

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 August 2010 (12.08.2010)

PCT

(10) International Publication Number
WO 2010/091413 A1

(51) International Patent Classification:
A01N 43/50 (2006.01)

(21) International Application Number:
PCT/US2010/023645

(22) International Filing Date:
9 February 2010 (09.02.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/151,079 9 February 2009 (09.02.2009) US
61/153,231 17 February 2009 (17.02.2009) US
61/153,224 17 February 2009 (17.02.2009) US
61/156,110 27 February 2009 (27.02.2009) US
61/156,239 27 February 2009 (27.02.2009) US

(71) Applicant (for all designated States except US): **ENANTA PHARMACEUTICALS, INC.** [US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **QIU, Yao-Ling** [US/US]; 29 Linda Road, Andover, MA 01810 (US). **WANG, Ce** [CN/US]; 220 School Street, Suite 9, Waltham, MA 02451 (US). **YING, Lu** [CN/US]; 24 Wilson Avenue, Belmont, MA 02478 (US). **PENG, Xiaowen** [CN/US]; 268 Grove Street, #2, Auburndale, MA (US). **OR, Yat, Sun** [US/US]; 169 Fayette Street, Watertown, MA 02472 (US).

(74) Agents: **HODA, Mahreen, Chaudhry** et al.; Elmore Patent Law Group, P.C., 515 Groton Road, Unit 1R, Westford, MA 01886 (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, 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, RO, RS, RU, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: LINKED DIBENZIMIDAZOLE DERIVATIVES

(57) Abstract: The present invention discloses linked dibenzimidazole derivatives, or pharmaceutically acceptable salts, esters, or prodrugs thereof, which inhibit RNA-containing virus, particularly the hepatitis C virus (HCV). Consequently, the compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.



WO 2010/091413 A1

LINKED DIBENZIMIDAZOLE DERIVATIVES

Inventors: Yao-Ling Qiu, Ce Wang, Lu Ying, Xiaowen Peng, and Yat Sun Or

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/151,079 filed February 9, 2009, U.S. Provisional Application No. 61/153,224, filed February 17, 2009, U.S. Provisional Application No. 61/156,239 filed February 27, 2009, U.S. Provisional Application No. 61/153,231 filed February 17, 2009 and U.S. Provisional Application No. 61/156,110 filed February 27, 2009. The entire teachings of the above applications are incorporated herein by reference.

TECHNICAL FIELD

5 The present invention relates to novel antiviral agents. More specifically, the present invention relates to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, methods for inhibiting HCV viral replication, methods for treating or preventing HCV infection, and processes for making the compounds.

10 BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have
15 been estimated at \$5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by
20 the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV
25 infection. However, adverse side effects are commonly associated with this treatment: flu-

like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K. L. (1997) *Hepatology* 26 (suppl 1): 71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of responders, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) *Science* 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non-A, non-B hepatitis (NANBH) (Kuo, G et al (1989) *Science* 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae*, such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) *Science* 244:359-362; Miller, R.H. and R.H. Purcell (1990) *Proc. Natl. Acad. Sci. USA* 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al 'An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' *RNA – A Publication of the RNA Society*. 1(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) *Virology* 2nd Edition,

p931-960; Raven Press, N.Y.). There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are several non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease. NS5A is a membrane-anchored phosphoprotein that is observed in basally phosphorylated (56 kDa) and hyperphosphorylated (58 kDa) forms. While its function has not fully been elucidated, NS5A is believed to be important in viral replication. The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. *et al* (1996) *EMBO J.* 15:1-22) encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.* (2000) *Journal of Virology*, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to be useful to treat HCV infection.

Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. *et al* (1996) *J. Virology* 70:3363-3371; Tanaka, T. *et al* (1995) *Biochem Biophys. Res. Commun.* 215:744-749; Tanaka, T. *et al* (1996) *J. Virology* 70:3307-3312; Yamada, N. *et al* (1996) *Virology* 223:255-261). The 3' NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, 284, 1; and in Rice, C. M. *Nature* 2005, 435, 374.

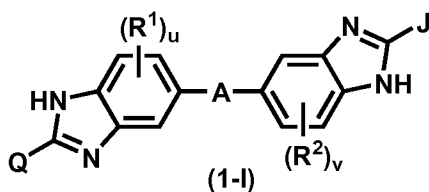
Based on the foregoing, there exists a significant need to identify compounds with the ability to inhibit HCV. A general strategy for the development of antiviral agents is to inactivate virally encoded proteins, including NS5A, that are essential for the replication of the virus. The relevant patent disclosures describing the synthesis of HCV NS5A

inhibitors are: US 2009/0202478; US 2009/0202483; WO 2009/020828; WO 2009/020825; WO 2009/102318; WO 2009/102325; WO 2009/102694; WO 2008/144380; WO 2008/021927; WO 2008/021928; WO 2008/021936; WO 2006/1333262; WO 2004/014852; WO 2008/070447; WO 2009/034390; WO 2006/079833; WO 2007/031791; WO 2007/070556; WO 2007/070600; WO 2008/064218; WO 2008/154601; WO 2007/082554; WO 2008/048589, the contents of each of which are expressly incorporated by reference herein.

SUMMARY OF THE INVENTION

The present invention relates to novel antiviral compounds represented herein below, pharmaceutical compositions comprising such compounds, and methods for the treatment or prophylaxis of viral (particularly HCV) infection in a subject in need of such therapy with said compounds. Compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents.

In its first principal aspect, the present invention provides a compound of Formula (1-I):



or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from the group consisting of: aryl, heteroaryl, heterocyclic, C₃-C₈ cycloalkyl, and C₃-C₈ cycloalkenyl, all optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, -R¹⁰, -OR¹¹, N(R¹¹)₂, -C(O)R¹¹, -CO₂R¹¹, -C(O)N(R¹¹)₂ and -N(R¹¹)C(O)R¹¹; A is preferably phenyl, 5-7-membered heteroaryl, 5-7-membered heterocyclic, C₅-C₇ cycloalkyl, or C₅-C₇ cycloalkenyl, all optionally substituted with one or more substituents independently selected from halogen and R¹⁰;

R¹⁰ at each occurrence is independently C₁-C₄ alkyl optionally substituted with one or more halogen atoms;

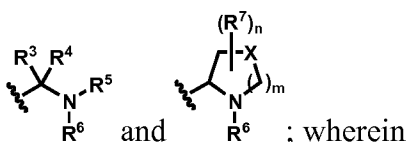
R^{11} at each occurrence is independently hydrogen or optionally substituted C_1 - C_8 alkyl;

R^1 and R^2 at each occurrence are each independently selected from the group consisting of: halogen, cyano, optionally substituted C_1 - C_4 alkyl, $-O-R^{11}$, $-NR^aR^b$,
 5 $-C(O)R^{11}$, $-CO_2R^{11}$, and $-C(O)NR^aR^b$, preferably halogen and optionally substituted C_1 - C_4 alkyl;

R^a and R^b at each occurrence are each independently hydrogen, optionally substituted C_1 - C_8 alkyl, or optionally substituted C_2 - C_8 alkenyl; or R^a and R^b taken together with the nitrogen atom to which they are attached form an optionally substituted
 10 heterocyclic or optionally substituted heteroaryl group;

u and v at each occurrence are each independently 0, 1, 2, or 3, preferably 0 or 1;

Q and J are each independently selected from:



R^3 and R^4 at each occurrence are each independently hydrogen, optionally
 15 substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl or optionally substituted C_3 - C_8 cycloalkyl, preferably hydrogen or optionally substituted C_1 - C_4 alkyl; or alternatively, R^3 and R^4 taken together with the carbon atom to which they are attached form optionally substituted C_3 - C_8 cycloalkyl or optionally substituted heterocyclic;

R^5 at each occurrence is independently hydrogen, optionally substituted C_1 - C_8
 20 alkyl, or optionally substituted C_3 - C_8 cycloalkyl, preferably hydrogen or optionally substituted C_1 - C_4 alkyl;

R^6 at each occurrence is independently selected from the group consisting of: hydrogen, $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$, preferably $-C(O)-R^{12}$;

R^{12} at each occurrence is independently selected from the group consisting of: $-O-$
 25 R^{11} , $-NR^aR^b$, $-R^{13}$, $-NR^cR^d$, $-CH(R^{13})NR^aR^b$, and $-CH(R^{13})NR^cR^d$, preferably optionally substituted C_1 - C_8 alkyl and $-O-R^{11}$;

R^{13} at each occurrence is independently selected from the group consisting of: optionally substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl, optionally substituted C_2 - C_8 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted
 30 C_3 - C_8 cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, and optionally

substituted heteroarylalkyl; preferably C₁-C₈ alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or O(C₁-C₄ alkyl);

R^c and R^d at each occurrence are each independently selected from the group consisting of: hydrogen, -R¹³, -C(O)-R¹³, -C(O)-OR¹³, -S(O)₂-R¹³, -C(O)N(R¹³)₂, and

5 -S(O)₂N(R¹³)₂;

m is 0, 1, or 2; preferably 1;

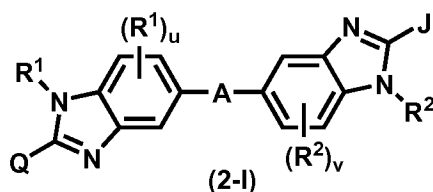
n is 0, 1, 2, 3, or 4; preferably 0, 1, or 2;

X at each occurrence is independently selected from O, S, S(O), SO₂, CH₂, CHR⁷, and C(R⁷)₂; preferably CH₂ or CHR⁷; provided that when m is 0, X is selected from CH₂,

10 CHR⁷, and C(R⁷)₂; or

R⁷ at each occurrence is independently selected from the group consisting of: halogen, cyano, -O-R¹¹, -NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted -C₁-C₄ alkyl, preferably methyl or halogen; or, two vicinal R⁷ groups are taken together with the two adjacent atoms to which they are attached form a fused, optionally substituted -C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably, a fused, optionally substituted cyclopropyl; or alternatively, two geminal R⁷ groups are taken together with the carbon atom to which they are attached form a spiro, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl.

20 In its second principal aspect, the present invention provides a compound of Formula (2-I):



or a pharmaceutically acceptable salt thereof, wherein:

A is an optionally substituted linear aliphatic group;

25 R¹ and R² at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C₁-C₄ alkyl, -O-R¹¹, -NR^aR^b, -C(O)R¹¹, -CO₂R¹¹, and -C(O)NR^aR^b; preferably hydrogen, halogen and optionally substituted C₁-C₄ alkyl;

R¹¹ at each occurrence is independently hydrogen or optionally substituted C₁-C₈ alkyl; and

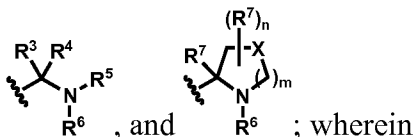
30

R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, and optionally substituted C_2 - C_8 alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl

5 group;

u and v at each occurrence are each independently 1, 2, or 3;

Q and J are each independently selected from:



10 consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl, and optionally substituted C_3 - C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1 - C_4 alkyl; or alternatively, R^3 and R^4 can be taken together with the carbon atom to which they are attached to form optionally substituted C_3 - C_8 cycloalkyl or optionally substituted heterocyclic;

15 R^5 at each occurrence is independently hydrogen, optionally substituted C_1 - C_8 alkyl, or optionally substituted C_3 - C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1 - C_4 alkyl;

R^6 at each occurrence is independently selected from the group consisting of $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$, preferably $-C(O)-R^{12}$, more preferably an optionally substituted amino acid acyl;

R^{12} at each occurrence is independently selected from the group consisting of: $-O-R^{11}$, $-NR^aR^b$, $-R^{13}$, and $-NR^cR^d$, preferably optionally substituted C_1 - C_8 alkyl and $-O-R^{11}$;

25 R^{13} at each occurrence is independently selected from the group consisting of hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; preferably optionally substituted C_1 - C_8 alkyl; more preferably C_1 - C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or $O(C_1$ - C_4 alkyl); and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, $-R^{13}$, $-C(O)-R^{13}$, $-C(O)-OR^{13}$, $-S(O)_2-R^{13}$, $-C(O)N(R^{13})_2$, and $-S(O)_2N(R^{13})_2$;

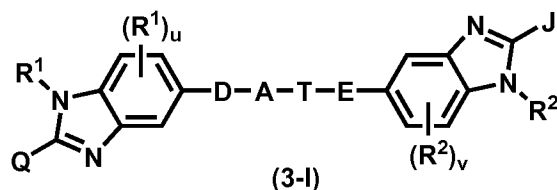
m is 0, 1, or 2, preferably 1;

n is 1, 2, 3, or 4, preferably 1 or 2;

X at each occurrence is independently selected from O, S, S(O), SO₂, and C(R⁷)₂, preferably CH₂ or CHR⁷; provided that when m is 0, X is C(R⁷)₂; and

R⁷ at each occurrence is independently selected from the group consisting of
 5 hydrogen, halogen, cyano, -O-R¹¹, -NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted -C₁-C₄ alkyl; preferably hydrogen, methyl or halogen; or two vicinal R⁷ groups can be taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably a fused, optionally substituted
 10 cyclopropyl; or alternatively, two geminal R⁷ groups can be taken together with the carbon atom to which they are attached to form a spiro, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl.

In its third principal aspect, the present invention provides a compound of Formula
 15 (3-I):



or a pharmaceutically acceptable salt thereof, wherein:

A is a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C₃-C₈ cycloalkyl, and C₃-C₈ cycloalkenyl, each optionally substituted;

20 D is absent or an optionally substituted aliphatic group;

T is absent or an optionally substituted linear aliphatic group containing zero to eight carbons;

E is absent or independently selected from optionally substituted aryl and optionally substituted heteroaryl;

25 wherein one or two of D, E, and T are absent;

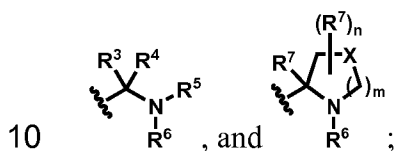
R¹ and R² at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C₁-C₄ alkyl, -O-R¹¹, -NR^aR^b, -C(O)R¹¹, -CO₂R¹¹, and -C(O)NR^aR^b; preferably hydrogen, halogen and optionally substituted C₁-C₄ alkyl;

R^{11} at each occurrence is independently hydrogen or optionally substituted C_1 - C_8 alkyl;

R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, and optionally substituted C_2 - C_8 alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

u and v at each occurrence are each independently 1, 2, or 3;

Q and J are each independently selected from:



R^3 and R^4 at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl, and optionally substituted C_3 - C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1 - C_4 alkyl; or alternatively, R^3 and R^4 can be taken together with the carbon atom to which they are attached to form optionally substituted C_3 - C_8 cycloalkyl or optionally substituted heterocyclic;

R^5 at each occurrence is independently hydrogen, optionally substituted C_1 - C_8 alkyl, or optionally substituted C_3 - C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1 - C_4 alkyl;

20 R^6 at each occurrence is independently selected from the group consisting of $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$, preferably $-C(O)-R^{12}$, more preferably an optionally substituted amino acid acyl;

R^{12} at each occurrence is independently selected from the group consisting of: $-O-R^{11}$, $-NR^aR^b$, $-R^{13}$, and $-NR^cR^d$, preferably optionally substituted C_1 - C_8 alkyl and $-O-R^{11}$;

25 R^{13} at each occurrence is independently selected from the group consisting of hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; preferably optionally substituted C_1 - C_8 alkyl; more preferably C_1 - C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or $O(C_1$ - C_4 alkyl); and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, $-R^{13}$, $-C(O)-R^{13}$, $-C(O)-OR^{13}$, $-S(O)_2-R^{13}$, $-C(O)N(R^{13})_2$, and $-S(O)_2N(R^{13})_2$;

m is 0, 1, or 2, preferably 1;

5 n is 1, 2, 3, or 4, preferably 1 or 2;

X at each occurrence is independently selected from O, S, S(O), SO₂, and $C(R^7)_2$, preferably CH₂ or CHR⁷; provided that when m is 0, X is $C(R^7)_2$; and

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, cyano, $-O-R^{11}$, $-NR^aR^b$, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted $-C_1-C_4$ alkyl; preferably hydrogen, methyl or halogen; or two vicinal R^7 groups can be taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably a fused, optionally substituted cyclopropyl; or alternatively two geminal R^7 groups can be taken together with the carbon atom to which they are attached to form a spiro, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl.

Each preferred group stated above can be taken in combination with one, any or all other preferred groups.

20 In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

25 In yet another aspect, the present invention provides a method of inhibiting the replication of a RNA-containing virus comprising contacting said virus with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. Particularly, this invention is directed to methods of inhibiting the replication of HCV.

30 In still another aspect, the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt

thereof. Particularly, this invention is directed to methods of treating or preventing infection caused by HCV.

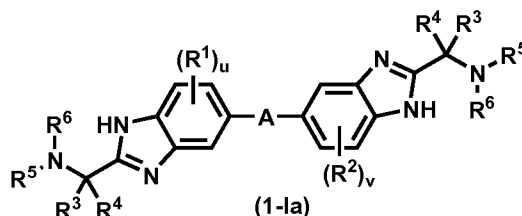
Yet another aspect of the present invention provides the use of a compound or combination of compounds of the present invention, or a therapeutically acceptable salt thereof, as defined hereinafter, in the preparation of a medicament for the treatment or prevention of infection caused by RNA-containing virus, specifically HCV.

DETAILED DESCRIPTION OF THE INVENTION

I. Compounds having Formula (1-I)

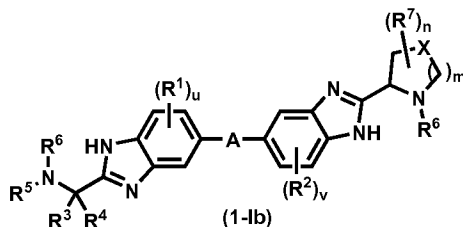
In certain aspects, the present invention relates to compounds of Formula (1-I) as illustrated above, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention relates to compounds of Formula (1-Ia), or a pharmaceutically acceptable salt thereof:



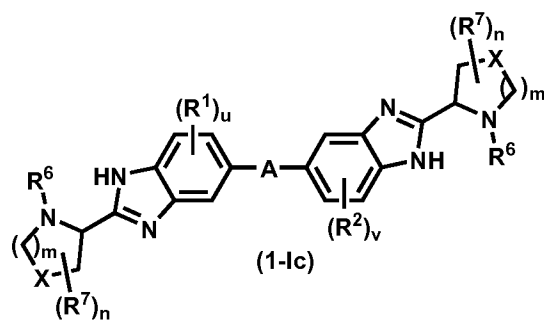
wherein A, u, v, R¹, R², R³, R⁴, R⁵ and R⁶ are as previously defined in Formula (1-I).

In another embodiment, the present invention relates to compounds of Formula (1-Ib), or a pharmaceutically acceptable salt thereof:



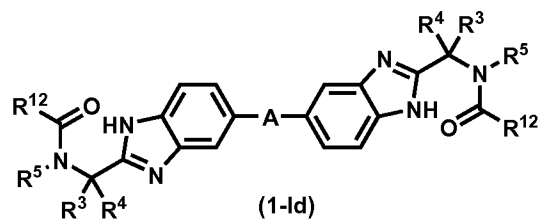
wherein A, u, v, m, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as previously defined in Formula (1-I).

In yet another embodiment, the present invention relates to compounds of Formula (1-Ic), or a pharmaceutically acceptable salt thereof:



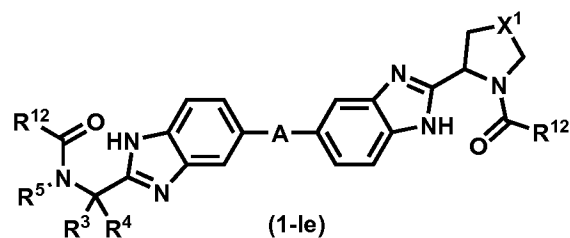
wherein A, u, v, m, n, R¹, R², R⁶, R⁷ and X are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-Id), or a pharmaceutically acceptable salt thereof:



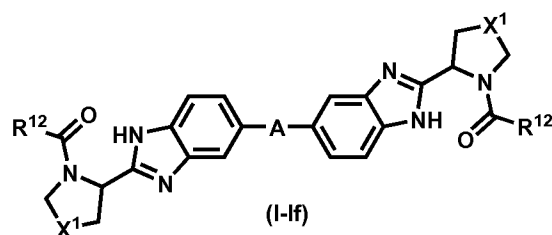
wherein A, R³, R⁴, R⁵ and R¹² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-Ie), or a pharmaceutically acceptable salt thereof:



wherein A, R³, R⁴, R⁵ and R¹² are as previously defined in Formula (1-I). and X¹ is CH₂, CHF, CH(OH), or CF₂.

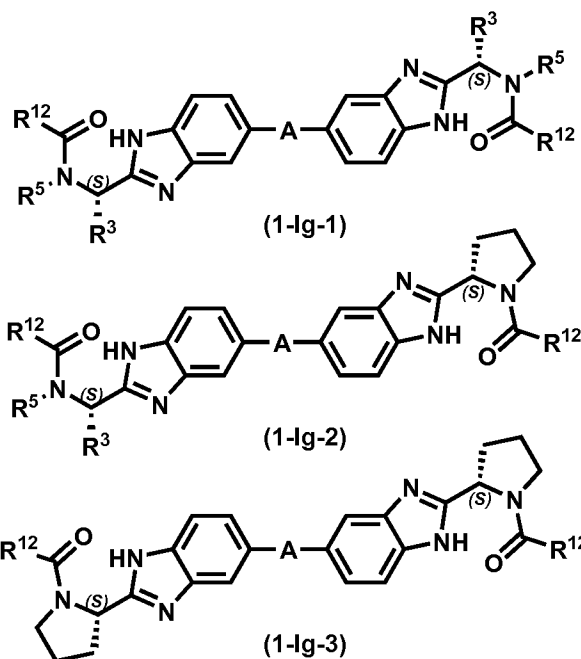
In still another embodiment, the present invention relates to compounds of Formula (1-If), or a pharmaceutically acceptable salt thereof:



wherein A, X¹ and R¹² are as previously defined in Formula (1-I).

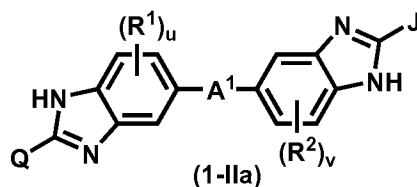
In an additional embodiment, the present invention relates to compounds of Formula (1-If), wherein R¹² is C₁-C₈ alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C₁-C₄ alkyl); or a pharmaceutically acceptable salt thereof.

In still another embodiment of the present invention, the absolute stereochemistry of the pyrrolidine and 2-benzimidazolylmethylamine moiety is represented by Formulae (1-Ig-1, 1-Ig-2 and 1-Ig-3):



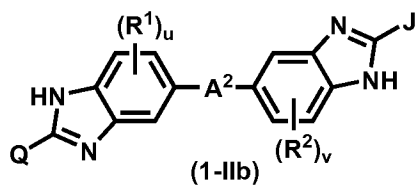
5 wherein A, R^3 , R^5 and R^{12} are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIa), or a pharmaceutically acceptable salt thereof:



10 wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (1-I) and A^1 is independently an aryl; preferably phenyl or naphthyl ring, optionally substituted with one or more substituents independently selected from halogen and R^{10} ; and R^{10} is as previously defined in Formula (1-I).

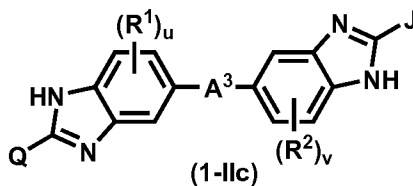
In still another embodiment, the present invention relates to compounds of Formula (1-IIb), or a pharmaceutically acceptable salt thereof:



15 wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (1-I) and A^2 is independently a heteroaryl, preferably 5-7-membered heteroaryl, optionally with one or

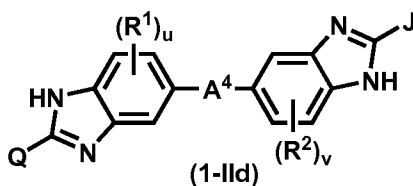
more substituents independently selected from halogen and R^{10} ; and R^{10} is as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIc), or a pharmaceutically acceptable salt thereof:



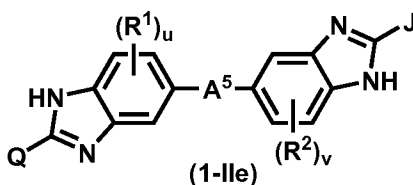
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (1-I) and A^3 is independently a heterocyclic, preferably 5-7-membered heterocyclic, optionally with one or more substituents independently selected from halogen and R^{10} ; and R^{10} is as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIId), or a pharmaceutically acceptable salt thereof:



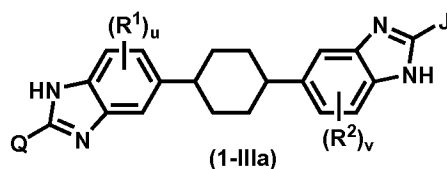
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (1-I) and A^4 is independently a C_3 - C_8 cycloalkyl, preferably 5-7-membered cycloalkyl, optionally with one or more substituents independently selected from halogen and R^{10} ; and R^{10} is as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIe), or a pharmaceutically acceptable salt thereof:



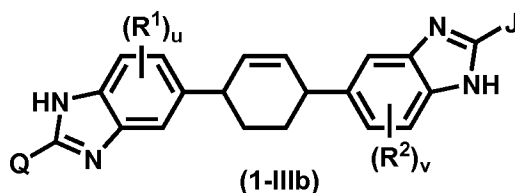
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (1-I) and A^5 is independently a C_3 - C_8 cycloalkenyl, preferably 5-7-membered cycloalkenyl, optionally substituted with one or more substituents independently selected from halogen and R^{10} ; and R^{10} is as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIf), or a pharmaceutically acceptable salt thereof:



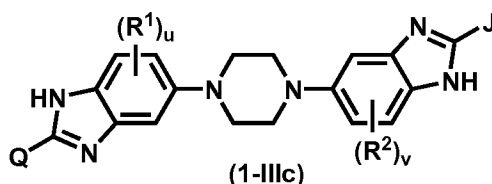
wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIb), or a pharmaceutically acceptable salt thereof:



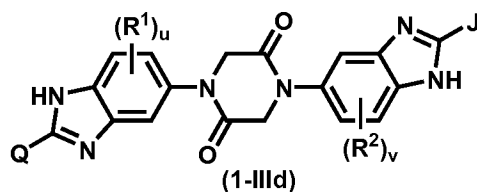
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIc), or a pharmaceutically acceptable salt thereof:



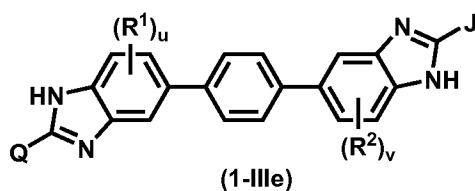
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIId), or a pharmaceutically acceptable salt thereof:



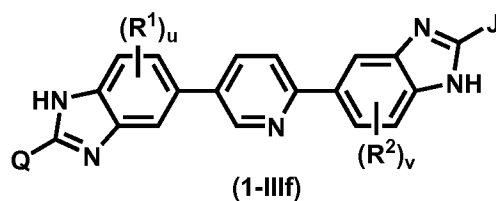
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIE), or a pharmaceutically acceptable salt thereof:



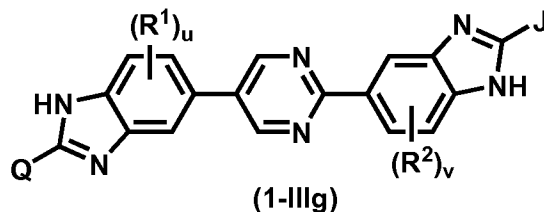
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIf), or a pharmaceutically acceptable salt thereof:



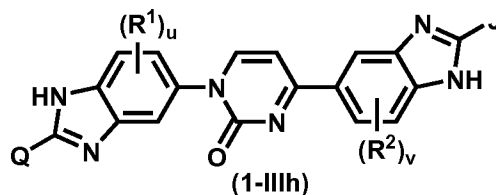
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

In still another embodiment, the present invention relates to compounds of Formula (1-IIIg), or a pharmaceutically acceptable salt thereof:



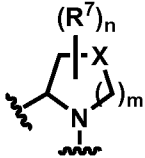
wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

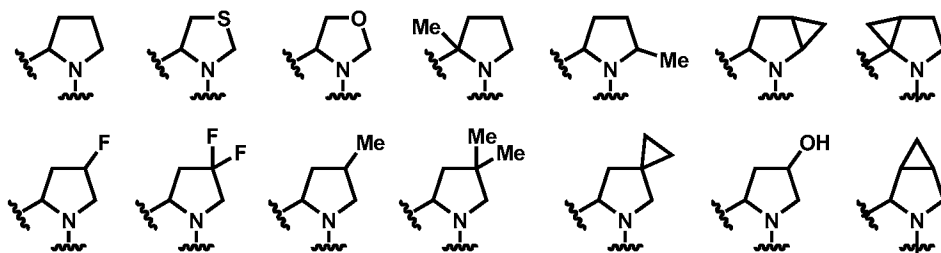
In still another embodiment, the present invention relates to compounds of Formula (1-IIIh), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R¹, and R² are as previously defined in Formula (1-I).

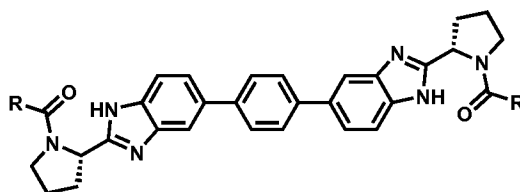
In still another embodiment, the present invention relates to compounds of

Formula (1-I), or a pharmaceutically acceptable salt thereof; wherein  at each occurrence is independently illustrated by one of the following groups:



Representative compounds of Formula (1-I) are those selected from compounds 1-1 to 1-360, 1-354a, 1-357a, and 1-361 to 1-372 compiled in the following tables:

Table 1: Compounds 1-1 to 1-219



Entry 1-		Entry 1-		Entry 1-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	

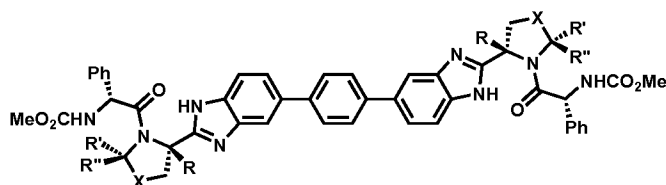
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	

91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	

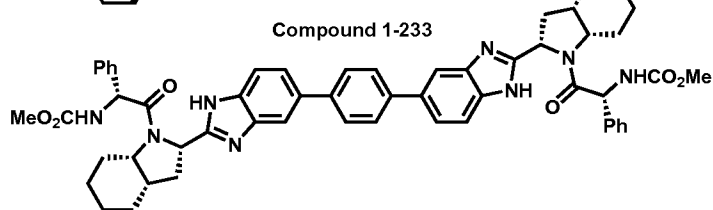
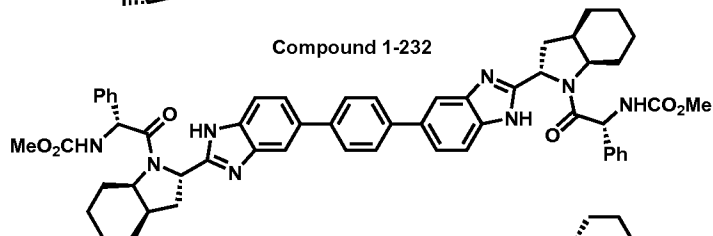
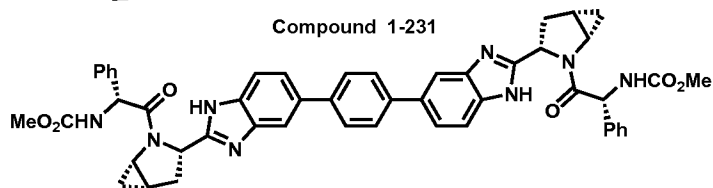
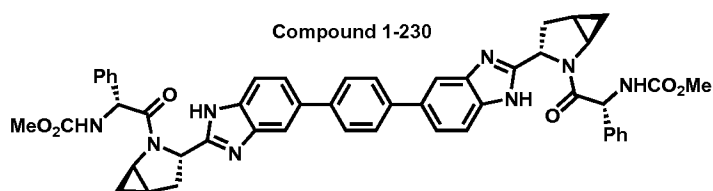
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	

175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Table 2: Compounds 1-220 to 1-229

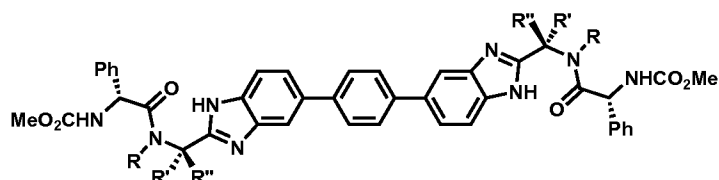


Entry 1-	R	R'	R''	X	Entry 1-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	



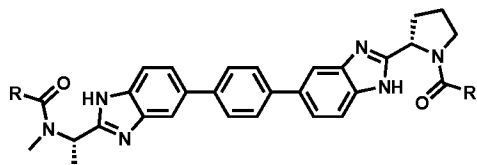
5

Table 3: Compounds 1-234 to 1-243



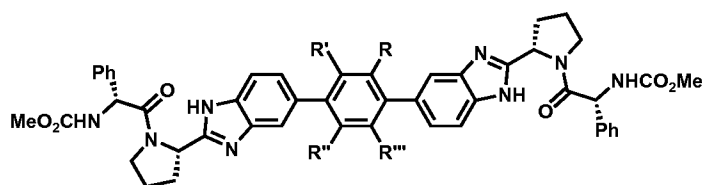
Entry 1-	R	R'	R''	Entry 1-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

Table 4: Compounds 1-244 to 1-263



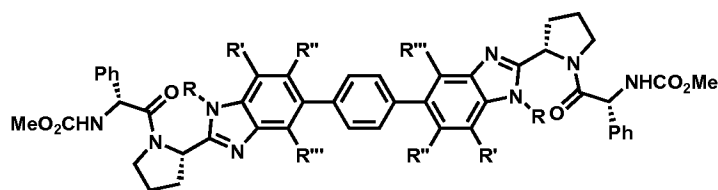
Entry 1-	R	R'	Entry 1-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 5: Compounds 1-264 to 1-283



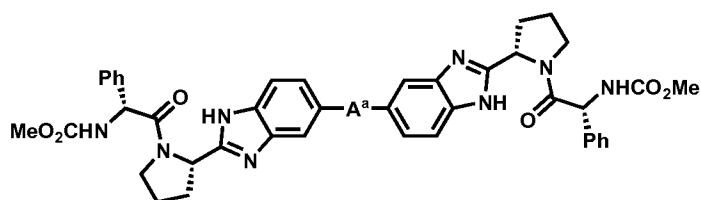
Entry 1-	R	R'	R''	R'''	Entry 1-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H
280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

Table 6: Compounds 1-284 to 1-309



Entry 1-	R	R'	R''	R'''	Entry 1-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

Table 7: Compounds 1-310 to 1-360



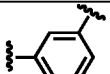
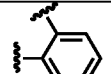
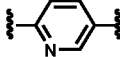
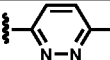
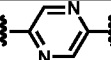
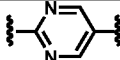
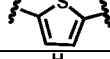
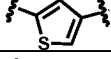
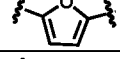
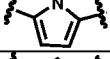
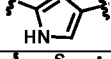
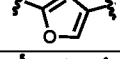
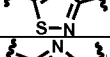
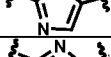
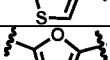
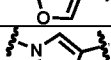
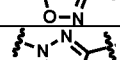
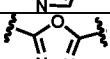
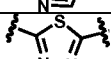
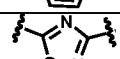
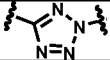
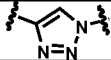
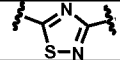
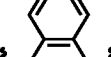
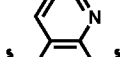
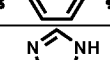
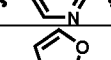
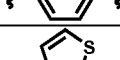
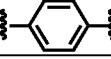
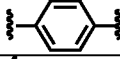
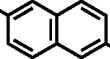
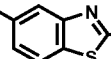
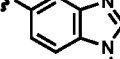
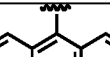
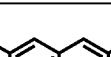
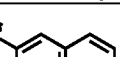
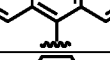
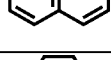
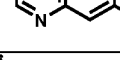
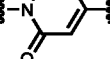
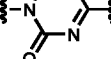
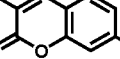
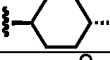
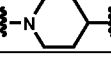
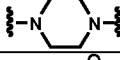
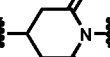
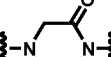
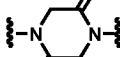
Entry 1-	A ^a	Entry 1-	A ^a	Entry 1-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	
337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	
358		359		360	

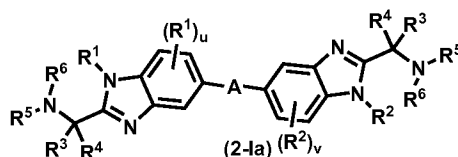
Table 8: Compounds 1-354a, 1-357a, and 1-361 to 1-372

1-354a	
1-357a	
1-361	
1-362	
1-363	
1-364	
1-365	
1-366	
1-367	
1-368	
1-369	
1-370	
1-371	
1-372	

II. Compounds having the Formula (2-I)

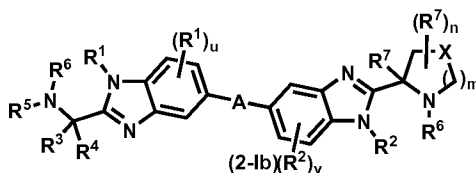
The present invention relates to compounds of Formula (2-I) as illustrated above, or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention relates to compounds of Formula (2-Ia),
5 or a pharmaceutically acceptable salt thereof:



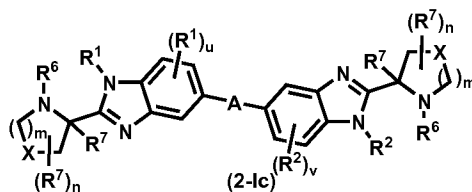
wherein A, u, v, R¹, R², R³, R⁴, R⁵ and R⁶ are as previously defined in Formula (2-I).

In another embodiment, the present invention relates to compounds of Formula (2-Ib), or a pharmaceutically acceptable salt thereof:



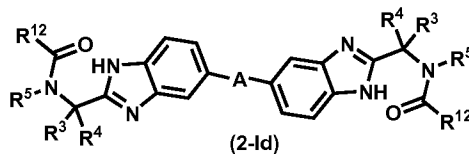
wherein A, u, v, m, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as previously defined in Formula (2-I).

