Provided herein are compounds, pharmaceutical compositions and combination therapies for treatment of hepatitis C.
Fused Ring Inhibitors of Hepatitis C
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Statement of Related Applications

[0001] This application claims the benefit of U.S. provisional applications 61/164,342 filed on March 27, 2009 and 61/214,883 filed on April 28, 2009.

Field of the Invention

[0002] The invention relates to compounds useful for inhibiting hepatitis C virus ("HCV") replication, particularly functions of the non-structural 5A ("NS5A") protein of HCV.

Background of the Invention

[0003] HCV is a single-stranded RNA virus that is a member of the Flaviviridae family. The virus shows extensive genetic heterogeneity as there are currently seven identified genotypes and more than 50 identified subtypes. In HCV infected cells, viral RNA is translated into a polyprotein that is cleaved into ten individual proteins. At the amino terminus are structural proteins: the core (C) protein and the envelope glycoproteins, E1 and E2, and p7, an integral membrane protein that follows E1 and E2. Additionally, there are six non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B, which play a functional role in the HCV lifecycle. (see, for example, Lindenbach, B.D. and Rice, CM. Nature. 436:933-938, 2005).

[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

[0005] The present standard of care treatment regimen for HCV infection involves interferon-alpha, alone or in combination with ribavirin. The treatment is cumbersome and sometimes has debilitating and severe side effects and many patients do not durably respond to treatment. New and effective methods of treating HCV infection are urgently needed.
Summary of the Invention

[0006] Essential features of the NS5A protein of HCV make it an ideal target for inhibitors. The present invention describes a class of compounds targeting the NS5A protein and methods of their use to treat HCV infection in humans.

[0007] In a first aspect, compounds of formula I are provided:

![Chemical Structure](image)

wherein:

D is either present or absent and if present selected from the group consisting of
-\(-\text{CR}_2\text{CR}_2^2\), -\(-\text{CR}_2^2\), -\(-\text{NR}^\text{N}\), -\(-\text{O}\) and -\(-\text{S}\) wherein:

\(\text{R}^\text{N}\) is H, -\(-\text{OH}\), \(-\text{CO}_\text{t}\text{CO}_\text{t}\) alkyl, \(-\text{CO}_\text{t}\text{CO}_\text{t}\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, and sulfonamide, and,

each \(\text{R}\) is independently selected from the group consisting of hydrogen, -\(-\text{OH}\), -\(-\text{CN}\), -\(-\text{NO}_2\), halogen, \(-\text{CO}_\text{t}\text{CO}_\text{t}\) alkyl, \(-\text{CO}_\text{t}\text{CO}_\text{t}\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

\(\text{A}\) and \(\text{E}\) are:

each independently -\(-\text{CR}_2\), -\(-\text{CR}_2^2\), -\(-\text{CR}^\text{CR}_2^2\), -\(-\text{CR}^\text{CR}_2^2\), -\(-\text{N}^\text{N}\), -\(-\text{CN}\), -\(-\text{NO}_2\), halogen, \(-\text{CO}_\text{t}\text{CO}_\text{t}\) alkyl, \(-\text{CO}_\text{t}\text{CO}_\text{t}\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

\(\text{R}\)'s either both on a single \(\text{C}\) or on adjoining \(\text{Cs}\), together with the \(\text{C}\)
or $C$ to which they are attached, optionally form a cycle, and
where two R's are possible on a C, the C may optionally be linked to a
single R with a double bond;
each a and b are independently 0, 1, 2, or 3 with the proviso that if D is present
both b's are not 0; and
$R^N$ and R may be replaced by a bond to D if D is present,
if D is absent, A and E can additionally each independently be a bond, -O-, -S-, 
-S(O)_, -S(O)_, -C(O)- or -N=, and
with the proviso that if W and W are both 5-membered rings, A and E are either
both a bond or both other than a bond;
each R is independently selected from the group consisting of -OH, -CN, -NO$_2$, halogen,
Ci to C$_{12}$ alkyl, Ci to C$_{12}$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl,
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate,
sulfonamide and amino;
each r is independently 0, 1, 2 or 3;
W and W are each independently selected from the group consisting of

and

$X^1$ is CH$_2$, NH, O or S.
$Y^1$, $Y^2$ and $Z^1$ are each independently CH or N,
$X^2$ is NH, O or S,
W and W are each independently optionally substituted with one or more
substituents selected from the group consisting of -OH, -CN, -NO$_2$, halogen,
Ci to C_{12} alkyl, Ci to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonam id e and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_{2}, halogen, Ci to C_{12} alkyl, Ci to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^{e}, R^{d}, R^{c} and R^{f} is independently selected from the group consisting of: hydrogen, Ci to C_{8} alkyl, Ci to C_{8} heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,

each of R^{e}, R^{d}, R^{c} and R^{f} may optionally be substituted by Ci to C_{8} alkyl, Ci to C_{8} heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R^{c} and R^{d} are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring,

and

R^{c} and R^{f} are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C_{8} alkyl, Ci to C_{8} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-\{U-(CR^4_2)\}_{1}NR^{5}_{-(CR^4_2)}\}_{1}O-(CR^4_2)_{1}-U-(CR^4_2)_{1}-R^{8}, and

\{U-(CR^4_2)\}_{1}NR^{5}_{-(CR^4_2)}\}_{1}O-(CR^4_2)_{1}-R^{8},\text{ where in,}

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)_{2}^{-},
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to C_{8} alkyl, Ci to C_{8} heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl and aralkyl,

R<sub>8</sub> is selected from the group consisting of hydrogen, Ci to C<sub>g</sub> alkyl, Ci to C<sub>g</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R<sup>81</sup>, -C(S)-R<sup>81</sup>, -C(O)-O-R<sup>81</sup>, -C(O)-N-R<sup>81</sup>, -S(O)<sub>2</sub>-R<sup>81</sup> and -S(O)<sub>2</sub>-N-R<sup>81</sup>, wherein each R<sub>81</sub> is independently chosen from the group consisting of hydrogen, Ci to C<sub>g</sub> alkyl, Ci to C<sub>g</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R<sub>7</sub> and R<sub>8</sub> together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0008] In a first embodiment of the first aspect, one or both of W and W are selected from the group consisting of

\[ \begin{align*}
    &\text{Z}^1 \text{Y}^1, \\
    &\text{Z}^1 \text{X}^1, \\
    &\text{X}^1 \text{Y}^1
\end{align*} \]

[0009] In a second embodiment of the first aspect, one or both of W and W are selected from the group consisting of

\[ \begin{align*}
    &\text{H}-\text{NH}, \\
    &\text{H}-\text{NH}, \\
    &\text{H}-\text{NH}, \\
    &\text{H}-\text{NH}, \\
    &\text{H}-\text{NH}, \\
    &\text{H}-\text{NH}
\end{align*} \]

[0010] In a third embodiment of the first aspect, R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub> and R<sub>f</sub> are each independently selected from the group consisting of: hydrogen, Ci to C<sub>g</sub> alkyl and Ci to C<sub>g</sub> heteroalkyl, wherein,

each hetero atom, if present, is independently N, O or S,

R<sub>c</sub> and R<sub>d</sub> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle, and

R<sub>e</sub> and R<sub>f</sub> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0011] In a fourth embodiment of the first aspect, one or both of R<sub>c</sub> and R<sub>d</sub> or R<sub>e</sub> and R<sub>f</sub> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.
In a fifth embodiment of the first aspect, \( R_c \) and \( R_d \) are joined and form a heterocyclic fused ring system selected from the group consisting of:

\[
\text{[Diagram showing various ring systems]}
\]

wherein \( R^N \) is selected from the group consisting of hydrogen, -OH, \( \text{C}_1 \) to \( \text{C}_{12} \) alkyl, \( \text{C}_1 \) to \( \text{C}_{12} \) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

In a sixth embodiment of the first aspect, \( R_e \) and \( R_f \) are joined and form a heterocyclic fused ring system selected from the group consisting of:

\[
\text{[Diagram showing various ring systems]}
\]

wherein \( R^N \) is selected from the group consisting of hydrogen, -OH, \( \text{C}_1 \) to \( \text{C}_{12} \) alkyl, \( \text{C}_1 \) to \( \text{C}_{12} \) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

In a second aspect of the invention, compounds have formula II:

\[
\text{[Chemical structure diagram]}
\]

wherein:

A and E are:

each independently a bond, -O-, -S-, -S(O\(_2\))-, -S(O)-, -C(O)-, -N=CR\(_2\)-.
-CR=, -CR₂CR₂-, -CR=CR-, -N=CR-, -(CR₂)₂aN(RN)⁻(CR₂)₂a⁻,
-(CR₂)₂aC(O)-N(RN)⁻(CR₂)₂a⁻, -(CR₂)₂aN(RN)⁻C(O)-(CR₂)₂a⁻ or
-(CR₂)bO-(CR₂)b⁻, wherein:
RN is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;
each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
wherein:
two R's either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond; and
each a and b are independently 0, 1, 2, or 3; and
with the proviso that if W and W' are both 5-membered rings, A and E are either both a bond or both other than a bond;
each Rₙ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;
each r is independently 0, 1, 2 or 3;

W and W' are each independently selected from the group consisting of

- CR=, CR₂, CR₂-, CR=CR-, N=CR-, (CR₂)₂aN(RN)⁻(CR₂)₂a⁻,
- (CR₂)₂aC(O)-N(RN)⁻(CR₂)₂a⁻, (CR₂)₂aN(RN)⁻C(O)-(CR₂)₂a⁻ or
- (CR₂)bO-(CR₂)b⁻, wherein:
RN is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;
each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
wherein:
two R's either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond; and
each a and b are independently 0, 1, 2, or 3; and
with the proviso that if W and W' are both 5-membered rings, A and E are either both a bond or both other than a bond;
each Rₙ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;
each r is independently 0, 1, 2 or 3;
and wherein:

$X_1$ is $\text{CH}_2$, $\text{NH}$, $\text{O}$ or $\text{S}$,

$Y_1$, $Y_2$ and $Z_1$ are each independently $\text{CH}$ or $\text{N}$,

$X_2$ is $\text{NH}$, $\text{O}$ or $\text{S}$,

$W$ and $W$ are each independently optionally substituted with one or more

substituents selected from the group consisting of -OH, -CN, -$\text{NO}_2$, halogen,
$\text{Ci}$ to $\text{C}_{12}$ alkyl, $\text{Ci}$ to $\text{C}_{12}$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl,
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carboxamoyl, substituted sulfonyl,
sulfonate, sulfonamide and amino, and

$\text{Cy}$ is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl,
heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms
are independently $\text{N}$, $\text{S}$ or $\text{O}$ and which is optionally substituted with one or
more substituents selected from the group consisting of -OH, -CN, -$\text{NO}_2$,
halogen, $\text{Ci}$ to $\text{C}_{12}$ alkyl, $\text{Ci}$ to $\text{C}_{12}$ heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carboxamoyl, substituted sulfonyl,
sulfonate, sulfonamide and amino;

each $R_c$, $R_d$, $R_e$ and $R_f$ is independently selected from the group consisting of: hydrogen,
$\text{Ci}$ to $\text{C}_g$ alkyl, $\text{Ci}$ to $\text{C}_g$ heteroalkyl, aralkyl and a 4- to 8-membered ring which may
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently $\text{N}$, $\text{O}$ or $\text{S}$,

each of $R_c$, $R_d$, $R_e$ and $R_f$ may optionally be substituted by $\text{Ci}$ to $\text{C}_g$ alkyl, $\text{Ci}$ to $\text{C}_g$
heteroalkyl, aralkyl, or a 4- to 8-membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is
independently $\text{N}$, $\text{O}$ or $\text{S}$,

$R_c$ and $R_d$ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and

$R_c$ and $R_f$ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;
Y and Y’ are each independently carbon or nitrogen; and

Z and Z’ are independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-\[U-(CR^4_2).NR^5(R^4_2).1_{17}U-(CR^4_2).NR^7-(CR^4_2).-R^8, \]

\[-U-(CR^4_2).-R^8, \]

wherein,

U is selected from the group consisting of \(-C(O)\), \(-C(S)\) and \(-S(O)_2\),

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, \(-C(O)-R^8\), \(-C(S)-R^8\), \(-C(O)-O-R^8\), \(-C(O)-N-R^8\), \(-S(O)_2-R^8\) and \(-S(O)_2-N-R^8\), wherein each R^8 is independently chosen from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R^7 and R^8 together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0015] In a first embodiment of the second aspect, compounds of formula Ha are provided:

\[ \text{IIa.} \]

[0016] In a second embodiment of the second aspect, compounds of formula lib are provided:

\[ \text{IIb.} \]
In a third embodiment of the second aspect, both A and E are -O-.

In a fourth embodiment of the second aspect, A is -O- and E is -CH₂⁻, -C(CH₃)₂⁻, -C(CH₂CH₃)⁻ or -C(O)-.

In a third aspect of the invention, compounds of formula III are provided:

![Chemical structure]

wherein:

D is either present or absent and if present selected from the group consisting of
-CR₂, -CR²⁻, -CR₂⁻, -NR⁻, -O⁻ and -S⁻ wherein Rᴺ is H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently -CR⁻, -CR=, -CR₂⁻, CR=CR⁻, -N=CR⁻,
-(CR₂)⁻N(Rᴺ)(CR₂)⁻⁻, -(CR₂)⁻C(O)-N(Rᴺ)(CR₂)⁻⁻,
-(CR₂)⁻N(Rᴺ)-C(O)-(CR₂)⁻⁻ or -(CR₂)⁻⁻O-(CR₂)⁻⁻, wherein:

Rᴺ is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:
two R's either both on a single C or on adjoining Cs, together with the C or C s to which they are attached, optionally form a cycle, and
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond;
each a and b are independently 0, 1, 2, or 3 with the proviso that if D is present
both b's are not 0; and
R^N and R may be replaced by a bond to D if D is present,
if D is absent, A and E can additionally each independently be a bond, -O-, -S-, 
-S(O_2)-, -S(O)-, -C(O)- or -N=, and
with the proviso that if W and W' are both 5-membered rings, A and E are either
both a bond or both other than a bond;
each R_i is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, 
C_i to C_{12} alkyl, C_i to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, 
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, 
sulfonamide and amino;
each r is independently 0, 1, 2 or 3;
X^1 is CH_2, NH, O or S.
Y^1 and Z^1 are each independently CH or N,
W and W' are each independently optionally substituted with one or more substituents
selected from the group consisting of -OH, -CN, -NO_2, halogen, C_i to C_{12} alkyl, C_i to 
C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, 
alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and 
amino, and
each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, 
C_i to C_{g} alkyl, C_i to C_{g} heteroalkyl, aralkyl and a 4- to 8- membered ring which may 
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of R^c, R^d, R^e and R^f may optionally be substituted by C_i to C_{g} alkyl, C_i to C_{g} 
heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, 
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is 
independently N, O or S.
R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and

R² and R⁷ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

- [U-(CR⁴₂)₂-NR⁵-C(R⁴₂)₃]⁻ U-(CR⁴₂)₋ NR⁷₋ (CR⁴₂)₋ R⁸⁻ and
- [U-(CR⁴₂)₂-NR⁵-C(R⁴₂)₃]⁻ U-(CR⁴₂)₋ O-(CR⁴₂)₋ R⁸⁻

wherein,

U is selected from the group consisting of -C(O)-, -C(S)-, and -S(O)₂⁻,
each R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R⁸ is selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R¹, -C(S)-R¹, -C(O)-O-R¹, -C(O)-N-R¹₂, -S(O)₂-R¹ and -S(O)₂⁻N-R¹₂, wherein each R¹ is independently chosen from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R⁷ and R⁸ together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0020] In a first embodiment of the third aspect, compounds of formula IIIa are provided:

[0021] In a second embodiment of the third aspect, compounds of formula IHB are provided:
In a third embodiment of the third aspect, both A and E are -O- and D is absent.

In a fourth embodiment of the third aspect, A is -O-, D is absent and E is -CH_2-, -C(CH_3)_2-, -C(CH_2CH_2)_2- or -C(O)-.

In a fifth embodiment of the third aspect, one or both of X^1 are -S-.

In a sixth embodiment of the third aspect, one or both of X^1 are -O-.

In a seventh embodiment of the third aspect, one or both of X^1 are -NH-.

In an eighth embodiment of the third aspect, one or both of Y^1 is -N-.

In a ninth embodiment of the third aspect, one or both of Z^1 is -N-.

In a fourth aspect of the invention, compounds of formula IV are provided:

wherein:

A is a bond, -CR_2-, -CR=, -CR=CR-, -CR=CR=, -N=CR-, -(CR_2)a-N(R^N)-(CR_2)b-, -O-, -S-, -S(O)_2-, -S(O)-, -C(O)-, -N=, -(CR_2)a-C(O)-N(R^N)-(CR_2)b-, -(CR_2)a-N(R^N)-C(O)-(CR_2)b- or -(CR_2)b-O-(CR_2)a-, wherein:

R^N is selected from the group consisting of H, -OH, Ci to Ci_2 alkyl, Ci to Ci_2 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, Ci to Ci_2 alkyl, Ci to Ci_2 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
wherein:

two R’s either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and where two R’s are possible on a C, the C may optionally be linked to a single R with a double bond;

each a and b are independently 0, 1, 2, or 3; and

with the proviso that if W and W are both 5-membered rings, A is a bond;

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, Ci to C_12 alkyl, Ci to C_2 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

W and W are each independently selected from the group consisting of

\[
\begin{align*}
&X^1, \\
&Y^1, \\
&Z^1, \\
&X^1 \rightarrow Y^1, \\
&X^2, \\
&Y^2, \\
&Z^2, \\
&X^2 \rightarrow Y^2, \\
&Z^1 \rightarrow Y^1, \\
&X^1 \rightarrow Z^1, \\
&X^2 \rightarrow Z^2,
\end{align*}
\]

and

\[
\begin{align*}
&X^1, \\
&Y^1, \\
&Z^1, \\
&X^1 \rightarrow Y^1, \\
&X^2, \\
&Y^2, \\
&Z^2, \\
&X^2 \rightarrow Y^2, \\
&Z^1 \rightarrow Y^1, \\
&X^1 \rightarrow Z^1, \\
&X^2 \rightarrow Z^2.
\end{align*}
\]

wherein:

X^1 is CH_2, NH, O or S.
Y^1, Y^2 and Z^1 are each independently CH or N,
X^2 is NH, O or S.

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen, Ci to C_12 alkyl, Ci to C_2 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and
Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R, amino; each Rᵣ, Rᵈ, Rᵉ and Rᶠ is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein, each hetero atom, if present, is independently N, O or S, each of Rᵣ, Rᵈ, Rᵉ and Rᶠ may optionally be substituted by Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S, Rᵣ and Rᵈ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and Rᵣ and Rᶠ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring; Y and Y’ are each independently carbon or nitrogen; and Z and Z’ are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids, -[U-(CR₂)₄]-NR₅-C(R₄₂)₄-U-(CR₂)₄-NR₇-(CR₄₂)₄-R₈, -U-(CR₂)₄-R₈, and -[U-(CR₂)₄]-NR₅-(CR₂)₄]-U-(CR₂)₄-O-(CR₂)₄-R₈ wherein, U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)₂⁻, each Rᵈ, Rᶠ and Rṣ is independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl, R₈ is selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R₈₁,
-C(S)-R_8^1, -C(O)-O-R_8^1, -C(O)-N-R_8^1_2, -S(O)_2-R_8^1 and -S(O)_2-N-R_8^1_2, wherein each R_8^1 is independently chosen from the group consisting of hydrogen, C_i to C_g alkyl, C_i to C_g heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl, optionally, R_7 and R_8 together form a 4-7 membered ring, each t is independently 0, 1, 2, 3, or 4, and u is 0, 1, or 2.

[0030] In a first embodiment of the fourth aspect, compounds of formula IVa are provided:

\[
\text{IVa.}
\]

[0031] In a second embodiment of the fourth aspect, compounds of formula IVb are provided:

\[
\text{IVb.}
\]

[0032] In a third embodiment of the fourth aspect, A is -S-.

[0033] In a fourth embodiment of the fourth aspect, A is -S(O)_2^-.

[0034] In a fifth embodiment of the fourth aspect, A is -O-.

[0035] In a sixth embodiment of the fourth aspect, A is -CH_2^-.

[0036] In a seventh embodiment of the fourth aspect, A is -CH_2CH_2^-.

[0037] In a fifth aspect of the embodiment, compounds of formula V are provided:

\[
\text{V}
\]

wherein:

A and E are:

RₐN is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

two R’s either both on a single C or on adjoining Cs, together with the C or C’s to which they are attached, optionally form a cycle, and

where two R’s are possible on a C, the C may optionally be linked to a single R with a double bond;

each a and b are independently o. 1, 2, or 3; and

with the proviso that A and E are either both a bond or both other than a bond;

each Rₙ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently o. 1, 2 or 3;

X¹ is CH₂, NH, O or S,

Y¹, and Z¹ are each independently CH or N,

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and
each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,

each of R^c, R^d, R^e and R^f may optionally be substituted by Ci to C_8 alkyl, Ci to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring,

and

R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

\[-[U-(CR^4_2)]_oU-(CR^4_2)_1U-(CR^4_2)_2-NR^7-(CR^4_2)_1-NR^5-(CR^4_2)_2,-R^8,-U-(CR^4_2)_1-R^8,\]

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\_2^-, each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^8\_1, -C(S)-R^8\_1, -C(O)-O-R^8\_1, -C(O)-N-R^8\_1, -S(O)_2-R^8\_1 and -S(O)_2-N-R^8\_1, wherein each R^8 is independently chosen from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R^7 and R^8 together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.
In a first embodiment of the fifth aspect, compounds of formula Va are provided:

\[ \text{Va.} \]

In a second embodiment of the fifth aspect, compounds of formula Vb are provided:

\[ \text{Vb.} \]

In a third embodiment of the fifth aspect, both A and E are -O-.

In a fourth embodiment of the fifth aspect, A is -O- and E is -CH\(_2\)-, -C(CH\(_3\))\(_2\)-, -C(CH\(_2\)\(_2\))\(_2\)- or -C(O)-.

In a fifth embodiment of the fifth aspect, one or both of X\(^1\) are -S-.

In a sixth embodiment of the fifth aspect, one or both of X\(^1\) are -O-.

In a seventh embodiment of the fifth aspect, one or both of X\(^1\) are -NH-.

In an eighth embodiment of the fifth aspect, one or both of Y\(^1\) are -N-.

In a ninth embodiment of the fifth aspect, one or both of Z\(^1\) is -N-.

