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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 June 2012 (21.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/083058 A2

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61K 31/4427* (2006.01)
C07D 401/12 (2006.01) *A61P 31/12* (2006.01)
C07D 403/04 (2006.01)

(21) International Application Number:
PCT/US2011/065239

(22) International Filing Date:
15 December 2011 (15.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/423,559 15 December 2010 (15.12.2010) US
61/425,946 22 December 2010 (22.12.2010) US

(71) Applicant *(for all designated States except US)*: **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KRUEGER, Allan C.** [US/US]; 7260 Presidential Drive, Gurnee, Illinois 60031 (US). **KATI, Warren M.** [US/US]; 152 Knob Hill Lane, Gurnee, Illinois 60031 (US). **MARING, Clarence J.** [US/US]; 1228 W. Borders Drive, Palatine, Illinois 60067 (US). **WAGNER, Rolf** [US/US]; 42530 Sheridan Oaks Drive, Antioch, Illinois 60002 (US). **HUTCHINS, Charles W.** [US/US]; 31005 Prairie Ridge Rd, Green Oaks, Illinois 600048 (US).

(74) Agent: **ZHANG, Xu**; Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064 (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, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/083058 A2

(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract: The present invention relates to anti-HCV compounds, compositions comprising the same and methods of using the same to treat HCV infection.

ANTI-VIRAL COMPOUNDS

FIELD

The present invention relates to anti-HCV compounds, compositions comprising the same and methods of using the same to treat HCV infection.

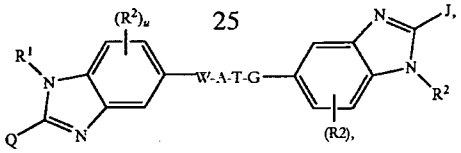
BACKGROUND

Hepatitis C virus ("HCV") is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome which encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY

The present invention relates to a compound of Formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein:

A is a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkenyl, wherein A preferably is substituted with –L–E or prefereably –L_3-D, wherein –L–E or –L_3-D are as defined below;

W is (a) absent; or (b) an optionally substituted aliphatic group; wherein W, if present, is substituted with –L–E or –L_3-D, wherein –L–E or –L_3-D are as defined below;

T is (a) absent; or (b) an optionally substituted linear aliphatic group containing zero to eight carbons; wherein T, if present, is substituted with –L–E or –L_3-D, wherein –L–E or –L_3-D are as defined below;

G is (a) absent; or (b) independently selected from optionally substituted aryl and optionally substituted heteroaryl; wherein G, if present, is substituted with –L–E or –L_3-D, wherein –L–E or –L_3-D are as defined below;

wherein one or two of W, G, and T can optionally be absent; and wherein at least one of A, W, T or G is substituted with L–E or –L_3-D are as defined below;

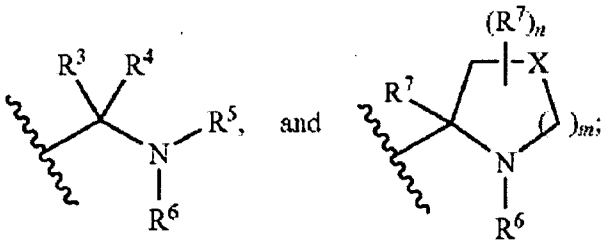
R^1 and R^2 at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C_1-C_4 alkyl, —O—R^{11}, —NR^aR^b, —$C(O)R^{11}$, —CO_2R^{11}, and —$C(O)NR^aR^b$; wherein at least one of R^1 and R^2 can be optionally substituted with –L–E or –L_3-D, wherein –L–E or –L_3-D are as defined below;

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; 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, cycloalkyl;

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};

R^{12} at each occurrence is independently selected from the group consisting of: —O—R^{11}, —NR^cR^d;

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; or

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 (R13)$_2$, and— $S(O)_2N(R^{13})_2$;

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), SO_2, and $C(R^7)_2$, provided that when m is 0, X is $C(R^7)_2$; or

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, —C_1-C_4 alkyl, cyano, —O —R^{11}, —NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted with —C_1-C_4 alkyl; 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 C_3-C_8, cycloalkyl or optionally substituted heterocyclic ring; 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 C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring;

-L–E are as follows:

E is (i) C_3-C_{14} carbocycle or 3- to 14-membered heterocycle, and is optionally substituted with one or more R_A; or (ii) E is –L_S–R_E;

L is –L_S–, –L_S–O–L_S'–, –L_S–C(O)–L_S'–, –L_S–$S(O)_2$–L_S'–, –L_S–S(O)–L_S'–, –L_S–$OS(O)_2$–L_S'–, –L_S–$S(O)_2$O–L_S'–, –L_S–OS(O)–L_S'–, –L_S–S(O)O–L_S'–, –L_S–C(O)O–L_S'–, –L_S–OC(O)–L_S'–, –L_S–OC(O)O–L_S'–, –L_S–C(O)N(R_B)–L_S'–, –L_S–N(R_B)C(O)–L_S'–, –L_S–C(O)N(R_B)O–L_S'–, –L_S–N(R_B)C(O)O–L_S'–, –L_S–OC(O)N(R_B)–L_S'–, –L_S–C(O)N(R_B)N(R_B')–L_S'–, –L_S–S–L_S'–, –L_S–C(S)–L_S'–, –L_S–C(S)O–L_S'–, –L_S–OC(S)–L_S'–, –L_S–C(S)N(R_B)–L_S'–, –L_S–N(R_B)–L_S'–, –L_S–N(R_B)C(S)–L_S'–, –L_S–N(R_B)S(O)–L_S'–, –L_S–N(R_B)$S(O)_2$–L_S'–, –L_S–$S(O)_2$N(R_B)–L_S'–, –L_S–S(O)N(R_B)–L_S'–, –L_S–C(S)N(R_B)O–L_S'–, –L_S–C(O)N(R_B)C(O)–L_S'–, –L_S–N(R_B)C(O)N(R_B')–L_S'–, –L_S–N(R_B)SO_2N(R_B')–L_S'–, –L_S–N(R_B)S(O)N(R_B')–L_S'–, or –L_S–C(S)N(R_B)N(R_B')–L_S'–;

L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L;

R_A is independently selected at each occurrence from halogen, oxo, thioxo, hydroxy, mercapto, nitro, cyano, amino, carboxy, formyl, phosphonoxy, or phosphono; or –L_S–R_E;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each

occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6 carbocycle or 3- to 6-membered heterocycle; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle; wherein each C_3-C_6 carbocycle or 3- to 6-membered heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_E is independently selected at each occurrence from –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)N($R_S$'$R_S$''), –N($R_S$)$SO_2R_S$', –$SO_2$N($R_S$$R_S$'), –N($R_S$)$SO_2$N($R_S$'$R_S$''), –N($R_S$)S(O)N($R_S$'$R_S$''), –OS(O)–$R_S$, –OS$(O)_2$–$R_S$, –S$(O)_2OR_S$, –S(O)O$R_S$, –OC(O)O$R_S$, –N($R_S$)C(O)O$R_S$', –OC(O)N($R_S$$R_S$'), –N($R_S$)S(O)–$R_S$', –S(O)N($R_S$$R_S$') or –C(O)N($R_S$)C(O)–$R_S$'; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

–L_3-D are follows:

L_3 is bond or –L_S–K–L_S'–, wherein K is selected from bond, –O–, –S–, –N(R_B)–, –C(O)–, –$S(O)_2$–, –S(O)–, –OS(O)–, –OS$(O)_2$–, –S$(O)_2$O–, –S(O)O–, –C(O)O–, –OC(O)–, –OC(O)O–, –

$C(O)N(R_B)$–, –$N(R_B)C(O)$–, –$N(R_B)C(O)O$–, –$OC(O)N(R_B)$–, –$N(R_B)S(O)$–, –$N(R_B)S(O)_2$–, –$S(O)N(R_B)$–, –$S(O)_2N(R_B)$–, –$C(O)N(R_B)C(O)$–, –$N(R_B)C(O)N(R_B')$–, –$N(R_B)SO_2N(R_B')$–, or –$N(R_B)S(O)N(R_B')$–;

D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle which is substituted with J and optionally substituted with one or more R_A, where J is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle and is optionally substituted with one or more R_A, or J is $–SF_5$; or D is hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $–L_S–R_E$, wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from $–O–R_S$, $–S–R_S$, $–C(O)R_S$, $–OC(O)R_S$, $–C(O)OR_S$, $–N(R_SR_S')$, $–S(O)R_S$, $–SO_2R_S$, $–C(O)N(R_SR_S')$, $–N(R_S)C(O)R_S'$, $–N(R_S)C(O)N(R_S'R_S'')$, $–N(R_S)SO_2R_S'$, $–SO_2N(R_SR_S')$, $–N(R_S)SO_2N(R_S'R_S'')$, $–N(R_S)S(O)N(R_S'R_S'')$, $–OS(O)–R_S$, $–OS(O)_2–R_S$, $–S(O)_2OR_S$, $–S(O)OR_S$, $–OC(O)OR_S$, $–N(R_S)C(O)OR_S'$, $–OC(O)N(R_SR_S')$, $–N(R_S)S(O)–R_S'$, $–S(O)N(R_SR_S')$, $–P(O)(OR_S)_2$, or $–C(O)N(R_S)C(O)–R_S'$; or C_1-C_6alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $C(O)OR_S$, or $–N(R_SR_S')$;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $–O–R_S$, $–S–R_S$, $–C(O)R_S$, $–OC(O)R_S$, $–C(O)OR_S$, $–N(R_SR_S')$, $–S(O)R_S$, $–SO_2R_S$, $–C(O)N(R_SR_S')$ or $–N(R_S)C(O)R_S'$; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono,

thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl; wherein two adjacent R_L, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –O–C_1-C_6 alkyl, –O–C_1-C_6 alkylene–O–C_1-C_6 alkyl, or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl.

In another aspect, the present invention relates to a pharmaceutical composition comprising (a) one or more of any of the compounds of Formula (I) or any salts, solvates or prodrugs thereof; and (b) at least one pharmaceutically acceptable carrier or at least one pharmaceutically acceptable excipient. Examples of suitable pharmaceutically acceptable carriers or excipients that can be used in said pharmaceutical compositions include, but are not limited to, sugars (e.g., lactose, glucose or sucrose), starches (e.g., corn starch or potato starch), cellulose or its derivatives (e.g., sodium carboxymethyl cellulose, ethyl cellulose or cellulose acetate), oils (e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil or soybean oil), glycols (e.g., propylene glycol), buffering agents (e.g., magnesium hydroxide or aluminum hydroxide), agar, alginic acid, powdered tragacanth, malt, gelatin, talc, cocoa butter, pyrogen-free water, isotonic saline, Ringer's solution, ethanol, phosphate buffer solutions, lubricants, coloring agents, releasing agents, coating agents, sweetening, flavoring or perfuming agents, preservatives, or antioxidants.

In addition to containing any one or more compounds of Formula (I) or any salts, solvates or prodrugs thereof, the pharmaceutical compositions of the present invention can also further contain one or more of the following: (a) one or more anti-HCV agents, such as an HCV polymerase inhibitor, HCV protease inhibitor, HCV helicase inhibitor, CD81 inhibitor, cyclophilin inhibitors, IRES inhibitors, or NS5A inhibitors; (b) one or more antiviral agents such as anti-HBV agents, anti-HIV agents, anti-hepatitis agents, anti-hepatitis D, anti-hepatitis E or anti-hepatitis G agents; (c) anti-bacterial agents; (d) anti-fungal agents; (e) immunomodulators, (f) anti-cancer or chemotherapeutic

agents; (g) anti-inflammatory agents; (h) antisense RNA; (i) antibodies; (j) agents for treating cirrhosis or inflammation of the liver; or (k) any combinations of (a)-(k).

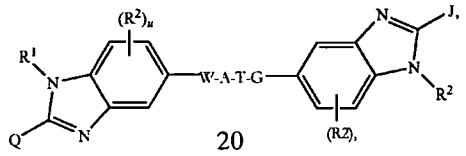
The present invention also relates to a method of treating HCV infection. The method involves administering to a patient in need of treatment, a therapeutically effective amount of the above-described pharmaceutical composition of the present invention to treat the HCV infection in said patient.

Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

In one aspect, the present invention relates to compounds having the structure of below Formula (I) or pharmaceutically acceptable salts thereof:

(I)



wherein:

A is a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkenyl, wherein A is substituted with –L–E or $-L_3$-D, which are defined hereinabove and below;

W is (a) absent; or (b) an optionally substituted aliphatic group; wherein W, when or if present, is substituted with –L–E or $-L_3$-D, which are defined hereinabove and below;

T is (a) absent; or (b) an optionally substituted linear aliphatic group containing zero to eight carbons; wherein T, when or if present, is substituted with –L–E or $-L_3$-D, which are defined hereinabove and below;

G is (a) absent; or (b) independently selected from optionally substituted aryl and optionally substituted heteroaryl; wherein G, when or if present, is substituted with –L–E or $-L_3$-D, which are defined hereinabove and below;

wherein one or two of W, G, and T can optionally be absent;

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, —$C(O)R^{11}$, —

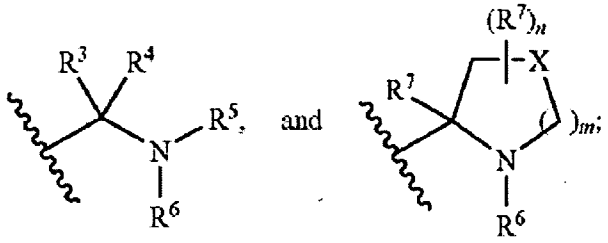
CO_2R^{11}, and —C(O)NR^aR^b; wherein at least one of R^1 and R^2 can be optionally substituted with –L–E or $–L_3$-D as defined below;

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, 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^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 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); or

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 ($R13)_2$, 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), SO_2, and $C(R^7)_2$, preferably CH_2 or CHR^7; provided that when m is 0, X is $C(R^7)_2$; or

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, —C_1-C_4 alkyl, 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 C_3-C_8, 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 C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl;

With respect to –L–E as used herein:

E is (i) C_3-C_{14} carbocycle or 3- to 14-membered heterocycle, and is optionally substituted with one or more R_A; or (ii) E is $-L_S-R_E$;

L is $-L_S-$, $-L_S-O-L_S'-$, $-L_S-C(O)-L_S'-$, $-L_S-S(O)_2-L_S'-$, $-L_S-S(O)-L_S'-$, $-L_S-OS(O)_2-L_S'-$, $-L_S-S(O)_2O-L_S'-$, $-L_S-OS(O)-L_S'-$, $-L_S-S(O)O-L_S'-$, $-L_S-C(O)O-L_S'-$, $-L_S-OC(O)-L_S'-$, $-L_S-OC(O)O-L_S'-$, $-L_S-C(O)N(R_B)-L_S'-$, $-L_S-N(R_B)C(O)-L_S'-$, $-L_S-C(O)N(R_B)O-L_S'-$, $-L_S-N(R_B)C(O)O-L_S'-$, $-L_S-OC(O)N(R_B)-L_S'-$, $-L_S-C(O)N(R_B)N(R_B')-L_S'-$, $-L_S-S-L_S'-$, $-L_S-C(S)-L_S'-$, $-L_S-C(S)O-L_S'-$, $-L_S-OC(S)-L_S'-$, $-L_S-C(S)N(R_B)-L_S'-$, $-L_S-N(R_B)-L_S'-$, $-L_S-N(R_B)C(S)-L_S'-$, $-L_S-N(R_B)S(O)-L_S'-$, $-L_S-N(R_B)S(O)_2-L_S'-$, $-L_S-S(O)_2N(R_B)-L_S'-$, $-L_S-S(O)N(R_B)-L_S'-$, $-L_S-C(S)N(R_B)O-L_S'-$, $-L_S-C(O)N(R_B)C(O)-L_S'-$, $-L_S-N(R_B)C(O)N(R_B')-L_S'-$, $-L_S-N(R_B)SO_2N(R_B')-L_S'-$, $-L_S-N(R_B)S(O)N(R_B')-L_S'-$, or $-L_S-C(S)N(R_B)N(R_B')-L_S'-$;

L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L;

R_A is independently selected at each occurrence from halogen, oxo, thioxo, hydroxy, mercapto, nitro, cyano, amino, carboxy, formyl, phosphonoxy, or phosphono; or $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6 carbocycle or 3- to 6-membered heterocycle; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle; wherein each C_3-C_6 carbocycle or 3- to 6-membered heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo,

phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_E is independently selected at each occurrence from –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)N($R_S$'$R_S$''), –N($R_S$)$SO_2R_S$', –$SO_2$N($R_S$$R_S$'), –N($R_S$)$SO_2$N($R_S$'$R_S$''), –N($R_S$)S(O)N($R_S$'$R_S$''), –OS(O)–$R_S$, –OS(O)$_2$–$R_S$, –S(O)$_2OR_S$, –S(O)O$R_S$, –OC(O)O$R_S$, –N($R_S$)C(O)O$R_S$', –OC(O)N($R_S$$R_S$'), –N($R_S$)S(O)–$R_S$', –S(O)N($R_S$$R_S$') or –C(O)N($R_S$)C(O)–$R_S$'; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

For –L_3-D:

L_3 is bond or –L_S–K–L_S'–, wherein K is selected from bond, –O–, –S–, –N(R_B)–, –C(O)–, –$S(O)_2$–, –S(O)–, –OS(O)–, –$OS(O)_2$–, –$S(O)_2$O–, –S(O)O–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(R_B)–, –N(R_B)C(O)–, –N(R_B)C(O)O–, –OC(O)N(R_B)–, –N(R_B)S(O)–, –N(R_B)$S(O)_2$–, –S(O)N(R_B)–, –$S(O)_2$N(R_B)–, –C(O)N(R_B)C(O)–, –N(R_B)C(O)N(R_B')–, –N(R_B)SO_2N(R_B')–, or –N(R_B)S(O)N(R_B')–; preferably, L_3 is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene; more preferably, L_3 is bond;

D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle which is substituted with J and optionally substituted with one or more R_A, where J is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle and is optionally substituted with one or more R_A, or J is $-SF_5$; or D is hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$, wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $C(O)OR_S$, or $-N(R_SR_S')$;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl; wherein two adjacent R_L, taken together with the atoms to which they are attached

and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

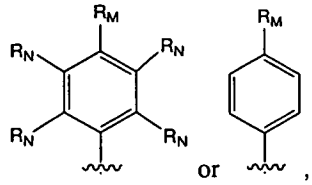
L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

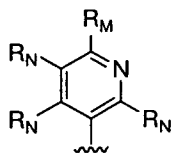
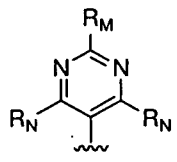
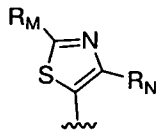
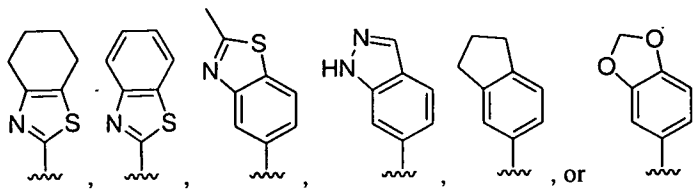
R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –O–C_1-C_6 alkyl, –O–C_1-C_6 alkylene–O–C_1-C_6 alkyl, or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl.

Preferably, -L-E comprises C_5-C_6 carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycle, each of which is optionally substituted with one or more R_A as defined above. Also preferably, the moiety comprises C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one or more R_L as defined above. More preferably, the moiety comprises C_5-C_6 carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, C_1-C_6alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein each of said C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl can be further independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6 carbocycle or 3- to 6-membered heterocycle. Highly preferably, the moiety comprises C_5-C_6 carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl.

In one example, -L-E comprises phenyl optionally substituted with one or more substituents selected from is halogen, hydroxy, mercapto, amino, carboxy, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein each of said C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. In another example, the moiety comprises C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with one or more substituents selected from

halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

In the above Formula I, D in -L_3-D preferably is selected from C_5-C_6 carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, and is optionally substituted with one or more substituents selected from R_L. More preferably, D is C_5-C_6 carbocycle (e.g., phenyl), 5- to 6-membered heterocycle (e.g., pyridinyl, pyrimidinyl, thiazolyl), or 6- to 12-membered bicycles (e.g., indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, benzo[d][1,3]dioxol-5-yl), and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$. Also preferably, D is phenyl, and is optionally substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D is  , and is optionally substituted with one or more R_M.

Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from

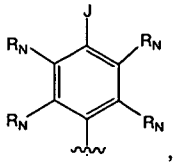
halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6 alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6 alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $-C(O)OR_S$, or $-N(R_SR_S')$. More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example, R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-R_E$ where L_S is a bond and R_E is $-N(R_SR_S')$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1$-C_6 alkyl$)_2$ (e.g., $-NMe_2$); $-N(C_1$-C_6 alkylene$-O-C_1$-C_6 alkyl$)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1$-C_6 alkyl$)(C_1$-C_6 alkylene$-O-C_1$-C_6 alkyl) (e.g. $-N(CH_3)(CH_2CH_2OMe)$);$-O-C_1$-C_6alkyl (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1$-C_6 haloalky l (e.g., $-OCF_3$, $-OCH_2CF_3$); $-O-C_1$-C_6alkylene–piperidine (e.g., $-O-CH_2CH_2-1$-piperidyl); $-N(C_1$-C_6alkyl$)C(O)OC_1$-C_6 alkyl (e.g., $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1$-C_6 alkyl$)SO_2C_1$-C_6 alkyl (e.g., $-N(CH_3)SO_2CH_3$); $-SO_2C_1$-C_6 alkyl (e.g., $-SO_2Me$); $-SO_2C_1$-C_6 haloalkyl (e.g., $-SO_2CF_3$); or $-S-C_1$-C_6 haloalkyl (e.g., SCF_3). Also preferably R_M is $-L_S-R_E$ where L_S is C_1-C_6 alkylene (e.g., $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) and R_E is $-O-R_S$, $-C(O)OR_S$, –

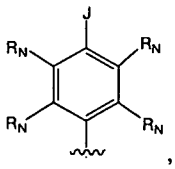
$N(R_S)C(O)OR_S'$, or $-P(O)(OR_S)_2$. For example R_M is $-C_1$-C_6 alkylene–O–R_S (e.g., $-C(CH_3)_2-CH_2-OMe$); $-C_1$-C_6 alkylene–$C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1$-C_6 alkylene–$N(R_S)C(O)OR_S'$ (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1$-C_6 alkylene–$P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). Also more preferably R_M is C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $-C(O)OR_S$, or $-N(R_SR_S')$. For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

More preferably, D is C_5-C_6 carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6 carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6 carbocycle or 3- to 6-membered heterocycle, wherein said C_3-C_6carbocycle or 3- to 6-membered heterocycle is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6 carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A, and preferably, J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Also preferably, D is C_5-C_6 carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or sipro bicycle comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently

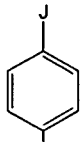
optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C(O)OR_S or –



$N(R_SR_S')$. Highly preferably, D is , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C(O)OR_S or –



$N(R_SR_S')$. Also preferably, D is , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle and 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C(O)OR_S or –



$N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, D is , and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C(O)OR_S or $-N(R_SR_S')$.

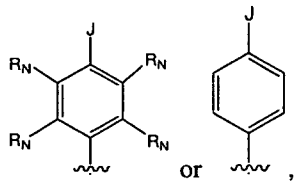
The present invention also features $-L_3$-D, wherein:

D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle which is substituted with J and optionally substituted with one or more R_A, where J is C_3-C_{15}carbocycle or 3- to 15-membered

heterocycle (e.g., a 3- to 6-membered monocycle, a 6- to 12-membered fused, bridged or spiro bicycle, a 10- to 15-memberd tricycle containing fused, bridged or spiro rings, or a 13- to 15-membered carbocycle or heterocycle) and is optionally substituted with one or more R_A, or J is $-SF_5$; or D is hydrogen or R_A; R_A and J are as defined herein;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, $=C(R_SR_S')$, or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle (e.g., 7- ot 12-membered carbocycle or heterocycle), each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, trimethylsilyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-C(O)OR_S$, or $-N(R_SR_S')$.

In one embodiment, D is a C_5-C_6 carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle, or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$ or $-N(R_SR_S')$, or (2) trimethylsilyl, $-O-R_S$, $-S-R_S$, $-C(O)R_S$; and J can also be optionally substituted with one or more R_A. Preferably, D is



or

, wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond.

As used herein, R_A preferably is halogen, hydroxy; mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ or $-L_A-C(O)N(R_S)C(O)-R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

According to another aspect of the invention, $-L_3$-D are defined as:

L_3 is bond or C_1-C_6 alkylene;

D is C_6-C_{10}carbocycle or 5- to 12-membered heterocycle, each of which is optionally R_M is independently selected at each occurrence from:

halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, SF_5, $-N(R_SR_S')$, $-O-R_S$, $-OC(O)R_S$, $-OC(O)OR_S$, $-OC(O)N(R_SR_S')$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-S(O)R_S$, $-SO_2R_S$, $-S(O)N(R_SR_S')$, $-SR_S$, $-Si(R_S)_3$, or $-P(O)(OR_S)_2$;

C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $-N(R_SR_S')$, $-O-R_S$, $-OC(O)R_S$, $-OC(O)OR_S$, $-OC(O)N(R_SR_S')$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-S(O)R_S$, $-SO_2R_S$, $-S(O)N(R_SR_S')$, $-SR_S$, or $-P(O)(OR_S)_2$; or

G_2, wherein G_2 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_{G2}, and each R_{G2} is independently selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-O-R_S$, $-C(O)OR_S$, $-C(O)R_S$, $-N(R_SR_S')$, or $-L_4-G_3$;

L_4 is a bond, C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, or $-N(R_B)S(O)N(R_B')-$;

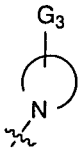
G_3 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_{G3}; and

R_{G3} is each independently, at each occurrence, halogen, $-C_1$-C_6alkyl, $-C(O)C_1$-C_6alkyl, $-C_1$-C_6 haloalkyl, $-O-C_1$-C_6alkyl, $-O-C_1$-C_6haloalkyl, C_3-C_6carbocycle, or 3- to 6-membered heterocycle. substituted with one or more R_M;

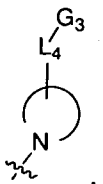
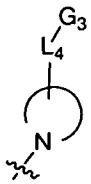
R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $-O-C_1$-C_6alkyl, $-O-C_1$-C_6haloalkyl, or 3- to 12-membered carbocycle or heterocycle; or 3- to 12-membered carbocycle or heterocycle; wherein each 3- to 12-membered carbocycle or heterocycle in R_S , R_S' or R_S'' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

As described hereinabove for this aspect of the invention, D preferably is C_6-C_{10}carbocycle or 3- to 12-membered heterocycle optionally substituted by one or more R_M. Preferably, D is C_6-C_{10}aryl (e.g., phenyl, naphthyl, indanyl), or 5- to 10-membered heteroaryl (pyridinyl, thiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, benzo[d][1,3]dioxol-5-yl), and D is substituted with one or more R_M. For example, in certain embodiments D is preferably phenyl substituted by one or more R_M, wherein each R_M is independently halogen (e.g., fluoro, chloro, bromo); C_1-C_6alkyl (e.g., tert-butyl); C_1-C_6alkyl substituted with one or more halogen (e.g., CF_3); $-O-R_S$ such as $-O-C_1$-C_6alkyl (e.g., $-O-CH_2CH_3$); or $-O-C_1$-C_6alkyl substituted at each occurrence with

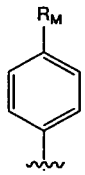
one or more halogen (e.g., –O–CF_3, –O–CH_2CHF_2) or –O–C_1-C_6alkyl (e.g., –O–$CH_2CH_2OCH_3$); –O–R_S (e.g., –O–C_1-C_6alkyl, such as –O–CH_2) substituted with 3- to 12-membered heterocycle (e.g., 3-ethyloxetan-3-yl, 1,3-dioxolan-4-yl); –O–R_S where R_S is an optionally substituted 3- to 12-membered carbocycle or heterocycle (e.g., cyclopentyl, cyclohexyl, phenyl, 1,3-dioxan-5-yl); –N(R_S)C(O)R_S' wherein R_S and R_S' are each independently C_1-C_6alkyl (e.g., –N(t-Bu)C(O)Me); SF_5; –SO_2R_S wherein R_S is C_1-C_6alkyl (e.g., –SO_2Me); or C_3-C_{12}carbocycle (e.g., cyclopropyl, cyclohexyl, phenyl).

