ANTI-VIRAL COMPOUNDS

This application claims the benefit from and incorporates herein by references the entire content of U.S. Provisional Application No. 61/140,318, filed December 23, 2008.

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.

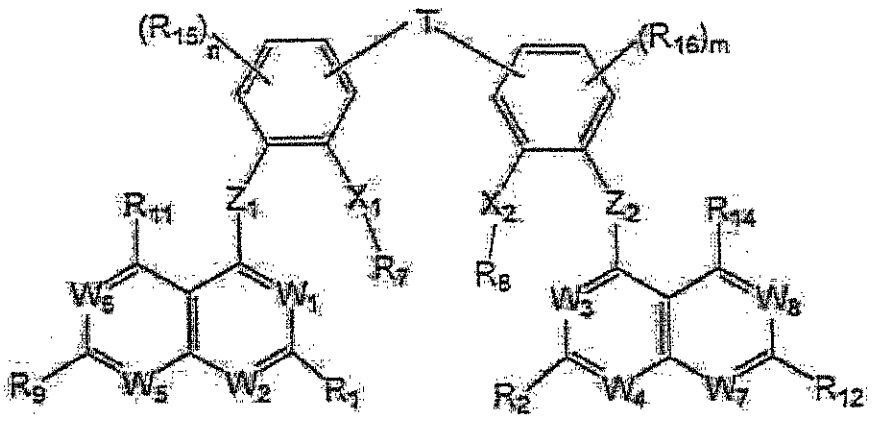
BACKGROUND

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

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



II

wherein:

X_1 and X_2 are each independently selected from a bond, $-CH_2-$, -O-, or -S-, and at least one of X_1 and X_2 is selected from $-CH_2-$, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

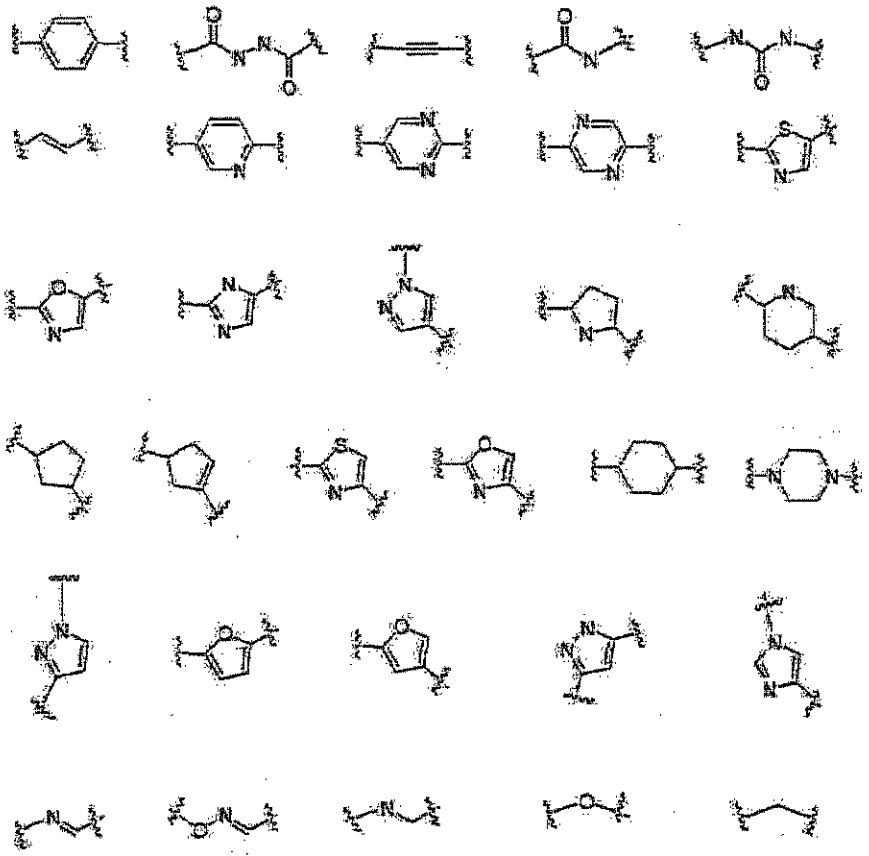
Z_1 and Z_2 are each selected from $-N(R_B)-$;

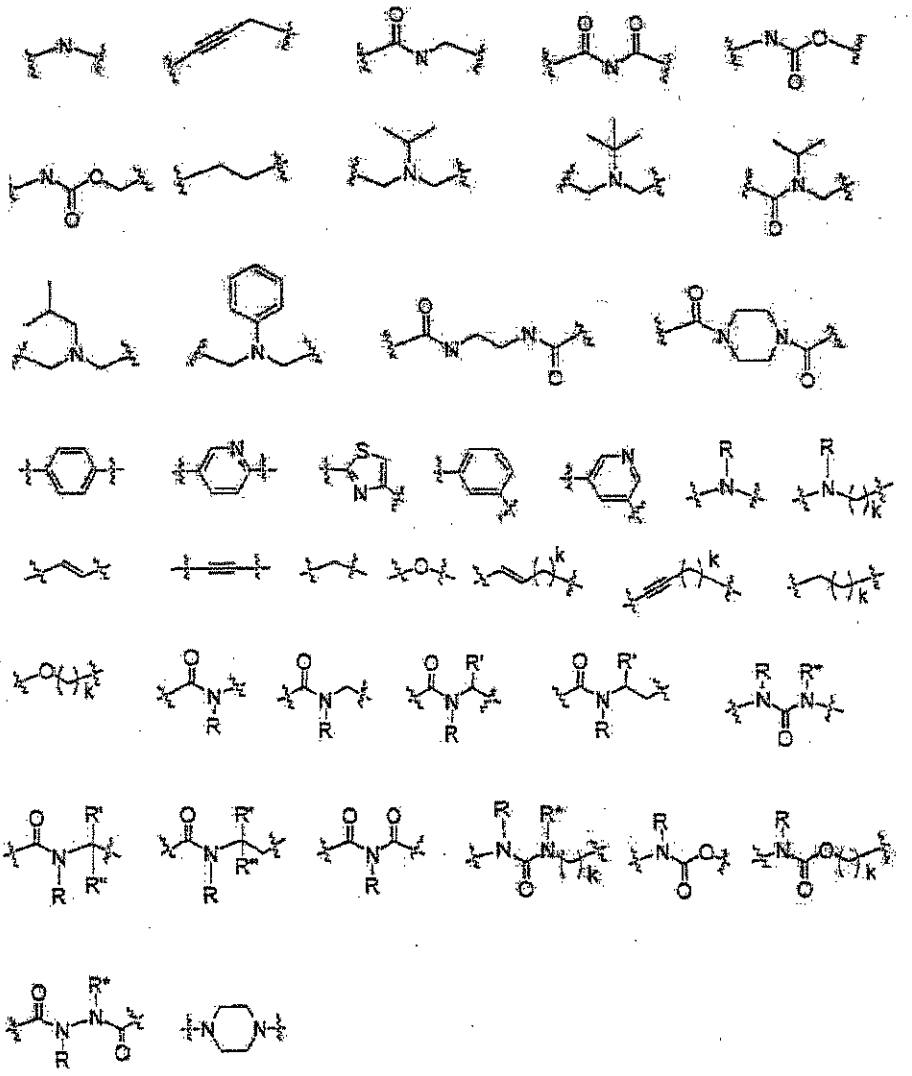
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or RA;

m and n are each 0;

T is selected from a bond, $-L_S-$, $-L_S-M-L_S-$, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -N(R_B)-, -C(O)N(R_B)-, -N(R_B)C(O)-, -N(R_B)C(O)N($R_{B'}$)-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, 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_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo;

thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

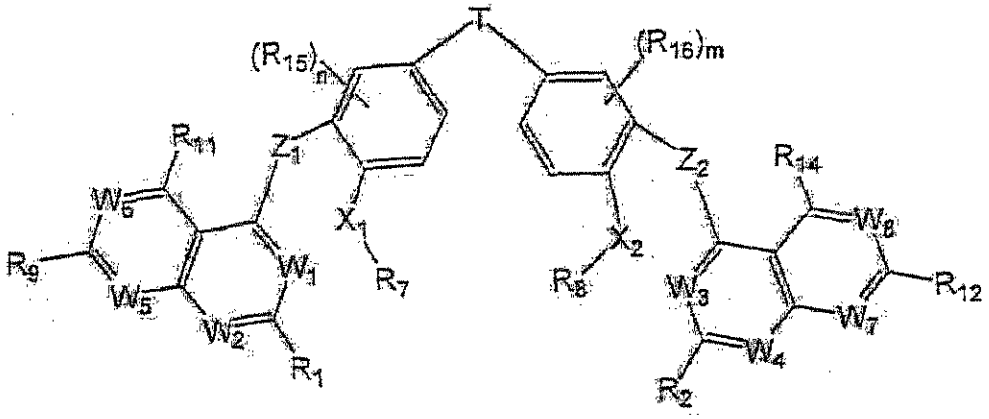
L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or-N($R_SR_{S'}$); and

R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

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



III

wherein:

X_1 and X_2 are each independently selected from a bond, -CH_2-, -O-, or -S-, and at least one of X_1 and X_2 is selected from -CH_2-, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

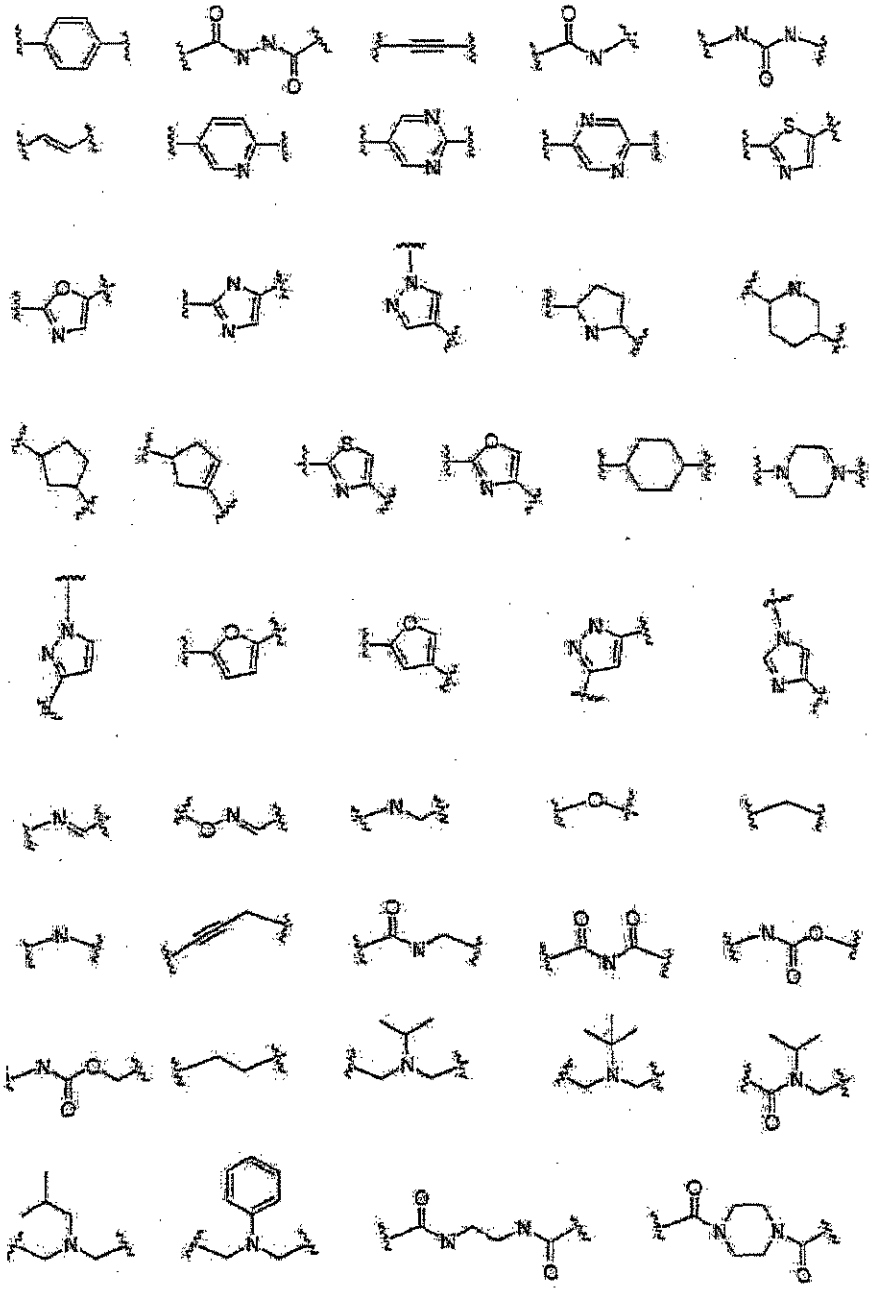
Z_1 and Z_2 are each selected from -N(R_B)-;

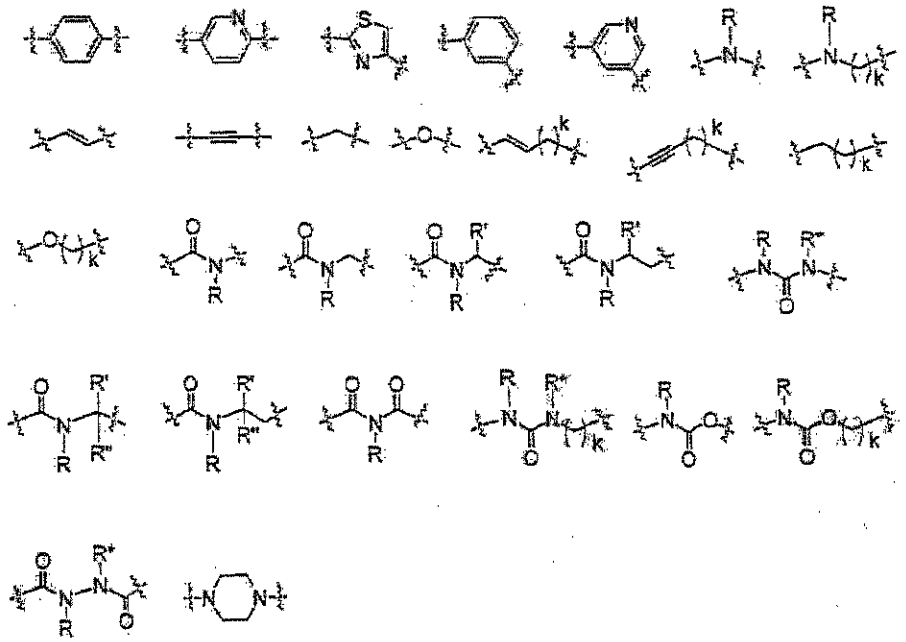
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or C(R_D), wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or R_A;

m and n are each 0;

T is selected from a bond, -L_S-, -L_S-M-L_S-, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R" are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -N(R_B)-, -C(O)N(R_B)-, -N(R_B)C(O)-, -N(R_B)C(O)N($R_{B'}$)-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, 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_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or -N(R_S $R_{S'}$); and

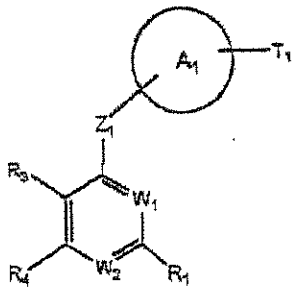
R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

In a third aspect, there is provided a pharmaceutical composition comprising a compound or salt as defined herein.

In a fourth aspect, there is provided the use of a compound or salt as defined herein for inhibiting HCV replication in a patient, in the manufacture of a medicament for treating HCV infection.

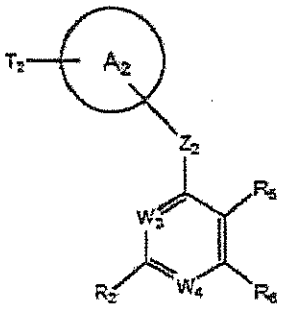
In a fifth aspect, there is provided a process of making a compound as defined herein, comprising the step of:

coupling a compound of Formula IV



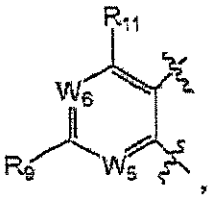
IV

to a compound of Formula V

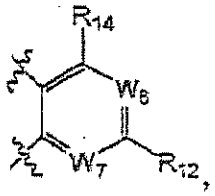


V

wherein T_1 is a carboxylic acid, an activated derivative, or an activated ester, T_2 is an amine or a substituted amine, A_1 is phenyl substituted with $-X_1$-R_7 and optionally substituted with one or more R_A, A_2 is phenyl substituted with $-X_2$-R_8 and optionally substituted with one or more R_A, R_3 and R_4, taken together with the carbon atoms to which they are attached, form



R_5 and R_6, taken together with the carbon atoms to which they are attached, form



, and

X_1, X_2, Z_1, Z_2, W_1, W_2, W_3, W_4, W_5, W_6, W_7, W_8, R_1, R_2, R_7, R_8, R_9, R_{11}, R_{12}, R_{14}, and R_A are as defined herein.

In a sixth aspect, there is provided a method of inhibiting HCV virus replication in vitro, comprising contacting cells infected with HCV virus with a compound or salt as defined herein.

The present disclosure features compounds of Formulae I, II and III, and pharmaceutically acceptable salts thereof. These compounds and salts are capable of inhibiting the replication of HCV.

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

The present disclosure further features methods of using the compounds or salts of the present disclosure to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus with a compound or salt of the present disclosure, thereby inhibiting the replication of HCV virus in the cells.

In addition, the present disclosure features methods of using the compounds or salts of the present disclosure, or compositions comprising the same, to treat HCV infection. The methods

comprise administering a compound or salt of the present disclosure, 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.

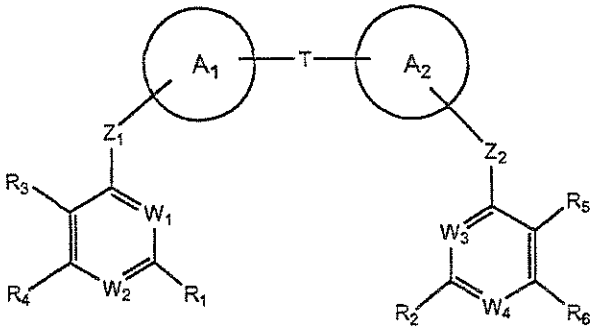
The present disclosure also features use of the compounds or salts of the present disclosure for the manufacture of medicaments for the treatment of HCV infection.

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

Other features, objects, and advantages of the present disclosure are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the disclosure, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the disclosure 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_1 is C_5-C_{10}carbocyclyl or 5- to 10-membered heterocyclyl, and is substituted with $-X_1$-R_7, wherein said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are optionally substituted with one or more R_A;

A_2 is C_5-C_{10}carbocyclyl or 5- to 10-membered heterocyclyl, and is substituted with $-X_2$-R_8, wherein said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are optionally substituted with one or more R_A;

X_1 and X_2 are each independently selected from a bond, $-L_S-$, $-O-$, $-S-$, or $-N(R_B)-$;

R_7 and R_8 are each independently selected from hydrogen, $-L_A$, C_5-C_{10}carbocyclyl, or 5- to 10-membered heterocyclyl, wherein at each occurrence said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are each independently optionally substituted with one or more R_A;

Z_1 and Z_2 are each independently selected from a bond, $-C(R_CR_{C'})-$, $-O-$, $-S-$, or $-N(R_B)-$;

W_1, W_2, W_3, and W_4 are each independently selected from N or $C(R_D)$, wherein R_D is independently selected at each occurrence from hydrogen or R_A;

R_1 and R_2 are each independently selected from hydrogen or R_A;

R_3 and R_4 are each independently selected from hydrogen or R_A; or R_3 and R_4, taken together with the carbon atoms to which they are attached, form a C_5-C_{10}carbocyclic or 5- to 10-membered heterocyclic ring, wherein said C_5-C_{10}carbocyclic and 5- to 10-membered heterocyclic ring are optionally substituted with one or more R_A;

R_5 and R_6 are each independently selected from hydrogen or R_A; or R_5 and R_6, taken together with the carbon atoms to which they are attached, form a C_5-C_{10}carbocyclic or 5- to 10-membered heterocyclic ring, wherein said C_5-C_{10}carbocyclic and 5- to 10-membered heterocyclic ring are optionally substituted with one or more R_A;

T is selected 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 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_5-C_{10}carbocycle, or 5- to 10-membered heterocycle, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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 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, phosphate, oxo, thioxo, formyl or cyano;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano;

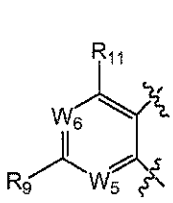
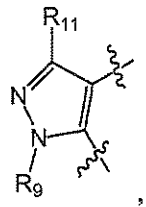
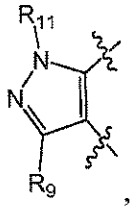
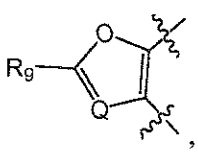
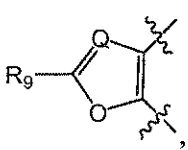
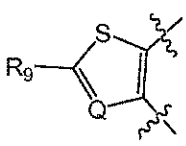
L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, C_2-C_6alkenylene, or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano;

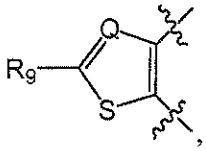
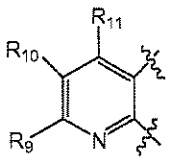
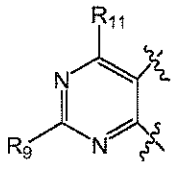
R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_{S'})$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_{S'})$, $-N(R_S)C(O)R_{S'}$, $-N(R_S)C(O)N(R_{S'}R_{S''})$, $-N(R_S)SO_2R_{S'}$, $-SO_2N(R_SR_{S'})$, $-N(R_S)SO_2N(R_{S'}R_{S''})$, $-N(R_S)S(O)N(R_{S'}R_{S''})$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_{S'}$, $-OC(O)N(R_SR_{S'})$, $-N(R_S)S(O)-R_{S'}$, $-S(O)N(R_SR_{S'})$, $-C(O)N(R_S)C(O)-R_{S'}$, C_3-C_6carbocyclyl, or 3- to 6-membered heterocyclyl, and said C_3-C_6carbocyclyl and 3- to 6-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except hydrogen), halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano; and

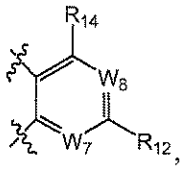
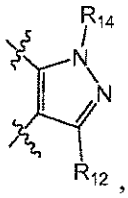
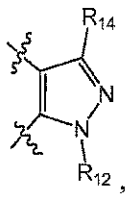
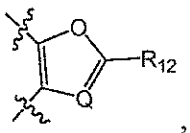
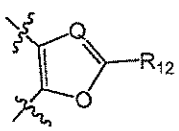
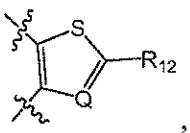
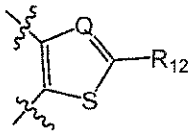
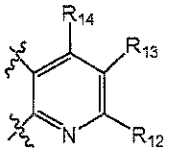
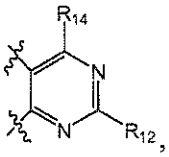
R_S, $R_{S'}$ and $R_{S''}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- to 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano.