In yet another embodiment, the present invention relates to compounds of Formula (2-Ic), or a pharmaceutically acceptable salt thereof:



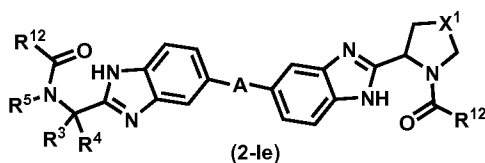
wherein A, u, v, m, n, R¹, R², R⁶, R⁷ and X are as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-Id), or a pharmaceutically acceptable salt thereof:



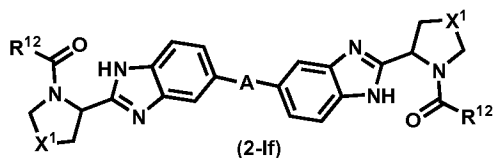
wherein A, R³, R⁴, R⁵ and R¹² are as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-Ie), or a pharmaceutically acceptable salt thereof:



wherein A, R³, R⁴, R⁵ and R¹² are as previously defined in Formula (2-I) and X¹ is CH₂, CHF, CH(OH), or CF₂.

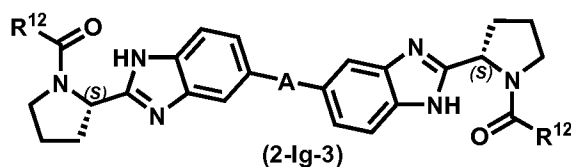
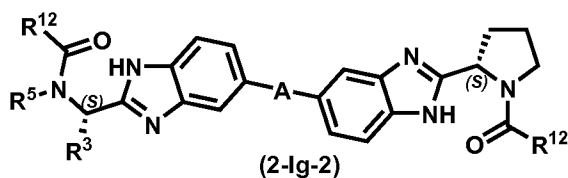
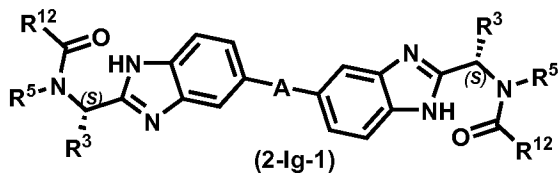
- In still another embodiment, the present invention relates to compounds of
 5 Formula (2-If), or a pharmaceutically acceptable salt thereof:



wherein A, X¹ and R¹² are as previously defined in Formula (2-I).

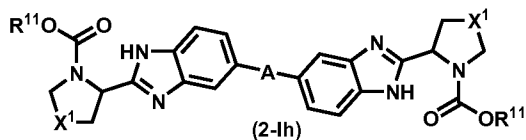
- In still another embodiment, the present invention relates to compounds of
 Formula (2-If), wherein R¹² is C₁-C₈ alkyl optionally substituted with amino, hydroxy,
 10 phenyl, protected amino, or O(C₁-C₄ alkyl); or a pharmaceutically acceptable salt thereof.

In still another embodiment of the present invention, the absolute stereochemistry
 of the pyrrolidine and 2-benzimidazolylmethylamine moiety is represented by Formulae
 (2-Ig-1, 2-Ig-2 and 2-Ig-3):



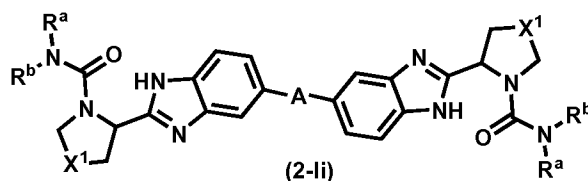
- 15 wherein A, R³, R⁵, and R¹² are as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of
 Formula (2-Ih), or a pharmaceutically acceptable salt thereof:



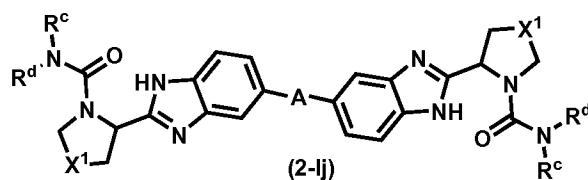
wherein A, X¹ and R¹¹ are as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-II), or a pharmaceutically acceptable salt thereof:



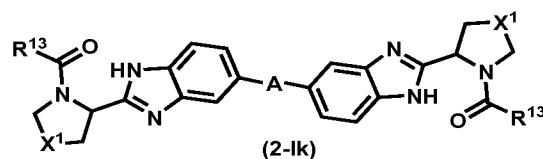
5 wherein A, X¹, R^a and R^b are as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-Ij), or a pharmaceutically acceptable salt thereof:



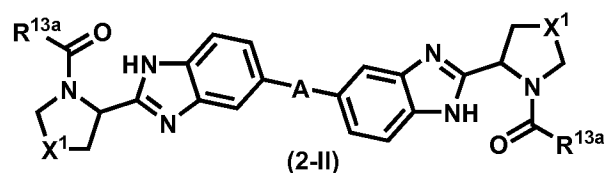
wherein A, X¹, R^c and R^d are as previously defined in Formula (2-I).

10 In still another embodiment, the present invention relates to compounds of Formula (2-Ik), or a pharmaceutically acceptable salt thereof:



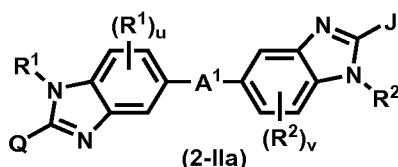
wherein A, X¹ and R¹³ are as previously defined in Formula (2-I).

15 In still another embodiment, the present invention relates to compounds of Formula (2-II), or a pharmaceutically acceptable salt thereof:



wherein A and X¹ are as previously defined in Formula (2-I) and R^{13a} at each occurrence is independently an optionally substituted C₁-C₈ alkyl; preferably C₁-C₈ alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C₁-C₄ alkyl).

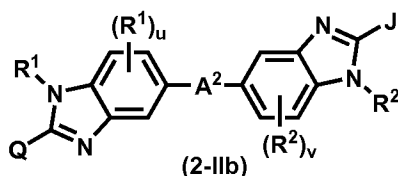
20 In still another embodiment, the present invention relates to compounds of Formula (2-IIa), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (2-I) and A¹ is C₁-C₈ alkyl, preferably C₃-C₆ alkyl, each optionally substituted.

In still another embodiment, the present invention relates to compounds of

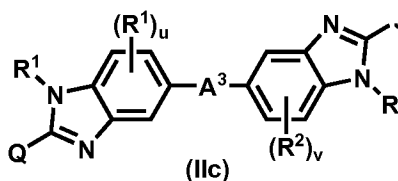
- 5 Formula (2-IIb), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (2-I) and A² is C₂-C₈ alkenyl, preferably C₃-C₆ alkenyl, each optionally substituted.

In still another embodiment, the present invention relates to compounds of

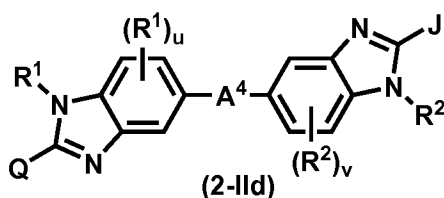
- 10 Formula (2-IIc), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (2-I) and A³ is C₂-C₈ alkynyl, preferably C₃-C₆ alkynyl, each optionally substituted.

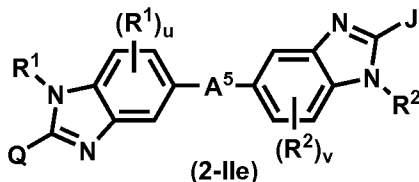
In still another embodiment, the present invention relates to compounds of

- 15 Formula (2-IIId), or a pharmaceutically acceptable salt thereof:



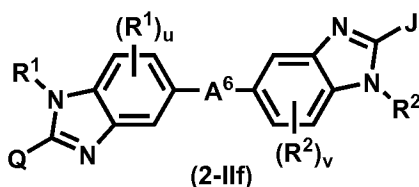
wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (2-I); and A⁴ is a linear aliphatic group containing a group selected from C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹),
 20 N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or C(O)N(R¹¹)S(O)₂N(R¹¹); and R¹¹ is as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-IIe), or a pharmaceutically acceptable salt thereof:



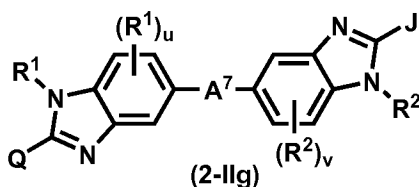
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I).; and A^5 is a linear aliphatic group containing an olefinic double bond and a group selected from $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-IIf), or a pharmaceutically acceptable salt thereof:



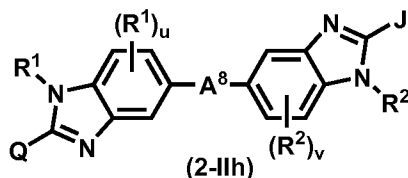
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I); and A^6 is a linear aliphatic group containing an alkynic triple bond and a group selected from $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-IIg), or a pharmaceutically acceptable salt thereof:



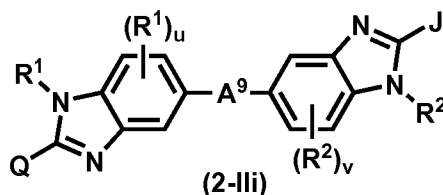
wherein Q, J, u, v, R^1 and R^2 are as previously defined for Formula (2-I); and A^7 is a linear aliphatic group containing one or more groups independently selected from O and $N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of Formula (2-IIh), or a pharmaceutically acceptable salt thereof:



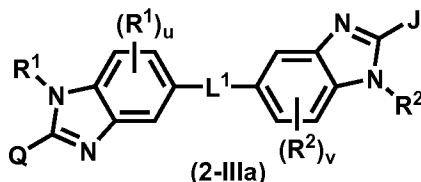
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I); and A^8 is a linear aliphatic group containing an olefinic double bond and one or more groups independently selected from O and $N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

5 In still another embodiment, the present invention relates to compounds of Formula (2-III), or a pharmaceutically acceptable salt thereof:



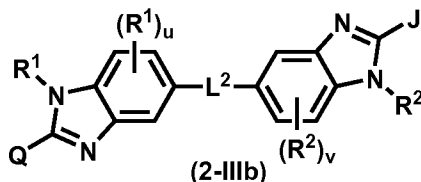
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I); and A^9 is a linear aliphatic group containing an alkynic triple bond and one or more groups independently selected from O and $N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

10 In still another embodiment, the present invention relates to compounds of Formula (2-IIIa), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I) and L^1 is selected from $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; and R^{11} is as previously defined in Formula (2-I).

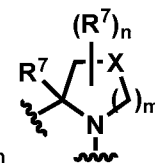
In still another embodiment, the present invention relates to compounds of Formula (2-IIIb), or a pharmaceutically acceptable salt thereof:



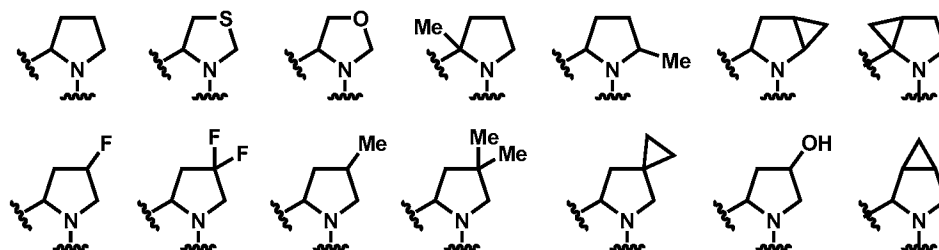
wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (2-I) and L^2 is a linear aliphatic group containing one to four carbons and two groups independently selected

from O, N(R¹¹), C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or C(O)N(R¹¹)S(O)₂N(R¹¹); and R¹¹ is as previously defined in Formula (2-I).

In still another embodiment, the present invention relates to compounds of

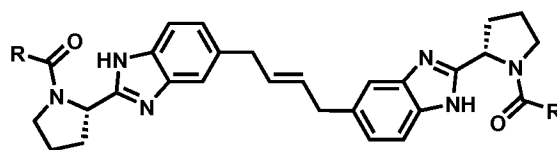


- 5 Formula (2-I), or a pharmaceutically acceptable salt thereof; wherein at each occurrence is independently illustrated by one of the following groups:



Representative compounds having the Formula (2-I) are those selected from compounds 2-1 to 2-352, 2-1a, 2-3a, and 2-353 to 2-357 compiled in the following tables:

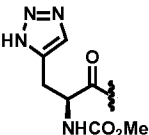
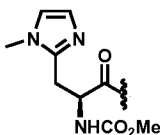
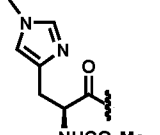
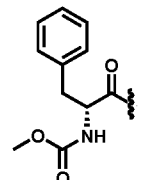
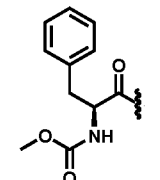
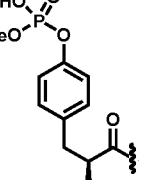
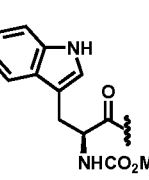
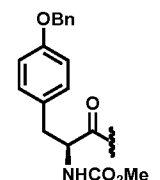
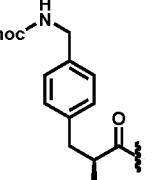
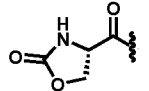
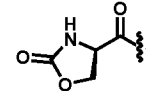
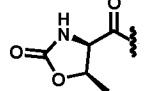
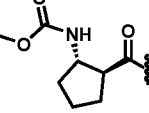
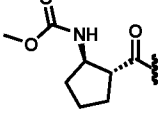
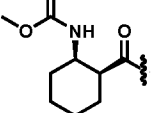
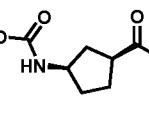
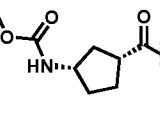
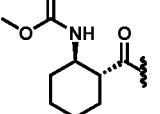
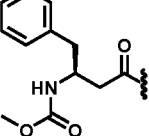
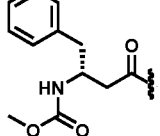
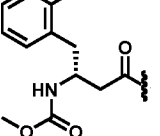
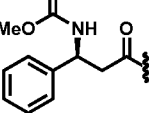
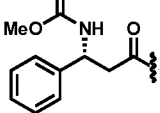
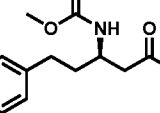
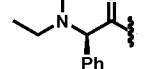
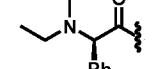
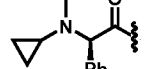
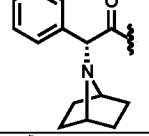
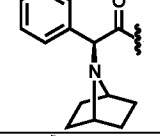
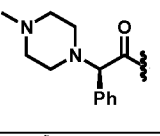
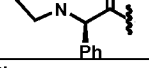
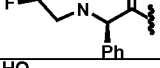
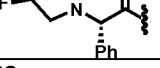
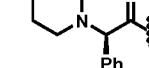
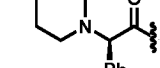
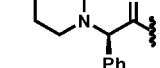
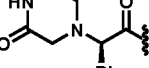
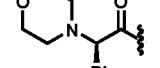
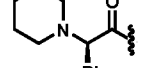
Table 9: Compounds 2-1 to 2-219

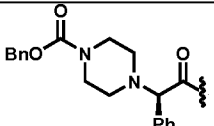
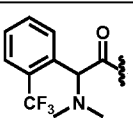
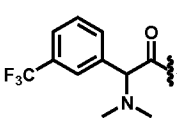
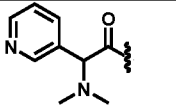
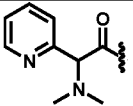
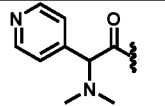
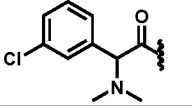
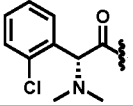
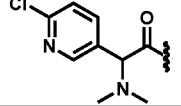
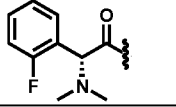
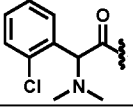
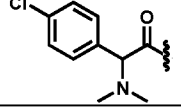
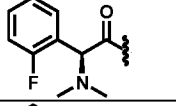
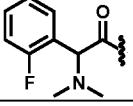
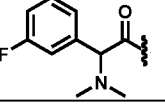
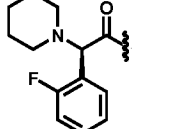
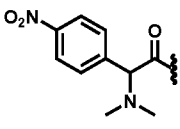
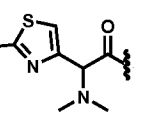
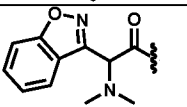
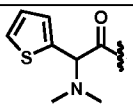
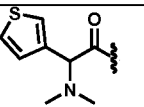
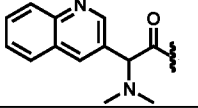
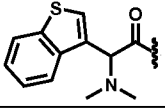
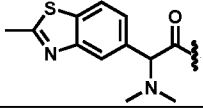
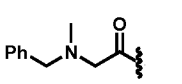
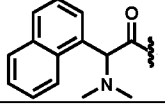
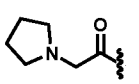
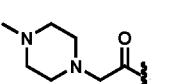
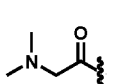
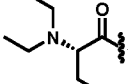
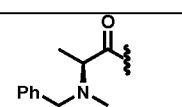
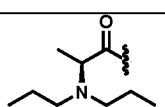
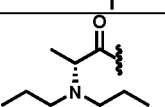
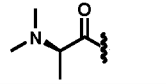
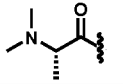
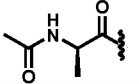
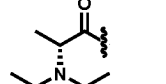
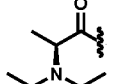
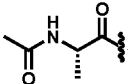
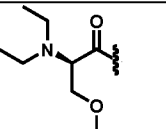
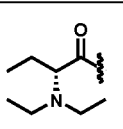
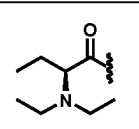
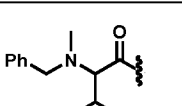
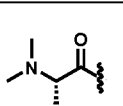
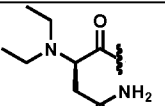
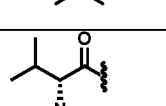
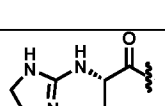
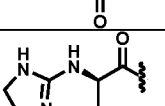


Entry 2-		Entry 2-		Entry 2-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	

25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	

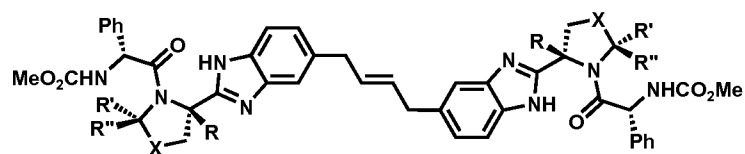
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	

115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	

154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	

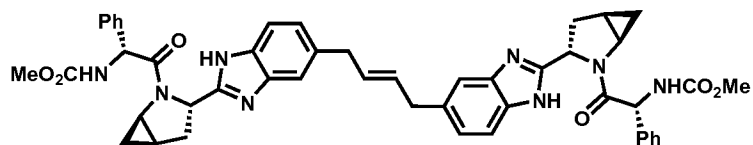
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Table 10: Compounds 2-220 to 2-229

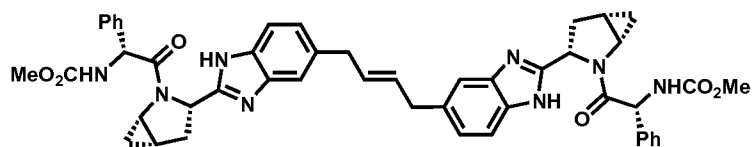


Entry 2-	R	R'	R''	X	Entry 2-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

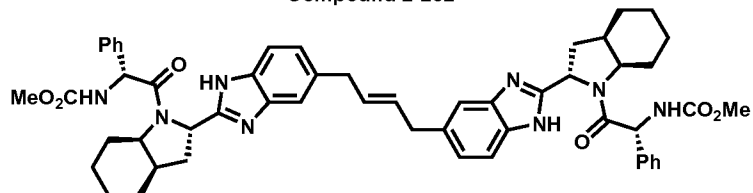
Compound 2-230



Compound 2-231



Compound 2-232



Compound 2-233

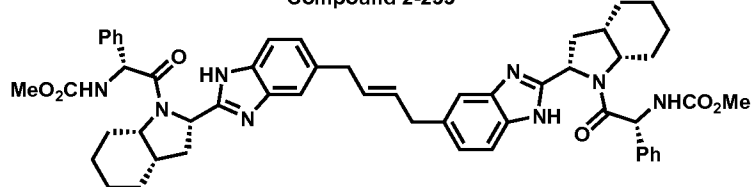
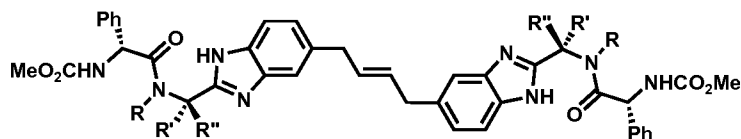


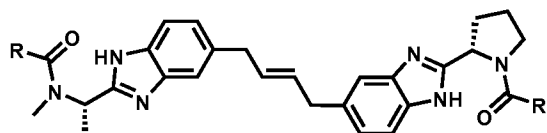
Table 11: Compounds 2-234 to 2-243



Entry 2-	R	R'	R''	Entry 2-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

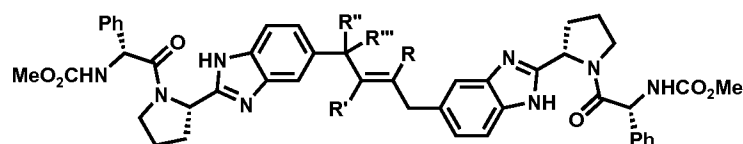
5

Table 12: Compounds 2-244 to 2-263



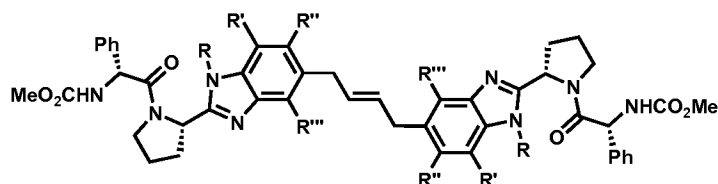
Entry 2-	R	R'	Entry 2-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 13: Compounds 2-264 to 2-283



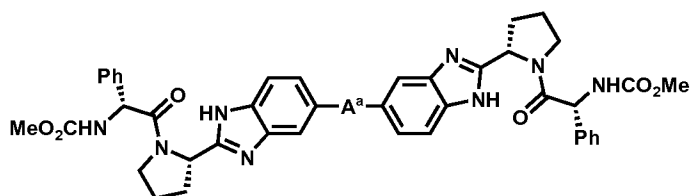
Entry 2-	R	R'	R''	R'''	Entry 2-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H
280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

Table 14: Compounds 2-284 to 2-309



Entry 2-	R	R'	R''	R'''	Entry 2-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

Table 15: Compounds 2-310 to 2-352



5

Entry 2-	A ^a	Entry 2-	A ^a	Entry 2-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	

334		335		336	
337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352					

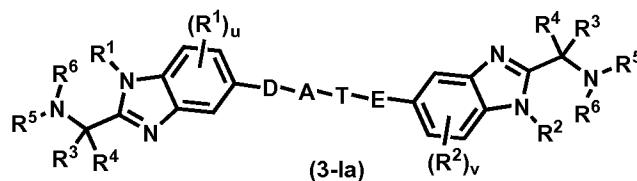
Table 16: Compounds 2-1a, 2-3a, and 2-353 to 2-357

2-1a	
2-3a	
2-353	
2-354	
2-355	
2-356	
2-357	

III. Compounds having the Formula (3-I)

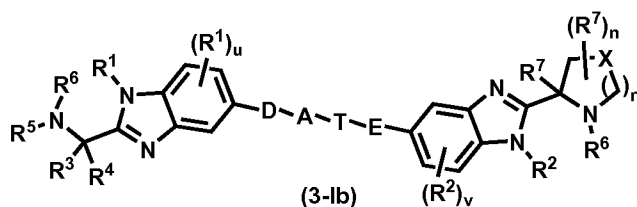
- 5 The present invention relates to compounds of Formula (3-I) as illustrated above, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention relates to compounds of Formula (3-Ia), or a pharmaceutically acceptable salt thereof:



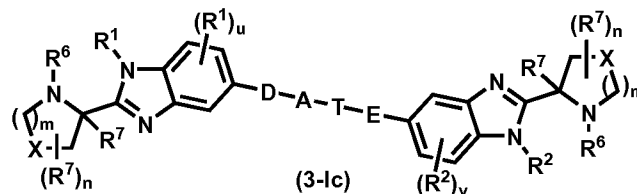
wherein A, D, E, T, u, v, R¹, R², R³, R⁴, R⁵ and R⁶ are as previously defined in Formula (3-I).

In another embodiment, the present invention relates to compounds of Formula (3-Ib), or a pharmaceutically acceptable salt thereof:



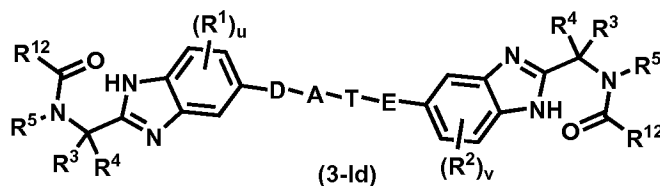
wherein A, D, E, T, u, v, m, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as previously defined in Formula (3-I).

In yet another embodiment, the present invention relates to compounds of Formula (3-Ic), or a pharmaceutically acceptable salt thereof:



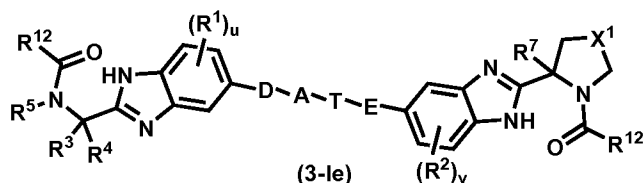
wherein A, D, E, T, u, v, m, n, R¹, R², R⁶, R⁷ and X are as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-Id), or a pharmaceutically acceptable salt thereof:



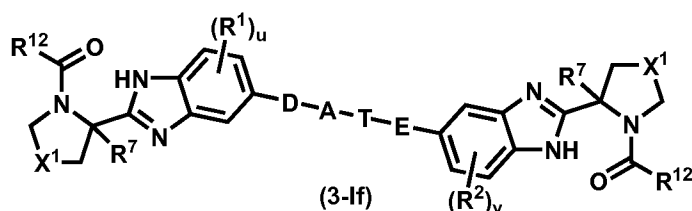
wherein A, D, E, T, u, v, R¹, R², R³, R⁴, R⁵ and R¹² are as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-Ie), or a pharmaceutically acceptable salt thereof:



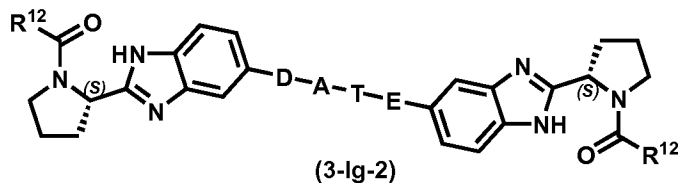
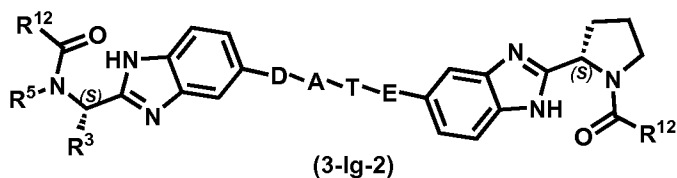
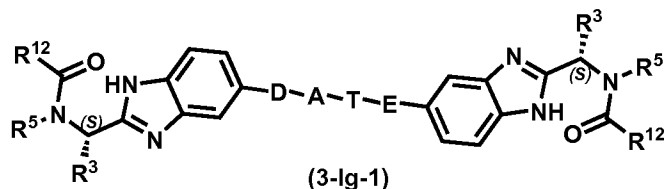
wherein A, D, E, T, u, v, R^1 , R^2 , R^3 , R^4 , R^5 , R^7 and R^{12} are as previously defined in Formula (3-I) and X^1 is independently CH_2 , CHF, CH(OH), or CF_2 .

In still another embodiment, the present invention relates to compounds of Formula (3-If), or a pharmaceutically acceptable salt thereof:



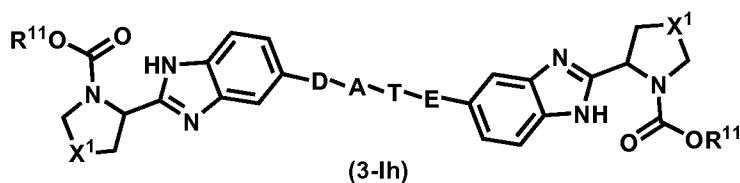
wherein A, D, E, T, u, v, X^1 , R^1 , R^2 , R^7 and R^{12} are as previously defined in Formula (3-I).

In still another embodiment of the present invention, the absolute stereochemistry of the pyrrolidine and 2-benzimidazolylmethylamine moiety is represented by Formula (3-Ig-1, 3-Ig-2 and 3-Ig-3):



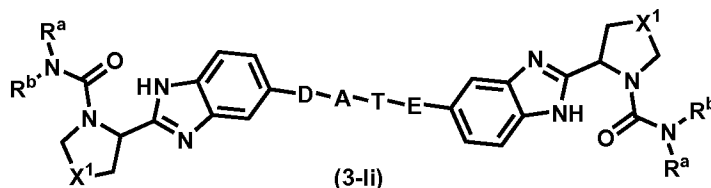
wherein A, D, E, T, R^3 , R^5 , and R^{12} are as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-Ih), or a pharmaceutically acceptable salt thereof:



wherein A, D, E, T, X¹ and R¹¹ are as previously defined in Formula (3-I)

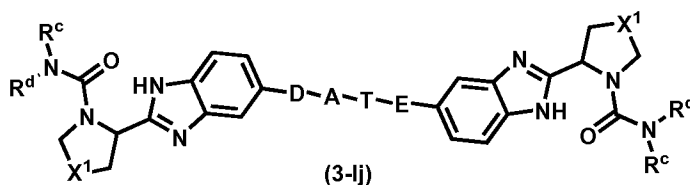
In still another embodiment, the present invention relates to compounds of Formula (3-Ii), or a pharmaceutically acceptable salt thereof:



5

wherein A, D, E, T, X¹, R^a and R^b are as previously defined in Formula (3-I).

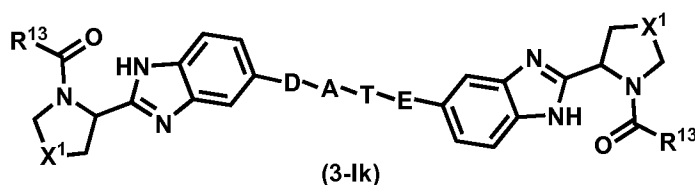
In still another embodiment, the present invention relates to compounds of Formula (3-Ij), or a pharmaceutically acceptable salt thereof:



10

wherein A, D, E, T, X¹, R^c and R^d are as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-Ik), or a pharmaceutically acceptable salt thereof:

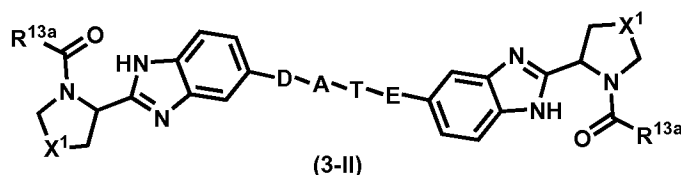


wherein A, D, E, T, X¹ and R¹³ are as previously defined in Formula (3-I)

15

In still another embodiment, the present invention relates to compounds of Formula (3-Ik), wherein R¹³ is C₁-C₈ alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C₁-C₄ alkyl); or a pharmaceutically acceptable salt thereof.

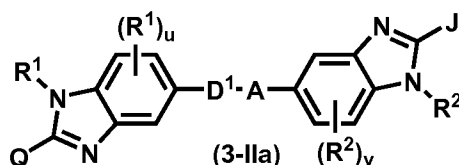
In still another embodiment, the present invention relates to compounds of Formula (3-II), or a pharmaceutically acceptable salt thereof:



20

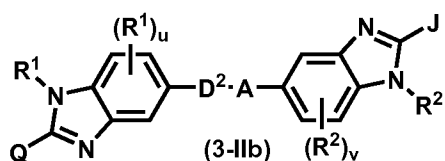
wherein A, D, E, T and X^1 are as previously defined in Formula (3-I) and $R^{1,5a}$ at each occurrence is independently an optionally substituted C_1 - C_8 alkyl; preferably C_1 - C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino or O(C_1 - C_4 alkyl).

- 5 In still another embodiment, the present invention relates to compounds of Formula (3-IIa), or a pharmaceutically acceptable salt thereof:



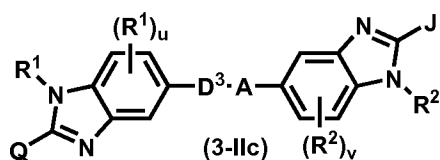
- wherein A, Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I) and D^1 is an optionally substituted C_1 - C_4 alkyl. In another embodiment, the compound has the Formula (3-IIa), wherein A is a heterocyclic; or a pharmaceutically acceptable salt thereof.
- 10

In still another embodiment, the present invention relates to compounds of Formula (3-IIb), or a pharmaceutically acceptable salt thereof:



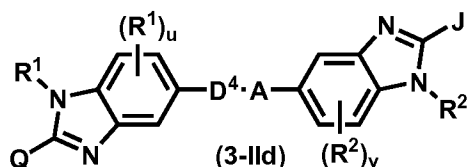
- wherein A, Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I) and D^2 is an optionally substituted C_2 - C_4 alkenyl.
- 15

In still another embodiment, the present invention relates to compounds of Formula (3-IIc), or a pharmaceutically acceptable salt thereof:



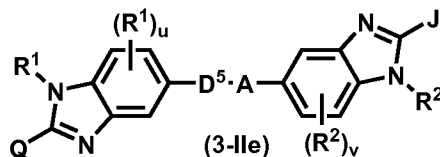
- wherein A, Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I) and D^3 is an optionally substituted C_2 - C_4 alkynyl.
- 20

In still another embodiment, the present invention relates to compounds of Formula (3-IId), or a pharmaceutically acceptable salt thereof:



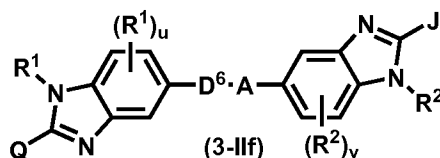
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and D⁴ is selected from O and N(R¹¹); and R¹¹ is as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-IIe), or a pharmaceutically acceptable salt thereof:



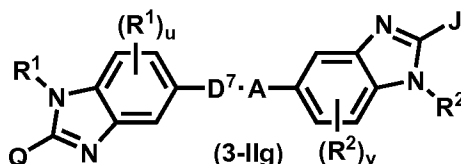
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and D⁵ is selected from C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ and C(O)N(R¹¹)S(O)₂N(R¹¹); and R¹¹ is as previously defined in Formula (3-I).

In still another embodiment, the present invention relates to compounds of Formula (3-IIf), or a pharmaceutically acceptable salt thereof:



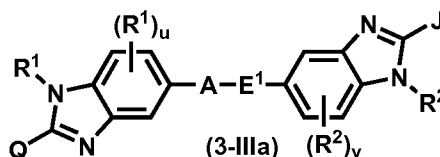
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and D⁶ is an optionally substituted C₃-C₈ cycloalkyl or optionally substituted C₃-C₈ cycloalkenyl.

In still another embodiment, the present invention relates to compounds of Formula (3-IIg), or a pharmaceutically acceptable salt thereof:



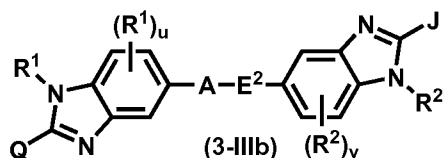
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and D⁷ is an optionally substituted heterocyclic.

In still another embodiment, the present invention relates to compounds of Formula (3-IIIa), or a pharmaceutically acceptable salt thereof:



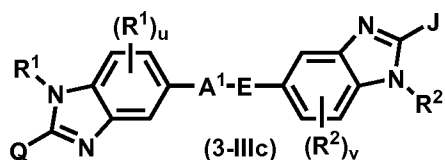
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and E¹ is an optionally substituted aryl.

In still another embodiment, the present invention relates to compounds of Formula (3-IIIb), or a pharmaceutically acceptable salt thereof:



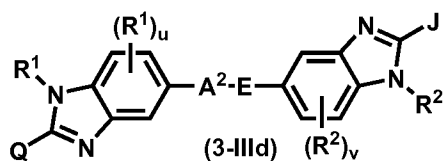
wherein A, Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I) and E² is an optionally substituted heteroaryl.

In still another embodiment, the present invention relates to compounds of Formula (3-IIIc), or a pharmaceutically acceptable salt thereof:



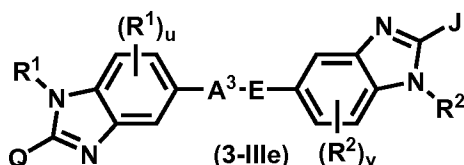
wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I); E is present and as previously defined for Formula (3-I); and A¹ is an optionally substituted aryl.

In still another embodiment, the present invention relates to compounds of Formula (3-IIId), or a pharmaceutically acceptable salt thereof:



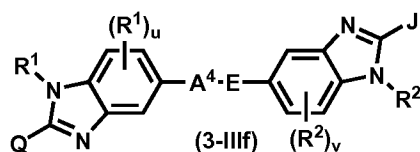
wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I); E is present and as previously defined in Formula (3-I); and A² is an optionally substituted heteroaryl.

In still another embodiment, the present invention relates to compounds of Formula (3-IIIE), or a pharmaceutically acceptable salt thereof:



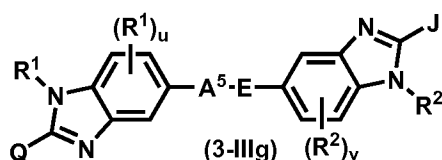
wherein Q, J, u, v, R¹ and R² are as previously defined in Formula (3-I); E is present and as previously defined in Formula (3-I); and A³ is an optionally substituted heterocyclic.

In still another embodiment, the present invention relates to compounds of Formula (3-IIIf), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I); E is present and as previously defined in Formula (3-I); and A^4 is an optionally substituted C_3 - C_8 cycloalkyl.

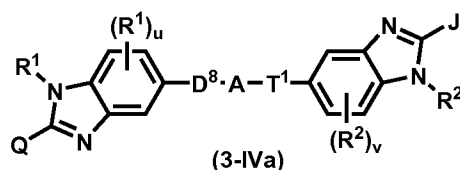
- 5 In still another embodiment, the present invention relates to compounds of Formula (3-III g), or a pharmaceutically acceptable salt thereof:



wherein Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I); E is present and as previously defined in Formula (3-I); and A^5 is an optionally substituted C_3 - C_8 cycloalkenyl.