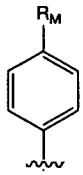
In certain embodiments of this aspect of the invention, D is preferably phenyl or pyridyl and is substituted by one or more R_M where one R_M is G_2. In certain embodiments where D is phenyl or pyridyl, D is substituted by G_2, G_2 is 3- to 12-membered heterocycle (e.g., pyridinyl, piperidinyl, pyrrolidinyl, azetidinyl, oxazolyl) and is optionally substituted with one or more halogen (e.g., fluoro, chloro), hydroxy, oxo, cyano, C_1-C_6alkyl (e.g., methyl), C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl (e.g., CF_3), C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –O–C_1-C_6alkyl (e.g., –O–CH_3), –C(O)OR_S (e.g., –C(O)OCH_3), –C(O)R_S (e.g., –C(O)CH_3), or –N(R_SR_S'); and D is further optionally substituted by one or more R_M where R_M is halogen (e.g., fluoro, chloro), C_1-C_6alkyl (e.g., methyl), C_1-C_6haloalkyl (e.g., CF_3), or –O–C_1-C_6alkyl (e.g., –O–CH_3). In certain other embodiments D is phenyl or pyridyl and G_2 is, for example, a monocyclic 3-8 membered carbocycle or monocyclic 4-8 membered heterocycle substituted with L_4–G_3 and optionally substituted with one or more R_{G2} wherein L_4, G_3 and R_{G2} are as defined herein. L_4, for example is a bond, a C_1-C_6 alkylene (e.g., –CH_2–, –CH_2CH_2–, –$CH_2CH_2CH_2$–, etc.), –O–, or –$S(O)_2$–. G_3 is for example a C_3-C_{12}carbocycle optionally substituted with one or more R_{G3}. R_{G2} and R_{G3} are each independently at each occurrence halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl. In certain embodiments G_2 is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl) attached to the parent molecular moiety through a nitrogen atom and substituted with one or two L_4–G_3 and optionally substituted with one or more R_{G2}. Thus, in certain embodiments where L_4 is a bond G_2 is  , where  is optionally substituted with R_{G2} and G_3 is optionally substituted with R_{G3}. Thus,  can be, for example, 3-phenylazetidin-1-yl, 3-phenylpyrrolidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-phenyl-3,6-

dihydropyridin-1(2H)-yl, 4,4-diphenylpiperidin-1-yl, 4-acetyl-4-phenylpiperidin-1-yl, 4-(4-methoxyphenyl)piperidin-1-yl, 4-(4-fluorophenyl)piperidin-1-yl, or 3-phenylpiperidin-1-yl, and wherein D can be further optionally substituted with one or more R_M (e.g., fluoro, chloro, methyl, methoxy).

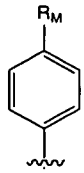
In certain other embodiments of this aspect of the invention, L_4 is a C_1-C_6 alkylene, –O–, or –$S(O)_2$–, and G_2 is  , where  is as defined above and is optionally substituted with R_{G2} and G_3 is as defined above and is optionally substituted with R_{G3}. Thus,  can be, for example, 4-tosylpiperazin-1-yl, 4-phenoxypiperidin-1-yl, 3-phenoxypyrrolidin-1-yl, 4-benzylpiperidin-1-yl, 4-phenethylpiperidin-1-yl, or 3-phenylpropyl)piperidin-1-yl.

In certain other embodiments of this aspect of the invention, D is phenyl or pyridyl, D is substituted by G_2 and G_2 is a spiro, bridged, or fused bicyclic carbocycle or heterocycle optionally substituted with L_4–G_3 and one or more R_{G2}, wherein D is optionally substituted with one or more R_M and R_M, L_4, G_3, and R_{G2} are as defined herein. In certain embodiments G_2 is  , wherein  is a spiro, bridged, or fused bicyclic nitrogen-containing heterocycle (e.g., 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl) attached to the parent molecular moiety through a nitrogen atom and optionally substituted with G_3 and one or more R_{G2}. Thus, G_2 is 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, or 1,4-dioxa-8-azaspiro[4.5]dec-8-yl; L_4 is a bond and D is optionally substituted with one or more R_M (e.g., fluoro, chloro, methyl, methoxy).

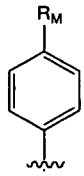
In certain embodiments of this aspect of the invention, D is  wherein R_M is as defined above in connection with Formula I_E, and D is optionally substituted by one or more additional R_M.



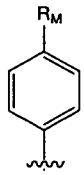
For instance, where D is , R_M can be fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, –O–(1,3-dioxan-5-yl), cyclopropyl, cyclohexyl, phenyl, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D can be optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



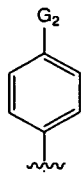
In certain embodiments of this aspect of the invention, D is wherein R_M is fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



In certain embodiments of this aspect of the invention, D is wherein R_M is cyclopropyl, cyclohexyl, or phenyl and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).

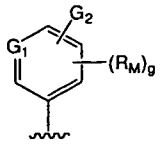
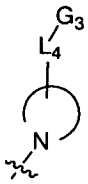
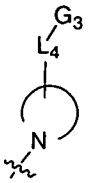
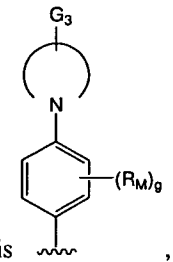
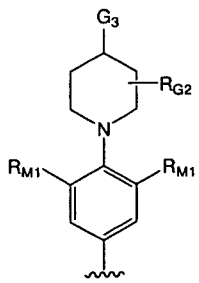


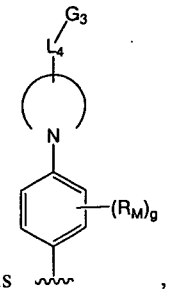
In certain embodiments of this aspect of the invention, D is wherein R_M is –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, or –O–(1,3-dioxan-5-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



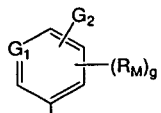
In certain embodiments of this aspect of the invention, D is wherein G_2 is pyridinyl (e.g., pyridin-2-yl), piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-

oxopiperidin-1-yl, 3,3-dimethylazetidin-1-yl, or oxazolyl (e.g., 1,3-oxazol-2-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).

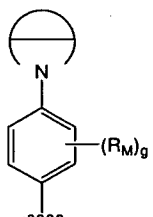
In another embodiment of this aspect of the invention, D is  wherein G_1 is N, C–H, or C–R_M; G_2 is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) attached to the parent molecular moiety through a nitrogen atom and substituted by L_4–G_3 and optionally substituted with one or more R_{G2}; L_4 is a bond, C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is aryl (e.g., phenyl), cycloalkyl (e.g., cyclohexyl), or heterocycle (e.g., thienyl) wherein each G_3 is optionally substituted with one or more R_{G3}; R_{G2} and R_{G3} at each occurrence are each independently halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl; g is 0, 1, 2, or 3; and R_M is as defined above in connection with Formula I_E. In one group of compounds according to this embodiment, D is  , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  and R_{G3} are as defined above. In a further subgroup of compounds of this embodiment, D is  wherein G_3 is phenyl optionally substituted with one or two R_{G3}; R_{M1} is each independently hydrogen, fluoro, chloro, or methyl; and R_{G2} is an optional substituent as described herein. In another group of



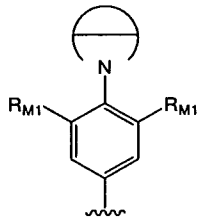
compounds according to this embodiment, D is , wherein L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  and R_{G3} are as defined above.



In yet another embodiment of this aspect of the invention, D is wherein G_1 is N, C–H, or C–R_M; G_2 is  , wherein  is a spiro, bridged, or fused bicyclic nitrogen-containing heterocycle (e.g., 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl) attached to the parent molecular moiety through a nitrogen atom and optionally substituted with L_4–G_3 and one or more R_{G2}; L_4 is a bond, C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is aryl (e.g., phenyl), cycloalkyl (e.g., cyclohexyl), or heterocycle (e.g., thienyl) wherein each G_3 is optionally substituted with one or more R_{G3}; R_{G2} and R_{G3} at each occurrence are each independently halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl; g is 0, 1, 2, or 3; and R_M is as defined above in connection with Formula I_E. In one group of compounds according to this embodiment, D is

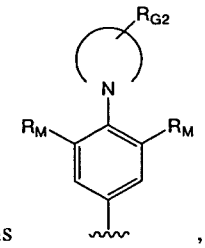


wherein g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  is as defined above. In a further subgroup of compounds D is

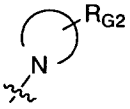


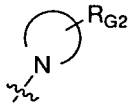
wherein R_{M1} is each independently hydrogen, fluoro, chloro, or methyl, and

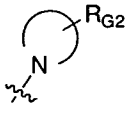
is as defined above (e.g., 3-azabicyclo[3.2.0]hept-3-yl, octahydro-2H-isoindol-2-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl).