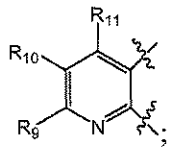
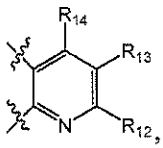
A_1 and A_2 are preferably independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles (e.g., phenyl, thiazolyl, thienyl, pyrrolidinyl or piperidinyl), and are each independently optionally substituted with one or more R_A. A_1 and A_2 are substituted with $-X_1$-R_7 and $-X_2$-R_8, respectively. The ring system in A_1 can be identical to, or different from, that in A_2. For instance, A_1 and A_2 can both be phenyl, or one is phenyl and the other is thiazolyl. Z_1 and T can be attached to A_1 via any two substitutable ring atoms on A_1, and Z_2 and T can be attached to A_2 via any two substitutable ring atoms on A_2. Two adjacent R_A on A_1 (or A_2), taken together with the ring atoms to which they are attached, may form a C_5-C_6carbocycle or a 5- to 6-membered heterocycle.

Preferably, R_3 and R_4, taken together with the carbon atoms to which they are attached, form a C_5-C_6carbocycle or a 5- to 6-membered heterocycle, which is optionally substituted with one or more R_A. Non-limiting examples of suitable 5- to 6-membered carbocycles or heterocycles include







or


, where W_5 and W_6 are independently N or $C(R_D)$, Q is N or $C(R_D)$, and R_D, R_9 and R_{11} are each independently selected from hydrogen or R_A. Preferred examples of suitable 5- to 6-membered heterocycles include  or , where R_9, R_{10}, and R_{11} are each independently selected from hydrogen or R_A.

Preferably, R_5 and R_6, taken together with the carbon atoms to which they are attached, also form a C_5-C_6carbocycle or a 5- to 6-membered heterocycle, which is optionally substituted with one or more R_A. Non-limiting examples of suitable 5- to 6-membered carbocycles or heterocycles include , , , , , , or , where W_7 and W_8 are each independently N or $C(R_D)$, Q is N or $C(R_D)$, and R_D, R_{12} and R_{14} are each independently selected from hydrogen or R_A. Preferred examples of suitable 5- to 6-membered heterocycles include  or , where R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen or R_A.

More preferably, R_3 and R_4, taken together with the carbon atoms to which they are attached, form ; and R_5 and R_6, taken together with the carbon atoms to which they are attached, form , where R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen or R_A. Preferably, R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen; halogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, or C_3-C_6carbocyclylC_1-C_6alkyl, each of which is independently optionally substituted at each occurrence

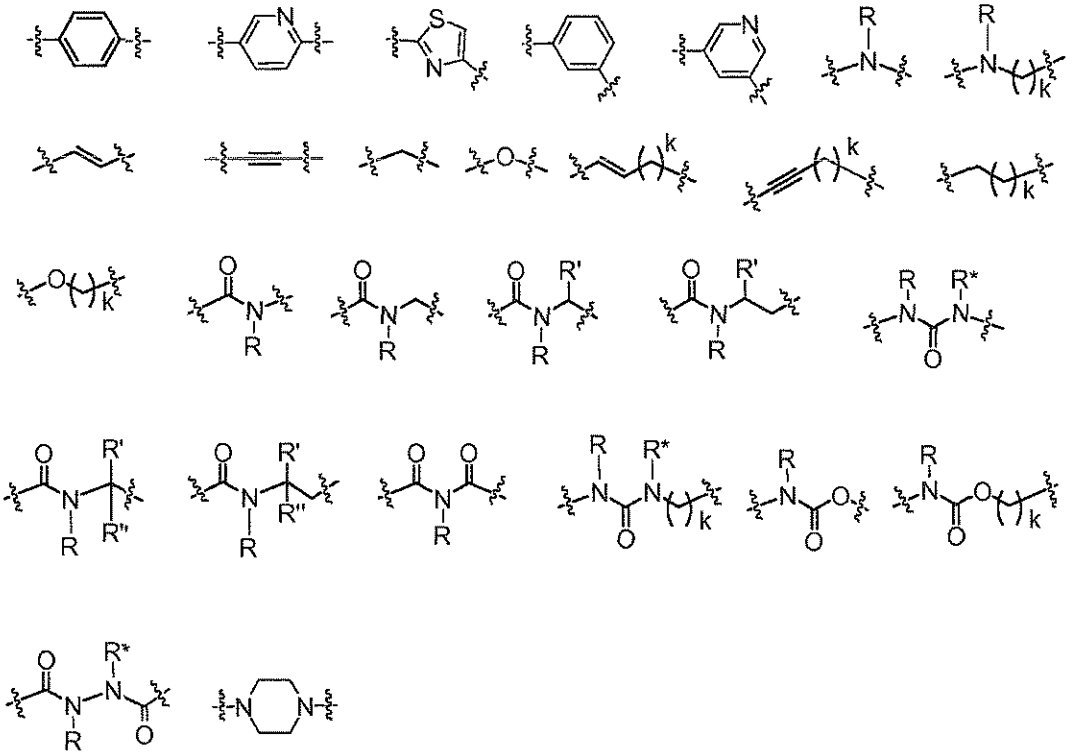
with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano. Highly preferably, R_9 and R_{12} are each independently selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl (e.g., C_3-C_6cycloalkyl), or C_3-C_6carbocyclylC_1-C_6alkyl (e.g., C_3-C_6cycloalkylC_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, phosphate, oxo, thioxo, formyl or cyano; and R_{10}, R_{11}, R_{13} and R_{14} are hydrogen.

R_7 and R_8 are preferably independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles, and are each independently optionally substituted with one or more R_A. The ring system in R_7 can be identical to, or different from, that in R_8. More preferably, both R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A (e.g., $-N(R_SR_{S'})$, such as $-NH_2$).

X_1 and X_2 are preferably independently selected from $-CH_2-$, $-O-$, or $-S-$.

Z_1 and Z_2 are preferably independently $-N(R_B)-$, such as $-NH-$ or $-N(C_1$-C_6alkyl$)-$.

T can be selected, without limitation, from the following moieties:



where k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl.

Preferably, T is selected from Table 4 described below.

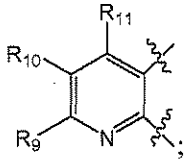
More preferably, T is $-L_S-N(R_T)-L_{S'}-$ (e.g., $-CH_2-N(R_T)-CH_2-$), or $-L_S-C(R_TR_T')-L_{S'}-$ (e.g., $-CH_2-C(R_TR_T')-CH_2-$). R_T is C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from

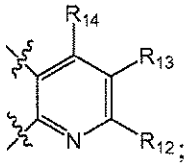
halogen, –O–R_S, –S–R_S, –N($R_S$$R_{S'}$), –OC(O)$R_S$, –C(O)O$R_S$, nitro, phosphate, oxo, thioxo, formyl or cyano; or R_T is C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- or 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except hydrogen), halogen, –O–R_B, –S–R_B, –N($R_B$$R_{B'}$), –OC(O)$R_B$, –C(O)O$R_B$, nitro, phosphate, oxo, thioxo, formyl or cyano. $R_{T'}$ is R_A, and preferably $R_{T'}$ is hydrogen. L_S, $L_{S'}$, R_A, R_B, $R_{B'}$, R_S, and $R_{S'}$ are as defined above.

In one embodiment, A_1 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl, thiazolyl, thienyl, pyrrolidinyl or piperidinyl), which is substituted with –X_1-R_7 and is optionally substituted with one or more R_A; and A_2 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl, thiazolyl, thienyl, pyrrolidinyl or piperidinyl), which is substituted with –X_2-R_8 and is optionally substituted with one or more R_A. R_3 and R_4, taken together with the carbon atoms to which they are attached, form a 5- to 6-membered carbocycle or heterocycle which is optionally substituted with one or more R_A. R_5 and R_6, taken together with the carbon atoms to which they are attached, also form a 5- to 6-membered carbocycle or heterocycle which is optionally substituted with one or more R_A. Preferably, both A_1 and A_2 are phenyl, and are substituted with –X_1-R_7 and –X_2-R_8, respectively, where X_1 and X_2 preferably are independently selected from –CH_2–, –O–, or –S–, and R_7 and R_8 preferably are phenyl and are each independently optionally substituted with one or more R_A.

In another embodiment, at least one of R_7 and R_8 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl), which is optionally substituted with one or more R_A. In still another embodiment, R_7 and R_8 are each independently selected from 5- to 6-membered carbocycles or heterocycles, and are each independently optionally substituted with one or more R_A.

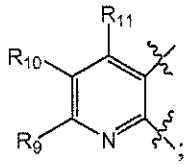
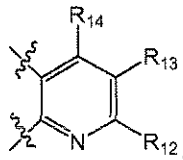
In a further embodiment, W_1, W_2, W_3 and W_4 are N, and Z_1 and Z_2 are independently –N(R_B)–. Preferably, Z_1 and Z_2 are independently selected from –NH–, –N(C_1-C_6alkly)–, –N(C_2-C_6alkenyl)–, –N(C_2-C_6alkynyl)–, –N(C_1-C_6haloalkyl)–, –N(C_2-C_6haloalkenyl)–, or –N(C_2-C_6haloalkynyl)–. More preferably, Z_1 and Z_2 are independently selected from –NH– or –N(C_1-C_6alkly)–.

In still another embodiment, R_3 and R_4, taken together with the carbon atoms to which they are attached, form 

; R_5 and R_6, taken together with the carbon atoms to which they are attached, form 

; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen or R_A; W_1, W_2, W_3 and W_4 are N; Z_1 and Z_2 are independently –N(R_B)– (e.g., –NH– or –

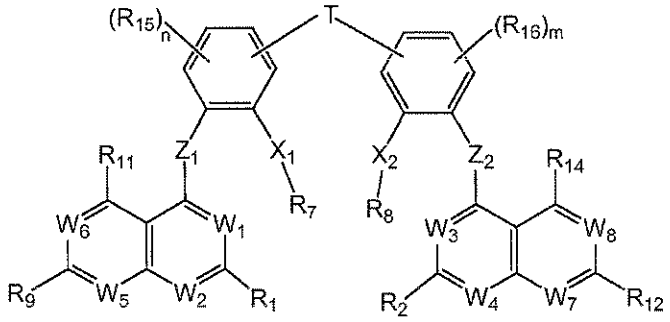
N(C_1-C_6alkly)–); and at least one of X_1 and X_2 is –CH_2–, –O–, or –S–. Preferably, at least one of R_7 and R_8 is phenyl, and is optionally substituted with one or more R_A. More preferably, R_1 and R_2 are hydrogen; and R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen; halogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, or C_3-C_6carbocyclylC_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, phosphate, oxo, thioxo, formyl or cyano. Highly preferably, R_9 and R_{12} are each independently selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl (e.g., C_3-C_6cycloalkyl), or C_3-C_6carbocyclylC_1-C_6alkyl (e.g., C_3-C_6cycloalkylC_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, phosphate, oxo, thioxo, formyl or cyano; and R_{10}, R_{11}, R_{13} and R_{14} are hydrogen.

In yet another embodiment, R_3 and R_4, taken together with the carbon atoms to which they are attached, form ; R_5 and R_6, taken together with the carbon atoms to which they are attached, form ; R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen or R_A; W_1, W_2, W_3 and W_4 are N; Z_1 and Z_2 are independently –N(R_B)– (e.g., –NH– or –N(C_1-C_6alkly)–); and X_1 and X_2 are each independently selected from –CH_2–, –O–, or –S–. Preferably, R_7 and R_8 are phenyl, and are each optionally substituted with one or more R_A. More preferably, R_1 and R_2 are hydrogen; and R_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each independently selected from hydrogen; halogen; C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, or C_3-C_6carbocyclylC_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, phosphate, oxo, thioxo, formyl or cyano. Highly preferably, R_9 and R_{12} are each independently C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl (e.g., C_3-C_6cycloalkyl), or C_3-C_6carbocyclylC_1-C_6alkyl (e.g., C_3-C_6cycloalkylC_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, phosphate, oxo, thioxo, formyl or cyano; and R_{10}, R_{11}, R_{13} and R_{14} are hydrogen.

In another embodiment, R_3 and R_4 are each independently selected from hydrogen or R_A, and/or R_5 and R_6 are each independently selected from hydrogen or R_A; and at least one of R_7 and R_8 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl), which is optionally substituted with one or more R_A. Preferably, R_7 and R_8 are each independently selected from 5- to 6-membered carbocycles or heterocycles, and are each independently optionally substituted with one or more R_A.

In still another embodiment, R_3 and R_4 are each independently selected from hydrogen or R_A, and/or R_5 and R_6 are each independently selected from hydrogen or R_A; A_1 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl, thiazolyl, thienyl, pyrrolidinyl or piperidinyl), which is substituted with $-X_1$-R_7 and is optionally substituted with one or more R_A; and A_2 is a 5- to 6-membered carbocycle or heterocycle (e.g., phenyl, thiazolyl, thienyl, pyrrolidinyl or piperidinyl), which is substituted with $-X_2$-R_8 and is optionally substituted with one or more R_A. Both A_1 and A_2 preferably are phenyl, and are substituted with $-X_1$-R_7 and $-X_2$-R_8, respectively. X_1 and X_2 preferably are independently selected from $-CH_2-$, $-O-$ or $-S-$. R_7 and R_8 preferably are each independently selected from 5- to 6-membered carbocycles or heterocycles, and are each independently optionally substituted with one or more R_A. More preferably, R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A. W_1, W_2, W_3 and W_4 preferably are N. Z_1 and Z_2 preferably are independently $-N(R_B)-$, such as $-NH-$, $-N(C_1$-C_6alkly$)-$, $-N(C_2$-C_6alkenyl$)-$, $-N(C_2$-C_6alkynyl$)-$, $-N(C_1$-C_6haloalkyl$)-$, $-N(C_2$-C_6haloalkenyl$)-$, or $-N(C_2$-C_6haloalkynyl$)-$. More preferably, Z_1 and Z_2 are independently selected from $-NH-$ or $-N(C_1$-C_6alkly$)-$.

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



II

wherein:

X_1 and X_2 are each independently selected from a bond, $-L_S-$, $-O-$, $-S-$, or $-N(R_B)-$;

R_7 and R_8 are each independently selected from hydrogen, $-L_A$, C_5-C_{10}carbocyclyl, or 5- to 10-membered heterocyclyl, wherein at each occurrence said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are each independently optionally substituted with one or more R_A;

Z_1 and Z_2 are each independently selected from a bond, $-C(R_CR_{C'})-$, $-O-$, $-S-$, or $-N(R_B)-$;

W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is independently selected at each occurrence from hydrogen or R_A;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or R_A;

m and n are each independently selected from 0, 1, 2, or 3;

T is selected 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 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_5-C_{10}carbocycle, or 5- to 10-membered heterocycle, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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 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, phosphate, oxo, thioxo, formyl or cyano;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano;

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_6carbocyclyl, or 3- to 6-membered heterocyclyl, and said C_3-C_6carbocyclyl and 3- to 6-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except

hydrogen), halogen, –O–R_B, –S–R_B, –N($R_BR_{B'}$), –OC(O)R_B, –C(O)OR_B, nitro, phosphate, oxo, thioxo, formyl or cyano; and

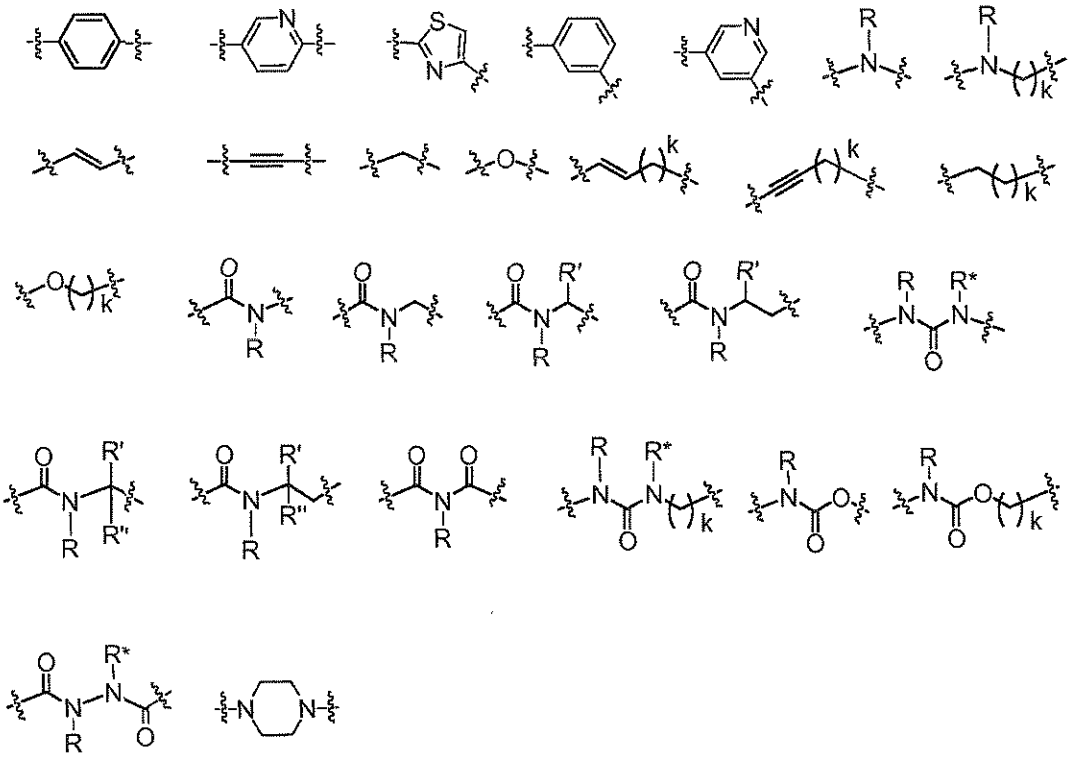
R_S, $R_{S'}$ and $R_{S''}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- to 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, –O–R_B, –S–R_B, –N($R_BR_{B'}$), –OC(O)R_B, –C(O)OR_B, nitro, phosphate, oxo, thioxo, formyl or cyano.

Z_1 and Z_2 are preferably independently –N(R_B)–, such as –NH– or –N(C_1-C_6alkyl)–.

X_1 and X_2 are preferably independently selected from –CH_2–, –O–, or –S.

R_7 and R_8 are preferably independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles, and are each independently optionally substituted with one or more R_A. The ring system in R_7 can be identical to, or different from, that in R_8. More preferably, both R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A (e.g., –N($R_SR_{S'}$) such as –NH_2).

T can be selected, without limitation, from the following moieties:



where k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl.

Preferably, T is selected from Table 4 described below.

More preferably, T is –L_S–N(R_T)–$L_{S'}$– (e.g., –CH_2–N(R_T)–CH_2–), or –L_S–C(R_TR_T')–$L_{S'}$– (e.g., –CH_2–C(R_TR_T')–CH_2–). R_T is C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl, each of which is

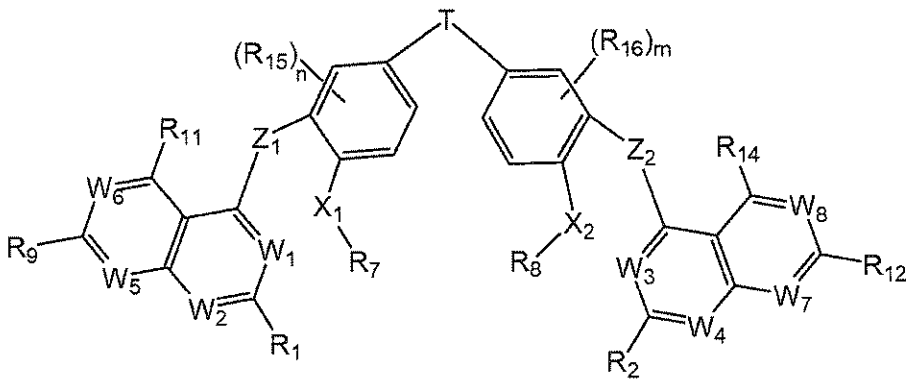
independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano; or R_T is C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, 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 C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except hydrogen), halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano. $R_{T'}$ is R_A, and preferably $R_{T'}$ is hydrogen. L_S, $L_{S'}$, R_A, R_B, $R_{B'}$, R_S, and $R_{S'}$ are as defined above.

In one embodiment, at least one of X_1 and X_2 is selected from $-CH_2-$, $-O-$, or $-S-$; at least one of R_7 and R_8 is selected from 5- to 6-membered carbocycles or heterocycles, and is optionally substituted with one or more R_A; and Z_1 and Z_2 are each independently $-N(R_B)-$ (e.g., $-NH-$ or $-N(C_1$-C_6alkyl$)-$).

In another embodiment, X_1 and X_2 are each independently selected from $-CH_2-$, $-O-$, or $-S-$; R_7 and R_8 are each independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles, and are each independently optionally substituted with one or more R_A; and Z_1 and Z_2 are each independently $-N(R_B)-$ (e.g., $-NH-$ or $-N(C_1$-C_6alkyl$)-$).

In still another embodiment, W_1, W_2, W_3, W_4 , W_5, and W_7 are N, and W_6 and W_8 are each independently $C(R_D)$; R_1 and R_2 are hydrogen; R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A; and R_9, R_{11}, R_{12}, R_{14}, and R_D are each independently selected at each occurrence from hydrogen; halogen; C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, or C_3-C_6carbocyclylC_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, phosphate, oxo, thioxo, formyl or cyano. Preferably, R_9 and R_{12} are each independently C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl (e.g., C_3-C_6cycloalkyl), or C_3-C_6carbocyclylC_1-C_6alkyl (e.g., C_3-C_6cycloalkylC_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, phosphate, oxo, thioxo, formyl or cyano; and R_{11}, R_{14} and R_D are hydrogen.