10

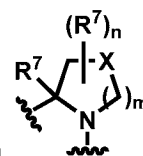
In still another embodiment, the present invention relates to compounds of Formula (3-IV a), or a pharmaceutically acceptable salt thereof:



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined in Formula (3-I) and D^8 and T^1 are each independently linear aliphatic group containing zero to six carbons, optionally contain one or more groups selected from O, $N(R^{11})$, $C(O)$, $S(O)_2$, $C(O)O$, and $C(O)N(R^{11})$; and R^{11} is as previously defined in Formula (3-I).

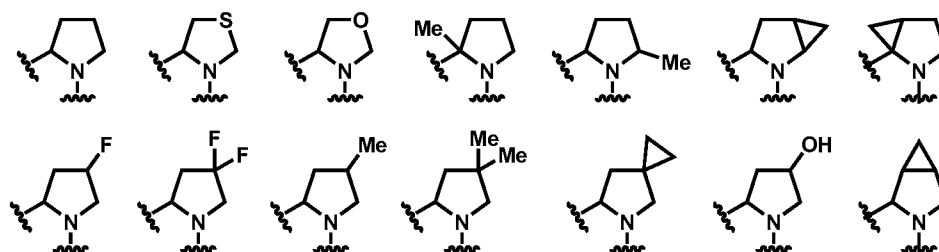
15

In still another embodiment, the present invention relates to compounds of



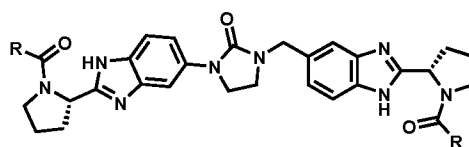
Formula (3-I), or a pharmaceutically acceptable salt thereof; wherein at each occurrence is independently illustrated by one of the following groups:

20



Representative compounds of the present invention are those selected from compounds 3-1 to 3-334 compiled in the following tables:

Table 17: Compounds 3-1 to 3-219



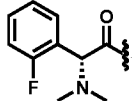
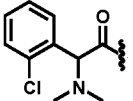
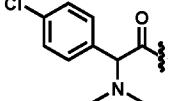
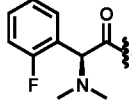
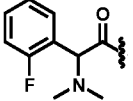
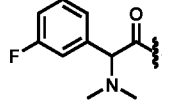
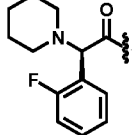
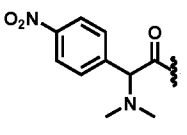
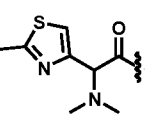
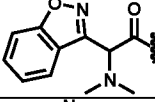
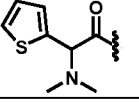
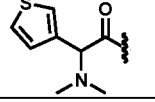
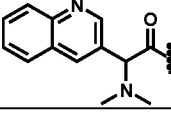
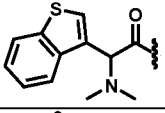
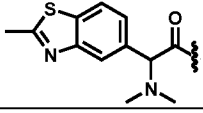
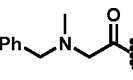
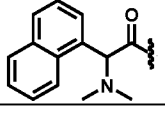
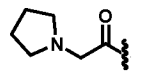
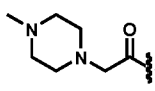
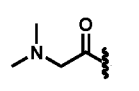
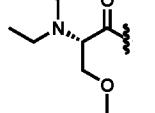
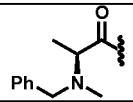
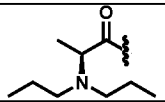
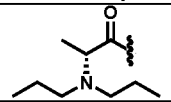
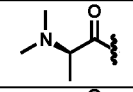
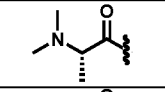
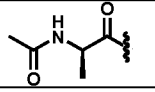
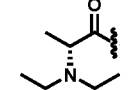
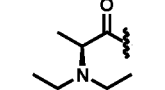
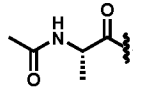
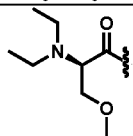
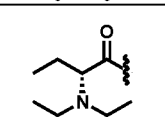
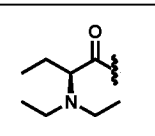
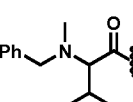
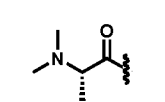
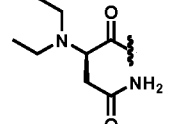
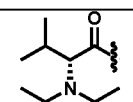
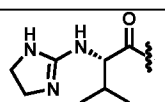
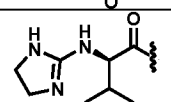
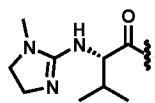
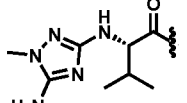
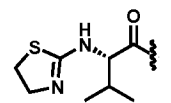
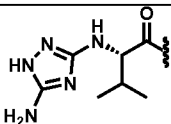
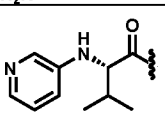
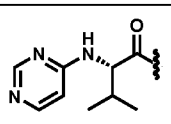
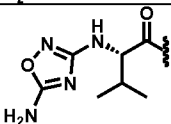
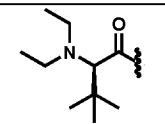
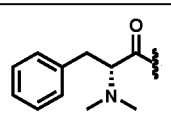
5

Entry 3-		Entry 3-		Entry 3-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	

37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	

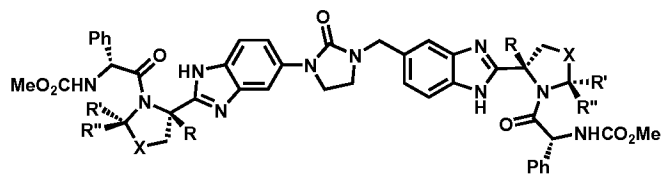
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	

121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	

163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	

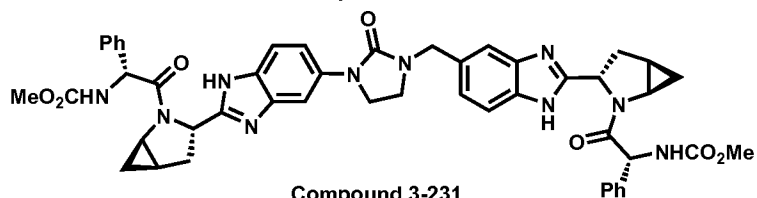
211		212		213	
214		215		216	
217		218		219	

Table 18: Compounds 3-220 to 3-229

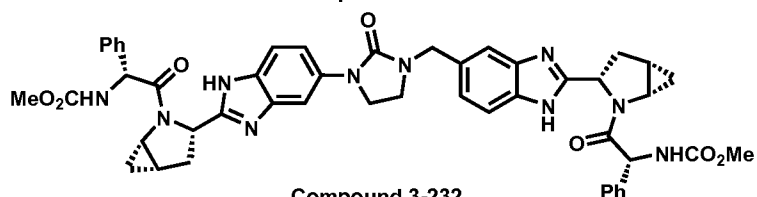


Entry 3-	R	R'	R''	X	Entry 3-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

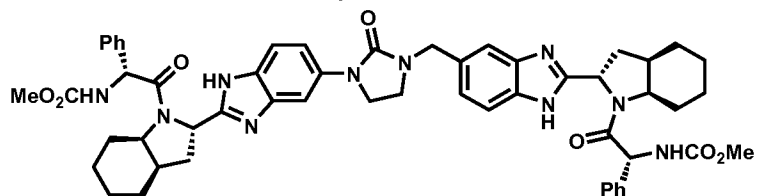
Compound 3-230



Compound 3-231



Compound 3-232



Compound 3-233

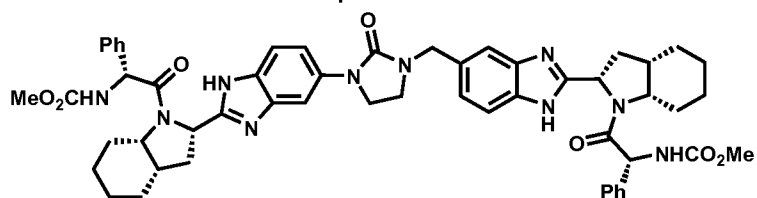
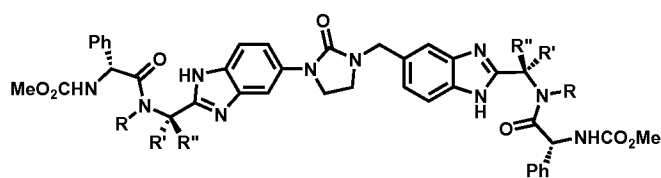


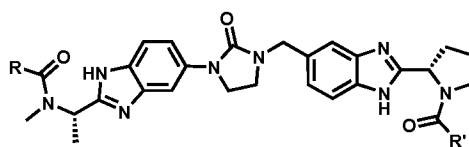
Table 19: Compounds 3-234 to 3-243



Entry 3-	R	R'	R''	Entry 3-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

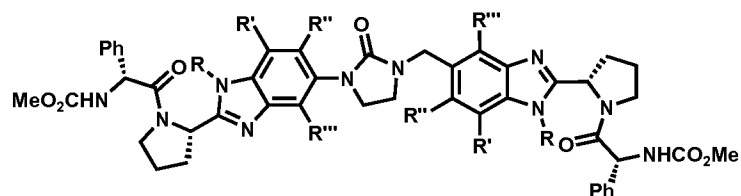
5

Table 20: Compounds 3-244 to 3-263



Entry 3-	R	R'	Entry 3-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

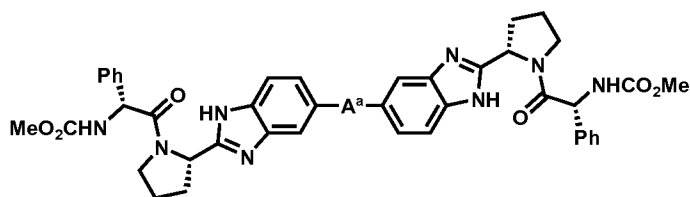
Table 21: Compounds 3-264 to 3-289



Entry 3-	R	R'	R''	R'''	Entry 3-	R	R'	R''	R'''
264	Me	H	H	H	265	H	CO ₂ H	H	H
266	H	F	H	H	267	H	H	CO ₂ H	H
268	H	H	F	H	269	H	H	H	CO ₂ H
270	H	H	H	F	271	H	CO ₂ Me	H	H
272	H	Cl	H	H	273	H	H	CO ₂ Me	H
274	H	H	Cl	H	275	H	H	H	CO ₂ Me
276	H	H	H	Cl	277	H	CONH ₂	H	H
278	H	Me	H	H	279	H	H	CONH ₂	H
280	H	H	Me	H	281	H	H	H	CONH ₂
282	H	H	H	Me	283	H	OMe	H	H

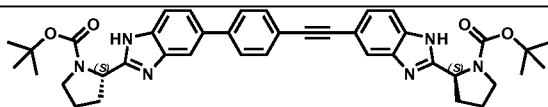
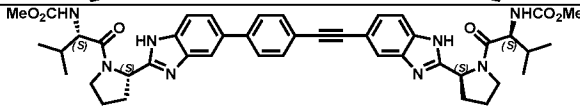
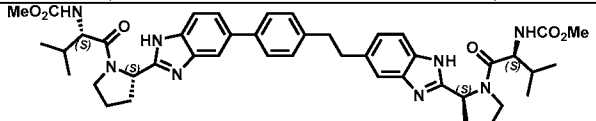
284	H	CF ₃	H	H	285	H	H	OMe	H
286	H	H	CF ₃	H	287	H	H	H	OMe
288	H	H	H	CF ₃	289	CO ₂ Me	H	H	H

Table 22: Compounds 3-290 to 3-334



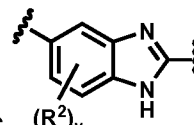
Entry 3-	A ^a	Entry 3-	A ^a	Entry 3-	A ^a
290		291		292	
293		294		295	
296		297		298	
299		300		301	
302		303		304	
305		306		307	
308		309		310	
311		312		313	
314		315		316	
317		318		319	
320		321		322	
323		324		325	
326		327		328	
329		330		331	
332		333		334	

Table 23: Compounds 3-335 to 3-337

3-335	
3-336	
3-337	

Compounds of Formulae (1-I), (2-I) and (3-I)

It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a



substituent at any given location. For example, in the structure $(R^2)_v$, R^2 may be attached to either the carbon atom in the benzimidazole ring or, alternatively, in Formula (1-I), R^2 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted benzimidazole.

It is intended that the definition of any substituent or variable (e.g., A, R^1 , R^2 , u, m, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

It will be yet appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. It will still be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

It should be understood that the compounds encompassed by the present invention are those that are suitably stable for use as pharmaceutical agent.

It will be further appreciated that reference herein to therapy and/or treatment includes, but is not limited to, prevention, retardation, prophylaxis, therapy and cure of the disease. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection includes treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

A further embodiment of the present invention includes pharmaceutical compositions comprising any single compound or a combination of two or more compounds delineated herein, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier or excipient.

5 Yet a further embodiment of the present invention is a pharmaceutical composition comprising any single compound or a combination of two or more compounds delineated herein, or a pharmaceutically acceptable salt thereof, in combination with one or more agents known in the art, with a pharmaceutically acceptable carrier or excipient.

It will be further appreciated that compounds of the present invention can be
10 administered as the sole active pharmaceutical agent, or used in combination with one or more agents to treat or prevent hepatitis C infections or the symptoms associated with HCV infection. Other agents to be administered in combination with a compound or combination of compounds of the present invention include therapies for disease caused by HCV infection that suppresses HCV viral replication by direct or indirect mechanisms.
15 These agents include, but not limited to, host immune modulators (for example, interferon-alpha, pegylated interferon-alpha, consensus interferon, interferon-beta, interferon-gamma, CpG oligonucleotides and the like); antiviral compounds that inhibit host cellular functions such as inosine monophosphate dehydrogenase (for example, ribavirin and the like); cytokines that modulate immune function (for example, interleukin 2, interleukin 6,
20 and interleukin 12); a compound that enhances the development of type 1 helper T cell response; interfering RNA; anti-sense RNA; vaccines comprising HCV antigens or antigen adjuvant combinations directed against HCV; agents that interact with host cellular components to block viral protein synthesis by inhibiting the internal ribosome entry site (IRES) initiated translation step of HCV viral replication or to block viral particle
25 maturation and release with agents targeted toward the viroporin family of membrane proteins such as, for example, HCV P7 and the like; and any agent or combination of agents that inhibit the replication of HCV by targeting other proteins of the viral genome involved in the viral replication and/or interfere with the function of other viral targets, such as inhibitors of NS3/NS4A protease, NS3 helicase, NS5B polymerase, NS4A protein
30 and NS5A protein.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise other inhibitor(s) of targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, NS4A protein, NS5A protein, and internal ribosome entry site (IRES).

Accordingly, one embodiment of the present invention is directed to a method for treating or preventing an infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents selected from the group consisting of a host immune modulator and a second or more antiviral agents, or a combination thereof, with a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

A further embodiment of the present invention is directed to a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver, with a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

Yet another embodiment of the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by hepatitis B (HBV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. An agent that treats patients for disease caused by hepatitis B (HBV) infection may be for example, but not limited thereto, L-deoxythymidine, adefovir, lamivudine or tenfovir, or any combination thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

A further embodiment of the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. The agent that treats patients for disease caused

by human immunodeficiency virus (HIV) infection may include, but is not limited thereto, ritonavir, lopinavir, indinavir, nelfmavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) or T-1249, or any combination thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

It can occur that a patient may be co-infected with hepatitis C virus and one or more other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) or hepatitis B virus (HBV). Thus also contemplated herein is combination therapy to treat such co-infections by co-administering a compound according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

In addition, the present invention provides the use of a compound or a combination of compounds of the invention, or a therapeutically acceptable salt thereof, and one or more agents selected from the group consisting of a host immune modulator and one or more additional antiviral agents, or a combination thereof, to prepare a medicament for the treatment of an infection caused by an RNA-containing virus in a patient, particularly hepatitis C virus. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant. Preferably said additional antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

When used in the above or other treatments, combination of compound or compounds of the present invention, together with one or more agents as defined herein above, can be employed in pure form or, where such forms exist, or as a pharmaceutically acceptable salt thereof. Alternatively, such combination of therapeutic agents can be administered as a pharmaceutical composition containing a therapeutically effective amount of the compound or combination of compounds of interest, or their pharmaceutically acceptable salt thereof, in combination with one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used for inhibiting the replication of an RNA-containing virus, particularly Hepatitis C virus (HCV), by contacting said virus with said pharmaceutical composition. In addition, such compositions are useful for the treatment or prevention of an infection caused by an RNA-containing virus, particularly Hepatitis C virus (HCV).

Hence, a still further embodiment of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus, particularly a hepatitis C virus (HCV), comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a compound or combination of compounds of the invention or a pharmaceutically acceptable salt thereof, and one or more agents as defined
5 hereinabove, with a pharmaceutically acceptable carrier.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or within a predetermined period of time, or the therapeutic agents can be given as a single unit dosage form.

10 Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV
15 inhibitor; and an HBV inhibitor.

Other agents that can be administered in combination with a compound of the present invention include a cytochrome P450 monooxygenase inhibitor (also referred to herein as a CYP inhibitor), which is expected to inhibit metabolism of the compounds of the invention. Therefore, the cytochrome P450 monooxygenase inhibitor would be in an
20 amount effective to inhibit metabolism of the compounds of this invention. Accordingly, the CYP inhibitor is administered in an amount sufficient to increase the bioavailability of a compound of the invention when the bioavailability is increased in comparison to the bioavailability in the absence of the CYP inhibitor.

In one embodiment, the invention provides methods for improving the
25 pharmacokinetics of a compound of the invention. The advantages of improving the pharmacokinetics of drugs are recognized in the art (see, for example, US Patent App. Nos. 2004/0091527; US 2004/0152625; and US 2004/0091527). Accordingly, one embodiment of this invention provides a method comprising administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention
30 provides a method comprising administering a compound of the invention and an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In a preferred embodiment, the CYP inhibitor preferably inhibits CYP3A4. Any CYP inhibitor that improves the pharmacokinetics of the relevant compound of the invention may be

used in a method of this invention. These CYP inhibitors include, but are not limited to, ritonavir (see, for example, WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

It will be understood that the administration of the combinations of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention is a pack comprising at least a compound of the invention and a CYP inhibitor and an information insert containing directions on the use of the combination of the invention. In an alternative embodiment of this invention, the pack further comprises one or more additional agents as described herein. The additional agent or agents may be provided in the same pack or in separate packs.

Another aspect of this involves a packaged kit for a patient to use in the treatment of HCV infection or in the prevention of HCV infection, comprising: a single or a plurality of pharmaceutical formulations of each pharmaceutical component; a container housing the pharmaceutical formulation (s) during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat or prevent HCV infection.

Accordingly, this invention provides kits for the simultaneous or sequential administration of a compound of the invention and a CYP inhibitor (and optionally an additional agent) or derivatives thereof are prepared in a conventional manner. Typically, such a kit will comprise, e. g. a composition of a compound of the invention and optionally the additional agent (s) in a pharmaceutically acceptable carrier (and in one or in a plurality of pharmaceutical formulations) and written instructions for the simultaneous or sequential administration.

In another embodiment, a packaged kit is provided that contains one or more dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package

insert, a label, and/or on other components of the kit, and the dosage form or forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil- plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle.

- 5 The present kits will also typically include means for packaging the individual kit components, i. e., the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

DEFINITIONS

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

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl.

The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl.

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

The terms "C₁-C₄ alkyl," "C₁-C₆ alkyl," "C₁-C₈ alkyl," "C₂-C₄ alkyl," or "C₃-C₆ alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and four, one and six, one and eight carbon atoms, or the like, respectively. Examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, heptyl and octyl radicals.

The terms "C₂-C₈ alkenyl," "C₂-C₄ alkenyl," "C₃-C₄ alkenyl," or "C₃-C₆ alkenyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight, or two to four carbon atoms, or the like, having at least one carbon-carbon

double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl, and the like.

The terms "C₂-C₈ alkynyl," "C₂-C₄ alkynyl," "C₃-C₄ alkynyl," or "C₃-C₆ alkynyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight, or two to four carbon atoms, or the like, having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, heptynyl, octynyl, and the like.

The term "C₃-C₈-cycloalkyl", or "C₅-C₇-cycloalkyl," as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring compound, and the carbon atoms may be optionally oxo-substituted. Examples of C₃-C₈-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₅-C₇-cycloalkyl include, but not limited to, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and the like.

The term "C₃-C₈ cycloalkenyl", or "C₅-C₇ cycloalkenyl" as used herein, refers to monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond, and the carbon atoms may be optionally oxo-substituted. Examples of C₃-C₈ cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₅-C₇ cycloalkenyl include, but not limited to, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like.

The term "arylalkyl", as used herein, refers to an aryl-substituted alkyl group. More preferred arylalkyl groups are aryl-C₁-C₆-alkyl groups.

The term "heteroarylalkyl", as used herein, refers to a heteroaryl-substituted alkyl group. More preferred heteroarylalkyl groups are heteroaryl-C₁-C₆-alkyl groups. It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group or an alicyclic group.

An "aliphatic" group is a non-aromatic moiety comprised of any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contains one or more units of unsaturation, e.g., double and/or triple bonds. Examples of aliphatic groups are functional groups, such as, O, OH, NH, NH₂, C(O), S(O)₂, C(O)O, C(O)NH, OC(O)O, OC(O)NH, OC(O)NH₂, S(O)₂NH, S(O)₂NH₂, NHC(O)NH₂, NHC(O)C(O)NH, NHS(O)₂NH, NHS(O)₂NH₂, C(O)NHS(O)₂,

C(O)NHS(O)₂NH or C(O)NHS(O)₂NH₂, and the like, groups comprising one or more functional groups, non-aromatic hydrocarbons (optionally substituted), and groups wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a functional group. Carbon atoms of an aliphatic group can be optionally oxo-

5 substituted. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, as used herein, aliphatic groups expressly include, for example, alkoxyalkyls, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Aliphatic groups may be

10 optionally substituted. A linear aliphatic group is a non-cyclic aliphatic group. It is to be understood that when a linear aliphatic group is said to “contain” or “include” or “comprise” one or more specified functional groups, the linear aliphatic group can be selected from one or more of the specified functional groups or a combination thereof, or a group wherein one or more carbons of a non-aromatic hydrocarbon (optionally

15 substituted) is replaced by a specified functional group. In some examples, the linear aliphatic group can be represented by the formula M-Y-M’, where M and M’ are each independently absent or an alkyl, alkenyl or alkynyl, each optionally substituted, and Y is a functional group. In some examples, Y is selected from the group consisting of C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹),

20 N(R¹¹)C(O)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or C(O)N(R¹¹)S(O)₂N(R¹¹); wherein R¹¹ is as previously defined. In another aspect of the invention, an exemplary linear aliphatic group is an alkyl, alkenyl or alkynyl, each optionally substituted, which is interrupted or terminated by a functional group such as described herein.

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

30 The terms “heterocyclic” or “heterocycloalkyl” can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may

optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted.

Representative heterocycloalkyl groups include, but are not limited to, 1,3-dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl,

5 piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted.

It is understood that any alkyl, alkenyl, alkynyl, alicyclic, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclic, aliphatic moiety or the like, described herein can also be
10 divalent group when used as a linkage to connect two groups or substituents, which can be at the same or different atom(s).

The term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -N₃, -CN, -NH₂, protected amino, oxo,
15 thioxo, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₈-alkenyl, -NH-C₂-C₈-alkynyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₈-alkenyl, -O-C₂-C₈-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₈-alkenyl, -C(O)-C₂-C₈-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -
20 C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₈-alkenyl, -CONH-C₂-C₈-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₈-alkenyl, -OCO₂-C₂-C₈-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -CO₂-C₁-C₁₂ alkyl, -CO₂-C₂-C₈ alkenyl, -CO₂-C₂-C₈ alkynyl, CO₂-C₃-C₁₂-cycloalkyl, -CO₂-
25 aryl, CO₂-heteroaryl, CO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₈-alkenyl, -OCONH-C₂-C₈-alkynyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)H, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₈-alkenyl, -NHC(O)-C₂-C₈-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-
30 C₂-C₈-alkenyl, -NHCO₂-C₂-C₈-alkynyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₈-alkenyl, -NHC(O)NH-C₂-C₈-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, -NHC(S)NH₂, -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₈-alkenyl, -NHC(S)NH-C₂-C₈-

alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₈-alkenyl, -NHC(NH)NH-C₂-C₈-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₈-alkenyl, -NHC(NH)-C₂-C₈-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₈-alkenyl, -C(NH)NH-C₂-C₈-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₈-alkenyl, -S(O)-C₂-C₈-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₈-alkenyl, -SO₂NH-C₂-C₈-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₈-alkenyl, -NHSO₂-C₂-C₈-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₈-alkenyl, -S-C₂-C₈-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthio-methyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

The term "halogen," as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

The term "hydrogen" includes hydrogen and deuterium. In addition, the recitation of an atom includes other isotopes of that atom so long as the resulting compound is pharmaceutically acceptable.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reaction. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate groups, for example.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions

during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999).

- 5 Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert-butoxy-carbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxy-carbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl, benzyl, triphenyl-methyl (trityl),
10 methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-(trimethylsilyl)-ethoxymethyl, methanesulfonyl, trimethylsilyl, triisopropylsilyl, and the like.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

- 15 The term "hydroxy prodrug group", as used herein, refers to a promoietty group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group in vivo. Hydroxy prodrug groups as
20 known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery, (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992).

- The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions
25 during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, methoxycarbonyl, t-butoxycarbonyl, 9-fluorenyl-methoxycarbonyl, benzyloxycarbonyl, and the like.
30

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a

nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

5 The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-
10 methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further
15 discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

 The term "protic solvent" as used herein, refers to a solvent that tends to provide
20 protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature
25 ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

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

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the Formula herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH (1999); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The term "subject" as used herein refers to an animal. Preferably, the animal is a mammal. More preferably, the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

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

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other

unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers or cis- and trans-isomers. Likewise, all tautomeric forms are also intended to be included. Tautomers may be in cyclic or acyclic. The configuration of any carbon-carbon double bond appearing
5 herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

Certain compounds of the present invention may also exist in different stable
10 conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of these compounds and mixtures thereof.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts
15 which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66:
20 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and
25 perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentane-propionate, digluconate,
30 dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate,

succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

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

The present invention also relates to solvates of the compounds of the present invention, for example hydrates.

This invention also encompasses pharmaceutical compositions containing, and methods of treating viral infections through administering, pharmaceutically acceptable prodrugs of compounds of the invention. For example, compounds of the invention having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs.

5 Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-
10 hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate
15 esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted
20 with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid
25 functionalities.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

30 As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose;

starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols
5 such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents,
10 sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The
15 pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-
20 articular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

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

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or

wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

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

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

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

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose,

mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents
5 such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also
10 comprise buffering agents.

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

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be
15 prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and
20 waxes.

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

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

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

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

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable
10 size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.*, and WO 98/43650 by Montgomery, all of which are incorporated herein by reference). A
15 discussion of pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

ANTIVIRAL ACTIVITY

An inhibitory amount or dose of the compounds of the present invention may range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50
20 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections, conditions are treated or prevented in a patient such as a human or another animal by administering to the patient a therapeutically effective amount of a compound of the
25 invention, in such amounts and for such time as is necessary to achieve the desired result.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives
30 an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total

daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

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

The compounds of the present invention described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically expipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general

health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

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

10 When the compositions of this invention comprise a combination of a compound of the Formula described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be
15 administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The said "additional therapeutic or prophylactic agents" includes but not limited to, immune therapies (eg. interferon), therapeutic vaccines, antifibrotic agents, anti-
20 inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (eg ribavirin and amantidine). The compositions
25 according to the invention may also be used in combination with gene replacement therapy.

COMBINATION AND ALTERNATION THERAPY FOR HCV

It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by
30 mutation of a gene that encodes for a protein such as an enzyme used in viral replication, and most typically in the case of HCV, RNA polymerase, protease, or helicase.

Recently, it has been demonstrated that the efficacy of a drug against a viral infection, such as HIV, can be prolonged, augmented, or restored by administering the

drug in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principal drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred

5 over alternation therapy because it induces multiple simultaneous stresses on the virus.

A compound of the present invention can also be administered in combination or alternation with antiviral agent. Exemplary antiviral agents include ribavirin, interferon, interleukin or a stabilized prodrug of any of them. More broadly described, the compound can be administered in combination or alternation with any of the anti-HCV drugs listed in

10 Table 24 below.

Table 24

Table of anti-Hepatitis C Compounds in Current Clinical Development		
Drug name	Drug category	Pharmaceutical Company
PEGASYS pegylated interferon alfa-2a	Long acting interferon	Roche
INFERGEN interferon alfacon-1	Long acting interferon	InterMune
OMNIFERON natural interferon	Long acting interferon	Viragen
ALBUFERON	Long acting interferon	Human Genome Sciences
REBIF interferon beta-1a	Interferon	Ares-Serono
Omega Interferon	Interferon	BioMedicine
Oral Interferon alpha	Oral Interferon	Amarillo Biosciences
Interferon gamma-1b	Anti-fibrotic	InterMune
IP-501	Anti-fibrotic	InterMune
Merimebodib VX-497	IMPDH inhibitor (inosine monophosphate dehydrogenase)	Vertex
AMANTADINE (Symmetrel)	Broad Antiviral Agent	Endo Labs Solvay
IDN-6556	Apoptosis regulation	Idun Pharma.
XTL-002	Monoclonal Antibody	XTL
HCV/MF59	Vaccine	Chiron
CIVACIR	Polyclonal Antibody Therapeutic vaccine	NABI Innogenetics
VIRAMIDINE	Nucleoside Analogue	ICN
ZADAXIN (thymosin alfa-1)	Immunomodulator	Sci Clone
CEPLENE (histamine)	Immunomodulator	Maxim
VX 950/LY 570310	Protease inhibitor	Vertex/Eli Lilly
ISIS 14803	Antisense	Isis Pharmaceutical/Elan
IDN-6556	Caspase inhibitor	Idun Pharmaceuticals
JTK 003	Polymerase Inhibitor	AKROS Pharma
Tarvacin	Anti-Phospholipid Therapy	Peregrine
HCV-796	Polymerase Inhibitor	ViroPharma/Wyeth
CH-6	Protease inhibitor	Schering
ANA971	Isatoribine	ANADYS
ANA245	Isatoribine	ANADYS

CPG 10101 (Actilon)	Immunomodulator	Coley
Rituximab (Rituxam)	Anti-CD20 Monoclonal Antibody	Genetech/IDEC
NM283 (Valopicitabine)	Polymerase Inhibitor	Idenix Pharmaceuticals
HepX TM -C	Monoclonal Antibody	XTL
IC41	Therapeutic Vaccine	Intercell
Medusa Interferon	Longer acting interferon	Flamel Technology
E-1	Therapeutic Vaccine	Innogenetics
Multiferon	Long Acting Interferon	Viragen
BILN 2061	Protease inhibitor	Boehringer-Ingelheim
TMC435350	Protease inhibitor	Tibotec/Medivir
Telaprevir (VX-950)	Protease inhibitor	Vertex
Boceprevir (SCH 503034)	Protease inhibitor	Schering-Plough
ACH-1625	Protease inhibitor	Achillion
ABT-450	Protease inhibitor	Abbott/Enanta
BI-201335	Protease inhibitor	Boehringer-Ingelheim
PHX-1766	Protease inhibitor	Phenomix
VX-500	Protease inhibitor	Vertex
MK-7009	protease inhibitor	Merck
R7227 (ITMN-191)	protease inhibitor	InterMune
Narlaprevir (SCH 900518)	Protease inhibitor	Schering/Merck
Alinia (nitazoxanide)	To be determined	Romark
ABT-072	Polymerase Inhibitor	Abbott
ABT-333	Polymerase Inhibitor	Abbott
Filibuvir (PF-00868554)	Polymerase Inhibitor	Pfizer
VCH-916	Polymerase Inhibitor	Vertex
R7128 (PSI6130)	Polymerase Inhibitor	Roche/Pharmasset
IDX184	Polymerase Inhibitor	Idenix
R1626	Polymerase inhibitor	Roche
MK-3281	Polymerase inhibitor	Merck
PSI-7851	Polymerase inhibitor	Pharmasset
ANA598	Polymerase inhibitor	Anadys Pharmaceuticals
BI-207127	Polymerase inhibitor	Boehringer-Ingelheim
GS-9190	Polymerase inhibitor	Gilead
VCH-759	Polymerase Inhibitor	Vertex
Clemizole	NS4B inhibitor	Eiger Biopharmaceuticals
A-832	NS5A inhibitor	ArrowTherapeutics
BMS-790052	NS5A inhibitor	Bristol-Myers-Squibb
ITX5061	Entry inhibitor	iTherx
GS-9450	Caspase inhibitor	Gilead
ANA773	TLR agonist	Anadys
CYT107	immunomodulator	Cytheris
SPC3649 (LNA-antimiR TM -122)	microRNA	Santaris Pharma
Debio 025	Cyclophilin inhibitor	Debiopharm
SCY-635	Cyclophilin inhibitor	Scynexis

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

5 ABBREVIATIONS

Abbreviations which may be used in the descriptions of the scheme and the examples that follow are: Ac for acetyl; AcOH for acetic acid; AIBN for

azobisisobutyronitrile; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc₂O for di-*tert*-butyl-dicarbonate; Boc for *t*-butoxycarbonyl; Bpoc for 1-methyl-1-(4-biphenyl)ethyl carbonyl; BtOH for 1-hydroxy-benzotriazole; Bz for benzoyl; Bn for benzyl; BocNHOH for *tert*-butyl N-hydroxycarbamate; *t*-BuOK for potassium *tert*-butoxide; Bu₃SnH for tributyltin hydride; BOP for (benzotriazol-1-yl)oxytris(dimethylamino)phosphonium Hexafluorophosphate; Brine for sodium chloride solution in water; Cbz for carbobenzyloxy; CDI for carbonyldiimidazole; CH₂Cl₂ for dichloromethane; CH₃ for methyl; CH₃CN for acetonitrile; Cs₂CO₃ for cesium carbonate; CuCl for copper (I) chloride; CuI for copper (I) iodide; dba for dibenzylidene acetone; dppb for diphenylphosphino butane; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC for N,N'-dicyclohexylcarbodiimide; DEAD for diethylazodicarboxylate; DIAD for diisopropyl azodicarboxylate; DIBAL-H for diisobutylaluminium hydride; DIPEA or (i-Pr)₂EtN for N,N-diisopropylethyl amine; Dess-Martin periodinane for 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; DMAP for 4-dimethylaminopyridine; DME for 1,2-dimethoxy-ethane; DMF for N,N-dimethylformamide; DMSO for dimethyl sulfoxide; DMT for di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl; DPPA for diphenylphosphoryl azide; EDC for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide; EDC HCl for N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide hydrochloride; EtOAc for ethyl acetate; EtOH for ethanol; Et₂O for diethyl ether; Fmoc for 9-fluorenylmethoxycarbonyl; Grubbs-1 catalyst for benzylidene-bis(tricyclohexylphosphine)dichlororuthenium; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Hexafluorophosphate; HCl for hydrogen chloride; HOBT for 1-hydroxybenzotriazole; K₂CO₃ for potassium carbonate; *n*-BuLi for *n*-butyl lithium; *i*-BuLi for *i*-butyl lithium; *t*-BuLi for *t*-butyl lithium; PhLi for phenyl lithium; LDA for lithium diisopropylamide; LiTMP for lithium 2,2,6,6-tetramethylpiperidinate; MeOH for methanol; Mg for magnesium; MOM for methoxymethyl; Ms for mesyl or -SO₂-CH₃; Ms₂O for methanesulfonic anhydride or mesyl-anhydride; NaBH₄ for sodium borohydride; NaBH₃CN for sodium cyanoborohydride; NaN(TMS)₂ for sodium bis(trimethylsilyl)amide; NaCl for sodium chloride; NaH for sodium hydride; NaHCO₃ for sodium bicarbonate or sodium hydrogen carbonate; Na₂CO₃ sodium carbonate; NaOH for sodium hydroxide; Na₂SO₄ for sodium sulfate; NaHSO₃ for sodium bisulfite or sodium hydrogen sulfite; Na₂S₂O₃ for sodium thiosulfate; NH₂NH₂ for hydrazine; NH₄HCO₃ for ammonium bicarbonate; NH₄Cl for

ammonium chloride; NMMO for N-methylmorpholine N-oxide; NaIO₄ for sodium periodate; Ni for nickel; OH for hydroxyl; OsO₄ for osmium tetroxide; Pd for palladium; Ph for phenyl; PMB for p-methoxybenzyl; POPd for dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(II); Pd₂(dba)₃ for tris(dibenzylidene-acetone) dipalladium (0); Pd(PPh₃)₄ for tetrakis(triphenylphosphine)palladium (0); PdCl₂(PPh₃)₂ for trans-dichlorobis(triphenyl-phosphine)palladium (II); Pt for platinum; Rh for rhodium; rt for room temperature; Ru for ruthenium; SEM for (trimethylsilyl)ethoxymethyl; TBAF for tetrabutylammonium fluoride; TBS for *tert*-butyl dimethylsilyl; TEA or Et₃N for triethylamine; Teoc for 2-trimethylsilyl-ethoxy-carbonyl; TFA for trifluoroacetic acid; THF for tetrahydrofuran; TMEDA for N,N,N',N'-tetramethylethylenediamine; TPP or PPh₃ for triphenyl-phosphine; Troc for 2,2,2-trichloroethyl carbonyl; Ts for tosyl or -SO₂-C₆H₄CH₃; Ts₂O for tolylsulfonic anhydride or tosyl-anhydride; TsOH for p-tolylsulfonic acid; TMS for trimethylsilyl; or TMSCl for trimethylsilyl chloride.