In still another embodiment of this aspect of the invention, D is 

, wherein

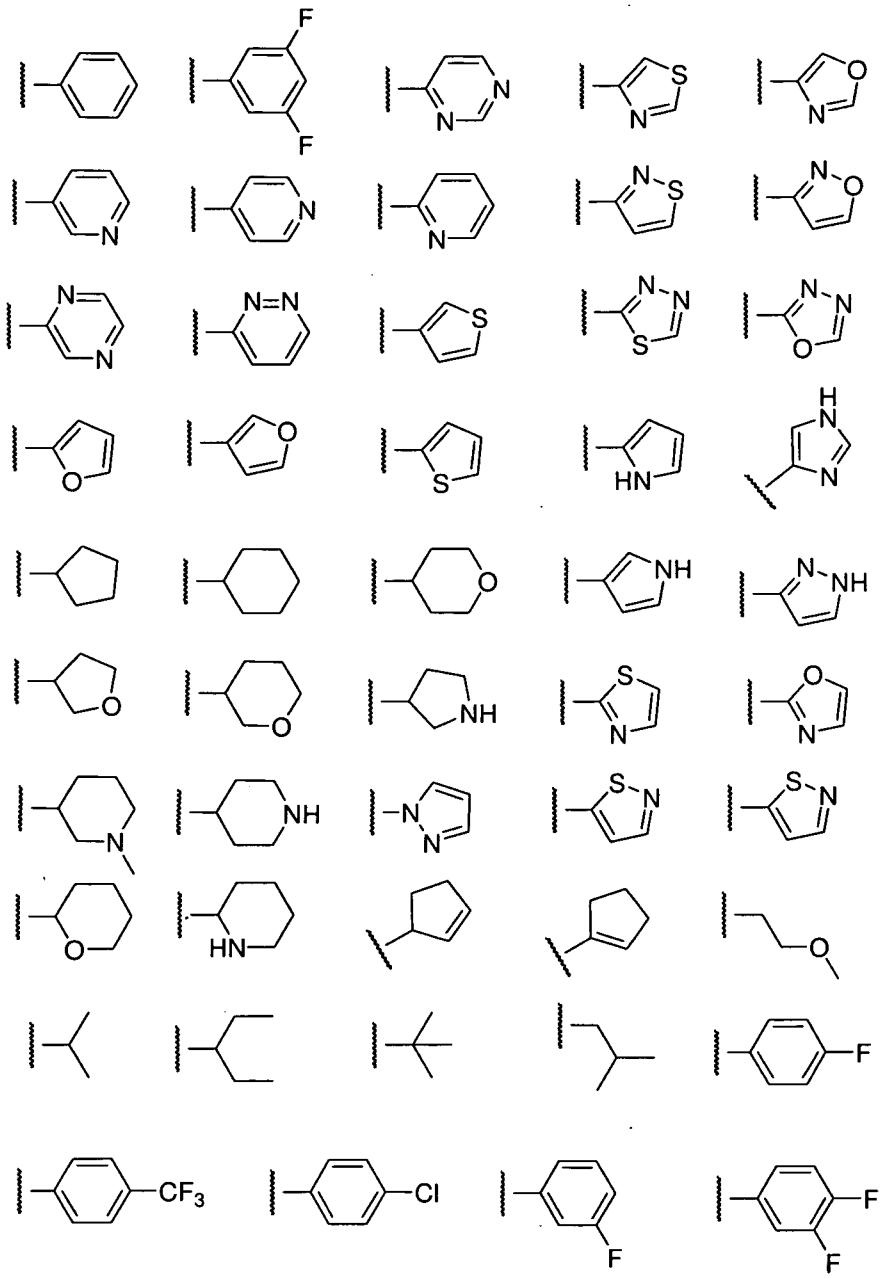


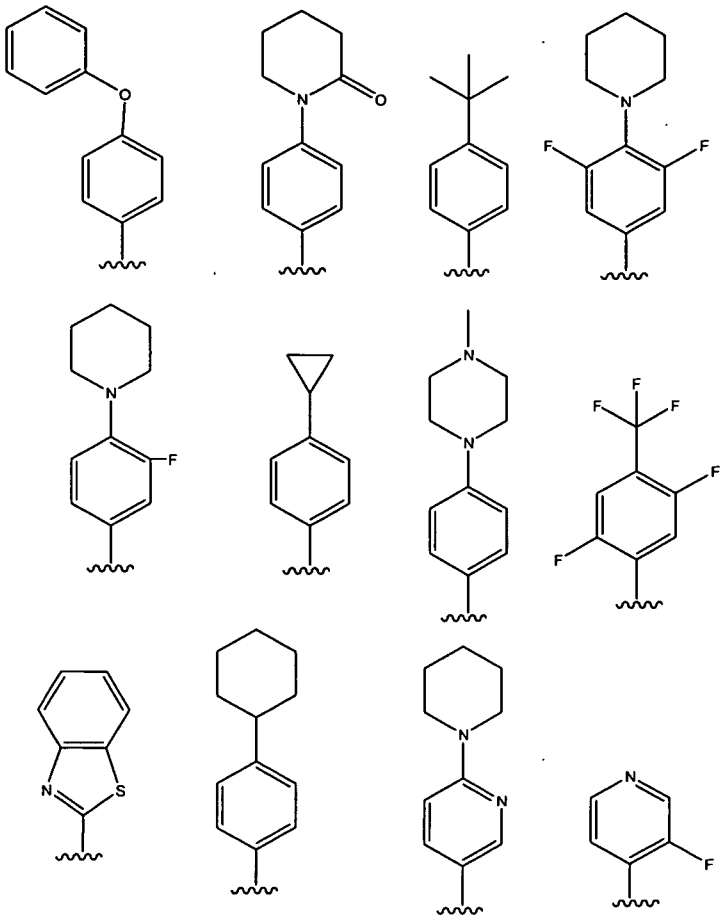
is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) substituted with one or more R_{G2}, wherein R_{G2} at each occurrence is each independently halogen, $-C(O)C_1$-C_6alkyl, $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-O-C_1$-C_6alkyl, or $-O-C_1$-C_6haloalkyl; and R_M is each independently halogen, $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-O-C_1$-C_6alkyl, or $-O-C_1$-C_6haloalkyl. In one group of compounds according to this embodiment, 

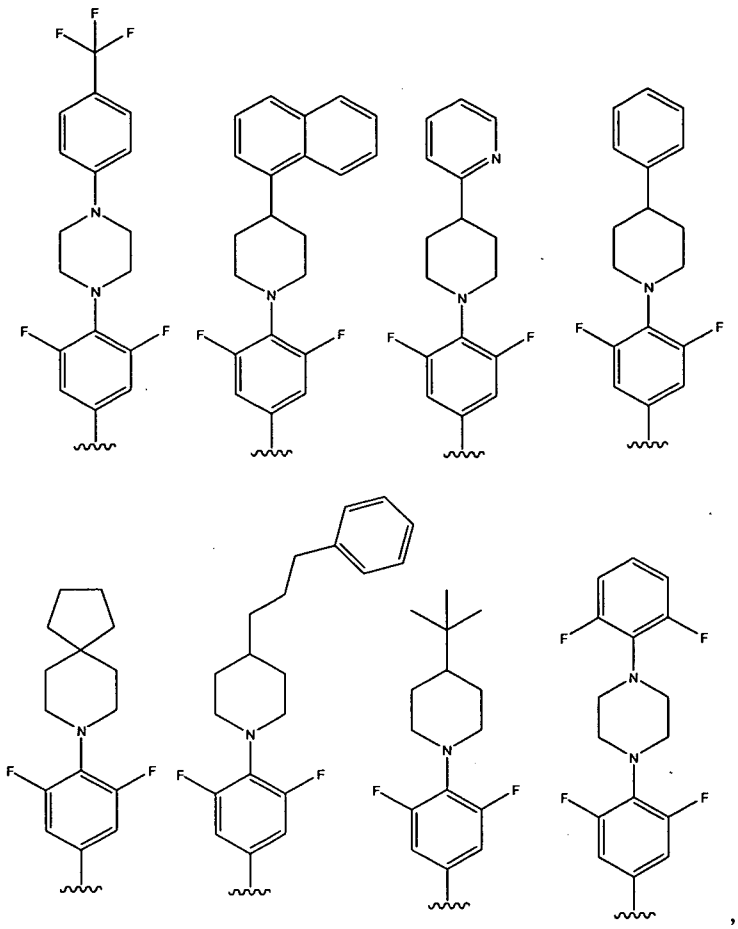
is azetidinyl, pyrrolidinyl, or piperidinyl substituted with one or two R_{G2}, wherein R_{G2} at each occurrence is each independently methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, or trifluoromethyl; and R_M is each independently fluoro, chloro, or methyl. For example 

is 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl.

Non-limited examples of D in $-L_3-D$ include:







wherein L_3 is preferably bond.

The term "alkenyl" as used in connection with the definition of –L–E or $-L_3$-D means a straight or branched hydrocarbyl chain containing one or more double bonds. Each carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety, relative to groups substituted on the double bond carbons. Non-limiting examples of alkenyl groups include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, and 3-butenyl.

The term "alkenylene" as used in connection with the definition of –L–E or $-L_3$-D refers to a divalent unsaturated hydrocarbyl chain which may be linear or branched and which has at least one carbon-carbon double bond. Non-limiting examples of alkenylene groups include —C(H)=C(H)—, —C(H)=C(H)—CH_2—, —C(H)=C(H)—CH_2—CH_2—, —CH_2—C(H)=C(H)—CH_2—, —C(H)=C(H)—$CH(CH_3)$—, and —CH_2—C(H)=C(H)—$CH(CH_2CH_3)$—.

The term "alkyl" as used in connection with the definition of –L–E or $-L_3$-D means a straight or branched saturated hydrocarbyl chain. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, iso-amyl, and hexyl.

The term "alkylene" as used in connection with the definition of –L–E or $-L_3$-D denotes a divalent saturated hydrocarbyl chain which may be linear or branched. Representative examples of

alkylene include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "alkynyl" as used in connection with the definition of –L–E or –L_3-D means a straight or branched hydrocarbyl chain containing one or more triple bonds. Non-limiting examples of alkynyl include ethynyl, 1-propynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

The term "alkynylene" as used in connection with the definition of –L–E or –L_3-D refers to a divalent unsaturated hydrocarbon group which may be linear or branched and which has at least one carbon-carbon triple bonds. Representative alkynylene groups include, by way of example, —C≡C—, —C≡C—CH_2—, —C≡C—CH_2—CH_2—, —CH_2—C≡C—CH_2—, —C≡C—$CH(CH_3)$—, and —CH_2—C≡C—$CH(CH_2CH_3)$—.

The term "carbocycle" or "carbocyclic" or "carbocyclyl" as used in connection with the definition of –L–E or –L_3-D refers to a saturated (e.g., "cycloalkyl"), partially saturated (e.g., "cycloalkenyl" or "cycloalkynyl") or completely unsaturated (e.g., "aryl") ring system containing zero heteroatom ring atom. "Ring atoms" or "ring members" are the atoms bound together to form the ring or rings. A carbocyclyl may be, without limitation, a single ring, two fused rings, or bridged or spiro rings. A substituted carbocyclyl may have either cis or trans geometry. Representative examples of carbocyclyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclopentadienyl, cyclohexadienyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, cyclohexenyl, phenyl, naphthyl, indanyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, isoindenyl, decalinyl, and norpinanyl. A carbocycle group can be attached to the parent molecular moiety through any substitutable carbon ring atom.

The term "carbocyclylalkyl" as used in connection with the definition of –L–E or –L_3-D refers to a carbocyclyl group appended to the parent molecular moiety through an alkylene group. For instance, C_3-C_6carbocyclylC_1-C_6alkyl refers to a C_3-C_6carbocyclyl group appended to the parent molecular moiety through C_1-C_6alkylene.

The term "cycloalkenyl" as used in connection with the definition of –L–E or –L_3-D as used in connection with the definition of –L–E or –L_3-D refers to a non-aromatic, partially unsaturated carbocyclyl moiety having zero heteroatom ring member. Representative examples of cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, and octahydronaphthalenyl.

The term "cycloalkyl" as used in connection with the definition of –L–E or –L_3-D refers to a saturated carbocyclyl group containing zero heteroatom ring member. Non-limiting examples of cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, decalinyl and norpinanyl.

The prefix "halo" as used in connection with the definition of –L–E or –L_3-D indicates that the substituent to which the prefix is attached is substituted with one or more independently selected

halogen radicals. For example, "C_1-C_6 haloalkyl" means a C_1-C_6 alkyl substituent wherein one or more hydrogen atoms are replaced with independently selected halogen radicals. Non-limiting examples of C_1-C_6 haloalkyl include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).

The term "heterocycle" or "heterocyclo" or "heterocyclyl" as used in connection with the definition of –L–E or –L_3-D refers to a saturated (e.g., "heterocycloalkyl"), partially unsaturated (e.g., "heterocycloalkenyl" or "heterocycloalkynyl") or completely unsaturated (e.g., "heteroaryl") ring system where at least one of the ring atoms is a heteroatom (i.e., nitrogen, oxygen or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur. A heterocycle may be, without limitation, a single ring, two fused rings, or bridged or spiro rings. A heterocycle group can be linked to the parent molecular moiety via any substitutable carbon or nitrogen atom(s) in the group.

A heterocyclyl may be, without limitation, a monocycle which contains a single ring. Non-limiting examples of monocycles include furanyl, dihydrofuranyl, tetrahydrofuranyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), and 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl and 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, and 1,3,4-dioxazolyl), oxathiolanyl, pyranyl (including 1,2-pyranyl and 1,4-pyranyl), dihydropyranyl, pyridinyl, piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), and pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, and 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl and p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

A heterocyclyl may also be, without limitation, a bicycle containing two fused rings, such as, for example, naphthyridinyl (including [1,8] naphthyridinyl, and [1,6] naphthyridinyl), thiazolpyrimidinyl, thienopyrimidinyl, pyrimidopyrimidinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, and pyrido[4,3-b]-pyridinyl), pyridopyrimidine, and pteridinyl. Other non-limiting examples of fused-ring heterocycles include benzo-fused

heterocyclyls, such as indolyl, isoindolyl, indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") and isoquinolinyl (also known as "2-benzazinyl")), benzimidazolyl, phthalazinyl, quinoxalinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") and quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including "chromenyl" and "isochromenyl"), benzothiopyranyl (also known as "thiochromenyl"), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", and "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", and "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, and 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl and 1,4-benzisoxazinyl), and tetrahydroisoquinolinyl.

A heterocyclyl may comprise one or more sulfur atoms as ring members; and in some cases, the sulfur atom(s) is oxidized to SO or SO_2. The nitrogen heteroatom(s) in a heterocyclyl may or may not be quaternized, and may or may not be oxidized to N-oxide. In addition, the nitrogen heteroatom(s) may or may not be N-protected.

The number of carbon atoms in a hydrocarbyl moiety can be indicated by the prefix "C_x-C_y," where x is the minimum and y is the maximum number of carbon atoms in the moiety. Thus, for example, "C_1-C_6alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6carbocycle means a carbocycle containing from 3 to 6 carbon ring atoms. A prefix attached to a multiple-component substituent only applies to the first component that immediately follows the prefix. To illustrate, the term "carbocyclylalkyl" contains two components: carbocyclyl and alkyl. Thus, for example, C_3-C_6 carbocyclyl C_1-C_6 alkyl refers to a C_3-C_6 carbocyclyl appended to the parent molecular moiety through a C_1-C_6 alkyl group.

Unless otherwise specified, when a moiety links two other elements in a depicted chemical structure, the leftmost-described component of the moiety is bound to the left element in the depicted structure, and the rightmost-described component of the moiety is bound to the right element in the depicted structure. To illustrate, if the chemical structure is –L–L_S–R_E and L_S is C_1-C_6 alkylene, then the chemical structure is –L–C_1-C_6 alkylene–R_E.

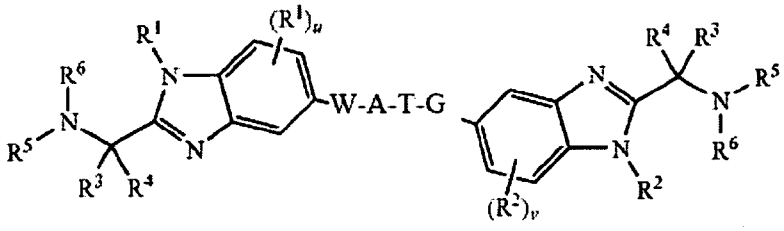
If a moiety in a depicted structure is a bond, then the element left to the moiety is joined directly to the element right to the linking element via a covalent bond. For example, if a chemical structure is depicted as –L–L_S–R_E and L_S is selected as bond, then the chemical structure will be –L–R_E. If two or more adjacent moieties in a depicted structure are bonds, then the element left to these moieties is joined directly to the element right to these linking elements via a covalent bond.