In a sixth aspect, compounds of formula VI are provided:

\[ \text{VI} \]

wherein:

A and E are:

-(CR$_2$)$_a$N(R$_N$)-C(O)-(CR$_2$)$_a$ or -(CR$_2$)$_b$-O-(CR$_2$)$_b$-, wherein:

R$_N$ is selected from the group consisting of H, -OH, Ci to Ci$_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO$_2$, halogen, Ci to Ci$_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

two R's either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and

where two R's are possible on a C, the C may optionally be linked to a single R with a double bond, and

each a and b are independently 0, 1, 2, or 3 with the proviso that both b's are not 0; and

each R$_r$ is independently selected from the group consisting of -OH, -CN, -NO$_2$, halogen, Ci to Ci$_3$ alkyl, Ci to Ci$_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

X$^1$ is CH$_2$, NH, O or S,

Y$^1$ and Z$^1$ are each independently CH or N,

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO$_2$, halogen, Ci to Ci$_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R$^c$, R$^d$, R$^e$ and R$^f$ is independently selected from the group consisting of: hydrogen, Ci to C$_8$ alkyl, Ci to C$_8$ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S.
each of Rₖ, R₉, Rₗ and Rₘ may optionally be substituted by Ci to C₉ alkyl, Ci to C₉ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S.
Rₖ and R₉ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and
Rₗ and Rₘ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
-\[U-(CR_{4}^{2}),-NR_{5}^{5}C(R_{4}^{2}),_{U}U-(CR_{4}^{2}),-NR_{7}^{7}-(CR_{4}^{2}),-R_{8}^{8}, -U-(CR_{4}^{2}),-R_{8}^{8}, \text{and} \]
-\[U-(CR_{4}^{2}),-NR_{5}^{5}-(CR_{4}^{2}),_{U}U-(CR_{4}^{2}),-O-(CR_{4}^{2}),-R_{8}^{8}, \text{wherein,} \]

U is selected from the group consisting of -C(O), -C(S)- and -S(O)₂⁻,
each R₄, R₅ and R₇ is independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
R₈ is selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R₈₁, -C(S)-R₈₁, -C(O)-O-R₈₁, -C(O)-N-R₈₁₂, -S(O)₂-R₈₁ and -S(O)₂-N-R₈₁₂, wherein each R₈₁ is independently chosen from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R₇ and R₈ together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

[0048] In a first embodiment of the sixth aspect, compounds of formula Via are provided:
In a second embodiment of the sixth aspect, compounds of formula VIb are provided:

![VIa](image)

In a third embodiment of the sixth aspect, compounds of formula VII are provided:

![VII](image)

In a fourth embodiment of the sixth aspect, compounds of formula VIla are provided:

![VIla](image)

In a fifth embodiment of the sixth aspect, compounds of formula VIIb are provided:

![VIIb](image)
In a sixth embodiment of the sixth aspect, compounds of formula VIII are provided:

\[ \text{VIII.} \]

In a seventh embodiment of the sixth aspect, compounds of formula Villa are provided:

\[ \text{VIIa.} \]

In an eighth embodiment of the sixth aspect, compounds of formula VIIIb are provided:

\[ \text{VIIIb.} \]

In a ninth embodiment of the sixth aspect, one or both of X\textsuperscript{1} are -O-.

In a tenth embodiment of the sixth aspect, one or both of X\textsuperscript{1} are -NH-.

In an eleventh embodiment of the sixth aspect, one or both of X\textsuperscript{1} are -S-.

In a twelfth embodiment of the sixth aspect, one or both of Z\textsuperscript{1} is -N-.

In a thirteenth embodiment of the sixth aspect, one or both of Y\textsuperscript{1} is -N-.

In a seventh aspect of the invention, compounds of formula IX are provided:

\[ \text{IX} \]

wherein:
A and E are each independently -CR= or -N= wherein R is selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, C₁₀ to C₁₂ alkyl, C to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; each Rᵢ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C to C₃ alkyl, C to C₃ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; 
each r is independently 0, 1, 2 or 3; 

X¹ is CH₂, NH, O or S, 

Y¹ and Z¹ are each independently CH or N, 

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, C to C₃ alkyl, C to C₃ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and 
each Rₑ, Rᵈ, Rₑ and Rᶠ is independently selected from the group consisting of: hydrogen, C to C₈ alkyl, C to C₈ heteroalkyl, aralkyl and a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein, 
each hetero atom, if present, is independently N, O or S, 
each of Rₑ, Rᵈ, Rₑ and Rᶠ may optionally be substituted by C to C₈ alkyl, C to C₈ heteroalkyl, aralkyl, or a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S, 
Rₑ and Rᵈ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and 
Rₑ and Rᶠ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, C1 to Cg alkyl, C1 to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-\[\text{U}-(\text{CR}^4_2)\text{NR}^5\text{C}(\text{R}^4_2)_1\text{U}-(\text{CR}^4_2)_2\text{NR}^7\text{C}(\text{R}^4_2)_1\text{R}^8\text{U}-(\text{CR}^4_2)_1\text{R}^8,\text{U}-(\text{CR}^4_2)_1\text{R}^8\text{and}\]

-\[\text{U}-(\text{CR}^4_2)\text{NR}^5\text{C}(\text{R}^4_2)_1\text{U}-(\text{CR}^4_2)_2\text{O}-(\text{CR}^4_2)_1\text{R}^8\text{wherein,}\]

\text{U} is selected from the group consisting of -C(O)-, -C(S)-, and -S(O)\_2^-, each \text{R}^4, \text{R}^5, and \text{R}^7 is independently selected from the group consisting of hydrogen, C1 to Cg alkyl, C1 to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, and aralkyl,

\text{R}^8 is selected from the group consisting of hydrogen, C1 to Cg alkyl, C1 to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, and aralkyl,

each t is independently 0, 1, 2, 3, or 4, and

\text{u is 0, 1, or 2.}

In a first embodiment of the seventh aspect compounds of formula IXa are provided:

[0062] In a first embodiment of the seventh aspect compounds of formula IXa are provided:

\[\text{IXa.}\]
[0063] In a second embodiment of the seventh aspect compounds of formula IXb are provided:

\[
\begin{align*}
&\text{IXb.}
\end{align*}
\]

[0064] In a third embodiment of the seventh aspect A and E are -N=.

[0065] In a fourth embodiment of the seventh aspect, one or both of X\(^1\) are -S-.

[0066] In a fifth embodiment of the seventh aspect, one or both of X\(^1\) are -O-.

[0067] In a sixth embodiment of the seventh aspect, one or both of X\(^1\) are -NH-.

[0068] In a seventh embodiment of the seventh aspect, one or both of Y\(^1\) are -N-.

[0069] In an eighth embodiment of the seventh aspect, one or both of Z\(^1\) is -N-.

[0070] In an eighth aspect of the invention, compounds of formula X are provided:

\[
\begin{align*}
&\text{X}
\end{align*}
\]

wherein:

E is -CR\(^2\)-, -CR=, -CR\(^2\)-CR\(^2\)-, -CR=CR=, -N=CR=, -(CR\(^2\))\(_a\)-N(R\(^N\))(CR\(^2\))\(_a\)-
-(CR\(^2\))\(_a\)-C(O)-N(R\(^N\))(CR\(^2\))\(_a\)-, -(CR\(^2\))\(_a\)-N(R\(^N\))-C(O)-(CR\(^2\))\(_a\)-, or -(CR\(^2\))\(_b\)-O-(CR\(^2\))\(_b\)-,

wherein:

R\(^N\) is selected from the group consisting of H, -OH, Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO\(_2\), halogen, Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
two R’s either both on a single C or on adjoining Cs, together with the C
or Cs to which they are attached, optionally form a cycle, and
where two R’s are possible on a C, the C may optionally be linked to a
single R with a double bond;
each a and b are independently 0, 1, 2, or 3;
each R³ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen,
Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl,
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate,
sulfonamide and amino;
each r is independently 0, 1, 2 or 3;
X¹ is CH₂, NH, O or S,
Y¹ and Z¹ are each independently CH or N,
W and W are each independently optionally substituted with one or more substituents
selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to
C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy,
alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
and
each R², R⁴, R⁵ and R⁶ is independently selected from the group consisting of: hydrogen,
Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of R², R⁴, R⁵ and R⁶ may optionally be substituted by Ci to C₈ alkyl, Ci to C₈
heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is
independently N, O or S,
R² and R⁴ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring,
and
R⁵ and R⁶ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-[U-(CR\(^4\)_2)\(\_\)NR\(^5\)-C(R\(^4\)_2)\(\_\)NR\(^7\)-C(R\(^4\)_2)\(\_\)R\(^8\), -U-(CR\(^4\)_2)\(\_\)R\(^8\), and

-[U-(CR\(^4\)_2)\(\_\)NR\(^5\)-C(R\(^4\)_2)\(\_\)U-(CR\(^4\)_2)\(\_\)O-(CR\(^4\)_2)\(\_\)R\(^8\), wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\(^2\)-, each R\(^4\), R\(^5\) and R\(^7\) is independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R\(^8\) is selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R\(^7\) and R\(^8\) together form a 4-7 membered ring,

each t is independently o, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0071] In a first embodiment of the eighth aspect, compounds of formula X\(_a\) are provided:
[0072] In a second embodiment of the eighth aspect, compounds of formula Xb are provided:

![Diagram](image)

Xb.

[0073] In a third embodiment of the eighth aspect, one or both of X¹ are -S-.

[0074] In a fourth embodiment of the eighth aspect, one or both of X¹ are -O-.

[0075] In a fifth embodiment of the eighth aspect, one or both of X¹ are -NH-.

[0076] In a sixth embodiment of the eighth aspect, one or both of Y¹ are -N-.

[0077] In a seventh embodiment of the eighth aspect, one or both of Z¹ is -N-.

[0078] In a ninth aspect of the invention, compounds of formula XI are provided:

![Diagram](image)

XI

wherein:

each \( R^a \) is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₂ alkyl, C₁ to C₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each \( r \) is independently 0, 1, 2 or 3;

X¹ is CH₂, NH, O or S,

Y¹ and Z¹ are each independently CH or N,

W and W are each independently optionally substituted with one or more substituents
selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C_{12} alkyl, Ci to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^e, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, Ci to C_g alkyl, Ci to C_g heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,
each of R^e, R^d, R^e and R^f may optionally be substituted by Ci to C_g alkyl, Ci to C_g heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R^e and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C_g alkyl, Ci to C_g heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-\{U-(CR^4_2),-NR^5-C(R^4_2),_1\}_{\text{U}}-(CR^4_2),-NR^7-(CR^4_2),-R^8, -U-(CR^4_2),-R^8, and
-\{U-(CR^4_2),-NR^5-(CR^4_2),_1\}_{\text{U}}-(CR^4_2),-O-(CR^4_2),-R^8,\}

\text{wherein,}

U is selected from the group consisting of -CO\text{--}, -C(S)\text{--} and -S(O)\text{--}²⁻, each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to C_g alkyl, Ci to C_g heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, Ci to C_g alkyl, Ci to C_g heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -CO\text{--}_1, -C(S)\text{--}_1, -C(O)-O-R^8_1, -C(O)-N-R^8_1^{12}, -S(O)_2-R^8_1 and -S(O)_2-N-R^8_1^{12}, \text{wherein each R^8 is independently chosen from the group consisting of hydrogen, Ci to
C<sub>g</sub> alkyl, C<sub>i</sub> to C<sub>g</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R<sup>7</sup> and R<sup>8</sup> together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

[0079] In a first embodiment of the ninth aspect, compounds of formula XIa are provided:

\[
\begin{align*}
\text{XIa.}
\end{align*}
\]

[0080] In a second embodiment of the ninth aspect, compounds of formula XIb are provided:

\[
\begin{align*}
\text{XIb.}
\end{align*}
\]

[0081] In a third embodiment of the ninth aspect, one or both of X<sup>1</sup> are -S-.

[0082] In a fourth embodiment of the ninth aspect, one or both of X<sup>1</sup> are -O-.

[0083] In a fifth embodiment of the ninth aspect, one or both of X<sup>1</sup> are -NH-.

[0084] In a sixth embodiment of the ninth aspect, one or both of Y<sup>1</sup> are -N-.

[0085] In a seventh embodiment of the ninth aspect, one or both of Z<sup>1</sup> is -N-. 
In a tenth aspect of the invention, compounds of formula XII are provided:

![Chemical Structure](image)

**XII. wherein:**

A' and E' are each independently -CR₂⁻, -CR=, -N(R⁻N)-, -O-, -S-, -S(O)₂-, -S(O)-, or -N=, wherein:

Rᴺ is selected from the group consisting of H, -OH, Ci to Cᵢ₂ alkyl, Ci to Cᵢ₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and

R is selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Cᵢ₂ alkyl, Ci to Cᵢ₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each Rᴬ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Cᵢ₂ alkyl, Ci to Cᵢ₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

X¹ is CH₂, NH, O or S.

Y¹ and Z¹ are each independently CH or N.

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Cᵢ₂ alkyl, Ci to Cᵢ₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each Rᶜ, Rᵈ, Rᵉ and Rᶠ is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of R_e, R_d, R_e and R_f may optionally be substituted by Ci to C_g alkyl, Ci to C_g heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S.
R_e and R_d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and
R_e and R_f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and
Z and Z' are independently selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
-[U-(CR^4_2).NR^5.C(R^4_2).]_U-(CR^4_2).NR^7.(CR^4_2).-R^8, -U-(CR^4_2).-R^8, and
-[U-(CR^4_2).NR^5.(CR^4_2).]_U-(CR^4_2).-O-(CR^4_2).-R^8, wherein,
U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\_2^-, each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
R^8 is selected from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^8_1, -C(S)-R^8_1, -C(O)-O-R^8_1, -C(O)-N-R^8_1, -S(O)\_2^2-R^8_1 and -S(O)\_2^2-N-R^8_1, wherein each R^8_1 is independently chosen from the group consisting of hydrogen, Ci to C_8 alkyl, Ci to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R^7 and R^8 together form a 4-7 membered ring,
each t is independently o, 1, 2, 3, or 4, and
u is 0, 1, or 2.
In a first embodiment of the tenth aspect, compounds of formula XIIa are provided:

![Diagram of XIIa]

In a second embodiment of the tenth aspect, compounds of formula XIIb are provided:

![Diagram of XIIb]

In a third embodiment of the tenth aspect, one or both of $X^1$ are -S-.

In a fourth embodiment of the tenth aspect, one or both of $X^1$ are -O-.

In a fifth embodiment of the tenth aspect, one or both of $X^1$ are -NH-.

In a sixth embodiment of the tenth aspect, one or both of $Y^1$ are -N-.

In a seventh embodiment of the tenth aspect, one or both of $Z^1$ is -N-.

In an eleventh aspect of the invention $Z$ and $Z'$ in any of the previous aspects are each 1-3 amino acids.

In a first embodiment of the eleventh aspect, the amino acids are all in the D or all in the L configuration.

In a second embodiment of the eleventh aspect, $Z$ and $Z'$ are each independently selected from the group consisting of

- $-[U-(CR^4_2),NR^5-(CR^4_2),]_1U-(CR^4_2),NR^7-(CR^4_2),-R^8,$
- $-U-(CR^4_2),-R^8$ and $-U[-(CR^4_2),NR^5-(CR^4_2),]_1U-(CR^4_2),-O-(CR^4_2),-R^8.$

In a third embodiment of the eleventh aspect, one or both of $Z$ and $Z'$ are

- $-[U-(CR^4_2),NR^5-(CR^4_2),]_1U-(CR^4_2),NR^7-(CR^4_2),-R^8.$
In a fourth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-U-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a fifth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-U-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a sixth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \([-\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a seventh embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In an eighth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a ninth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a tenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In an eleventh embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 2 \, n)_n\text{C}(O)-\text{R}^{81}\).

In a twelfth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7\text{C}(O)-\text{R}^{81}\).

In a thirteenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7-(\text{CR} \, 2 \, n)_n\text{C}(O)-\text{O}-\text{R}^{81}\).

In a fourteenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{NR}^7\text{C}(O)-\text{O}-\text{R}^{81}\).

In a fifteenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a sixteenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \(-\text{C}(O)-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

In a seventeenth embodiment of the eleventh aspect, one or both of \(Z\) and \(Z'\) are:
- \([-\text{U}-(\text{CR} \, 4 \, 2)_2-,\text{NR}^5-(\text{CR} \, 4 \, 2)_2-,\text{O}-(\text{CR} \, 4 \, 2)_2-,\text{R}^8\).

...
[0112] In an eighteenth embodiment of the eleventh aspect, one or both of Z and Z’ are 
-U-(CR 4 2 ),-NR 5 -(CR 4 2 ),-O-(CR 4 2 ),-R 8 .

[0113] In a nineteenth embodiment of the eleventh aspect, one or both of Z and Z’ are 
-C(O)-(CR 4 2 ),-NR 5 -(CR 4 2 )-C(O)-(CR 4 2 ),-O-(CR 4 2 )-R 8 .

[0114] In a twentieth embodiment of the eleventh aspect, one or both of Z and Z’ are 
-U-(CR 4 2 )t-O-(CR 4 2 )t-R 8 .

[0115] In a twenty-first embodiment of the eleventh aspect, one or both of Z and Z’ are 
-C(O)-(CR 4 2 )t-O-(CR 4 2 )t-R 8 .

[0116] In a twenty-second embodiment of the eleventh aspect, one or both of Z and Z’ are 
-C(O)-(CR 4 2 )n-NR 7 -R 7 wherein R 7 and R 8 together form a 4-7 membered ring.

[0117] A twelfth aspect of the invention provides a pharmaceutical composition 
comprising the compounds of the invention.

[0118] A thirteenth aspect of the invention provides use of the compounds of the 
invention in the manufacture of a medicament.

[0119] In a first embodiment of the thirteenth aspect the medicament is for the treatment 
of hepatitis C.

[0120] A fourteenth aspect of the invention provides a method of treating hepatitis C 
comprising administering to a subject in need thereof, a therapeutically effective amount of a 
compound of the invention.

Detailed Description

[0121] Unless otherwise stated, the following terms used in this application, including the 
specification and claims, have the definitions given below. It must be noted that, as used in 
the specification and the appended claims, the singular forms "a," "an" and "the" include 
plural referents unless the context clearly dictates otherwise. Definition of standard 
chemistry terms may be found in reference works, including Carey and Sundberg (2007) 
LLC, New York. The practice of the present invention will employ, unless otherwise 
indicated, conventional methods of synthetic organic chemistry, mass spectroscopy, 
preparative and analytical methods of chromatography, protein chemistry, biochemistry, 
recombinant DNA techniques and pharmacology.
The term "alkanoyl" as used herein contemplates a carbonyl group with a lower alkyl group as a substitutent.

The term "alkenyl" as used herein contemplates substituted or unsubstituted, straight and branched chain alkene radicals, including both the E- and Z-forms, containing from two to eight carbon atoms. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, -NO₂, -CO₂R, -C(O)R, -O-R, -N(R)₂, -N(R)C(O)R, -N(R)S(O)₂R, -SR, -C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₃R, -S(O)₂N(R)₂, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

The term "alkoxy" as used herein contemplates an oxygen with a lower alkyl group as a substituent and includes methoxy, ethoxy, butoxy, trifluromethoxy and the like. It also includes divalent substituents linked to two separated oxygen atoms such as, without limitation, -O-(CH₂)₄-O-, -O-CF₂-O-, -O-(CH₂)₄O-(CH₂CH₂-O)₂L₄⁻ and -(O-CH₂CH₂-O)L₄⁻.

The term "alkoxycarbonyl" as used herein contemplates a carbonyl group with an alkoxy group as a substitutent.

The term "alkyl" as used herein contemplates substituted or unsubstituted, straight and branched chain alkyl radicals containing from one to fifteen carbon atoms. The term "lower alkyl" as used herein contemplates both straight and branched chain alkyl radicals containing from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert- butyl and the like. The alkyl group may be optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -C(O)₂R, -C(O)R, -O-R, -N(R)₂, -N(R)C(O)R, -N(R)S(O)₂R, -SR, -C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₃R, -S(O)₂N(R)₂, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

The term "alkylene," "alkenylene" and "alkynylene" as used herein refers to the groups "alkyl," "alkenyl" and "alkynyl" respectively, when they are divalent, i.e., attached to two atoms.

The term "alkylsulfonyl" as used herein contemplates a sulfonyl group which has a lower alkyl group as a substitutent.

The term "alkynyl" as used herein contemplates substituted or unsubstituted, straight and branched carbon chain containing from two to eight carbon atoms and having at least one carbon-carbon triple bond. The term alkynyl includes, for example ethynyl,
1-propynyl, 2-propynyl, 1-butynyl, 3-methyl-1-butynyl and the like. The alkynyl group may be optionally substituted with one or more substituents selected from halo, -CN, -NO₂, -CO₂R, -C(O)R, -OR, -N(Rₙ)₂, -N(Rₙ)C(O)R, -N(Rₙ)S(O)₂R, -SR, -C(O)N(Rₙ)₂, -OC(O)R, -OC(O)N(Rₙ)₂, -OS(O)₂R, -SO₃R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0130] The term "amino" as used herein contemplates a group of the structure -NRₙ₂.

[0131] The term "amino acid" as used herein contemplates a group of the structure

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{R}
\end{array}
\quad \text{or} \quad
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{R}
\end{array}
\]

in either the D or the L configuration and includes but is not limited to the twenty "standard" amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine and histidine. The present invention also includes, without limitation, D-configuration amino acids, beta-amino acids, amino acids having side chains as well as all non-natural amino acids known to one skilled in the art.

[0132] The term "aralkyl" as used herein contemplates a lower alkyl group which has as a substituent an aromatic group, which aromatic group may be substituted or unsubstituted. The aralkyl group may be optionally substituted with one or more substituents selected from halogen, -CN, -NO₂, -CO₂R, -C(O)R, -OR, -N(Rₙ)₂, -N(Rₙ)C(O)R, -N(Rₙ)S(O)₂R, -SR, -C(O)N(Rₙ)₂, -OC(O)R, -OC(O)N(Rₙ)₂, -OS(O)₂R, -SO₃R, -S(O)₂N(Rₙ)₂, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0133] The terms "aryl," "aromatic group" or "aromatic ring" as used herein contemplates substituted or unsubstituted single-ring and multiple aromatic groups (for example, phenyl, pyridyl and pyrazole, etc.) and polycyclic ring systems (naphthyl and quinolinyl, etc.). The polycyclic rings may have two or more rings in which two atoms are common to two adjoining rings (the rings are "fused") wherein at least one of the rings is aromatic, e.g., the other rings can be cycloalkyls, cycloalkenyls, aryl, heterocycles and/or heteroaryls. The aryl group may be optionally substituted with one or more substituents selected from halogen, alkyl, -CN, -NO₂, -CO₂R, -C(O)R, -OR, -N(Rₙ)₂, -N(Rₙ)C(O)R, -N(Rₙ)S(O)₂R, -SR, -C(O)N(Rₙ)₂, -OC(O)R, -OC(O)N(Rₙ)₂, -OS(O)₂R, -SO₃R, -SO₃R,…
-S(O)2NR, -SiR3, -P(O)R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0134] The term "arylsulfonyl" as used herein contemplates a sulfonyl group which has as a substituent an aryl group. The term is meant to include, without limitation, monovalent as well as multiply valent aryls (eg, divalent aryls).