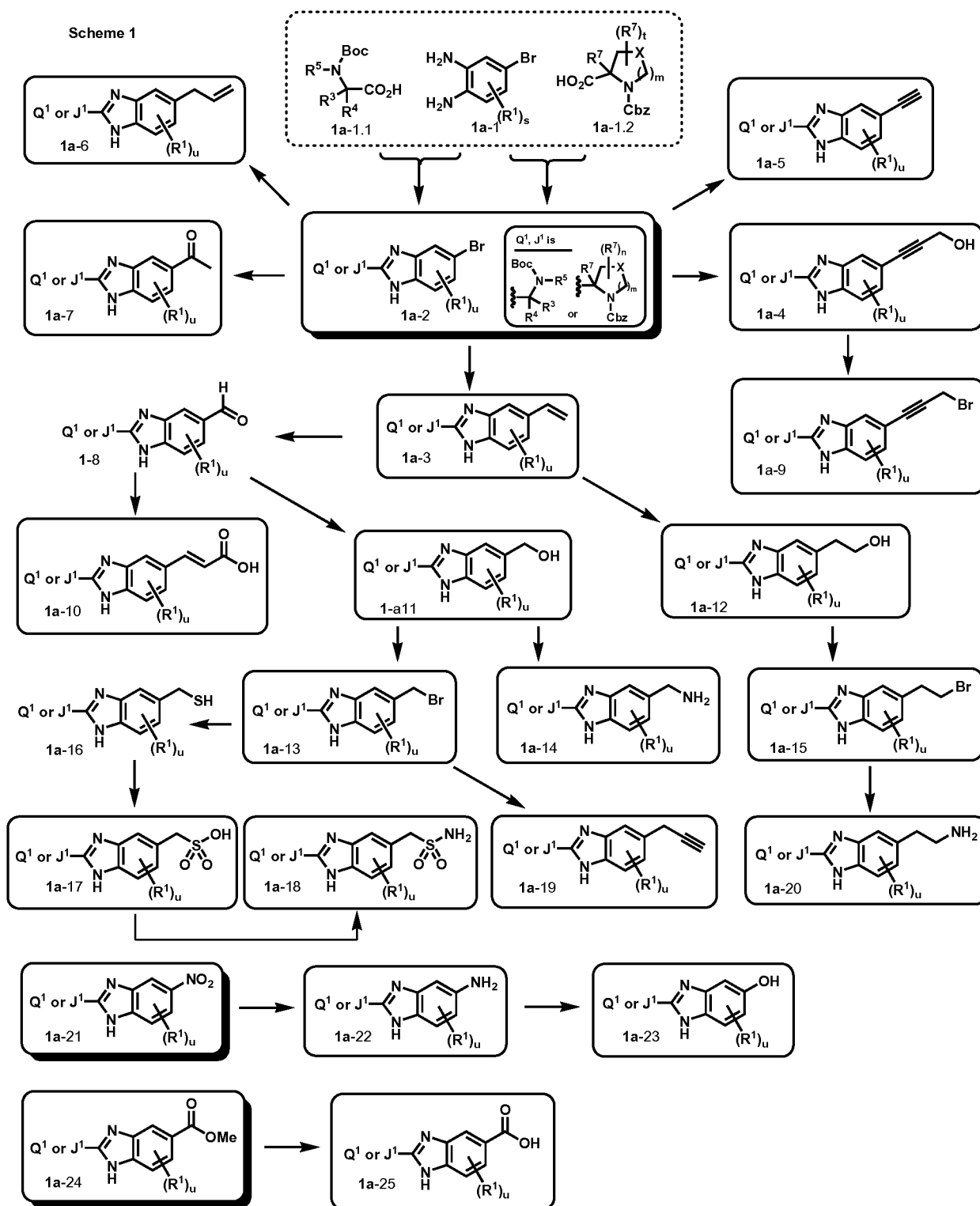
SYNTHETIC METHODS

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

The compounds of the present invention may be prepared via several different synthetic routes from a variety of benzimidazole related intermediates. A retro-synthesis of those title compounds include direct formation of a suitably linked dibenzimidazole core structure followed by attachment of a suitable R⁶ group, plus some functional group manipulations in between and/or after.

A general synthesis and further elaboration of some benzimidazole related intermediates are summarized in Scheme 1.

The synthesis starts from the construction of an optionally substituted benzimidazole **1a-2**, which may be obtained by condensation of an amino acid or its derivative **1a-1.1** or **1a-1a.2** and an *o*-phenylenediamine **1a-1** under the conditions to those skilled in the art. The benzimidazole ring closure may be realized either in one pot by heat, optionally in the presence of an acid and/or with a dehydration reagent such as polyphosphoric acid; or in two steps: 1) amide formation between diamine **1a-1** and amino acid **1a-1.1** or **1a-1.2** in the presence of a condensation reagent such as EDC HCl, DCC or the like; or through mixed anhydride approach by reacting acid **1a-1.1** or **1a-1.2** with a chloroformate such as methyl chloroformate, isobutyl chloroformate, or the like, in the presence of a base such as TEA, DIPEA, DMAP, N-methylmorpholine, or the like, followed by treating the mixed anhydride with diamine **1a-1**; and 2a) the heterocyclic ring closure in the presence of an acid such as acetic acid, sulfuric acid or the like or a dehydration reagent such as HATU or the like, optionally with heat.



Optionally, the NH group in the newly formed benzimidazole ring of **1a-2** may be protected with an amino protecting group, such as SEM (i.e. SEM-Cl, NaH), Boc, Cbz, Teoc, Troc, or the like. The protected benzimidazole **1a-2** may be subjected to lithium-halogen exchange with various (*n*-, *s*-, or *t*-) butyl lithium and the resulting lithiate can be trapped with a nucleophile, i.e. a halide such as various allyl halide to give the allylated

1a-6 as a key intermediate. Alternatively, **1a-6** may be obtained from the Stille reaction conditions to those skilled in the art (see reviews: A. Anastasia, et al, *Handbook of Organopalladium Chemistry for Organic Synthesis* 2002, 1, 311; F. Bellina, et al, *Synthesis* 2004, 2419; M. G. Organ, et al, *Synthesis* 2008, 2776; A. T. Lindhardt, et al, *Chem. - A European J.* 2008, 14, 8756; E. A. B. Kantchev, et al, *Angew. Chem. Int. Ed.* 2007, 46, 2768; V. Farina, et al, *Advances in Metal-Organic Chem.* 1996, 5, 1), using an allylstanne such as allyltributylstanne as the allyl donor. Analogously a key vinyl intermediate **1a-3** may be prepared by Stille reaction from bromide **1a-2** with tributylvinylstanne. Also, Sonogashira coupling between bromide **1a-2** and propargyl alcohol or trimethylsilylacetylene can generate propargyl alcohol **1a-4** or alkyne **1a-5** after removal of TMS. Further bromination of intermediate **1a-4** may form the propargyl bromide **1a-9**. In addition, benzimidazole bromide **1a-2** may be converted to methyl ketone **1a-7** by coupling with tributyl(1-ethoxyvinyl)tin under Stille coupling conditions followed by acidic hydrolysis.

Further elaboration of the benzimidazole intermediates starts from the vinyl intermediate **1a-3**, which may be transformed to aldehyde **1a-8** through ozonolysis cleavage or to alcohol **1a-12** by hydroboration-oxidation sequence. Alcohol **1a-12** may be converted to bromide **1a-15** by the well-known bromination procedure, which can be further functionalized to amine **1a-20** through azide substitution followed by reduction. Aldehyde **1a-8** can then either be reduced to alcohol **1a-11**, or be converted to α , β -unsaturated acid **1a-10** through Horner-Wadsworth-Emmons aldehyde homologation reaction followed by saponification. Alcohol **1a-11** may be similarly converted to the corresponding amine intermediate **1a-14** and bromide intermediate **1a-13** as described previously. Bromide **1a-13** can be homologated to alkyne intermediate **1a-19** with a metal acetylide. In addition, bromide **1a-13** may be also transformed to thiol **1a-16** through nucleophilic substitution, which can be further oxidized to sulfonic acid **1a-17**. Sulfonamide **1a-18** may then be derived from **1a-17** through the sulfonyl chloride activation process.

The compounds of the present invention may also be derived from nitrobenzimidazole **1a-21**, which can be prepared from the corresponding 4-nitro-1,2-diaminobenzene using the similar procedures described above. Intermediate **1a-21** can be converted to amine **1a-22** through NO_2 -reduction (i.e. H_2 , catalytical Pd). Diazotization of amine **1a-22** with a nitrite such as sodium nitrite, isobutyl nitrite, or the like, in an aqueous

acid such as acetic acid, hydrochloric acid, sulfuric acid, or the like, optionally in the presence of a copper or copper salt, may afford hydroxy **1a-23**.

Analogously, esterbenzimidazole **1a-24**, which can be prepared from the corresponding 4-methyl-1,2-diaminobenzoate using the procedures described above, may be hydrolyzed to the corresponding carboxylic acid **1a-25**.

It should be noted that optionally the NH group of all the benzimidazole related intermediates listed above may be protected with an amino protecting group, such as SEM (i.e. SEM-Cl, NaH), Boc, Cbz, Teoc, Troc, or the like.

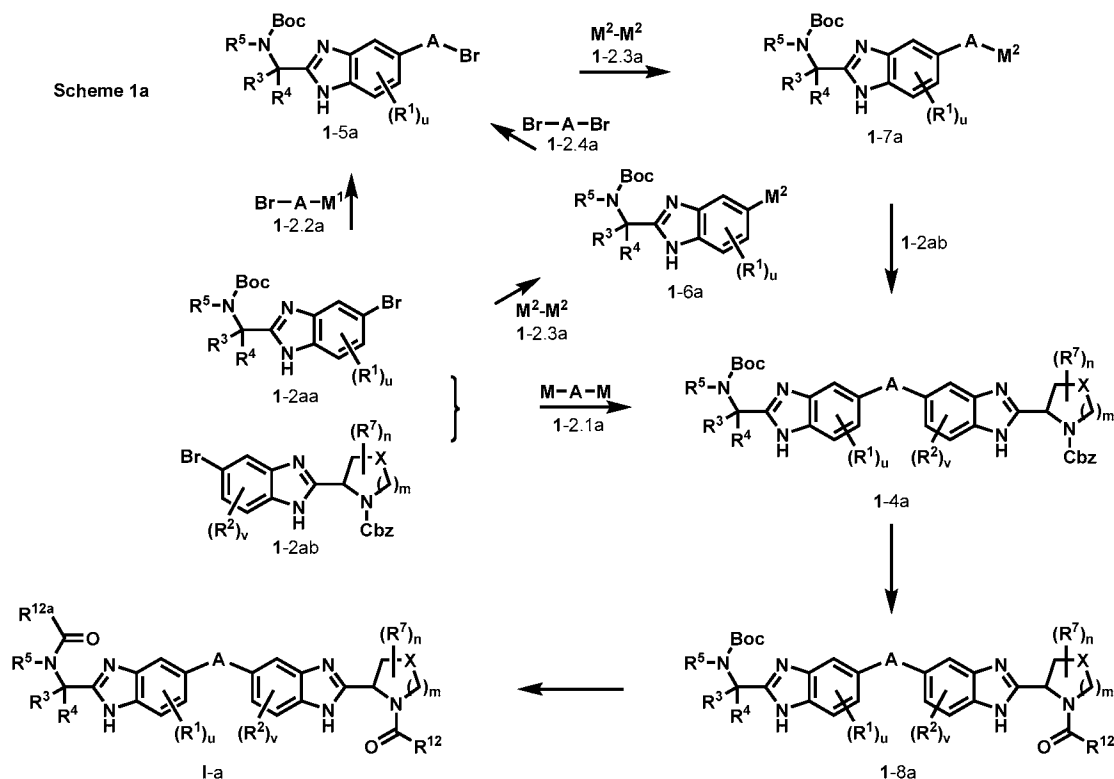
With suitably substituted benzimidazoles in hand, such as those listed in Scheme 1, the compounds of the present invention may be prepared through various coupling strategy or a combination of strategies to connect two fragments with a suitable cyclic linker or formation of a cyclic linker. The said strategy includes, but not limited to, Stille coupling, Suzuki coupling, Sonogashira coupling, Heck coupling, Buchwald amidation, Buchwald amination, amide coupling, ester bond formation, William etherification, Buchwald etherification, alkylation, pericyclic reaction with different variations, or the like.

As illustrated in Schemes 1a, 1b, 2 and 3, in which s and t at each occurrence are each independently 0, 1, 2 or 3; M, M¹, and M² at each occurrence are each independently a boron, tin, silicon, zinc, zirconium, or copper species; PG is a hydroxy or amino protection group; and R^{12a} at each occurrence are each independently R¹². The bromides **1-2aa** and **1-2ab** may be coupled with partner **1-2.1a**, a bismetallated reagent such as 1,3-benzenediboronic acid, 1,4-benzene-diboronic acid, 2,5-thiophenediboronic acid, 2,5-bis(trimethylstannyl)thiophene, 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene, 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene, 1,4-di(1,3,2-dioxaborolan-2-yl)benzene, 2,5-bis(methoxy-methyl)-1,4-phenylenediboronic acid, or the like, under Suzuki or Stille conditions described in Scheme 1 to provide the linked dibenzimidazole core **1-4a**.

Alternatively, bromobenzimidazole **1-2aa** may be converted to intermediate **1-5a** by selectively reacting with metallic reagent **1-2.2a** under the Suzuki or Stille conditions described previously. Yet alternatively, intermediate **1-5a** may be prepared by reacting **1-2aa** with dimetallic agent **1-2.3a** to afford organometallic **1-6a**, followed by coupling with dibromide **1-2.4a**, both may be under the previously described Suzuki and Stille reaction conditions. The bromide **1-5a** may be further converted to organometallic **1-7a** with dimetallic agent **1-2.3a** using the conditions described above to prepare **1-6a**. Under the

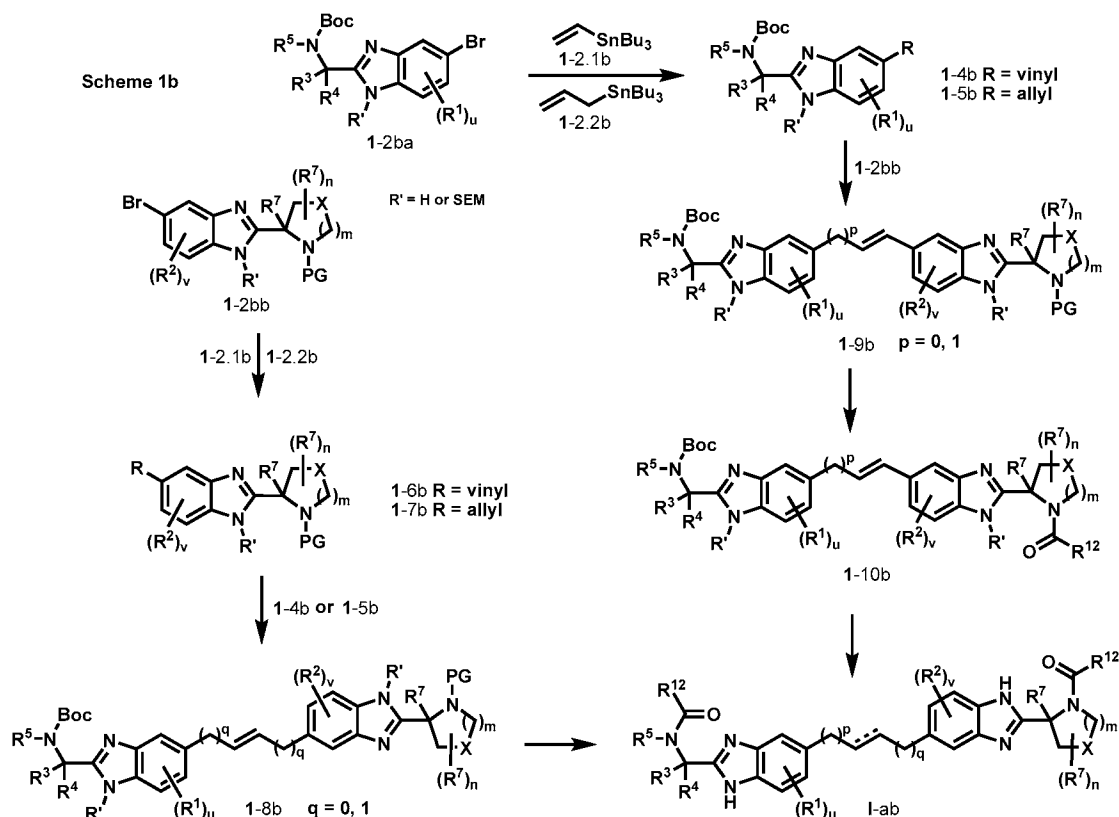
Suzuki or Stille conditions, bromide **1-2ab** may be coupled with organometallic **1-7a** to afford the linked dibenzimidazole core **1-4a**.

Core **1-4a** may then serve as a common intermediate for further derivatizations to **1-8a** in two steps: 1) mono-deprotection of the linear or cyclic amine moiety may be accomplished, for example, treatment to hydrogenolytic conditions under Pd catalyst in the presence of a base such as potassium carbonate to remove the Cbz protection group; and 2) the released amine functionality may be acylated with an carboxylic acid under standard acylation conditions, for example a coupling reagent such as HATU in combination with an organic base such as DIPEA can be used in this regard; alternatively, the released amine may be reacted with an isocyanate, carbamoyl chloride or chloroformate to provide an urea or carbamate. Various carboxylic acids including amino acids in racemic or optical form are commercially available, and/or can be synthesized in racemic or optical form, see references cited in reviews by D. Seebach, et al, *Synthesis* 2009, 1; C. Cativiela and M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* 2007, 18, 569; 2000, 11, 645; and 1998, 9, 3517; and experimental examples compiled in patent application WO 2008/021927A2 by C. Bachand, et al, from BMS, which is incorporated herein by reference. **1-8a** may be further deprotected under hydrolytic conditions in the presence of an acid such as TFA or hydrogen chloride to remove the Boc protection group and the released amine functionality can be further derivatized to the title compound **I-a** using the conditions described above.



As shown in Schem 1b, the bromides **1-2ba** and **1-2bb** may be converted to vinylic **1-4b** and **1-6b**, or allylic **1-5b** and **1-7b** with a vinylstanne such as tributylvinylstanne **1-2.1b** or an allylstanne such as allyltributylstanne **1-2.2b** using the reaction conditions described in Scheme 1. The intermediates **1-4b** and **1-5b** can be crossed-linked with intermediates **1-6b** and **1-7b** using transition metal catalyzed Hoveyda-Grubbs metathesis reaction conditions which are known to those skilled in the art (see J. D. Waetzig, et al, *Chemtracts* 2006, 19, 157; C. L. Dwyer, *Metal-Catalysis in Industrial Organic Processes* 2006, 201; S. T. Diver, et al, *Chem. Review* 2004, 104, 1317; A. J. Vernall, et al, *Aldrichimica Acta* 2003, 36, 93; S. T. Connon, et al, *Angew. Chem. Int. Ed.* 2003, 42, 1900; S. E. Gibson, et al, *Topics in Organometallic Chemistry* 1998, 1(Alkene Metathesis in Organic Synthesis), 155; Y. Schrodi, et al, *Aldrichimica Acta* 2007, 40, 45), giving the corresponding olefin **1-8b**, a core structure of a linked dibenzimidazole. Alternatively and additionally, intermediates **1-4b** and **1-5b** may be coupled with bromide **1-3b** under the well-known Heck reaction conditions (reviewed by M. Arisawa, *Chem. Pharm. Bull.* 2007, 55, 1099; P. Guiry, et al, *Current Org. Chem.* 2004, 8, 781; J. T. Link, *Org. React.* 2002, 60, 167; S. Braese, et al, *Metal-Catalyzed Cross-Coupling Reactions* 1998, 99) to give olefin **1-9b**, another core structure of a linked dibenzimidazole. The structural cores **1-8b** and **1-9b** then may be served as common intermediates for further derivatizations to

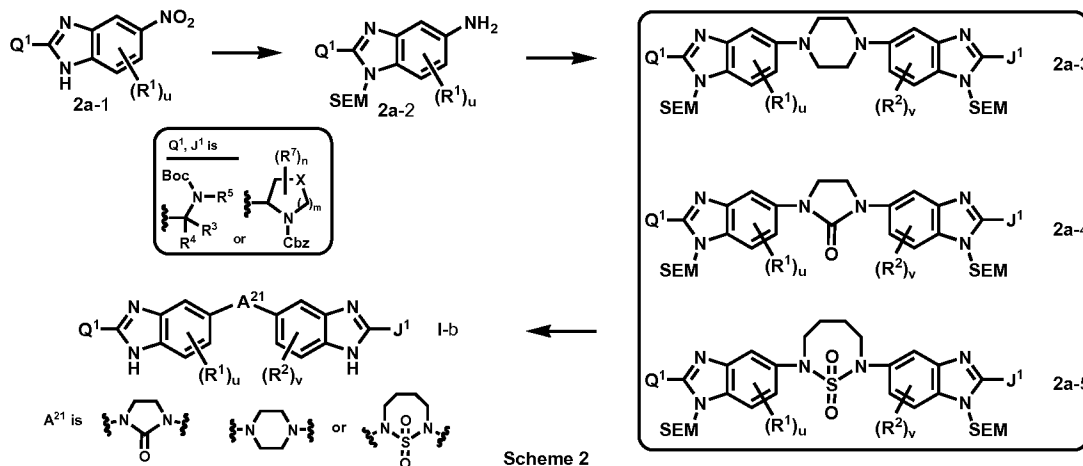
the title compounds **I-ab** of the present invention using the procedures similar to that described in Scheme 1a.



The compounds of the present invention may also be derived from

- 5 nitrobenzimidazole **2a-1**, which can be prepared from the corresponding 4-nitro-1,2-diaminobenzene using the procedures described in Scheme 1. As shown in Scheme 2, **2a-1** can be converted to amine **2a-2** in two-steps: 1) NH-protection (i.e. SEM-Cl, NaH); and 2) NO₂-reduction (i.e. H₂, catalytical Pd). Alkylation of **2a-2** with an alkylating reagent such as 1,2-dihaloethane, ethylene tosylate, or the like, in the presence of a base such as
- 10 NaHCO₃, K₂CO₃, pyridine, Et₃N, DMAP, DBU or the like, may provide the bis-ethylenylated (piperidine)-linked dibenzimidazole **2-3** through the mono-ethylenylated intermediate. The latter with two secondary ethylenediamine may be used to form the 5-membered heterocycle **2a-4** by reacting with CDI, phosgene, triphosgene, or the like, optionally in the presence of a base such as pyridine, Et₃N, DMAP, DBU or the like.
- 15 Similarly **2a-2** was alkylated with 1,4-diiodobutane followed by sulfonylation with sulfonyl chloride in the presence of a base such as NaHCO₃, K₂CO₃, pyridine, Et₃N, DMAP, DBU or the like, may provide the 7-membered heterocycle **2a-5**. The linked dibenzimidazole **2a-3**, **2a-4**, or **2a-5** can be further converted to the title compound **I-b** using the conditions described in Scheme 1, it is noteworthy that the SEM-group can be

removed at the same time when deprotecting the Boc-protection in acid as described above.



Alternatively as shown Scheme 3, intermediate **2a-3** may be obtained by the

- 5 Buchwald-Hartwig amination process (see references by S. L. Buchwald et al, *J. Organomet. Chem.* 1999, 576, 125; J. F. Hartwig, *Angew. Chem., Int. Ed.* 1998, 37, 2046; V. T. Abaev et al, *Russian Chem. Reviews* 2008, 77, 177; and J. F. Hartwig, *Modern Arene Chemistry* 2002, 107-168; S. L. Buchwald, et al, *Angew. Chem., Int. Ed.* 2008, 47, 6338) from bromobenz-imidazole **3a-1**, which can be prepared similarly to that of bromides **1a-2**
- 10 and **1a-3** after SEM-protecting as described above, and an amine such as piperazine or the like, using a transition metal catalyst such as palladium acetate in the presence of a base such as sodium *t*-butoxide (see S. M. Pyke, et al, *J. Org. Chem.* 2008, 73, 8880; and R. Dorta, et al, *JACS* 2008, 130, 6848). Also two molecules of bromide **3a-1** may be reacted
- 15 with glycine anhydride (piperazine-2,5-dione), imidazolidin-2-one, [1,2,5]-thiazolidine-1,1-dioxide under the Buchwald amidation reaction conditions (see C. C. Mauger, et al, *Aldrichimica Acta* 2006, 39, 17; S. L. Buchwald, et al, *JACS* 2009, 131, 78; *Accounts Chem. Res.* 2008, 41, 1439; H. C. Ma, et al, *Synlett* 2008, 1335; J. H. M. Lange, *Tetrahedron Lett.* 43, 1101; S. L. Buchwald, et al, *JACS* 2002, 124, 7421), to give the diamide, urea, or sulfonamide-linked dibenzimidazole **3a-2**, **3a-3**, or **3a-4**. Additionally,
- 20 bromide **3a-1** may be subjected to lithium-halogen exchange with various (*n*-, *s*-, or *t*-)butyl lithium and the resulting lithiate can be trapped with a dihalide such as 1,4-dibromocyclohexane, 1,4-dichlorocyclohexane, 3,6-dibromocyclohexene, 3,6-dichlorocyclohexene, to give the cycloalkyl-linked dibenzimidazoles **3a-5** and **3a-6**. Also olefins **3a-6** can be saturated under hydrogenolytic conditions with a Pd catalyst to give
- 25 **3a-6**. Intermediates **3a-2**, **3a-3**, **3a-4**, **3a-5**, and **3a-6** may be then converted to the title compound **I-c** using the procedures described previously.

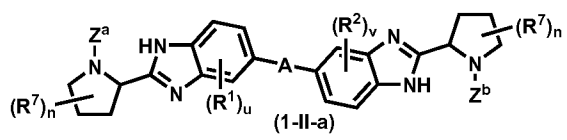


5



comprising the steps of:

10



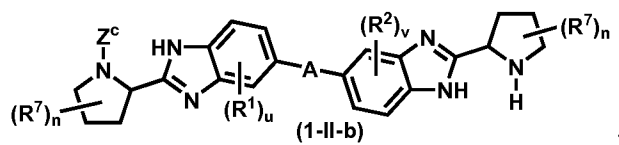
via a transition-metal catalyzed cross-coupling reaction;

wherein:

A, n, u, v, R^1 , R^2 , and R^7 are as defined in claim 1;

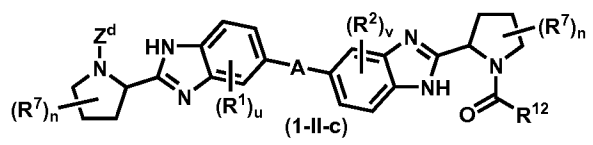
- 5 Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$, R^{12} is C_1 - C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1-C_4$ alkyl);

ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (II-b):



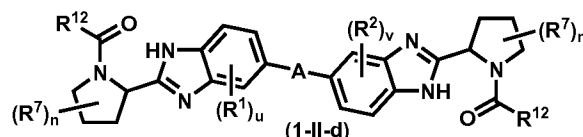
wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$;

iii) capping the released amino group of a compound of Formula (II-b) with $LG-C(O)-R^{12}$, wherein LG is a leaving group; to give the compound of Formula (II-c):



wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and

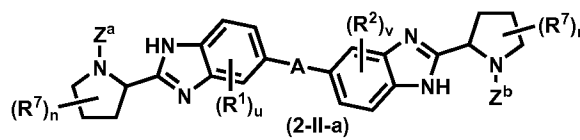
iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (II-d):



In another aspect, the invention is a process of making a compound having the Formula

20 (2-I) comprising the steps of:

i) preparing a compound of Formula (2-II-a):



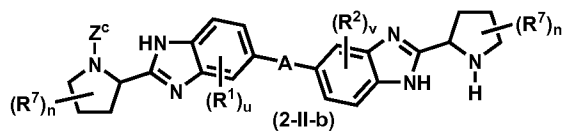
via a transition-metal catalyzed cross-coupling or metathesis reaction; amide or urea formation; ester or carbamate formation; or ether formation;

wherein:

A, n, u, v, R^1 , R^2 , and R^7 are as defined in claim 18;

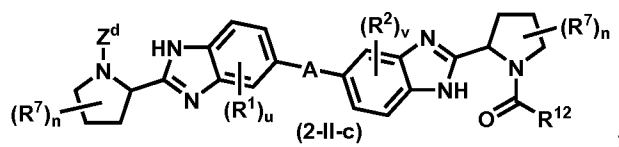
Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$; R^{12} is C_1 - C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1-C_4$ alkyl);

ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (II-b):



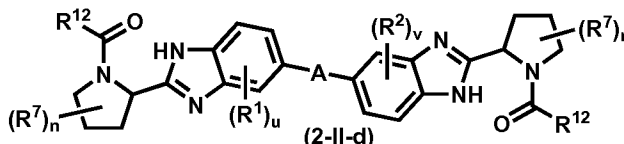
wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$;

iii) capping the released amino group of a compound of Formula (II-b) with $LG-C(O)-R^{12}$, wherein LG is a leaving group; to give the compound of Formula (II-c):



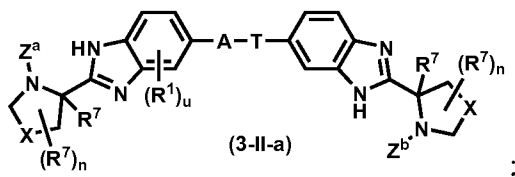
wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and

iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (II-d):



In yet another aspect, the invention is a process of making a compound having the Formula (3-I) comprising the steps of:

i) preparing a compound of Formula (3-II-a):

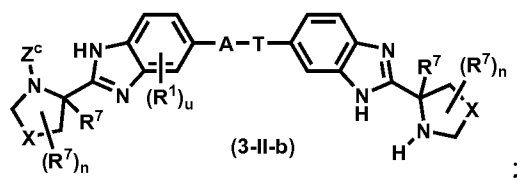


via a transition-metal catalyzed cross-coupling reaction; amide or urea formation; ester or carbamate formation; or ether formation;

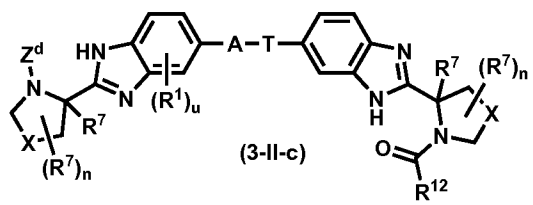
wherein

A, T, n, u, v, R^1 , R^2 , and R^7 are as defined in claim 33;

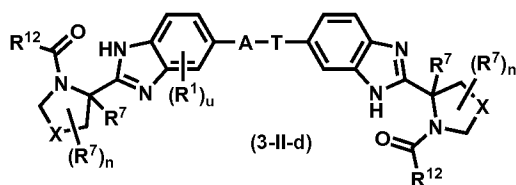
- Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$;
- ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (3-II-b):



- 5 wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$; R^{12} is C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1-C_4$ alkyl);
- iii) capping the released amino group of a compound of Formula (II-b) with $LG-C(O)-R^{12}$, wherein LG is a leaving group; to give the compound of Formula (3-II-c):



- 10 wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and
- iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (3-II-d):



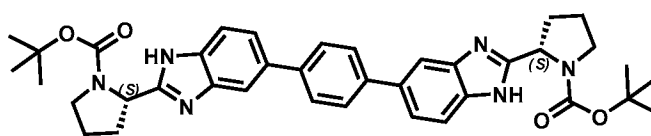
- 15 It will be appreciated that, with appropriate manipulation and protection of any chemical functionality, synthesis of compounds of the present invention is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts "Protective Groups in Organic Synthesis", 3rd Ed (1999), J
- 20 Wiley and Sons.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

EXAMPLES

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

Although the invention has been described with respect to various preferred
10 embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

Example 1-1.

Step 1a. A mixture of *N*-Boc-L-proline (5.754 g, 26.7 mmol) and TEA (3.73 mL, 26.7 mmol) in THF (60 mL) at -20°C was treated with ethyl chloroformate (2.55 mL, 26.7 mmol) for 30 minutes before a slow addition of 4-bromo-1,2-diaminobenzene (5.00 g, 26.7 mmol) in THF (20 mL). It was then kept at -20°C for 1 hour and then slowly
20 warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a dark brown foam (10.7 g). ESIMS $m/z = 384.18, 386.18 [\text{M}+\text{H}]^+$.

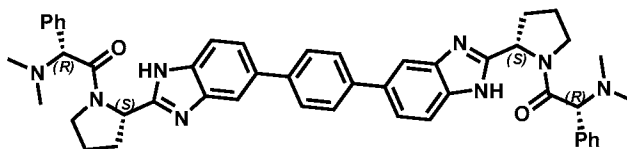
Step 1b. A solution of the crude compound from step 1a (10.7 g, theo. 26.7 mmol) in
25 glacial acetic acid (100 mL) was heated at 50°C for 2 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous NaHCO_3). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown foam (5.78 g, 59%). ESIMS $m/z = 366.17, 368.17 [\text{M}+\text{H}]^+$.

30 ^1H NMR (CDCl_3) 10.96, 10.93 (2 s, 1H), 7.81, 7.30 (2 s, 1H), 7.53, 7.17 (2d, $J = 8.5$ Hz,

1H), 7.23, 7.03 (2d, $J = 8.5$ Hz, 1H), 5.09, 5.07 (2s, 1H), 3.42-3.49 (m, 2H), 2.75-2.85 (m, 1H), 2.13-2.23 (m, 2H), 1.97-2.00 (m, 1H), 1.48 (s, 9H).

Step 1c. A mixture of the compound from step 1b (0.500 g, 1.37 mmol), benzene-1,4-diboronic acid (0.103 g, 0.621 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (35.8 mg, 31.0 μmol) in ethanol (6 mL), toluene (6 mL) and aqueous Na_2CO_3 (2 M, 0.4 mL) was degassed and heated to reflux under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous NaHCO_3). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a yellow solid (0.158 g, 23%). ESIMS $m/z = 649.50$ $[\text{M}+\text{H}]^+$.

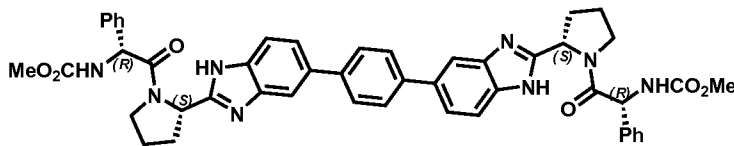
Example 1-2.



Step 2a. A solution of the compound from step 1c (79.0 mg, 0.122 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS $m/z = 449.39$ $[\text{M}+\text{H}]^+$.

Step 2b. A mixture of the crude compound from step 2a (0.122 mmol at most) and (R)-dimethylamino phenyl acetic acid (prepared according to WO 2008/021927, 54.5 mg, 0.305 mmol) in DMF (3 mL) was treated with HATU (0.102 g, 0.268 mmol) in the presence of DIPEA (0.30 mL, 2.44 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by reverse phase HPLC (C_{18} , $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{TFA}$) to give the title compound as its TFA salts and as a white solid (0.116 g, 2 steps 78%). ESIMS $m/z = 771.70$ $[\text{M}+\text{H}]^+$.

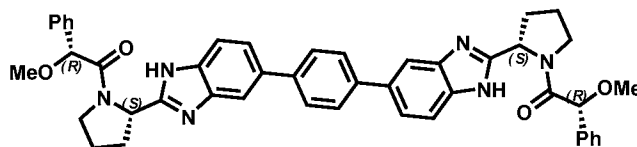
Example 1-3.



A mixture of the crude compound from step 2a (0.122 mmol at most) and (R)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 76.4 mg, 0.366 mmol) in DMF (3 mL) was treated with HATU (0.102 g, 0.268 mmol) in the presence of DIPEA (0.30 mL, 2.44 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography

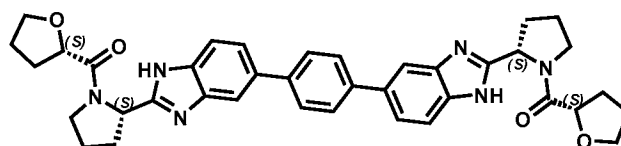
(silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (82.4 mg, 2 steps 81%). ESIMS m/z = 831.59 [M+H]⁺.

Example 1-20.



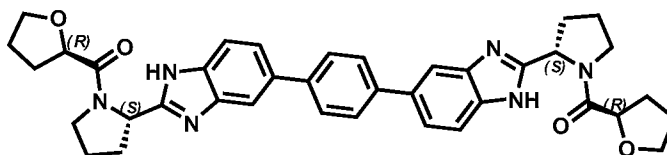
- 5 A mixture of the crude compound from step 2a (0.0786 mmol at most) and (*R*)- α -methoxy phenyl acetic acid (32.7 mg, 0.197 mmol) in DMF (2 mL) was treated with HATU (68.7 mg, 0.181 mmol) in the presence of DIPEA (0.27 mL, 1.572 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (33.0 mg, 2 steps 56%). ESIMS m/z = 745.05 [M+H]⁺.

Example 1-25.

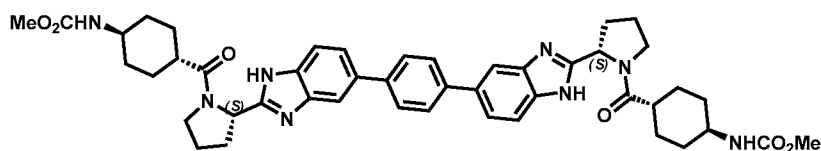


- A mixture of the crude compound from step 2a (0.077 mmol at most) and (*S*)-tetrahydrofuran-2-carboxylic acid (22mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil, which was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (40 mg, 2 steps 82%). ESIMS m/z = 645.00 [M+H]⁺.

Example 1-26.

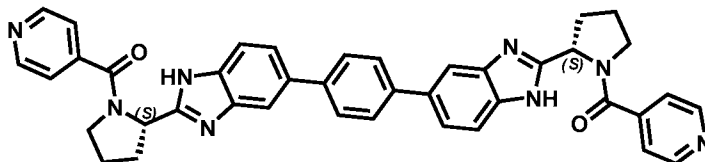


- 20 A mixture of the crude compound from step 2a (0.077 mmol at most) and (*R*)-tetrahydrofuran-2-carboxylic acid (22mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (16 mg, 2 steps 32%). ESIMS m/z = 645.06 [M+H]⁺.

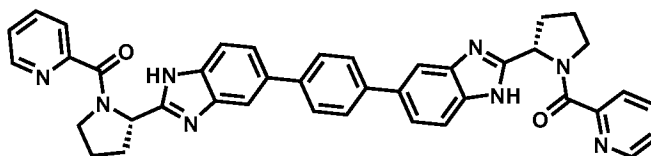
Example 1-42.

Step 42a. A mixture of *trans*-4-aminocyclohexanecarboxylic acid (500 mg, 3.5 mmol) in aqueous sodium hydroxide (1M, 3.5 mL) was added sodium carbonate (371 mg, 3.5 mmol) and methyl chloroformate (0.3 mL, 3.9 mmol). The resulting solution was stirred at room temperature for 2 hours before being extracted with dichloromethane. The aqueous phase was acidified with hydrochloric acid (1M, 7 mL) and the resulting cloudy suspension was extracted with EtOAc. The organic phase was separated, dried (Na₂SO₄) and concentrated to afford the crude desired product as white solid (546 mg, 78%). ESIMS $m/z = 224.01$ [M+Na]⁺.

Step 42b. A mixture of the crude compound from step 2a (0.077 mmol at most) and the compound from step 42a (39 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (41 mg, 2 steps 62%). ESIMS $m/z = 815.03$ [M+H]⁺.

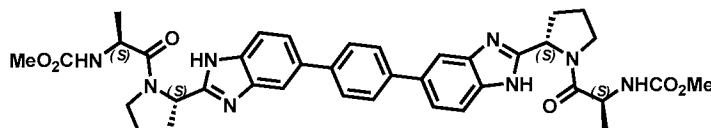
Example 1-52.