When a chemical formula is used to describe a moiety, the dash(s) indicates the portion of the moiety that has the free valence(s).

If a moiety is described as being "optionally substituted", the moiety may be either substituted or unsubstituted. If a moiety is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that moiety may be either unsubstituted, or substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the moiety, whichever is less. Thus, for example, if a moiety is described as a heterocycle optionally substituted with up to three non-hydrogen radicals, then any heterocycle with less than three substitutable positions will be optionally substituted by up to only as many non-hydrogen radicals as the heterocycle has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) will be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to two non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to two non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only one non-hydrogen radical.

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

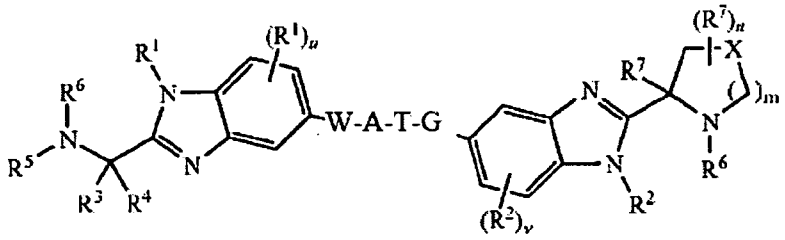
(Ia)



wherein A, W, G, T, u, v, R^1, R^2, R^3, R^4, R^5 and R^6 are as previously defined above.

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

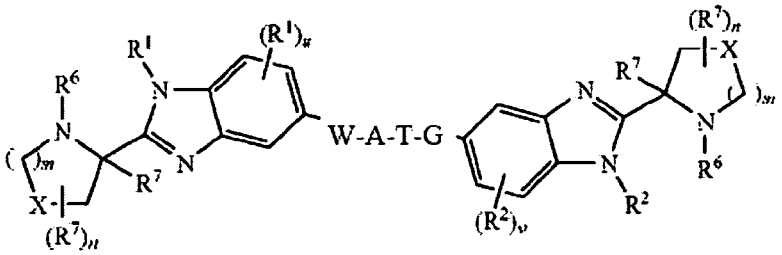
(Ib)



wherein A, W, G, T, u, v, m, n, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as previously defined above.

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

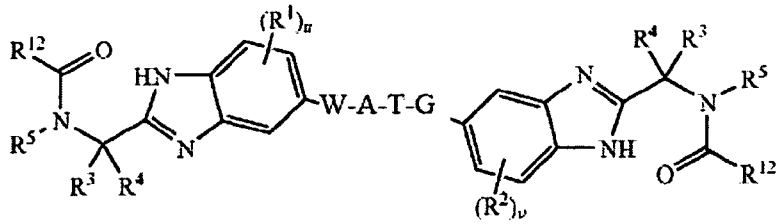
(Ic)



wherein A, W, G, T, u, v, m, n, R^1, R^2, R^6, R^7 and X are as previously defined above.

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

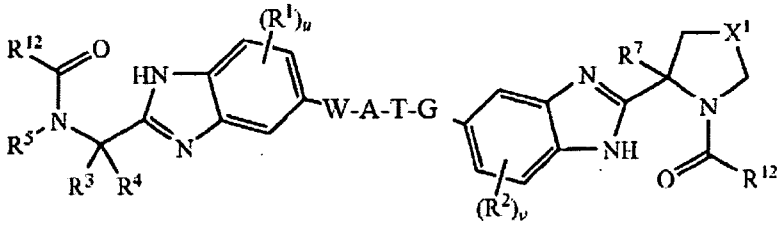
(Id)



wherein A, W, G, T, u, v, R^1, R^2, R^3, R^4, R^5 and R^{12} are as previously defined above.

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

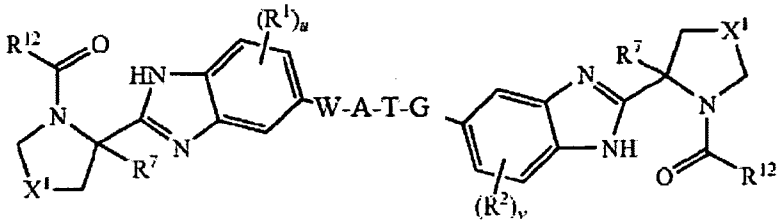
(Ie)



wherein A, W, G, T, u, v, R^1, R^2, R^3, R^4, R^5, R^7 and R^{12} are as previously defined above 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 (If), or a pharmaceutically acceptable salt thereof:

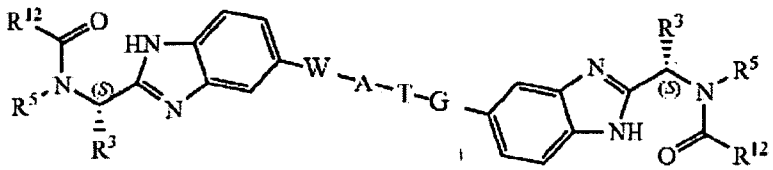
(If)



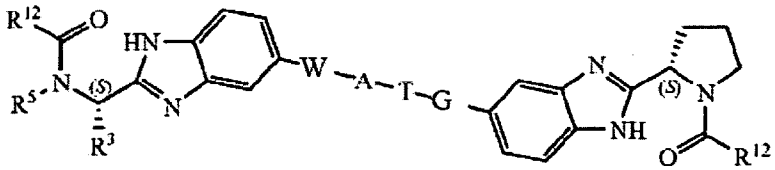
wherein A, W, G, T, u, v, X^1, R^1, R^2, $R^7$and R^{12} are as previously defined above.

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

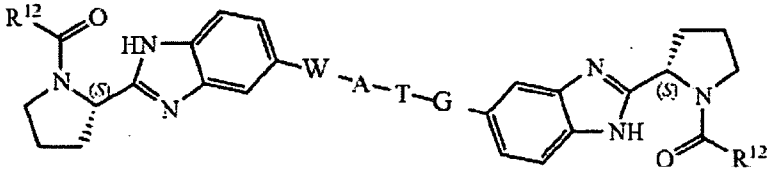
(Ig-1)



(Ig-2)



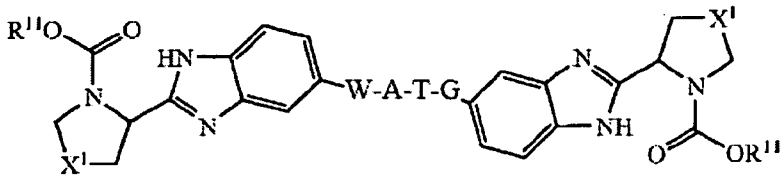
(Ig-3)



wherein A, W, G, T, R^3, R^5, and R^{12} are as previously defined above.

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

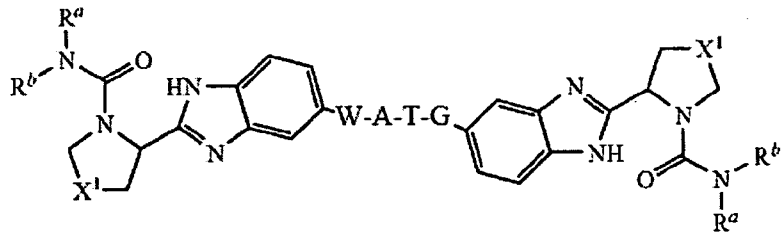
(Ih)



wherein A, W, G, T, X^1, and R^{11} are as previously defined above.

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

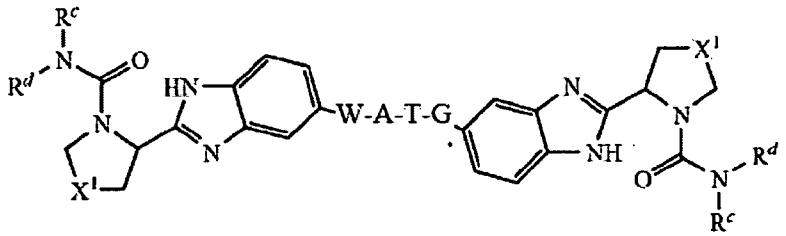
(Ii)



wherein A, W, G, T, X^1, R^a, and R^b are as previously defined above.

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

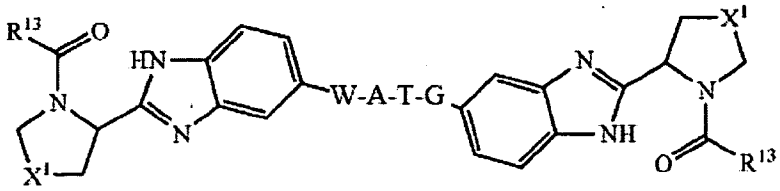
(Ij)



wherein, A, W, G, T, X^1, R^c and R^d are as previously defined above.

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

(Ik)

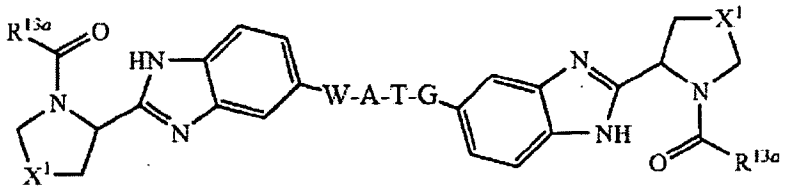


wherein A, Y, Z, X^1, and R^{13} are as previously defined above.

In still another embodiment, the present invention relates to compounds of Formula (Ik), wherein R^{13} is C_1-C_8 alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C_1 - C_4 alkyl); or a pharmaceutically acceptable salt thereof.

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

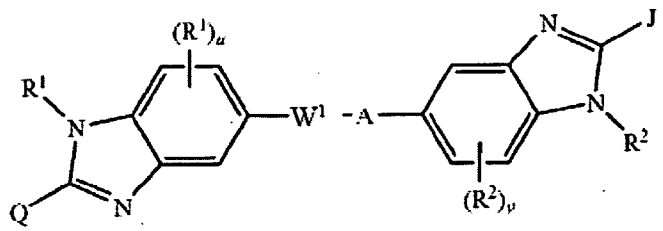
(Il)



wherein A, W, G, T and X^1 are as previously defined above and R^{13a} at each occurrence is independently and optionally substituted C_1-C_8 alkyl; preferably is C_1-C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or O(C_1 - C_4 alkyl).

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

(I-IIa)

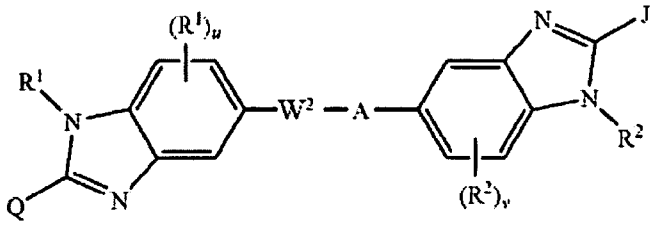


wherein A, Q, J, u, v, R^1, and R^2 are as previously defined above and W^1 is an optionally substituted C_1-C_4 alkyl and wherein at least A or W^1 is substituted with –L–E or $-L_3$-D as defined herein.

In another embodiment, the compound has the Formula (I-IIa), wherein A is a heterocyclic; or a pharmaceutically acceptable salt thereof and and wherein A is substituted with –L–E or $-L_3$-D as defined herein.

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

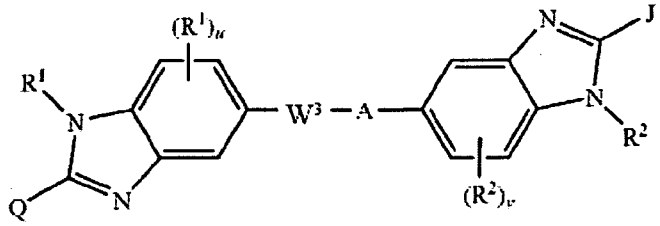
(I-IIb)



wherein A, Q, J, u, v, R^1, and R^2 are as previously defined above and W^2 is an optionally substituted C_2-C_4 alkenyl and wherein at least A or W^2 is substituted with –L–E or $-L_3$-D as defined herein.

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

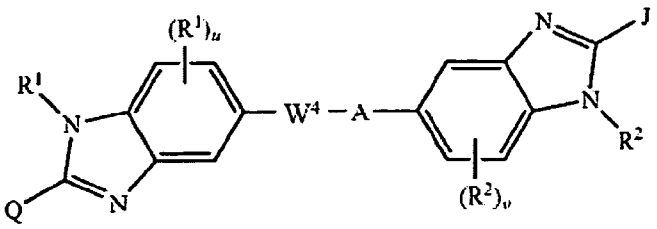
(I-IIc)



wherein A, Q, J, u, v, R^1, and R^2 are as previously defined above and W^3 is an optionally substituted C_2-C_4 alkenyl and wherein at least A or W^3 is substituted with –L–E or $-L_3$-D as defined herein.

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

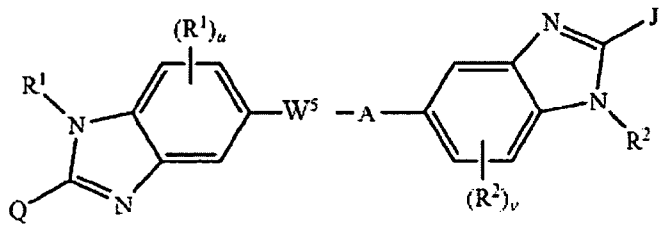
(I-IId)



wherein A, Q, J, u, v, R^1, and R^2 are as previously defined above and W^4 is selected from O and $N(R^{11})$; and R^{11} is as previously defined above, and wherein at least A or W^5 is substituted with –L–E or $-L_3$-D as defined herein.