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



III

wherein:

X_1 and X_2 are each independently selected from a bond, $-L_S-$, $-O-$, $-S-$, or $-N(R_B)-$;

R_7 and R_8 are each independently selected from hydrogen, $-L_A$, C_5-C_{10}carbocyclyl, or 5- to 10-membered heterocyclyl, wherein at each occurrence said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are each independently optionally substituted with one or more R_A;

Z_1 and Z_2 are each independently selected from a bond, $-C(R_CR_{C'})-$, $-O-$, $-S-$, or $-N(R_B)-$;

W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is independently selected at each occurrence from hydrogen or R_A;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or R_A;

m and n are each independently selected from 0, 1, 2, or 3;

T is selected 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 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_5-C_{10}carbocycle, or 5- to 10-membered heterocycle, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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 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, phosphate, oxo, thioxo, formyl or cyano;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-

C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano;

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_6carbocyclyl, or 3- to 6-membered heterocyclyl, and said C_3-C_6carbocyclyl and 3- to 6-membered heterocyclyl are each independently optionally substituted at each occurrence with one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except hydrogen), halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano; and

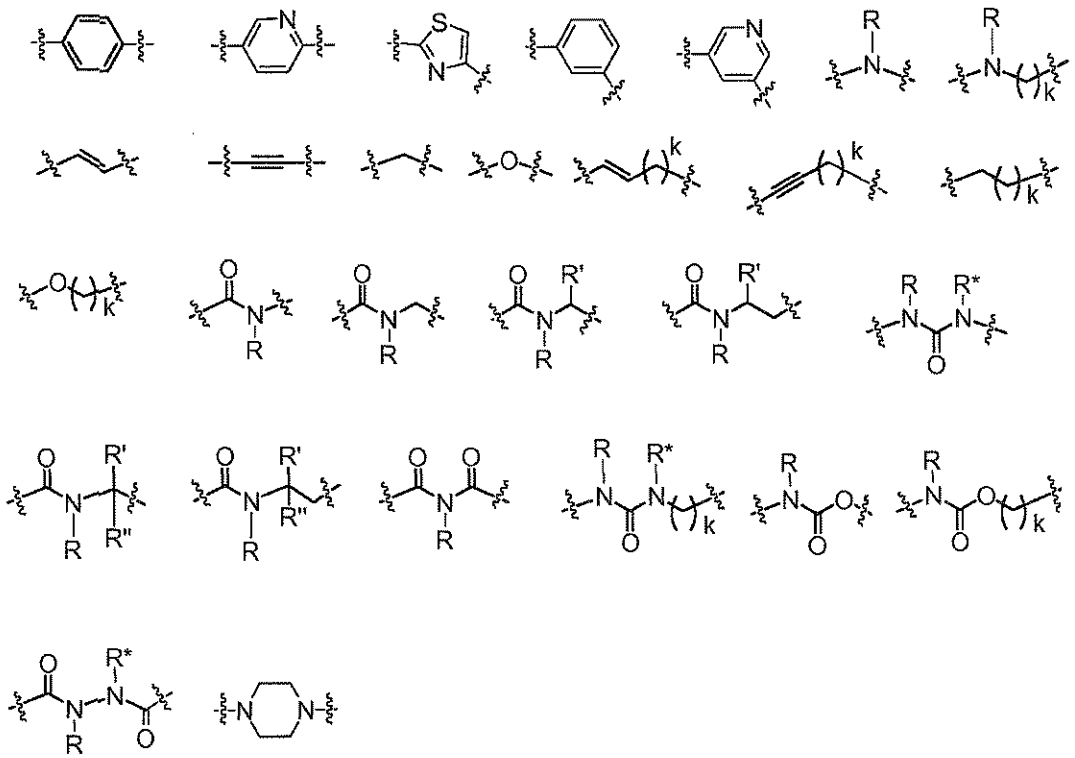
R_S, $R_{S'}$ and $R_{S''}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl, C_3-C_6carbocyclylC_1-C_6alkyl, 3- to 6-membered heterocyclyl, or (3- to 6-membered heterocyclyl)C_1-C_6alkyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano.

Z_1 and Z_2 are preferably each independently $-N(R_B)-$, such as $-NH-$ or $-N(C_1$-C_6alkyl$)-$.

X_1 and X_2 are preferably independently selected from $-CH_2-$, $-O-$, or $-S-$.

R_7 and R_8 are preferably independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles, and are each independently optionally substituted with one or more R_A. The ring system in R_7 can be identical to, or different from, that in R_8. More preferably, both R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A (e.g., $-N(R_SR_{S'})$ such as $-NH_2$).

T can be selected, without limitation, from the following moieties:



where k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl.

Preferably, T is selected from Table 4 described below.

More preferably, T is $-L_S-N(R_T)-L_{S'}-$ (e.g., $-CH_2-N(R_T)-CH_2-$), or $-L_S-C(R_TR_T')-L_{S'}-$ (e.g., $-CH_2-C(R_TR_T')-CH_2-$). R_T is 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, $-O-R_S$, $-S-R_S$, $-N(R_SR_{S'})$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, phosphate, oxo, thioxo, formyl or cyano; or R_T is 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 C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, R_S (except hydrogen), halogen, $-O-R_B$, $-S-R_B$, $-N(R_BR_{B'})$, $-OC(O)R_B$, $-C(O)OR_B$, nitro, phosphate, oxo, thioxo, formyl or cyano. $R_{T'}$ is R_A, and preferably $R_{T'}$ is hydrogen. L_S, $L_{S'}$, R_A, R_B, $R_{B'}$, R_S, and $R_{S'}$ are as defined above.

In one embodiment, at least one of X_1 and X_2 is selected from $-CH_2-$, $-O-$, or $-S-$; at least one of R_7 and R_8 is selected from 5- to 6-membered carbocycles or heterocycles, and is optionally substituted with one or more R_A; and Z_1 and Z_2 are each independently $-N(R_B)-$ (e.g., $-NH-$ or $-N(C_1$-C_6alkyl$)-$).

In another embodiment, X_1 and X_2 are each independently selected from $-CH_2-$, $-O-$, or $-S-$; R_7 and R_8 are each independently selected from C_5-C_6carbocycles or 5- to 6-membered heterocycles, and are each independently optionally substituted with one or more R_A; and Z_1 and Z_2 are each independently $-N(R_B)-$ (e.g., $-NH-$ or $-N(C_1$-C_6alkyl$)-$).

In still another embodiment, W_1, W_2, W_3, W_4 , W_5, and W_7 are N, and W_6 and W_8 are each independently $C(R_D)$; R_1 and R_2 are hydrogen; R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A; and R_9, R_{11}, R_{12}, R_{14}, and R_D are each independently selected at each occurrence from hydrogen; halogen; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclylalkyl, or C_3-C_6carbocyclylC_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, phosphate, oxo, thioxo, formyl or cyano. Preferably, R_9 and R_{12} are each independently C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6carbocyclyl (e.g., C_3-C_6cycloalkyl), or C_3-C_6carbocyclylC_1-C_6alkyl (e.g., C_3-C_6cycloalkylC_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, phosphate, oxo, thioxo, formyl or cyano; and R_{11}, R_{14} and R_D are hydrogen.

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 acid, 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 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 compounds of the invention includes each conformational isomer of these compounds and mixtures thereof.

Certain compounds of the invention may also exist in zwitterionic form and the invention includes 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., A_1, A_2, Z_1, Z_2, R_1 or R_2). 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 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_6cycloalkyl means a saturated hydrocarbyl ring 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_6carbocyclylC_1-C_6alkyl refers to a C_3-C_6carbocyclyl appended to the parent molecular moiety through a C_1-C_6alkyl group.

When words are used to describe a linking element between two other elements of a depicted chemical structure, the leftmost-described component of the linking element is the component that is bound to the left element in the depicted structure. To illustrate, if the chemical structure is A_1-T-A_2 and T is described as $-N(R_B)S(O)-$, then the chemical will be A_1-$N(R_B)$-S(O)–A_2.

If a linking element in a depicted structure is a bond, then the left element in the depicted structure is joined directly to the right element in the depicted structure. For example, if a chemical structure is depicted as $-L_S-M-L_S-$, where M is selected as a bond, then the chemical structure will be $-L_S-L_S-$. For another example, if a chemical moiety is depicted as $-L_S-R_E$ where L_S is selected as a bond, then the chemical moiety will be $-R_E$.

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.

The term "alkenyl" 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" 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" 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" 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" 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" 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" 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 carbocyclyl group can be attached to the parent molecular moiety through any substitutable carbon ring atom. Where a carbocyclyl group is a divalent moiety, such as A_1 and A_2 in Formula I, it can be attached to the remaining molecular moiety through any two substitutable ring atoms.

The term "carbocyclylalkyl" 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" 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" 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" 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_6haloalkyl" means a C_1-C_6alkyl substituent wherein one or more hydrogen atoms are replaced with independently selected halogen radicals. Non-limiting examples of C_1-C_6haloalkyl 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" 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 heterocyclyl group can be linked to the parent molecular moiety via any substitutable carbon or nitrogen atom(s) in the group. Where a heterocyclyl group is a divalent moiety, such as A_1 and A_2 in Formula I, it can be attached to the remaining molecular moiety through any two substitutable ring atoms.

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")), 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 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.

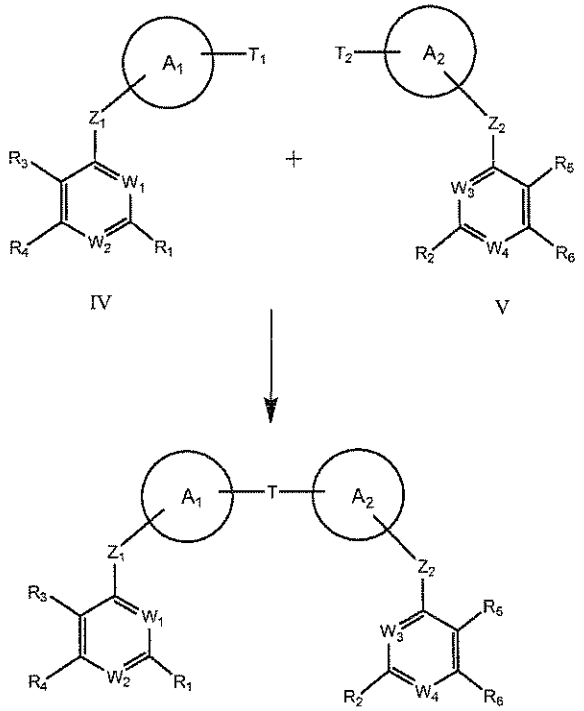
The term "prodrug" refers to derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active *in vivo*. A prodrug of a compound may be formed 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 term "N-protecting group" or "N-protected" refers to those groups capable of protecting an amino group against undesirable reactions. Commonly used N-protecting groups are described in Greene and Wuts, PROTECTING GROUPS IN CHEMICAL SYNTHESIS (3rd ed., John Wiley & Sons, NY (1999). Non-limiting examples of N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, or 4-nitrobenzoyl; sulfonyl groups such as benzenesulfonyl or p-toluenesulfonyl; sulfenyl groups such as phenylsulfenyl (phenyl-S-) or triphenylmethylsulfenyl (trityl-S-); sulfinyl groups such as p-methylphenylsulfinyl (p-methylphenyl-S(O)-) or t-butylsulfinyl (t-Bu-S(O)-); carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl,

4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloro-ethoxy-carbonyl, phenoxycarbonyl, 4-nitro-phenoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, or phenylthiocarbonyl; alkyl groups such as benzyl, p-methoxybenzyl, triphenylmethyl, or benzyloxymethyl; p-methoxyphenyl; and silyl groups such as trimethylsilyl. Preferred N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

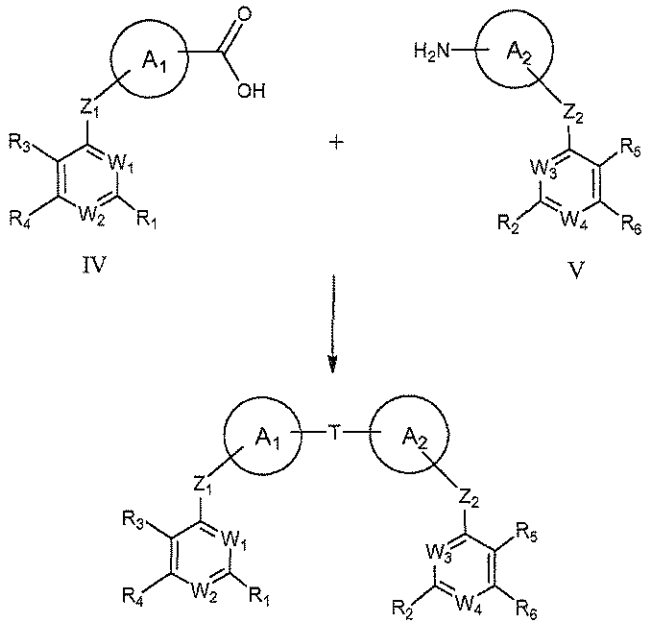
The compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as showed in Scheme I, where A_1, A_2, Z_1, Z_2, W_1, W_2, W_3, W_4, R_1, R_2, R_3, R_4, R_5, R_6 and T are as defined hereinabove. Compounds of Formulae IV and V can be prepared according to the processes described in U.S. Patent Application Publication Nos. 20070232627, 20070197558 and 20070232645, and WO2008/133753.



Scheme I

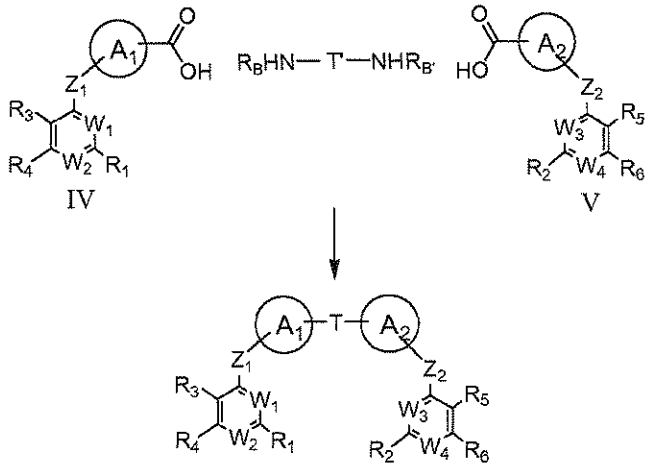
As a non-limiting example, the compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as shown in Scheme II, where T_1 is a carboxylic acid as shown or an activated derivative such as an acid chloride or an activated ester (e.g., N-hydroxysuccinimide or pentafluorophenyl esters), and T_2 is an amine or substituted amine.

Amide bond coupling reagents such as DCC, EDAC, PyBOP, and HATU may be employed with the option of adding an amine base such as triethylamine or Hunig's base in a solvent such as DMF, DMSO, THF, or dichloromethane.



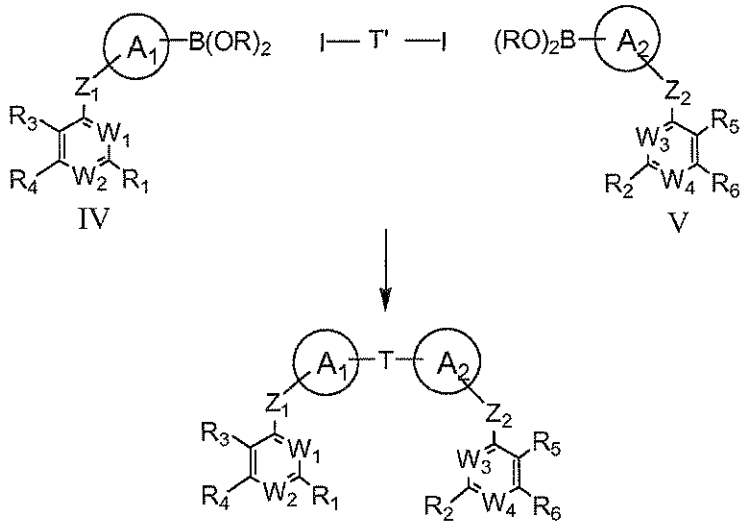
Scheme II

As another non-limiting example, the compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as shown in Scheme III, where T_1 and T_2 are carboxylic acids or activated derivatives such as acid chlorides or activated esters (e.g., N-hydroxysuccinimide or pentafluorophenyl esters) by reaction with an amine or substituted amine as shown. Amide bond coupling reagents such as DCC, EDAC, PyBOP, and HATU may be employed with the option of adding an amine base such as triethylamine or Hunig's base in a solvent such as DMF, DMSO, THF, or dichloromethane. Couplings may be conducted concurrently to give symmetric products or sequentially to give non-symmetric products. R_B and $R_{B'}$ are as defined hereinabove, and $-C(O)N(R_B)-T'-N(R_{B'})C(O)-$ is T.



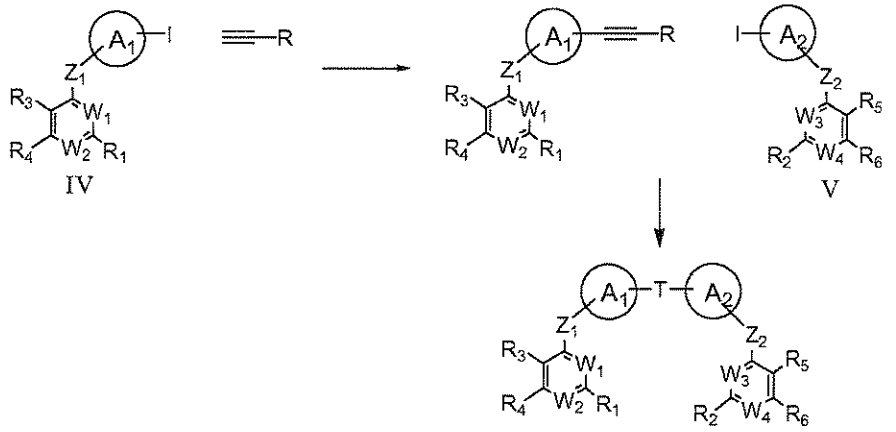
Scheme III

As yet another non-limiting example, the compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as shown in Scheme IV, where T_1 and T_2 are independently boronic acids or esters as shown by reaction with heterocyclic or carbocyclic halides (iodide shown in Scheme IV) or triflates and a transition metal catalyst. T' is a heterocyclic or carbocyclic, and R can be, without limitation, independently selected at each occurrence from hydrogen or L_A, and L_A is as defined hereinabove. Alternatively, alkyl stannanes (such a tributyl- or trimethylstannanes) may be employed in place of the boronates and coupled with halides or triflates under analogous conditions. Pd catalysts such as $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ may be employed or generated in situ using a Pd (II) catalyst such $Pd(OAc)_2$ or $Pd_2(dba)_3$ and organophosphorous ligands, such as PPh_3 or $P(t\text{-}Bu)_3$. Reactions may be conducted with addition of a base such K_2CO_3 or K_3PO_4 in a solvent such as THF or DMF. Couplings may be conducted concurrently to give symmetric products or sequentially to give non-symmetric products.



Scheme IV

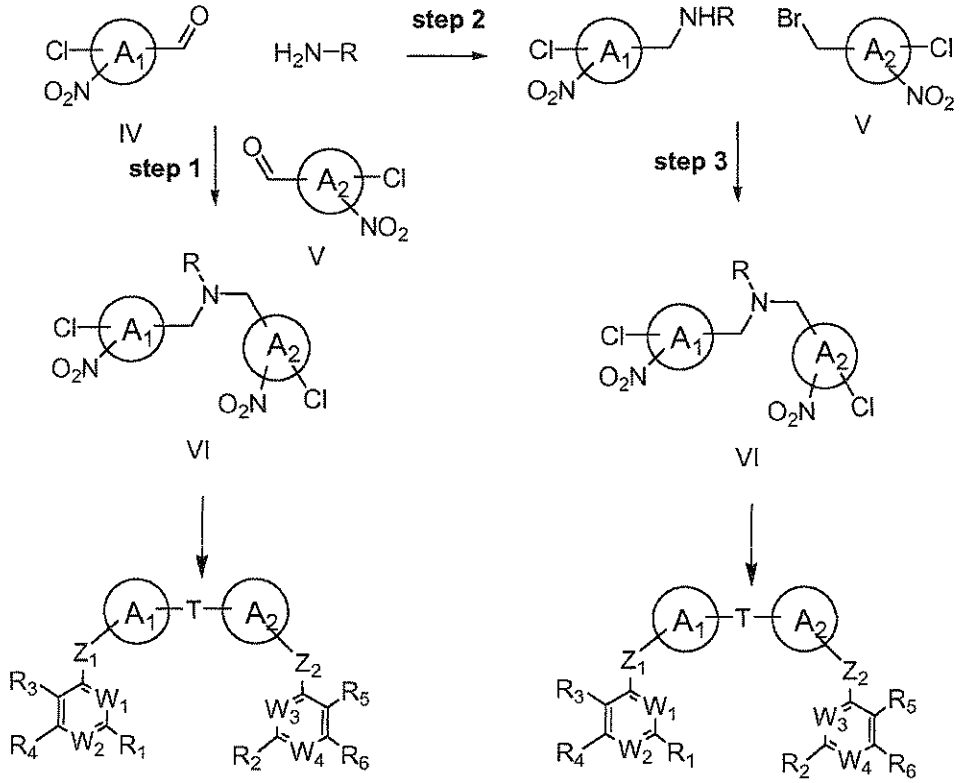
As still another non-limiting example, the compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as shown in Scheme V, where T_1 and T_2 are halides (iodide as shown) by reaction with an alkyne, where R may be trimethylsilyl (TMS) or another suitable protecting group, by Sonogashira reaction using a suitable catalyst. Pd catalysts such as $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ may be employed or generated in situ using a Pd (II) catalyst such $Pd(OAc)_2$ or $Pd_2(dba)_3$ and organophosphorous ligands, such as PPh_3 or $P(t\text{-}Bu)_3$. Alternatively, a Cu (I) catalyst may be employed, such as Cu (I) iodide. Reactions may be conducted with addition of a base such K_2CO_3 or K_3PO_4 or an amine base such as triethylamine or Hunig's base in a solvent such as THF or DMF. The TMS protecting group may be removed using a base such as K_2CO_3 in a solvent such as methanol or THF. A second Sonogashira reaction with V may be conducted under the analogous conditions to the first coupling. Couplings may be conducted concurrently to give symmetric products or sequentially to give non-symmetric products.