A mixture of the crude compound from step 2a (0.077 mmol at most) and isonicotinic acid (24mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (39 mg, 2 steps 76%). ESIMS $m/z = 658.99$ [M+H]⁺.

Example 1-54.

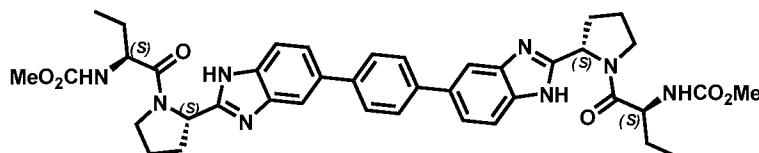
A mixture of the crude compound from step 2a (0.077 mmol at most) and picolinic acid (24mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (38 mg, 2 steps 74%). ESIMS m/z = 659.02 [M+H]⁺.

Example 1-62.



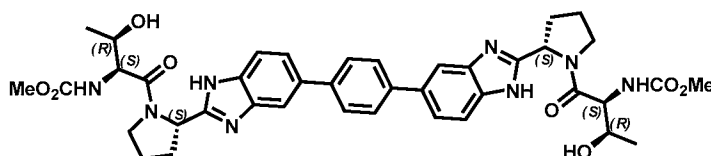
A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-(methoxycarbonylamino)propanoic acid (prepared according to WO 2008/021927, 28 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (52 mg, 2 steps 96%). ESIMS m/z = 707.06 [M+H]⁺.

Example 1-67.



A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-(methoxycarbonylamino)butanoic acid (prepared according to WO 2008/021927, 31 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (50.5 mg, 2 steps 89%). ESIMS m/z = 734.97 [M+H]⁺.

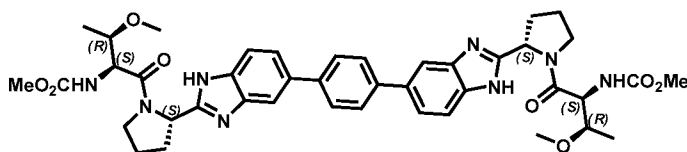
Example 1-70.



A mixture of the crude compound from step 2a (0.077 mmol at most) and (2S,3S)-3-hydroxy-2-(methylperoxymethylamino)butanoic acid (prepared according to WO

2008/021927, 30 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (48 mg, 2 steps 81%). ESIMS m/z = 767.08 [M+H]⁺.

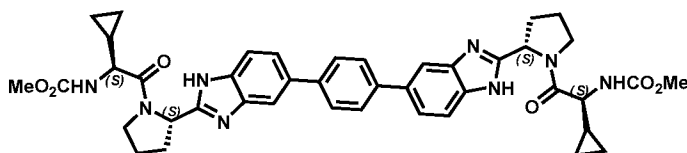
Example 1-72.



A mixture of the crude compound from step 2a (78.7 μmol at most) and (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (prepared according to WO

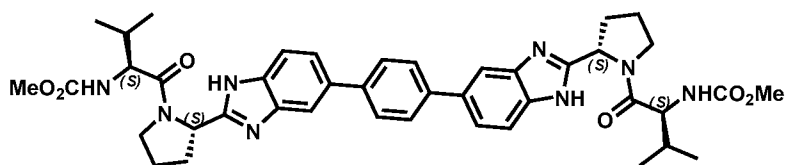
2008/021927, 34.6 mg, 0.181 mmol) in DMF (3 mL) was treated with HATU (65.8 mg, 0.173 mmol) in the presence of DIPEA (0.20 mL, 1.57 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (50.2 mg, 2 steps 80%). ESIMS m/z = 795.54 [M+H]⁺.

Example 1-78.



A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-cyclopropyl-2-(methoxycarbonylamino)acetic acid (prepared according to WO 2008/021927, 30 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (55 mg, 2 steps 95%). ESIMS m/z = 759.36 [M+H]⁺.

Example 1-83.

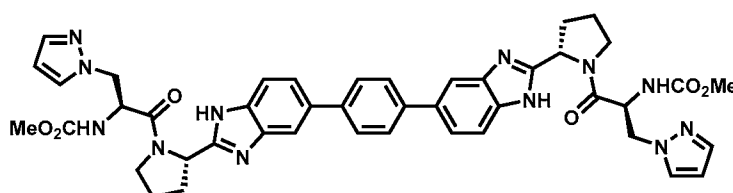


A mixture of the crude compound from step 2a (0.156 mmol at most) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (prepared according to WO 2008/021927, 68.2 mg,

0.386 mmol) in DMF (3 mL) was treated with HATU (0.136 g, 0.358 mmol) in the presence of DIPEA (0.39 mL, 3.12 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (98.3 mg, 2 steps 83%).

5 ESIMS m/z = 763.22 [M+H]⁺.

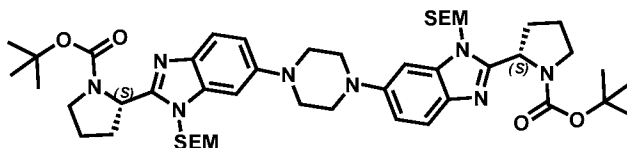
Example 1-114.



A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (prepared with similar procedure as that of **42a**, 41 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (40 mg, 2 steps 64%). ESIMS m/z = 838.96 [M+H]⁺.

15

Example 1-354a.

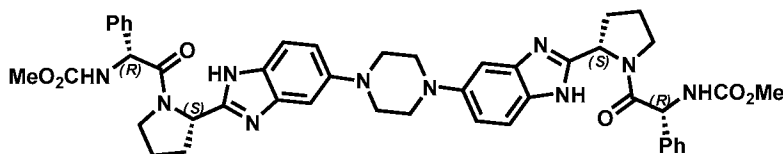


Step 354a-a. A solution of the compound from step 1b (2.18 g, 5.95 mmol) in DMF (50 mL) was treated with NaH (60% in mineral oil, 0.273 g, 6.84 mmol) for 1 hour before a slow addition of 2-(trimethylsilyl)ethoxymethyl chloride (1.05 mL, 5.95 mmol). The mixture was kept stirring for 3 hours before being diluted with EtOAc and quenched with saturated NH₄Cl. The organics were washed with water and brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow oil (2.75 g, 94%). ESIMS m/z = 496.33, 498.33 [M+H]⁺.

25 **Step 354a-b.** A mixture of the compound from step 354a-a (0.200 g, 0.403 mmol), piperazine (11.6 mg, 0.134 mmol), 2-diphenylphosphono-2'-(N, N-dimethylamino)biphenyl (29.6 mg, 73.2 μmol), sodium *t*-butoxide (39.9 mg, 0.403 mmol) and Pd₂(dba)₃ (24.6 mg, 26.8 μmol) in toluene (6 mL) was degassed and heated at 80 °C under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc

- water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a brown oil (0.102 g, 81%). The regiochemistry of the SEM-group was not determined. ESIMS $m/z = 917.79$ $[\text{M}+\text{H}]^+$.

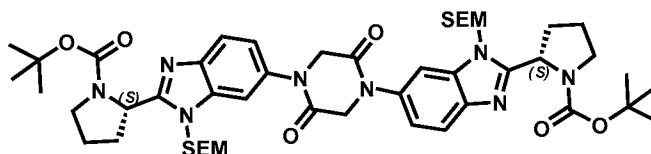
5

Example 1-354.

Step 354a. A solution of the compound from step 354a-b (100 mg, 0.109 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at 50 °C for 2 hours. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS $m/z = 457.37$ $[\text{M}+\text{H}]^+$.

10

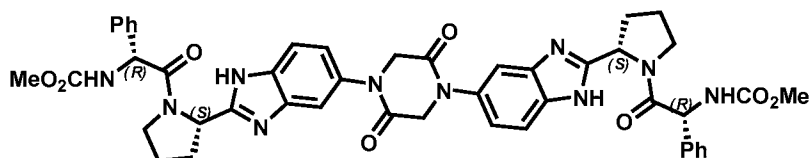
Step 354b. The title compound was synthesized from the compound from step 354a using a procedure similar to that described in Example 3. ESIMS $m/z = 839.34$ $[\text{M}+\text{H}]^+$.

Example 1-357a.

A mixture of the compound from step 354a-a (0.360 g, 0.726 mmol), glycine anhydride (27.6 mg, 0.242 mmol), (1R,2R)-N¹,N²-dimethylcyclohexane-1,2-diamine (15.2 μL , 96.3 μmol), potassium phosphate (0.174 g, 0.822 mmol) and CuI (9.2 mg, 48.3 μmol) in toluene (4 mL) was degassed and heated at 100 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (47.9 mg, 21%). The regiochemistry of the SEM-group was not determined. ESIMS $m/z = 945.91$ $[\text{M}+\text{H}]^+$.

15

20

Example 1-357.

25

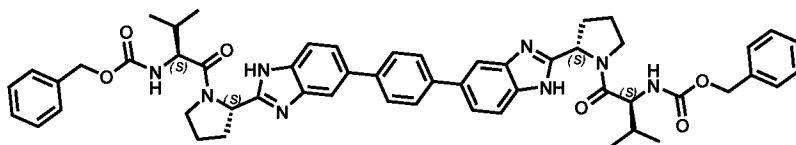
Step 357a. A solution of the compound from Example 357a (47.9 mg, 50.7 μmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at 50 °C for 2 hours. The

volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS $m/z = 485.44 [M+H]^+$.

Step 357b. The title compound was synthesized from the compound from step 357a using a procedure similar to that described in Example 3. ESIMS $m/z = 867.69 [M+H]^+$.

5

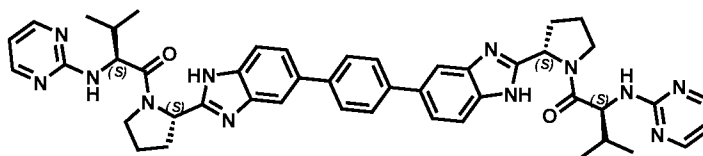
Example 1-361.



A mixture of the crude compound from step 2a (0.309 mmol at most) and (S)-2-(benzyloxy-carbonylamino)-3-methylbutanoic acid (0.178 g, 0.710 mmol) in DMF (3 mL) was treated with HATU (0.258 g, 0.679 mmol) in the presence of DIPEA (0.58 mL, 4.63 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (0.257 g, 2 steps 91%). ESIMS $m/z = 915.52 [M+H]^+$.

10

Example 1-362.

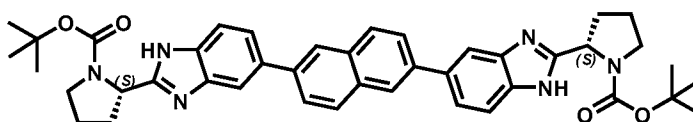


Step 362a. A mixture of the title compound from example 361 (0.128 g, 0.140 mmol) and Pd(OH)₂ on carbon (20% wt., 64.0 mg) in ethanol (12 mL) was treated with H₂ balloon overnight. The mixture was filtered through celite and the filtrate was concentrated to give the crude desired compound as a white solid (73.7 mg, 82%). ESIMS $m/z = 647.47 [M+H]^+$.

Step 362b. A mixture of the compound from step 362a (73.7 mg, 0.114 mmol), 2-bromopyrimidine (0.124 g, 0.741 mmol) and DIPEA (47 μ L, 0.376 mmol) in toluene (4 mL) and DMSO (1 mL) was degassed and heated to 90 °C under N₂ overnight. The volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (29.0 mg, 32%). ESIMS $m/z = 803.41 [M+H]^+$.

25

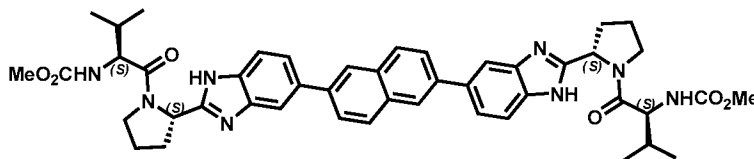
Example 1-363.



Step 363a. A mixture of the compound from step 1b (1 g, 2.73 mmol), bis-(pinacolato)-diboron (763 mg, 3.0 mmol), potassium acetate (402 mg, 4.0 mmol) in 1,4-dioxane (9.1 mL) was added tetrakis(triphenylphosphine)palladium(0) (158 mg, 0.14 mmol). The resulting solution was degassed and then heated at 80 °C under N₂ overnight before being
5 evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et₃N in ethyl acetate) to give the desired compound as a yellow solid (680 mg, 60%). ESIMS m/z = 414.24 [M+H]⁺.

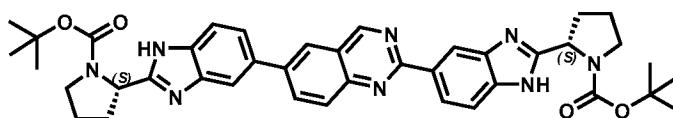
Step 363b. A mixture of the compound from step 363a (0.400 g, 0.969 mmol), 2,6-dibromo-naphthalene (0.126 g, 0.440 mmol), NaHCO₃ (0.296 g, 3.52 mmol) and
10 Pd(PPh₃)₄ (25.4 mg, 22.0 μmol) in DME (12 mL) and water (4 mL) was degassed and heated at 85 °C under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (0.268 g, 87%).
15 ESIMS m/z = 699.31 [M+H]⁺.

Example 1-364.

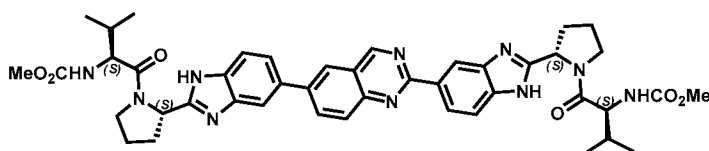


The title compound was synthesized from the compound of Example 363 using procedures similar to that described in step 2b and Example 83. ESIMS m/z = 813.55 [M+H]⁺.

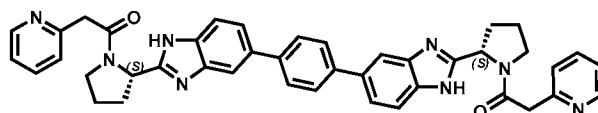
Example 1-365.



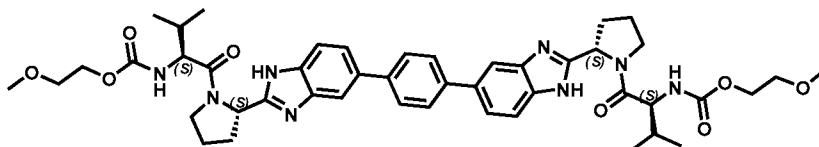
A mixture of the compound from step 363a (47.2 mg, 0.114 mmol), 2,6-dibromoquinazoline (15.0 mg, 52.0 μmol) and Pd(PPh₃)₄ (6.0 mg, 5.2 μmol) in ethanol (3 mL), toluene (3 mL) and aqueous Na₂CO₃ (2 M, 0.2 mL) was degassed and heated to
25 reflux under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous NaHCO₃). The organics were washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a yellow solid (28.3 mg, 36%). ESIMS m/z = 701.32 [M+H]⁺.

Example 1-366.

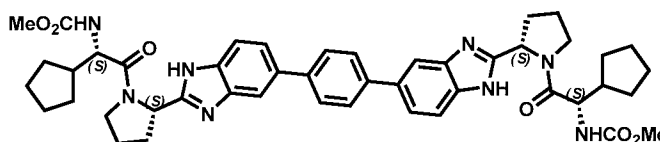
The title compound was synthesized from the compound from Example 365 using procedures similar to that described in step 2b and Example 83. ESIMS m/z = 815.53 $[M+H]^+$.

Example 1-367.

A mixture of the crude compound from step 2a (0.077 mmol at most) and 2-(pyridin-2-yl)-acetic acid (33 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH_2Cl_2 -MeOH) to give the title compound as a yellow solid (14 mg, 2 steps 26%). ESIMS m/z = 686.98 $[M+H]^+$.

Example 1-368.

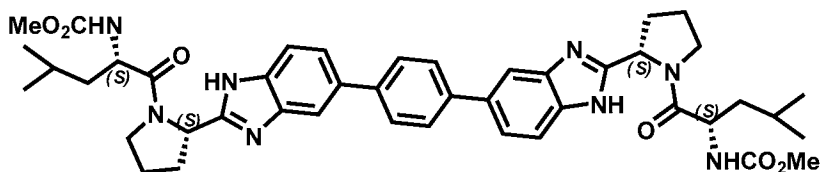
A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-((2-methoxyethoxy)carbonylamino)-3-methylbutanoic acid (prepared with similar procedure as that of **42a**, 42 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH_2Cl_2 -MeOH) to give the title compound as a yellow solid (45 mg, 2 steps 69%). ESIMS m/z = 851.12 $[M+H]^+$.

Example 1-369.

A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-cyclopentyl-2-(methoxycarbonylamino) acetic acid (prepared with similar procedure as that of **42a**, 35 mg, 0.19 mmol) in DMF (2 mL) was treated with HATU (73 mg, 0.19

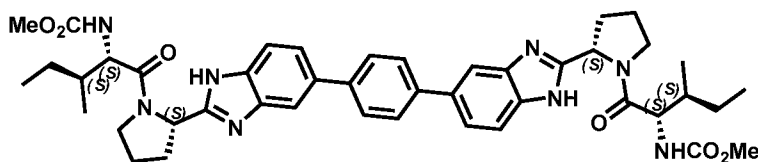
mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (51 mg, 2 steps 63%). ESIMS m/z = 815.13 [M+H]⁺.

5

Example 1-370.

A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid (prepared with similar procedure as that of **42a**, 32 mg, 0.19 mmol) in acetonitrile (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (55 mg, 2 steps 90%). ESIMS m/z = 790.99 [M+H]⁺.

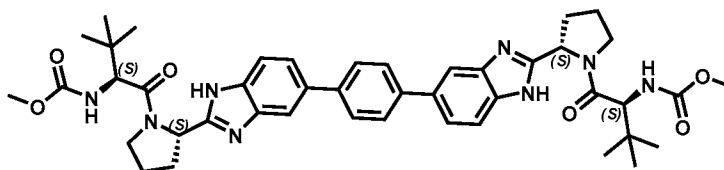
10

Example 1-371.

15

A mixture of the crude compound from step 2a (0.077 mmol at most) and (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (prepared with similar procedure as that of **42a**, 32 mg, 0.19 mmol) in acetonitrile (2 mL) was treated with HATU (73 mg, 0.19 mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (58.5 mg, 2 steps 95%). ESIMS m/z = 790.99 [M+H]⁺.

20

Example 1-372.

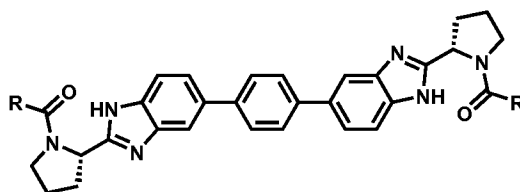
25

A mixture of the crude compound from step 2a (0.077 mmol at most) and (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (prepared with similar procedure as that of **42a**, 32 mg, 0.19 mmol) in acetonitrile (2 mL) was treated with HATU (73 mg, 0.19

mmol) in the presence of DIPEA (0.22 mL, 1.6 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a yellow solid (52 mg, 2 steps 85%). ESIMS m/z = 790.99 [M+H]⁺.

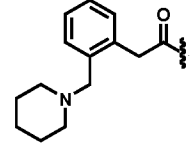
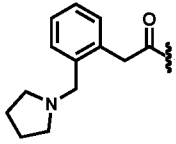
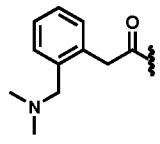
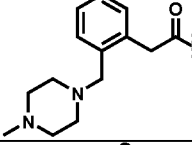
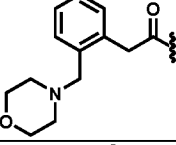
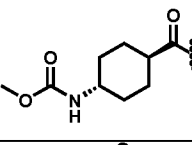
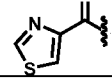
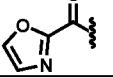
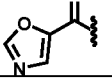
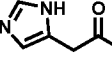
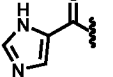
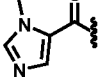
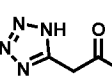
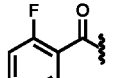
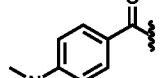
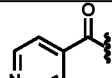
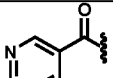
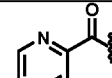
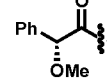
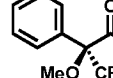
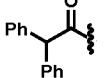
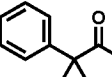
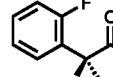
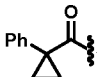
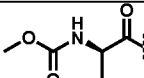
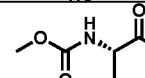
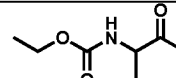
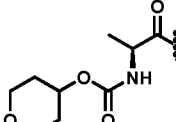
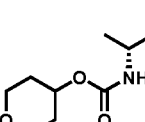
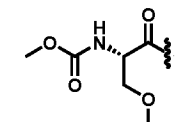
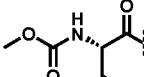
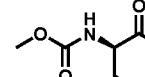
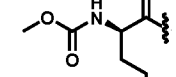
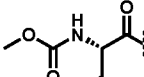
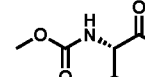
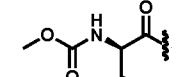
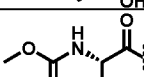
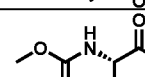
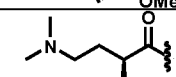
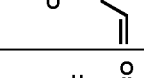
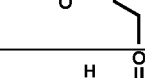
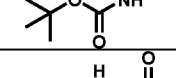
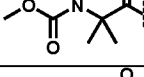
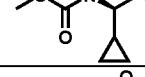
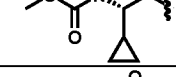
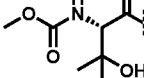
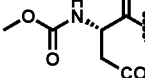
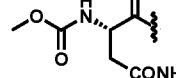
- 5 The remaining compounds of examples 1-4 to 1-360 may be prepared using procedures similar to those described in examples 1-1, 1-2, 1-3, 1-20, 1-25, 1-26, 1-42, 1-52, 1-54, 1-62, 1-67, 1-70, 1-72, 1-78, 1-83, 1-114, 1-354, 1-354a, 1-357, 1-357a, 1-361 to 1-372, and/or procedures described in the Synthetic Methods.

Table 1a: Examples 1-4 to 1-219

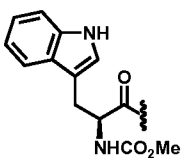
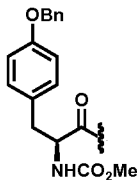
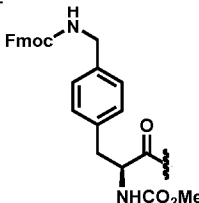
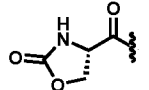
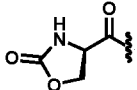
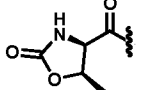
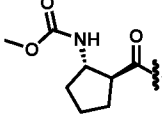
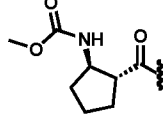
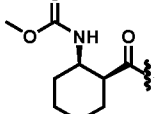
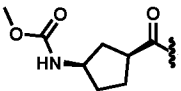
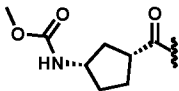
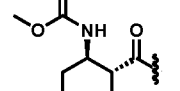
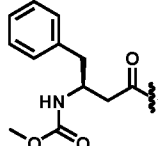
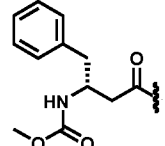
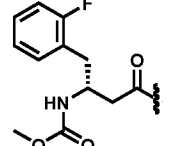
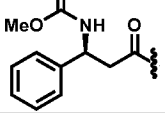
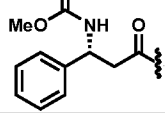
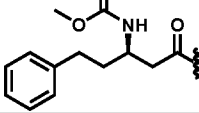
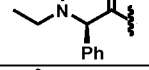
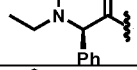
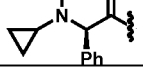
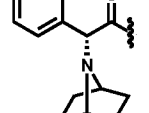
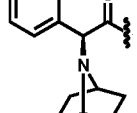
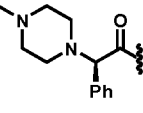
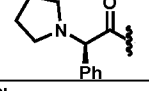
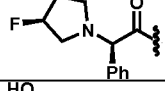
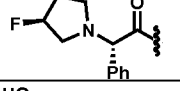
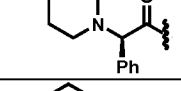
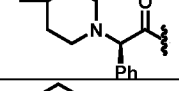
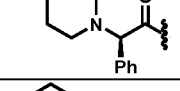
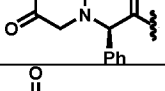
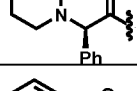
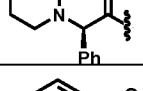
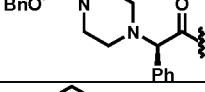
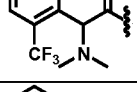
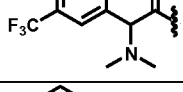
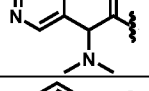
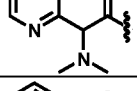
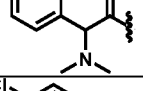
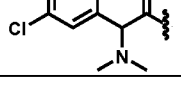
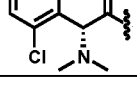
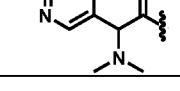


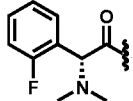
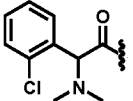
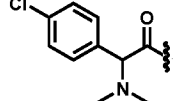
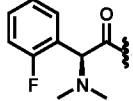
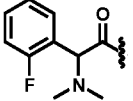
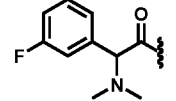
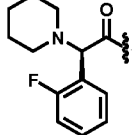
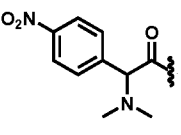
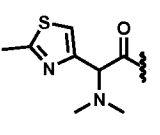
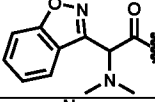
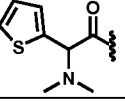
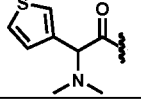
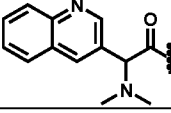
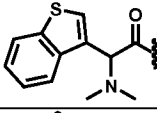
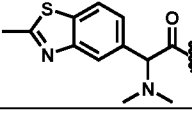
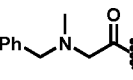
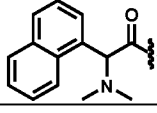
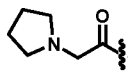
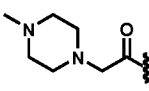
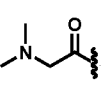
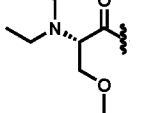
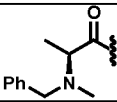
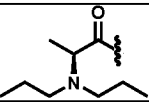
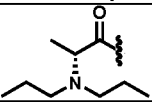
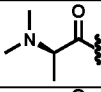
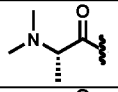
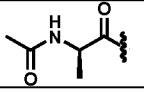
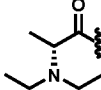
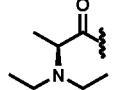
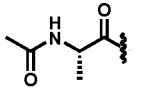
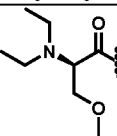
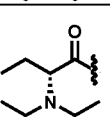
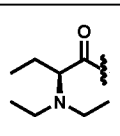
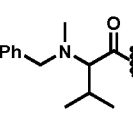
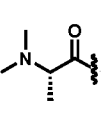
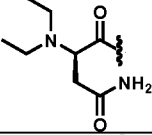
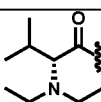
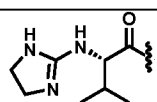
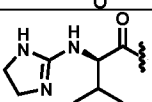
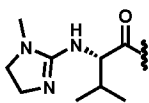
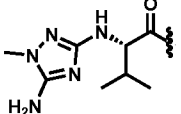
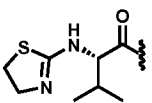
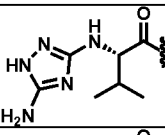
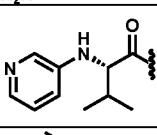
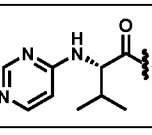
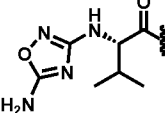
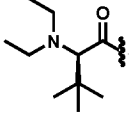
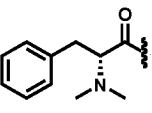
10

Example 1-		Example 1-		Example 1-	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	

37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	

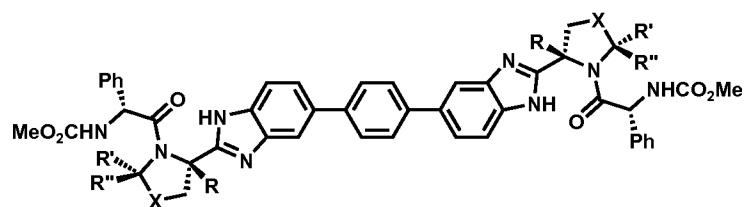
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	

121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	

163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	

211		212		213	
214		215		216	
217		218		219	

Table 2: Examples 1-220 to 1-229.



Example 1-	R	R'	R''	X	Example 1-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

Table 3: Examples 1-230 to 1-233.

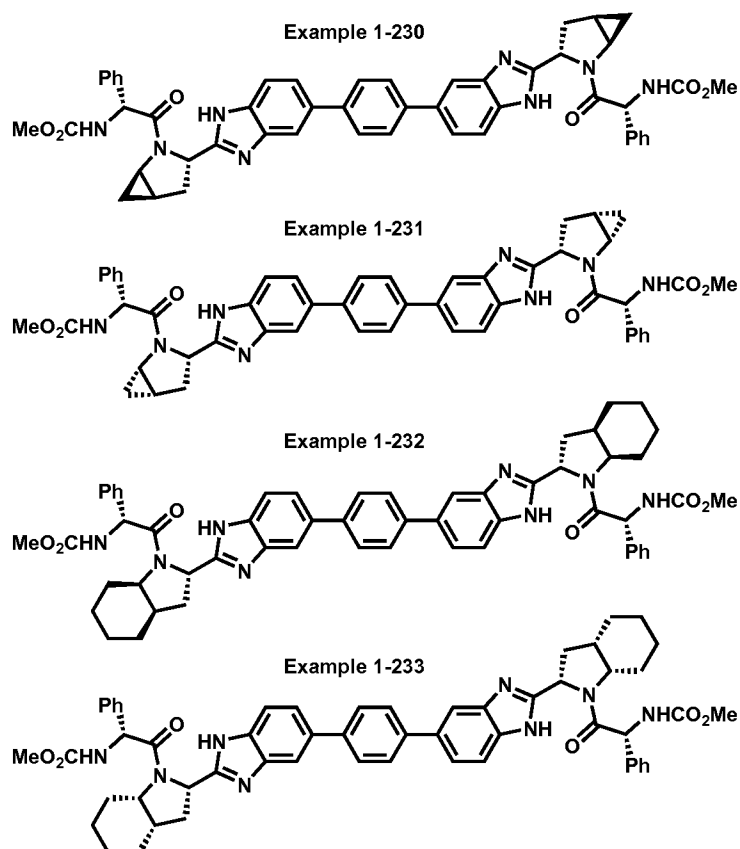
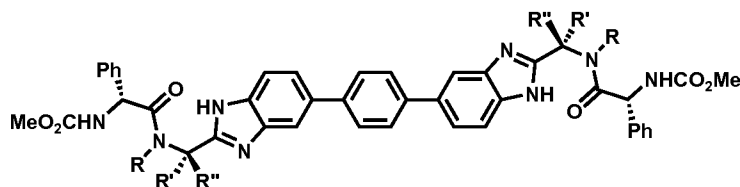
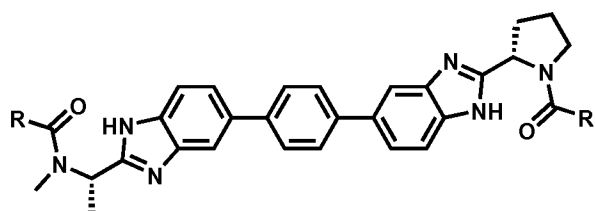


Table 4: Examples 1-234 to 1-243.



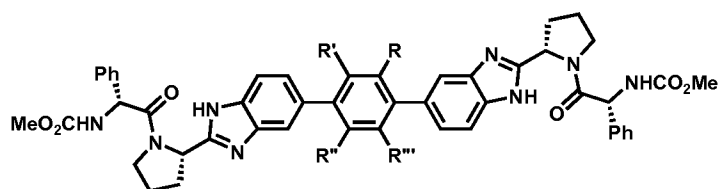
Example 1-	R	R'	R''	Example 1-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

Table 5: Examples 1-244 to 1-263.



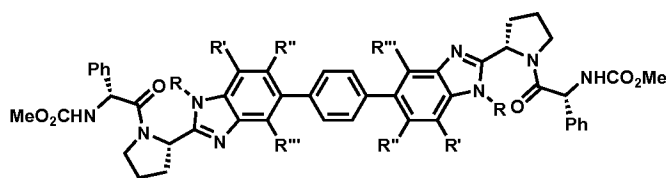
Example 1-	R	R'	Example 1-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 6: Examples 1-264 to 1-283.



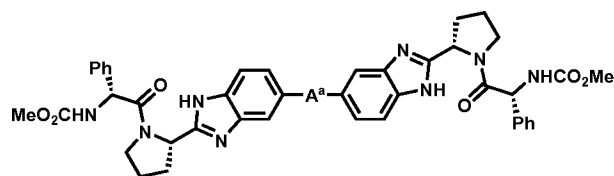
Example 1-	R	R'	R''	R'''	Example 1-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H
280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

Table 7: Examples 1-284 to 1-309.



Example 1-	R	R'	R''	R'''	Example 1-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

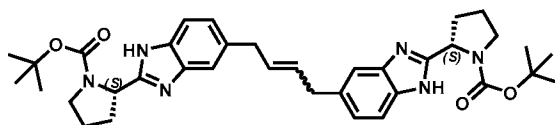
Table 8: Examples 1-310 to 1-360.



Example 1-	A ^a	Example 1-	A ^a	Example 1-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	

337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	
358		359		360	

Example 2-1a.



Step 1a-a. A mixture of *N*-Boc-L-proline (5.754 g, 26.7 mmol) and TEA (3.73 mL, 26.7 mmol) in THF (60 mL) at -20°C was treated with ethyl chloroformate (2.55 mL, 26.7 mmol) for 30 minutes before a slow addition of 4-bromo-1,2-diaminobenzene (5.00 g, 26.7 mmol) in THF (20 mL). It was then kept at -20°C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a dark brown foam (10.7 g). ESIMS $m/z = 384.18, 386.18 [\text{M}+\text{H}]^+$.

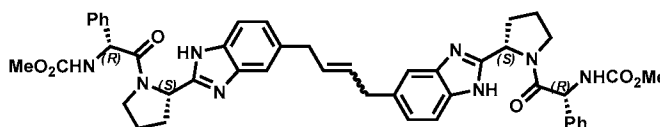
Step 1a-b. A solution of the crude compound of step 1a-a (10.7 g, theo. 26.7 mmol) in glacial acetic acid (100 mL) was heated at 50°C for 2 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous NaHCO_3). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown foam (5.78 g, 59%). ESIMS $m/z = 366.17, 368.17 [\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3) 10.96, 10.93 (2 s, 1H), 7.81, 7.30 (2 s, 1H), 7.53, 7.17 (2d, $J = 8.5$ Hz,

1H), 7.23, 7.03 (2d, $J = 8.5$ Hz, 1H), 5.09, 5.07 (2s, 1H), 3.42-3.49 (m, 2H), 2.75-2.85 (m, 1H), 2.13-2.23 (m, 2H), 1.97-2.00 (m, 1H), 1.48 (s, 9H).

Step 1a-c. A mixture of the compound of step 1a-b (0.250 g, 0.683 mmol), allyltributylstannane (0.26 mL, 0.820 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (39.4 mg, 34.1 μmol) in toluene (6 mL) was degassed and heated to 110 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous NaHCO_3). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compounds as a colorless oil (0.127 g, 60%). ESIMS $m/z = 328.23$ $[\text{M}+\text{H}]^+$.

Step 1a-d. A mixture of the compound of step 1a-c (0.100 g, 0.306 mmol) and Grubbs-1 Catalyst (12.5 mg, 15.2 μmol) in CH_2Cl_2 (6 mL) was degassed and heated to reflux under N_2 for 3 days. The volatiles were evaporated and the residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a colorless oil (8.7 mg). ESIMS $m/z = 627.28$ $[\text{M}+\text{H}]^+$.

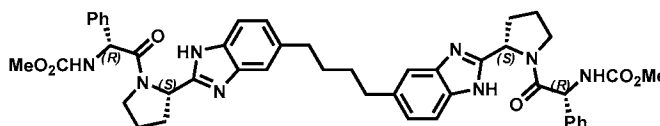
Example 2-3a.



Step 3a-a. A solution of the compound of Example 1a-a (8.7 mg, 13.8 μmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) rt for 30 min. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS $m/z = 427.39$ $[\text{M}+\text{H}]^+$.

Step 3a-b. A mixture of the crude compound of step 3a-a (13.8 μmol at most) and (R)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 7.2 mg, 34.5 μmol) in DMF (3 mL) was treated with HATU (12.0 mg, 31.7 μmol) in the presence of DIPEA (34.4 μL , 0.276 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2 -MeOH) to give the title compound as a very light yellow solid (8.8 mg, 2 steps 79%). ESIMS $m/z = 809.30$ $[\text{M}+\text{H}]^+$.

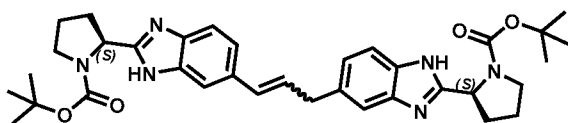
Example 2-310.



A mixture of the compound of example 3a (5.8 mg, 7.1 μ mol) and Pd(OH)₂ on carbon (20%, 15.0 mg) in ethanol (3 mL) was treated with H₂ balloon overnight. It was filtered through celite and the filtrate was concentrated. The residue was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (5.0

5 mg, 86%). ESIMS m/z = 811.34 [M+H]⁺.

Example 2-353.

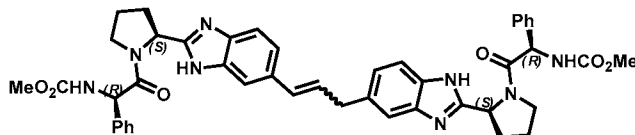


A mixture of the compound of step 1a-b (0.156 g, 0.427 mmol), the compound of step 1a-c (0.127 g, 0.388 mmol), triethylamine (0.56 mL, 3.88 mmol), tri-*o*-tolylphosphine (15.2

10 mg, 48.5 μ mol) and Pd(OAc)₂ (4.4 mg, 19.4 μ mol) in CH₃CN (6 mL) was degassed and heated to 80 °C under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous NaHCO₃). The organics were washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow

15 oil (0.165 g, 70%). ESIMS m/z = 613.47 [M+H]⁺.