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

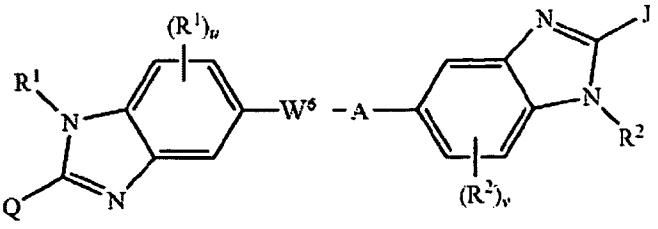
(I-IIe)



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and W^5 is selected from C(O), $S(O)_2$, C(O)O, C(O)N(R^{11}), OC(O)O, OC(O)N(R^{11}), $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$; and R^{11} is as previously defined above and wherein at least A or W^5 is substituted with –L–E or $-L_3$-D as defined herein.

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

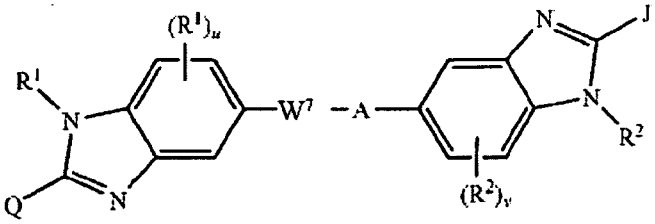
(I-IIf)



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and W^6 is an optionally substituted C_3-C_8 cycloalkyl or optionally substituted C_3-C_8 cycloalkenyl, wherein at least A or W^6 is substituted with –L–E or $-L_3$-D as defined herein.

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

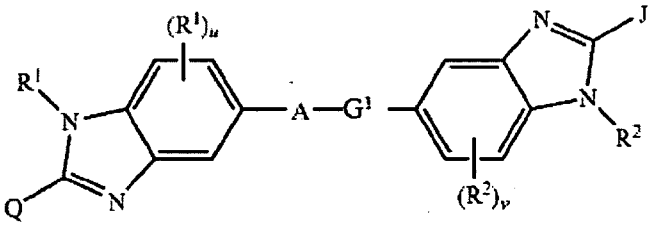
(I-IIg)



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and W^7 is an optionally substituted heterocyclic and wherein at least A or W^7 is substituted with –L–E or $-L_3$-D as defined herein.

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

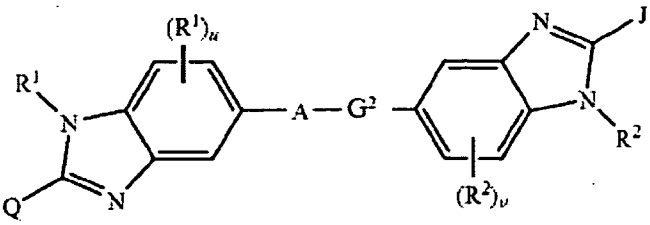
(I-IIIa)



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and G^1 is an optionally substituted aryl.

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

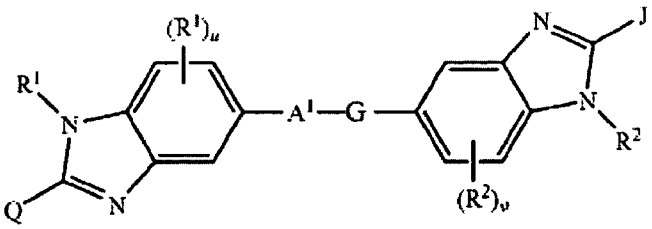
(I-IIIb)



wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and G^2 is an optionally substituted aryl and wherein at least A or G^2 is substituted with –L–E or $-L_3$-D as defined herein.

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

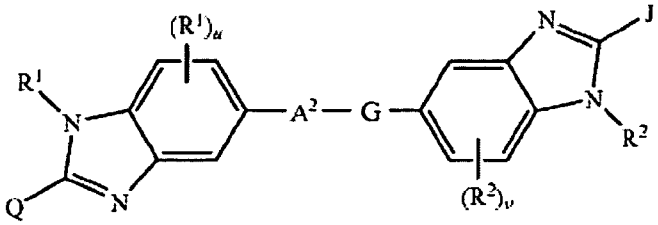
(I-IIIc)



wherein Q, J, u, v, R^1 and R^2 are as previously defined above; G is present and as previously defined above; and A^1 is an optionally substituted aryl and wherein at least G or A^1 is substituted with –L–E or $-L_3$-D as defined herein.

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

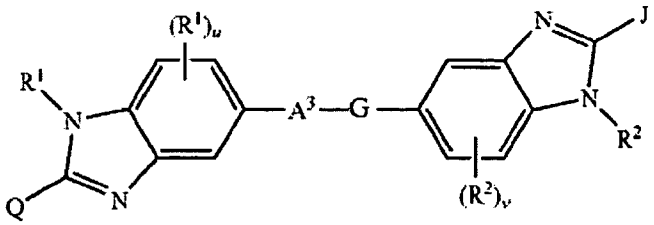
(I-IIId)



wherein Q, J, u, v, R^1 and R^2 are as previously defined above; G is present and as previously defined above; and A^2 is an optionally substituted heteroaryl and wherein at least G or A^2 is substituted with –L–E or $-L_3$-D as defined herein.

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

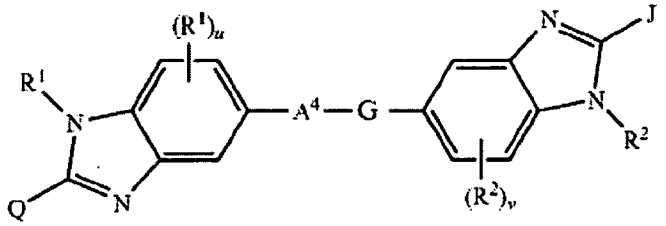
(I-IIIe)



wherein Q, J, u, v, R^1 and R^2 are as previously defined above; G is present and as previously defined above; and A^3 is an optionally substituted heterocyclic and wherein at least G or A^3 is substituted with –L–E or $–L_3$-D as defined herein.

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

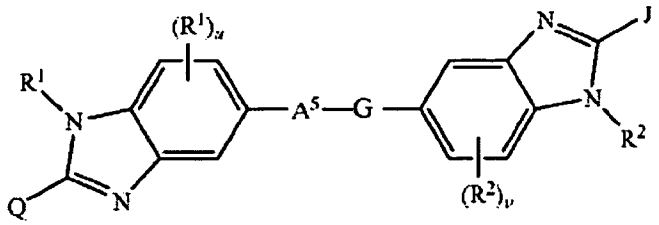
(I-IIIf)



wherein Q, J, u, v, R^1 and R^2 are as previously defined above; G is present and as previously defined above; and A^4 is an optionally substituted C_3-C_8 cycloalkyl and wherein at least G or A^4 is substituted with –L–E or $–L_3$-D as defined herein.

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

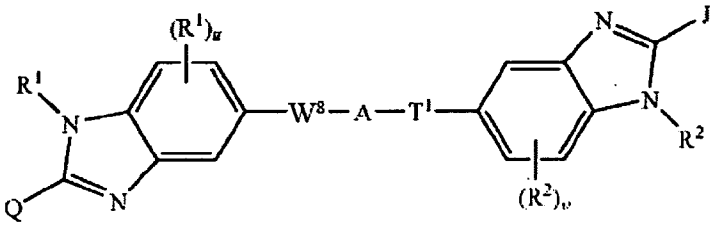
(I-IIIg)



wherein Q, J, u, v, R^1 and R^2 are as previously defined above; G is present and as previously defined above; and A^5 is an optionally substituted C_3-C_8 cycloalkyl and and wherein at least G or A^5 is substituted with –L–E or –L_3-D as defined herein.

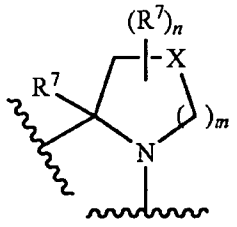
In still another embodiment, the present invention relates to compounds of Formula (I-IVa), or a pharmaceutically acceptable salt thereof:

(I-IVa)

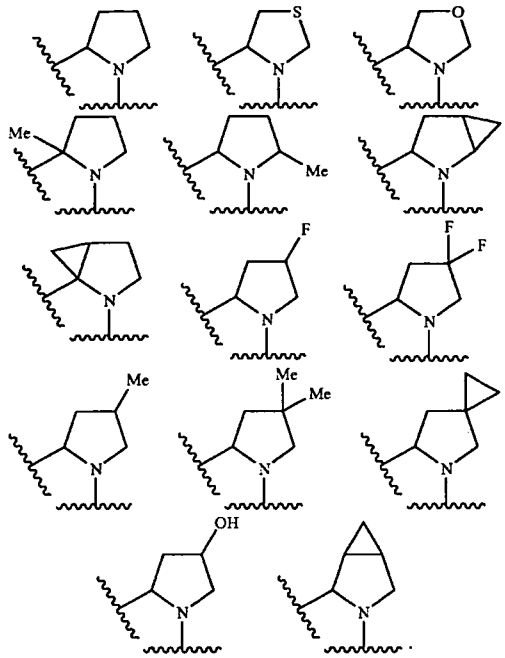


wherein A, Q, J, u, v, R^1 and R^2 are as previously defined above and W^8 and T^1 are each independently linear aliphatic group containing zero to six carbons, optionally contain one or more groups selected from O, N(R^{11}), C(O), S(O)$_2$, C(O)O, and C(O)N(R^{11}); and R^{11} is as previously defined above, and wherein at least one of A, W^8 or T^1 is substituted with –L–E or –L_3-D as defined herein.

In still another embodiment, the present invention relates to compounds of Formula (I), or a pharmaceutically acceptable salt thereof; wherein



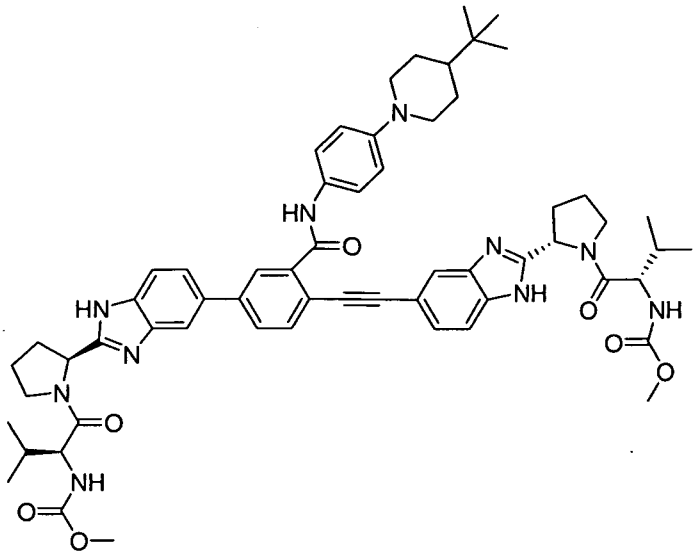
at each occurrence is independently illustrated by one of the following groups:

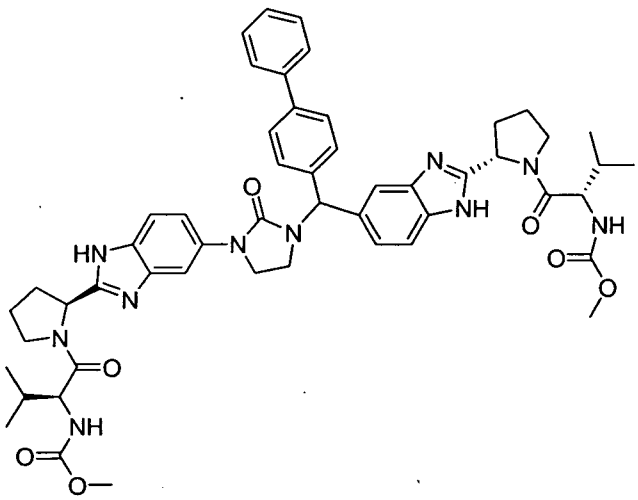


Except for the above definitions provided for –L–E or $-L_3$-D, the remaining substitutents in the compounds having the above Formula I as well as other formulae described above are to be interpreted according to the meaning provided for the substitutents in US Patent Publication 2010/0221215, the contents of which are herein incorporated by reference.

Methods for making compounds of Formula I as well as other formulae described above are described in US Patent Publication 2010/0221215 (see the description of compounds having the formula I) and US Application No. 12/959,941 filed on December 3, 2010, the contents of which are herein each incorporated by reference.

In one embodiment, the present invention features the below compounds.