[0135] The term "carbamoyl" as used herein contemplates a group of the structure

\[
\begin{align*}
\text{C} & \quad \text{NR}^2
\end{align*}
\]

[0136] The term "carbonyl" as used herein contemplates a group of the structure

\[
\begin{align*}
\text{C} & \quad \text{O}
\end{align*}
\]

[0137] The term "carboxyl" as used herein contemplates a group of the structure

\[
\begin{align*}
\text{C} & \quad \text{O}
\end{align*}
\]

[0138] The term "cycloalkyl" as used herein contemplates substituted or unsubstituted cyclic alkyl radicals containing from three to twelve carbon atoms and includes cyclopropyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkyl" also includes polycyclic systems having two rings in which two or more atoms are common to two adjoining rings (the rings are "fused"). The cycloalkyl group may be optionally substituted with one or more substituents selected from halo, -CN, -NO2, -CO2R, -C(O)R, -O-R, -N(R)2, -N(R)C(O)R, -N(R)S(O)2R, -SR, -C(O)N(R)2, -OC(O)R, -OC(O)N(R)2, -SOR, -SO2R, -S(O)2N(R)2, phosphate, phosphonate, alkyl, cycloalkenyl, aryl and heteroaryl.

[0139] The term "cycloalkenyl" as used herein contemplates substituted or unsubstituted cyclic alkenyl radicals containing from four to twelve carbon atoms in which there is at least one double bond between two of the ring carbons and includes cyclopentenyl, cyclohexenyl and the like. The term "cycloalkenyl" also includes polycyclic systems having two rings in which two or more atoms are common to two adjoining rings (the rings are "fused"). The cycloalkenyl group may be optionally substituted with one or more substituents selected from halo, -CN, -NO2, -CO2R, -C(O)R, -O-R, -N(R)2, -N(R)C(O)R, -N(R)S(O)2R, -SR,
-C(O)N(R N) 2, -OC(O)R, -OC(O)N(R N) 2, -SOR, -SO 2 R, -S(O) 2 N(R N) 2, phosphate, phosphonate, alkyl, cycloalkenyl, aryl and heteroaryl.

[0140] The term "halo" or "halogen" as used herein includes fluorine, chlorine, bromine and iodine.

[0141] The term "heteroalkyl" as used herein contemplates an alkyl with one or more heteroatoms.

[0142] The term "heteroatom", particularly within a ring system, refers to N, O and S.

[0143] The term "heterocyclic group," "heterocycle" or "heterocyclic ring" as used herein contemplates substituted or unsubstituted aromatic and non-aromatic cyclic radicals having at least one heteroatom as a ring member. Preferred heterocyclic groups are those containing five or six ring atoms which includes at least one hetero atom and includes cyclic amines such as morpholino, piperidino, pyrrolidino and the like and cyclic ethers, such as tetrahydrofuran, tetrahydropyran and the like. Aromatic heterocyclic groups, also termed "heteroaryl" groups, contemplates single-ring hetero-aromatic groups that may include from one to three heteroatoms, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, oxadiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrimidine and the like. The term heteroaryl also includes polycyclic hetero-aromatic systems having two or more rings in which two or more atoms are common to two adjoining rings (the rings are "fused") wherein at least one of the rings is a heteroaryl, e.g., the other rings can be cycloalkyls, cycloalkenyls, aryl, heterocycles and/or heteroaryls. Examples of polycyclic heteroaromatic systems include quinoline, isoquinoline, cinnoline, tetrahydroisoquinoline, quinoxaline, quinazoline, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, indazole, purine, benzotriazole, pyrrolepyridine, pyrazolopyridine and the like. The heterocyclic group may be optionally substituted with one or more substituents selected from the group consisting of halo, alkyl, -CN, -NO 2, -CO 2 R, -C(O)R, -O-R, -N(R N) 2, -N(R N)C(0)R, -N(R N)S(O) 2 R, -SR, -C(0)N(R N) 2, -OC(O)R, -OC(O)N(R N) 2, -SOR, -SO 2 R, -SO 3 R, -S(O) 2 N(R N) 2, -SiR 3, -P(O)R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0144] The term "oxo" as used herein contemplates an oxygen atom attached with a double bond.

[0145] By "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material which is not biologically or otherwise undesirable, i.e., the material may be
administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0146] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention which is made with counterions understood in the art to be generally acceptable for pharmaceutical uses and which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lact acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylyamine and the like. Also included are salts of amino acids such as arginates and the like, and salts of organic acids like glucurmic or galactunoric acids and the like (see, e.g., Berge et al. 1977, J. Pharm. Sci. 66:1-19).

[0147] The terms "phosphate" and "phosphonate" as used herein refer to the moieties having the following structures, respectively:

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OR} \\
\text{OR} \\
\text{O} \\
\text{P} \\
\end{array} \]

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OR} \\
\text{OR} \\
\end{array} \]

[0148] The terms "salts" and "hydrates" refers to the hydrated forms of the compound that would favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which those skilled in the art may take into account in the selection
include the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity, flowability and manufacturability of the resulting bulk drug.

[0149] The term sulfonamide as used herein contemplates a group having the structure

\[ \text{O} \quad \text{S} \quad \text{NR}^N_2 \quad \text{O} \]

[0150] The term "sulfonate" as used herein contemplates a group having the structure

\[ \text{O} \quad \text{S} \quad \text{OR}^s \quad \text{O} \]

wherein \( R^s \) is selected from the group consisting of hydrogen, \( \text{C}_1\text{-C}_{10} \text{ alkyl}, \) \( \text{C}_2\text{-C}_1\text{O alkyl}, \) \( \text{C}_2\text{-C}_1\text{O alkenyl}, \) \( \text{C}_1\text{-C}_{10} \text{ alkanoyl or C}_1\text{-C}_{10} \text{ alkoxy carbonyl}. \)

[0151] The term "sulfonyl" as used herein contemplates a group having the structure

\[ \text{O} \quad \text{S} \quad \text{O} \]

[0152] "Substituted sulfonyl" as used herein contemplates a group having the structure

\[ \text{O} \quad \text{S} \quad \text{R} \quad \text{O} \]

including, but not limited to alkylsulfonyl and arylsulfonyl.

[0153] The term "thiocarbonyl," as used herein, means a carbonyl wherein an oxygen atom has been replaced with a sulfur.

[0154] Each \( R \) is independently selected from hydrogen, -OH, -CN, -NO\(_2\), halogen, \( \text{C}_1 \) to \( \text{C}_2 \) alkyl, \( \text{C}_1 \) to \( \text{C}_2 \) heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, amino and oxo.

[0155] Each \( R^N \) is independently selected from the group consisting of hydrogen, -OH, \( \text{C}_1 \) to \( \text{C}_2 \) alkyl, \( \text{C}_1 \) to \( \text{C}_2 \) heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl,
sulfonate and sulfonamide. Two $R^N$ may be taken together with $C$, $O$, $N$ or $S$ to which they are attached to form a five to seven membered ring which may optionally contain a further heteroatom.

[0156] The compounds of the present invention may be used to inhibit or reduce the activity of HCV, particularly HCVs NS5A protein. In these contexts, inhibition and reduction of activity of the NS5A protein refers to a lower level of the measured activity relative to a control experiment in which the cells or the subjects are not treated with the test compound. In particular aspects, the inhibition or reduction in the measured activity is at least a 10% reduction or inhibition. One of skill in the art will appreciate that reduction or inhibition of the measured activity of at least 20%, 50%, 75%, 90% or 100% or any number in between, may be preferred for particular applications.

[0157] In a first aspect, compounds of formula I are provided:

\[ \text{I} \]

wherein:

D is either present or absent and if present selected from the group consisting of

- $\text{CR}_2$- $\text{CR}_2$- , $\text{CR}^2_2$- , $\text{NR}^N$- , $\text{O}$- and $\text{S}$- wherein:

$R^N$ is $\text{H}$, $\text{-OH}$, $\text{C}$ to $\text{C}_2$ alkyl, $\text{C}$ to $\text{C}_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and,

each $R$ is independently selected from the group consisting of hydrogen, $\text{-OH}$, $\text{-CN}$, $\text{-NO}_2$, halogen, $\text{C}$ to $\text{C}_2$ alkyl, $\text{C}$ to $\text{C}_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently $\text{-CR}_2$-, $\text{-CR}=\text{-CR}_2$-, $\text{-CR=CR}_2$-, $\text{-N=CR}_2$-, $\text{-S}$- $\text{-N=CR}_2$- , $\text{-N=CR}=\text{-CR}_2$-, $\text{-N=CR}_2$-, $\text{-N=CR=CR}_2$-, $\text{-(CR}_2-a\text{-N}}(\text{R}^N)\text{-}-(\text{CR}_2-a\text{-})\text{-C(O)}\text{-N}-(\text{R}^N)\text{-}-(\text{CR}_2-a\text{-})\text{,}$

$\text{-(CR}_2-a\text{-N}}(\text{R}^N)\text{-}-(\text{CR}_2-a\text{-})\text{-C(O)}\text{-N}-(\text{R}^N)\text{-}-(\text{CR}_2-a\text{-})\text{-}-(\text{CR}_2-a\text{-})\text{-O}-(\text{CR}_2-a\text{-})\text{,}$ wherein:

$R^N$ is selected from the group consisting of $\text{H}$, $\text{-OH}$, $\text{C}$ to $\text{C}_2$ alkyl, $\text{C}$ to $\text{C}_2$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and
sulfonamide;
each R is independently selected from the group consisting of hydrogen, -OH, 
-CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,
wherein:
two R’s either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and where two R’s are possible on a C, the C may optionally be linked to a single R with a double bond;
each a and b are independently 0, 1, 2, or 3 with the proviso that if D is present both b’s are not 0; and
Rᴺ and R may be replaced by a bond to D if D is present,
if D is absent, A and E can additionally each independently be a bond, -O-, -S-, 
-S(O₂) -, -S(O) -, -C(O) - or -N=, and
with the proviso that if W and W are both 5-membered rings, A and E are either both a bond or both other than a bond;
each Rᵃ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, 
Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;
each r is independently 0, 1, 2 or 3;

W and W are each independently selected from the group consisting of
X₁ is CH₂, NH, O or S,
Y₁, Y₂ and Z₁ are each independently CH or N,
X₂ is NH, O or S,
W and W are each independently optionally substituted with one or more
substituents selected from the group consisting of -OH, -CN, -NO₂, halogen,
Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl,
aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,
sulfonate, sulfonamide and amino, and
Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl,
heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms
are independently N, S or O and which is optionally substituted with one or
more substituents selected from the group consisting of -OH, -CN, -NO₂,
halogen, Ci to C₅ alkyl, Ci to C₅ heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted
sulfonyl, sulfonate, sulfonamide and amino;
each Rₑ, Rᵈ, Rₑ and Rᶠ is independently selected from the group consisting of: hydrogen,
Ci to C₉ alkyl, Ci to C₉ heteroalkyl, aralkyl and a 4- to 8- membered ring which may
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of Rₑ, Rᵈ, Rₑ and Rᶠ may optionally be substituted by Ci to C₉ alkyl, Ci to C₉
heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is
independently N, O or S.
Rₑ and Rᵈ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring,
and
Rₑ and Rᶠ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and
Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₉
alkyl, C\textsubscript{i} to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids, $\text{-}[U-(CR^4_2)_j]\text{-}$NR\textsuperscript{s}-(R\textsuperscript{4}_2)_k$, and $\text{-}[U-(CR^4_2)_j]\text{-}$S(O)(R\textsuperscript{8}_1)$, wherein, $U$ is selected from the group consisting of -C(O)-, -C(S)- and -S(O)$^2$, each $R^4$, $R^5$ and $R^7$ is independently selected from the group consisting of hydrogen, C\textsubscript{i} to C\textsubscript{g} alkyl, C\textsubscript{i} to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl, $R^8$ is selected from the group consisting of hydrogen, C\textsubscript{i} to C\textsubscript{g} alkyl, C\textsubscript{i} to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl, optionally, $R^7$ and $R^8$ together form a 4-7 membered ring, each $t$ is independently 0, 1, 2, 3, or 4, and $u$ is 0, 1, or 2.

[0158] In a first embodiment of the first aspect, one or both of $W$ and $W$ are selected from the group consisting of.

[0159] In a second embodiment of the first aspect, one or both of $W$ and $W$ are selected from the group consisting of.

[0160] In a third embodiment of the first aspect, $R^e, R^d, R^e$ and $R^f$ are each independently selected from the group consisting of: hydrogen, C\textsubscript{i} to C\textsubscript{g} alkyl and C\textsubscript{i} to C\textsubscript{g} heteroalkyl, wherein, each hetero atom, if present, is independently N, O or S.
R<sup>c</sup> and R<sup>d</sup> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle, and

R<sup>e</sup> and R<sup>f</sup> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

[0161] In a fourth embodiment of the first aspect, one or both of R<sup>c</sup> and R<sup>d</sup> or R<sup>e</sup> and R<sup>f</sup> are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

[0162] In a fifth embodiment of the first aspect, R<sup>c</sup> and R<sup>d</sup> are joined and form a heterocyclic fused ring system selected from the group consisting of:

![Chemical Structures](Chemical_Structures.png)

wherein R<sup>N</sup> is selected from the group consisting of hydrogen, -OH, C<sub>i</sub> to C<sub>2</sub> alkyl, C<sub>i</sub> to C<sub>2</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[0163] In a sixth embodiment of the first aspect, R<sup>e</sup> and R<sup>f</sup> are joined and form a heterocyclic fused ring system selected from the group consisting of:

![Chemical Structures](Chemical_Structures.png)

wherein R<sup>N</sup> is selected from the group consisting of hydrogen, -OH, C<sub>i</sub> to C<sub>12</sub> alkyl, C<sub>i</sub> to C<sub>12</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.
In a second aspect of the invention, compounds have formula II:

wherein:

A and E are:

  - Rᴺ is selected from the group consisting of H, -OH, C₁₂ to C₂₅ alkyl, C₁ to C₁₀ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, alkanoyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;
  - each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, C₁ to C₂₅ alkyl, C₁ to C₁₀ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, alkanoyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

- two R’s either both on a single C or on adjoining Cs, together with the C or Cs to which they are attached, optionally form a cycle, and where two R’s are possible on a C, the C may optionally be linked to a single R with a double bond; and

- each a and b are independently 0, 1, 2, or 3; and

with the proviso that if W and W are both 5-membered rings, A and E are either both a bond or both other than a bond;

- each Rₐ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₀ alkyl, C₁ to C₁₀ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

- each r is independently 0, 1, 2 or 3;
W and W are each independently selected from the group consisting of

and , wherein:

X \(^1\), Y \(^1\), Y \(^2\) and Z \(^1\) are each independently CH or N,
X \(^2\) is NH, O or S,
W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO \(_2\), halogen, Ci to C\(_{12}\) alkyl, Ci to C\(_{12}\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and
Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO \(_2\), halogen, Ci to C\(_{13}\) alkyl, Ci to C\(_{12}\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;
each R\(^c\), R\(^d\), R\(^e\) and R\(^f\) is independently selected from the group consisting of: hydrogen, Ci to C\(_g\) alkyl, Ci to C\(_g\) heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of R\(^c\), R\(^d\), R\(^e\) and R\(^f\) may optionally be substituted by Ci to C\(_g\) alkyl, Ci to C\(_g\) heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and

R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-\[U-(\text{CR}^{4}_2)_{\text{a}}-\text{NR}^{5}_{\text{a}}-\text{C}(\text{CR}^{4}_2)_{\text{b}}-\text{R}^{8}_{\text{a}}-\text{U-(CR}^{4}_2)_{\text{c}}-\text{R}^{8}_{\text{c}}\]
-\[U-(\text{CR}^{4}_2)-\text{NR}^{5}_{\text{a}}-\text{C}(\text{CR}^{4}_2)_{\text{b}}-\text{O-(CR}^{4}_2)_{\text{c}}-\text{R}^{8}_{\text{c}}\]

wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\_2^-, each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^8\_1, -C(S)-R^8\_1, -C(O)-O-R^8\_1, -C(O)-N-R^8\_12, -S(O)\_2-N-R^8\_12, wherein each R^8\_1 is independently chosen from the group consisting of hydrogen, Ci to Cg alkyl, Ci to Cg heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R^7 and R^8 together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

each u is 0, 1, or 2.

In a first embodiment of the second aspect, compounds of formula Ha are provided:
[0166] In a second embodiment of the second aspect, compounds of formula IIb are provided:

\[ \text{IIb.} \]

[0167] In a first embodiment of the second aspect, both A and E are \(-\text{O}-\).

[0168] In a second embodiment of the second aspect, A is \(-\text{O}-\) and E is \(-\text{CH}_2, -\text{C(CH}_3)_2, -\text{C(CH}_2\text{CH}_2)-\) or \(-\text{C(O)}-\).

[0169] In a third aspect of the invention, compounds of formula III are provided:

\[ \text{wherein:} \]

D is either present or absent and if present selected from the group consisting of
\(-\text{CR}_2\text{CR}_2^-, -\text{CR}^-, -\text{NR}^N-, -\text{O}-\) and \(-\text{S}-\) wherein \(R^N\) is \(\text{H}, -\text{OH}, \text{Ci to Ci}_2\text{ alkyl, Ci to Ci}_2\text{ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO\(_2\), halogen, Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; A and E are:

each independently \(-\text{CR}_2^-, -\text{CR}^-, -\text{CR}_2\text{CR}_2^-, -\text{CR}=\text{CR}^-, -\text{N}=\text{CR}^-, -\text{(CR}_2\text{)}^a\text{-N(R}^N\text{)}^2-(\text{CR}_2\text{)}^a\text{-}, -(\text{CR}_2\text{)}^a\text{-C(O)}^-(\text{R}^N\text{)}^2-(\text{CR}_2\text{)}^a\text{), -(CR}_2\text{)}^a\text{-N(R}^N\text{)}^2-(\text{C(O)}^-(\text{CR}_2\text{)}^a\text{), -(CR}_2\text{)}^a\text{-N(R}^N\text{)}^2-(\text{CR}_2\text{)}^a\text{), -(CR}_2\text{)}^a\text{-O-(CR}_2\text{)}^a\text{), where in: R}^N\text{ is selected from the group consisting of H, -OH, Ci to Ci}_2\text{ alkyl, Ci to Ci}_2\text{ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;\}
each R is independently selected from the group consisting of hydrogen, -OH, 
-CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, 
heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, 
carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, 
wherein: 
two R’s either both on a single C or on adjoining Cs, together with the C 
or Cs to which they are attached, optionally form a cycle, and 
where two R’s are possible on a C, the C may optionally be linked to a 
single R with a double bond; 
each a and b are independently 0, 1, 2, or 3 with the proviso that if D is present 
both b’s are not 0; and 
Rᴺ and R may be replaced by a bond to D if D is present, 
if D is absent, A and E can additionally each independently be a bond, -O-, -S-, 
-S(O)₂-, -S(O)₃-, -C(O)- or -N=, and 
with the proviso that if W and W’ are both 5-membered rings, A and E are either 
both a bond or both other than a bond; 
each R³ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, 
Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, 
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, 
sulfonamide and amino; 
each r is independently 0, 1, 2 or 3; 
X¹ is CH₂, NH, O or S, 
Y¹, and Z¹ are each independently CH or N, 
W and W’ are each independently optionally substituted with one or more substituents 
selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to 
C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, 
alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and 
amino, and 
each R⁵, R⁶, R⁷ and R⁸ is independently selected from the group consisting of: hydrogen, 
Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may 
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S.
each of R\(^e\), R\(^d\), R\(^e\) and R\(^f\) may optionally be substituted by Ci to C\(_8\) alkyl, Ci to C\(_8\) heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S.

R\(^e\) and R\(^d\) are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

R\(^e\) and R\(^f\) are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C\(_8\) alkyl, Ci to C\(_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

\[-[U-(CR\(^4\)_2)\_NR\(^5\)C(R\(^4\)_2)]_7U-(CR\(^4\)_2)\_NR\(^6\)C(R\(^4\)_2)-R\(^8\), \]-U-(CR\(^4\)_2)\_R\(^8\), and

\[-[U-(CR\(^4\)_2)\_NR\(^7\)C(R\(^4\)_2)]_7U-(CR\(^4\)_2)-O-(CR\(^4\)_2)-R\(^8\),\]

wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\(^2\)-,
each R\(^4\), R\(^5\) and R\(^7\) is independently selected from the group consisting of hydrogen, Ci to C\(_8\) alkyl, Ci to C\(_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R\(^8\) is selected from the group consisting of hydrogen, Ci to C\(_8\) alkyl, Ci to C\(_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R\(^8\)_1,

-C(S)-R\(^8\)_1, -C(O)-O-R\(^8\)_1, -C(O)-N-R\(^8\)_2, -S(O)\(^2\)-R\(^8\)_1 and -S(O)\(^2\)-N-R\(^8\)_2, wherein each R\(^8\)_1 is independently chosen from the group consisting of hydrogen, Ci to C\(_8\) alkyl, Ci to C\(_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R\(^7\) and R\(^8\) together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0170] In a first embodiment of the third aspect, compounds of formula IIia are provided:
In a second embodiment of the third aspect, compounds of formula IHb are provided:

IIIa.

In a third embodiment of the third aspect, both A and E are -O- and D is absent.

In a fourth embodiment of the third aspect, A is -O-, D is absent and E is -CH₂-, -C(CH₃)₂-, -C(CH₂CH₂)- or -C(O)-.

In a fifth embodiment of the third aspect, one or both of X₁ are -S-.

In a sixth embodiment of the third aspect, one or both of X₁ are -O-.

In a seventh embodiment of the third aspect, one or both of X₁ are -NH-.

In an eighth embodiment of the third aspect, one or both of Y₁ are -N-.

In a ninth embodiment of the third aspect, one or both of Z₁ is -N-.