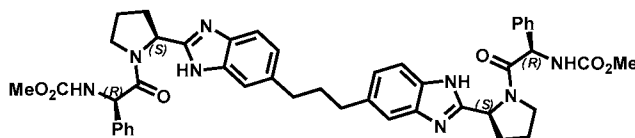
Example 2-354.



The title compound was synthesized from the compound from Example 353 using procedures similar to that described in Example 3a. ESIMS m/z = 795.56 [M+H]⁺.

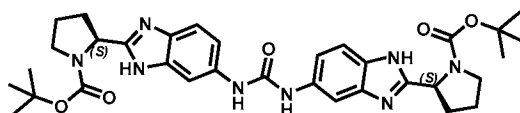
20

Example 2-355.



The title compound was synthesized from the compound from Example 354 using procedures similar to that described in Example 310. ESIMS m/z = 797.69 [M+H]⁺.

Example 2-356.



25

Step 356a. A mixture of *N*-Boc-L-proline (7.03 g, 32.6 mmol) and TEA (4.55 mL, 32.6 mmol) in THF (60 mL) at -20 °C was treated with *iso*-butyl chloroformate (4.27 mL, 32.6

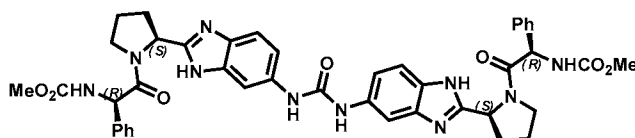
mmol) for 30 minutes before a slow addition of 4-nitro-1,2-diaminobenzene (5.00 g, 32.6 mmol) in THF (20 mL). It was then kept at -20°C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4),
5 filtered and evaporated to give the crude desired compound as a dark brown foam which was directly used in the next step. ESIMS $m/z = 351.23$ $[\text{M}+\text{H}]^+$.

Step 356b. A mixture of the compound from step 356a (32.6 mmol at most) and Pd on carbon (10%, 500 mg) in ethanol (200 mL) was treated with H_2 balloon overnight. The mixture was filtered through celite and the filtrate was concentrated to give the crude
10 desired compound as a dark purple foam which was directly used in the next step. ESIMS $m/z = 321.25$ $[\text{M}+\text{H}]^+$.

Step 356c. A solution of the crude compound from step 356b (32.6 mmol at most) in glacial acetic acid (60 mL) was heated at 40°C for 3 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous NaHCO_3). The organics
15 were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, CH_2Cl_2 -MeOH) to give the desired compound as a purple foam (7.02 g, 3 steps 71%). ESIMS $m/z = 303.28$ $[\text{M}+\text{H}]^+$.

Step 356d. A mixture of the compound from step 356c (0.200 g, 0.662 mmol), CDI (53.7 mg, 0.331 mmol) and triethylamine (0.11 mL, 0.794 mmol) in THF (5 mL) was kept
20 stirring under N_2 overnight. The volatiles were evaporated and the residue was purified by flash column chromatography (silica, CH_2Cl_2 -MeOH) to give the title compound as a light purple solid (0.115 g, 55%). ESIMS $m/z = 631.54$ $[\text{M}+\text{H}]^+$.

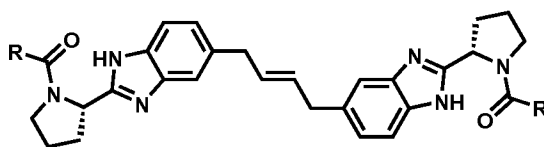
Example 2-357.



25 The title compound was synthesized from the compound from Example 356 using procedures similar to that described in Example 3a. ESIMS $m/z = 813.65$ $[\text{M}+\text{H}]^+$.

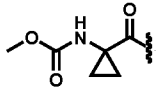
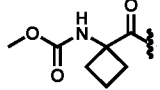
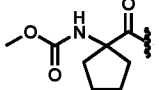
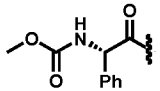
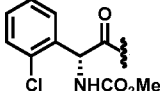
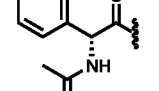
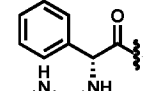
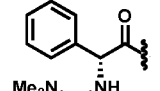
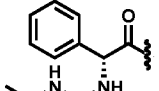
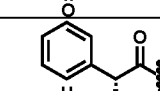
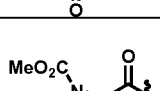
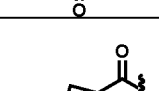
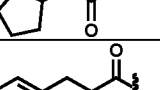
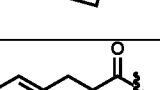
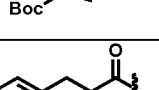
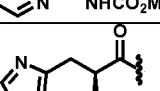
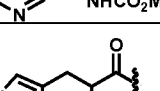
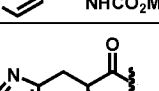
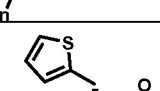
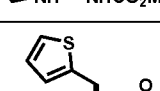
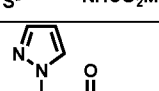
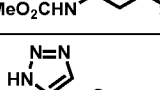
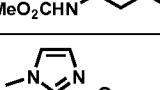
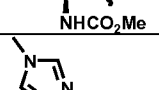
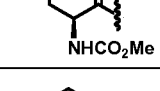
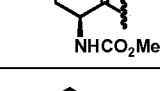
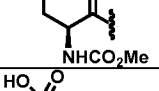
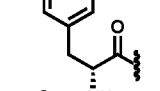
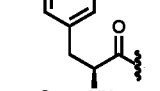
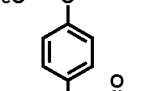
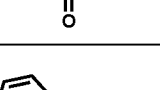
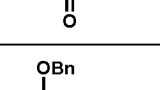
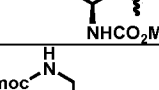
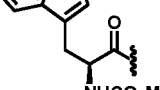
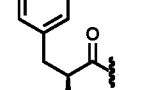
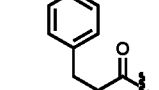
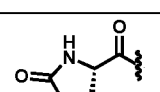
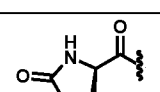
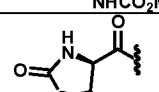
The remaining compounds of examples 1-352 may be prepared using procedures similar to those described in examples 1a, 3a, 310, 353-357, and/or as described in the Synthetic Methods.

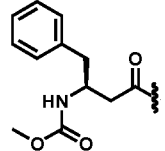
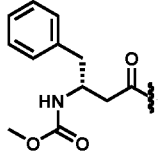
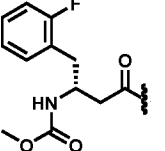
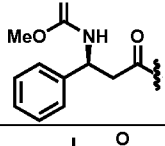
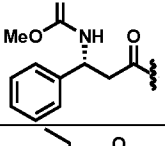
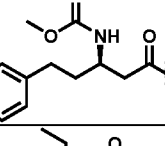
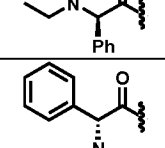
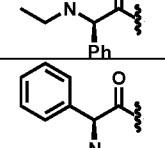
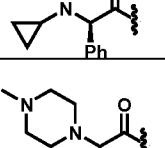
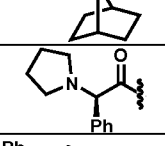
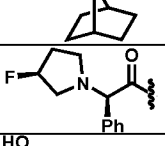
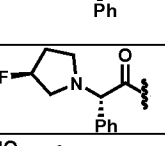
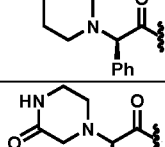
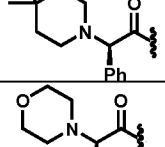
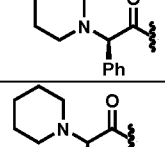
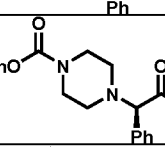
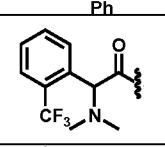
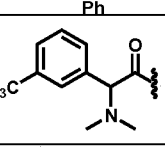
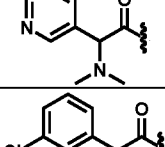
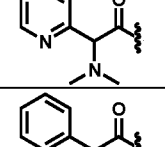
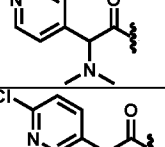
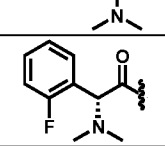
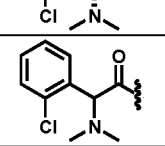
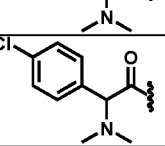
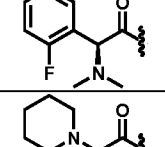
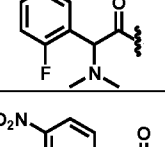
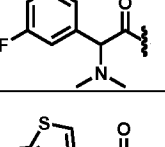
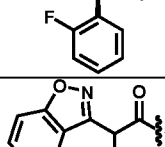
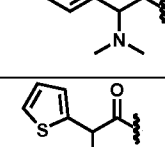
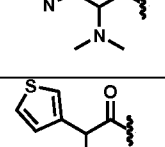
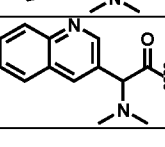
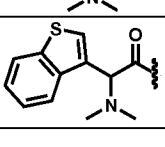
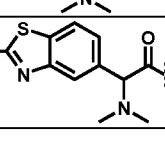
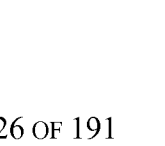
Table 9: Examples 2-1 to 2-219



Example 2-		Example 2-		Example 2-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	

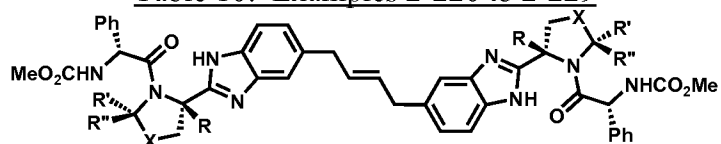
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	

94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	

133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	

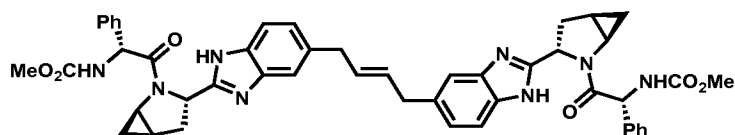
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Table 10: Examples 2-220 to 2-229

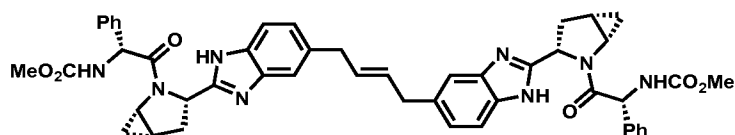


Example 2-	R	R'	R''	X	Example 2-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

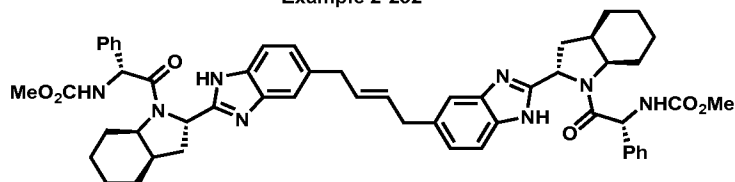
Example 2-230



Example 2-231



Example 2-232



Example 2-233

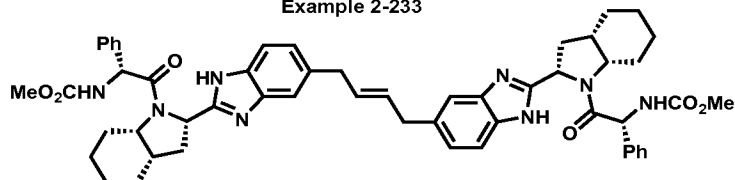
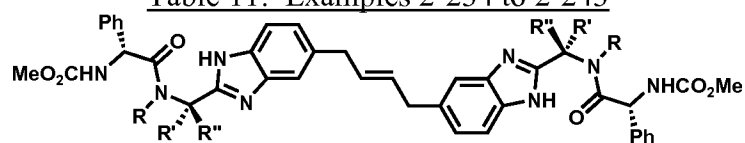
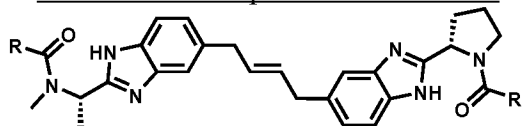


Table 11: Examples 2-234 to 2-243



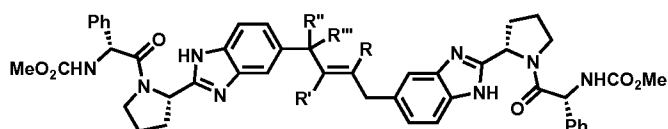
Example 2-	R	R'	R''	Example 2-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

Table 12: Examples 2-244 to 2-263



Example 2-	R	R'	Example 2-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

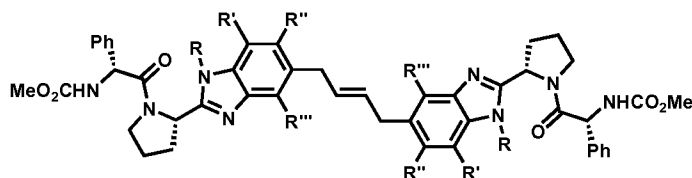
Table 13: Examples 2-264 to 2-283



Example 2-	R	R'	R''	R'''	Example 2-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H

280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

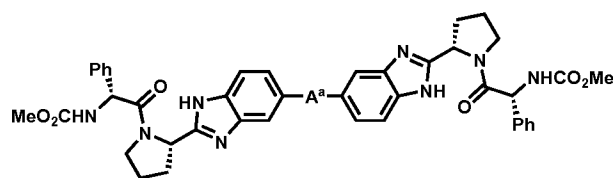
Table 14: Examples 2-284 to 2-309



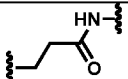
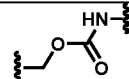
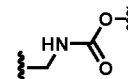
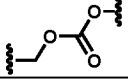
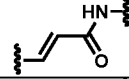
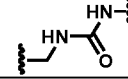
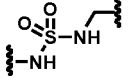
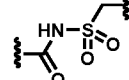
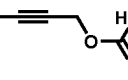
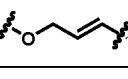
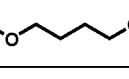
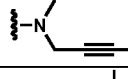
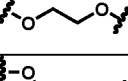
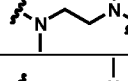
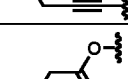
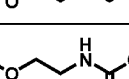
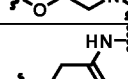
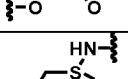
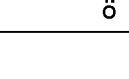
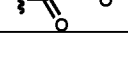
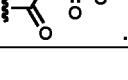
Example 2-	R	R'	R''	R'''	Example 2-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

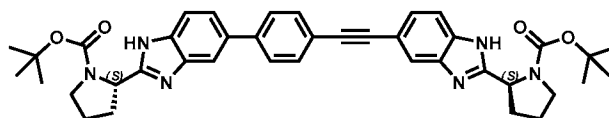
5

Table 15: Examples 2-310 to 2-352



Example 2-	A ^a	Example 2-	A ^a	Example 2-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	

331		332		333	
334		335		336	
337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352					

Example 3-335.

Step 335a. A mixture of *N*-Boc-L-proline (5.754 g, 26.7 mmol) and TEA (3.73 mL, 26.7 mmol) in THF (60 mL) at -20°C was treated with ethyl chloroformate (2.55 mL, 26.7 mmol) for 30 minutes before a slow addition of 4-bromo-1,2-diaminobenzene (5.00 g, 26.7 mmol) in THF (20 mL). It was then kept at -20°C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a dark brown foam (10.7 g). ESIMS $m/z = 384.18, 386.18$ $[\text{M}+\text{H}]^+$.

Step 335b. A solution of the crude compound from step 335a (10.7 g, 26.7 mmol at most) in glacial acetic acid (100 mL) was heated at 50°C for 2 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - aqueous NaHCO_3). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown foam (5.78 g, 59%). ESIMS $m/z = 366.17, 368.17$ $[\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3) 10.96, 10.93 (2 s, 1H), 7.81, 7.30 (2 s, 1H), 7.53, 7.17 (2d, $J = 8.5$ Hz, 1H), 7.23, 7.03 (2d, $J = 8.5$ Hz, 1H), 5.09, 5.07 (2s, 1H), 3.42-3.49 (m, 2H), 2.75-2.85 (m, 1H), 2.13-2.23 (m, 2H), 1.97-2.00 (m, 1H), 1.48 (s, 9H).

Step 335c. A mixture of the compound from step 335b (1 g, 2.73 mmol), bis-(pinacolato)-diboron (763 mg, 3.0 mmol), potassium acetate (402 mg, 4.0 mmol) in 1,4-dioxane (9.1 mL) was added tetrakis(triphenylphosphine)palladium(0) (158 mg, 0.14 mmol). The resulting solution was degassed and then heated at 80 °C under N₂ overnight before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et₃N in ethyl acetate) to give the desired compound as a yellow solid (680 mg, 60%). ESIMS m/z = 414.24 [M+H]⁺.

Step 335d. A mixture of the compound from step 335c (0.250 g, 0.605 mmol), 1-bromo-4-iodobenzene (0.257 g, 0.908 mmol), NaHCO₃ (0.203 g, 2.42 mmol) and Pd(PPh₃)₄ (34.9 mg, 30.2 μmol) in DME (12 mL) and water (4 mL) was degassed and heated at 85 °C under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a very light yellow solid (0.246 g, 92%). ESIMS m/z = 442.00, 444.00 [M+H]⁺.

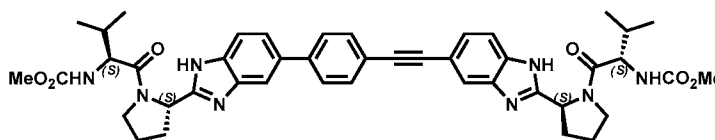
Step 335e. A mixture of the compound from step 1b (2.010 g, 5.488 mmol), trimethylsilyl-acetylene (2.33 mL, 16.46 mmol), CuI (0.110 g, 0.576 mmol) and Pd(PPh₃)₂Cl₂ (0.308 g, 0.439 mmol) in Et₃N (50 mL) was degassed and then heated at 80 °C under N₂ overnight before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et₃N in ethyl acetate) to give the desired compound as a yellow foam (1.140 g, 54%). ESIMS m/z = 384.22 [M+H]⁺.

Step 335f. A suspension of the compound from step 335e (1.140 g, 2.972 mmol) and K₂CO₃ (1.027 g, 7.430 mmol) in methanol (30 mL) was stirred at rt for 2 hour. The volatiles were evaporated off. The residue was partitioned (EtOAc - H₂O). The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et₃N in ethyl acetate) to give the desired compound as a yellow foam (0.792 g, 86%). ESIMS m/z = 312.18 [M+H]⁺.

Step 335g. A mixture of the compound from step 335d (97.0 mg, 0.219 mmol), the compound from step 335f (75.0 mg, 0.241 mmol), CuI (1.2 mg, 6.5 μmol) and Pd(PPh₃)₄ (34.9 mg, 30.2 μmol) in CH₃CN (4 mL) and triethylamine (4 mL) was degassed and heated at 90 °C under N₂ overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na₂SO₄), filtered and evaporated. The residue was purified by flash column chromatography (silica,

hexanes-ethyl acetate) to give the title compound as a light yellow solid (0.108 g, 73%). ESIMS $m/z = 673.18 [M+H]^+$.

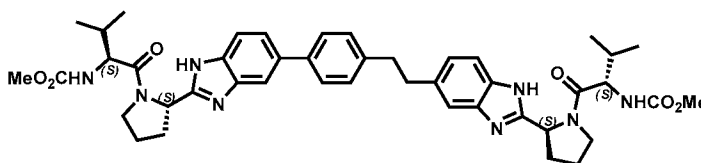
Example 3-336.



5 **Step 336a.** A solution of the compound from Example 335 (0.108 g, 0.161 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step.

Step 336b. A mixture of the crude compound from step 336a (0.161 mmol at most) and
 10 (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (prepared according to WO 2008/021927, 59.0 mg, 0.337 mmol) in DMF (3 mL) was treated with HATU (0.122 g, 0.321 mmol) in the presence of DIPEA (0.40 mL, 3.21 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown syrup. It was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (0.102
 15 g, 2 steps 81%). ESIMS $m/z = 787.26 [M+H]^+$.

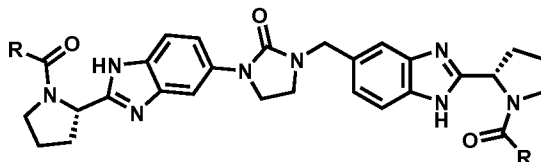
Example 3-337.

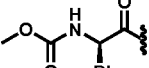
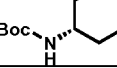
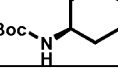
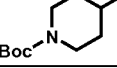
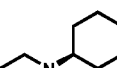
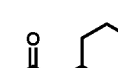
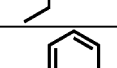
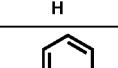
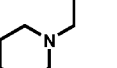
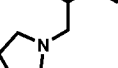
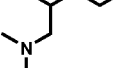


A mixture of the title compound from example 336 (18.1 mg, 23.0 μ mol) and Pd(OH)₂ on carbon (20% wt., 36.0 mg) in ethanol (3 mL) was treated with H₂ balloon overnight. The
 20 mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by flash column chromatography (silica, CH₂Cl₂-MeOH) to give the title compound as a white solid (12.7 mg, 70%). ESIMS $m/z = 791.34 [M+H]^+$.

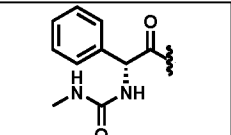
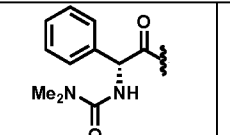
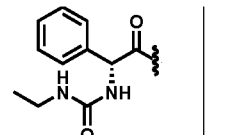
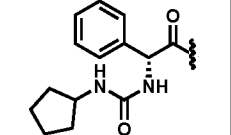
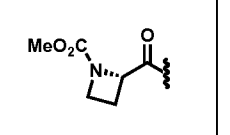
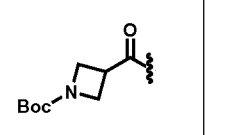
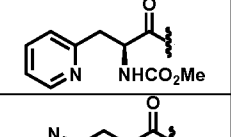
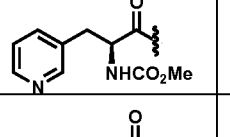
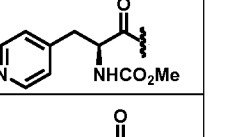
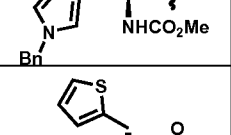
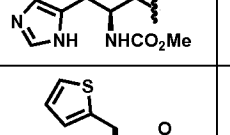
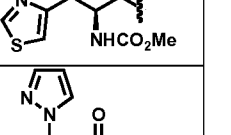
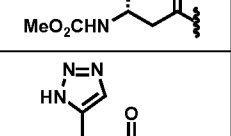
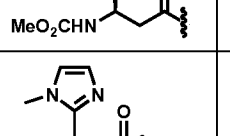
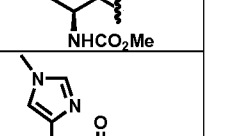
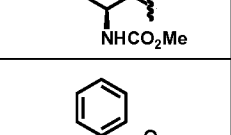
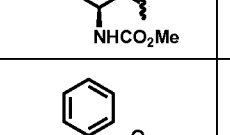
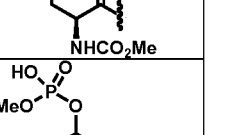
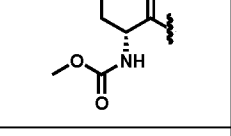
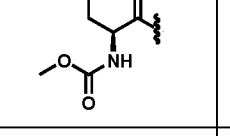
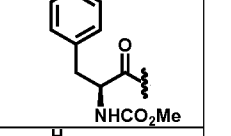
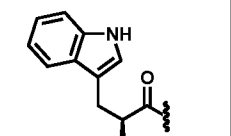
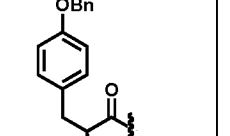
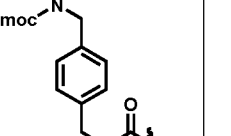
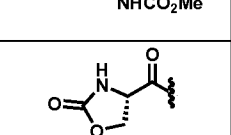
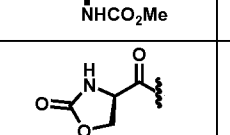
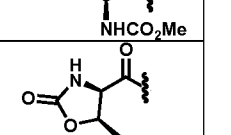
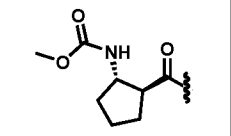
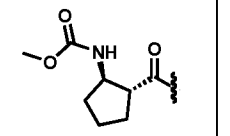
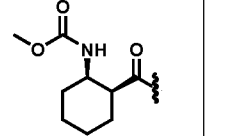
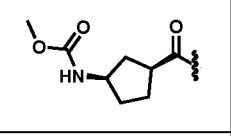
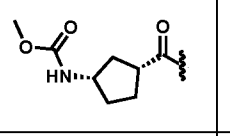
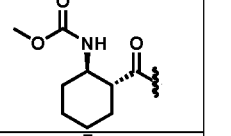
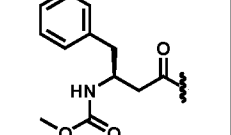
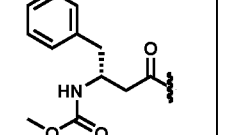
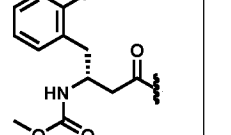
The title compounds of examples 1-334 may be prepared using procedures similar to those described in examples 335-337, and/or as described in the Synthetic Method.

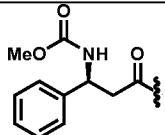
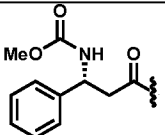
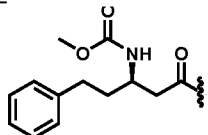
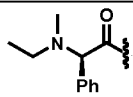
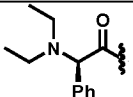
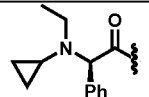
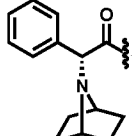
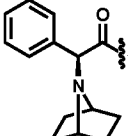
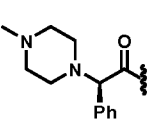
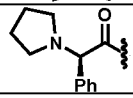
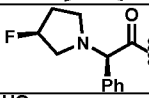
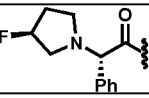
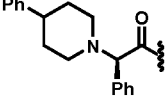
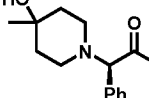
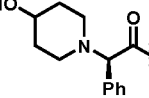
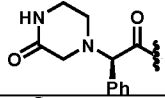
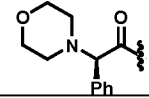
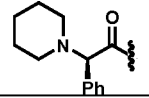
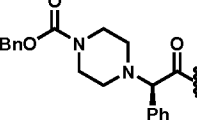
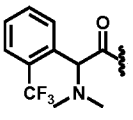
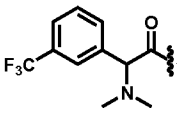
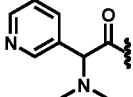
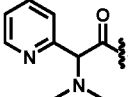
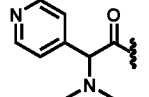
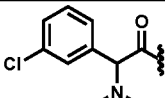
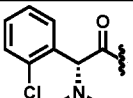
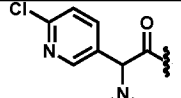
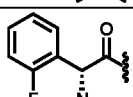
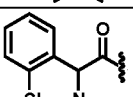
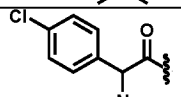
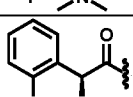
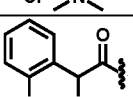
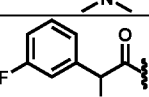
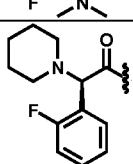
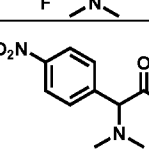
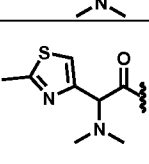
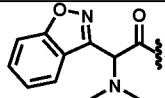
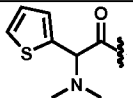
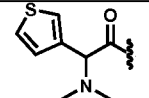
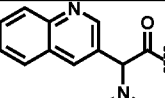
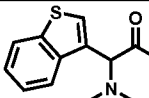
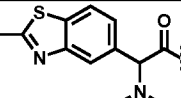
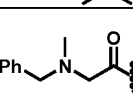
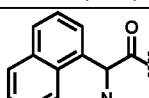
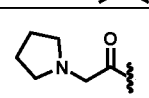
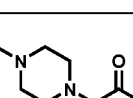
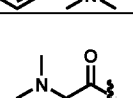
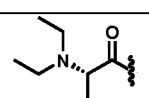
25 Table 16: Examples 3-1 to 3-219



Example 3-		Example 3-		Example 3-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	

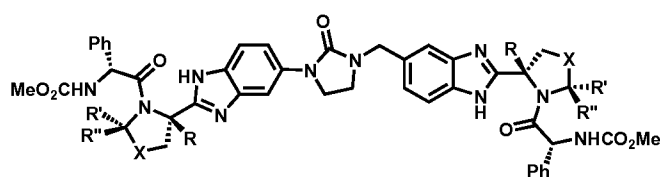
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	

100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	

136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	

184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

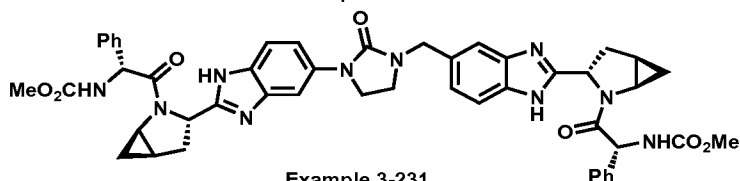
Table 17: Examples 3-220 to 3-229



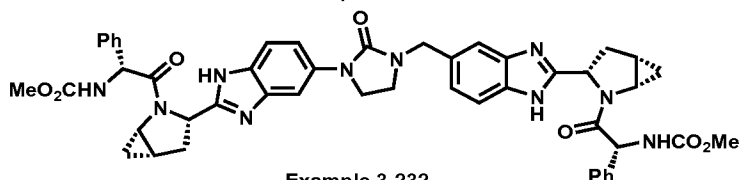
Example 3-	R	R'	R''	X	Example 3-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	

224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

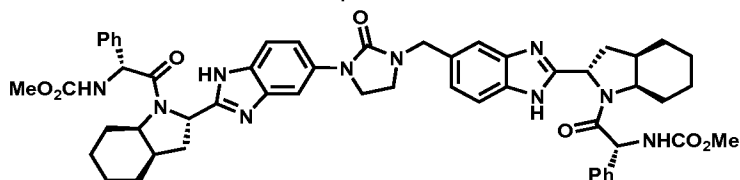
Example 3-230



Example 3-231



Example 3-232



Example 3-233

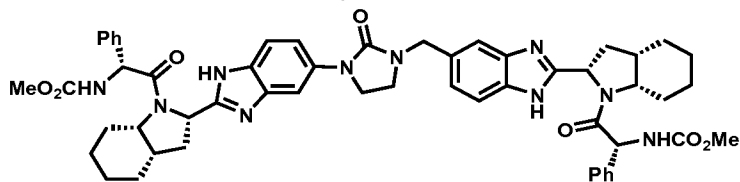
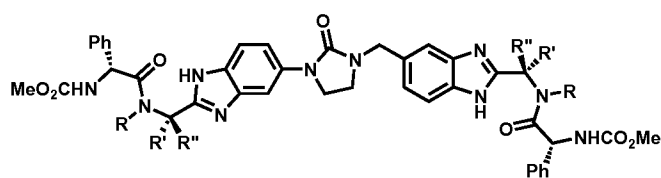
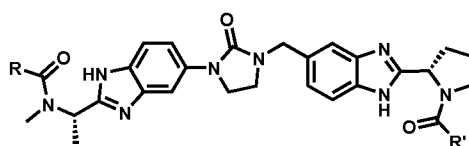


Table 18: Examples 3-234 to 3-243



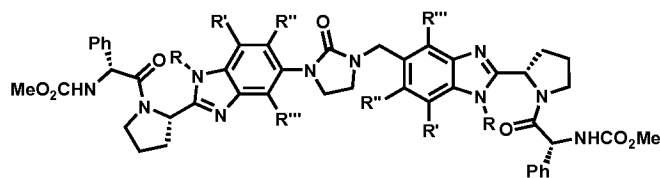
Example 3-	R	R'	R''	Example 3-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

Table 19: Examples 3-244 to 3-263



Example 3-	R	R'	Example 3-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

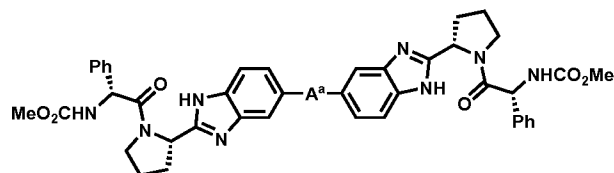
Table 20: Examples 3-264 to 3-289



Example 3-	R	R'	R''	R'''	Example 3-	R	R'	R''	R'''
264	Me	H	H	H	265	H	CO ₂ H	H	H
266	H	F	H	H	267	H	H	CO ₂ H	H
268	H	H	F	H	269	H	H	H	CO ₂ H
270	H	H	H	F	271	H	CO ₂ Me	H	H
272	H	Cl	H	H	273	H	H	CO ₂ Me	H
274	H	H	Cl	H	275	H	H	H	CO ₂ Me

276	H	H	H	Cl	277	H	CONH ₂	H	H
278	H	Me	H	H	279	H	H	CONH ₂	H
280	H	H	Me	H	281	H	H	H	CONH ₂
282	H	H	H	Me	283	H	OMe	H	H
284	H	CF ₃	H	H	285	H	H	OMe	H
286	H	H	CF ₃	H	287	H	H	H	OMe
288	H	H	H	CF ₃	289	CO ₂ Me	H	H	H

Table 21: Examples 3-290 to 3-334



Example 3-	A ^a	Example 3-	A ^a	Example 3-	A ^a
290		291		292	
293		294		295	
296		297		298	
299		300		301	
302		303		304	
305		306		307	
308		309		310	
311		312		313	
314		315		316	
317		318		319	
320		321		322	
323		324		325	
326		327		328	
329		330		331	
332		333		334	

BIOLOGICAL ACTIVITY

1. HCV Replicon Cell Lines

HCV replicon cell lines (kindly provided by R. Bartenschlager) isolated from colonies as described by Lohman et. al. (Lohman et al. (1999) Science 285: 110-113, expressly incorporated by reference in its entirety) and used for all experiments. The HCV replicon has the nucleic acid sequence set forth in EMBL Accession No.: AJ242651, the coding sequence of which is from nucleotides 1801 to 8406.

The coding sequence of the published HCV replicon was synthesized and subsequently assembled in a modified plasmid pBR322 (Promega, Madison, WI) using standard molecular biology techniques. One replicon cell line ("SGR 11-7") stably expresses HCV replicon RNA which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the neomycin phosphotransferase gene (neo), (iii) the IRES from encephalomyocarditis virus (EMCV), and (iv) HCV NS2 to NS5B genes and the HCV 3'UTR. Another replicon cell line ("Huh-luc/neo-ET") described by Vrolijk et. al. (Vrolijk et. al. (2003) Journal of Virological Methods 110:201-209, expressly incorporated by reference in its entirety) stably expresses HCV replicon RNA which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the firefly luciferase reporter gene, (iii) the ubiquitin gene, (iv) the neomycin phosphotransferase gene (neo), (v) the IRES from encephalomyocarditis virus (EMCV), and (vi) HCV NS3 to NS5B genes that harbor cell culture adaptive mutations (E1202G, T1280I, K1846T) and the HCV 3'UTR.

These cell lines were maintained at 37°C, 5% CO₂, 100% relative humidity in DMEM (Cat# 11965-084, Invitrogen), with 10% fetal calf serum ("FCS", Invitrogen), 1% non-essential amino acids (Invitrogen), 1% of Glutamax (Invitrogen), 1% of 100X penicillin/streptomycin (Cat# 15140-122, Invitrogen) and Geneticin (Cat# 10131-027, Invitrogen) at 0.75 mg/ml or 0.5 mg/ml for 11-7 and Huh-luc/neo-ET cells, respectively.

2. HCV Replicon Assay - qRT-PCR

EC₅₀ values of single agent compounds and combinations were determined by HCV RNA detection using quantitative RT-PCR, according to the manufacturer's instructions, with a TaqMan® One-Step RT-PCR Master Mix Reagents Kit (Cat# AB 4309169, Applied Biosystems) on an ABI Model 7500 thermocycler. The TaqMan primers used for detecting and quantifying were obtained from Integrated DNA

Technologies. HCV RNA was normalized to GAPDH RNA levels in drug-treated cells, which was detected and quantified using the Human GAPDH Endogenous Control Mix (Applied Biosystems, AB 4310884E). Total cellular RNA was purified from 96-well plates using the RNeasy 96 kit (Ambion, Cat# AM1812). Chemical agent

cytotoxicity was evaluated using an MTS assay according to the manufacturer's directions (Promega).

3. HCV Replicon Assay - Luciferase

Since clinical drug resistance often develops in viral infections following single agent therapies, there is a need to assess the additive, antagonistic, or synergistic

properties of combination therapies. We used the HCV replicon system to assess the potential use of the compound of the present invention or in combination therapies with Interferon alpha, cyclosporine analogs and inhibitors targeting other HCV proteins. The acute effects of a single or combinations of drugs are studied in the "Huh-luc/neo-ET" replicon with each chemical agent titrated in an X or Y direction in a 6 point two-fold dilution curve centered around the EC50 of each drug. Briefly, replicon cells are seeded at 7,000 cells per well in 90 ul DMEM (without phenol red, Invitrogen Cat.# 31053-036) per well with 10% FCS, 1% non-essential amino acids, 1% of Glutamax and 1% of 100X penicillin/streptomycin and incubated overnight at 37°C, 5% CO₂, 100% relative humidity. 16-20h after seeding cells, test compounds previously solubilized and titrated in dimethyl sulfoxide ("DMSO") from each X plate and Y plate are diluted 1:100 in DMEM (without phenol red, Invitrogen Cat.# 31053-036) with 10% FCS, 1% non-essential amino acids, 1% of Glutamax and 1% of 100X penicillin/streptomycin and added directly to the 96-well plate containing cells and growth medium at a 1:10 dilution for a final dilution of compound and DMSO of 1:1000 (0.2% DMSO final concentration). Drug treated cells are incubated at 37°C, 5% CO₂, 100% relative humidity for 72 hours before performing a luciferase assay using 100 ul per well BriteLite Plus (Perkin Elmer) according to the manufacturer's instructions. Data analysis utilizes the method published by Prichard and Shipman (Antiviral Research, 1990. 14:181-205). Using this method, the combination data are analyzed for antagonistic, additive, or synergistic combination effects across the entire combination surface created by the diluted compounds in combination.