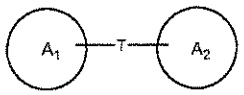
Scheme V

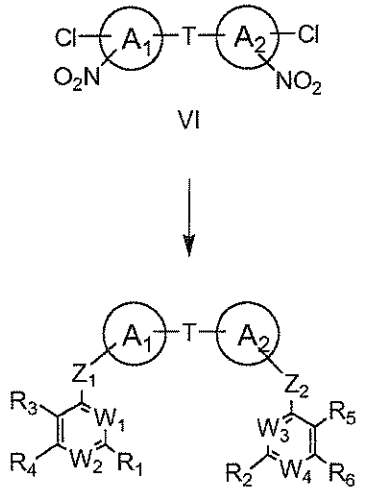
As a further non-limiting example, the compounds of the present invention can be prepared by coupling a compound of Formula IV to a compound of Formula V as shown in Scheme VI. Formula IV and V are both aldehydes, and can be reacted with an amine to form Formula VI (step 1) by reductive amination using a suitable reducing agent such as $NaCNBH_3$ or $NaBH(OAc)_3$, in a solvent such as THF or ethanol with or without the addition of acetic acid. R may be, without limitation, C_1-C_6alkyl such as tert-buyl or isopropyl, C_6-C_{10}carbocycle such as phenyl, or 6- to 10-membered heterocycle. Alternatively, R may be a protecting group, such as benzyl or 2,4-dimethoxy benzyl, which may be removed from VI using hydrogenolysis or by treatment with an acid, such as TFA or HCl. Alternatively, V may contain an alkyl halide, such as the bromide shown, and reacted with the product of reductive amination (step 2) of aldehyde IV with the amine to form VI (step 3). The alkylation using halide V may be conducted in the presence of a base, such as NaH, NaOH,

Hunig's base, or NaHMDS in a solvent such as THF or DMF. The halide and nitro substituted compounds VI may be reacted with alkyl, aryl, or heteroaryl alcohols, thiols, phenols, or thiophenols using a base such as K_2CO_3 or Hunig's base in a solvent such as THF or DMF. Nitro groups may be reduced to amino groups, using Pd or Raney Ni catalyzed hydrogenation or using Fe in the presence of NH_4Cl, HCl, or acetic acid, and further functionalized to compounds I using the processes described in U.S. Patent Application Publication Nos. 20070232627, 20070197558 and 20070232645, and WO2008/133753. T is $-CH_2-N(R)-CH_2-$ or -CH2-NH-CH2-.



Scheme VI

In addition, the compounds of Formula I can be directly prepared from  or an activated derivative thereof. For example, the compounds of the present invention can be prepared from a compound of Formula VI as shown in Scheme VII, which can be prepared through Schemes I-V by substituting chloro and nitro for IV and V. The halide and nitro substituted compounds VI may be reacted with alkyl, aryl, or heteroaryl alcohols, thiols, phenols, or thiophenols using a base such as K_2CO_3 or Hunig's base in a solvent such as THF or DMF. Nitro groups may be reduced to amino groups, using Pd or Raney Ni catalyzed hydrogenation or using Fe in the presence of NH_4Cl, HCl, or acetic acid, and further functionalized to compounds I using the processes described in U.S. Patent Application Publication Nos. 20070232627, 20070197558 and 20070232645, and WO2008/133753.



VI

Scheme VII

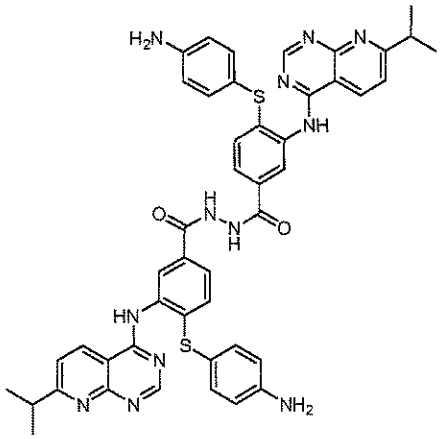
The compounds having Formulae II and III can be similarly prepared according to the above schemes, as appreciated by those skilled in the art.

If a moiety described herein (e.g., $-NH_2$ or –OH) is not compatible with the synthetic methods, the moiety may be protected with a suitable protecting group that is stable to the reaction conditions used in the methods. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and methods for protecting or deprotecting moieties are well know in the art, examples of which can be found in Greene and Wuts, *supra*. Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art based on the present invention.

It should be understood that the above-described embodiments and schemes and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

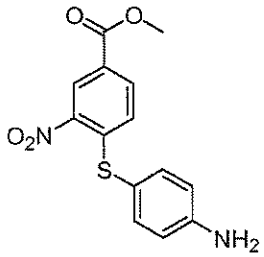
Example 1

4-(4-aminophenylthio)-N'-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzoyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzohydrazide



Example 1A

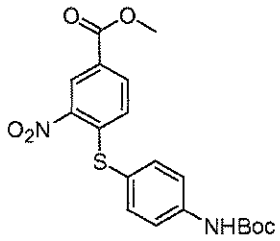
4-(4-Amino-phenylsulfanyl)-3-nitro-benzoic acid methyl ester



A mixture of 4-chloro-3-nitrobenzoic acid methyl ester (15.0 g, 68 mmol), 4-aminothiophenol (8.8 g, 68 mmol) and K_2CO_3 (11.8 g, 85 mmol) in DMF (150 mL) was heated at 90 °C for 1.5 hours, cooled to room temperature, and then poured into H_2O (450 mL) under stirring. The aqueous mixture was extracted with ethyl acetate (400 mL). The extract was washed with H_2O (3 times) and brine, dried over $MgSO_4$, and evaporated to give the crude product as orange crystal. The crude product was suspended in 150 mL of *i*-Pr_2O and stirred at room temperature for 1 hour. The crystal was collected by filtration, washed with *i*-Pr_2O and dried at 60 °C for 3 days under reduced pressure gave purified title compound as orange crystal (18.6 g, 90% yield).

Example 1B

4-(4-*tert*-Butoxycarbonylamino-phenylsulfanyl)-3-nitro-benzoic acid methyl ester

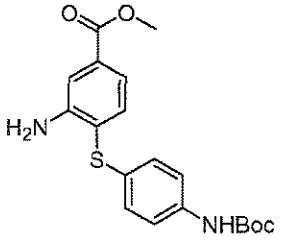


A solution of the product from Example 1A (18.5 g, 61 mmol) and di-tert-butyl dicarbonate (26.8 g, 122 mmol) in *p*-dioxane (280 mL) was heated at 90 °C for 3 hours. An additional di-tert-butyl dicarbonate (26.8 g, 122 mmol) was added and the mixture was heated at 90 °C for 3 hours. A

second additional di-tert-butyl dicarbonate (13.4 g, 61 mmol) was added and the mixture was heated at 90 °C for 4 hours. The reaction mixture was cooled to room temperature, and then evaporated. The residue was diluted with *i*-Pr_2O (250 mL) and the mixture was stirred at room temperature for 1 hour. The resulting crystal was collected by filtration, washed with *i*-Pr_2O and dried at 60 °C overnight under reduced pressure gave the title compound as yellow crystal (22.8 g, 93% yield).

Example 1C

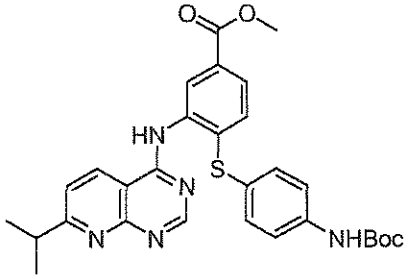
3-Amino-4-(4-*tert*-butoxycarbonylamino-phenylsulfanyl)-benzoic acid methyl ester



A suspension of the product from Example 1B (22.8 g, 56 mmol), Fe powder (16.4 g, 282 mmol) and NH_4Cl (15.1 g, 282 mmol) in aqueous EtOH [prepared from EtOH (228 mL) and H_2O (228 mL)] was gradually heated to reflux and gently refluxed for 2 hours. The reaction mixture was cooled to room temperature and filtered through celite pad. The filtrate was evaporated. The aqueous residue was portioned between Ethyl acetate and H_2O, made basic to pH 9 with K_2CO_3, and then filtered through celite pad. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$ and evaporated. The oily residue was crystallized in the treatment with *i*-Pr_2O (200 mL) and stirred at room temperature for 30 minutes. The resulting crystal was collected by filtration, washed with *i*-Pr_2O and dried at 60 °C overnight under reduced pressure gave the title compound as colorless crystal (13.9 g, 66% yield).

Example 1D

4-(4-*tert*-Butoxycarbonylamino-phenylsulfanyl)-3-(7-isopropyl-pyrido[2,3-*d*]pyrimidin-4-ylamino)-benzoic acid methyl ester

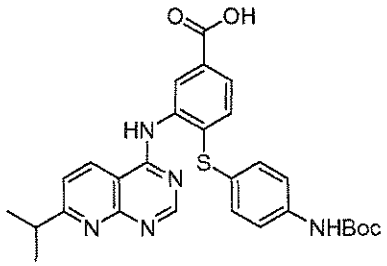


A suspension of *N'*-(3-cyano-6-isopropyl-pyridin-2-yl)-*N,N*-dimethyl-formamidine (2.00 g, 9.3 mmol) and the product from Example 1C (3.46 g, 9.3 mmol) in AcOH (40 mL) was heated at 120 °C for 20 minutes under N_2. After cooling to room temperature, the reaction mixture was portioned

between ethyl acetate (150 mL) and H_2O (200 mL), and then made basic to pH 9 with K_2CO_3 under stirring. The organic layer was separated, washed with 10% $NaHCO_3$, H_2O and brine, dried over $MgSO_4$, and evaporated to give a pale brown oil. The oily residue was separated by silica gel column chromatography (ethyl acetate/*n*-hexane = 5/1) gave yellow crystal. Further purification by washing with cold ethyl acetate (15 mL) gave the title compound as slightly yellow crystal (3.27 g, 65% yield).

Example 1E

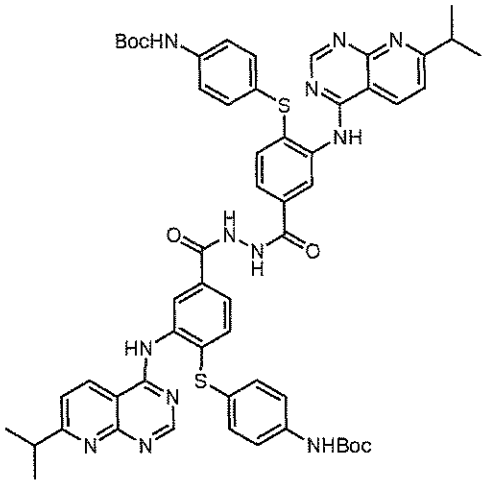
4-(4-*tert*-Butoxycarbonylamino-phenylsulfanyl)-3-(7-isopropyl-pyrido[2,3-*d*]pyrimidin-4-ylamino)-benzoic acid



To a solution of the product from Example 1D (3.25 g, 6.0 mmol) in THF (32.5 mL) was added aqueous LiOH [prepared from LiOH monohydrate (1.02 g, 24 mmol) and H_2O (10 mL)] dropwise at room temperature. The mixture was stirred at room temperature for 26 hours, and then evaporated. The aqueous mixture was diluted with 100 mL of H_2O, washed with ethyl acetate (50 mL), and then carefully acidified to pH 4-5 with 10% HCl at 5 °C under stirring. The resulting solid was collected by filtration, washed with H_2O, and dried at 60 °C overnight under reduced pressure gave the title compound as pale yellow crystal (3.09 g, 98% yield).

Example 1F

tert-butyl 4,4'-(4,4'-(hydrazine-1,2-diylbis(oxomethylene))bis(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4,1-phenylene))bis(sulfanediyl)bis(4,1-phenylene)dicarbamate



To a solution of the product from Example 1E (106 mg, 0.200 mmol) in DMSO (1.0 mL) at room temperature were added Hunig's base (87 µl, 0.499 mmol), hydrazine hydrate (5.0 mg, 0.100 mmol), and HATU (118 mg, 0.310 mmol) and the reaction was stirred at room temperature overnight. Diluted with water and isolated the solid by filtration. Purification by chromatography on silica gel eluting with 0-10% methanol in dichloromethane gave the title compound (50 mg, 47% yield).

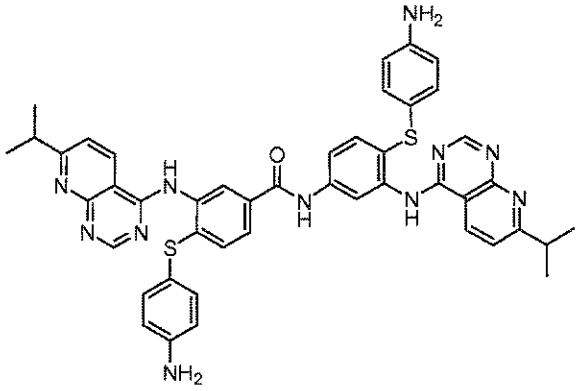
Example 1G

4-(4-aminophenylthio)-N'-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzoyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzohydrazide

The product from Example 1F (50 mg, 0.047 mmol) was dissolved in THF (1.0 mL) and 4 M HCl in dioxane (0.5 m) was added and the reaction was stirred at room temperature overnight. Collected product by filtration, dissolved in methanol and added to $NaHCO_3$ solution, and extracted with ethyl acetate. Dried over $MgSO_4$, filtered and evaporated. Purification by chromatography on silica gel eluting with 0-10% methanol in dichloromethane gave the title compound as a yellow solid (6 mg, 15% yield). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.33 (d, J=6.99 Hz, 12 H) 3.16 - 3.29 (m, 2 H) 5.60 (s, 4 H) 6.63 (d, J=8.46 Hz, 4 H) 6.84 (d, J=8.09 Hz, 2 H) 7.14 (d, J=8.46 Hz, 4 H) 7.63 (d, J=8.46 Hz, 2 H) 7.73 (d, J=8.46 Hz, 2 H) 7.87 (s, 2 H) 8.58 (s, 2 H) 8.87 (d, J=8.46 Hz, 2 H) 10.13 (s, 2 H) 10.45 (s, 2 H). MS (ESI) *m/z* 859 $(M + H)^+$.

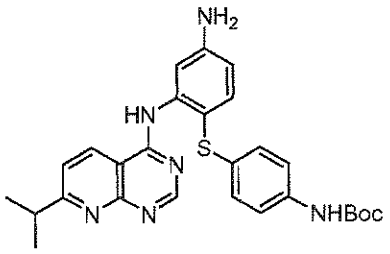
Example 2

4-(4-aminophenylthio)-N-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide



Example 2A

tert-butyl 4-(4-amino-2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenylthio)phenylcarbamate



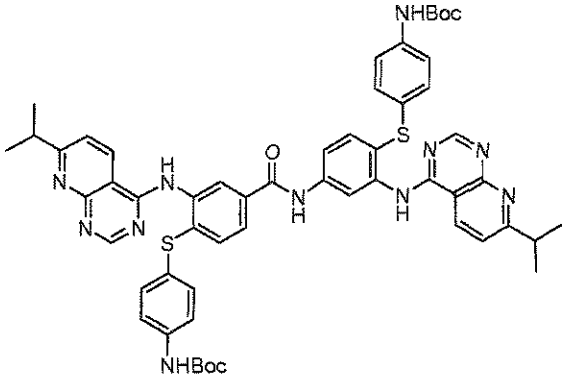
To a solution of the product from Example 1E (0.5 g, 0.941 mmol) in DMSO (5.0 mL) at room temperature were added Hunig's base (0.493 ml, 2.82 mmol), sodium azide (0.153 g, 2.351 mmol), and HATU (0.465 g, 1.223 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was diluted with ethyl acetate and washed with water and brine. The organic was dried over $MgSO_4$, filtered and concentrated. The crude product was used without further purification.

A solution of the product from the first step (0.524 g, 0.941 mmol) in toluene (50 ml) was stirred at 100 °C for 30 minutes. The reaction was cooled and 2-(trimethylsilyl)ethanol (1.349 ml, 9.41 mmol) was added and the mixture was heated at 50 °C for 1.5 hours. The reaction was cooled and evaporated. The crude product used without further purification.

To a solution of the crude product from the second step in THF (9.41 ml) at room temperature was added TBAF (4.71 ml, 4.71 mmol) and the reaction was stirred at room temperature for 5 hours. The reaction was diluted with ethyl acetate and washed with water, and brine. The organic was dried over $MgSO_4$, filtered and concentrated. The product was purified by chromatography on silica gel eluting with a gradient starting with dichloromethane and ending with ethyl acetate gave the title compound as a yellow solid (340 mg, 72% yield).

Example 2B

4-(4-(tert-butoxycarbonylamino)phenylthio)-N-(4-(4-(tert-butoxycarbonylamino)phenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide



To a solution of the product from Example 1E (50 mg, 0.094 mmol) in DMSO (0.5 mL) at room temperature were added Hunig's base (49.3 µl, 0.282 mmol), the product from Example 2A (47.3 mg, 0.094 mmol), and HATU (42.9 mg, 0.113 mmol) and the reaction was stirred at room

temperature overnight. The reaction was diluted with ethyl acetate and washed with water. The organic was dried over $MgSO_4$, filtered and concentrated. The crude product was used without further purification.

Example 2C

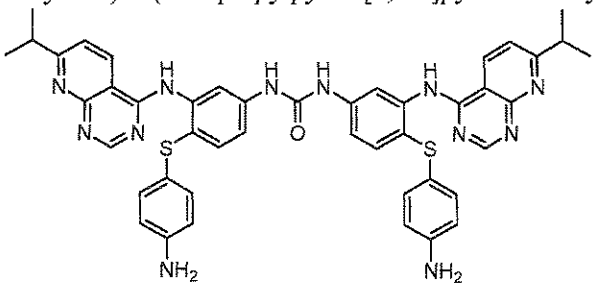
4-(4-aminophenylthio)-N-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide

To a solution of Reactant 1 (96 mg, 0.094 mmol) in Dichloromethane (2 ml) at rt was added TFA (2 ml) and the reaction was stirred at rt for 30 minutes. The reaction was evaporated.

The crude product was added to a reverse phase column and was eluted with a gradient starting with 5% acetonitrile in water (0.1% TFA) and ending with 75% acetonitrile in water (0.1% TFA). Most of the solvent was evaporated. Extracted with ethyl acetate and washed with saturated $NaHCO_3$. Dry $MgSO_4$, filtered, evaporated and concentrated to give the title compound (15.7 mg, 20% yield). ^1H NMR (300 MHz, DMSO-D6) δ ppm 1.33 (d, J=6.62 Hz, 12 H) 3.12 - 3.27 (m, 2 H) 5.43 (s, 2 H) 5.59 (s, 2 H) 6.54 (d, J=8.46 Hz, 2 H) 6.63 (d, J=8.82 Hz, 2 H) 6.87 (d, J=8.46 Hz, 1 H) 6.92 (d, J=8.82 Hz, 1 H) 7.06 (d, J=8.46 Hz, 2 H) 7.13 (d, J=8.46 Hz, 2 H) 7.52 - 7.66 (m, 3 H) 7.78 (d, J=8.09 Hz, 1 H) 7.88 (d, J=2.21 Hz, 1 H) 7.94 (s, 1 H) 8.55 (s, 1 H) 8.58 (s, 1 H) 8.84 (d, J=8.82 Hz, 1 H) 8.87 (d, J=8.46 Hz, 1 H) 10.04 (s, 1 H) 10.16 (s, 1 H) 10.27 (s, 1 H). MS (ESI) *m/z* 816 $(M+H)^+$.

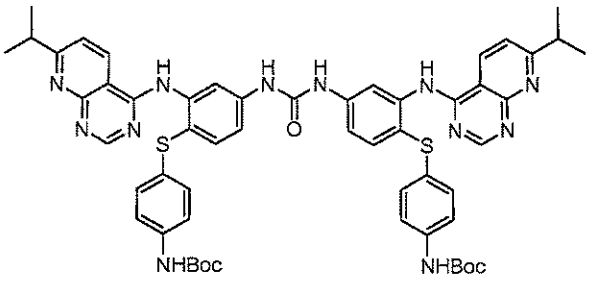
Example 3

1,3-bis(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)urea



Example 3A

tert-butyl 4,4'-(4,4'-carbonylbis(azanediyl)bis(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4,1-phenylene))bis(sulfanediyl)bis(4,1-phenylene)dicarbamate



To a solution of the product from Example 1E (0.05 g, 0.094 mmol) in DMSO (0.5 mL) at room temperature were added Hunig's base (0.049 ml, 0.282 mmol), sodium azide (0.015 g, 0.235 mmol), and HATU (0.046 g, 0.122 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction was diluted with ethyl acetate and washed with water (2X) and brine. The organic was dried over MgSO4, filtered and concentrated. The crude product was used without further purification.

A solution of the product from the first step (0.052 g, 0.094 mmol) in toluene (4.70 ml) was stirred at 100 °C for 30 minutes. The reaction was cooled and evaporated. THF (1 mL) and the product from Example 2A (0.047 g, 0.094 mmol) were added and the mixture was heated at 50 °C for 1.5 hours. The reaction was cooled and evaporated to give the title compound which was used without further purification.

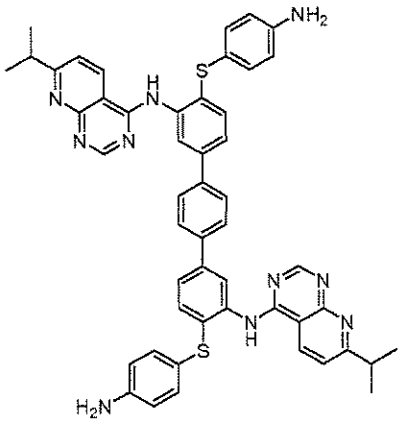
Example 3B

1,3-bis(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)urea

To a solution of the product from Example 3A (97 mg, 0.094 mmol) in dichloromethane (1 mL) at room temperature was added TFA (1 mL) and the reaction was stirred at room temperature for 30 minutes. The reaction was evaporated. Purification by reverse phase (C18) chromatography eluting with a gradient starting with 95:5 water (0.1% TFA):acetonitrile and ending with 1:1 water (0.1% TFA):acetonitrile. Most of the solvent was evaporated. Extracted with ethyl acetate and washed with saturated $NaHCO_3$. Dry $MgSO_4$, filtered, evaporated and concentrated to give the title compound (35.5 mg, 45% yield). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.33 (d, J=6.99 Hz, 6 H) 3.13 - 3.29 (m, 1 H) 5.38 (s, 2 H) 6.51 (d, J=8.46 Hz, 2 H) 6.94 (d, J=8.46 Hz, 1 H) 7.03 (d, J=8.46 Hz, 2 H) 7.23 (dd, J=8.82, 2.21 Hz, 1 H) 7.60 (d, J=8.82 Hz, 1 H) 7.66 (d, J=2.21 Hz, 1 H) 8.55 (s, 1 H) 8.74 - 8.92 (m, 2 H) 9.97 (s, 1 H). MS (ESI) *m/z* 831 $(M + H)^+$.