In a fourth aspect of the invention, compounds of formula IV are provided:

IV

wherein:

A is a bond, -CR₂-, -CR=, -CR₂=CR₂-, -CR=CR-, -N=CR-, -(CR₂)a-N(R(N)-)(CR₂)a-, -O-, -S-, -S(O)₂-, -S(O)-, -C(O)-, -N=, -(CR₂)a-C(O)-N(R(N)-)(CR₂)a-, -(CR₂)a-N(R(N)-)(CR₂)a-, or -(CR₂)b-O-(CR₂)b-, wherein:

Rₙ is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂
heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

two R's either both on a single C or on adjoining Cs, together with the C or C's to which they are attached, optionally form a cycle, and

where two R's are possible on a C, the C may optionally be linked to a single R with a double bond;

each a and b are independently 0, 1, 2, or 3; and

with the proviso that if W and W are both 5-membered rings, A is a bond;

each R is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

W and W are each independently selected from the group consisting of

\[ \text{X}^1 \text{Z}^1 \text{Y}^1 \text{X}^2 \text{Z}^2 \text{Y}^2 \text{X}^2 \text{Z}^2 \text{Y}^2 \text{X}^2 , \]

and

\[ \text{X}^1 \text{Cy} \text{Z}^1 \text{Y}^1 \text{Cy} \text{Z}^1 \text{Y}^1 \text{Cy} \text{Z}^1 \text{Y}^1 \text{Cy} \text{Z}^1 \text{Y}^1 \text{Cy} , \]

wherein:

\[ \text{X}^1 \text{is CH}_2, \text{NH, O or S}. \]
Y₁, Y₂ and Z₁ are each independently CH or N,
X₂ is NH, O or S,
W and W are each independently optionally substituted with one or more
substituents selected from the group consisting of -OH, -CN, -NO₂, halogen,
Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl,
aryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl,
sulfonate, sulfonamide and amino, and
Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl,
heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms
are independently N, S or O and which is optionally substituted with one or
more substituents selected from the group consisting of -OH, -CN, -NO₂,
halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted
sulfonyl, sulfonate, sulfonamide and amino;
each R₁, R₂, R₃ and R₄ is independently selected from the group consisting of: hydrogen,
Ci to C₂ alkyl, Ci to C₂ heteroalkyl, aralkyl and a 4- to 8-membered ring which may
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of R₅, R₆, R₇ and R₈ may optionally be substituted by Ci to C₂ alkyl, Ci to C₂
heteroalkyl, aralkyl, or a 4- to 8-membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is
independently N, O or S.
R₅ and R₆ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring,
and
R₇ and R₈ are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;
Y and Y’ are each independently carbon or nitrogen; and
Z and Z’ are independently selected from the group consisting of hydrogen, Ci to C₈
alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3
amino acids,
-[U-(CR₂)₅]-NR₅-C(R₂)₅]-U-(CR₂)₅]-NR₇-(CR₂)₅]-R₈,-U-(CR₂)₅]-R₈, and
-[U-(CR\textsuperscript{4}2),-NR\textsuperscript{5}-(CR\textsuperscript{4}2),10U-(CR\textsuperscript{4}2),-O-(CR\textsuperscript{4}2),-R\textsuperscript{8}], wherein,

\(U\) is selected from the group consisting of \(-\text{C}(\text{O})\), \(-\text{C}(\text{S})\) and \(-\text{S}(\text{O})\textsuperscript{2}\),

each \(R^4\) \(R^5\) and \(R^7\) is independently selected from the group consisting of hydrogen, \(\text{C}_8\) alkyl, \(\text{C}_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

\(R^8\) is selected from the group consisting of hydrogen, \(\text{C}_8\) alkyl, \(\text{C}_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, \(-\text{C}(\text{O})\textsuperscript{-}\text{R}^8\), \(-\text{C}(\text{S})\textsuperscript{-}\text{R}^8\), \(-\text{C}(\text{O})\textsuperscript{-}\text{O}\textsuperscript{2}\text{R}^8\) and \(-\text{C}(\text{O})\textsuperscript{-}\text{N}\textsuperscript{2}\text{R}^8\), wherein each \(R^8\) is independently chosen from the group consisting of hydrogen, \(\text{C}_8\) alkyl, \(\text{C}_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, \(R^7\) and \(R^8\) together form a 4-7 membered ring,

each \(t\) is independently \(0, 1, 2, 3,\) or \(4,\) and

\(u\) is \(0, 1,\) or \(2.\)

[0180] In a first embodiment of the fourth aspect, compounds of formula IVa are provided:

\[\text{IVa.}\]

[0181] In a second embodiment of the fourth aspect, compounds of formula IVb are provided:

\[\text{IVb.}\]

[0182] In a third embodiment of the fourth aspect, \(A\) is \(-\text{S}-.\)

[0183] In a fourth embodiment of the fourth aspect, \(A\) is \(-\text{S(O)}\textsuperscript{2}-.\)

[0184] In a fifth embodiment of the fourth aspect, \(A\) is \(-\text{O}-.\)

[0185] In a sixth embodiment of the fourth aspect, \(A\) is \(-\text{CH}\textsuperscript{2}-.\)

[0186] In a seventh embodiment of the fourth aspect, \(A\) is \(-\text{CH}\textsuperscript{2}-\text{CH}_2-.\)
In a fifth aspect of the embodiment, compounds of formula V are provided:

wherein:

A and E are:

each independently a bond, -CR₂⁻, -CR=, -CR₂CR₂⁻, -CR=CR⁻, -N=CR⁻,
-(CR₂)ₐC(O)-N(R)⁻(CR₂)ₐ⁻, -(CR₂)ₐ-N(R⁻)-C(O)-(CR₂)ₐ⁻
-(CR₂)ₐ-N(R⁻)(CR₂)ₐ⁻, -(CR₂)VO-(CR₂)⁻V⁻, -O⁻, -S⁻, -S(O⁻)⁻, -S(O)⁻,
-C(O)⁻ or -N⁻, wherein:

R⁻ is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, and amino,

wherein:

two R's either both on a single C or on adjoining Cs, together with the C or C's to which they are attached, optionally form a cycle, and

where two R's are possible on a C, the C may optionally be linked to a single R with a double bond;

each a and b are independently 0, 1, 2, or 3; and

with the proviso that A and E are either both a bond or both other than a bond;

each R⁺ is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, and amino;

each r is independently 0, 1, 2 or 3;

X⁻ is CH₂, NH, O or S.
Y\textsuperscript{1} and Z\textsuperscript{1} are each independently CH or N.

W and W' are each independently optionally substituted with one or more substituents
selected from the group consisting of -OH, -CN, -NO\textsubscript{2}, halogen, Ci to C\textsubscript{12} alkyl, Ci to
C\textsubscript{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy,
alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and
amino, and

each R\textsuperscript{c}, R\textsuperscript{d}, R\textsuperscript{e} and R\textsuperscript{f} is independently selected from the group consisting of: hydrogen,
Ci to C\textsubscript{g} alkyl, Ci to C\textsubscript{g} heteroalkyl, aralkyl and a 4- to 8- membered ring which may
be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,
each of R\textsuperscript{c}, R\textsuperscript{d}, R\textsuperscript{e} and R\textsuperscript{f} may optionally be substituted by Ci to C\textsubscript{g} alkyl, Ci to C\textsubscript{g}
heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl,
heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is
independently N, O or S,

R\textsuperscript{c} and R\textsuperscript{d} are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring,

and

R\textsuperscript{e} and R\textsuperscript{f} are optionally joined to form a 4- to 8-membered heterocycle which is
optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are each independently selected from the group consisting of hydrogen, Ci to C\textsubscript{g}
alanyl, Ci to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3
amino acids,

\[-[U-(CR\textsubscript{4})_2],-NR\textsubscript{5}-C(R\textsubscript{4})_2,1\textsuperscript{U}-U-(CR\textsubscript{4})_2,-NR\textsubscript{7}-(CR\textsubscript{4})_2,-R\textsubscript{8}, -U-(CR\textsubscript{4})_2,-R\textsubscript{8}, \text{ and} \]

\[-[U-(CR\textsubscript{4})_2],-NR\textsubscript{5}-(CR\textsubscript{4})_2,1\textsuperscript{U}-U-(CR\textsubscript{4})_2,-O-(CR\textsubscript{4})_2,-R\textsubscript{8}, \text{ wherein,} \]

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)\textsubscript{2} -, 
each R\textsuperscript{4}, R\textsuperscript{5} and R\textsuperscript{7} is independently selected from the group consisting of
hydrogen, Ci to C\textsubscript{g} alkyl, Ci to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl and aralkyl,

R\textsubscript{8} is selected from the group consisting of hydrogen, Ci to C\textsubscript{g} alkyl, Ci to C\textsubscript{g}
heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R\textsuperscript{81},
-C(S)-R\textsubscript{81}, -C(O)-O-R\textsubscript{81}, -C(O)-N-R\textsubscript{812}, -S(O)\textsubscript{2}-R\textsubscript{81} and -S(O)\textsubscript{2}-N-R\textsubscript{812}, wherein each R\textsubscript{81} is independently chosen from the group consisting of hydrogen, C\textsubscript{i} to C\textsubscript{g} alkyl, C\textsubscript{i} to C\textsubscript{g} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl, optionally, R\textsubscript{7} and R\textsubscript{8} together form a 4-7 membered ring, each t is independently 0, 1, 2, 3, or 4, and u is 0, 1, or 2.

[0188] In a first embodiment of the fifth aspect, compounds of formula Va are provided:

\[ \text{Va.} \]

[0189] In a second embodiment of the fifth aspect, compounds of formula Vb are provided:

\[ \text{Vb.} \]

[0190] In a third embodiment of the fifth aspect, both A and E are -O-.

[0191] In a fourth embodiment of the fifth aspect, A is -O- and E is -CH\textsubscript{2}-, -C(CH\textsubscript{3})\textsubscript{2}-, -C(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{-} or -C(O)-.

[0192] In a fifth embodiment of the fifth aspect, one or both of X\textsubscript{1} are -S-.

[0193] In a sixth embodiment of the fifth aspect, one or both of X\textsubscript{1} are -O-.

[0194] In a seventh embodiment of the fifth aspect, one or both of X\textsubscript{1} are -NH-.

[0195] In an eighth embodiment of the fifth aspect, one or both of Y\textsubscript{1} are -N-.

[0196] In a ninth embodiment of the fifth aspect, one or both of Z\textsubscript{1} is -N-.

[0197] In a sixth aspect, compounds of formula VI are provided:
wherein:

A and E are:

-(CR\(_2\))\(_a\)-N(R\(_N\))-(CR\(_2\))\(_a\)-, ... 

R\(_N\) is selected from the group consisting of H, -OH, Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, 
-CN, -NO\(_2\), halogen, Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

two R's either both on a single C or on adjoining Cs, together with the C 
or C's to which they are attached, optionally form a cycle, and 
where two R's are possible on a C, the C may optionally be linked to a 
single R with a double bond, and 

each a and b are independently 0, 1, 2, or 3 with the proviso that both b's are not 0; and 

each R\(^a\) is independently selected from the group consisting of -OH, -CN, -NO\(_2\), halogen, 
Ci to Ci\(_2\) alkyl, Ci to Ci\(_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, 
aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, 
sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

X\(^1\) is CH\(_2\), NH, O or S,

Y\(^1\) and Z\(^1\) are each independently CH or N,
W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁₂ to C₁₂ alkyl, C₁₂ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R₅, R⁴, R³ and R² is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,
each of R₅, R⁴, R³ and R² may optionally be substituted by Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,
R³ and R⁴ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and
R⁵ and R⁴ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;
Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-U-(CR ⁴₂),-NR ⁵(CR ⁴₂),₁U-(CR ⁴₂),-NR ⁷(CR ⁴₂),₂R,₈, -U-(CR ⁴₂),₃R,₈, and

-U-(CR ⁴₂),-NR ⁵(CR ⁴₂),₁U-(CR ⁴₂),-O-(CR ⁴₂),₂R,₈, wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)₂⁻,
each R⁴, R₅ and R⁷ is independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R⁸ is selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R ⁸¹, -C(S)-R ⁸¹, -C(O)-O-R ⁸¹, -C(O)-N-R ⁸¹₂, -S(O)₂-R ⁸¹ and -S(O)₂-N-R ⁸¹₂, wherein
each R₈ is independently chosen from the group consisting of hydrogen, C₄ to C₉ alkyl, C₄ to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R⁷ and R⁸ together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0198] In a first embodiment of the sixth aspect, compounds of formula Via are provided:

[0199] In a second embodiment of the sixth aspect, compounds of formula Vlb are provided:

[0200] In a third embodiment of the sixth aspect, compounds of formula VII are provided:

[0201] In a fourth embodiment of the sixth aspect, compounds of formula Vila are provided:
In a fifth embodiment of the sixth aspect, compounds of formula VIIb are provided:

![VIIa](image)

In a sixth embodiment of the sixth aspect, compounds of formula VIII are provided:

![VIII](image)

In a seventh embodiment of the sixth aspect, compounds of formula Villa are provided:

![Villa](image)

In an eighth embodiment of the sixth aspect, compounds of formula VIIIb are provided:
In a ninth embodiment of the sixth aspect, one or both of $X^1$ are -O-.

In a tenth embodiment of the sixth aspect, one or both of $X^1$ are -NH-.

In an eleventh embodiment of the sixth aspect, one or both of $X^1$ are -S-.

In a twelfth embodiment of the sixth aspect, one or both of $Z^1$ is -N-.

In a thirteenth embodiment of the sixth aspect, one or both of $Y^1$ is -N-.

In a seventh aspect of the invention, compounds of formula IX are provided:

\[
\begin{align*}
\text{wherein:} & \\
A \text{ and } E \text{ are each independently } -\text{CR}= \text{ or } -\text{N}= \text{ wherein } R \text{ is selected from the group} \\
& \text{consisting of hydrogen, } -\text{OH}, -\text{CN}, -\text{NO}_2, \text{halogen, } \text{Ci to Ci}_2 \text{ alkyl,} \\
& \text{Ci to } C_{13} \text{ heteroalkyl, cyloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy,} \\
& \text{alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and} \\
& \text{amino; } \\
& \text{each } R^0 \text{ is independently selected from the group consisting of } -\text{OH}, -\text{CN}, -\text{NO}_2, \text{halogen,} \\
& \text{Ci to } C_{12} \text{ alkyl, Ci to Ci}_2 \text{ heteroalkyl, cyloalkyl, heterocycle, aryl, heteroaryl,} \\
& \text{aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate,} \\
& \text{sulfonamide and amino; } \\
& \text{each } r \text{ is independently } 0, 1, 2 \text{ or } 3; \\
& X^1 \text{ is } \text{CH}_2, \text{NH, O or S,} \\
& Y^1 \text{ and } Z^1 \text{ are each independently } \text{CH or N,}
\end{align*}
\]
W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R⁵, R⁶, R⁷ and R⁸ is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,
each of R⁵, R⁶, R⁷ and R⁸ may optionally be substituted by Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl, or a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R⁵ and R⁶ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and

R⁷ and R⁸ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;

Y and Y’ are each independently carbon or nitrogen; and

Z and Z’ are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)₂⁻, each R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R⁸ is selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R⁸₁, -C(S)-R⁸₁, -C(O)-O-R⁸₁, -C(O)-N-R⁸₁₂, -S(O)₂-R⁸₁ and -S(O)₂-N-R⁸₁₂, wherein
each $R^8$ is independently chosen from the group consisting of hydrogen, $C_i$ to $C_g$ alkyl, $C_i$ to $C_g$ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, $R^7$ and $R^8$ together form a 4-7 membered ring,

each $t$ is independently 0, 1, 2, 3, or 4, and

$u$ is 0, 1, or 2.

[0212] In a first embodiment of the seventh aspect compounds of formula IXa are provided:

IXa.

[0213] In a second embodiment of the seventh aspect compounds of formula IXb are provided:

IXb.

[0214] In a third embodiment of the seventh aspect $A$ and $E$ are -N=.

[0215] In a fourth embodiment of the seventh aspect, one or both of $X^1$ are -S-.

[0216] In a fifth embodiment of the seventh aspect, one or both of $X^1$ are -O-.

[0217] In a sixth embodiment of the seventh aspect, one or both of $X^1$ are -NH-.

[0218] In a seventh embodiment of the seventh aspect, one or both of $Y^1$ are -N-.

[0219] In an eighth embodiment of the seventh aspect, one or both of $Z^1$ is -N-.

[0220] In an eighth aspect of the invention, compounds of formula X are provided:
wherein:

\[ E \text{ is } -CR_2^-, -CR=, -CR_2^2-, -CR=CR-, -N=CR-, -(CR_2)_a-N(R^N)\text{-(CR}_2)_a^- \]

\[ -(CR_2)_a-C(O)-N(R^N)-(CR_2)_a^-, -(CR_2)_a-N(R^N)-C(O)-(CR_2)_a^-, \text{ or } -(CR_2)_b-O-(CR_2)_b^- \]

wherein:

- \( R^N \) is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

- each \( R \) is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

- wherein:

  - two \( R \)'s either both on a single \( C \) or on adjoining \( Cs \), together with the \( C \) or \( Cs \) to which they are attached, optionally form a cycle, and

  - where two \( R \)'s are possible on a \( C \), the \( C \) may optionally be linked to a single \( R \) with a double bond;

- each \( a \) and \( b \) are independently 0, 1, 2, or 3;

- each \( R^a \) is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

- each \( r \) is independently 0, 1, 2 or 3;

- \( X^1 \) is CH₂, NH, O or S,

- \( Y^1 \) and \( Z^1 \) are each independently CH or N,

- \( W \) and \( W \) are each independently optionally substituted with one or more substituents.
selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyle, sulfonate, sulfonamide and amino, and

each R⁵, R⁶, R⁷ and R⁸ is independently selected from the group consisting of: hydrogen, Ci to C₉ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,

each of R⁵, R⁶, R⁷ and R⁸ may optionally be substituted by Ci to C₉ alkyl, Ci to C₉ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S.

R⁵ and R⁶ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

R⁷ and R⁸ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

-[U-(CR₂)₄]-NR₅-C(R₄)₂₋₁U-(CR₄)₂₋₁NR₇-(CR₄)₂₋₁-R₈₋₁, -U-(CR₂)₄₋₁-R₈₋₁, and

-U-(CR₂)₄₋₁-NR₅-(CR₄)₂₋₁U-(CR₄)₂₋₁-O-(CR₂)₄₋₁-R₈₋₁, wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O)₂⁻,

each R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R⁸ is selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R₈₁, -C(S)-R₈₁, -C(O)-O-R₈₁, -C(O)-N-R₈₁, -S(O)₂-R₈₁ and -S(O)₂-N-R₈₁, wherein each R₈₁ is independently chosen from the group consisting of hydrogen, Ci to
C<sub>g</sub> alkyl, C<sub>i</sub> to C<sub>g</sub> heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R<sup>7</sup> and R<sup>8</sup> together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0221] In a first embodiment of the eighth aspect, compounds of formula X<sub>a</sub> are provided:

![Chemical structure](image1)

X<sub>a</sub>.

[0222] In a second embodiment of the eighth aspect, compounds of formula X<sub>b</sub> are provided:

![Chemical structure](image2)

X<sub>b</sub>.

[0223] In a third embodiment of the eighth aspect, one or both of X<sup>1</sup> are -S-.

[0224] In a fourth embodiment of the eighth aspect, one or both of X<sup>1</sup> are -O-.

[0225] In a fifth embodiment of the eighth aspect, one or both of X<sup>1</sup> are -NH-.

[0226] In a sixth embodiment of the eighth aspect, one or both of Y<sup>1</sup> are -N-.

[0227] In a seventh embodiment of the eighth aspect, one or both of Z<sup>1</sup> is -N-.

[0228] In a ninth aspect of the invention, compounds of formula X<sub>I</sub> are provided:

![Chemical structure](image3)

X<sub>I</sub>.
wherein:

each R is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, Ci to Cl₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

X is CH₂, NH, O or S,

Y and Z are each independently CH or N,

W and W are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to Cl₂ alkyl, Ci to Cl₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R, R₄, R₅ and R₆ is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,

each of R₄, R₅, R₆ and R₇ may optionally be substituted by Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S.

R₄ and R₅ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

R₄ and R₅ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y’ are each independently carbon or nitrogen; and

Z and Z’ are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3
amino acids,

\[-[U-(CR_2^2),-NR^5-C(r_2),]_u-U-(Cr_2^2),-NR^7-(Cr_2),-R^8, \text{ and} \]
\[-[U-(CR_2^2),-NR^5-(CR_4^2),]_u-U-(CR_2^2),-O-(CR_2^2),-R^8,\] wherein,

U is selected from the group consisting of \(-C(O)-\), \(-C(S)-\), and \(-S(O)_2-\),
each \(R^4\), \(R^5\), and \(R^7\) is independently selected from the group consisting of
hydrogen, \(\text{C}_8\) alkyl, \(\text{C}_8\) heteroalkyl, cycloalkyl, heterocycle, aryl,
heteroaryl and aralkyl,

\(R^8\) is selected from the group consisting of hydrogen, \(\text{C}_8\) alkyl, \(\text{C}_8\) heteroalkyl,
cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, \(-C(O)-R^8_1\),
\(-C(S)-R^8_1\), \(-C(O)-O-R^8_1\), \(-C(O)-N-R^8_2\), \(-S(O)_2-R^8_1\) and \(-S(O)_2-N-R^8_{12}\), wherein
each \(R^8_1\) is independently chosen from the group consisting of hydrogen, \(\text{C}_8\) alkyl,
\(\text{C}_8\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, \(R^7\) and \(R^8\) together form a 4-7 membered ring,
each \(t\) is independently \(0\), \(1\), \(2\), \(3\), or \(4\), and

\(u\) is \(0\), \(1\), or \(2\).

[0229] In a first embodiment of the ninth aspect, compounds of formula XIa are provided:

\[
\begin{align*}
\text{XIa.}
\end{align*}
\]

[0230] In a second embodiment of the ninth aspect, compounds of formula XIb are provided:

\[
\begin{align*}
\text{XIb.}
\end{align*}
\]
In a third embodiment of the ninth aspect, one or both of X₁ are -S-.

In a fourth embodiment of the ninth aspect, one or both of X₁ are -O-.

In a fifth embodiment of the ninth aspect, one or both of X₁ are -NH-.

In a sixth embodiment of the ninth aspect, one or both of Y₁ are -N-.

In a seventh embodiment of the ninth aspect, one or both of Z₁ is -N-.

