ANTI-VIRAL COMPOUNDS

This claims the benefit of U.S. Provisional Application No. 61/169,449, filed April 15, 2009, and U.S. Provisional Application No. 61/222,591, filed July 2, 2009, the content of which are fully incorporated by reference.

FIELD

The present invention relates to compounds effective in inhibiting replication of Hepatitis C virus ("HCV"). The present invention also relates to compositions comprising these compounds and methods of using these compounds to treat HCV infection.

BACKGROUND

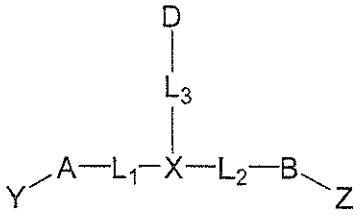
HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. HCV has enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins in one single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides encoding 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 disclosure~~invention~~ features compounds of Formulae I, I_A, I_B and I_C, and pharmaceutically acceptable salts thereof. These compounds and salts are capable of inhibiting the replication of HCV and therefore can be used to treat HCV infection.

In a first aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

A and B are each independently C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and are each independently optionally substituted with one or more R_A;

D is C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is optionally substituted with one or more R_A; or D is R_D;

X is N;

L_1 and L_2 are each independently selected from a 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 substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

L_3 is bond;

Y is selected from $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, or $-L_K-E$;

R_1 and R_2 are each independently R_C, and R_5 is R_B; or R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_3, R_4, R_6, and R_7 are each independently R_C; or R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, or $-L_K-E$;

R_8 and R_9 are each independently R_C, and R_{12} is R_B; or R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10}, R_{11}, R_{13}, and R_{14} are each independently R_C; or R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

L_K is independently selected at each occurrence from a bond; $-N(R_B)C(O)-L_S-$; $-C(O)N(R_B)-L_S-$; or C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

E is independently selected at each occurrence from C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is independently optionally substituted at each occurrence with one or more R_A;

T and T' are each independently selected at each occurrence from a bond, $-L_S-$, $-L_S-M-L_S'-$, $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from a bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $-L_A$, 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, optionally form a C_3-C_{10}carbocycle or 3- to 10-membered heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from R_A;

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$$R_S$'), –C(O)N($R_S$)C(O)–$R_S$', C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_F is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, 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;

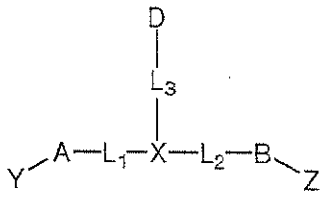
L_A is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

L_S, L_S' and L_S'' are each independently selected at each occurrence from a 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 substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen or R_T;

R_T is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_F, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

In a second aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

A and B are each independently phenyl, and are each independently optionally substituted with one or more R_A;

D is C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is optionally substituted with one or more R_A; or D is selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

X is N;

L_1 and L_2 are $-(CH_2)-$, and are each independently optionally substituted with one or more substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

L_3 is bond;

Y is selected from $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$ or $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$;

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$ or $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

T is each independently selected at each occurrence from a bond, $-L_S-$, $-L_S-M-L_S'-$, $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from a bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, -

$N(R_B)C(O)O–$, $–OC(O)N(R_B)–$, $–N(R_B)S(O)–$, $–N(R_B)S(O)_2–$, $–S(O)N(R_B)–$, $–S(O)_2N(R_B)–$, $–C(O)N(R_B)C(O)–$, $–N(R_B)C(O)N(R_B')–$, $–N(R_B)SO_2N(R_B')–$, $–N(R_B)S(O)N(R_B')–$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from R_A;

R_E is independently selected at each occurrence from $–O–R_S$, $–S–R_S$, $–C(O)R_S$, $–OC(O)R_S$, $–C(O)OR_S$, $–N(R_SR_S')$, $–S(O)R_S$, $–SO_2R_S$, $–C(O)N(R_SR_S')$, $–N(R_S)C(O)R_S'$, $–N(R_S)C(O)N(R_S'R_S'')$, $–N(R_S)SO_2R_S'$, $–SO_2N(R_SR_S')$, $–N(R_S)SO_2N(R_S'R_S'')$, $–N(R_S)S(O)N(R_S'R_S'')$, $–OS(O)–R_S$, $–OS(O)_2–R_S$, $–S(O)_2OR_S$, $–S(O)OR_S$, $–OC(O)OR_S$, $–N(R_S)C(O)OR_S'$, $–OC(O)N(R_SR_S')$, $–N(R_S)S(O)–R_S'$, $–S(O)N(R_SR_S')$, $–C(O)N(R_S)C(O)–R_S'$, C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $–O–R_B$, $–S–R_B$, $–N(R_BR_B')$, $–OC(O)R_B$, $–C(O)OR_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_F is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, 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_A is independently selected at each occurrence from 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, R_T, $–O–R_S$, $–S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

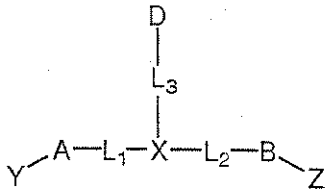
L_S, L_S' and L_S'' are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, C_2-C_6alkenylene, or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more substituents selected from

halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen or R_T;

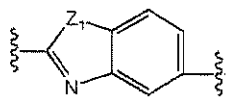
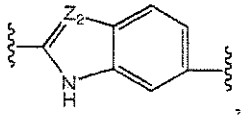
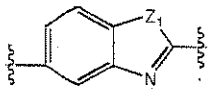
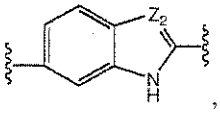
R_T is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_F, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

In a third aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

A is  or , B is  or , Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_2 is independently selected at each occurrence from N or CH, wherein A and B are each independently optionally substituted with one or more R_A;

D is C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is optionally substituted with one or more R_A; or D is selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

X is N;

L_1 and L_2 are -(CH_2)-, and are each independently optionally substituted with one or more substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

L_3 is bond;

Y is selected from –C($R_1$$R_2$)N($R_5$)–T–$R_D$ or –C($R_3$$R_4$)C($R_6$$R_7$)–T–$R_D$,

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $-C(R_8R_9)N(R_{12})-T-R_D$ or $-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

T is each independently selected at each occurrence from a bond, $-L_S-$, $-L_S-M-L_S'-$, $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from a bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from R_A;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-C(O)N(R_S)C(O)-R_S'$, C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $-O-R_B$, $-S-R_B$, $-N(R_BR_B')$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_F is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, 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;

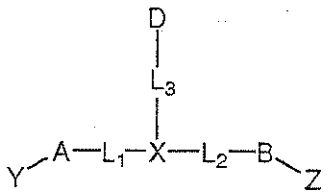
L_A is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

L_S, L_S' and L_S'' are each independently selected at each occurrence from a 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 substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen or R_T;

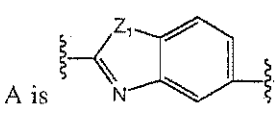
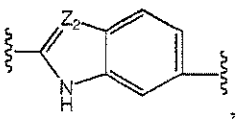
R_T is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_F, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

In a fourth aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

A is  or , Z_1 is selected from O, S, NH or CH_2, Z_2 is selected from N or CH, and A is optionally substituted with one or more R_A;

B is phenyl, and is optionally substituted with one or more R_A;

D is C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is optionally substituted with one or more R_A; or D is selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from halogen, R_T, –O–R_S, –

$S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

X is N;

L_1 and L_2 are $-(CH_2)-$, and are each independently optionally substituted with one or more substituents selected from halogen, R_T, $–O–R_S$, $–S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

L_3 is bond;

Y is selected from $–C(R_1R_2)N(R_5)–T–R_D$ or $–C(R_3R_4)C(R_6R_7)–T–R_D$,

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $–N(R_B)C(O)C(R_8R_9)N(R_{12})–T–R_D$ or $–N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

T is each independently selected at each occurrence from a bond, $–L_S–$, $–L_S–M–L_S'–$, $–L_S–M–L_S'–M'–L_S''–$, wherein M and M' are each independently selected at each occurrence from a bond, $–O–$, $–S–$, $–N(R_B)–$, $–C(O)–$, $–S(O)_2–$, $–S(O)–$, $–OS(O)–$, $–OS(O)_2–$, $–S(O)_2O–$, $–S(O)O–$, $–C(O)O–$, $–OC(O)–$, $–OC(O)O–$, $–C(O)N(R_B)–$, $–N(R_B)C(O)–$, $–N(R_B)C(O)O–$, $–OC(O)N(R_B)–$, $–N(R_B)S(O)–$, $–N(R_B)S(O)_2–$, $–S(O)N(R_B)–$, $–S(O)_2N(R_B)–$, $–C(O)N(R_B)C(O)–$, $–N(R_B)C(O)N(R_B')–$, $–N(R_B)SO_2N(R_B')–$, $–N(R_B)S(O)N(R_B')–$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_T;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_T;

R_D is each independently selected at each occurrence from R_A;

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$$R_S$'), –C(O)N($R_S$)C(O)–$R_S$', C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_F is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, 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_A is independently selected at each occurrence from 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, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

L_S, L_S' and L_S'' are each independently selected at each occurrence from a 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 substituents selected from halogen, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen or R_T;

R_T is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_F, –O–R_B, –S–R_B, –N($R_B$$R_B$'), –OC(O)$R_B$, –C(O)O$R_B$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

The present disclosure~~invention~~ also features compositions comprising the compounds or salts of the present disclosure~~invention~~. The compositions can also include other therapeutic agents, such as HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

The present disclosure~~invention~~ further features methods of using the compounds or salts of the present disclosure~~invention~~ to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus

with a compound or salt of the present disclosure~~invention~~, thereby inhibiting the replication of HCV virus in the cells.

In addition, the present disclosure~~invention~~ features methods of using the compounds or salts of the present disclosure~~invention~~, or compositions comprising the same, to treat HCV infection. The methods comprise administering a compound or salt of the present disclosure~~invention~~, or a pharmaceutical composition comprising the same, to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

The present disclosure~~invention~~ also features use of the compounds or salts of the present disclosure~~invention~~ for the manufacture of medicaments for the treatment of HCV infection.

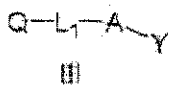
Furthermore, the present disclosure~~invention~~ features processes of making the compounds or salts of the disclosure~~invention~~.

In a fifth aspect, there is provided a process of making a compound as defined above, comprising the step of: coupling a compound of Formula II



II

to a compound of Formula III



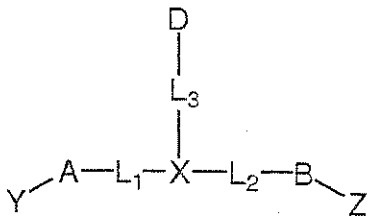
III ,

wherein Q is halo, and A, D, L_1, L_3, and Y are as defined above.

Other features, objects, and advantages of the present disclosure~~invention~~ are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the disclosure~~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

The present invention features compounds having Formula I, and pharmaceutically acceptable salts thereof,



I

wherein:

A and B are each independently C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and are each independently optionally substituted with one or more R_A;

D is C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is optionally substituted with one or more R_A; or D is R_D;

X is $C(R_C)$ or N;

L_1 and L_2 are each independently selected from a 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 substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, –

R_8 and R_9 are each independently R_C, and R_{12} is R_B; or R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10}, R_{11}, R_{13}, and R_{14} are each independently R_C; or R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

L_K is independently selected at each occurrence from a bond; $-N(R_B)C(O)-L_S-$; $-C(O)N(R_B)-L_S-$; or C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

E is independently selected at each occurrence from C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, and is independently optionally substituted at each occurrence with one or more R_A;

T and T' are each independently selected at each occurrence from a bond, $-L_S-$, $-L_S-M-L_S'-$, $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from a bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $-L_A$, 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, optionally form a C_3-C_{10}carbocycle or 3- to 10-membered heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from ~~hydrogen or~~ R_A;

$N(R_B)C(O)O–$, $–OC(O)N(R_B)–$, $–N(R_B)S(O)–$, $–N(R_B)S(O)_2–$, $–S(O)N(R_B)–$, $–S(O)_2N(R_B)–$, $–C(O)N(R_B)C(O)–$, $–N(R_B)C(O)N(R_B')–$, $–N(R_B)SO_2N(R_B')–$, $–N(R_B)S(O)N(R_B')–$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from ~~hydrogen or~~ R_A;

R_E is independently selected at each occurrence from $–O–R_S$, $–S–R_S$, $–C(O)R_S$, $–OC(O)R_S$, $–C(O)OR_S$, $–N(R_SR_S')$, $–S(O)R_S$, $–SO_2R_S$, $–C(O)N(R_SR_S')$, $–N(R_S)C(O)R_S'$, $–N(R_S)C(O)N(R_S'R_S'')$, $–N(R_S)SO_2R_S'$, $–SO_2N(R_SR_S')$, $–N(R_S)SO_2N(R_S'R_S'')$, $–N(R_S)S(O)N(R_S'R_S'')$, $–OS(O)–R_S$, $–OS(O)_2–R_S$, $–S(O)_2OR_S$, $–S(O)OR_S$, $–OC(O)OR_S$, $–N(R_S)C(O)OR_S'$, $–OC(O)N(R_SR_S')$, $–N(R_S)S(O)–R_S'$, $–S(O)N(R_SR_S')$, $–C(O)N(R_S)C(O)–R_S'$, C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $–O–R_B$, $–S–R_B$, $–N(R_BR_B')$, $–OC(O)R_B$, $–C(O)OR_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

R_F is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, 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_A is independently selected at each occurrence from 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, R_T, $–O–R_S$, $–S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

L_S, L_S' and L_S'' are each independently selected at each occurrence from a 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 substituents selected from

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $-C(R_8R_9)N(R_{12})-T-R_D$ or $-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

T is each independently selected at each occurrence from a bond, $-L_S-$, $-L_S-M-L_S'-$, $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from a bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_F;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from ~~hydrogen or~~ R_A;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-C(O)N(R_S)C(O)-R_S'$, C_3-C_{10}carbocyclyl, or 3- to 10-membered heterocyclyl, wherein said C_3-C_{10}carbocyclyl and 3- to 10-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $-O-R_B$, $-S-R_B$, $-N(R_BR_B')$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

$S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, phosphonoxy, phosphono, oxo, thioxo, formyl or cyano;

X is N;

L_1 and L_2 are $-(CH_2)-$, and are each independently optionally substituted with one or more substituents selected from halogen, R_T, $–O–R_S$, $–S–R_S$, $–N(R_SR_S')$, $–OC(O)R_S$, $–C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

L_3 is bond;

Y is selected from $–C(R_1R_2)N(R_5)–T–R_D$ or $–C(R_3R_4)C(R_6R_7)–T–R_D$,

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

Z is selected from $–N(R_B)C(O)C(R_8R_9)N(R_{12})–T–R_D$ or $–N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 8-membered heterocyclic ring which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 8-membered carbocyclic or heterocyclic ring which is optionally substituted with one or more R_A;

T is each independently selected at each occurrence from a bond, $–L_S–$, $–L_S–M–L_S'–$, $–L_S–M–L_S'–M'–L_S''–$, wherein M and M' are each independently selected at each occurrence from a bond, $–O–$, $–S–$, $–N(R_B)–$, $–C(O)–$, $–S(O)_2–$, $–S(O)–$, $–OS(O)–$, $–OS(O)_2–$, $–S(O)_2O–$, $–S(O)O–$, $–C(O)O–$, $–OC(O)–$, $–OC(O)O–$, $–C(O)N(R_B)–$, $–N(R_B)C(O)–$, $–N(R_B)C(O)O–$, $–OC(O)N(R_B)–$, $–N(R_B)S(O)–$, $–N(R_B)S(O)_2–$, $–S(O)N(R_B)–$, $–S(O)_2N(R_B)–$, $–C(O)N(R_B)C(O)–$, $–N(R_B)C(O)N(R_B')–$, $–N(R_B)SO_2N(R_B')–$, $–N(R_B)S(O)N(R_B')–$, C_3-C_{10}carbocycle, or 3- to 10-membered heterocycle, and wherein said C_3-C_{10}carbocycle and 3- to 10-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

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

R_B and R_B' are each independently selected at each occurrence from hydrogen or R_T;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, or R_F;

R_D is each independently selected at each occurrence from ~~hydrogen or~~ R_A;