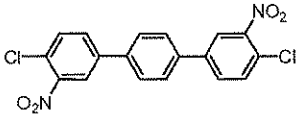
Example 4

4,4"-(4-amino-phenylsulfanyl)-N*3*,N*3"*-(7-isopropylpyrido[2,3-d]pyrimidin-4-yl)-[1,1';4',1"]terphenyl-3,3"-diamine



Example 4A

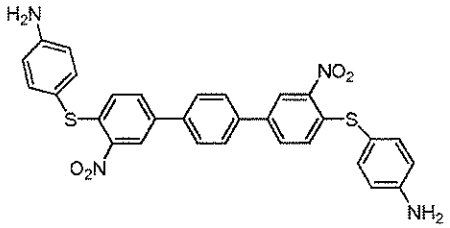
4,4"-Dichloro-3,3"-dinitro-[1,1';4',1"]terphenyl



1,4-diiodobenzene (200 mg, 0.606 mmol), 4-chloro-3-nitrophenylboronic acid (256 mg, 1.273 mmol), and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol), were added to a flask followed by Na_2CO_3 (321 mg, 3.03 mmol). DMF (6.0 mL) and water (1.0 mL) were added and the mixture was bubbled with N_2 for ten minutes. Heated solution to 110 °C for 30 min in a microwave reactor. A large amount of precipitate formed. Water and dichloromethane were added and the mixture was extracted with dichloromethane. Dried over $MgSO_4$, filtered and concentrated to give the title compound as a light brown solid. (250 mg), which was used without further purification.

Example 4B

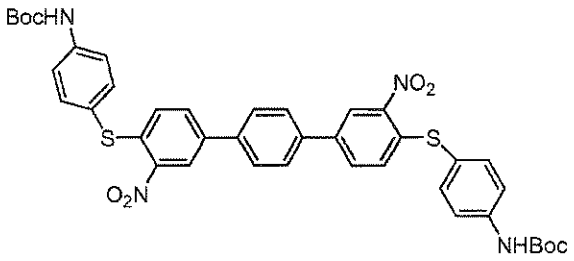
4,4"-(4-amino-phenylsulfanyl)-3,3"-dinitro-[1,1';4',1"]terphenyl



To a solution of the product from Example 4A (250 mg, 0.642 mmol) in DMF (3.0 mL) were added 4-aminobenzenethiol (161 mg, 1.285 mmol) and potassium carbonate (266 mg, 1.927 mmol) and the mixture was heated to 90 °C for 1.5 hours and then stirred at room temperature overnight. The mixture was extracted with dichloromethane and washed with water. A precipitate formed in the dichloromethane extract solution and this brown solid was collected by filtration and air dried to provide the title compound (90 mg, 25% yield).

Example 4C

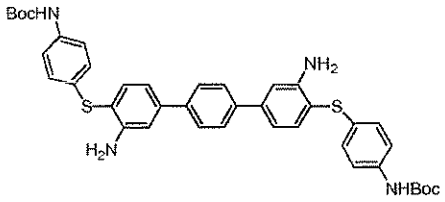
4,4"-(4-*tert*-butoxycarbonylamino-phenylsulfanyl)-3,3"-dinitro-[1,1';4',1"]terphenyl



The product from Example 4B (75 mg, 0.132 mmol) was suspended in dioxane (4.0 mL) and di-tert-butyl dicarbonate was added (100 mg, 0.457 mmol) and the mixture was heated to 90 °C. After 2 hours, more di-tert-butyl dicarbonate (190 mg, 0.867 mmol) was added and the mixture was heated at 90 °C overnight. The reaction was evaporated to give the title compound as a brown semi-solid, which was used without further purification.

Example 4D

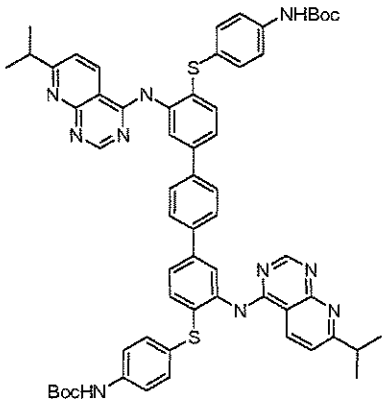
4,4"-(4-*tert*-butoxycarbonylamino-phenylsulfanyl)-[1,1';4',1"]terphenyl-3,3"-diamine



To a suspension of the product from Example 4C (100 mg, 0.130 mmol) in THF (2.0 mL), EtOH (2.0 mL), and water (0.6 mL) mixture were added Fe (72.8 mg, 1.304 mmol) and ammonium chloride (34.9 mg, 0.652 mmol) and the mixture was heated at 90 °C for 1.5 hours. DMF was added and the mixture was heated to 50-60 °C and the mixture was filtered and solids were rinsed with warm DMF. Then DMF filtrate was evaporated to a brown semi-solid. The solid was extracted with ethyl acetate and washed with water. Dried over $MgSO_4$, filtered and evaporated to yield the title compound as a brown solid (90 mg) and the product was used without further purification.

Example 4E

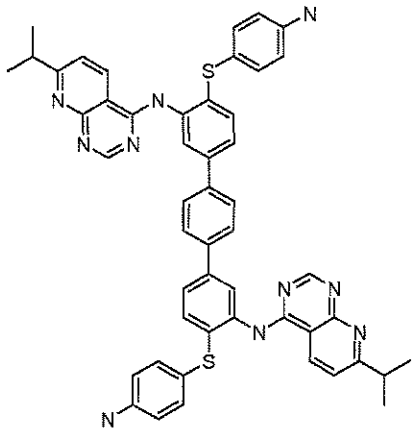
4,4"-(4-*tert*-butoxycarbonylamino-phenylsulfanyl)-N*3*,N*3"*-(7-isopropylpyrido[2,3-d]pyrimidin-4-yl)-[1,1';4',1"]terphenyl-3,3"-diamine



To a suspension of the product from Example 4D (80 mg, 0.113 mmol) in AcOH (3.0 mL) was added (E)-N'-(3-cyano-6-isopropylpyridin-2-yl)-N,N-dimethylformimidamide (53.8 mg, 0.249 mmol) and the mixture was placed into a preheated oil bath at 120 °C for 15 minutes. The reaction was cooled and the mixture was extracted with dichloromethane and washed with saturated Na_2CO_3. Dried over $MgSO_4$, filtered and evaporated to yield the title compound as a brown solid (110 mg) and the product was used without further purification.

Example 4F

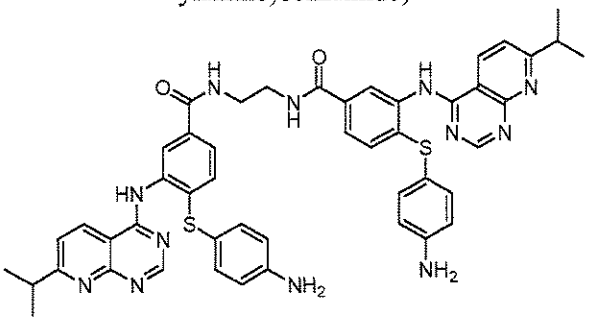
4,4"-(4-amino-phenylsulfanyl)-N*3*,N*3"*-(7-isopropylpyrido[2,3-d]pyrimidin-4-yl)-[1,1';4',1"]terphenyl-3,3"-diamine



The product of Example 4E (110 mg, 0.105 mmol) was dissolved in dichloromethane (0.3 mL) and TFA (2.7 mL) and the solution was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue was extracted with 30% MeOH in dichloromethane and washed with 1N Na_2CO_3. Dried over $MgSO_4$, filtered and evaporated. Purification by chromatography on silica gel eluting with 0-10% MeOH in dichloromethane gave the title compound as a light yellow solid (22 mg, 25% yield). 1H NMR (300MHz, DMSO-d_6) : δ 10.10 (s, 2H), 8.88 (d, J=8.1 Hz, 2H), 8.56 (s, 2H), 7.78 (m, 2H), 7.73 (s, 4H), 7.61 (m, 4H), 7.14 (d, J=8.5 Hz, 4H), 6.91 (d, J=7.7Hz, 2H), 6.61 (d, J=8.2 Hz, 4H), 5.53 (s, 4H), 3.20 (m, 2H), 1.34 (d, J=7.0 Hz, 12H). MS (ESI) *m/z* 849 $(M+H)^+$.

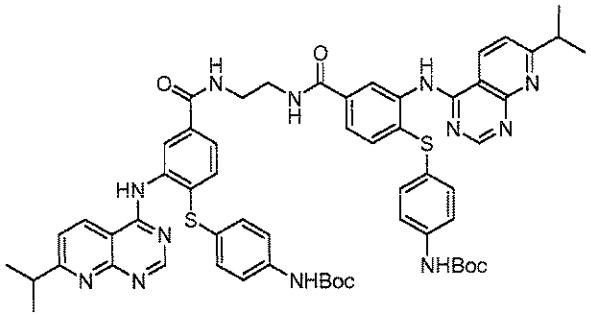
Example 5

N,N'-(ethane-1,2-diyl)bis(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide)



Example 5A

tert-butyl 4,4'-(4,4'-(ethane-1,2-diylbis(azanediyl))bis(oxomethylene)bis(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4,1-phenylene))bis(sulfanediyl)bis(4,1-phenylene)dicarbamate



To a solution of the product from Example 1E (50 mg, 0.094 mmol) in DMSO (2.0 mL) were added ethylenediamine (6.4 μL, 0.095 mmol), HATU (39.5 mg, 0.104 mmol), Hunigs base (50 μL, 0.282 mmol), and the mixture was stirred at room temperature until the starting material was consumed. Additional product from Example 1E (50 mg, 0.094 mmol), HATU (39.5 mg, 0.104 mmol), and Hunigs base (50 μL, 0.282 mmol) were added and the reaction was stirred for 2 hours. The reaction was diluted with ethyl acetate and washed with HCl (aq. 1M). Dried over Na_2SO_4, filtered and evaporated. Purification by chromatography on silica gel eluting with (4% to 7% methanol in dichloromethane) gave the title compound (100 mg, 91% yield) as a light yellow solid. ^1H NMR (500 MHz, DMSO-D6) δ ppm 1.32 (d, J=6.87 Hz, 12 H) 1.46 (s, 18 H) 3.39 (s, 4 H) 6.94 (d, J=8.09 Hz, 2 H) 7.30 (d, J=8.70 Hz, 4 H) 7.48 (d, J=8.54 Hz, 4 H) 7.59 (d, J=8.09 Hz, 2 H) 7.66 (d, J=8.09 Hz, 2 H) 7.84 (s, 2 H) 8.54 (s, 2 H) 8.56 (s, 2 H) 8.81 (d, J=8.39 Hz, 2 H) 9.53 (s, 2 H) 10.12 (s, 2 H). MS (ESI) *m/z* 1088 $(M + H)^+$.

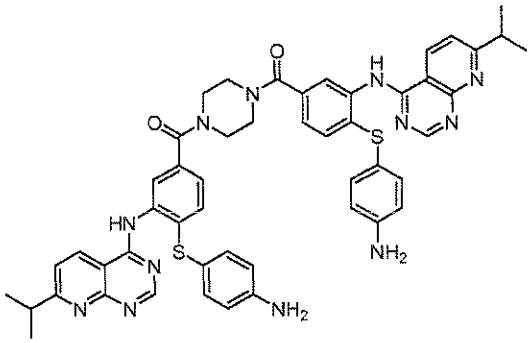
Example 5B

N,N'-(ethane-1,2-diyl)bis(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide)

The product from Example 5A was dissolve in dichloromethane (2.0 mL) and TFA (2.0 mL) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated and NH_4OH was added and the mixture was evaporated to dryness. Purification by prep TLC (10% methanol in dichloromethane) gave the title compound (28 mg, 36% yield) as a yellow solid. ^1H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (d, J=6.99 Hz, 12 H) 5.55 (s, 4 H) 6.60 (d, J=8.46 Hz, 4 H) 6.75 (d, J=8.09 Hz, 2 H) 7.10 (d, J=8.46 Hz, 4 H) 7.57 (s, 4 H) 7.76 (s, 2 H) 8.50 (s, 4 H) 8.80 (d, J=5.52 Hz, 2 H). MS (ESI) *m/z* 888 $(M + H)^+$.

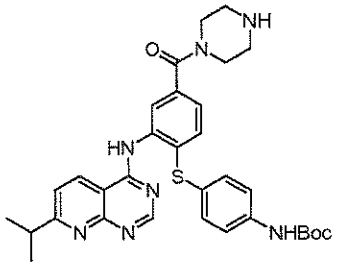
Example 6

piperazine-1,4-diylbis((4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)methanone)



Example 6A

tert-butyl 4-(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4-(piperazine-1-carbonyl)phenylthio)phenylcarbamate

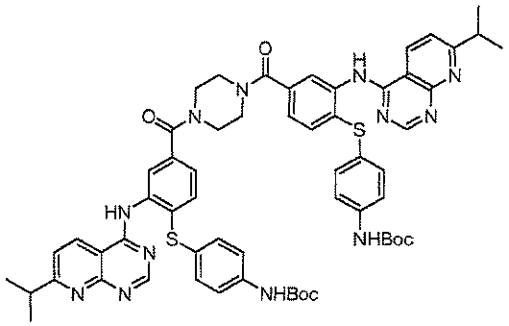


To a solution of the product from Example 1E (100 mg, 0.188 mmol) in DMSO (2.0 mL) were added piperazine (16 mg, 0.188 mmol), HATU (79 mg, 0.207 mmol) and Hunigs base (100 µL, 0.564 mmol) and the mixture was stirred at room temperature until the starting material was consumed. Additional product from Example 1E (100 mg, 0.188 mmol), HATU (79 mg, 0.212 mmol), and Hunigs base (100 µL, 0.564 mmol), were added and the reaction was stirred for 2 hours. The reaction was diluted with ethyl acetate and washed water. Dried over Na_2SO_4, filtered and

evaporated. Purification by chromatography on silica gel eluting with (10% methanol in dichloromethane) gave the title compound (150 mg) as a yellow solid.

Example 6B

tert-butyl 4,4'-(4,4'-(piperazine-1,4-diylbis(oxomethylene))bis(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4,1-phenylene))bis(sulfanediyl)bis(4,1-phenylene)dicarbamate



To a solution of the product from Example 6A (20 mg, 0.033 mmol) in DMF (1.0 mL) and pyridine (1.0 mL) were added EDAC (32 mg, 0.167 mmol) and the product from Example 1E (17.7 mg, 0.033 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was suspended in methanol. The solid was collected using centrifugation gave the title compound (22 mg, 57% yield).

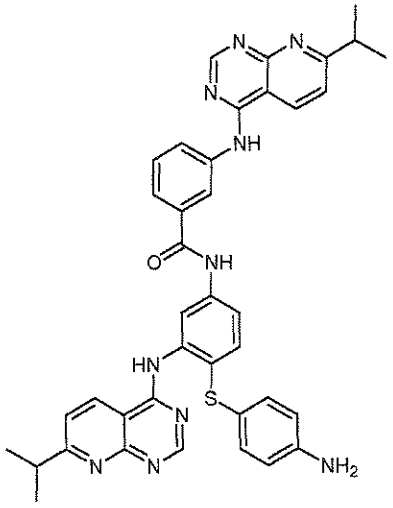
Example 6C

piperazine-1,4-diylbis((4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)methanone)

The product from Example 6B was dissolved in TFA (1.0 mL) and dichloromethane (1.0 mL) and the mixture was then allowed to stir at room temperature for 1 hour. The solvent was evaporated and NH_4OH was added and the mixture was evaporated to dryness. Purification by precipitation from methanol gave the title compound (12 mg, 94% yield) as a yellow solid. ^1H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (d, J=6.62 Hz, 12 H) 3.14 - 3.24 (m, 2 H) 3.54 (s, 8 H) 5.60 (s, 4 H) 6.61 (d, J=8.46 Hz, 4 H) 6.79 (d, J=5.15 Hz, 2 H) 7.13 (d, J=8.46 Hz, 4 H) 7.23 (s, 2 H) 7.41 (s, 2 H) 7.61 (d, J=6.99 Hz, 2 H) 8.56 (s, 2 H) 8.84 (d, J=6.25 Hz, 2 H) 10.11 (s, 2 H). MS (ESI) *m/z* 914 $(M + H)^+$.

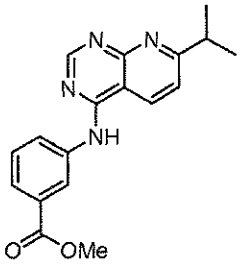
Example 7

N-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide



Example 7A

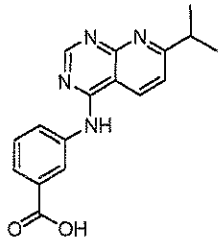
methyl 3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzoate



To methyl 3-aminobenzoate (0.50 g, 3.31 mmol) in acetic acid (10 mL) was added (E)-N'-(3-cyano-6-isopropylpyridin-2-yl)-N,N-dimethylformimidamide (0.71 g, 3.31 mmol) and the mixture was stirred at 120 °C for 25 minutes. Reaction mixture was cooled to room temperature and a solid formed. Water was added and solid was collected by filtration. Purification by chromatography on silica gel eluting with 0-30% methanol in dichloromethane gave the title compound (1.05 g, 98% yield).

Example 7B

3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzoic acid

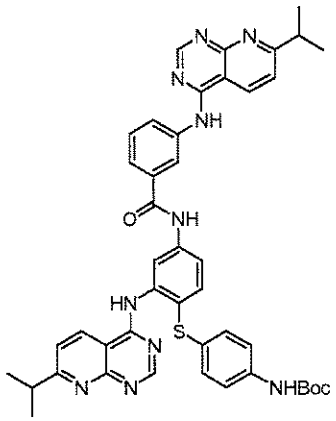


The product from Example 7A (1.0 g, 3.26 mmol) was dissolved in THF (12.0 mL) and water (12.0 mL) and LiOH (390 mg, 16.29 mmol) was added and the reaction was stirred at room

temperature overnight. Reaction was neutralized with 1 N HCl and extracted with ethyl acetate. Dried over Na_2SO_4, filtered and concentrated to give the title compound (1.5 g).

Example 7C

tert-butyl 4-(2-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)-4-(3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamido)phenylthio)phenylcarbamate



To a solution of the product from Example 7B (25.8 mg, 0.084 mmol) in DMSO (2.0 mL) were added the product from Example 2A (40 mg, 0.084 mmol), HATU (31.8 mg, 0.084 mmol), and Hunigs base (56 µL, 0.318 mmol), and the mixture was stirred at room temperature for 24 hours. Additional HATU (39.5 mg, 0.104 mmol), and Hunigs base (50 µL, 0.282 mmol) were added and the reaction was stirred for 48 hours. Added more HATU (39.5 mg, 0.104 mmol) and heated at 45 °C for 8 hours. Added more HATU (39.5 mg, 0.104 mmol) and stirred overnight at room temperature. Water was added and the product was collected by filtration. Purification by chromatography on silica gel eluting with (0% to 5% methanol in dichloromethane) gave the title compound (40 mg, 63% yield).

Example 7D

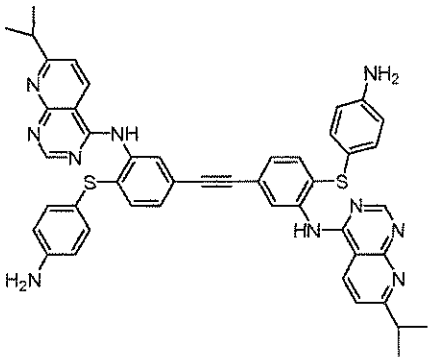
N-(4-(4-aminophenylthio)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)phenyl)-3-(7-isopropylpyrido[2,3-d]pyrimidin-4-ylamino)benzamide

The product from Example 7C (40 mg, 0.050 mmol) was dissolved in dioxane (2.0 mL) and 4M HCl in dioxane (0.25 mL) was added. This solution was stirred at room temperature overnight. The solid HCl salt of the product was filtered off then dissolved in methanol and added to saturated $NaHCO_3$. Extracted with ethyl acetate and evaporated. Purification by chromatography on silica gel eluting with (0% to 30% methanol in dichloromethane) gave the title compound (13 mg, 37% yield). ^{1}H NMR (300 MHz, DMSO-D6) d ppm 1.36 (dd, *J*=6.80, 4.23 Hz, 12 H) 3.20 - 3.30 (m, 2 H) 6.57 (d, *J*=8.46 Hz, 2 H) 7.04 - 7.12 (m, 3 H) 7.60 - 7.70 (m, 2 H) 7.82 - 7.95 (m, 3 H) 8.00 - 8.08 (m, 2 H)

8.29 (s, 1 H) 8.83 - 8.93 (m, 2 H) 9.09 (d, *J*=12.50 Hz, 1 H) 9.17 (d, *J*=7.72 Hz, 1 H) 10.58 (s, 1 H) 11.38 (s, 1 H) 11.69 (s, 1 H). MS (ESI) *m/z* 693 $(M + H)^+$.

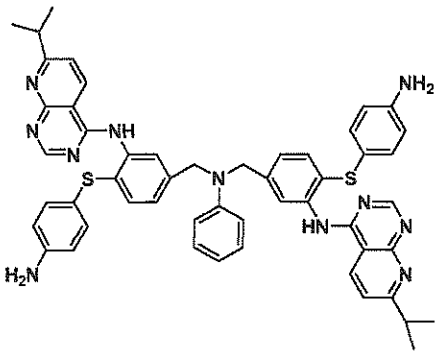
Example 8

N,N'-(5,5'-(ethyne-1,2-diyl)bis(2-(4-aminophenylthio)-5,1-phenylene))bis(7-isopropylpyrido[2,3-d]pyrimidin-4-amine)

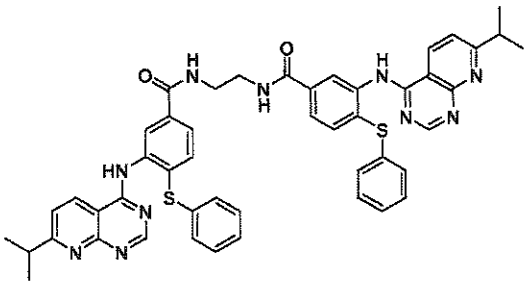


The title compound can be prepared by first coupling 1-fluoro-4-iodo-2-nitrobenzene with ethynyltrimethylsilane by Sonogashira reaction using a suitable catalyst. Pd catalysts such as $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ may be employed or generated in situ using a Pd (II) catalyst such $Pd(OAc)_2$ or $Pd_2(dba)_3$ and organophosphorous ligands, such as PPh_3 or $P(t\text{-}Bu)_3$. Alternatively, a Cu (I) catalyst may be employed, such as Cu (I) iodide. Reactions may be conducted with addition of a base such K_2CO_3 or K_3PO_4 or an amine base such as triethylamine or Hunig's base in a solvent such as THF or DMF. The trimethylsilyl (TMS) protecting group may be removed using a base such as K_2CO_3 in a solvent such as methanol or THF to produce 4-ethynyl-1-fluoro-2-nitrobenzene. A second Sonogashira reaction between 1-fluoro-4-iodo-2-nitrobenzene and 4-ethynyl-1-fluoro-2-nitrobenzene may be conducted under the analogous conditions to the first coupling to form 1,2-bis(4-fluoro-3-nitrophenyl)ethyne. Couplings may be conducted concurrently to give symmetric products or sequentially to give non-symmetric products. The fluoride and nitro substituted product may be reacted with alkyl, aryl, or heteroaryl alcohols, thiols, phenols, or thiophenols using a base such as K_2CO_3 or Hunig's base in a solvent such as THF or DMF. Nitro groups may be reduced to amino groups, using Pd or Raney Ni catalyzed hydrogenation or using Fe in the presence of NH_4Cl, HCl, or acetic acid, and further functionalized to the title compound using the processes described in U.S. Patent Application Publication Nos. 20070232627, 20070197558 and 20070232645, and WO2008/133753. Similarly, 1-chloro-4-iodo-2-nitrobenzene may be used as the starting material to prepare the title compound of this Example.