In a tenth aspect of the invention, compounds of formula XII are provided:

\[
\begin{align*}
\text{XII, wherein:} \\
\text{A'} \text{ and E'} \text{ are each independently } -\text{CR}_2^-, -\text{CR}=, -\text{N(R}_N^N)-, -\text{O}-, -\text{S}-, \\
-\text{S(O}_2^-)-, -\text{S(O)}-, \text{ or } -\text{N}=, \text{ wherein:} \\
\text{R}_N^N \text{ is selected from the group consisting of } \text{H}, -\text{OH}, \text{Ci to } \text{Ci}_2 \text{ alkyl, Ci to } \text{Ci}_2 \text{ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and} \\
\text{R} \text{ is selected from the group consisting of hydrogen, } -\text{OH}, -\text{CN}, -\text{NO}_2, \text{halogen, Ci to } \text{Ci}_2 \text{ alkyl, Ci to } \text{Ci}_2 \text{ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;} \\
\text{each } \text{R}^r \text{ is independently selected from the group consisting of } -\text{OH}, -\text{CN}, -\text{NO}_2, \text{halogen, Ci to } \text{Ci}_2 \text{ alkyl, Ci to } \text{Ci}_2 \text{ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;} \\
\text{each } \text{r} \text{ is independently } 0, 1, 2 \text{ or } 3; \\
\text{X}^1 \text{ is } \text{CH}_2, \text{NH, O or S,} \\
\text{Y}^1 \text{ and } \text{Z}^1 \text{ are each independently } \text{CH} \text{ or N,} \\
\text{W and W are each independently optionally substituted with one or more substituents}
\end{align*}
\]
selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carboxamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each Rᵣ, Rᵈ, Rᵉ and Rᶠ is independently selected from the group consisting of: hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

each hetero atom, if present, is independently N, O or S,

each of Rᵣ, Rᵈ, Rᵉ and Rᶠ may optionally be substituted by Ci to C₉ alkyl, Ci to C₉ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each hetero atom, if present, is independently N, O or S.

Rᵣ and Rᵈ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

Rᵣ and Rᶠ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

- [U- (CR ²)₂]-NR ⁵-C(R ⁴)₂]-U-(CR ⁴)₂]-NR ⁷-(CR ⁴)₂]-R ⁸, -U-(CR ⁴)₂]-R ⁸, and
- [U- (CR ²)₂]-NR ⁵-(CR ⁴)₂]-U-(CR ⁴)₂]-O-(CR ⁴)₂]-R ⁸, wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O) ₂⁻,

each R ⁴, R ⁵ and R ⁷ is independently selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R ⁸ is selected from the group consisting of hydrogen, Ci to C₉ alkyl, Ci to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R ⁸₁, -C(S)-R ⁸₁, -C(O)-O-R ⁸₁, -C(O)-N-R ⁸₁₂, -S(O) ₂⁻R ⁸₁ and -S(O) ₂⁻N-R ⁸₁₂, wherein each R ⁸₁ is independently chosen from the group consisting of hydrogen, Ci to
C₉ alkyl, C₁ to C₉ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R⁷ and R⁸ together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

[0237] In a first embodiment of the tenth aspect, compounds of formula XIIa are provided:

![Diagram XIIa]

[0238] In a second embodiment of the tenth aspect, compounds of formula XIIb are provided:

![Diagram XIIb]

[0239] In a third embodiment of the tenth aspect, one or both of X¹ are -S-.
[0240] In a fourth embodiment of the tenth aspect, one or both of X¹ are -O-.
[0241] In a fifth embodiment of the tenth aspect, one or both of X¹ are -NH-.
[0242] In a sixth embodiment of the tenth aspect, one or both of Y¹ are -N-.
[0243] In a seventh embodiment of the tenth aspect, one or both of Z¹ is -N-.
[0244] In an eleventh aspect of the invention Z and Z' in any of the previous aspects are each 1-3 amino acids.
[0245] In a first embodiment of the eleventh aspect, the amino acids are all in the D or all in the L configuration.
In a second embodiment of the eleventh aspect, Z and Z' are each independently selected from the group consisting of
\[-U-(CR_4^2)_{-}\text{NR}^5\cdot(CR_2^4)_{-}U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8,
\]-U-(CR_4^2)_{-}R^8 and -[U-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}U-(CR_4^2)_{-}\text{O}(CR_4^2)_{-}R^8.

In a third embodiment of the eleventh aspect, one or both of Z and Z' are
\[-U-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a fourth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-U-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a fifth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a sixth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-[C(O)-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a seventh embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}U-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In an eighth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-[C(O)-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}C(O)-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a ninth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_{-}\text{NR}^5\cdot(CR_4^2)_{-}\text{C}(O)-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In a tenth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_{-}\text{NR}^7\cdot(CR_4^2)_{-}R^8.

In an eleventh embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_n\text{NR}^7\cdot(CR_4^2)_n\text{C}(O)-R^8.

In an twelfth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_n\text{NR}^7\cdot(C(O)-R^8.

In a thirteenth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_n\text{NR}^7\cdot(C(O)-R^8.

In a fourteenth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-C(O)-(CR_4^2)_n\text{NR}^7\cdot(C(O)-O-R^8.

In a fifteenth embodiment of the eleventh aspect, one or both of Z and Z' are
\[-U-(CR_4^2)_{-}R^8.
In a sixteenth embodiment of the eleventh aspect, one or both of Z and Z' are -C(O)-(CR$_2^4$)$_{2t}$-R$_8$.

In a seventeenth embodiment of the eleventh aspect, one or both of Z and Z' are -[U-(CR$_2^4$)$_{2t}$]-NR$_5$-(CR$_2^4$)$_{2t}$]-U-(CR$_2^4$)$_{2t}$]-O-(CR$_2^4$)$_{2t}$]-R$_8$.

In an eighteenth embodiment of the eleventh aspect, one or both of Z and Z' are -U-(CR$_2^4$)$_{2t}$]-NR$_5$-(CR$_2^4$)$_{2t}$]-U-(CR$_2^4$)$_{2t}$]-O-(CR$_2^4$)$_{2t}$]-R$_8$.

In a nineteenth embodiment of the eleventh aspect, one or both of Z and Z' are -C(O)-(CR$_2^4$)$_{2t}$]-NR$_5$-(CR$_2^4$)$_{2t}$]-C(O)-(CR$_2^4$)$_{2t}$]-O-(CR$_2^4$)$_{2t}$]-R$_8$.

In a twentieth embodiment of the eleventh aspect, one or both of Z and Z' are -U-(CR$_2^4$)$_{2t}$]-O-(CR$_2^4$)$_{2t}$]-R$_8$.

In a twenty-first embodiment of the eleventh aspect, one or both of Z and Z' are -C(O)-(CR$_2^4$)$_{2t}$]-O-(CR$_2^4$)$_{2t}$]-R$_8$.

In a twenty-second embodiment of the eleventh aspect, one or both of Z and Z' are -C(O)-(CR$_2^4$)$_{2t}$]-NR$_7$-R$_8$ wherein R$_7$ and R$_8$ together form a 4-7 membered ring.

A twelfth aspect of the invention provides a pharmaceutical composition comprising the compounds of the invention.

A thirteenth aspect of the invention provides use of the compounds of the invention in the manufacture of a medicament.

In a first embodiment of the thirteenth aspect the medicament is for the treatment of hepatitis C.

A fourteenth aspect of the invention provides a method of treating hepatitis C comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the invention.

**General Synthesis**

The following abbreviations are used throughout this application:

- **ACN** Acetonitrile
- **AcOH** Acetic acid
- **aq** Aqueous
- **Bn** Benzyl
- **BnOH** Benzyl alcohol
- **Boc** t-Butoxycarbonyl
- **Cbz** Benzoxycarbonyl
Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹HNMR spectra were recorded on a Bruker 400 MHz or 500 MHz NMR spectrometer. Significant peaks are tabulated in the order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons.

The following examples are provided by way of illustration only and not by way of limitation. Those skilled in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental errors and deviations should, of course, be allowed for.

Liquid chromatography mass spectra (LC-MS) were obtained using an electrospray ionization (ESI) source in either the positive or negative mode.

The compounds were named using ChemDraw program from Cambridge Soft Inc.

The compounds of formula I in this invention can be prepared following the synthetic strategies outlined in Scheme A. The synthesis generally starts with the tricyclic central core A-I, which is either available from commercial sources, prepared following literature reports or prepared as disclosed here. The cyclic core can be prepared bearing the suitable substituents. The flanking W and W' moieties, along with the groups attached to them, may be constructed through a stepwise functional group transformations of G and G' in parallel (route A) or one side at a time (route B and then route C or vice versa). The W and W' and respective moieties attached to them can be introduced through a cross coupling step. Once the central core scaffold is in place, further elaboration of the two ends yields additional compounds.
The preparations of the various claimed chemical series are further illustrated in the schemes outlined below and in greater details in the Example section. These reactions are often carried out using known procedures, methods or analogous methods thereof. Examples of such known methods include those described in a general reference text such as Comprehensive Organic Transformations; Volumes 1-10, 1974-2002, Wiley Interscience; Comprehensive Organic Synthesis Volumes 1-9, Ed. B. M. Trost, I. Fleming, 1991, Pergamon. Using 9,10-dihydro-9,10-ethanoanthracene, 5,10-dimethyl-5,10-dihydrophenazine, phenoxathine and dibenzo[l,5]dioxocine systems as examples, we show some of the ways how W and W groups are installed.
As shown in Scheme B, compound B-I is converted to the corresponding α-bromoketone B-2, followed by reacting with N-substituted-L-Pro-OH and ring formation, to give bis-imidazole derivative B-3 which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-imidazole analogs of B-3.
As described in Scheme C, the regioisomer of B-3 with respect to the substitution pattern on the imidazole moiety is synthesized. Coupling of C1 and (5)-2-halo-l-(pyrrolidin-2-yl)ethanone C-2, followed by ring formation, gives bis-imidazole C-4, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Alternatively, C-4 can be obtained by condensing C-2 and bis-imidamide C-7. Moreover, (5)-2-halo-l-(pyrrolidin-2-yl)ethanone C-2 can be replaced with other α-halo ketones derived from N-substituted D- or L-amino acids to generate bis-imidazole analogs of C-4.

[0280] As illustrated in Scheme D, bis-triflate D-I is readily converted to the corresponding carboxylic acid D-2 via a palladium-mediated carbonylation, followed by saponification. Subsequently, the carboxylic acid residues are converted to thio-amides D-3, followed by treatment with N-substituted 2-bromo-2-((5)-pyrrolidin-2-yl)acetaldehyde D-4 to give bis-thiazole analog D-5, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, 2-bromo-2-((5)-pyrrolidin-2-yl)acetaldehyde D-4 can be replaced with other 2-bromo-2-substituted acetaldehydes, derived from N-substituted D- or L-amino acids to generate bis-thiazole analogs of D-5.
Scheme E

E-1

E-2

E-3

E-4

E-5

E-6

E-7
As depicted in Scheme E, the regio-isomer of bis-thioazole D-5 with respect to the substitution pattern on the thiazole moiety is prepared. Reduction of E-I, followed by condensation and hydrolysis, gives bis-substituted acetaldehyde E-4. Bromination of E-4, followed by cyclization with N-substituted (5)-pyrrolidine-2-carbothioamide E-6, affords bis-thiazole E-7, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted (5)-pyrrolidine-2-carbothioamide E-6 can be replaced with other thio-amides derived from N-substituted D- or L- amino acids to give bis-thiazole analogs of E-7.
As outlined in Scheme F, bis-carboxylic acid F-I is converted to \(N_3N'\)-diacylhydrazide F-3 through a three step sequence of amide formation, de-protection and amide formation. Ring cyclization of F-3 gives either bis-thiodiazole F-4 or bis-oxadiazole F-5 when the proper de-hydration reagents are used. Both F-4 and F-5 can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate analogs of F-4 and F-5, respectively.

\[
\begin{align*}
\text{Cl} & \quad \text{G-1} & \quad 1 \text{NaN₃, DMF} \\
\quad & \quad 2 \text{SnCl₄, DCM} \\
\quad & \quad \text{G-2} \\
\quad & \quad \text{DEPBT, DIEA, DMF} \\
\quad & \quad \text{G-3} \quad \text{R = Boc or Cbz} \\
\quad & \quad \text{DEAD, PPh₃, THF} \\
\quad & \quad \text{G-4} \quad \text{R = Boc or Cbz}
\end{align*}
\]

Scheme G

As shown in Scheme G, \(\alpha\)-chloro ketone G-I is converted to the corresponding \(\alpha\)-amino ketone G-2. Amide formation of G-2 with N-substituted L-Pro-OH, followed by dehydration, affords bis-oxazole G-4, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-oxazole analogs of G-4.
As outlined in Scheme H, the regioisomer of G-4 with respect to the substitution pattern on the oxazole moiety is prepared. Amide formation of bis-carboxylic acid H-I with (S)-2-amino-l-(pyrrolidin-2-yl)ethanone H-2, followed by dehydration, gives bis-oxazole H-4, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, (S)-2-amino-l-(pyrrolidin-2-yl)ethanone H-2 can be replaced with other α-amino ketones derived from N-substituted D- or L-amino acids to generate bis-oxazole analogs of H-4.
Scheme I
As shown in Scheme I, reduction of 1-1 and the subsequent N-alkylation give 1-2, which is readily converted to the corresponding bis-triflate 1-3. Stille coupling of 1-3, followed by α-bromination, O-alkylation and ring formation affords bis-imidazole 1-6, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-imidazole analogs of 1-6.
As described in Scheme J, O-alkylation of J-I, followed by ring cyclization, gives bis-imidazole J-2, which can be selectively oxidized to yield the corresponding sulfoxide J-3 and sulphone J-4. J-2, J-3 and J-4 can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate analogs of J-2, J-3 and J-4, respectively.
Analogs built on a dibenzo[1,5]dioxocine scaffold are prepared by using the synthetic route outlined in Scheme K or a variation of it. A properly substituted aryl ether K-2, prepared from the reduction of K-I, is cyclized to give dioxocine compound K-3 under the catalysis of a palladium catalyst such as Pd(dppf)Cl₂. Treatment of K-3 with chloroacetyl chloride under the standard Friedal-Craft reaction condition yields bischloromethylketone K-4. Similarly to what has been described above, bis-imidazole compound K-5 is obtained by reacting K-4 with an N-substituted-L-Pro-OH in two steps. The N-substituted L-Pro-OH used in this Scheme K can be substituted with other N-substituted D- or L-amino acids to generate bis-imidazole analogs bearing corresponding 2-substituents off the 2-position of the imidazole.

The following schemes exemplify some of the synthetic routes that are used for the preparation of compounds and their analogs included in this invention. Those skilled in the art will understand that alternative routes may also be used to reach the same and similarly functionalized intermediates and target molecules. Alternative reagents for a given transformation are also possible.
Example 1. Preparation of 1-5, dimethyl qS,2'S)-l,l'- 2S,2'S)-2,2'-(5,5'-fdibenzo[b,el][l,41dioxine-2,7-diyl]bis-flH-imidazole-5. 2-diyl))bispyrrolidine-2,l-diyl)dicarbamate

**Scheme 1**

**Example 1. Preparation of 1-5, dimethyl qS,2'S)-l,l'- 2S,2'S)-2,2'-(5,5'-fdibenzo[b,el][l,41dioxine-2,7-diyl]bis-flH-imidazole-5. 2-diyl))bispyrrolidine-2,l-diyl)dicarbamate**

[0289] **Step 1.** A solution of dibenzo-/?-dioxine (1-1) (5.0 g, 27.14 mmol) and chloroacetyl chloride (4.5 mL, 57 mmol) in dichloromethane (50 mL) was added over 20 min to a stirred suspension of aluminum chloride (14.5 g, 108.6 mmol) in dichloromethane (300 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 15 min and allowed to warm up to room temperature over 30 min. The reaction mixture was then heated at 50 °C for 3 h and stirring continued at rt overnight. The reaction was cooled to 0 °C and quenched carefully with ice-cold water (250 mL). The volatiles were removed in vacuo and the precipitate formed was collected by vacuum filtration and washed with ethyl ether and dried at 50 °C in...
vacuo to afford crude product 1-2 (8.85 g, 97% yield), which was used in the next step without further purification. ¹H NMR (CDCl₃, 300MHz) δ 7.82-7.50 (m, 4H), 7.20 (m, 2H), 5.18 (s, 4H) ppm.

[0290]  Step 2. General Procedure A -synthesis of an imidazole from an α-bromoketone (or α-chloroketone) and a carboxylic acid.

[0291]  a. Diisopropylethylamine (6.85 mL, 39.58 mmol) was added to a stirred suspension of chloromethyl ketone 1-2 (5.54 g, 16.49 mmol), N-Boc-L-proline (7.80 g, 36.28 mmol), and KI (1.09 g, 6.6 mmol) in DMF (30 mL), and the mixture was stirred at 50 °C for 3 h. The cooled reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over MgSO₄ and then filtered. The volatiles were removed in vacuo, and the crude product was purified by flash column chromatography (SiO₂, 1/1 EtOAc/hexanes) to afford ketoester 1-3 (6.85 g, 60% yield) as a light yellow solid.

[0292]  b. Ketoester 1-3 from above (4.85 g, 6.98 mmol) was taken up in xylene (20 mL) and placed in a 100 mL pressure vessel. Ammonium acetate (5.34 g, 69.8 mmol) and triethylamine (5 mL) were added and the reaction mixture was heated at 140 °C for 2 h. The cooled mixture was diluted with ethyl acetate (150 mL) and then washed with saturated NaHCO₃ aqueous solution followed by brine. The organic layer was dried over MgSO₄, filtered and volatiles were removed in vacuo. The crude product was purified by flash column chromatography (SiO₂, EtOAc) to afford product 1-4A (3.15 g, 69% yield) as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 7.40-6.60 (m, 8H), 7.44 (m, 2H), 4.98 (m, 2H), 3.60-1.85 (m, 12H), 1.47 (s, 18H) ppm. LC-MS (ESI): m/z 653 [M-H]⁻.

[0293]  Step 3. General Procedure B -deprotection and re-acylation. To a stirred solution of compound 1-4A (194 mg, 0.296 mmol) in dioxane (3 mL) was added 4.0 N HCl in dioxane (3 mL). After stirring at rt for 4 h, the reaction mixture was concentrated and the residue was dried in vacuo to give an HCl salt, which was used for the next step without further purification. LC-MS (ESI) m/z: 455 (M+H)⁺. The HCl salt obtained was dissolved in DMF (3 mL). To the resulting mixture were sequentially added DIEA (388 mg, 3.0 mmol), N-Moc-L-Val-OH (116 mg, 0.66 mmol) and HATU (251 mg, 0.66 mmol). After stirring at rt for 2 h, the reaction mixture was poured into water (50 mL) and the resulting suspension was extracted with DCM several times (20 mL x 3). The extracts were combined, washed with
brine and dried with anhydrous MgSO₄. The solvent was removed and the residue was purified by preparative HPLC and to give compound 1-5. LC-MS (ESI): m/z 769 (M+H)+.

**Example 2. Preparation of 1-4B**

![Chemical Structure of 1-4B]

[0294] Following General Procedure A described above for the synthesis of 1-4 and substituting N-Boc-L-proline with N-Boc-L-pipecolic acid in Step a, compound 1-4B (0.82 g) was obtained in 60% yield. LC-MS (ESI): m/z 681 [M-H]⁻.

**Example 3. Preparation of 1-5B**

![Chemical Structure of 1-5B]

[0295] Following General Procedure B and substituting compound 1-4B for 1-4A, compound 1-5B was obtained. LC-MS (ESI): m/z 797 [M+H]+.

**Example 4. Preparation of 1-4C**

![Chemical Structure of 1-4C]

[0296] Following General Procedure A described above for synthesis of 1-4A and replacing N-Boc-L-proline with N-Boc-L-thiaproline, the corresponding ketoester 1-3C was obtained in 37% yield. ¹H NMR (CDCl₃, 300MHz) δ 7.56 (d, 2H), 7.56 (d, 2H), 7.44 (s, 2H), 5.53-5.16 (m, 4H), 4.98 (m, 1H), 4.88 (m, 1H), 4.73-4.48 (m, 4H), 3.44 (m, 4H), 1.48 (s, 18H) ppm. LC-MS (ESI): m/z 729 [M-H]⁻.

[0297] Treatment of 1-3C with NH₃OAc under conditions as described in General Procedure A resulted in 1-4C (0.27 g) in 35% yield. ¹H NMR (CDCl₃, 300MHz) δ 7.18 (m, 6H), 6.81(s, 2H), 5.48 (m, 2H), 4.68 (m, 4H), 4.44 (br s, 2H), 3.43 (m, 4H), 1.48 (s, 18H) ppm. LC-MS (ESI): m/z 689 [M-H]⁻.
Example 5. Preparation of 1-5C

Following procedure B and substituting compound 1-4C for 1-4A, the title compound was obtained. LC-MS (ESI): m/z 805 [M+H]+.

Example 6. Preparation of 1-4D

Following General Procedure A described above for synthesis of 1-4A, and replacing N-Boc-L-proline with 4-N-Boc-3(5)-morpholine carboxylic acid, compound 1-4D was obtained in 70% yield. LC-MS (ESI): m/z 686 [M-H]+.

Example 7. Preparation of 1-5D

Following procedure B and substituting compound 1-4D for 1-4A, compound 1-5D was obtained. LC-MS (ESI): m/z 801 [M+H]+.

Example 8. Preparation of 1-4E

Following General Procedure A described above for synthesis of 1-4A, and replacing N-Boc-L-proline with N-Boc-L-alanine, compound 1-4E was obtained in 72% yield in two steps. LC-MS (ESI): m/z 601 [M-H]−.
Example 9. Preparation of 1-5E

Following General Procedure B and substituting compound 1-4E for 1-4A, the title compound was obtained. LC-MS (ESI): m/z 111 [M+H]+.

Scheme 5

Example 10. (2S,25")-tert-butyl 2,2'(5,5'-(9 H-xanthene-2,7-diyl)bisq H-imidazole-5,2-divD)dipyrrolidine-l-carboxylate (5-3)

Step 1. Referring to Scheme 5, bromoacetyl chloride (4.59 ml, 54.9 mmol) was added dropwise to a solution of 9H-xanthene (5g, 27.4 mmol) and AlCl₃ (8.05 g, 60.4 mmol), DCM (100 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and left to stir for 72 h. The reaction mixture was poured onto ice (400 mL), extracted with DCM (2 x 200 mL). The combined organic phase was washed with brine (400 mL), dried over MgSO₄, filtered and evaporated to dryness. The crude material was precipitated in EtOAc and filtered to give 1,1'-(9H-xanthene-2,7-diyl)bis(2-bromoethanone) (5-2) as a white solid (4.27 g, 36.7% yield). LC-MS (ESI): m/z 425.9 (M+H)+.
Step 2. Following General Procedure A as described in the synthesis of 1-4A, and substituting 1,1''-(9H-xanthene-2,7-diyl)bis(2-bromoethanone) (5-2) for 1,1''-(dibenzo[b,e][l,4]dioxine-2,7-diyl)bis(2-chloroethanone) (1-2) in Step 2a of the procedure, compound 5-3 was obtained as a brown solid in 35% yield. LC-MS (ESI): m/z 653.7 (M+H)+; 651.8 (M-H)-.