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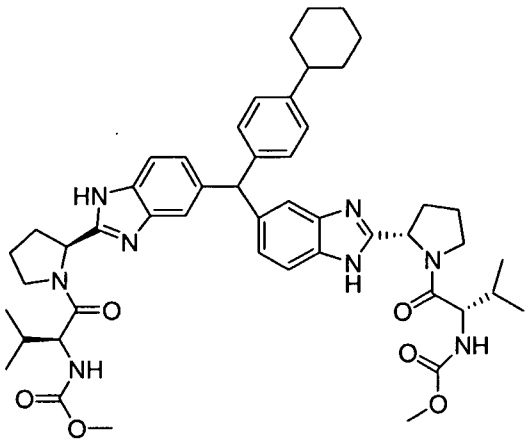
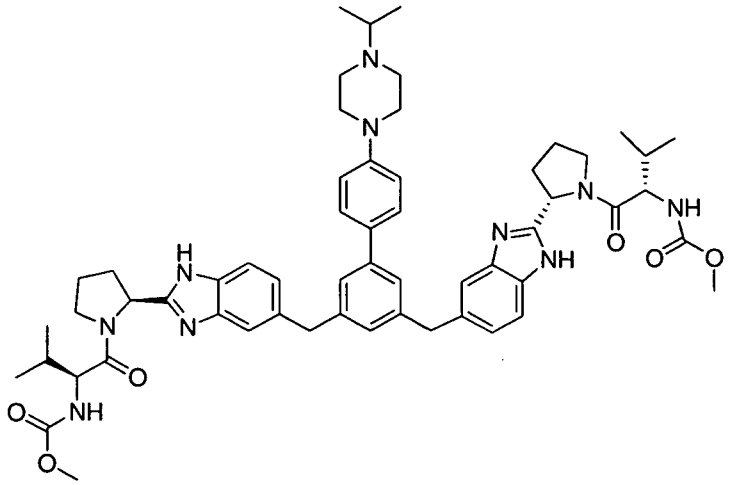
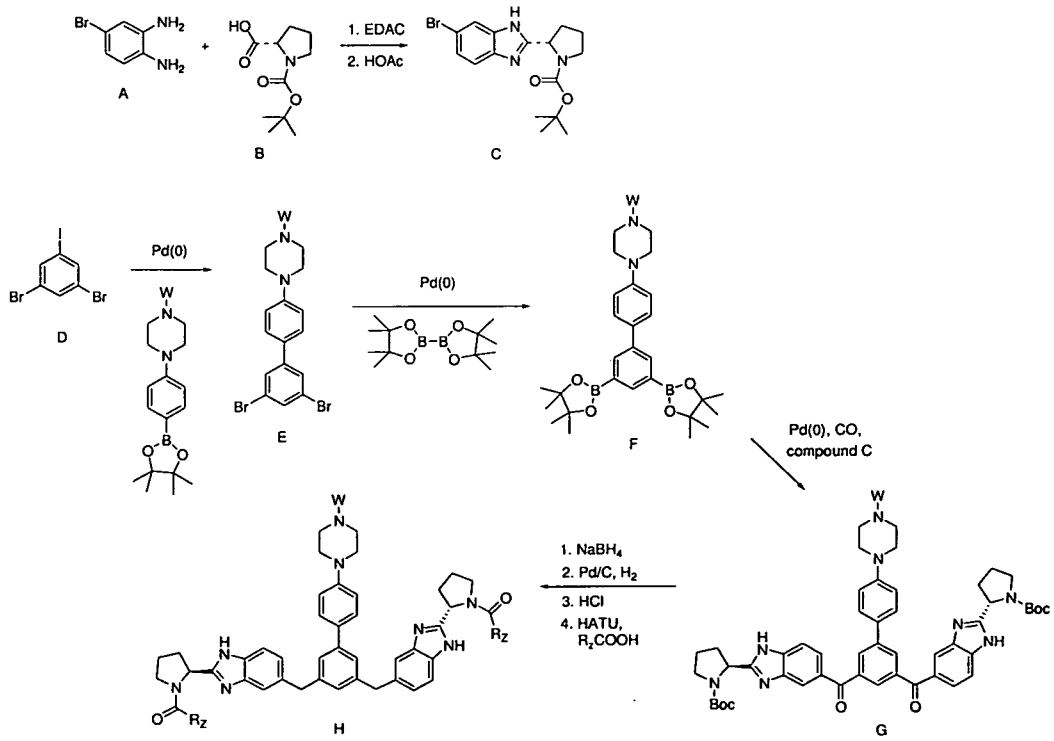




In another embodiment, the compounds of the invention can be prepared according to the following scheme:



wherein R_Z can be, for example, R^{12}; and wherein W can be, for example, hydrogen or R_A.

The compounds of the present invention can be used in the form of salts. Depending on the particular compound, a salt of a compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability under certain conditions or desired solubility in water or oil. In some instances, a salt of a compound may be useful for the isolation or purification of the compound.

Where a salt is intended to be administered to a patient, the salt preferably is pharmaceutically acceptable. Pharmaceutically acceptable salts include, but are not limited to, acid addition salts, base addition salts, and alkali metal salts.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Examples of suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroionic, nitric, carbonic, sulfuric, and phosphoric acid. Examples of suitable organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, b-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts and organic salts. Non-limiting examples of suitable metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other pharmaceutically acceptable metal salts. Such salts may be made, without limitation, from aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc. Non-limiting examples of suitable organic salts can be made from tertiary amines and quaternary amine, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as alkyl halides (e.g., methyl, ethyl, propyl, butyl, decyl, lauryl, myristyl, and stearyl chlorides/bromides/iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

The compounds or salts of the present invention may exist in the form of solvates, such as with water (i.e., hydrates), or with organic solvents (e.g., with methanol, ethanol or acetonitrile to form, respectively, methanolate, ethanolate or acetonitrilate).

The compounds or salts of the present invention may also be used in the form of prodrugs. Some prodrugs are aliphatic or aromatic esters derived from acidic groups on the compounds of the invention. Others are aliphatic or aromatic esters of hydroxyl or amino groups on the compounds of the invention. Phosphate prodrugs of hydroxyl groups are preferred prodrugs.

The compounds of the invention may comprise asymmetrically substituted carbon atoms known as chiral centers. These compounds may exist, without limitation, as single stereoisomers (e.g., single enantiomers or single diastereomer), mixtures of stereoisomers (e.g. a mixture of enantiomers or diastereomers), or racemic mixtures. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that is substantially free from other stereoisomers (e.g., substantially free from other enantiomers or diastereomers). By "substantially free," it means that at least 80% of the compound in a composition is the described stereoisomer; preferably, at least 90% of the compound in a composition is the described stereoisomer; and more preferably, at least 95%, 96%, 97%, 98% or 99% of the compound in a composition is the described stereoisomer. Where the stereochemistry of a chiral carbon is not specified in the chemical structure of a compound, the chemical structure is intended to encompass compounds containing either stereoisomer of the chiral center.

Individual stereoisomers of the compounds of this invention can be prepared using a variety of methods known in the art. These methods include, but are not limited to, stereospecific synthesis, chromatographic separation of diastereomers, chromatographic resolution of enantiomers, conversion of enantiomers in an enantiomeric mixture to diastereomers followed by chromatographically separation of the diastereomers and regeneration of the individual enantiomers, and enzymatic resolution.

Stereospecific synthesis typically involves the use of appropriate optically pure (enantiomerically pure) or substantial optically pure materials and synthetic reactions that do not cause racemization or inversion of stereochemistry at the chiral centers. Mixtures of stereoisomers of compounds, including racemic mixtures, resulting from a synthetic reaction may be separated, for example, by chromatographic techniques as appreciated by those of ordinary skill in the art. Chromatographic resolution of enantiomers can be accomplished by using chiral chromatography resins, many of which are commercially available. In a non-limiting example, racemate is placed in solution and loaded onto the column containing a chiral stationary phase. Enantiomers can then be separated by HPLC.

Resolution of enantiomers can also be accomplished by converting enantiomers in a mixture to diastereomers by reaction with chiral auxiliaries. The resulting diastereomers can be separated by column chromatography or crystallization/re-crystallization. This technique is useful when the compounds to be separated contain a carboxyl, amino or hydroxyl group that will form a salt or covalent bond with the chiral auxiliary. Non-limiting examples of suitable chiral auxiliaries include chirally pure amino acids, organic carboxylic acids or organosulfonic acids. Once the diastereomers

are separated by chromatography, the individual enantiomers can be regenerated. Frequently, the chiral auxiliary can be recovered and used again.

Enzymes, such as esterases, phosphatases or lipases, can be useful for the resolution of derivatives of enantiomers in an enantiomeric mixture. For example, an ester derivative of a carboxyl group in the compounds to be separated can be treated with an enzyme which selectively hydrolyzes only one of the enantiomers in the mixture. The resulting enantiomerically pure acid can then be separated from the unhydrolyzed ester.

Alternatively, salts of enantiomers in a mixture can be prepared using any suitable method known in the art, including treatment of the carboxylic acid with a suitable optically pure base such as alkaloids or phenethylamine, followed by precipitation or crystallization/re-crystallization of the enantiomerically pure salts. Methods suitable for the resolution/separation of a mixture of stereoisomers, including racemic mixtures, can be found in ENANTIOMERS, RACEMATES, AND RESOLUTIONS (Jacques *et al.*, 1981, John Wiley and Sons, New York, NY).

A compound of this invention may possess one or more unsaturated carbon-carbon double bonds. All double bond isomers, such as the cis (Z) and trans (E) isomers, and mixtures thereof are intended to be encompassed within the scope of a recited compound unless otherwise specified. In addition, where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms.

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

Certain compounds of the invention may also exist in zwitterionic form and the invention encompasses each zwitterionic form of these compounds and mixtures thereof.

The compounds of the present invention are generally described herein using standard nomenclature. For a recited compound having asymmetric center(s), it should be understood that all of the stereoisomers of the compound and mixtures thereof are encompassed in the present invention unless otherwise specified. Non-limiting examples of stereoisomers include enantiomers, diastereomers, and cis-transisomers. Where a recited compound exists in various tautomeric forms, the compound is intended to encompass all tautomeric forms. Certain compounds are described herein using general formulas that include variables (e.g., R_A or R_B). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence. If moieties are described as being "independently" selected from a group, each moiety is selected independently from the other. Each moiety therefore can be identical to or different from the other moiety or moieties.

The term "pharmaceutically acceptable" is used adjectivally to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product.

The term "therapeutically effective amount" refers to the total amount of each active substance that is sufficient to show a meaningful patient benefit, e.g. a reduction in viral load.

The term "prodrug" refers to derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active *in vivo*. A prodrug of a compound may be formed in a conventional manner by reaction of a functional group of the compound (such as an amino, hydroxy or carboxy group). Prodrugs often offer advantages of solubility, tissue compatibility, or delayed release in mammals (see, Bungard, H., DESIGN OF PRODRUGS, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Examples of prodrugs include, but are not limited to, acetate, formate, benzoate or other acylated derivatives of alcohol or amine functional groups within the compounds of the invention.

The term "solvate" refers to the physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association often includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, and methanolates.

The present invention also features pharmaceutical compositions comprising the compounds of the invention. A pharmaceutical composition of the present invention can comprise one or more compounds of the invention.

In addition, the present invention features pharmaceutical compositions comprising pharmaceutically acceptable salts, solvates, or prodrugs of the compounds of the invention. Without limitation, pharmaceutically acceptable salts can be zwitterions or derived from pharmaceutically acceptable inorganic or organic acids or bases. Preferably, a pharmaceutically acceptable salt retains the biological effectiveness of the free acid or base of the compound without undue toxicity, irritation, or allergic response, has a reasonable benefit/risk ratio, is effective for the intended use, and is not biologically or otherwise undesirable.

The present invention further features pharmaceutical compositions (a) one or more compounds of the present invention (namely, one or more of compounds having Formula (I) or salts, solvates or prodrugs thereof; and (b) another therapeutic agent. By way of illustration not limitation, these other therapeutic agents can be selected from antiviral agents (e.g., anti-HIV agents, anti-HBV agents, or other anti-HCV agents such as HCV protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, IRES inhibitors or NS5A inhibitors), anti-bacterial agents, anti-fungal agents, immunomodulators, anti-cancer or chemotherapeutic agents, anti-inflammation agents, antisense

RNA, siRNA, antibodies, or agents for treating cirrhosis or inflammation of the liver. Specific examples of these other therapeutic agents include, but are not limited to, ribavirin, α-interferon, β-interferon, pegylated interferon-α, pegylated interferon-lambda, ribavirin, viramidine, R-5158, nitazoxanide, amantadine, Debio-025, NIM-811, R7128, R1626, R4048, T-1106, PSI-7851, PF-00868554, ANA-598, IDX184, IDX102, IDX375, GS-9190, VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052, BMS-791325, BMS-650032, GS-9132, ACH-1095, AP-H005, A-831, A-689, AZD2836, telaprevir, boceprevir, ITMN-191, BI-201335, VBY-376, VX-500 (Vertex), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche), PSI-7851 (Pharmasset), MK-3281 (Merck), PF-868554 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), ABT-450 (Abbott/Enanta), ABT-072 (Abbott), ABT-333 (Abbott), Albuferon (Novartis), ritonavir, another cytochrome P450 monooxygenase inhibitor, or any combination thereof.

In one embodiment, a pharmaceutical composition of the present invention comprises (a) one or more compounds of the present invention (namely, one or more of compounds having Formula (I)), or salts, solvates or prodrugs thereof; and (b) one or more other antiviral agents.

In another embodiment, a pharmaceutical composition of the present invention comprises (a) one or more compounds of the present invention (namely, one or more of compounds having Formula (I)), or salts, solvates or prodrugs thereof; and (b) and one or more other anti-HCV agents, such as an agent selected from HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, IRES inhibitors, or NS5A inhibitors.