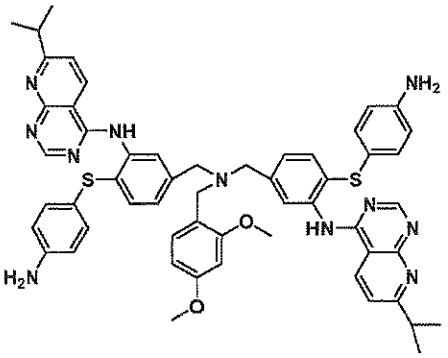
The following compounds were also prepared according to the processes described herein:



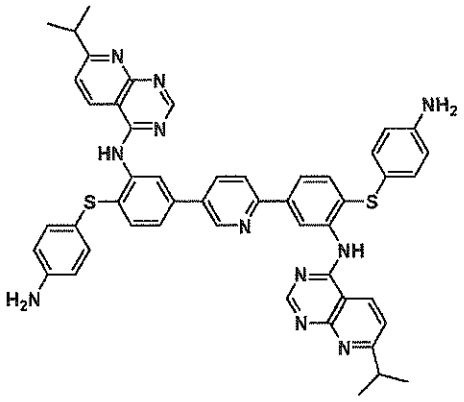
Example 9



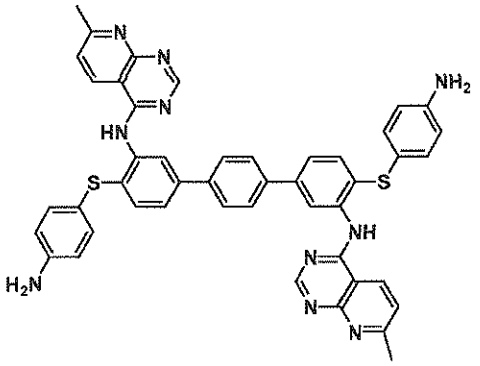
Example 10



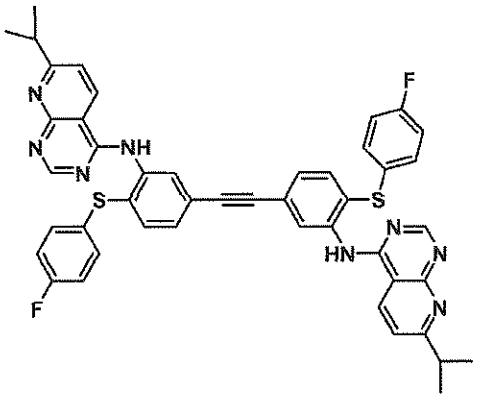
Example 11



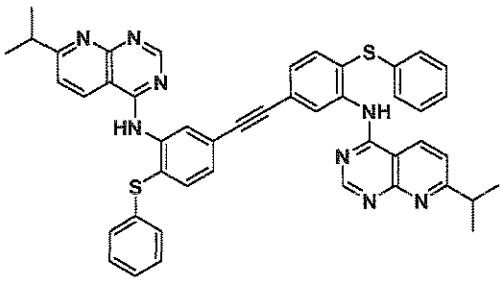
Example 12



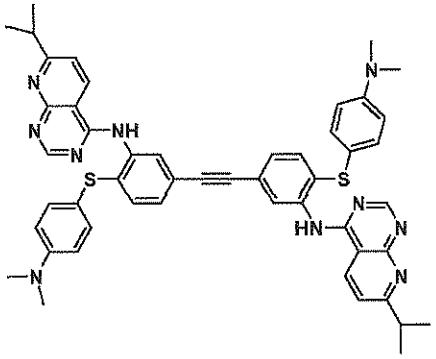
Example 13



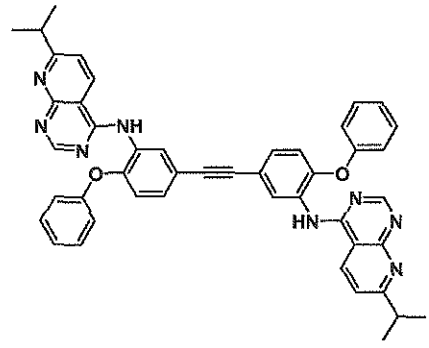
Example 14



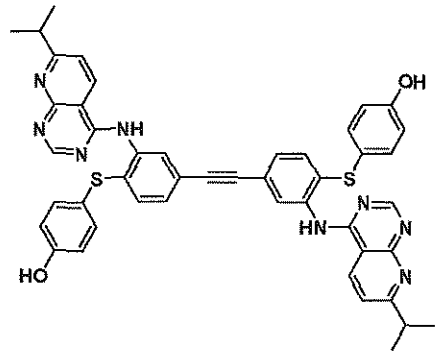
Example 15



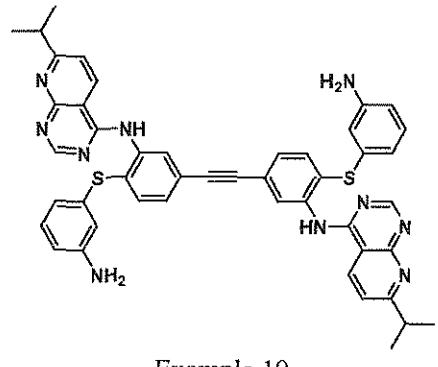
Example 16



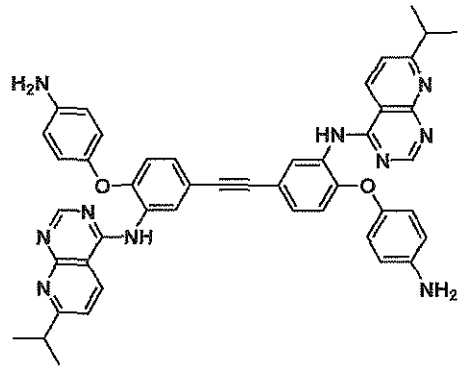
Example 17



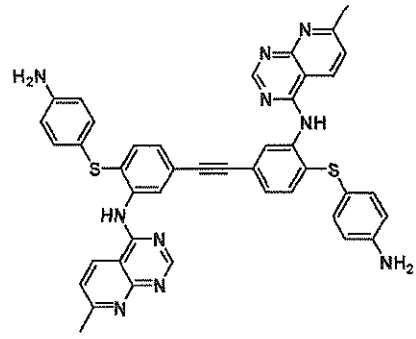
Example 18



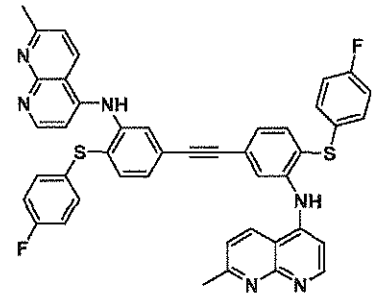
Example 19



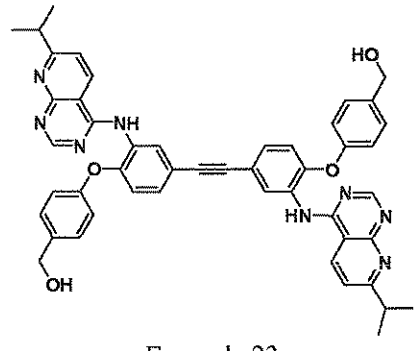
Example 20



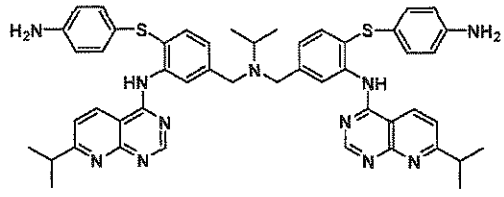
Example 21



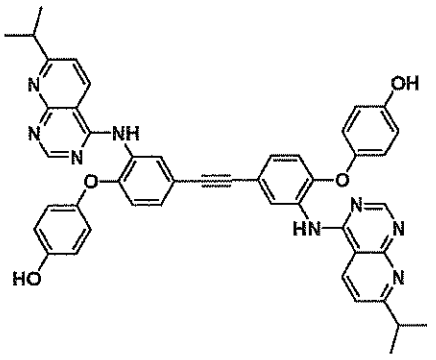
Example 22



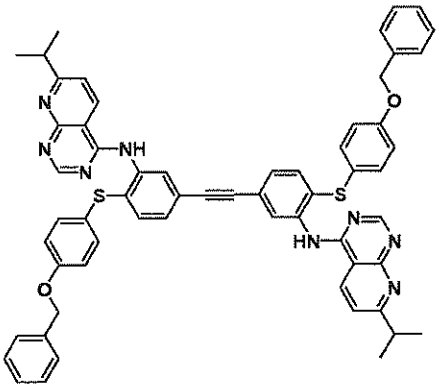
Example 23



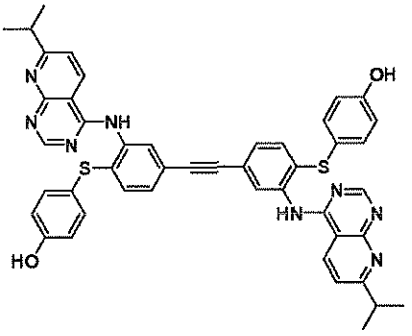
Example 24



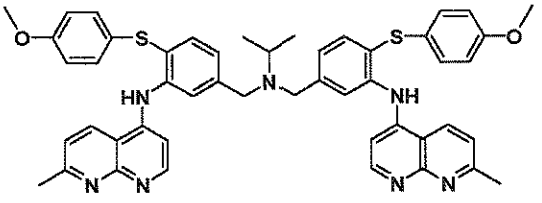
Example 25



Example 26

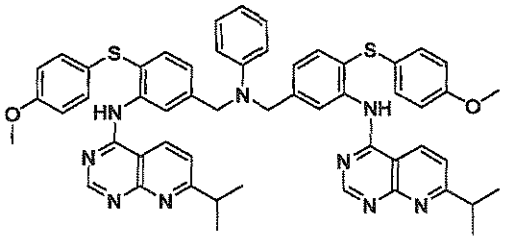


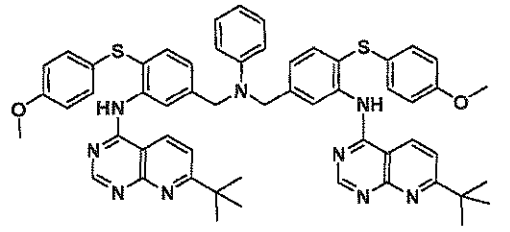
Example 27

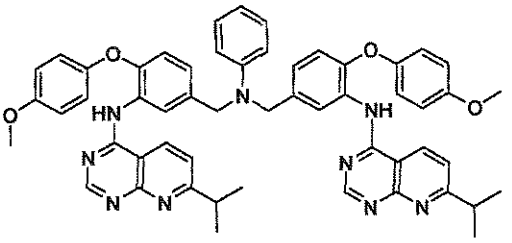


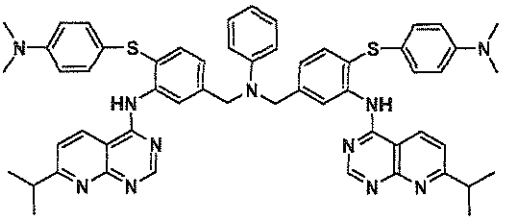
Example 28

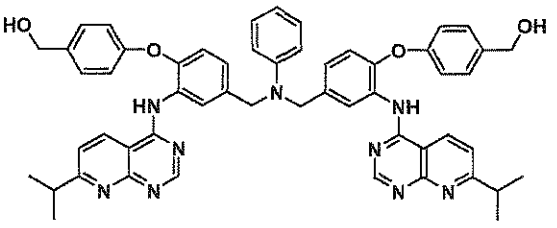
In addition, the following compounds can be prepared according to the present invention:



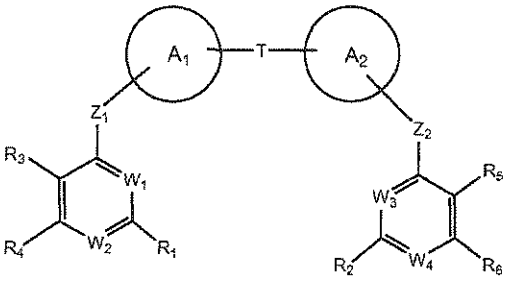








Likewise, the following compounds of Formula I can be similarly prepared according to the present invention,



I

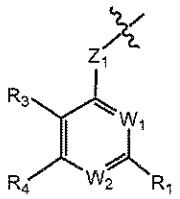
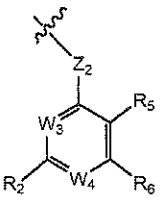
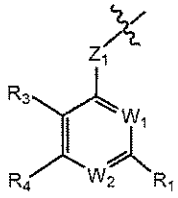
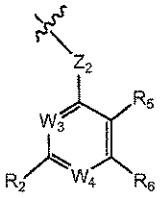
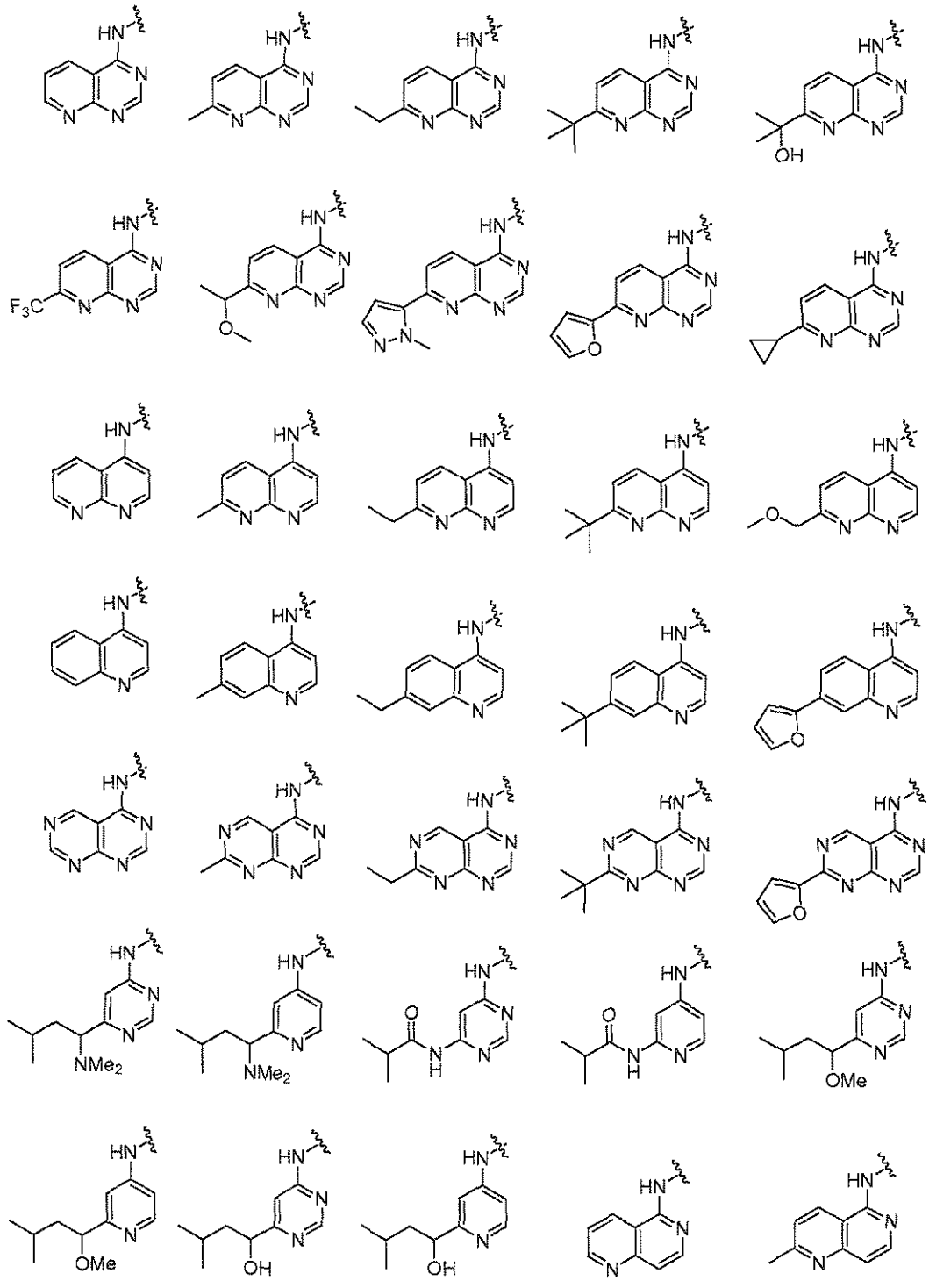
wherein  and  are each independently selected from Table 1; $-X_1-R_7$ and $-X_2-R_8$ are each independently selected from Tablet 2; A_1 and A_2 are each independently selected from Table 3, or A_1 is selected from Table 3a and A_2 is selected from Table 3b; and T is selected from Table 4.

Table 1.  and 



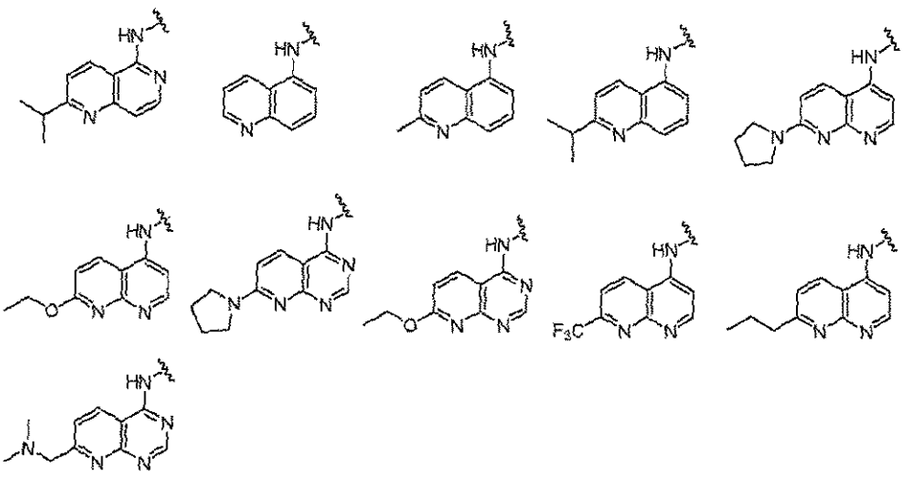


Table 2. -X_1-R_7 and –X_2-R_8

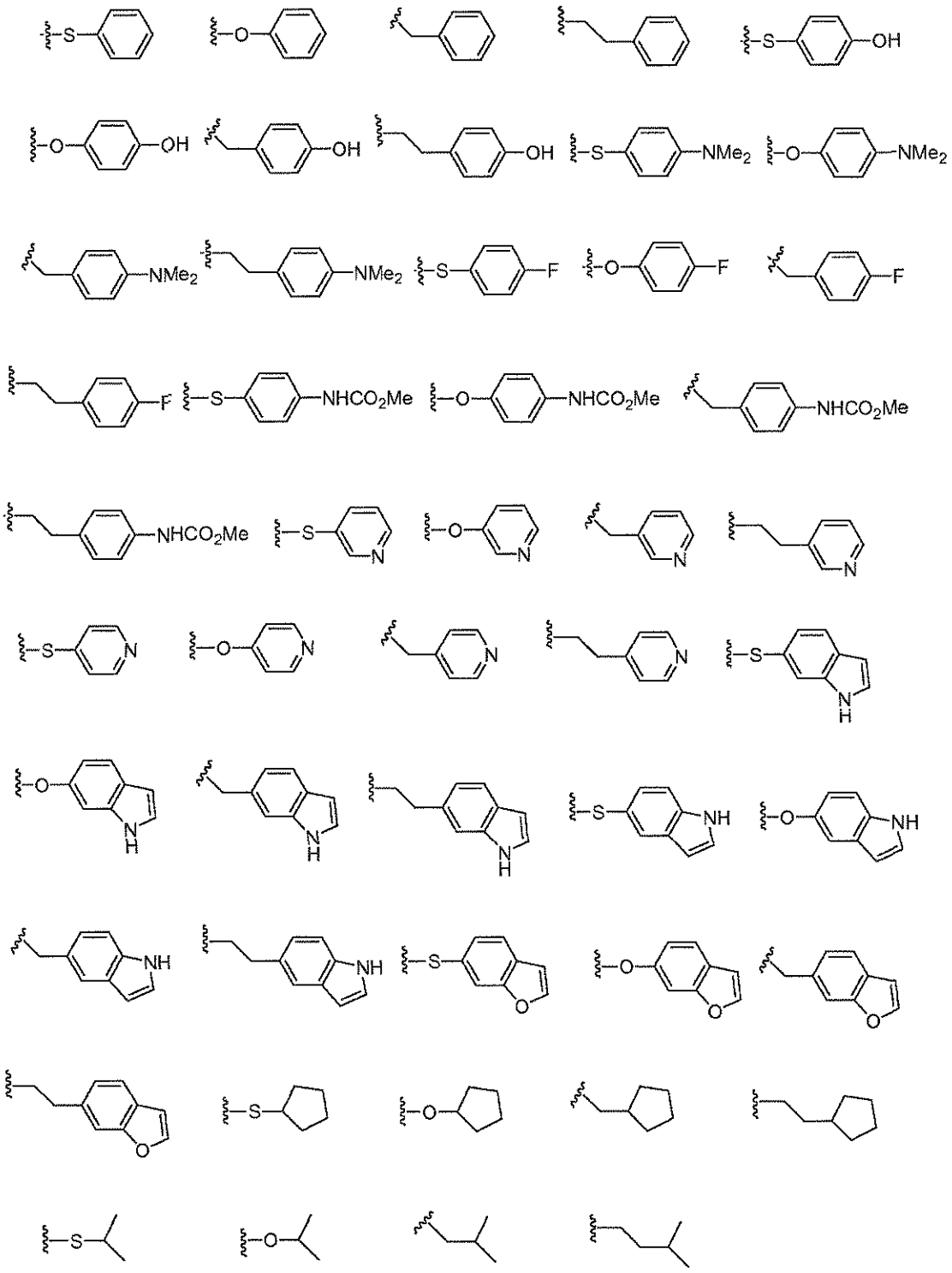


Table 3. A_1 and A_2

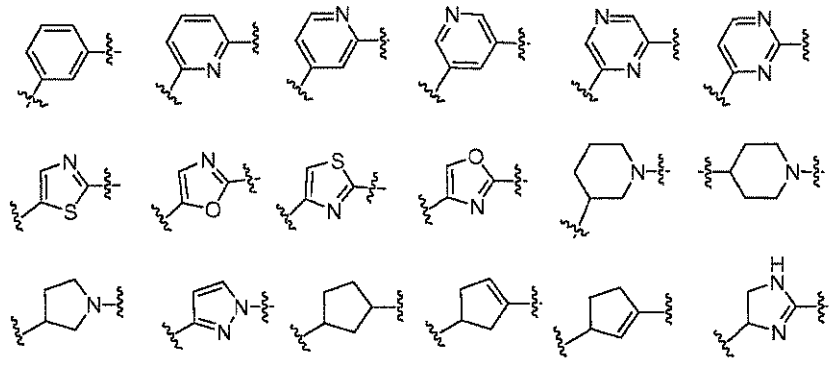


Table 3a. A_1

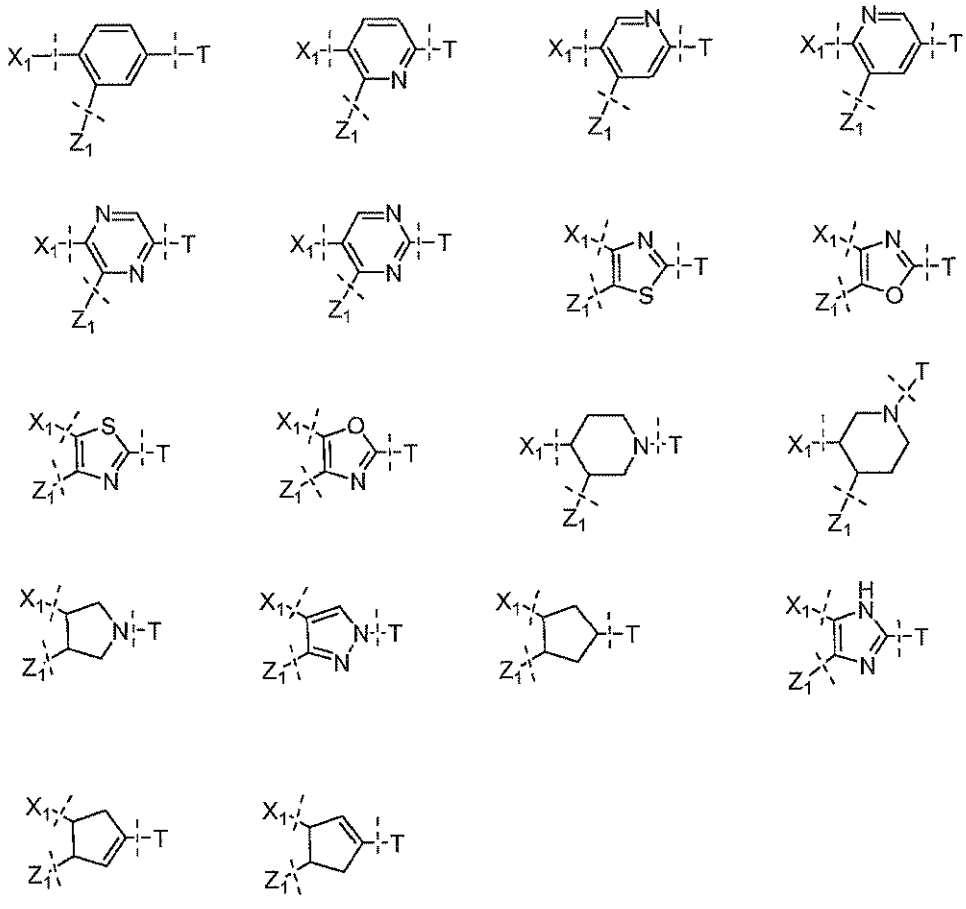


Table 3b. A_2

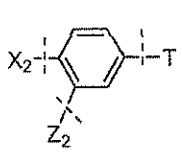
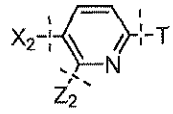
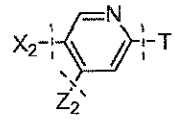
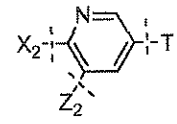
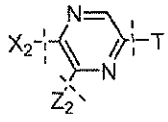
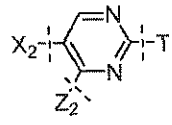
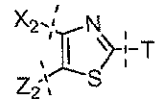
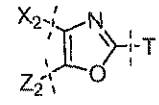
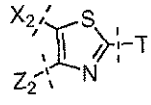
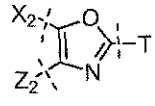
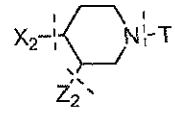
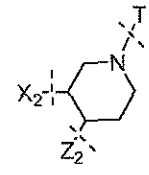
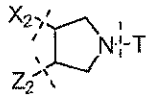
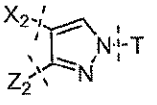
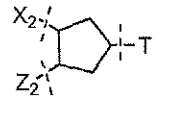
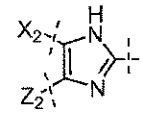
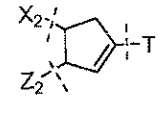
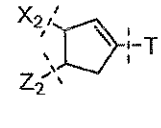
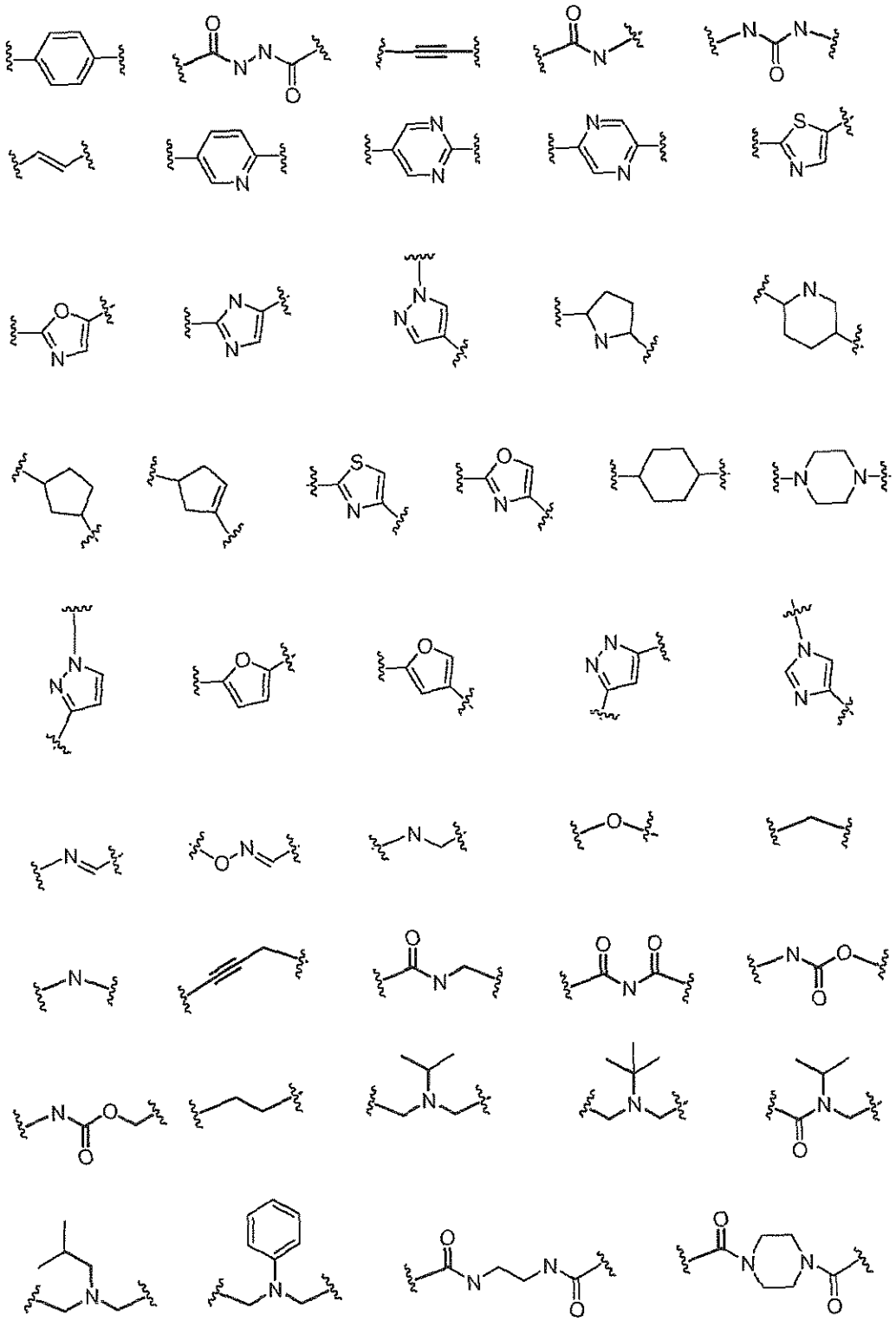
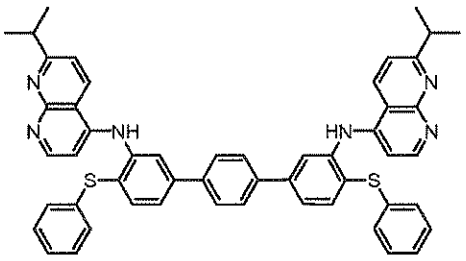



















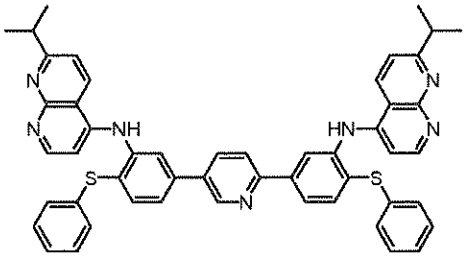
Table 4. –T–

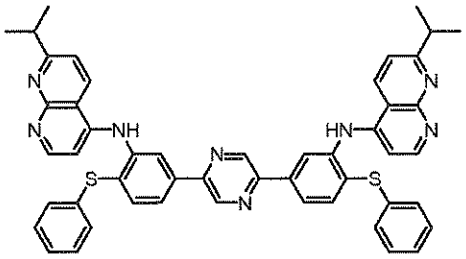


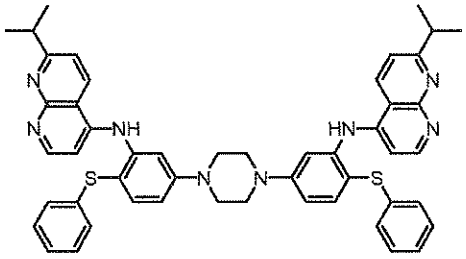
Likewise, the compounds in Table 5 can be prepared according to the present invention:

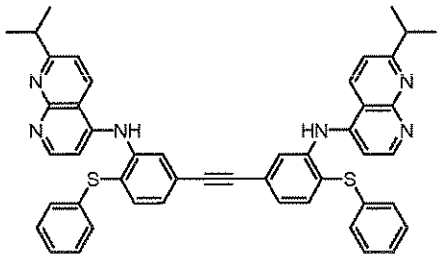
Table 5

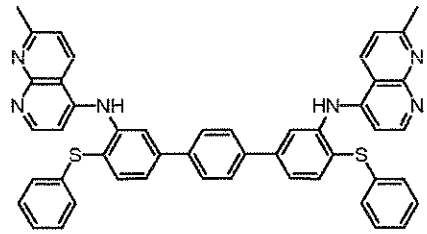


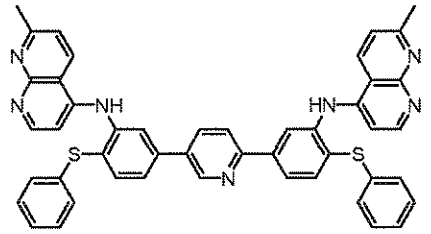


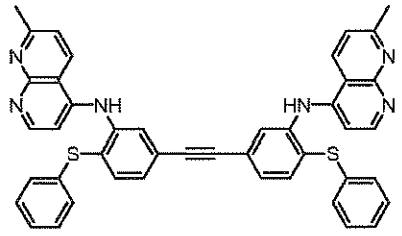


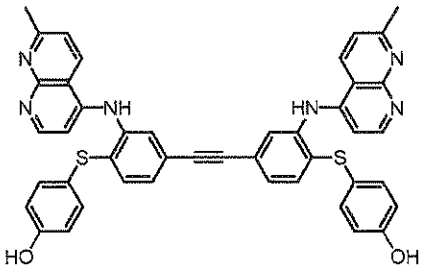


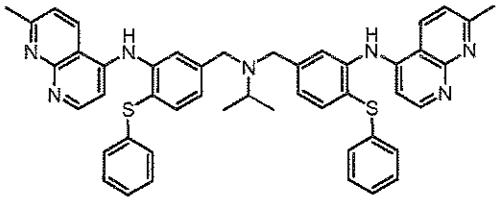


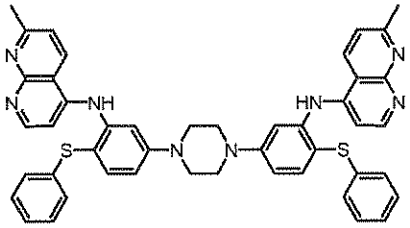


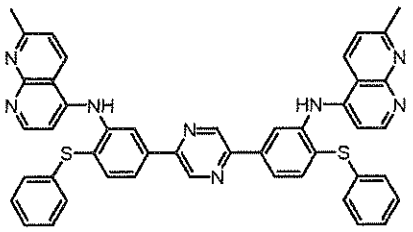


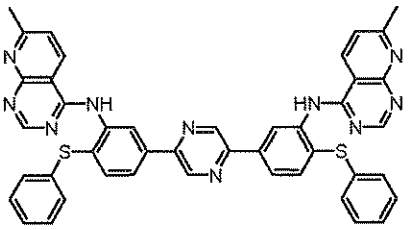


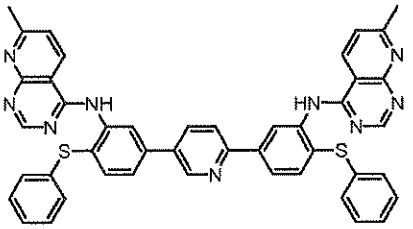


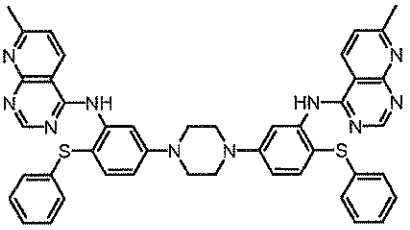


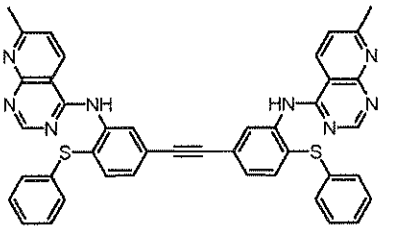


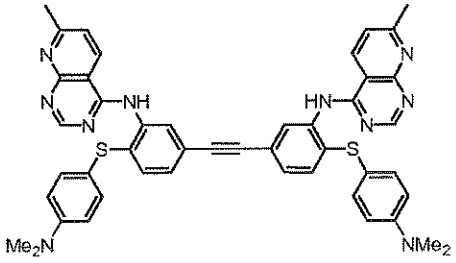


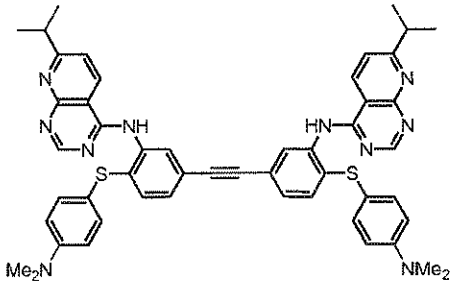


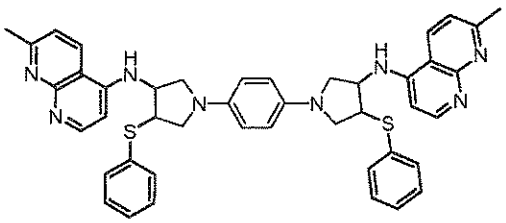


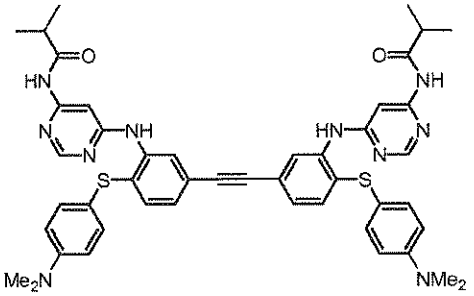


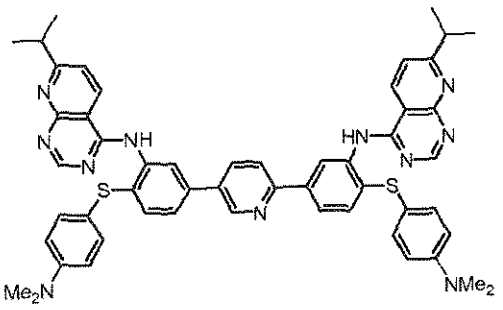


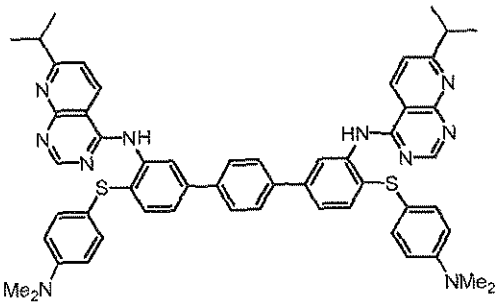


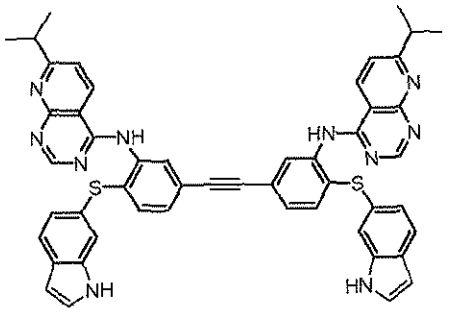


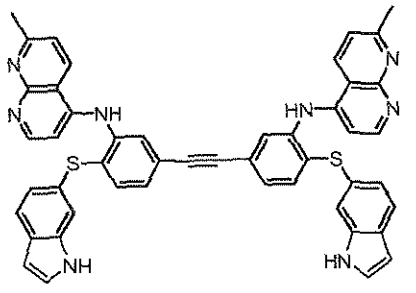


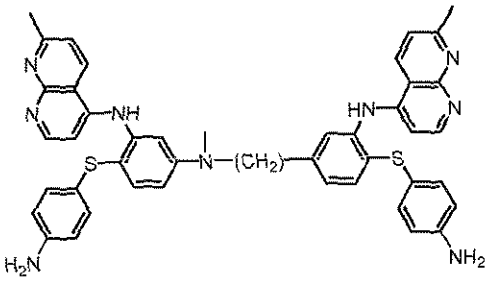


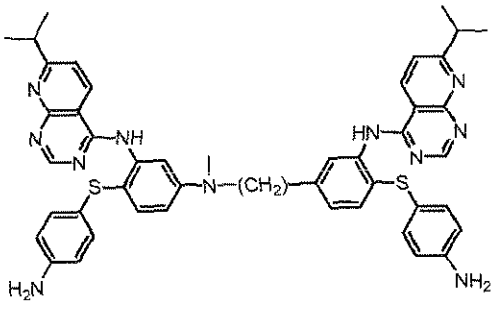


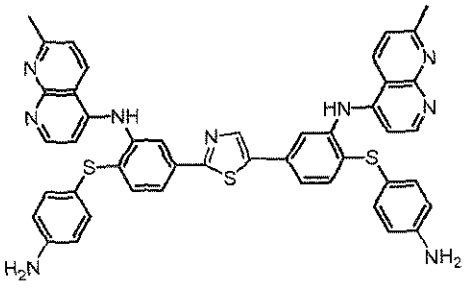


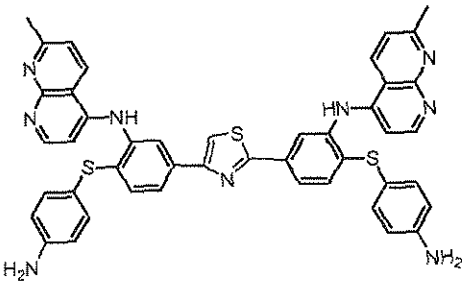


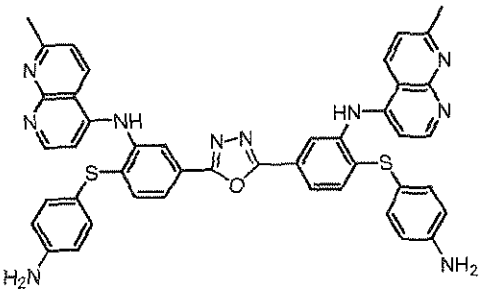


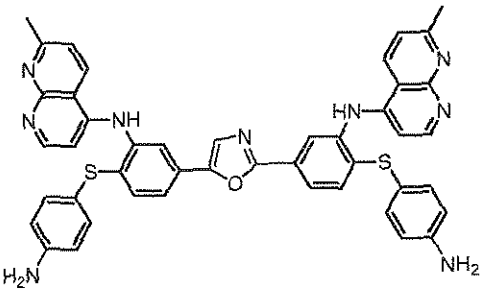


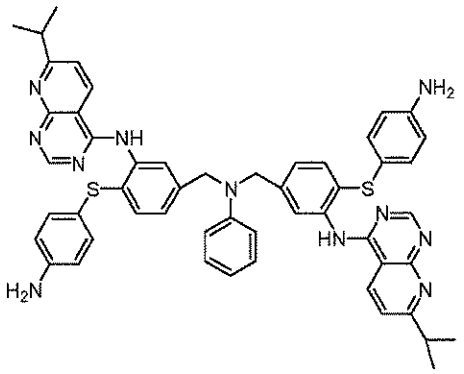












The inhibitory activities of the compounds of the present invention can be evaluated using a variety of assays known in the art. For instance, two stable subgenomic replicon cell lines can be used for compound characterization in cell culture: one derived from genotype 1a-H77 and the other derived from genotype 1b-Con1. The replicon constructs can be bicistronic subgenomic replicons. The genotype 1a replicon construct contains NS3-NS5B coding region derived from the H77 strain of HCV (1a-H77). The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. These two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the NS3-NS5B coding region with addition of adaptive mutations. The 1b-Con1 replicon construct is identical to the 1a-H77 replicon, except that the NS3-NS5B coding region is derived from the 1b-Con1 strain and that the replicon contains different adaptive mutations. Replicon cell lines can be maintained in Dulbecco's modified Eagles medium (DMEM) containing 10% (v/v) fetal bovine serum (FBS), 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), and 200 mg/ml G418 (Invitrogen).