Example 11. Dimethyl (2S,2'S)-l,l''--((2S,2'S)-2,2''-(5,5''-(9H-xanthene-2,7-diyl)bisimidazole-5,2-diyl))bis(pyrrolidine-2,4-diyl))bis(3-methyl-l-oxobutane-2,l-diyl)dicarbamate (5-4)

Following General Procedure B, product 5-4 was obtained in 2 steps from 5-3 as a white solid (161 mg, 59% yield) from 5-3. LC-MS (ESI): m/z 767.0 (M+H)+; 765.2 (M-H)-.

Example 12. Dimethyl (qR,l'R)-2,2''-((2S,2'S)-2,2''-(5,5''-(9H-xanthene-2,7-diyl)bisimidazole-5,2-diyl))bis(fpyrrolidine-2,1-diyl))bisf2-oxo-l-phenylethane-2,1-diyl)dicarbamate (5-5)

Following General Procedure B and using N-Moc-D-phenylglycine as the coupling amino acid, product 5-5 was obtained as a white solid (209 mg, 67% yield). LC-MS (ESI): m/z 835.1 (M+H)+; 833.0 (M-H)-.

Other compounds bearing the same 2,7-disubstituted xanthenes scaffold are prepared similarly and listed in Table 1.
Example 13. Dimethyl-(2S,2'S)-l,l'-(2,2'-((5,5'-α,β-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(lH-imidazole-5,2-diyl))dipyrrolidine-2,1-diyl)bisf3-methyl-1-oxobutane-2,1-diyl)dicarbamate (6-4)

[0308] Step 1. General Procedure C: preparation of an arylborate from an aryl bromide, aryl iodide or aryl trifluoromethyl. Referring to Scheme 6, a solution of 2,8-dibromo-10,11-dihydrodibenzo[b,f]oxepine (6-1) (prepared according to procedures reported in WO2005090337) (435 mg, 1.229 mmol), potassium acetate (627 mg, 6.39 mmol), bis(pinacolato)diboron (1.31 g, 5.16 mmol) and Pd(dppf)Cl₂ (90 mg, 0.123 mmol) in dioxane (15 mL) was degassed and heated at 90 °C overnight. Reaction mixture was allowed to cool to room temperature and then filtered through celite, adsorbed on SiO₂ and then purified by column chromatography (SiO₂, 0-100% DCM/isohexanes) to give 2,8-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-11-l-dihydrodibenzo[b,f]oxepine (6-2) (169 mg, 31 % yield) as a white solid. ¹H NMR (CDCl₃) δ 7.63-7.57 (4H, m), 7.17-7.13 (2H, m), 3.13 (24H, s), 1.33 (24H, s) ppm. LC-MS (ESI): m/z 449.0 (M+H)⁺.

[0309] Step 2. Preparation of 2-(2S,2'S)-3-tert-butyl-2,2'-((5,5'-α,β-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(lH-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (6-3). General Procedure D: A mixture of 6-2 (300 mg, 0.669 mmol), (S)-3-tert-butyl-2-(5-iodo-l H-imidazol-2-yl)pyrrolidine-1-carboxylate (486 mg, 1.339 mmol), NaHCO₃ (450 mg, 5.36 mmol) and Pd(dppf)Cl₂ (98 mg, 0.134 mmol) in DME (4.5 mL), water (1.5 mL) was degassed and then heated at 80 °C for 18 h. Water (40 ml) was then added and the mixture extracted with 20% MeOH/CHCl₃ (3 x 50 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The product was purified by gel chromatography (Companion, 40 g cartridge, 0-10% MeOH/DCM+1% NH₃) to give -300 mg brown oil. Further purification by gel chromatography eluting with 10% MeOH in DCM containing 1% NH₃ gave 2-(2S,2'S)-3-tert-butyl-2,2'-((5,5'-α,β-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(lH-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (6-3) as a clear oil (210 mg, 47% yield). LC-MS (ESI): m/z 667.1 (M+H)⁺; 666.2 (M-H)⁻.

[0310] Step 3. Compound 6-4 was prepared using General Procedure B to give the product as a white solid (69 mg, 38% yield). LC-MS (ESI): m/z 782.0 (M+H)⁺.
Example 14. Dimethyl-\(\alpha\) \(\text{R},\text{R}^{'},\text{R}^{''}\)\(-2,2\'-\((\text{2S},\text{2}'\text{S})\)-2,2\'-\((\text{5},\text{5}')\)-q \(\text{0},\text{ll}\)\)-

Prepared by using General Procedure B, the title product 6-5 was obtained as a white solid (15 mg, 9\% yield). LC-MS (ESI): \(m/z\) 849.4 (M+H)+.
Example 15. Preparation of dimethyl (2S,2'S)-1J'-((2S,2'S)-2,2'-(5,5'-(9-oxo-9H-xanthene-2,6-diyl)bisflH-imidazole-5,2-(iiyl))bisfpyrroli(iine-2,1-(iiyl))bisf3-methyl-1-oxobutane-2,1-diyl)dicarbamate (7-5).

Step 1. General Procedure E -synthesis of xanthen-9-one. Referring to Scheme 7, to a solution of 4-bromo-2-chlorobenzoic acid (18.4 g, 83.9 mmol) and 4-bromophenol (24 g, 109 mmol) in nitrobenzene was added cesium carbonate (82 g, 251.7 mmol). The resulting solution was heated at 170 °C with a condenser for 1 day. The reaction mixture was cooled to 70 °C and filtered at this temperature. The residue was washed with toluene. The organic layer was removed by vacuum distillation till a thick dark residue remained. To the dark residue was added aqueous HCl (IN, 400 mL) and DCM (200 mL). The resulting solution
was stirred until dark oil dispersed into DCM solution. The mixture was filtered. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to afford the crude product. The residue was purified by column chromatography on silica gel, eluted first with DCM and then with a mixture of DCM and MeOH to give 7-1.

**Step 2.** Compound 7-1 (16 g, 5:3 ratio, 44.3 mmol) was treated with concentrated sulfuric acid (95 mL). The solution was heated at 105 °C for 2 h. The reaction mixture was cooled and poured into ice water. The product precipitated out and was collected by filtration, washed with Et₂O and H₂O. The solid was dried and further purified by flash column chromatography on silica gel (eluents: Hex:AcOEt = 9:1 (v/v) to AcOEt 100% and to DCM alone) to afford 7-2 (12 g).

**Step 3.** Compound 7-4 was prepared according to conditions described in general procedure C. LC-MS (ESI): m/z 667.3 (M+H)⁺.

**Step 4.** Compound 7-5 was prepared according to conditions described in general procedure B. LC-MS (ESI): m/z 781.3 (M+H)⁺.

**Example 16. Preparation of 7-7**

**Step 1.** To a solution of compound 7-4 (1.6 g, 2.39 mmol) in anhydrous THF (40 mL) was added lithium borohydride (1.0 g, 45.6 mmol). The resulting solution was warmed up to 60 °C. After stirring for 3 h, the reaction was cooled to room temperature and slowly transferred to another bottle that was charged with chlorotrimethylsilane (3.0 mL, 23.6 mmol) in THF (100 mL). The mixture was stirred for an additional 20 mins at rt, and quenched by addition of methanol (10 mL). After removal of all the solvents by vacuum, 7-6 was obtained. LC-MS (ESI): m/z 667.3 (M+H)⁺.

**Step 2.** Treatment of 7-6 under the conditions of general procedure B afforded compound 7-7. LC-MS (ESI): m/z 161 (M+H)⁺.
Example 17. Preparation of 8-3

[0318] Step 1. Referring to Scheme 8, trimethylaluminum (2.4 mL, 2 M in hexanes, 4.80 mmol) was added dropwise to a degassed stirred solution of 2,6-dibromo-9H-xanthen-9-one 7-2 (500 mg, 1.412 mmol) in toluene (8 mL) at 0 °C. The resulting solution was allowed to warm up to rt and left to stir for 16 h. The crude reaction mixture was poured into ice-cold 1M HCl aq (200 mL), and the aqueous layer was washed with DCM (2 x 150 mL), dried over MgSO₄, filtered and solvents were removed in vacuo to give 2,6-dibromo-9,9-dimethyl-9H-xanthene 8-1 (482 mg, 93 % yield) as a white solid. 1H NMR (CDCl₃) δ 7.77-7.74 (IH, m), 7.55-7.51 (IH, m), 7.44-7.40 (IH, m), 7.33-7.29 (2H, m), 7.06-7.02 (IH, m), 1.58 (6H, s) ppm.

[0319] Step 2. The product 8-2 was prepared using general procedure C and obtained as a white solid (280 mg, 53% yield). 1H NMR (DMSO) δ 7.78-7.76 (IH, m), 7.60-7.53 (2H, m), 7.43-7.39 (IH, m), 7.29-7.27 (IH, m), 7.07-7.04 (IH, m), 1.31-1.28 (24H, m) ppm. LC-MS (ESI): m/z 463.2 (M+H)+.

[0320] Step 3. (2R,2'S)-tert-butyl-2,2'-((5,5'-(9,9-dimethyl-9H-xanthene-2,6-diyl)bis(Imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (8-3) Compound 8-3 was prepared using general procedure D to give the product as a brown solid (183 mg, 47% yield). LC-MS (ESI): m/z 681.26 (M+H)+.

Example 18. Preparation of 8-4

[0321] Compound 8-4 was prepared using general procedure C to give the product as a white solid (42 mg, 21% yield). LC-MS (ESI): m/z 795.54 (M+H)+.
Example 19. Preparation of 9-4

[0322] **Step 1.** To a solution of 9-1 (1.3 g, 3.70 mmol) in anhydrous DCM (40 mL) was added Et$_2$Zn (1.0 M in heptane, 18.5 mL) at rt. Diiodomethane (2.97 mL, 37 mmol) was then added drop-wisely. The reaction mixture was heated up to reflux. After stirring overnight, the reaction was cooled to rt and diluted with DCM, washed with brine, saturated NH$_4$Cl and water and dried over sodium sulfate. After removing the solvents, the crude mixture was purified by flash column chromatography (Hexane: Ethyl acetate = 30:1 (v/v)) to afford compound 9-2 (0.50 g).

[0323] **Step 2.** General Procedure D. To a solution of 9-2 (350 mg, 0.959 mmol) in dioxane (20 mL) was added bis(pinacolato)diboron (584 mg, 2.3 mmol), [1,1’-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-DCM (39 mg, 0.048 mmol) and potassium acetate (565 mg, 5.75 mmol). The resulting solution was bubbled with N$_2$ for 15 minutes, then heated at 85°C overnight. The solvent was removed in vacuo and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phases were washed with brine, water and dried over Na$_2$SO$_4$. The solvents were removed by vacuum to afford t crude 9-3 (450 mg). LC-MS (ESI): m/z 461 (M+H)$^+$. 

[0324] **Step 3.** To a solution of the crude 9-3 (0.959 mmol) in THF (10 mL) was added (S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (766 mg, 2.11 mmol), dichloro[l,r-bis(diphenylphosphino)ferrocene]palladium(II) (40 mg, 0.049 mmol) and 2 M sodium carbonate (4 mL). The resulting solution was bubbled with N$_2$ for 15 mins, then heated at 85°C overnight. The solvent was removed in vacuo, and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM:Methanol = 20:1 (v/v)) to afford compound 9-4 (110 mg). LC-MS (ESI): m/z 340 (M+2H)$^{2+}$.

Example 20. Preparation of 9-5

[0325] To a solution of the 9-4 (20 mg, 0.0295 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.3 mL). The reaction was stirred for 3 h at rt. The reaction was concentrated to afford compound de-Boc-9-4 (20 mg). LCMS (ESI): m/z 240 1/2(M+2H)$^{2+}$

To a solution of de-Boc-9-4 (20 mg) in DMF (2 mL), DIPEA (24 µL, 0.138 mmol), N-Moc-L-Val-OH (12 mg, 0.068 mmol) and HATU (26 mg, 0.068 mmol) was added. After one h stirring, the reaction was diluted with methanol and directly subject to prep-HPLC.
(Phenomenex, C18-Luna column, H$_2$O-MeCN, 0.1% HCO$_2$H) to provide 9-5 (12.0 mg). LC-MS (ESI): m/z 397 (M + 2H)$^{2+}$. $^1$H NMR (300 MHz, CD$_3$OD) δ 7.87 (s, 1H), 7.80 (s, 1H), 7.52 (d, $J$ = 8.2 Hz, 1H), 7.38 (d, $J$ = 8.2 Hz, 1H), 7.36 (s, 1H), 7.22 (s, 1H), 7.08 (d, $J$ = 9.2 Hz, 1H), 6.98 (d, $J$ = 8.2 Hz, 1H), 5.23-5.20 (m, 2H), 4.23 (d, $J$ = 7.1 Hz, 2H), 4.10-4.07 (m, 2H), 3.94-3.88 (m, 2H), 3.65 (s, 6H), 2.60-2.55 (m, 2H), 2.38-2.05 (m, 8H), 1.68-1.50 (m, 4H), 0.98-0.88 (m, 12H) ppm.
Example 21. Preparation of 10-6

[0326] Step 1. Referring to Scheme 10, methylmagnesium iodide (14.12 mL, 3 M in Et₂O, 42.4 mmol) was added to a stirred solution of 2,6-dibromo-9H-xanthen-9-one (9-2) (10 g, 28.2 mmol) in THF (30 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched with saturated NH₄Cl solution (250 mL) and stirred for 30 min. The volatiles were removed in vacuo. The residue was taken up in CHCl₃ (200 mL), and the organic layer was separated and the aqueous phase was extracted with CHCl₃ (2 x 200 mL) and combined organics was dried over MgSO₄, filtered and solvents removed in vacuo to crude product (9.46 g). The crude reaction was taken up in EtOAc (200 mL) and AcOH was added (20 mL) and the reaction mixture was stirred at room temperature for 3 h, the volatiles removed in vacuo and the residue was precipitated from isohexanes to give 2,6-dibromo-9-methylene-9H-xanthene (9-1) (6.43 g, 64.7% yield).

[0327] Step 2. Borane-THF complex (36.5 mL, 1M THF, 36.5 mmol) was added to a stirred solution of 2,6-dibromo-9-methylene-9H-xanthene (9-1) (6.43 g, 18.27 mmol) in THF (75 mL) at 0 °C. The mixture was allowed to warm up to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C and a mixture of hydrogen peroxide (35 wt% in water) (5.76 mL, 65.8 mmol) and NaOH (25.6 mL, 2 M aq, 51.1 mmol) was added cautiously. The mixture was allowed to warm up to rt over 30 min. The reaction mixture was then poured into water (200 mL) and extracted with DCM (3 x 150 mL). The combined organics were washed with water (2 x 200 mL), brine (200 mL), dried over MgSO₄, filtered and volatiles removed in vacuo to give a yellow solid. The crude product was purified by column chromatography (SiO₂, 0-100% EtOAc/isohexanes) to afford (2,6-dibromo-9H-xanthen-9-yl)methanol (10-1) (2.5 g, 37.0% yield) as a yellow solid. ¹H NMR (CDCl₃) δ 7.42-7.39 (IH, m), 7.37-7.35 (IH, m), 7.28-7.27 (IH, m), 7.25-7.21 (IH, m), 7.16-7.12 (IH, m), 7.00-6.97 (IH, m), 4.00 (IH, t, J = 5.9 Hz), 1.46 (2H, d, J = 5.9 Hz) ppm.

[0328] Step 3. Phosphorus pentoxide (5.04 g, 35.5 mmol) was added portion-wisely to a stirred solution of (2,6-dibromo-9H-xanthen-9-yl)methanol (10-1) (1.01 g, 2.73 mmol) in toluene (100 mL) and the suspension was heated under reflux for 20 min. The mixture was allowed to cool to rt and toluene was removed by decantation. The residual solid was washed with toluene (2 x 100 mL) by further decantation. The combined organics were cooled in an ice bath and brine (400 mL) was added slowly. The layers were separated and the organic washed with water (300 mL), brine (300 mL), dried over MgSO₄ and evaporated to dryness,
to give a yellow oily solid. The product was purified by column chromatography (SiO₂, 0-
10% EtOAc/isohexanes) to give 2,7-dibromodibenzo[b,f]oxepine (10-2) (763 mg, 79% yield)
as a clear oil. \(^1\)H NMR (CDCl₃) \(\delta\) 7.41-7.36 (IH, m), 7.33-7.31 (IH, m), 7.29-7.24 (2H, m),
7.04-6.99 (2H, m), 6.68-6.57 (2H, m) ppm.

[0329] Step 4. A solution of 2,7-dibromodibenzo[b,f]oxepine (10-2) (663 mg, 1.88
mmol) in EtOAc (40 mL) was degassed under N₂. Pt/C 10% by wt (200 mg) was added and
the reaction was evacuated and placed under H₂ gas. After 2 h reaction mixture was degassed
and filtered through Celite® 545 (eluant EtOAc) and solvent was removed in vacuo to give a
yellow oil. The compound was dissolved in petroleum ether and passed through a short pad
of SiO₂, eluting with isohexanes 400 mL. Solvent was removed in vacuo, to give 2,7-
dibromo-10,11-dihydrodibenzo[b,f]oxepine (10-3) (542 mg, 81% yield) as a colorless oil.
\(^1\)H NMR (CDCl₃) \(\delta\) 7.33-7.32 (IH, m), 7.29-7.24 (2H, m), 7.18-7.14 (IH, m), 7.04-6.96 (2H, m),
3.08 (4H, s) ppm.

[0330] Step 5. Compound 10-4 was prepared using General Procedure C to give the
product as a white solid (360 mg, 53% yield). LC-MS (ESI): \(m/z\) 449.51 (M+H)⁺.

[0331] Step 6. Preparation of (2S,2'-?)-tert-butyl 2,2'-(5,5'-(10,1 1-
dihydrodibenzo[b,f]oxepine-2,7-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate
(10-5). Compound 10-5 was prepared using general procedure D to give the product as brown
oil (59 mg, 11%). LC-MS (ESI): \(m/z\) 667.34 (M+H)⁺.

[0332] Step 7. Product 10-6 was prepared using general procedure C to give the product
as a white solid (6 mg, 11% yield). LC-MS (ESI): \(m/z\) 781.69 (M+H)⁺.
Example 22. Preparation of 11-8

[0333] Step 1. Referring to Scheme 11, to a solution of 4-bromo-2-chlorobenzoic acid (18.4 g, 83.9 mmol) and 4-bromophenol (24 g, 109 mmol) in nitrobenzene was added cesium carbonate (82 g, 251.7 mmol). The resulting solution was heated at 170 °C with condenser for 1 day. The reaction mixture was cooled to 70 °C and filtrated at this temperature. The residue was washed with toluene. The organic layer was removed by vacuum distillation till a thick dark residue remained. The dark residue was added to aqueous HCl (IN, 400 mL) and DCM (200 mL). The resulting solution was stirred until the dark oil dispersed into DCM solution. The mixture was filtered. The organic layer was dried (Na$_2$SO$_4$) and concentrated to afford the crude product. The residue was purified by column chromatography on silica gel, eluted first with DCM and then with a mixture of DCM and MeOH in 10:1 (v/v) ratio to give 11-1 along with the
corresponding des-iodo compound 11-1 (16 g, 5:3 ratio). LC-MS (ESI): m/z 419 (M+H)⁺ for 11-1, m/z 293 (M+H)⁺ for 11-1’. The mixture was used in the next step.

[0334] Step 2. The mixture of 11-1 and 11-1’ (16 g, 5:3 ratio, 44.3 mmol) was treated with concentrated sulfuric acid (95 mL). The solution was heated at 105 °C for 2 h. The reaction mixture was cooled down and poured into ice water. The product was precipitated out and was collected by filtration, washed with Et₂O and H₂O. The solid was dried and further purified by flash column chromatography on silica gel (eluents: Hex:AcOEt = 9:1 (v/v) to AcOEt 100%, and then to DCM) to afford 11-2 (7 g) and 11-2’ (5 g). LC-MS (ESI): m/z 401 (M+H)⁺ for 11-2, m/z 275 (M+H)⁺ for 11-2’.

[0335] Step 3. To a solution of iodide 11-2 (6.5 g, 16.2 mmol) and tri-w-butyl(l-ethoxyvinyl)stannane (6.02 mL, 17.8 mmol) in dioxane (70 mL) was added Pd(PPh₃)₂Cl₂ (0.57 g, 0.81 mmol). The resulting solution was bubbled with N₂ for 15 min and heated at 80 °C for 17 h. The reaction mixture was treated with H₂O (24 mL) and cooled to 0 °C. To the solution was added NBS (3.17 g, 17.8 mmol) in portions over 15 min. After about 30 min stirring, the volatiles were removed in vacuo and the residue was partitioned between DCM and water. The aqueous layer was back extracted with DCM. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude mixture was purified by flash column chromatography (Hex:AcOEt = 5:1 (v/v) to 1:1 (v/v) and DCM:MeOH = 9:1 (v/v)) to afford a mixture of 11-3 (4.6 g pure). ¹H NMR (300 MHz, CDCl₃) δ 8.90 (s, IH), 8.41 (dd, IH), 8.22 (d, IH), 7.76 (s, IH), 7.59 (m, 2H), 4.58 (s, 0.5H), 4.44 (s, 1.5H) ppm.

[0336] Step 4. A solution of 11-3 (3.3 g, 8.33 mmol) in CH₃CN (15 mL) was added dropwise over 5 minutes to a solution of N-Cbz-L-proline (2.26 g, 9.16 mmol) and triethylamine (1.74 mL, 12.5 mmol) in CH₃CN (30 mL). The resulting mixture was stirred for 90 min. The volatiles were removed in vacuo and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM to DCM:MeOH = 10:1 (v/v)) to afford the ketoester intermediate (3.4 g). LC-MS (ESI): m/z 564 (M+H)⁺.