The compounds of the present invention may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present invention inhibit HCV replicon and in another embodiment the compounds of the present invention inhibit NS5A.

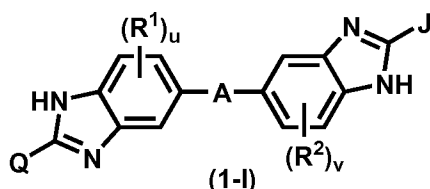
- The compounds of the present invention can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present invention can inhibit multiple genotypes of HCV. In one embodiment, compound of the present invention are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. Table 25 shows the EC₅₀ values of representative compounds of the present invention against the HCV 1b genotype from the above described qRT-PCR or luciferase assay. EC₅₀ ranges against HCV 1b are as follows: A >10 nM; B 1-10 nM; C < 1nM.

Table 25: Genotype-1b replicon EC₅₀

Principal Invention	Example	Range	Principal Invention	Example	Range	Principal Invention	Example	Range
First	1-2	C	First	1-3	C	First	1-20	C
First	1-25	A	First	1-26	A	First	1-42	A
First	1-52	A	First	1-54	A	First	1-62	C
First	1-67	C	First	1-70	C	First	1-72	C
First	1-78	C	First	1-83	C	First	1-114	C
First	1-354	C	First	1-357	A	First	1-361	A
First	1-362	C	First	1-364	C	First	1-366	C
First	1-367	C	First	1-368	A	First	1-369	C
First	1-370	C	First	1-371	C	First	1-372	C
Second	2-3a	C	Second	2-310	C	Second	2-354	C
Second	2-355	C	Second	2-357	A	Third	3-336	C
Third	3-337	C						

WHAT IS CLAIMED IS:

1. A compound represented by Formula (1-I):



- 5 or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from the group consisting of: aryl, heteroaryl, heterocyclic, C₃-C₈ cycloalkyl, and C₃-C₈ cycloalkenyl, all optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, -R¹⁰, -OR¹¹, N(R¹¹)₂, -C(O)R¹¹, -CO₂R¹¹, -C(O)N(R¹¹)₂, and -N(R¹¹)C(O)R¹¹;

- 10 R¹⁰ at each occurrence is independently C₁-C₄ alkyl optionally with one or more halogen atoms;

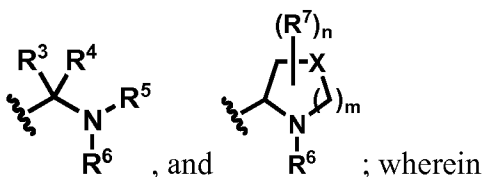
R¹¹ at each occurrence is independently hydrogen or optionally substituted C₁-C₈ alkyl;

- 15 R¹ and R² at each occurrence are each independently selected from the group consisting of: halogen, cyano, optionally substituted C₁-C₄ alkyl, -O-R¹¹, -NR^aR^b, -C(O)R¹¹, -CO₂R¹¹, and -C(O)NR^aR^b;

- 20 R^a and R^b at each occurrence are each independently hydrogen, optionally substituted C₁-C₈ alkyl, or optionally substituted C₂-C₈ alkenyl; or R^a and R^b taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

u and v at each occurrence are each independently 0, 1, 2, or 3;

Q and J at each occurrence are each independently selected from:



- 25 R³ and R⁴ at each occurrence are each independently hydrogen, optionally substituted C₁-C₈ alkyl, optionally substituted C₂-C₈ alkenyl or optionally substituted C₃-C₈ cycloalkyl; or alternatively, R³ and R⁴ taken together with the carbon atom to which they are attached form optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic;

R^5 at each occurrence is independently hydrogen, optionally substituted C_1 - C_8 alkyl, or optionally substituted C_3 - C_8 cycloalkyl;

R^6 at each occurrence is independently selected from the group consisting of: hydrogen, $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$;

5 R^{12} at each occurrence is independently selected from the group consisting of: $-O-R^{11}$, $-NR^aR^b$, $-R^{13}$, $-NR^cR^d$, $-CH(R^{13})NR^aR^b$ and $-CH(R^{13})NR^cR^d$;

R^{13} at each occurrence is independently selected from the group consisting of: optionally substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl, optionally substituted C_2 - C_8 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted C_3 - C_8 cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;

R^c and R^d at each occurrence are each independently selected from the group consisting of: hydrogen, $-R^{13}$, $-C(O)-R^{13}$, $-C(O)-OR^{13}$, $-S(O)_2-R^{13}$, $-C(O)N(R^{13})_2$, and $-S(O)_2N(R^{13})_2$;

m is 0, 1, or 2;

n is 0, 1, 2, 3, or 4;

X at each occurrence is independently selected from O, S, S(O), SO_2 , CH_2 , CHR^7 , and $C(R^7)_2$; provided that when m is 0, X is selected from CH_2 , CHR^7 , and $C(R^7)_2$; and

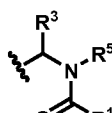
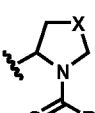
20 R^7 at each occurrence is independently selected from the group consisting of: halogen, cyano, $-O-R^{11}$, $-NR^aR^b$, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted $-C_1$ - C_4 alkyl; optionally, two vicinal R^7 groups taken together with the two adjacent atoms to which they are attached form a fused, optionally substituted $-C_3$ - C_8 cycloalkyl or optionally substituted heterocyclic ring; or alternatively
25 and optionally, two geminal R^7 groups taken together with the carbon atom to which they are attached form a spiro, optionally substituted C_3 - C_8 cycloalkyl or optionally substituted heterocyclic ring.

2. A compound of claim 1, wherein A is independently an aryl, optionally substituted
30 with one or more substituents independently selected from halogen and R^{10} ; or a pharmaceutically acceptable salt.

3. A compound of claim 1, wherein A is independently a heteroaryl, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 5 4. A compound of claim 1, wherein A is independently a heterocyclic, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 10 5. A compound of claim 1, wherein A is independently a C₃-C₈ cycloalkyl, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 15 6. A compound of claim 1, wherein A is independently a C₃-C₈ cycloalkenyl, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 20 7. A compound of claim 1, wherein A is independently a phenyl, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 25 8. A compound of claim 1, wherein A is independently a 5-7-membered heteroaryl, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
- 30 9. A compound of claim 1, wherein A is independently a 5-7-membered heterocyclic, optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
10. A compound of claim 1, wherein A is independently a C₅-C₇ cycloalkyl or C₅-C₇ cycloalkenyl, both optionally substituted with one or more substituents independently selected from halogen and R¹⁰; or a pharmaceutically acceptable salt thereof.
11. A compound of claim 1, wherein u and v at each occurrence are each independently 0 or 1; and when present, R¹ and R² at each occurrence are each

independently halogen or optionally substituted C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

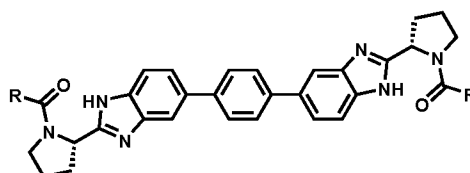
12. A compound of claim 1, wherein Q and J at each occurrence are each

- 5 independently selected from:  and ; wherein X at each occurrence is independently CH₂, CF₂, CHF, or CH(OH); or a pharmaceutically acceptable salt thereof.

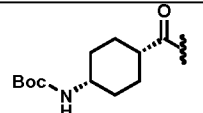
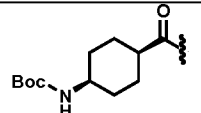
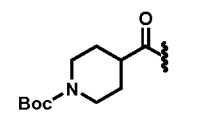
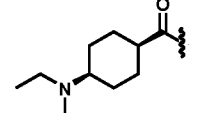
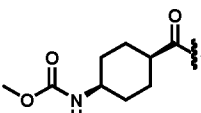
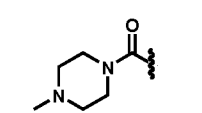
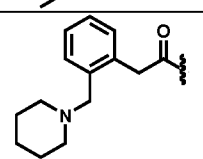
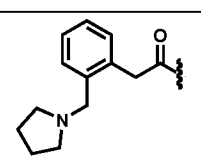
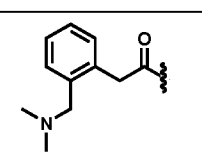
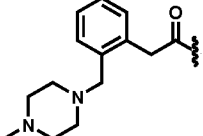
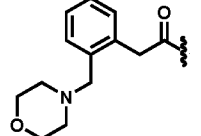
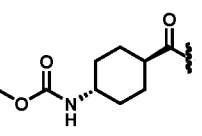
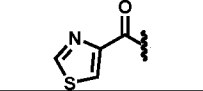
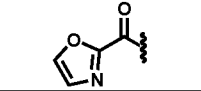
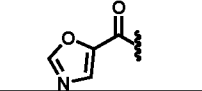
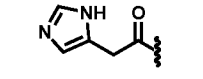
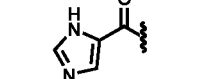
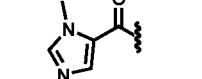
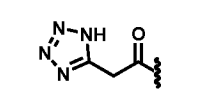
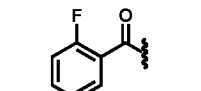
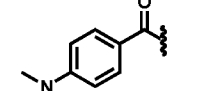
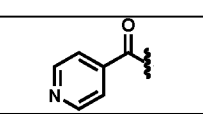
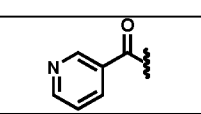
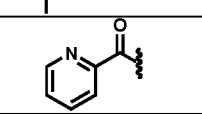
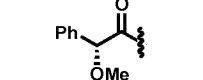
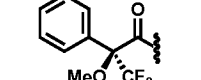
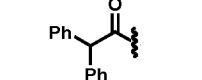
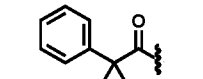
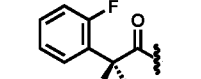
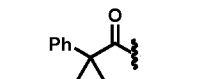
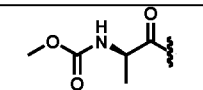
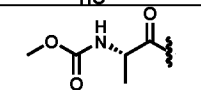
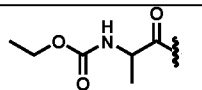
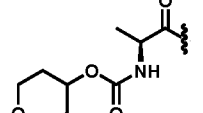
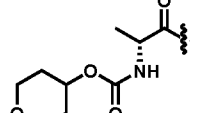
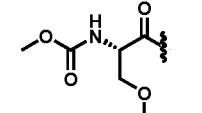
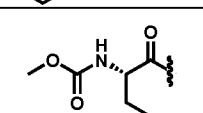
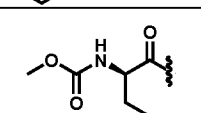
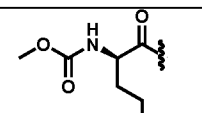
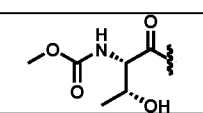
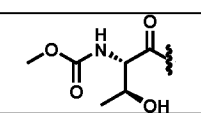
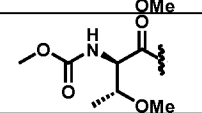
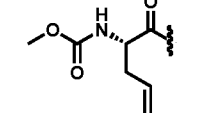
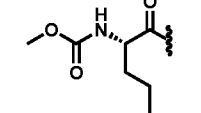
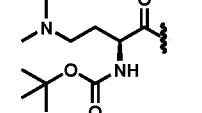
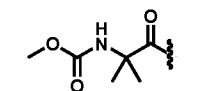
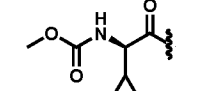
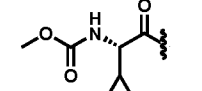
13. A compound according to claim 1 selected from the group of compounds 1-1 to 1-360 compiled in the following tables:

10

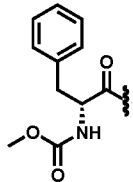
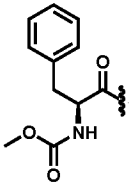
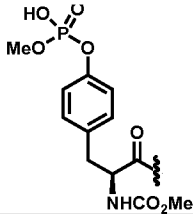
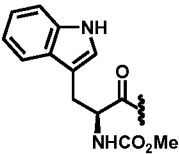
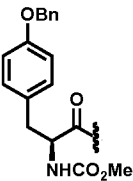
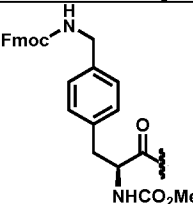
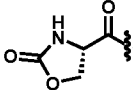
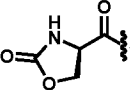
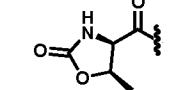
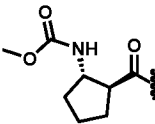
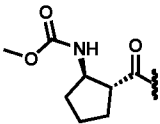
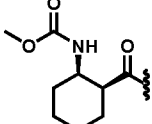
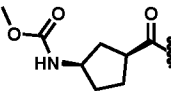
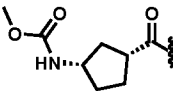
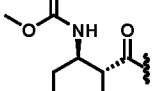
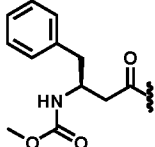
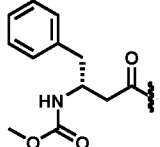
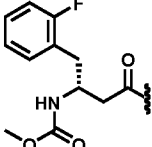
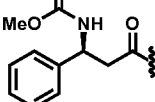
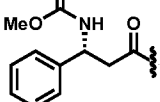
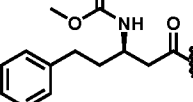
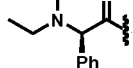
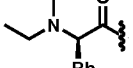
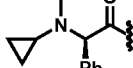
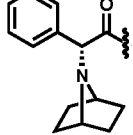
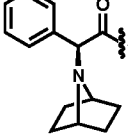
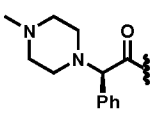
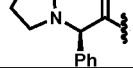
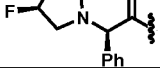
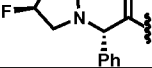
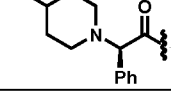
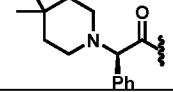
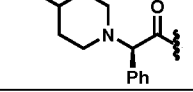
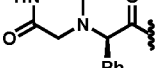
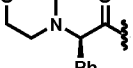
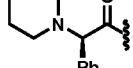
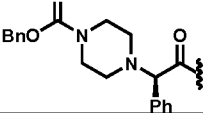
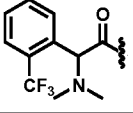
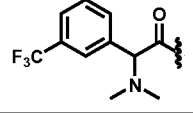
Compounds 1-1 to 1-219



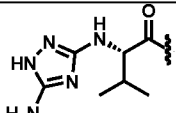
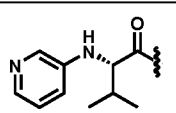
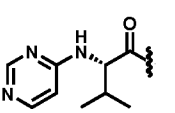
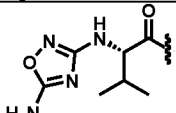
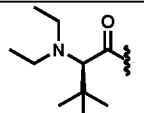
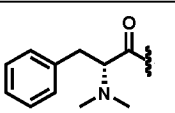
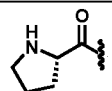
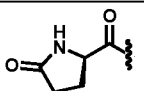
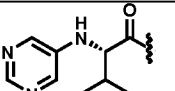
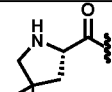
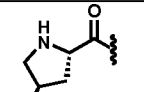
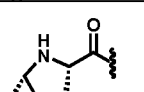
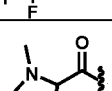
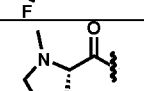
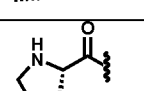
Entry 1-		Entry 1-		Entry 1-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	

31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	

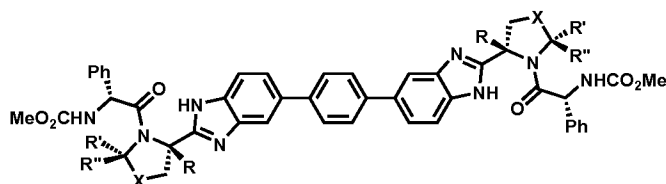
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	

118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	

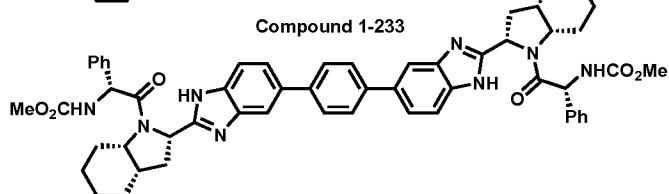
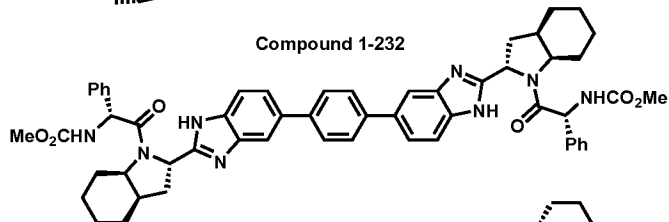
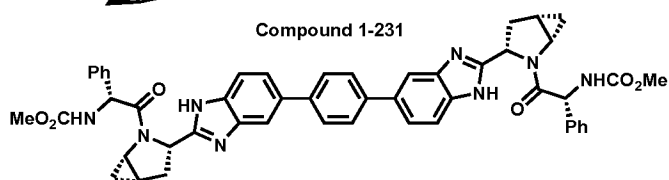
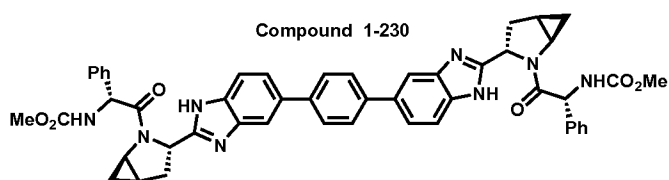
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	

205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

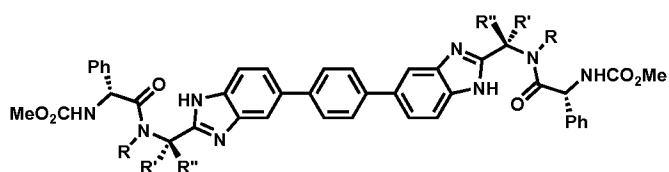
Compounds 1-220 to 1-229



Entry 1-	R	R'	R''	X	Entry 1-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	



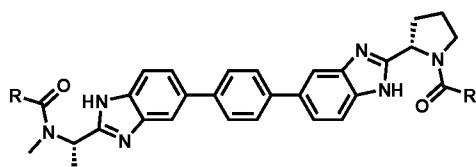
Compounds 1-234 to 1-243



Entry 1-	R	R'	R''	Entry 1-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

5

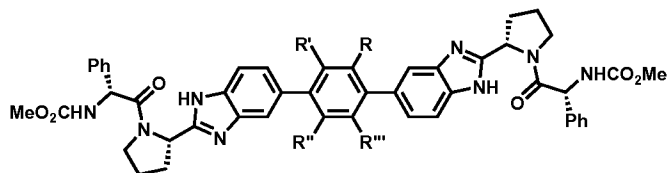
Compounds 1-244 to 1-263



Entry 1-	R	R'	Entry 1-	R	R'
244			245		

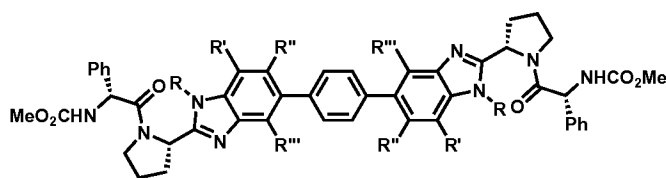
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Compounds 1-264 to 1-283



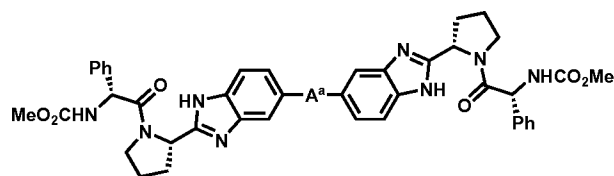
Entry 1-	R	R'	R''	R'''	Entry 1-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H
280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

Compounds 1-284 to 1-309



Entry 1-	R	R'	R''	R'''	Entry 1-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

Compounds 1-310 to 1-360

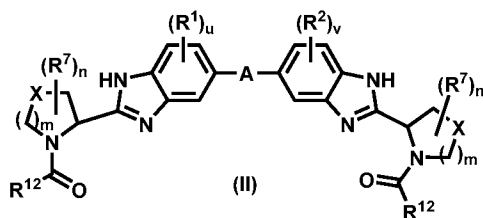


5

Entry 1-	A ^a	Entry 1-	A ^a	Entry 1-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	

337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	
358		359		360	

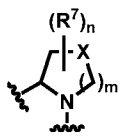
14. A compound of claim 1, represented by Formula (1-II), or a pharmaceutically acceptable salt thereof:



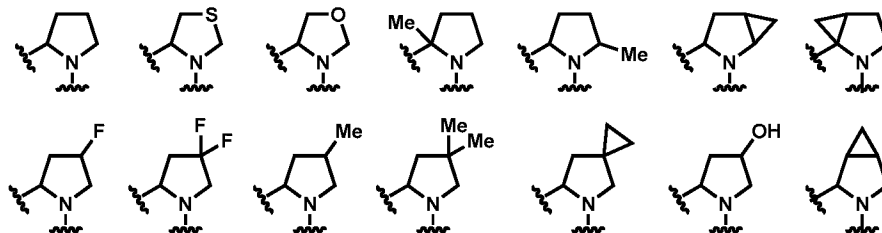
5

15. A compound of claim 14, wherein A is independently a phenyl, 6-membered heteroaryl, bicyclic aryl, or bicyclic heteroaryl; u is 0; v is 0; m is 1; n is 0, 1 or 2; X at each occurrence is independently CH₂, CF₂, CHF, or C(R⁷)₂; R¹² at each occurrence is independently C₁-C₈ alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C₁-C₄ alkyl); R⁷ at each occurrence is independently methyl, fluoro or hydroxy; or two vicinal R⁷ groups taken together with the two adjacent atoms to which they are attached form a fused, optionally substituted cyclopropyl; or alternatively two geminal R⁷ groups taken together with the carbon atom to which they are attached form a spiro, optionally substituted cyclopropyl; or a pharmaceutically acceptable salt thereof.

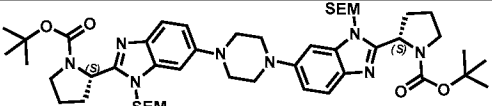
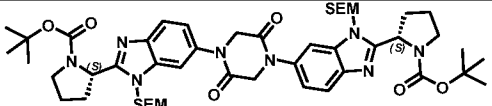
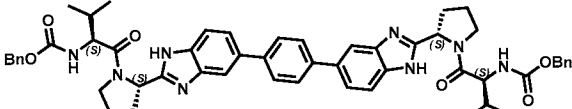
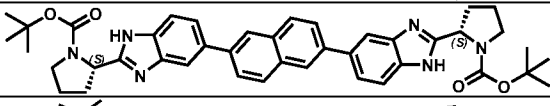
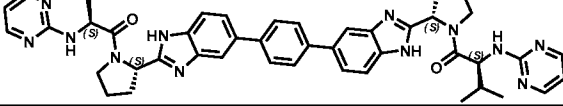
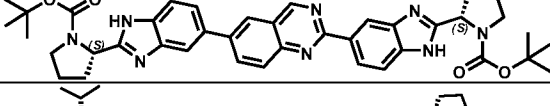
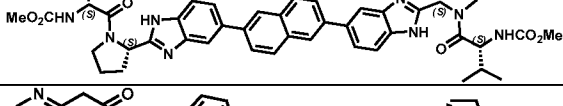
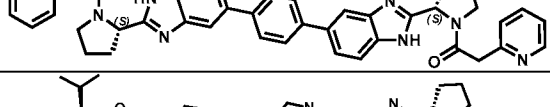
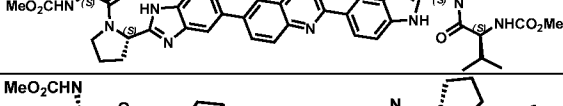
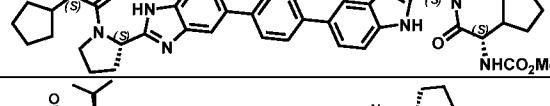
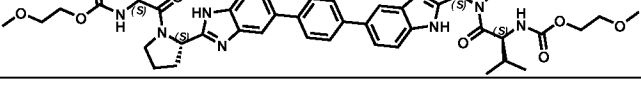
15



16. The compound of claim 1, wherein  is selected from the group listed below, or a pharmaceutically acceptable salt thereof:

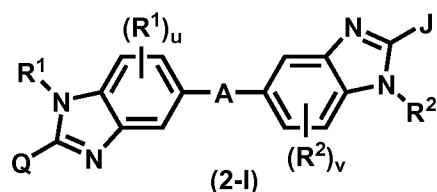


17. A compound according to claim 1 selected from the following table:

1-354a	
1-357a	
1-361	
1-362	
1-363	
1-364	
1-365	
1-366	
1-367	
1-368	
1-369	

1-370	
1-371	
1-372	

18. A compound represented by Formula (2-I):



or a pharmaceutically acceptable salt thereof, wherein:

5 A is an optionally substituted linear aliphatic group;

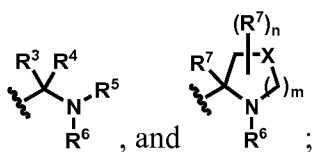
R^1 and R^2 at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C_1 - C_4 alkyl, $-O-R^{11}$, $-NR^aR^b$, $-C(O)R^{11}$, $-CO_2R^{11}$, and $-C(O)NR^aR^b$;

10 R^{11} at each occurrence is independently hydrogen or optionally substituted C_1 - C_8 alkyl;

R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, and optionally substituted C_2 - C_8 alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

u and v are each independently 1, 2, or 3;

Q and J are each independently selected from:



20 R^3 and R^4 at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_2 - C_8 alkenyl, and optionally substituted C_3 - C_8 cycloalkyl; or alternatively, R^3 and R^4 can be

taken together with the carbon atom to which they are attached to form optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic;

R⁵ at each occurrence is independently hydrogen, optionally substituted C₁-C₈ alkyl, or optionally substituted C₃-C₈ cycloalkyl;

- 5 R⁶ is selected from the group consisting of -C(O)-R¹², -C(O)-C(O)-R¹², -S(O)₂-R¹², and -C(S)-R¹²;

R¹² at each occurrence is independently selected from the group consisting of -O-R¹¹, -NR^aR^b, -R¹³, and -NR^cR^d; wherein

- 10 R¹³ at each occurrence is independently selected from the group consisting of: hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, -R¹³, -C(O)-R¹³, -C(O)-OR¹³, -S(O)₂-R¹³, -C(O)N(R¹³)₂, and -S(O)₂N(R¹³)₂;

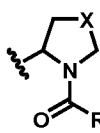
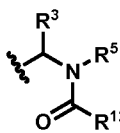
- 15 m is 0, 1, or 2;

n is 1, 2, 3, or 4;

X at each occurrence is independently selected from O, S, S(O), SO₂, and C(R⁷)₂; provided that when m is 0, X is C(R⁷)₂; and

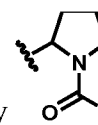
- 20 R⁷ at each occurrence is independently selected from the group consisting of: hydrogen, halogen, cyano, -O-R¹¹, -NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted -C₁-C₄ alkyl; or two vicinal R⁷ groups can be taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; or alternatively two geminal R⁷ groups can be taken together with the carbon atom to
 25 which they are attached to form a spiro, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring.

19. The compound of claim 18, wherein Q and J are each independently selected from:



wherein X is independently CH₂, CF₂, CHF, or CH(OH); or a

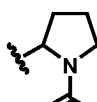
- 30 pharmaceutically acceptable salt thereof.



20. The compound of claim 18, wherein Q and J are each independently ; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 18, wherein u and v at each occurrence are each 1; and R¹ and R² at each occurrence are each independently selected from the group consisting of hydrogen, halogen or optionally substituted C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

22. The compound of claim 18, wherein Q and J at each occurrence are each



10 independently ; and R¹ and R² are each hydrogen; or a pharmaceutically acceptable salt thereof.

23. The compound of claim 18, wherein A is selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, and C₂-C₈ alkynyl, each optionally substituted; or a pharmaceutically acceptable salt.

15

24. The compound of claim 18, wherein A is a linear aliphatic group containing a group selected from C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or C(O)N(R¹¹)S(O)₂N(R¹¹); or a pharmaceutically acceptable salt thereof.

20

25. The compound of claim 19, wherein A is a linear aliphatic group containing an olefinic double bond and a group selected from C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or C(O)N(R¹¹)S(O)₂N(R¹¹); or a pharmaceutically acceptable salt thereof.

25

26. The compound of claim 19, wherein A is a linear aliphatic group containing an alkynic triple bond and a group selected from C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹), N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹),

30

$N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; or a pharmaceutically acceptable salt thereof.

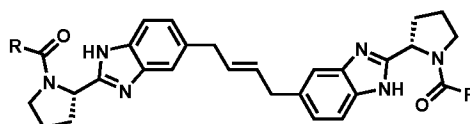
27. The compound of claim 18, wherein A is a linear aliphatic group containing one or two groups independently selected from O and $N(R^{11})$; or a pharmaceutically acceptable salt thereof.

28. A compound of claim 18, wherein A is a group independently selected from $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; or a pharmaceutically acceptable salt thereof.

29. A compound of claim 18, wherein A is a linear aliphatic group containing one to four carbons and two groups independently selected from the group consisting of O, $N(R^{11})$, $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$; or a pharmaceutically acceptable salt thereof.

30. The compound according to claim 18 selected from the group of compounds 2-1 to 2-393 compiled in the following tables:

Compounds 2-1 to 2-219



Entry 2-		Entry 2-		Entry 2-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	

16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	

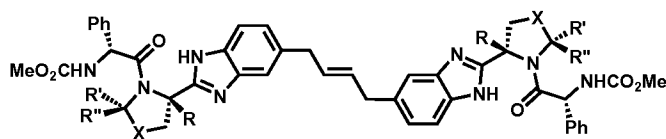
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	

112		113		114	
115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	

151		152		153	
154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	

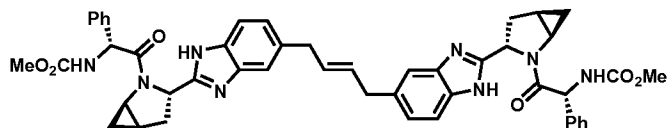
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Compounds 2-220 to 2-229

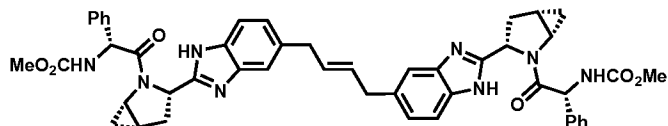


Entry 2-	R	R'	R''	X	Entry 2-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

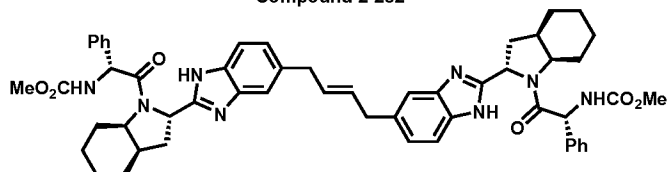
Compound 2-230



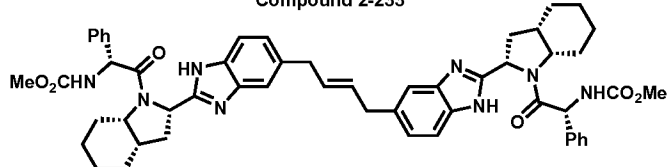
Compound 2-231



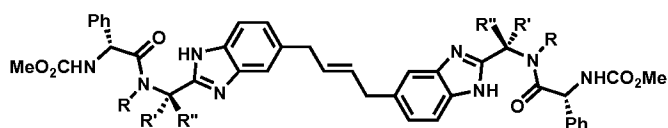
Compound 2-232



Compound 2-233



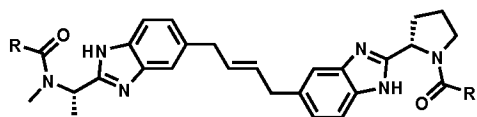
Compounds 2-234 to 2-243



Entry 2-	R	R'	R''	Entry 2-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

5

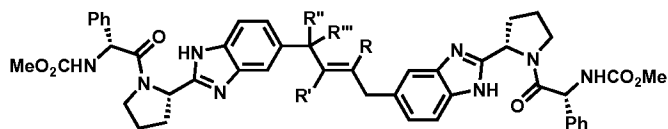
Compounds 2-244 to 2-263



Entry 2-	R	R'	Entry 2-	R	R'
244			245		
246			247		

248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

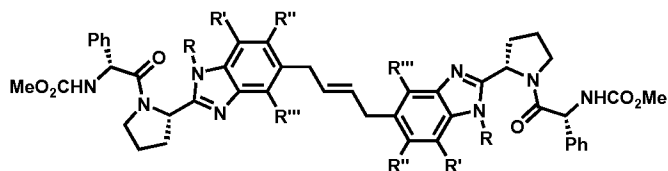
Compounds 2-264 to 2-283



Entry 2-	R	R'	R''	R'''	Entry 2-	R	R'	R''	R'''
264	F	H	H	H	265	F	H	F	H
266	F	F	H	H	267	Me	H	H	H
268	Me	Me	H	H	269	Me	H	Me	H
270	CF ₃	H	H	H	271	CF ₃	H	CF ₃	H
272	CF ₃	CF ₃	H	H	273	CO ₂ Me	H	H	H
274	CONH ₂	H	H	H	275	CO ₂ H	H	H	H
276	CH ₂ OH	H	H	H	277	CH ₂ NMe ₂	H	H	H
278	NMe ₂	H	H	H	279	OMe	H	H	H
280	OCF ₃	H	H	H	281	NHCO ₂ Me	H	H	H
282	Cl	H	H	H	283	Cl	H	Cl	H

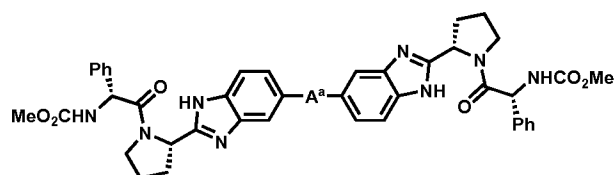
5

Compounds 2-284 to 2-309



Entry 2-	R	R'	R''	R'''	Entry 2-	R	R'	R''	R'''
284	Me	H	H	H	285	H	CO ₂ H	H	H
286	H	F	H	H	287	H	H	CO ₂ H	H
288	H	H	F	H	289	H	H	H	CO ₂ H
290	H	H	H	F	291	H	CO ₂ Me	H	H
292	H	Cl	H	H	293	H	H	CO ₂ Me	H
294	H	H	Cl	H	295	H	H	H	CO ₂ Me
296	H	H	H	Cl	297	H	CONH ₂	H	H
298	H	Me	H	H	299	H	H	CONH ₂	H
300	H	H	Me	H	301	H	H	H	CONH ₂
302	H	H	H	Me	303	H	OMe	H	H
304	H	CF ₃	H	H	305	H	H	OMe	H
306	H	H	CF ₃	H	307	H	H	H	OMe
308	H	H	H	CF ₃	309	CO ₂ Me	H	H	H

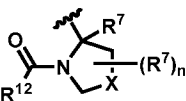
Compounds 2-310 to 2-352



Entry 2-	A ^a	Entry 2-	A ^a	Entry 2-	A ^a
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	
337		338		339	
340		341		342	

343		344		345	
346		347		348	
349		350		351	
352					

31. A compound of claim 18, wherein A is independently optionally substituted C₂-C₈ alkenyl or optionally substituted C₂-C₈ alkynyl; R¹ and R² are each hydrogen; Q and J are



each independently R^{12} $(R^n)_n$; wherein n is 1 or 2; X at each occurrence is

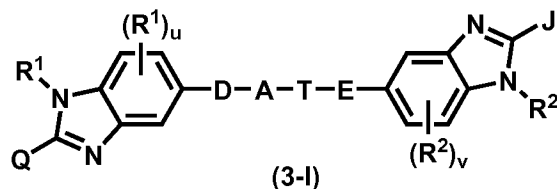
independently CH₂, CF₂, CHF, or C(R⁷)₂; R¹² at each occurrence is independently C₁-C₈ alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C₁-C₄ alkyl); R⁷ at each occurrence is independently hydrogen, methyl, fluoro or hydroxy; or optionally, two vicinal R⁷ groups taken together with the two adjacent atoms to which they are attached form a fused, optionally substituted cyclopropyl; or alternatively, two geminal R⁷ groups taken together with the carbon atom to which they are attached form a spiro, optionally substituted cyclopropyl; or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 18 selected from the group of compounds 2-1a, 2-3a, and 2-353 to 2-357 compiled in the following table:

2-1a	
2-3a	
2-353	
2-354	
2-355	

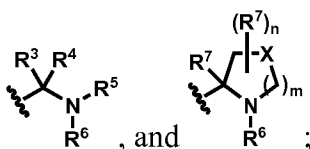
2-356	
2-357	

33. A compound represented by Formula (3-I):



or a pharmaceutically acceptable salt thereof, wherein:

- 5 A is a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C₃-C₈ cycloalkyl, and C₃-C₈ cycloalkenyl, each optionally substituted;
- D is absent or an optionally substituted aliphatic group;
- T is absent or an optionally substituted linear aliphatic group containing zero to eight carbons;
- 10 E is absent or independently selected from optionally substituted aryl and optionally substituted heteroaryl;
- Wherein one or two of D, E, and T are absent;
- R¹ and R² at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C₁-C₄ alkyl, -O-R¹¹, -NR^aR^b, -C(O)R¹¹, -CO₂R¹¹, and -C(O)NR^aR^b;
- 15 R¹¹ at each occurrence is independently hydrogen or optionally substituted C₁-C₈ alkyl;
- R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C₁-C₈ alkyl, and optionally substituted C₂-C₈ alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are
- 20 attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl group;
- u and v are each independently 1, 2, or 3;
- Q and J are each independently selected from:



R³ and R⁴ at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C₁-C₈ alkyl, optionally substituted C₂-C₈ alkenyl, and optionally substituted C₃-C₈ cycloalkyl; or alternatively, R³ and R⁴ can be taken together with the carbon atom to which they are attached to form optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic;

R⁵ at each occurrence is independently hydrogen, optionally substituted C₁-C₈ alkyl, or optionally substituted C₃-C₈ cycloalkyl;

R⁶ is selected from the group consisting of -C(O)-R¹², -C(O)-C(O)-R¹², -S(O)₂-R¹², and -C(S)-R¹²;

R¹² at each occurrence is independently selected from the group consisting of: -O-R¹¹, -NR^aR^b, -R¹³, and -NR^cR^d; wherein

R¹³ at each occurrence is independently selected from the group consisting of: hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, -R¹³, -C(O)-R¹³, -C(O)-OR¹³, -S(O)₂-R¹³, -C(O)N(R¹³)₂, and -S(O)₂N(R¹³)₂;

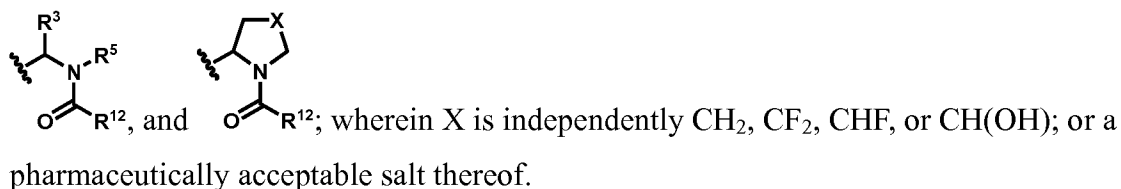
m is 0, 1, or 2;

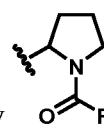
n is 1, 2, 3, or 4;

X at each occurrence is independently selected from O, S, S(O), SO₂, and C(R⁷)₂; provided that when m is 0, X is C(R⁷)₂; and

R⁷ at each occurrence is independently selected from the group consisting of: hydrogen, halogen, cyano, -O-R¹¹, -NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted -C₁-C₄ alkyl; or two vicinal R⁷ groups can be taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring; or alternatively two germinal R⁷ groups can be taken together with the carbon atom to which they are attached to form a spiro, optionally substituted C₃-C₈ cycloalkyl or optionally substituted heterocyclic ring.

34. The compound of claim 33, wherein Q and J are each independently selected from:



5 35. The compound of claim 33, wherein Q and J are each independently ; and R¹ and R² are each hydrogen; or a pharmaceutically acceptable salt thereof.

36. The compound of claim 33, wherein T and E are each absent and D is independently optionally substituted C₁-C₄ alkyl, optionally substituted C₂-C₄ alkenyl or
10 optionally substituted C₂-C₄ alkynyl; or a pharmaceutically acceptable salt thereof.

37. The compound of claim 33, wherein T and E are each absent and D is selected from O, N(R¹¹), C(O), S(O)₂, C(O)O, C(O)N(R¹¹), OC(O)O, OC(O)N(R¹¹), S(O)₂N(R¹¹),
N(R¹¹)C(O)N(R¹¹), N(R¹¹)C(O)C(O)N(R¹¹), N(R¹¹)S(O)₂N(R¹¹), C(O)N(R¹¹)S(O)₂ or
15 C(O)N(R¹¹)S(O)₂N(R¹¹); or a pharmaceutically acceptable salt thereof.

38. The compound of claim 33, wherein T and E are each absent and D is independently optionally substituted C₃-C₈ cycloalkyl or optionally substituted C₃-C₈ cycloalkenyl; or a pharmaceutically acceptable salt thereof.

20

39. The compound of claim 33, wherein T and E are each absent and D is independently optionally substituted heterocyclic; or a pharmaceutically acceptable salt thereof.

25 40. The compound of claim 33, wherein D and T are each absent and E is independently optionally substituted aryl or optionally substituted heteroaryl; or a pharmaceutically acceptable salt thereof.

41. The compound of claim 33, wherein D and T are each absent and E is present; A is independently optionally substituted aryl or optionally substituted heteroaryl; or a pharmaceutically acceptable salt thereof.

5 42. The compound of claim 33, wherein D and T are each absent, E is present; and A is independently optionally substituted C₃-C₈ cycloalkyl or optionally substituted C₃-C₈ cycloalkenyl; or a pharmaceutically acceptable salt thereof.

43. The compound of claim 33, wherein D and T are each absent; E is present and A is
10 independently optionally substituted heterocyclic; or a pharmaceutically acceptable salt thereof.

44. The compound of claim 33, wherein E is absent, D and T are each independently a
15 linear aliphatic group containing zero to six carbons, optionally comprising one or more groups selected from O, N(R¹¹), C(O), S(O)₂, C(O)O, and C(O)N(R¹¹); or a pharmaceutically acceptable salt thereof.

45. The compound of claim 36, wherein A is heterocyclyl; or a pharmaceutically acceptable salt thereof.

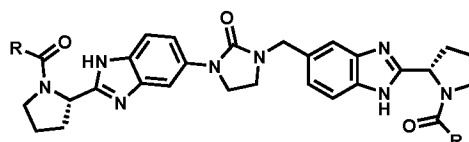
20 46. The compound of claim 36, wherein A is independently optionally substituted aryl or optionally substituted heteroaryl; or a pharmaceutically acceptable salt thereof.

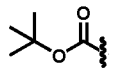
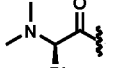
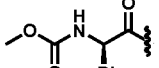
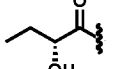
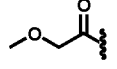
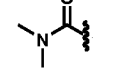
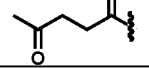
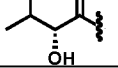
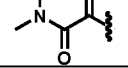
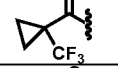
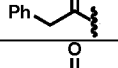
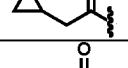
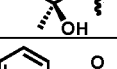
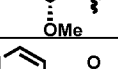
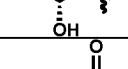
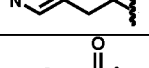
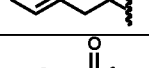
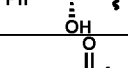
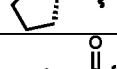
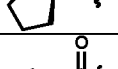
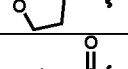
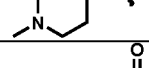
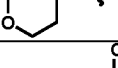
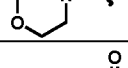
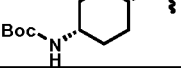
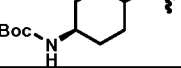
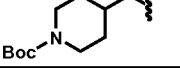
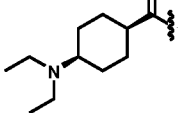
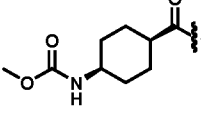
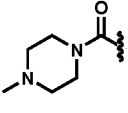
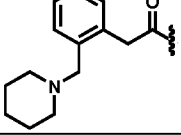
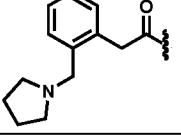
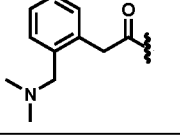
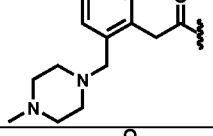
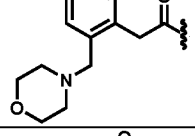
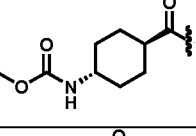
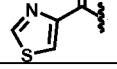
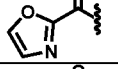
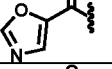
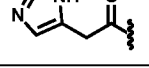
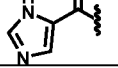
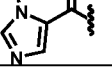
47. The compound of claim 36, wherein A is independently optionally substituted C₃-
25 C₈ cycloalkyl or optionally substituted C₃-C₈ cycloalkenyl; or a pharmaceutically acceptable salt thereof.

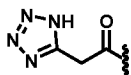
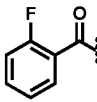
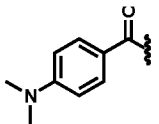
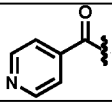
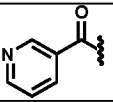
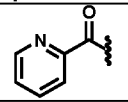
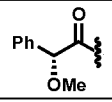
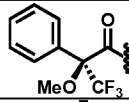
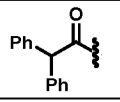
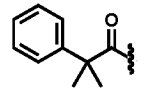
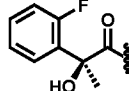
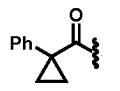
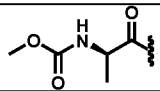
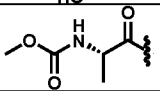
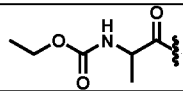
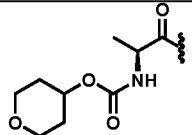
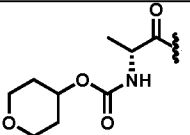
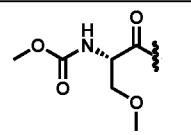
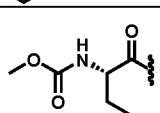
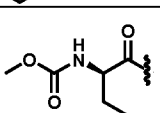
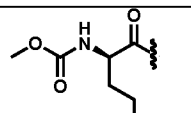
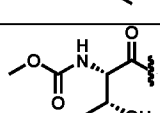
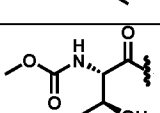
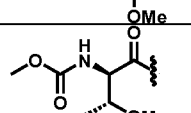
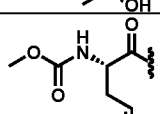
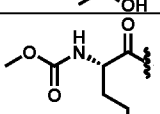
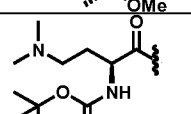
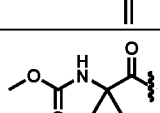
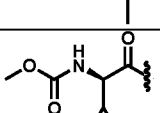
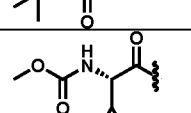
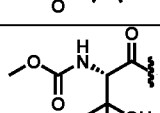
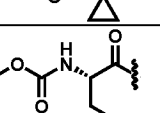
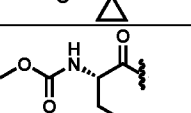
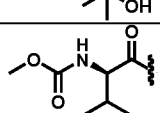
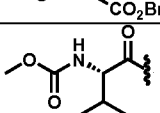
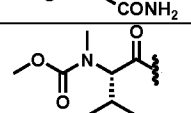
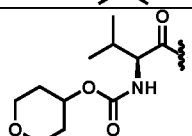
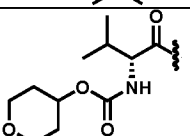
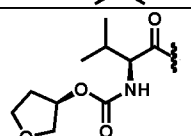
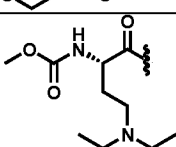
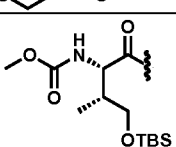
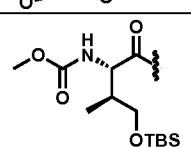
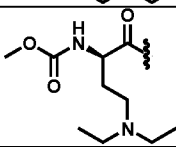
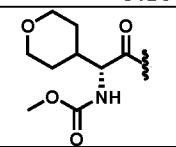
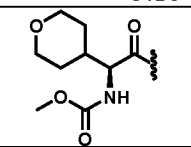
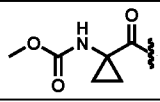
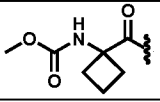
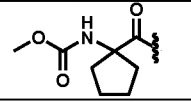
48. The compound according to claim 33 selected from the group of compounds 3-1 to 3-334 compiled in the following tables:

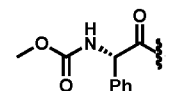
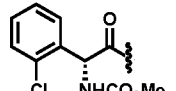
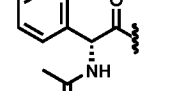
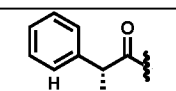
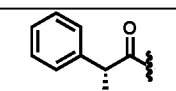
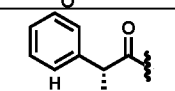
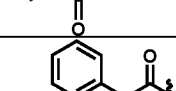
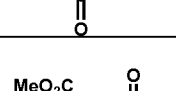
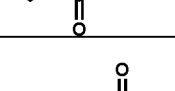
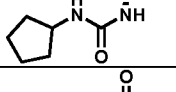
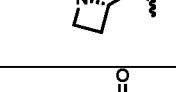
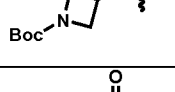
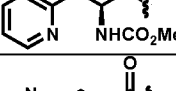
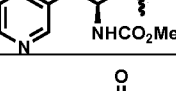
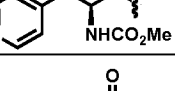
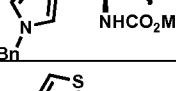
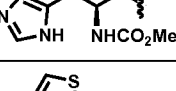
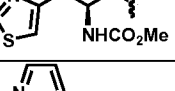
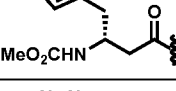
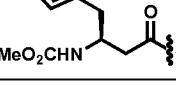
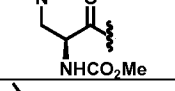
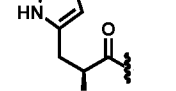
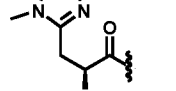
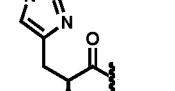
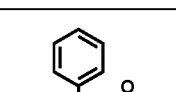
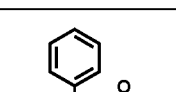
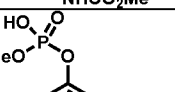
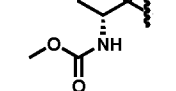
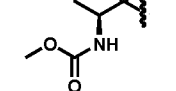
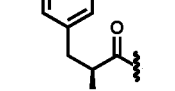
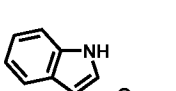
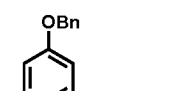
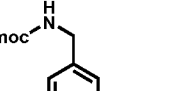
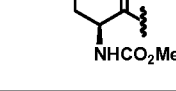
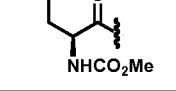
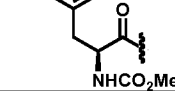
30

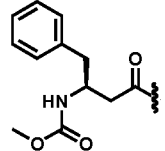
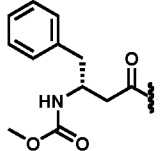
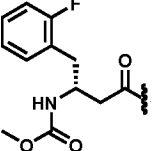
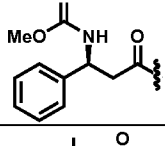
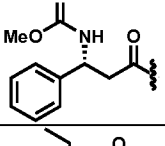
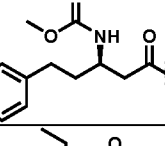
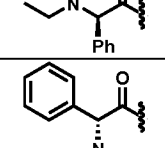
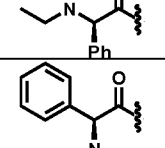
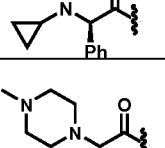
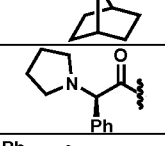
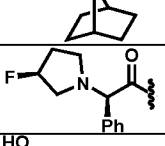
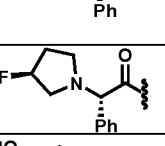
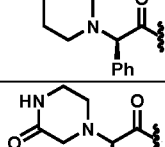
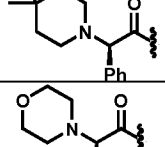
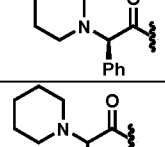
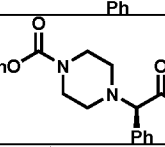
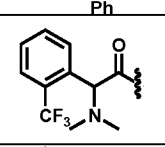
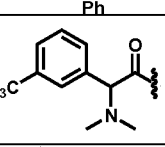
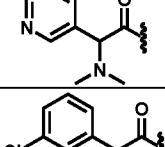
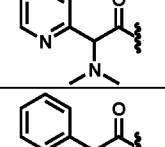
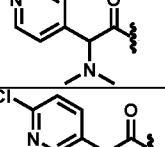
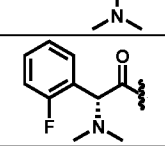
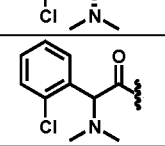
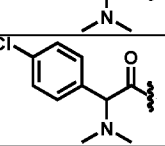
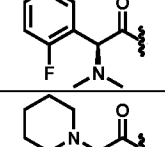
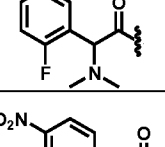
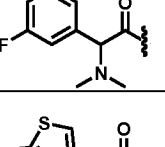
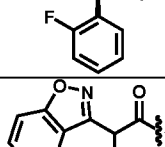
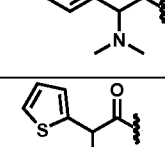
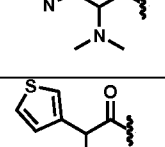
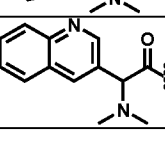
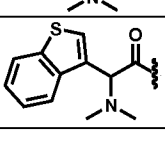
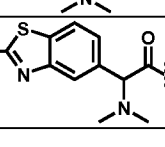
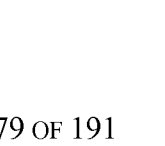
Compounds 3-1 to 3-219

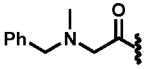
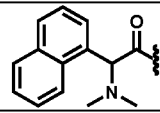
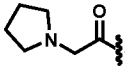
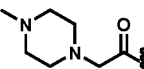
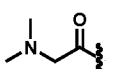
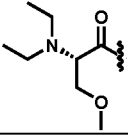
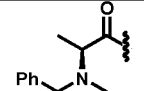
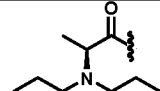
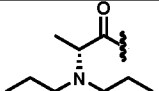
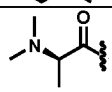
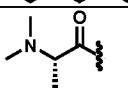
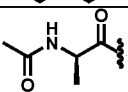
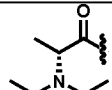
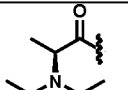
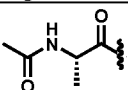
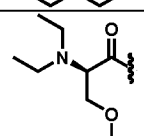
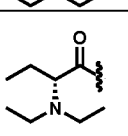
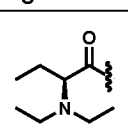
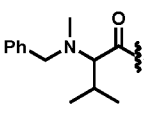
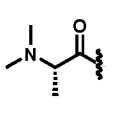
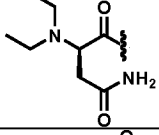
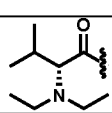
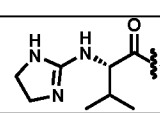
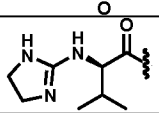
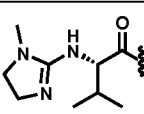
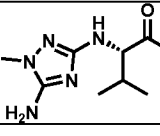
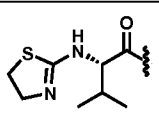
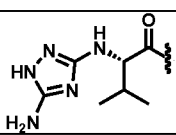
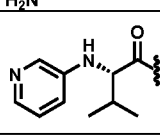
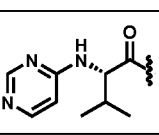
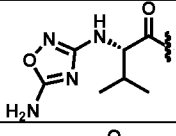
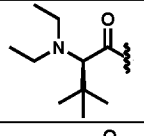
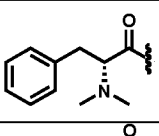
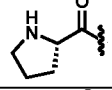
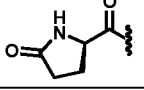
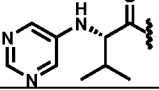
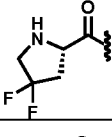
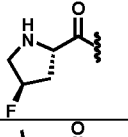
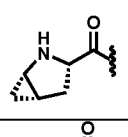
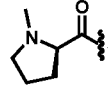
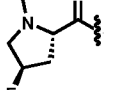
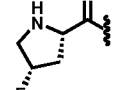


Entry 3-		Entry 3-		Entry 3-	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	

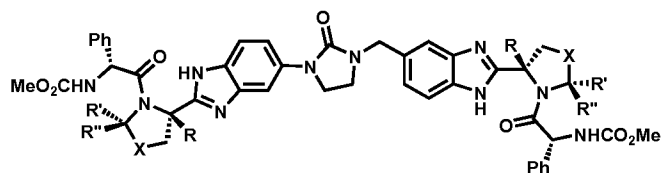
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	

97		98		99	
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	
121		122		123	
124		125		126	
127		128		129	
130		131		132	

133		134		135	
136		137		138	
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	

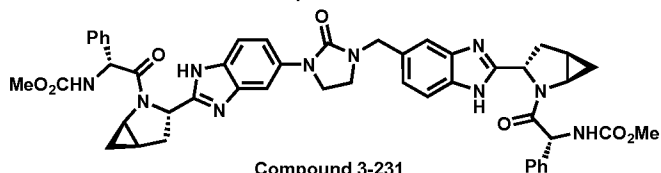
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Compounds 3-220 to 3-229

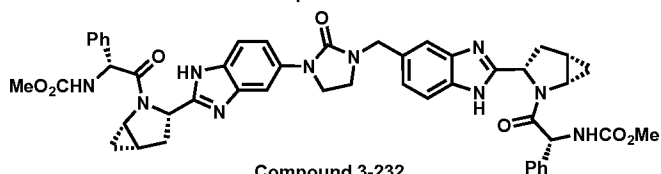


Entry 3-	R	R'	R''	X	Entry 3-	R	R'	R''	X
220	Me	H	H	CH ₂	221	H	H	H	CF ₂
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH ₂	227	H	H	H	
228	H	H	Ph	CH ₂	229	H	H	H	

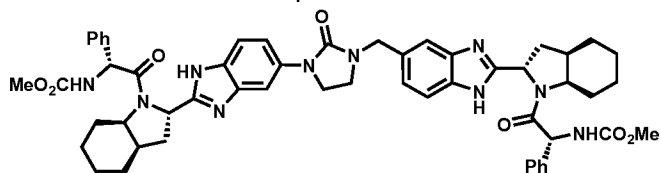
Compound 3-230



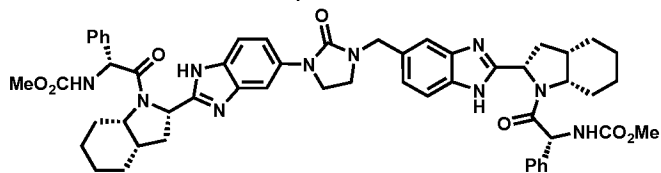
Compound 3-231



Compound 3-232

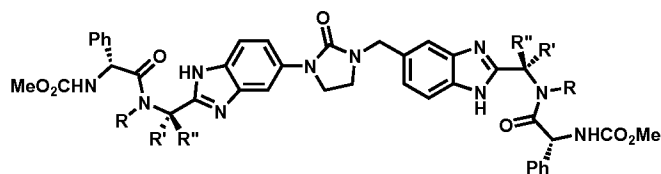


Compound 3-233



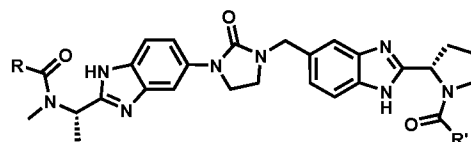
5

Compounds 3-234 to 3-243



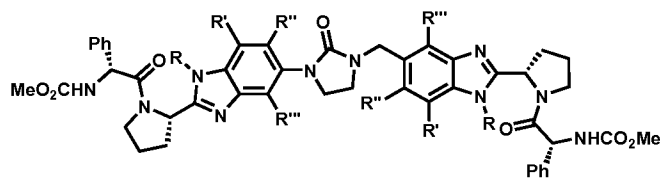
Entry 3-	R	R'	R''	Entry 3-	R	R'	R''
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	CHMe ₂	H	243	Me	Et	H

Compounds 3-244 to 3-263



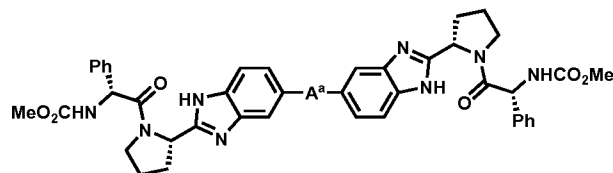
Entry 3-	R	R'	Entry 3-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Compounds 3-264 to 3-289



Entry 3-	R	R'	R''	R'''	Entry 3-	R	R'	R''	R'''
264	Me	H	H	H	265	H	CO ₂ H	H	H
266	H	F	H	H	267	H	H	CO ₂ H	H
268	H	H	F	H	269	H	H	H	CO ₂ H
270	H	H	H	F	271	H	CO ₂ Me	H	H
272	H	Cl	H	H	273	H	H	CO ₂ Me	H
274	H	H	Cl	H	275	H	H	H	CO ₂ Me
276	H	H	H	Cl	277	H	CONH ₂	H	H
278	H	Me	H	H	279	H	H	CONH ₂	H
280	H	H	Me	H	281	H	H	H	CONH ₂
282	H	H	H	Me	283	H	OMe	H	H
284	H	CF ₃	H	H	285	H	H	OMe	H
286	H	H	CF ₃	H	287	H	H	H	OMe
288	H	H	H	CF ₃	289	CO ₂ Me	H	H	H

Compounds 3-290 to 3-334

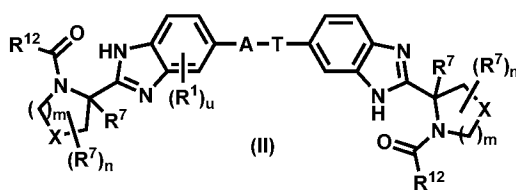


5

Entry 3-	A ^a	Entry 3-	A ^a	Entry 3-	A ^a
290		291		292	
293		294		295	
296		297		298	
299		300		301	
302		303		304	
305		306		307	
308		309		310	

311		312		313	
314		315		316	
317		318		319	
320		321		322	
323		324		325	
326		327		328	
329		330		331	
332		333		334	

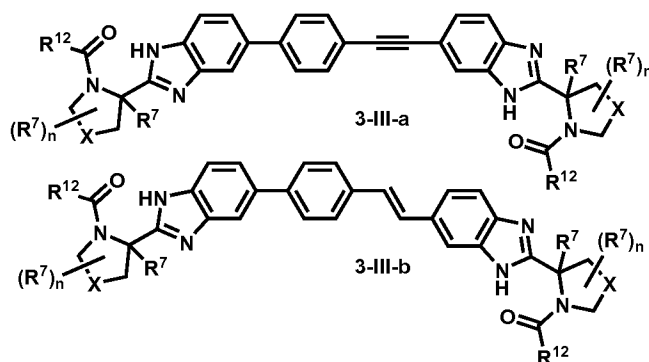
49. A compound of claim 33, represented by Formula (3-II), or a pharmaceutically acceptable salt thereof:



5

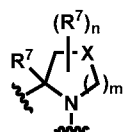
50. A compound of claim 49, wherein m is 1; n is 1 or 2; u is 1 or 2; A is optionally substituted phenyl or optionally substituted monocyclic heteroaryl; T is optionally substituted C₂-C₄ alkenyl or optionally substituted C₂-C₄ alkynyl; R¹ at each occurrence is independently hydrogen or halogen; X at each occurrence is each independently CH₂, CHF, CH(OH), CHMe, CF₂, or C(R⁷)₂; wherein R⁷ at each occurrence is independently hydrogen or methyl; alternatively, the two geminal R⁷ groups are taken together with the carbon to which they are attached to form a spiro C₃-C₈ cycloalkyl; or yet alternatively, two vicinal R⁷ groups can be taken together with the two adjacent atoms to which they are attached to form a fused C₃-C₈ cycloalkyl; and R¹² at each occurrence is independently optionally substituted C₁-C₈ alkyl; or a pharmaceutically acceptable salt thereof.

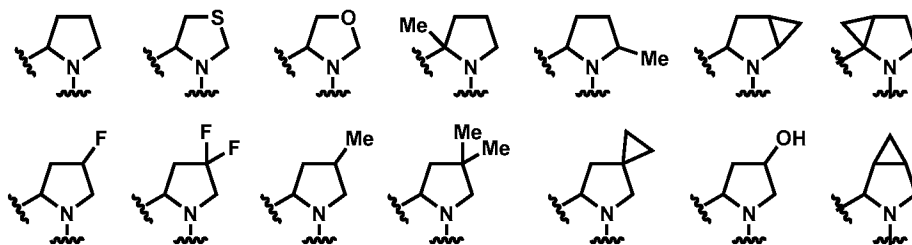
51. A compound of claim 33 represented by Formula (3-III-a) or (3-III-b):



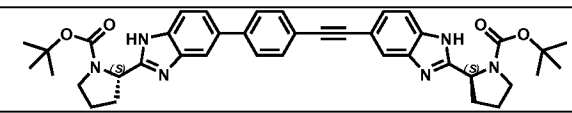
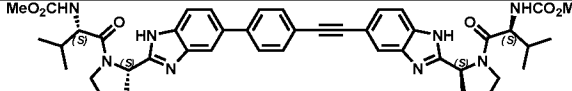
wherein n is 1 or 2; X at each occurrence is independently CH_2 , CHF , $\text{CH}(\text{OH})$, CHMe , CF_2 , or $\text{C}(\text{R}^7)_2$; wherein R^7 at each occurrence is independently hydrogen or methyl; alternatively, the two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro cyclopropyl; or yet alternatively, two vicinal R^7 groups can be taken together with the two adjacent atoms to which they are attached to form a fused cyclopropyl; and R^{12} at each occurrence is independently C_1 - C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $\text{O}(\text{C}_1$ - C_4 alkyl); or a pharmaceutically acceptable salt thereof.

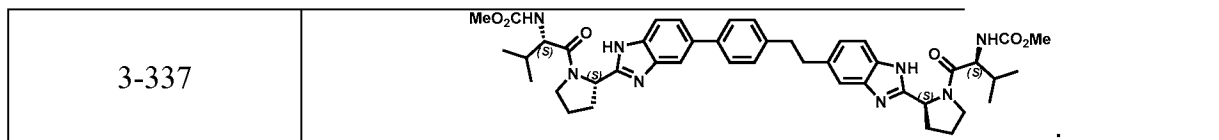
10

52. The compound of claim 33, wherein  is selected from the group listed below, or a pharmaceutically acceptable salt thereof:



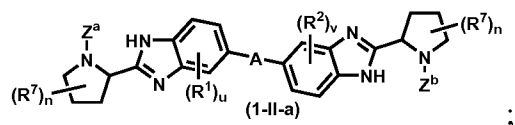
15 53. A compound according to claim 33 selected from the group of compounds 3-335 to 3-337 compiled in the following tables:

3-335	
3-336	



54. A process of making a compound according to claim 1 comprising the steps of:

i) preparing a compound of Formula (1-II-a):



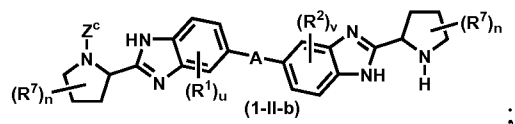
5 via a transition-metal catalyzed cross-coupling reaction;

wherein:

A, n, u, v, R¹, R², and R⁷ are as defined in claim 1;

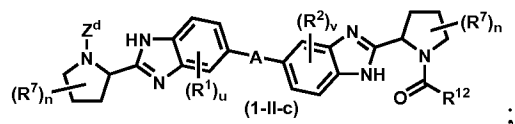
Z^a and Z^b are each independently an amino protecting group or -C(O)-R¹², R¹² is C₁-C₈ alkyl optionally substituted with amino, hydroxy, protected amino, or O(C₁-C₄ alkyl);

ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (II-b):



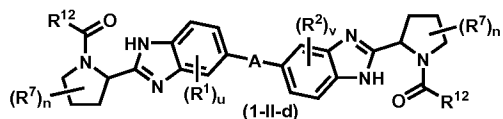
15 wherein Z^c is hydrogen, an amino protecting group or -C(O)-R¹²;

iii) capping the released amino group of a compound of Formula (II-b) with LG-C(O)-R¹², wherein LG is a leaving group; to give the compound of Formula (II-c):



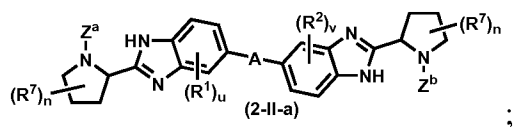
20 wherein Z^d is an amino protecting group -C(O)-R¹²; and

iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (II-d):



55. A process of making a compound according to claim 18 comprising the steps of:

- i) preparing a compound of Formula (2-II-a):



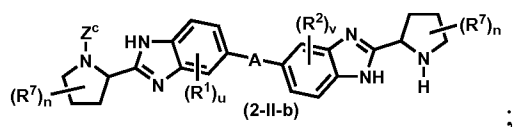
via a transition-metal catalyzed cross-coupling or metathesis reaction; amide or urea formation; ester or carbamate formation; or ether formation;

5 wherein:

A, n, u, v, R^1 , R^2 , and R^7 are as defined in claim 18;

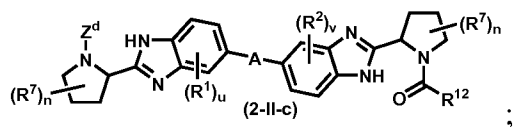
Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$; R^{12} is C_1 - C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1-C_4$ alkyl);

- 10 ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (II-b):



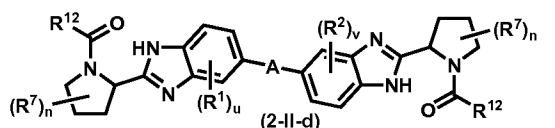
wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$;

- 15 iii) capping the released amino group of a compound of Formula (II-b) with $LG-C(O)-R^{12}$, wherein LG is a leaving group; to give the compound of Formula (II-c):



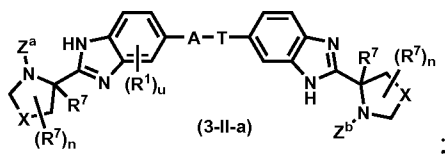
wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and

- 20 iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (II-d):



56. A process of making a compound according to claim 33 comprising the steps of:

- 25 i) preparing a compound of Formula (3-II-a):



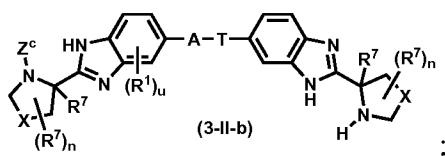
via a transition-metal catalyzed cross-coupling reaction; amide or urea formation; ester or carbamate formation; or ether formation;

wherein:

5 A, T, n, u, v, R¹, R², and R⁷ are as defined in claim 33;

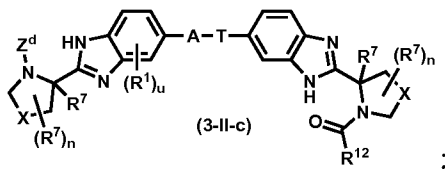
Z^a and Z^b are each independently an amino protecting group or -C(O)-R¹²;

ii) when Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (II-a) to give the corresponding amine of Formula (3-II-b):



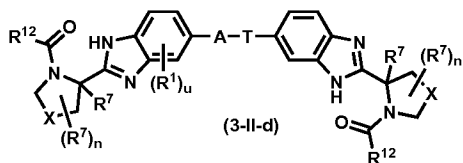
wherein Z^c is hydrogen, an amino protecting group or -C(O)-R¹²; R¹² is C₁-C₈ alkyl optionally substituted with amino, hydroxy, protected amino, or O(C₁-C₄ alkyl);

iii) capping the released amino group of a compound of Formula (II-b) with LG-C(O)-R¹², wherein LG is a leaving group; to give the compound of Formula (3-II-c):



wherein Z^d is an amino protecting group -C(O)-R¹²; and

iv) repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (3-II-d):



57. A pharmaceutical composition comprising a compound or a combination of compounds according to any one of claims 1 to 53 or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

58. A method of inhibiting the replication of an RNA-containing virus comprising contacting said virus with a therapeutically effective amount of a compound or combination of compounds of any one of claims 1 to 53, or a pharmaceutically acceptable salt thereof.

5

59. A method of treating or preventing infection caused by an RNA-containing virus comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of any one claims 1 to 53, or a pharmaceutically acceptable salt thereof.

10

60. The method of claim 59, wherein the RNA-containing virus is hepatitis C virus.

61. The method of claim 59, further comprising the step of co-administering one or more agents selected from the group consisting of a host immune modulator and an antiviral agent, or a combination thereof.

15

62. The method of claim 61, wherein the host immune modulator is selected from the group consisting of interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, consensus interferon, a cytokine, and a vaccine.

20

63. The method of claim 61, wherein the antiviral agent inhibit replication of HCV by inhibiting host cellular functions associated with viral replication.

64. The method of claim 61, wherein the antiviral agent inhibits the replication of HCV by targeting proteins of the viral genome.

25

65. The method of claim 61, wherein said antiviral agent is an inhibitor of a HCV viral protein, a replication process or a combination thereof, wherein said targeting protein or replication process is selected from the group consisting of helicase, protease, polymerase, metalloprotease, NS4A, NS4B, NS5A, assembly, entry, and IRES.

30

66. The method of claim 59, further comprising the step of co-administering an agent or combination of agents that treat or alleviate symptoms of HCV infection selected from cirrhosis, inflammation of the liver and a combination thereof.

67. The method of claim 59, further comprising the step of co-administering one or more agents that treat patients for disease caused by hepatitis B (HBV) infection.

5 68. The method of claim 59, further comprising the step of co-administering one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection.

69. The pharmaceutical composition of claim 57, further comprising an agent selected
10 from interferon, pegylated interferon, ribavirin, amantadine, an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site inhibitor.

70. The composition of claim 57, further comprising a cytochrome P450
15 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof.

71. The composition of claim 70, wherein the cytochrome P450 monooxygenase inhibitor is ritonavir.

20 72. A method of treating hepatitis C viral infection in a subject in need thereof comprising co-administering to said subject a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof, and a compound of any one of claims 1 to 53 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/23645

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A01N 43/50; A61K 31/415 (2010.01)
 USPC - 514/396-397

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
USPC- 514/396-397Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/234.5; 514/235.8 (see keywords below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB
Google: Scholar/patents: bis-benzimidazole antiviral hepatitis dibenzimidazole**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,141,574 B2 (BEAULIEU et al.) 28 November 2006 (28.11.2006) col 2, ln 29-46, ln 58-63; col 3, ln 1, ln 33, ln 43-46, ln 48-60; col 5, ln 13-14, ln 15-55; col 13, ln 32, ln 35, ln 60-67; col 25, ln 10-15	1-72
Y	BRESSANELLI et al. Crystal Structure of the RNA-dependent RNA polymerase of hepatitis C virus, PNAS, 09 November 1999, Vol 96, pp 13034-13039; pg 13034, abstract; pg 13034, col 1, para 1-3; col 2, para 3; pg 13035, Fig 1; pg 13036, col 1, para 1; col 2, para 2; pg 13037, Fig 3; pg 13038, Fig 4	1-72
Y	US 5,935,982 A (DYKSTRA et al.) 10 August 1999 (10.08.1999) col 2, ln 1-60; col 3, ln 16-25	1-17, 33-54, 57-72
Y	US 2007/02299068 A1 (KARP et al.) 27 December 2007 (27.12.2007) para [0017], [0041], [0045]-[0051], [0473]	18-32, 55
Y	US 2006/0058317 A1 (GRAVESTOCK et al.) 16 March 2006 (16.03.2006) para [0211], [0213]-[0214], [0222], [0251]-[0252], [0236]-[0239]	54-57
Y	US 2006/0003942 A1 (TUNG et al.) 05 January 2006 (05.01.2006) para [0004], [0044]-[0045]	66-68, 70-72

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

18 March 2010 (18.03.2010)

Date of mailing of the international search report

01 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774