The inhibitory effects of the compounds of the invention on HCV replication can be determined by measuring activity of the luciferase reporter gene. For example, replicon-containing cells can be seeded into 96 well plates at a density of 5000 cells per well in 100 μl DMEM containing 5% FBS. The following day compounds can be diluted in dimethyl sulfoxide (DMSO) to generate a 200x stock in a series of eight half-log dilutions. The dilution series can then be further diluted 100-fold in the medium containing 5% FBS. Medium with the inhibitor is added to the overnight cell culture plates already containing 100 μl of DMEM with 5% FBS. In assays measuring inhibitory activity in the presence of human plasma, the medium from the overnight cell culture plates can be replaced with DMEM containing 40% human plasma and 5% FBS. The cells can be incubated for three days in the tissue culture incubators and are then lysed for RNA extraction. For the luciferase assay, 30 μl of Passive Lysis buffer (Promega) can be added to each well, and then the plates are incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) can be added to each well, and luciferase activity can be measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of HCV RNA replication can be calculated for each compound

concentration and the IC_{50} and/or EC_{50} value can be calculated using nonlinear regression curve fitting to the 4-parameter logistic equation and GraphPad Prism 4 software.

When evaluated using the above method, representative compounds of the present invention inhibited HCV replicon replication with IC_{50} values in the range of from about 0.1 nM to about 100 μM. IC_{50} refers to 50% inhibitory concentration. Cytotoxicity of the compounds of the present invention can also be evaluated using methods known in the art. When tested, the TC_{50} values of representative compounds of the present invention were often greater than the corresponding IC_{50} values of the compounds. TC_{50} refers to 50% toxicity concentration. Table 6 lists the IC_{50} values of the compounds of Examples 1-28 when tested using HCV replicons.

Table 6

Example	IC_{50} for replicon 1b-Con1
1	0.1 nM – 10 nM
2	0.1 nM – 10 nM
3	10 nM – 100 nM
4	0.1 nM – 10 nM
5	0.1 nM – 10 nM
6	0.1 nM – 10 nM
7	100 nM – 10 μM
8	less than 0.1 nM
9	less than 0.1 nM
10	100 nM – 10 μM
11	0.1 nM – 10 nM
12	0.1 nM – 10 nM
13	0.1 nM – 10 nM
14	0.1 nM – 10 nM
15	0.1 nM – 10 nM
16	0.1 nM – 10 nM
17	0.1 nM – 10 nM
18	0.1 nM – 10 nM
19	0.1 nM – 10 nM
20	0.1 nM – 10 nM
21	0.1 nM – 10 nM
22	10 nM – 100 nM
23	0.1 nM – 10 nM
24	0.1 nM – 10 nM
25	0.1 nM – 10 nM
26	0.1 nM – 10 nM
27	0.1 nM – 10 nM
28	10 nM – 100 nM

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, each of which has a formula independently selected from selected from Formulae I, II or III.

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 comprising a compound of the invention (or a salt, solvate or prodrug thereof) and 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), Albuferon (Novartis), ritonavir, another cytochrome P450 monooxygenase inhibitor, or any combination thereof.

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

In another embodiment, a pharmaceutical composition of the present invention comprises one or more compounds of the present invention (or salts, solvates or prodrugs thereof), and one or more other anti-HCV agents. For example, a pharmaceutical composition of the present invention can comprise a compounds of the present invention having Formula I, II or III (or (or a salts, solvate or prodrug thereof), and 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 one or more compounds of the present invention (or salts, solvates or prodrugs thereof), and 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, 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 invention (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 (or a salt, solvate or prodrug 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 all 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 (or a salt, solvent or prodrug 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.

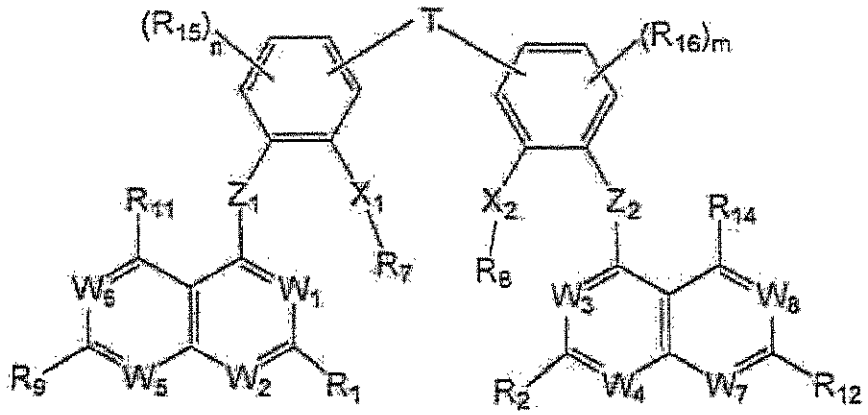
The present invention further features methods of using the pharmaceutical compositions of the present invention to treat HCV infection. The methods typically comprise administering a pharmaceutical composition of the present invention to an HCV patient, thereby reducing the HCV viral level in the blood 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 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 II, or a pharmaceutically acceptable salt thereof,



II

wherein:

X_1 and X_2 are each independently selected from a bond, $-CH_2-$, -O-, or -S-, and at least one of X_1 and X_2 is selected from $-CH_2-$, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

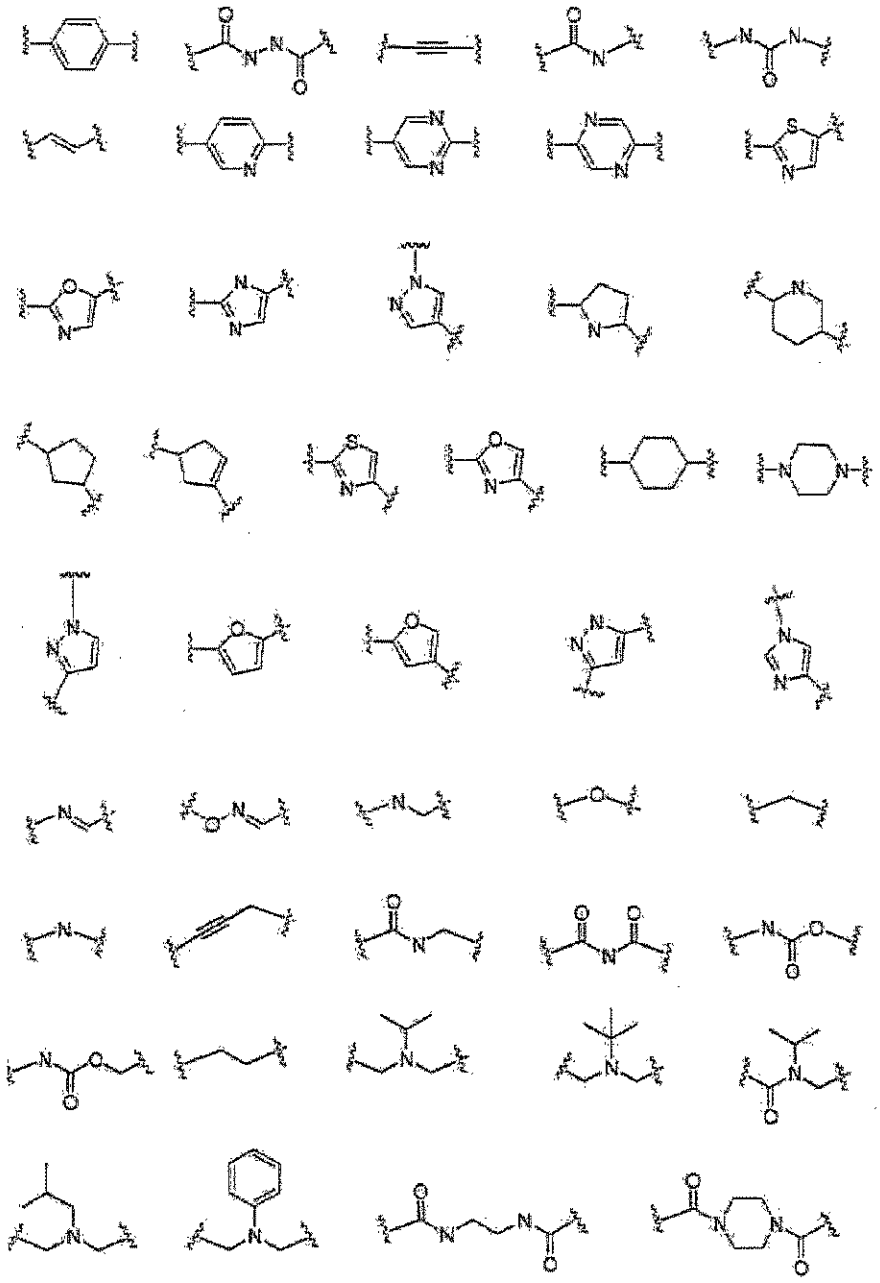
Z_1 and Z_2 are each selected from $-N(R_B)-$;

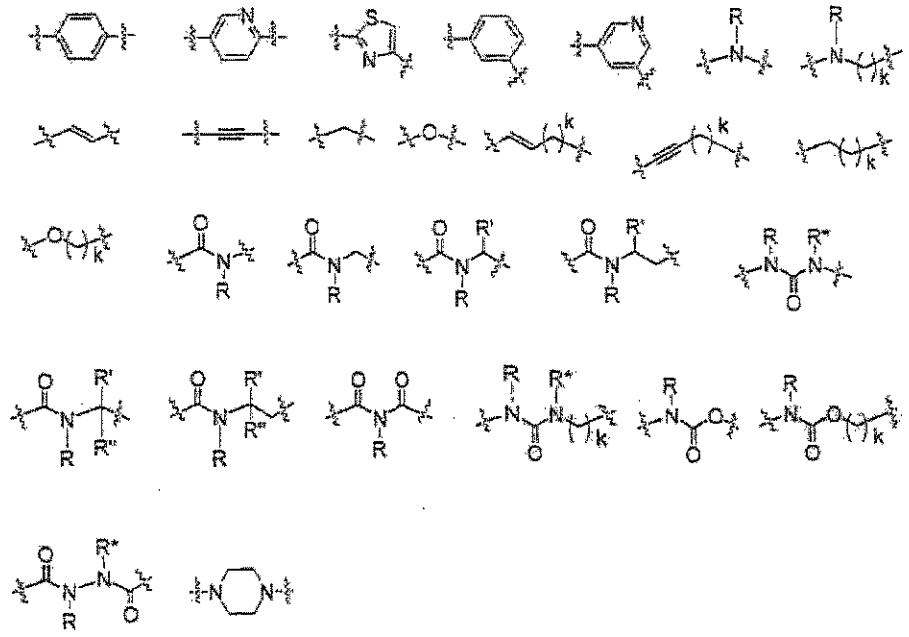
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or RA;

m and n are each 0;

T is selected from a bond, -L_S-, -L_S-M-L_S-, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R" are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -$N(R_B)$-, -$C(O)N(R_B)$-, -$N(R_B)C(O)$-, -$N(R_B)C(O)N(R_{B'})$-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, 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_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or-N($R_SR_{S'}$); and

R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

2. The compound or salt of claim 1, wherein:

X_1 and X_2 are each independently selected from -CH_2-, -O-, or -S-; and

R_7 and R_8 are each independently selected C_6aryl optionally substituted with one or more R_A.

3. The compound or salt of claim 1, wherein:

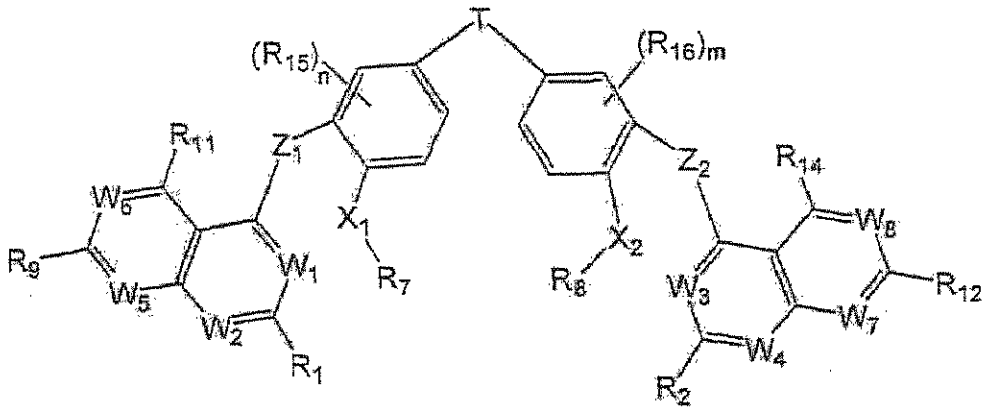
W_1, W_2, W_3, W_4, W_5, and W_7 are N, and W_6 and W_8 are each independently C(R_D);

R_1 and R_2 are hydrogen;

R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A; and

R_9, R_{11}, R_{12}, and R_{14} are each independently selected at each occurrence from hydrogen; halogen; or C_1-C_6alkyl, or C_2-C_6alkynyl.

4. A compound of Formula III, or a pharmaceutically acceptable salt thereof,



III

wherein:

X_1 and X_2 are each independently selected from a bond, $-CH_2-$, -O-, or -S-, and at least one of X_1 and X_2 is selected from $-CH_2-$, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

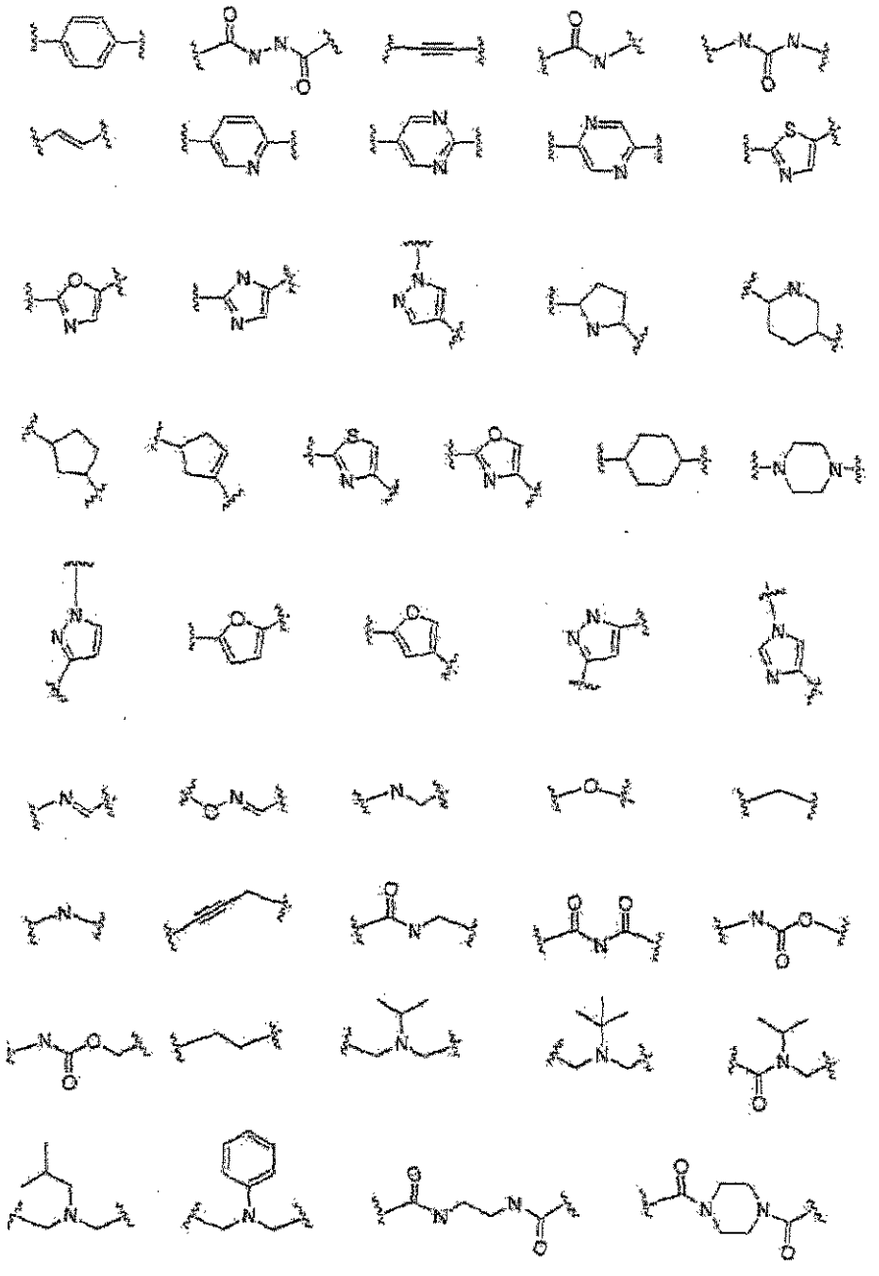
Z_1 and Z_2 are each selected from $-N(R_B)-$;

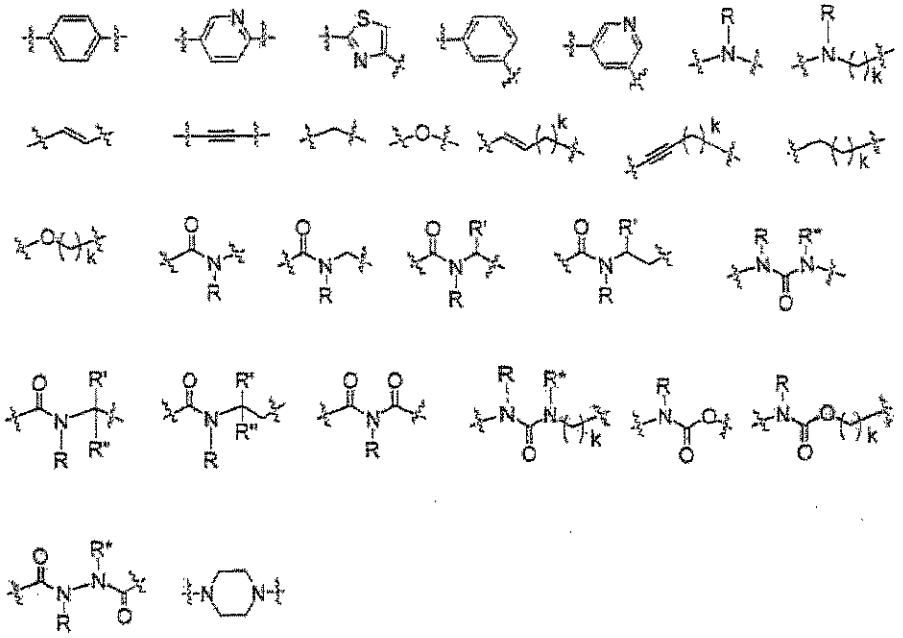
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or R_A;

m and n are each 0;

T is selected from a bond, $-L_S-$, $-L_S-M-L_S-$, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -N(R_B)-, -C(O)N(R_B)-, -N(R_B)C(O)-, -N(R_B)C(O)N($R_{B'}$)-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, 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_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or -N(R_S $R_{S'}$); and

R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

5. The compound or pharmaceutically acceptable salt thereof of claim 4, wherein:

X_1 and X_2 are each independently selected from -CH_2-, -O-, or -S-; and

R_7 and R_8 are each independently selected C_6aryl optionally substituted with one or more R_A.

6. The compound or pharmaceutically acceptable salt thereof of claim 4, wherein:

W_1, W_2, W_3, W_4, W_5, and W_7 are N, and W_6 and W_8 are each independently C(R_D);

R_1 and R_2 are hydrogen;

R_7 and R_8 are phenyl, and are each independently optionally substituted with one or more R_A; and

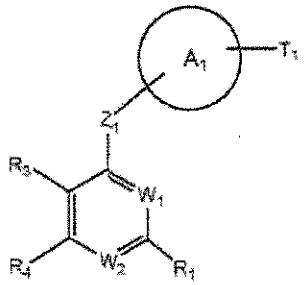
R_9, R_{11}, R_{12}, and R_{14} are each independently selected at each occurrence from hydrogen; halogen; or C_1-C_6alkyl, or C_2-C_6alkynyl.

7. A pharmaceutical composition comprising a compound or salt of claim 1 or 4.

8. Use of a compound or salt of claim 1 or claim 4 for inhibiting HCV replication in a patient, in the manufacture of a medicament for treating HCV infection.

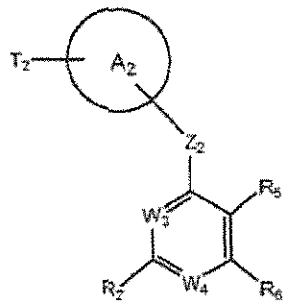
9. A process of making a compound of claim 1 or 4, comprising the step of:

coupling a compound of Formula IV



IV

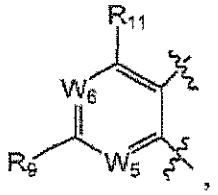
to a compound of Formula V



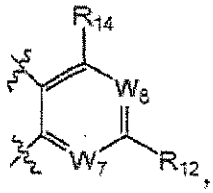
V

wherein T_1 is a carboxylic acid, an activated derivative, or an activated ester, T_2 is an amine or a substituted amine, A_1 is phenyl substituted with $-X_1$-R_7 and optionally substituted with one or more R_A, A_2 is phenyl substituted with $-X_2$-R_8

and optionally substituted with one or more R_A, R_3 and R_4, taken together with the carbon atoms to which they are attached, form



R_5 and R_6, taken together with the carbon atoms to which they are attached, form



, and

X_1, X_2, Z_1, Z_2, W_1, W_2, W_3, W_4, W_5, W_6, W_7, W_8, R_1, R_2, R_7, R_8, R_9, R_{11}, R_{12}, R_{14}, and R_A are as defined in claim 1 or 4.

10. A method of inhibiting HCV virus replication in vitro, comprising contacting cells infected with HCV virus with a compound or salt of claim 1 or 4.