The solution of ketoester from above (3.4 g, 6.03 mmol), ammonium acetate (6.97 g, 90.5 mmol) and triethylamine (12.6 mL, 90.5 mmol) in xylene (70 mL) was placed in a sealed tube and heated at 140 °C with stir for 2 h. The solvent was removed in vacuo, and the residue was partitioned between water and AcOEt. The aqueous layer was extracted with AcOEt. The combined organic phase was dried (Na₂SO₄), filtered and concentrated. The crude mixture
was purified by flash column chromatography (DCM:MeOH = 10:1 (v/v)) to afford compound 11-4 (2.0 g). LC-MS (ESI): m/z 544 (M+H)+.

[0337] Step 5. To a solution of 11-4 (1.9 g, 3.5 mmol) in dioxane (35 mL) was added bis(pinacolato)diboron (2.22 g, 8.75 mmol), tetrakis(triphenylphosphine)palladium (202 mg, 0.175 mmol) and potassium acetate (1.03 g, 10.5 mmol). The resulting solution was degassed by bubbling with N₂ for 15 min, and then heated at 95 °C for 5 h. The reaction mixture was filtered through a pad of Celite. The organic solvent was removed in vacuo. The residue was purified by flash column chromatography (DCM:MeOH = 10:1 (v/v)) to afford compound 11-5 (1.5 g). LC-MS (ESI): m/z 510 (M+H)+.

[0338] Step 6. To a solution of 11-5 (1.5 g, 2.5 mmol) in THF (30 mL) was added (S)-tert-butyl 2-(5-iodo-lH-imidazol-2-yl)pyrrolidine-l-carboxylate (1.0 g, 2.78 mmol), dichloro[l,l'-bis(diphenylphosphino)] ferrocene] palladium(II) (102 mg, 0.125 mmol) and sodium carbonate (2 M, 12 mL). The resulting solution was bubbled with N₂ for 15 min, then refluxed overnight. The solvent was removed in vacuo and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM:MeOH = 9:1 (v/v)) to afford compound 11-6 (1.3 g). LC-MS (ESI): m/z 351 (M+2H)+.

[0339] Step 7. By treating a sample of compound 11-6 under the conditions of General Procedure B, compound 11-8 was synthesized. LC-MS (ESI): m/z 758.3 (M+H)+.

Example 23. Preparation of 11-10

[0340] Step 1. Compound 11-8 was treated with H₂ in the presence of Pd/C for the removal of Cbz protecting group to give 11-9. LC-MS (ESI): m/z 624.3 (M+H)+.

[0341] Step 2. Following conditions in General Procedure B, 11-9 was converted to compound 11-10. ¹H NMR (300 MHz, CDCl₃) δ 8.28 (bs, 2H), 8.20 (s, IH), 8.05 (d, IH), 7.82 (m, 2H), 7.42-7.32 (m, 5H), 7.20 (m, 2H), 6.36 (bs, IH), 5.60 (d, IH), 5.52 (m, IH), 5.32 (m, 2H), 4.40 (t, IH), 4.03 - 3.85 (m, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 3.32 (m, IH), 2.60 (m, IH), 2.42 - 2.08 (m, 7H), 1.92 (m, IH), 1.09 - 0.90 (m, 6H) ppm; LC-MS (ESI): m/z 815.8 (M+H)+.
Example 24. Preparation of 11-12

Following the procedures described for steps in Scheme 11 and substituting 4-bromo-2,5-dichloro-5-nitrobenzoic acid for 4-bromo-2chloro-5-nitrobenzoic acid in step 1. Compounds 11-11 and 11-12 were obtained. LC-MS (ESI): m/z 735.3 (M+H)+ for 11-11 and LC-MS (ESI): m/z 850.3 (M+H)+ for 11-12.
Scheme 12

1. 4.0N HCl in dioxane  
2. HATU, DIPEA

12-1 + NH₄OAc → 12-2
12-2 + NH₄OAc → 12-3
12-3 + 12-5 → 12-4
Example 25. Preparation of 12-5

[0343] Step 1. Referring to Scheme 12, to a solution of 12-1 (200 mg, 1.31 mmol) in CS₂
(20 mL), AlCl₃ (876 mg, 6.57 mmol) and 2-chloroacetyl chloride (964 mg, 8.54 mmol) were
added at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was added to H₂O (50 mL).
The mixture was extracted with EtOAc for several times (3 x 50 mL) and the extracts were
combined and dried with anhydrous Na₂SO₄. The solvent was removed and the residue was
purified by silica gel column chromatography (Petroleum ether/EtOAc = 10:1 (v/v)) to give
12-2 (140 mg, 35% yield). LC-MS (ESI): m/z 305 (M+H)+.

[0344] Step 2. To a solution of 12-2 (140 mg, 0.459 mmol) in DCM (10 mL), (S)-N-BoC-
Pro-OH (197 g, 0.917 mmol) and Et₃N (0.26 mL, 1.84 mmol) were added at rt. After stirring
at rt overnight, the reaction mixture was concentrated and the residue was dried in vacuo to
give crude 12-3 (100 mg), which was used for the next step without further purification. LC-
MS (ESI): m/z 663 (M+H)+.

[0345] Step 3. To a solution of crude 12-3 (100 mg, 0.124 mmol) in toluene (20 mL) was
added NH₄OAc (95.0 mg, 1.24 mmol). After refluxing overnight, the reaction mixture was
concentrated and the residue was purified by silica gel column chromatography (Petroleum
Ether/EtOAc = 3:1 (v/v)) to give 12-4 (34 mg, 45% yield) as a yellow solid. LC-MS (ESI):
m/z 623 (M+H)+.

[0346] Step 4. To a stirred solution of compound 12-4 (33 mg, 0.050 mmol) in dioxane
(1 mL) was added 4 N HCl in dioxane (2 mL). After stirring at rt for 2 h, the reaction mixture
was concentrated and the residue was dried in vacuo to give an HCl salt, which was used for
the next step without further purification.

[0347] To a mixture of the HCl salt in DMF (2 mL) was added DIPEA (0.1 mL, 0.5
mmol), followed by N-Moc-L-Val-OH (22 mg, 0.13 mmol) and HATU (50 mg, 0.13 mmol).
After stirred at rt for 30 min, the reaction mixture was poured into water. The solid was
filtrated and purified by preparative HPLC to give 12-5 (10 mg, 27%) as an off-white solid.
¹H NMR (500 MHz, CD₃OD) δ 7.92 (s, 2H), 7.25 (d, J = 7.0, 2H), 7.16 (s, 2H), 6.91 (d, J =
6.5, 2H), 5.21 (s, 2H), 4.22 (d, J = 6.5, 2H), 4.09 (s, 2H), 3.91 (s, 2H), 3.65 (s, 6H), 2.55 (s,
2H), 2.28 (s, 2H), 2.17 (s, 2H), 2.07 (d, J = 6.0, 2H), 1.00 - 0.88 (m, 12H) ppm; LC-MS
(ESI): m/z 737 (M+H)+.
Example 26. Preparation of 13-5

Step 1. Referring to Scheme 13, a solution of 4-bromoaniline (10 g, 58.1 mmol) in DMF (30 mL) was added dropwise to a solution of potassium t-butoxide (19.57 g, 174 mmol) in DMF (60 mL) at -60 °C, followed immediately by a solution of 1-bromo-4-nitrobenzene (11.74 g, 58.1 mmol) in DMF (45 mL). The mixture was stirred for 5 min, and then a cooled mixture of AcOH (45 mL) and DMF (45 mL) was added in one portion. The mixture was allowed to warm to room temperature, and poured into water (500 mL) and extracted with EtOAc (3 x 300 mL), the organics were combined and washed with water (3 x 500 mL), brine (500 mL) and the organic layer was dried over MgSO₄, filtered and concentrated in vacuo to afford a crude brown solid. The product was purified by silica gel chromatography (SiO₂, 0-10% EtOAc/isohexane) to afford 13-1 as brown solid (10 g, 48.3 % yield).

Step 2. 5-bromo-N-(4-bromophenyl)-2-nitrosoaniline (13-1) (10 g, 28.1 mmol) in AcOH (300 mL) was heated under reflux for 1.5 h. Water (400 mL) was then added and the brown precipitate formed was collected by filtration after washing with water (2 x 200 mL). The product was purified by silica gel chromatography (SiO₂, hexanes/DCM = 1/1 (v/v)) to afford a brown solid, 2,7-dibromophenazine 13-2 (1.52 g, 16 % yield).

1H NMR (CDCl₃) δ 8.43 (2H, dd, J 2.2, 0.4 Hz), 8.10 (2H, dd, J 9.2, 0.4 Hz), 7.91 (2H, dd, J 9.2, 2.2 Hz) ppm. LC-MS (ESI): m/z 338.6 (M+H)⁺.

Step 3. To a solution of 2,7-dibromophenazine (13-2) (1.52 g, 4.50 mmol) in dry dioxane (75 mL) under N₂ was added tributyl(l-ethoxyvinyl)stannane (3.34 ml, 9.89 mmol) and Pd(dppf)Cl₂ (0.316 g, 0.450 mmol). The resultant mixture was heated at 100°C for 4 h in a sealed tube. The crude reaction mixture was filtered through CELITE™545, and the volatiles were removed in vacuo. The crude brown solid was triturated with isohexanes and filtered to give 2,7-bis(l-ethoxyvinyl)phenazine as a brown solid (1.27 g, 88 % yield).

1H NMR (CDCl₃) δ 8.55-8.53 (2H, m), 8.19-8.15 (2H, m), 8.11-8.07 (2H, m), 4.98 (2H, d, J = 3 Hz), 4.49 (2H, d, J = 3 Hz), 4.03 (4H, q, J = 7 Hz), 1.50 (6H, t, J = 7 Hz) ppm. LC-MS (ESI): m/z 322.1 (M+H)⁺.

N-Bromosuccinimide (1.41 l g, 7.93 mmol) was added to a stirred solution of 2,7-bis(l-ethoxyvinyl)phenazine (1.27 g, 3.96 mmol) in THF (95 mL) and water (20 mL) and left to stir at rt for 1 h. The reaction mixture was filtered and the yellow solid collected was washed with water and dried under vacuum to afford 1,1'- (phenazine-2,7-diyl)bis(2-bromoethanone) (13-3) (991 mg, 59.2 % yield) as a yellow solid.

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$^1$H NMR (CDCl$_3$) $\delta$ 8.93-8.91 (2H, m), 8.47-8.46 (2H, m), 8.41-8.37 (2H, m), 4.66 (4H, s) ppm. LC-MS (ESI): $m/z$ 423.8 (M+H)$^+$.  

[0352] **Step 4.** The bisimidazole compound 13-4, (2S,2'S)-tert-butyl 2,2'-(5,5′-(phenazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate was prepared under the conditions of general procedure A. LC-MS (ESI): $m/z$ 651.1 (M+H)$^+$.  

[0353] **Step 5.** Compound 13-5, Dimethyl (2S,2'S)-1,1,r-(2S,2′S)-2,2′-(5,5′-(phenazine-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate. This product was prepared using general procedure B to give an orange solid (57 mg, 88% yield). LC-MS (ESI): $m/z$ 765.2 (M+H)$^+$; 763.1 (M-H)$^-$.  


Example 27. Preparation of 14-5

[0354] Step 1. Referring to Scheme 14, cesium carbonate (6.20 g, 19.0 mmol) was added to a solution of methyl 5-bromo-2-hydroxybenzoate (4.0 g, 17.3 mmol) in DMF (20 mL) and the mixture was stirred for 30 mins. 4-bromo-2-fluoro-l-nitrobenzene (3.81 g, 17.3 mmol) was then added and the mixture was heated at 60 °C for 3 h. After cooling at the completion of the reaction, the mixture was poured into water (500 mL) and extracted with ether (2 x 250 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give crude 14-1 as brown oil (5.85 g, 78% yield).

[0355] Step 2. The crude product from above was dissolved in AcOH (12 mL) and treated with iron powder (320 mesh, 4.55 g, 81 mmol) at 115 °C for 40 mins. The reaction mixture was cooled to rt, poured into water (300 mL) and extracted with EtOAc (2x200 mL). The combined organic extracts were sequentially washed with water (300 mL), aq. NaHCO₃ (300 mL) and brine (200 mL) and concentrated in vacuo. The residue was taken up in minimal amount of Et₂O and precipitated with addition of hexanes. Precipitate was collected by filtration to give 14-2 as a white solid in 72% yield. LC-MS (ESI): m/z 368.2 (M-H)-.

[0356] Step 3. Compound 14-3 was prepared in 69% by treating 14-2 under General Procedure C.

[0357] Step 4. Compound 14-4 was obtained in 64% yield by treating 14-3 under General Procedure D. LC-MS (ESI): m/z 682.8 (M+H)+.

[0358] Step 5. Compound 14-5 was obtained in 45% yield by treating 14-4 under General Procedure B. LC-MS (ESI): m/z 796 (M+H)+.
Example 28. Preparation of 15-6

Step 1. Referring to Scheme 15, 4-Bromoaniline and paraformaldehyde were added to TFA (23 mL) at -15 °C. After stirred at rt for 24 h, the reaction mixture was slowly added to a stirred mixture of ice and 30% aqueous NH3 (40 mL). The entire mixture (solid and solution) was extracted with DCM (3 x 10 mL), the extracts were dried over MgSO4, filtered and concentrated in vacuo to afford 15-1 (2.35 g, 57%, yellow solid).

Step 2. Compound 15-1 was suspended in a mixture of TFAA (4 mL) and DCM (8 mL) and stirred at rt in a sealed vessel overnight. LC-MS indicated the presence of trifluoracetylated product and the absence of starting 15-1. The reaction was then quenched with H2O and basified with aqueous NaHCO3. The mixture was extracted with DCM (3x100 mL). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The residue was dissolved in EtOH (40 mL) with sodium hydroxide (800 mg) and stirred at rt for 2 h. The reaction was concentrated under reduced pressure and the residue dissolved in a mixture of water and DCM. The organic layer was dried over MgSO4, filtered and concentrated in vacuo to give product 15-2 in 57% yield.

Step 3. NaH (60% mineral oil dispersion, 0.103 g, 4.29 mmol) was added to a solution of 15-2 (0.75 g, 2.04 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 45 mins at rt. MeI (0.638 g, 4.50 mmol) was added at 0 °C, and the reaction mixture stirred at rt overnight. The reaction was cooled down to rt and quenched with water. The aqueous layer was extracted with DCM (3 x 50 mL) and Et2O (2 x 50 mL), respectively. The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography eluted with mixed solvents of hexanes and DCM in 9:1 (v/v) ratio to give 15-3 (0.634 g, 78% yield). LC-MS (ESI): m/z 397.1 (M+H)+.

Step 4. Compound 15-4 was prepared in 66% by treating 15-3 under general procedure C.

Step 5. Compound 15-5 was obtained in 54% yield by treating 15-4 under general procedure D. LC-MS (ESI): m/z 709.6 (M+H)+.

Step 6. Compound 15-6 was obtained in 32% yield by treating 15-5 under general procedure B. LC-MS (ESI): m/z 823.5 (M+H)+.

[0365]
Example 29. Preparation of 16-6

[0366]  Step 1. Referring to Scheme 16, to a solution of acid 4-bromo-4-fluorobenzoic acid (6 g) and 4-bromoaniline (7 g) in DMSO (75 mL) was added potassium tert-butoxide (1.3 g) at rt. After stirring for three days, the reaction was diluted with water (300 mL) and extracted with diethyl ether (3x100 mL). The aqueous layer was acidified by 2 M HCl to pH 1, extracted by ethyl acetate (with 10% MeOH). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to provide the crude product, which was recrystallized in MeOH to provide 16-1 (1.2 g, red solid, 12% yield). LC-MS (ESI): m/z 372 (M+H)⁺.

[0367]  Step 2. Compound 16-1 (1.2 g) was dissolved in cone. H₂SO₄ (6 mL) and the solution was warmed up to 110 °C. After stirring for one h, the reaction was cooled to rt and slowly transferred to ice-water (100 mL). The yellow precipitation from ice-water solution was filtered to afford 16-2 (900 mg), which was used without further purification. LC-MS (ESI): m/z 352 (M+H)⁺.

[0368]  Step 3. To a solution of 16-2 (900 mg) in dry DMF (20 mL) was added sodium hydride (60% dispersion, 355 mg) at rt. The reaction was stirred for 1 h and dimethyl sulfate (482 mg) was added. After stirring overnight, the reaction was quenched with ice-water. The yellow precipitation from ice-water solution was filtered to afford 16-3 (900 mg) without further purification. LC-MS (ESI): m/z 366 (M+H)⁺.

[0369]  Step 4. To a solution of 16-3 (100 mg, 0.272 mmol) in 24 mL of dioxane was added bis(pinacolato)diboron (166 mg, 0.653 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (111 mg, 0.014 mmol) and potassium acetate (160 mg, 1.63 mmol) under N₂ atmosphere. The reaction mixture was stirred at 80 °C overnight, and then cooled to rt and diluted with dichloromethane (150 mL) and then aq. phase was extracted with dichloromethane. The organic phase was washed with water, dried over sodium sulfate and concentrated in vacuo to give crude 16-4 (140 mg). LC-MS (ESI): m/z 462 (M+H)⁺.

[0370]  Step 5. To a solution of 16-4 (140 mg, 0.272 mmol) in 3.2 mL of THF and 2M Na₂CO₃ (3/1 v/v ) was added (S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.598 mmol), dichloro [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (111 mg, 0.014 mmol) and sodium bicarbonate (2.7 g, 32 mmol) under N₂ atmosphere. The reaction mixture was stirred at 80 °C overnight and diluted with dichloromethane (120 mL). The organic phase was washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was further purified
by silica gel column chromatography (Hexane / acetone = 1:1 (v/v)) to give 16-5 (110 mg, 43%) as a yellow solid. LC-MS (ESI): m/z 680 (M+H)⁺.

[0371] **Step 6.** To a stirred solution of 16-5 (55 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL). After 3 h, the reaction was concentrated to dryness to provide de-Boc- -16-5. de-Boc- 16-5 was dissolved in DMF (2 mL) and DIPEA (100 µL), N-Moc-L-Val-OH (18 mg) and DMTMM (20 mg) were added subsequently. After one h stirring, the reaction was diluted with water. The reaction was extracted with dichloromethane. The combined extracts were washed with brine and water, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by prep-HPLC (Phenomenex, C18-Luna column, H₂O-MeCN, 0.1% HCO₃H) to provide 16-6 (6.0 mg, 6.5% yield). ¹H NMR (300 MHz, CD₃OD) 58.77-8.69 (m, IH), 8.56 - 8.45 (m, IH), 8.31 - 8.18 (m, 3H), 8.06 - 8.01 (m, IH), 7.96 (s, IH), 7.74 - 7.71 (m, IH), 5.33 - 5.26 (m, 2H), 4.27-4.24 (m, 2H), 4.17 - 4.04 (m, 3H), 3.99 - 3.80 (m, 2H), 3.70 - 3.60 (m, 6H), 2.62 - 2.55 (m, 2H), 2.38 - 2.05 (m, 8H), 1.03 - 0.86 (m, 12H) ppm; LC-MS (ESI): m/z 794 (M+H)⁺.

**Biological Activity**

[0372] Biological activity of the compounds of the invention was determined using an HCV replicon assay. The HCV lb_Huh-Luc/Neo-ET cell line persistently expressing a bicistronic genotype 1b replicon in Huh 7 cells was obtained from ReBLikon GMBH. This cell line was used to test compound inhibition using luciferase enzyme activity readout as a measurement of compound inhibition of replicon levels.

[0373] On Day 1 (the day after plating cells), each compound is added in triplicate to the cells. Plates are incubated for 72 h prior to determining luciferase levels. Enzyme activity was measured using a Bright-Glo Kit (cat. number E2620) manufactured by Promega Corporation. The following equation was used to generate a percent control value for each compound.

\[ \text{% Control} = \left( \frac{\text{Compound Luciferase Level}}{\text{Control Luciferase Level}} \right) \times 100 \]

[0374] The EC50 value was determined using GraphPad Prism and the following equation:

\[ Y = \text{Bottom asymptote} + (\text{Top asymptote} - \text{Bottom asymptote}) \times \left( \frac{1}{1 + 10^A \cdot ((\text{LogEC}50 - X) \times \text{HillSlope})} \right) \]

[0375] EC50 values of compounds are determined several times in the replicon assay to generate average EC5₀ values.
Example compounds of the disclosed invention are illustrated in Table 1. The table shows inhibitory activity of many of the example compounds with respect to HCV Ib. The biological activity is indicated as being *, **, *** or ****, which corresponds to EC\textsubscript{50} ranges of >1000 nM, 999 nM to 10 nM, 9.9 nM to 1 nM, or <1 nM respectively. The tables further provide mass spectrometry results for the synthesized example compounds.

**Pharmaceutical Compositions**

A twelfth aspect of the invention provides a pharmaceutical composition comprising the compounds of the invention. In a first embodiment, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients or vehicles, and optionally other therapeutic and/or prophylactic ingredients. Such excipients are known to those of skill in the art. The compounds of the present invention include, without limitation, basic compounds such as free bases and pharmaceutically acceptable salts of these compounds. A thorough discussion of pharmaceutically acceptable excipients and salts is available in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990).

Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc.

The invention includes a pharmaceutical composition comprising a compound of the present invention including isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic and/or prophylactic ingredients.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate and the like.

For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule nonaqueous solution, suspension or syrup. Tablets and capsules are
preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used carriers such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents and the like.

[0382] A thirteenth aspect of the invention provides use of the compounds of the invention in the manufacture of a medicament.

[0383] In a first embodiment of the thirteenth aspect the medicament is for the treatment of hepatitis C.

[0384] A fourteenth aspect of the invention provides a method of treating hepatitis C comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the invention, optionally in a pharmaceutical composition. A pharmaceutically or therapeutically effective amount of the composition will be delivered to the subject. The precise effective amount will vary from subject to subject and will depend upon the species, age, the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, the effective amount for a given situation can be determined by routine experimentation. The subject may be administered as many doses as is required to reduce and/or alleviate the signs, symptoms or causes of the disorder in question, or bring about any other desired alteration of a biological system. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of this invention for a given disease.

**Combination Therapy**

[0385] The compounds of the present invention and their isomeric forms and pharmaceutically acceptable salts thereof are useful in treating and preventing HCV infection alone or when used in combination with other compounds targeting viral or cellular elements or functions involved in the HCV lifecycle. Classes of compounds useful in the invention may include, without limitation, all classes of HCV antivirals. For combination therapies, mechanistic classes of agents that may be useful when combined with the compounds of the
present invention include, for example, nucleoside and non-nucleoside inhibitors of the HCV polymerase, protease inhibitors, helicase inhibitors, NS4B inhibitors and medicinal agents that functionally inhibit the internal ribosomal entry site (IRES) and other medicaments that inhibit HCV cell attachment or virus entry, HCV RNA translation, HCV RNA transcription, replication or HCV maturation, assembly or virus release. Specific compounds in these classes and useful in the invention include, but are not limited to, macrocyclic, heterocyclic and linear HCV protease inhibitors such as telaprevir (VX-950), boceprevir (SCH-503034), nαlaprevir (SCH-900518), ITMN-191 (R-7227), TMC-435350 (a.k.a. TMC-435), MK-7009, BI-201335, BI-2061 (ciluprevir), BMS-650032, ACH-1625, ACH-1095 (HCV NS4A protease co-factor inhibitor), VX-500, VX-813, PHX-1766, PHX2054, IDX-136, IDX-316, ABT-450 EP-013420 (and congeners) and VBY-376; the Nucleosidic HCV polymerase (replicase) inhibitors useful in the invention include, but are not limited to, R7128, PSI-7851, IDX-184, IDX-102, R1479, UNX-0819, PSI-6130, PSI-938 and PSI-879 and various other nucleoside and nucleotide analogs and HCV inhibitors including (but not limited to) those derived as 2'-C-methyl modified nucleos(t)ides, 4'-aza modified nucleos(t)ides, and 7'-deaza modified nucleos(t)ides. Non-nucleosidic HCV polymerase (replicase) inhibitors useful in the invention, include, but are not limited to, HCV-796, HCV-371, VCH-759, VCH-916, VCH-222, ANA-598, MK-3281, ABT-333, ABT-072, PF-00868554, BI-207127, GS-9190, A-837093, JKT-109, GL-59728 and GL-60667.  

[0386] In addition, NS5A inhibitors of the present invention may be used in combination with cyclophyllin and immunophyllin antagonists (eg, without limitation, DEBIO compounds, NM-81 1 as well as cyclosporine and its derivatives), kinase inhibitors, inhibitors of heat shock proteins (e.g., HSP90 and HSP70), other immunomodulatory agents that may include, without limitation, interferons (-alpha, -beta, -omega, -gamma, -lambda or synthetic) such as Introne A™, Roferon-A™, Canferon-A300™, Advaferon™, Infergen™, Humoferon™, Sumiferon MP™, Alfaferone™, IFN-β™, Feron™ and the like; polyethylene glycol derivatized (pegylated) interferon compounds, such as PEG interferon-α-2a (Pegasys™), PEG interferon-α-2b (PEGIntron™), pegylated IFN-α-conl and the like; long acting formulations and derivatizations of interferon compounds such as the albumin-fused interferon, Albuferon™, Locterot™ and the like; interferons with various types of controlled delivery systems (e.g. ITCA-638, omega-interferon delivered by the DUROS™ subcutaneous delivery system); compounds that stimulate the synthesis of interferon in cells, such as resiquimod and the like; interleukins; compounds that enhance the development of
type 1 helper T cell response, such as SCV-07 and the like; TOLL-like receptor agonists such as CpG-IO1Ol (actilon), isotorabine, ANA773 and the like; thymosin α-1; ANA-245 and ANA-246; histamine dihydrochloride; propagermanium; tetrachlorodecaoxide; ampligen; IMP-321; KRN-7000; antibodies, such as civacir, XTL-6865 and the like and prophylactic and therapeutic vaccines such as InnoVac C, HCV E1E2/MF59 and the like. In addition, any of the above-described methods involving administering an NS5A inhibitor, a Type I interferon receptor agonist (e.g., an IFN-α) and a Type II interferon receptor agonist (e.g., an IFN-γ) can be augmented by administration of an effective amount of a TNF-α antagonist. Exemplary, non-limiting TNF-α antagonists that are suitable for use in such combination therapies include ENBREL™, REMICADE™ and HUMIRA™.

[0387] In addition, NS5A inhibitors of the present invention may be used in combination with antiprotozoans and other antivirals thought to be effective in the treatment of HCV infection, such as, without limitation, the prodrug nitazoxanide. Nitazoxanide can be used as an agent in combination the compounds disclosed in this invention as well as in combination with other agents useful in treating HCV infection such as peginterferon alfa-2a and ribavarin (see, for example, Rossignol, JF and Keeffe, EB, Future Microbiol. 3:539-545, 2008).

[0388] NS5A inhibitors of the present invention may also be used with alternative forms of interferons and pegylated interferons, ribavirin or its analogs (e.g., tarabavirin, levoviron), microRNA, small interfering RNA compounds (e.g., SIRPLEX-140-N and the like), nucleotide or nucleoside analogs, immunoglobulins, hepatoprotectants, anti-inflammatory agents and other inhibitors of NS5A. Inhibitors of other targets in the HCV lifecycle include NS3 helicase inhibitors; NS4A co-factor inhibitors; antisense oligonucleotide inhibitors, such as ISIS-14803, AVI-4065 and the like; vector-encoded short hairpin RNA (shRNA); HCV specific ribozymes such as heptazyme, RPI, 13919 and the like; entry inhibitors such as HepeX-C, HuMax-HepC and the like; alpha glucosidase inhibitors such as celgosivir, UT-231B and the like; KPE-02003002 and BIVN 401 and IMPDH inhibitors. Other illustrative HCV inhibitor compounds include those disclosed in the following publications: U.S. Pat. No. 5,807,876; U.S. Pat. No. 6,498,178; U.S. Pat. No. 6,344,465; U.S. Pat. No. 6,054,472; WO97/40028; WO98/40381; WO00/56331, WO 02/04425; WO 03/007945; WO 03/010141; WO 03/000254; WO 01/32153; WO 00/06529; WO 00/18231; WO 00/10573; WO 00/13708; WO 01/85172; WO 03/037893; WO 03/037894; WO 03/037895; WO 02/100851; WO 02/100846; EP 1256628; WO 99/01582; WO 00/09543; WO02/18369; WO98/17679,

Combination therapy can be sequential, that is treatment with one agent first and then a second agent (for example, where each treatment comprises a different compound of the invention or where one treatment comprises a compound of the invention and the other comprises one or more biologically active agents) or it can be treatment with both agents at the same time (concurrently). Sequential therapy can include a reasonable time after the completion of the first therapy before beginning the second therapy. Treatment with both agents at the same time can be in the same daily dose or in separate doses. Combination therapy need not be limited to two agents and may include three or more agents. The dosages for both concurrent and sequential combination therapy will depend on absorption,
distribution, metabolism and excretion rates of the components of the combination therapy as well as other factors known to one of skill in the art. Dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules may be adjusted over time according to the individual's need and the professional judgment of the person administering or supervising the administration of the combination therapy.

[0391] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[0392] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the invention as defined in the appended claims.
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We claim:

1. A compound having formula I:

\[
\begin{array}{c}
\text{I} \\
\text{wherein:}
\end{array}
\]

D is either present or absent and if present selected from the group consisting of

- \(\text{CR}_2\text{CR}_2^-\), -\(\text{CR}_2^-\), -\(\text{NR}^-\), -O- and -S- wherein \(\text{R}^N\) is \(\text{H}\), -OH, \(\text{Ci}\) to \(\text{Ci}_2\) alkyl, \(\text{Ci}\) to \(\text{Ci}_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each \(\text{R}\) is independently selected from the group consisting of hydrogen, -OH, -CN, -NO\(_2\), halogen, \(\text{Ci}\) to \(\text{Ci}_2\) alkyl, \(\text{Ci}\) to \(\text{Ci}_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently -\(\text{CR}_2^-\), -\(\text{CR}=-\), -\(\text{CR}_2\text{CR}_2^-\), -\(\text{CR}=\text{CR}^-\), -\(\text{N}=\text{CR}^-\),

-\((\text{CR}_2^-)\text{N}(\text{R}^N)-(\text{CR}_2^-)\text{a}^-\), -(\(\text{CR}_2\text{a}^-\))\text{(O)}\text{N}(\text{R}^N)-(\text{CR}_2\text{a}^-),

-\((\text{CR}_2\text{a}^-)\text{N}(\text{R}^N)\text{(O)}\text{(CR}_2\text{a}^-)\text{or-(CR}_2\text{a}^-)\text{b-O-(CR}_2\text{a}^-)\text{b}^-,\) wherein:

\(\text{R}^N\) is selected from the group consisting of \(\text{H}\), -OH, \(\text{Ci}\) to \(\text{Ci}_2\) alkyl, \(\text{Ci}\) to \(\text{Ci}_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each \(\text{R}\) is independently selected from the group consisting of hydrogen, -OH, -CN, -NO\(_2\), halogen, \(\text{Ci}\) to \(\text{Ci}_2\) alkyl, \(\text{Ci}\) to \(\text{Ci}_2\) heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

two \(\text{R}\)'s either both on a single \(\text{C}\) or on adjoining \(\text{Cs}\), together with the \(\text{C}\) or \(\text{Cs}\) to which they are attached, optionally form a cycle, and

where two \(\text{R}\)'s are possible on a \(\text{C}\), the \(\text{C}\) may optionally be linked to a single \(\text{R}\) with a double bond;

each \(\text{a}\) and \(\text{b}\) are independently \(\text{o}, \text{1}, \text{2}, \text{or 3}\) with the proviso that if \(\text{D}\) is present
both b's are not 0; and

R\textsuperscript{N} and R may be replaced by a bond to D if D is present,

if D is absent, A and E can additionally each independently be a bond, -O-, -S-, -S(O\textsubscript{2})-, -S(O)-, -C(O)- or -N=, and

with the proviso that if W and W are both 5-membered rings, A and E are either
both a bond or both other than a bond;

each R\textsuperscript{a} is independently selected from the group consisting of -OH, -CN, -NO\textsubscript{2}, halogen, C\textsubscript{i} to C\textsubscript{12} alkyl, C\textsubscript{i} to C\textsubscript{2} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each r is independently 0, 1, 2 or 3;

W and W are each independently selected from the group consisting of

\[ \text{and} \]

\[ \text{wherein:} \]

X\textsuperscript{1} is CH\textsubscript{2}, NH, O or S,

Y\textsuperscript{1}, Y\textsuperscript{2} and Z\textsuperscript{1} are each independently CH or N,

X\textsuperscript{2} is NH, O or S,

W and W are each independently optionally substituted with one or more substituents
selected from the group consisting of -OH, -CN, -NO\textsubscript{2}, halogen, C\textsubscript{i} to C\textsubscript{2} alkyl, C\textsubscript{i} to C\textsubscript{2} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate,
sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, Ci to C₁₂ alkyl, Ci to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each Rᵣ, Rᵈ, Rᵉ and Rᶠ is independently selected from the group consisting of: hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl and a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,
each hetero atom, if present, is independently N, O or S,
each of Rᵣ, Rᵈ, Rᵉ and Rᶠ may optionally be substituted by Ci to C₈ alkyl, Ci to C₈ heteroalkyl, aralkyl, or a 4- to 8-membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each hetero atom, if present, is independently N, O or S,

Rᵉ and Rᵈ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring, and

Rᵉ and Rᶠ are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5-membered heterocycle or heteroaryl ring;

Y and Y' are each independently carbon or nitrogen; and

Z and Z' are independently selected from the group consisting of hydrogen, Ci to C₈ alkyl, Ci to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

- [U-(CR ² ₂)-NR ⁵-C(R ² ₂)]₁₋₇[U-(CR ² ₂)-NR ⁷-(CR ² ₂)]₁₋₇-R ⁸, -U-(CR ² ₂)-R ⁸, and
- [U-(CR ² ₂)-NR ⁵-(CR ² ₂)]₁₋₇[U-(CR ² ₂)-O-(CR ² ₂)]₁₋₇-R ⁸, wherein,

U is selected from the group consisting of -C(O)-, -C(S)- and -S(O) ²⁻.
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_i to C_g alkyl, C_i to C_g heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_i to C_8 alkyl, C_i to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{\text{81}}, -C(S)-R^{\text{81}}, -C(O)-O-R^{\text{81}}, -C(O)-N-R^{\text{81}}, -S(O)_{2}-R^{\text{81}} and -S(O)_{2}-N-R^{\text{81}}, wherein each R^{\text{81}} is independently chosen from the group consisting of hydrogen, C_i to C_8 alkyl, C_i to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

optionally, R^7 and R^8 together form a 4-7 membered ring,

each t is independently 0, 1, 2, 3, or 4, and

each u is 0, 1, or 2.

2. The compound of claim 1 wherein one or both of W and W' are selected from the

3. The compound of claim 2 wherein one or both of W and W' are selected from the

4. The compound of any of the preceding claims wherein

R^c, R^d, R^e and R^f are each independently selected from the group consisting of: hydrogen, C_i to C_8 alkyl and C_i to C_8 heteroalkyl, wherein,

each hetero atom, if present, is independently N, O or S,
R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle, and

R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

5. The compound of claim 4 wherein one or both of R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

6. The compound of claim 4 wherein R^c and R^d are joined and form a heterocyclic fused ring system selected from the group consisting of:

![Diagrams of heterocyclic fused ring systems]

and wherein R^N is selected from the group consisting of hydrogen, -OH, C_i to C_{12} alkyl, C_i to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

7. The compound of claim 4 or claim 6 wherein R^e and R^f are joined and form a heterocyclic fused ring system selected from the group consisting of:

![More diagrams of heterocyclic fused ring systems]

and wherein R^N is selected from the group consisting
of hydrogen, -OH, C\textsubscript{i} to C\textsubscript{12} alkyl, C\textsubscript{1} to C\textsubscript{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

8. The compound of claim 1 having formula II:

9. The compound of claim 8 having formula Ha:

10. The compound of claim 8 having formula lib:

11. The compound of claim 1 having formula III:
12. The compound of claim 11 having formula IIa:

![Chemical Structure IIa](image)

13. The compound of claim 11 having formula IIb:

![Chemical Structure IIb](image)

14. The compound of any one of claims 1-7, 11-13 wherein both A and E are -O- and D is absent.

15. The compound of any one of claims 1-7, 11-13 wherein A is -O-, D is absent and E is -CH₂-, -C(CH₃)₂-, -C(CH₂CH₃)₂- or -C(O)-.

16. The compound of claim 1 having formula IV:

![Chemical Structure IV](image)

17. The compound of claim 14 having formula IVa:

![Chemical Structure IVa](image)
18. The compound of claim 14 having formula IVb:

![IVb](image)

19. The compound of any one of claims 16, 17 or 18 wherein A is -S-.

20. The compound of any one of claims 16, 17 or 18 wherein A is -S(O)_2-.

21. The compound of any one of claims 16, 17 or 18 wherein A is -O-.

22. The compound of any one of claims 16, 17 or 18 wherein A is -CH_2-.

23. The compound of any one of claims 16, 17 or 18 wherein A is -CH_2-CH_2-.

24. The compound of claim 1 having formula V:

![V](image)

25. The compound of claim 24 having formula Va:

![Va](image)

26. The compound of claim 24 having formula Vb:

![Vb](image)
27. The compound of claim 1 having formula VI:

![Chemical Structure VI](image)

28. The compound of claim 27 having formula Via:

![Chemical Structure Via](image)

29. The compound of claim 27 having formula Vlb:

![Chemical Structure Vlb](image)

30. The compound of claim 1 having formula VII:

![Chemical Structure VII](image)

31. The compound of claim 30 having formula Vila:

![Chemical Structure Vila](image)
32. The compound of claim 30 having formula VIIb:

![Formula VIIb]

33. The compound of claim 1 having formula VIII:

![Formula VIII]

34. The compound of claim 33 having formula Villa:

![Formula Villa]

35. The compound of claim 33 having formula VIIIb:

![Formula VIIIb]

36. The compound of claim 1 having formula IX:

![Formula IX]
37. The compound of claim 36 having formula IXa:

38. The compound of claim 36 having formula IXb:

39. The compound of any one of claims 36, 37 or 38 wherein A and E are N.

40. The compound of claim 1 having formula X:

41. The compound of claim 40 having formula Xa:
42. The compound of claim 40 having formula Xb:

43. The compound of claim 1 having formula XI:

44. The compound of claim 43 having formula Xla:

45. The compound of claim 43 having formula Xlb:
46. The compound of claim 1 having formula XII:

![Chemical Structure](image)

XII, wherein:

A' and E' are each independently -CR₂₉₂, -CR=, -N(R>N), -O-, -S-, -S(O)₂-, -S(O)-, or -N=, wherein:

Rᴺ is selected from the group consisting of H, -OH, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide; and

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO₂, halogen, Ci to Ci₂ alkyl, Ci to Ci₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino.

47. The compound of claim 46 having formula XIIa:

![Chemical Structure](image)

XIIa.

48. The compound of claim 46 having formula XIIb:

![Chemical Structure](image)

XIIb.

49. The compound of any one of claims 9-48 wherein one of Y and Y' is N.

50. The compound of any one of claims 9-48 wherein both of Y and Y' are N.
51. The compound of any one of claims 11-13 or 24-48 wherein one or both of X¹ are
   -S-.

52. The compound of any one of claims 11-13 or 24-48 wherein one or both of X¹ are
   -O-.

53. The compound of any one of claims 11-13 or 24-48 wherein one or both of X¹ are
   -NH-.

54. The compound of any one of claims 11-13 or 24-48 wherein one or both of Z¹ is -N-. 

55. The compound of any one of claims 11-13 or 24-48 wherein one or both of Y¹ is -N-. 

56. The compound according to any one of claims 1-55 wherein Z and Z' are each 1-3
   amino acids.

57. The compound of any one of claims 1-55 wherein Z and Z' are each independently
   selected from the group consisting of
   -[U-(CR⁴₂),NR⁵-(CR⁴₂)₄]-R⁸, -U-(CR⁴₂),R⁸ and
   -U-(CR⁴₂)₁t-NR⁵-(CR⁴₂)₄]-R⁸.

58. The compound of claim 57 wherein one or both of Z and Z' are
   -[U-(CR⁴₂)₄t-NR⁵-(CR⁴₂)₄]-R⁸.

59. The compound of claim 58 wherein one or both of Z and Z' are
   -U-(CR⁴₂),-NR⁵-(CR⁴₂),U-(CR⁴₂),R⁸.

60. The compound of claim 58 wherein one or both of Z and Z' are
   -U-(CR⁴₂),-NR⁵-(CR⁴₂),R⁸.

61. The compound of claim 58 wherein either one or both of Z and Z' are
   -[C(O)-(CR⁴₂)₁t-NR⁵-(CR⁴₂)₄]-R⁸.

62. The compound of claim 61 wherein one or both of Z and Z' are
   -C(O)-(CR⁴₂),-NR⁵-(CR⁴₂),U-(CR⁴₂),R⁸.

63. The compound of claim 58 wherein one or both of Z and Z' are
   -[C(O)-(CR⁴₂),-NR⁵-(CR⁴₂)₄]-R⁸.
64. The compound of claim 63 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_t-NR^5-(CR_4^{f_2})_t-C(O)-(CR_4^{f_2})_t-NR^7-(CR_4^{f_2})_t-R^8\).

65. The compound of claim 63 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_t-NR^7-(CR_4^{f_2})_t-R^8\).

66. The compound of claim 65 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_n-NR^7-(CR_4^{f_2})_n-C(O)-R^{81}\).

67. The compound of claim 66 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_n-NR^7-C(O)-R^{81}\).

68. The compound of claim 65 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_n-NR^7-(CR_4^{f_2})_n-C(O)-O-R^{81}\).

69. The compound of claim 68 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_n-NR^7-C(O)-O-R^{81}\).

70. The compound of claim 57 wherein one or both of Z and \( Z' \) are 
\(-U-(CR_4^{f_2})_t-R^8\).

71. The compound of claim 70 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_t-R^8\).

72. The compound of claim 57 wherein one or both of Z and \( Z' \) are 
\(-[U-(CR_4^{f_2})_t-NR^5-(CR_4^{f_2})_t-O-(CR_4^{f_2})_t-R^8].\)

73. The compound of claim 72 wherein one or both of Z and \( Z' \) are 
\(-U-(CR_4^{f_2})_t-NR^5-(CR_4^{f_2})_t-U-(CR_4^{f_2})_t-O-(CR_4^{f_2})_t-R^8\).

74. The compound of claim 73 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_t-NR^5-(CR_4^{f_2})_t-C(O)-(CR_4^{f_2})_t-O-(CR_4^{f_2})_t-R^8\).

75. The compound of claim 72 wherein one or both of Z and \( Z' \) are 
\(-U-(CR_4^{f_2})_t-O-(CR_4^{f_2})_t-R^8\).

76. The compound of claim 75 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_t-O-(CR_4^{f_2})_t-R^8\).

77. The compound of claim 57 wherein one or both of Z and \( Z' \) are 
\(-C(O)-(CR_4^{f_2})_n-NR^7-R^8\) wherein \( R^7 \) and \( R^8 \) together form a 4-7 membered ring.
78. A pharmaceutical composition comprising any one of the compounds of claims 1-77.

79. The use of the compound of any one of claims 1-77 in the manufacture of a medicament.

80. The use of a compound of claim 79 wherein the medicament is for the treatment of hepatitis C.

81. A method of treating hepatitis C comprising administering to a subject in need thereof, a therapeutically effective amount of any one of the compounds of claims 1-78.
INTERNATIONAL SEARCH REPORT

A CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01 N 37/00; A61 K 31/21 (201 0.01)
USPC - 514/510-511
According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/510-511

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/281, 286, 289, 568-569, 576-577, 656, 661-662, 764-766

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB.USPT.USOCAPAB.JPAB), Google
Search Terms Used
fused tricyclic hcv inhibitor, bridged fused tricyclic, dihydroanthracene, fluorene, dihydrophenazme

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 4,371,690 A (ANDERSON et al) 01 February 1983 (01 02 1983) col 1-4</td>
<td>1-2, 4, 11-13, 27-32</td>
</tr>
<tr>
<td>Y</td>
<td>US 3,453,315 A (RIGAUDY) 01 July 1969 (01 07 1969) col 1 in 20-30</td>
<td>8-10, 24-26</td>
</tr>
<tr>
<td>Y</td>
<td>US 5,288,914 A (KIRCHHOFF) 22 February 1994 (22 02 1994) col 5, 21</td>
<td>43-48</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

Date of the actual completion of the international search
04 May 2010 (04 05 2010)

Date of mailing of the international search report
17 JUN 2010

Name and mailing address of the ISA/US
Mail Stop PCT, Attn ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Authorized officer
Lee W. Young
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos** because they relate to subject matter not required to be searched by this Authority, namely

2. **Claims Nos** because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be earned out, specifically

3. **Claims Nos** 7, 14-15, 17-23 and 49-81 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- No protest accompanied the payment of additional search fees