In yet another embodiment, a pharmaceutical composition of the present invention comprises (a) one or more compounds of the present invention (namely, one or more of compounds having Formula (I)), or salts, solvates or prodrugs thereof; and (b) one or more other antiviral agents, such as anti-HBV, anti-HIV agents, or anti-hepatitis A, anti-hepatitis D, anti-hepatitis E or anti-hepatitis G agents. Non-limiting examples of anti-HBV agents include adefovir, lamivudine, and tenofovir. Non-limiting examples of anti-HIV drugs include ritonavir, lopinavir, indinavir, nelfinavir, 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-1249, or other HIV protease, reverse transcriptase, integrase or fusion inhibitors. Any other desirable antiviral agents can also be included in a pharmaceutical composition of the present invention, as appreciated by those skilled in the art.

A pharmaceutical composition of the present invention typically includes a pharmaceutically acceptable carrier or excipient. Non-limiting examples of suitable pharmaceutically acceptable

carriers/excipients include sugars (e.g., lactose, glucose or sucrose), starches (e.g., corn starch or potato starch), cellulose or its derivatives (e.g., sodium carboxymethyl cellulose, ethyl cellulose or cellulose acetate), oils (e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil or soybean oil), glycols (e.g., propylene glycol), buffering agents (e.g., magnesium hydroxide or aluminum hydroxide), agar, alginic acid, powdered tragacanth, malt, gelatin, talc, cocoa butter, pyrogen-free water, isotonic saline, Ringer's solution, ethanol, or phosphate buffer solutions. Lubricants, coloring agents, releasing agents, coating agents, sweetening, flavoring or perfuming agents, preservatives, or antioxidants can also be included in a pharmaceutical composition of the present invention.

The pharmaceutical compositions of the present invention can be formulated based on their routes of administration using methods well known in the art. For example, a sterile injectable preparation can be prepared as a sterile injectable aqueous or oleagenous suspension using suitable dispersing or wetting agents and suspending agents. Suppositories for rectal administration can be prepared by mixing drugs with a suitable nonirritating excipient such as cocoa butter or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drugs. Solid dosage forms for oral administration can be capsules, tablets, pills, powders or granules. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose lactose or starch. Solid dosage forms may also comprise other substances in addition to inert diluents, such as lubricating agents. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or elixirs containing inert diluents commonly used in the art. Liquid dosage forms may also comprise wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents. The pharmaceutical compositions of the present invention can also be administered in the form of liposomes, as described in U.S. Patent No. 6,703,403. Formulation of drugs that are applicable to the present invention is generally discussed in, for example, Hoover, John E., REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, PA: 1975), and Lachman, L., eds., PHARMACEUTICAL DOSAGE FORMS (Marcel Decker, New York, N.Y., 1980).

Any compound described herein (i.e, any compounds having a formula (I) – Formula (XXII)), or a pharmaceutically acceptable salt thereof, can be used to prepared pharmaceutical compositions of the present invention.

The present invention further features methods of using the compounds of the present (namely, one or more of compounds having Formula (I)), or salts, solvates or prodrugs thereof to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus with an effective amount of a compound of the present invention (namely, one or more of compounds having Formula (I) or salts, solvates or prodrugs thereof thereby inhibiting the replication of HCV virus in the

cells. As used herein, "inhibiting" means significantly reducing, or abolishing, the activity being inhibited (e.g., viral replication). In many cases, representative compounds of the present invention can reduce the replication of HCV virus (e.g., in an HCV replicon assay as described above) by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more.

The compounds of the present invention may inhibit one or more HCV subtypes. Examples of HCV subtypes that are amenable to the present invention include, but are not be limited to, HCV genotypes 1, 2, 3, 4, 5 and 6, including HCV genotypes 1a, 1b, 2a, 2b, 2c or 3a. In one embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of HCV genotype 1a. In another embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of HCV genotype 1b. In still another embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of both HCV genotypes 1a and 1b.

The present invention also features methods of using the compounds of the present invention (or salts, solvates or prodrugs thereof) to treat HCV infection. The methods typically comprise administering a therapeutic effective amount of a compound of the present invention (or a salt, solvate or prodrug thereof), or a pharmaceutical composition comprising the same, to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient. As used herein, the term "treating" refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition, or one or more symptoms of such disorder or condition to which such term applies. The term "treatment" refers to the act of treating. In one embodiment, the methods comprise administering a therapeutic effective amount of two or more compounds of the present invention (or salts, solvates or prodrugs thereof), or a pharmaceutical composition comprising the same, to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient.

A compound of the present invention (or a salt, solvate or prodrug thereof) can be administered as the sole active pharmaceutical agent, or in combination with another desired drug, such as other anti-HCV agents, anti-HIV agents, anti-HBV agents, anti-hepatitis A agents, anti-hepatitis D agents, anti-hepatitis E agents, anti-hepatitis G agents, or other antiviral drugs. Any compound described herein, or a pharmaceutically acceptable salt thereof, can be employed in the methods of the present invention.

A compound of the present invention (namely, one or more of compounds having Formula (I) or salts, solvates or prodrugs thereof can be administered to a patient in a single dose or divided doses. A typical daily dosage can range, without limitation, from 0.1 to 200 mg/kg body weight, such as from 0.25 to 100 mg/kg body weight. Single dose compositions can contain these amounts or submultiples thereof to make up the daily dose. Preferably, each dosage contains a sufficient amount of a compound of the present invention that is effective in reducing the HCV viral load in the blood or liver of the patient. The amount of the active ingredient, or the active ingredients that are combined,

to produce a single dosage form may vary depending upon the host treated and the particular mode of administration. It will be understood that the specific dose level 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, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The present invention further features methods of using the pharmaceutical compositions of the present invention to treat HCV infection. The methods typically comprise administering a pharmaceutical composition of the present invention to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient. Any pharmaceutical composition described herein can be used in the methods of the present invention.

In addition, the present invention features use of the compounds or salts of the present invention for the manufacture of medicaments for the treatment of HCV infection. Any compound described herein, or a pharmaceutically acceptable salt thereof, can be used to make medicaments of the present invention.

The compounds of the present invention can also be isotopically substituted. Preferred isotopic substitution include substitutions with stable or nonradioactive isotopes such as deuterium, ^{13}C, ^{15}N or ^{18}O. Incorporation of a heavy atom, such as substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. In one example, at least 10 mol % of hydrogen in a compound of the present invention is substituted with deuterium. In another example, at least 25 mole % of hydrogen in a compound of the present invention is substituted with deuterium. In a further example, at least 50, 60, 70, 80 or 90 mole % of hydrogen in a compound of the present invention is substituted with deuterium. The natural abundance of deuterium is about 0.015%. Deuterium substitution or enrichment can be achieved, without limitation, by either exchanging protons with deuterium or by synthesizing the molecule with enriched or substituted starting materials. Other methods known in the art can also be used for isotopic substitutions.

The compounds of the present invention can also be isotopically substituted. Preferred isotopic substitution include substitutions with stable or nonradioactive isotopes such as deuterium, ^{13}C, ^{15}N or ^{18}O. Incorporation of a heavy atom, such as substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. In one example, at least 10 mol % of hydrogen in a compound of the present invention is substituted with deuterium. In another example, at least 25 mole % of hydrogen in a compound of the present invention is substituted with deuterium. In a further example, at least 50, 60, 70, 80 or 90 mole % of hydrogen in a compound of the present invention is substituted with deuterium. The natural abundance of deuterium is about 0.015%. Deuterium substitution or enrichment can be achieved, without limitation, by either exchanging protons with deuterium or by synthesizing the molecule with

enriched or substituted starting materials. Other methods known in the art can also be used for isotopic substitutions.

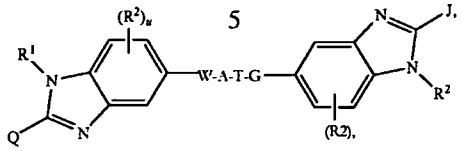
The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference.

The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A compound of Formula (I) or pharmaceutically acceptable salts thereof:

(I)



wherein:

A is a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkenyl, wherein A is substituted with –L–E or –L_3-D, which are defined below;

W is (a) absent; or (b) an optionally substituted aliphatic group; wherein W, when present, is substituted with –L–E or –L_3-D, which are defined below;

T is (a) absent; or (b) an optionally substituted linear aliphatic group containing zero to eight carbons; wherein T, when present, is substituted with –L–E or –L_3-D, which are defined below;

G is (a) absent; or (b) independently selected from optionally substituted aryl and optionally substituted heteroaryl; wherein G, when present, is substituted with –L–E or –L_3-D, which are defined below;

wherein one or two of W, G, and T can optionally be absent;

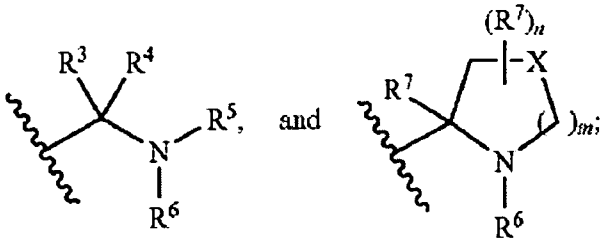
R^1 and R^2 at each occurrence are each independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C_1-C_4 alkyl, —O—R^{11}, —NR^aR^b, —$C(O)R^{11}$, —CO_2R^{11}, and —$C(O)NR^aR^b$; wherein at least one of R^1 and R^2 can be optionally substituted with –L–E or –L_3-D as defined below;

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; 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, cycloalkyl;

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};

R^{12} at each occurrence is independently selected from the group consisting of: —O—R^{11}, —NR^cR^d;

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; or

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 (R13)$_2$, and— $S(O)_2N(R^{13})_2$;

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), SO_2, and $C(R^7)_2$, provided that when m is 0, X is $C(R^7)_2$; or

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, —C_1-C_4 alkyl, cyano, —O —R^{11}, —NR^aR^b, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted with —C_1-C_4 alkyl; 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 C_3-C_8, cycloalkyl or optionally substituted heterocyclic ring; 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 C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring;

L–E or –L_3-D are as follows:

E is (i) C_3-C_{14} carbocycle or 3- to 14-membered heterocycle, and is optionally substituted with one or more R_A; or (ii) E is $-L_S-R_E$;

L is $-L_S-$, $-L_S-O-L_S'-$, $-L_S-C(O)-L_S'-$, $-L_S-S(O)_2-L_S'-$, $-L_S-S(O)-L_S'-$, $-L_S-OS(O)_2-L_S'-$, $-L_S-S(O)_2O-L_S'-$, $-L_S-OS(O)-L_S'-$, $-L_S-S(O)O-L_S'-$, $-L_S-C(O)O-L_S'-$, $-L_S-OC(O)-L_S'-$, $-L_S-OC(O)O-L_S'-$, $-L_S-C(O)N(R_B)-L_S'-$, $-L_S-N(R_B)C(O)-L_S'-$, $-L_S-C(O)N(R_B)O-L_S'-$, $-L_S-N(R_B)C(O)O-L_S'-$, $-L_S-OC(O)N(R_B)-L_S'-$, $-L_S-C(O)N(R_B)N(R_B')-L_S'-$, $-L_S-S-L_S'-$, $-L_S-C(S)-L_S'-$, $-L_S-C(S)O-L_S'-$, $-L_S-OC(S)-L_S'-$, $-L_S-C(S)N(R_B)-L_S'-$, $-L_S-N(R_B)-L_S'-$, $-L_S-N(R_B)C(S)-L_S'-$, $-L_S-N(R_B)S(O)-L_S'-$, $-L_S-N(R_B)S(O)_2-L_S'-$, $-L_S-S(O)_2N(R_B)-L_S'-$, $-L_S-S(O)N(R_B)-L_S'-$, $-L_S-C(S)N(R_B)O-L_S'-$, $-L_S-C(O)N(R_B)C(O)-L_S'-$, $-L_S-N(R_B)C(O)N(R_B')-L_S'-$, $-L_S-N(R_B)SO_2N(R_B')-L_S'-$, $-L_S-N(R_B)S(O)N(R_B')-L_S'-$, or $-L_S-C(S)N(R_B)N(R_B')-L_S'-$;

L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L;

R_A is independently selected at each occurrence from halogen, oxo, thioxo, hydroxy, mercapto, nitro, cyano, amino, carboxy, formyl, phosphonoxy, or phosphono; or $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6 carbocycle or 3- to 6-membered heterocycle; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle; wherein each C_3-C_6 carbocycle or 3- to 6-membered heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, -

SO_2R_S, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl;

L_3 is bond or $-L_S-K-L_S'-$, wherein K is selected from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, or $-N(R_B)S(O)N(R_B')-$;

D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle which is substituted with J and optionally substituted with one or more R_A, where J is C_3-C_{12} carbocycle or 3- to 12-membered heterocycle and is optionally substituted with one or more R_A, or J is $-SF_5$; or D is hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$, wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)N($R_S$'$R_S$''), –N($R_S$)$SO_2R_S$', –$SO_2$N($R_S$$R_S$'), –N($R_S$)$SO_2$N($R_S$'$R_S$''), –N($R_S$)S(O)N($R_S$'$R_S$''), –OS(O)–$R_S$, –$OS(O)_2$–$R_S$, –$S(O)_2OR_S$, –S(O)O$R_S$, –OC(O)O$R_S$, –N($R_S$)C(O)O$R_S$', –OC(O)N($R_S$$R_S$'), –N($R_S$)S(O)–$R_S$', –S(O)N($R_S$$R_S$'), –$P(O)(OR_S)_2$, or –C(O)N($R_S$)C(O)–$R_S$'; or C_1-C_6alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6 carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C(O)OR_S, or –N($R_S$$R_S$');

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; or C_3-C_6 carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl; wherein two adjacent R_L, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

L_S and L_S' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –O–C_1-C_6 alkyl, –O–C_1-C_6 alkylene–O–C_1-C_6 alkyl, or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl.