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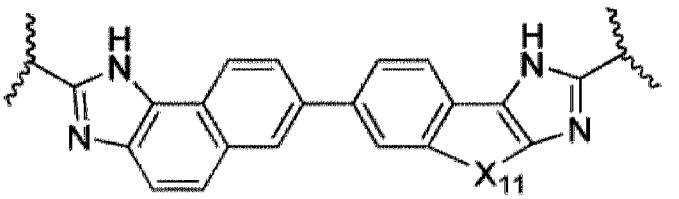
(54) Titre : COMPOSES ANTIVIRAUX
(54) Title: ANTIVIRAL COMPOUNDS

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b}$$

**(I)**



**($W^{1a}$)**

(57) Abrégé/Abstract:
It is provided an anti-viral compound of formula (I):

(see formula I)

wherein $W^{1a}$ is

(see formula $W^{1a}$),

composition containing same, for treating hepatitis C (HCV).

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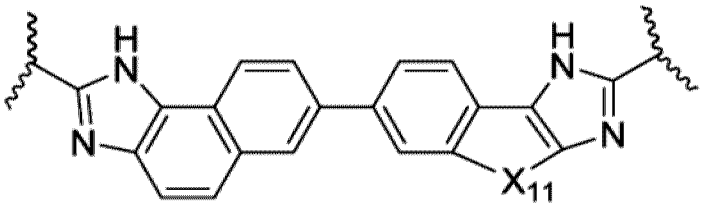
**ABSTRACT :**

It is provided an anti-viral compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b}\ (I)$$

wherein $W^{1a}$ is




,

composition containing same, for treating hepatitis C (HCV).



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# DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 5
CONTENANT LES PAGES 1 À 252

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# JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 5
CONTAINING PAGES 1 TO 252

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

# ANTIVIRAL COMPOUNDS

## PRIORITY OF INVENTION

## BACKGROUND OF THE INVENTION

Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

There is a need for new HCV therapeutic agents. In particular, there is a need for HCV therapeutic agents that have broad activity against HCV genotypes (e.g. genotypes 1a, 1b, 2a, 3a, 4a ). There is also a particular need for agents that are less susceptible to viral resistance. Resistance mutations to inhibitors have been described for HCV NS5A for genotypes 1a and 1b in Antimicrobial Agents and Chemotherapy, September 2010, Volume 54, p. 3641-3650.

## SUMMARY OF THE INVENTION

In one embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$P^{1a}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

$P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl,



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heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, (cycloalkyl)alkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, arylalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl-, oxo, and -$P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group,



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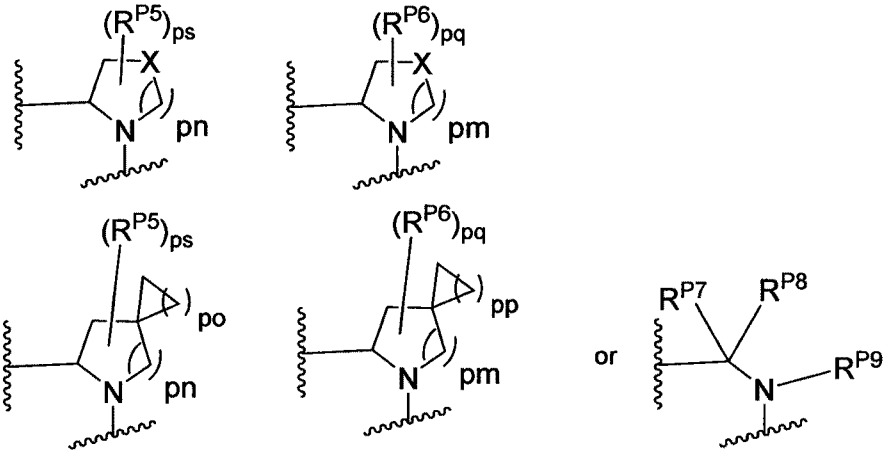
heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $P^0$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;



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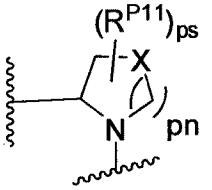
$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyalkyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy,



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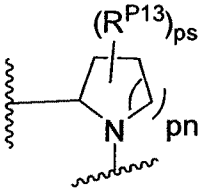
cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

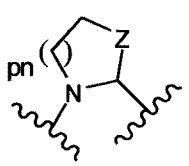
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:



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wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

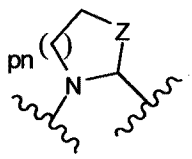
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;



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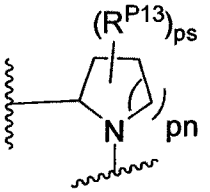
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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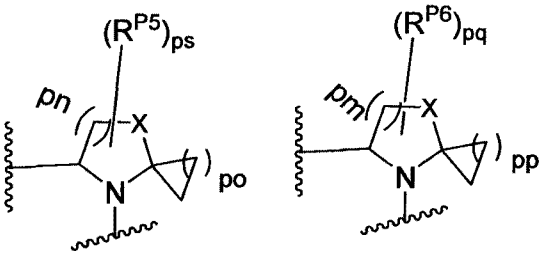


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

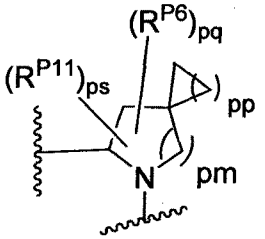
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to



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six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

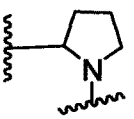
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



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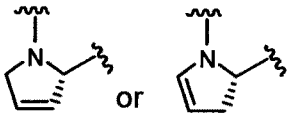
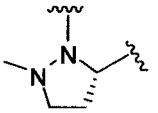
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



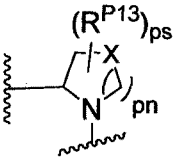
which is optionally substituted, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonylwith one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:



ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl,



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formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the



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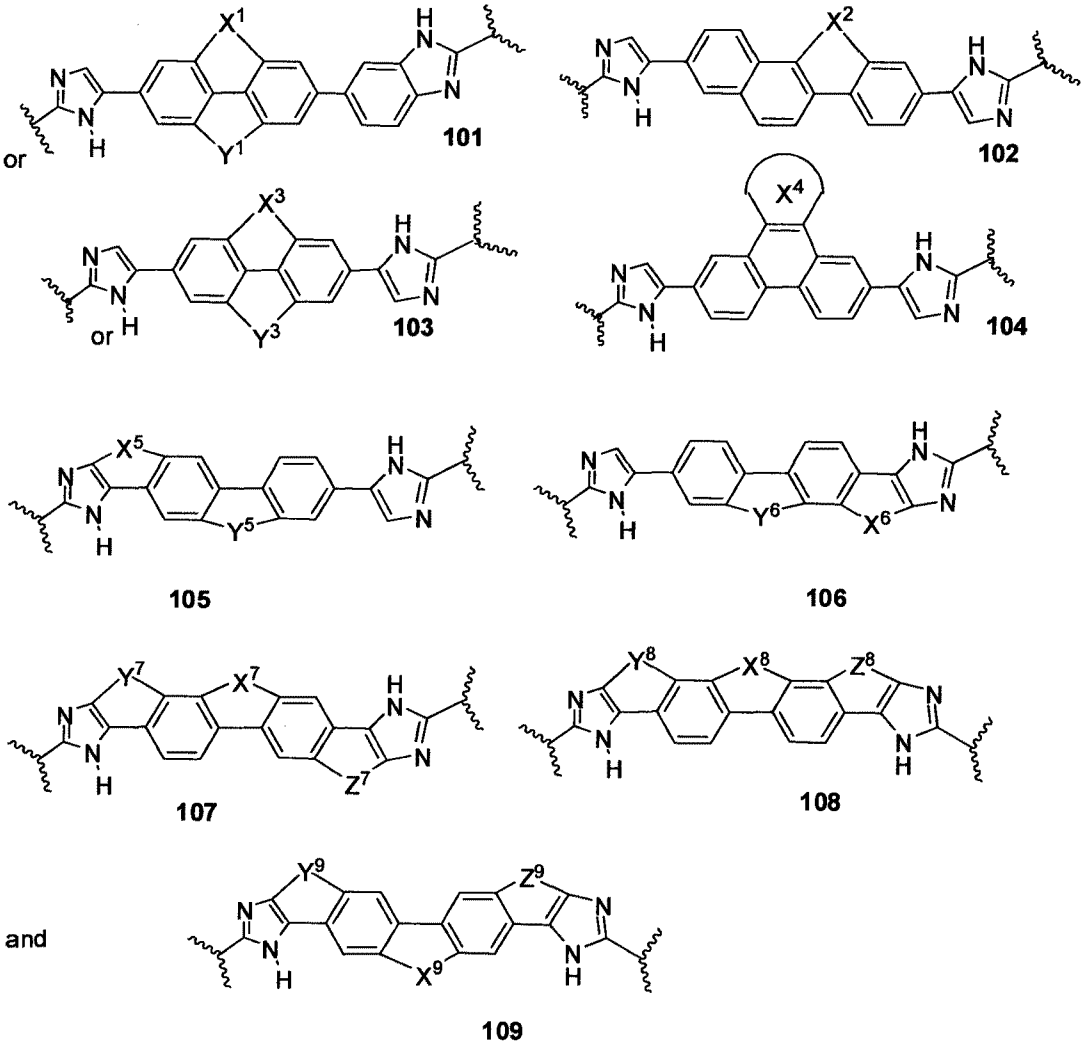
heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl; and

$W^{1a}$ is selected from:




wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and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wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^1$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^1$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^2$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^3$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^3$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^4$ is a six membered aromatic or heteroaromatic or five membered heteroraromatic ring;

$X^5$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^5$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^6$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^6$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Z^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$Z^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;



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$Y^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, --O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-; and

$Z^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, --O-, -S- $CH_2-$, - $CH_2-S-$, -OC(O)-, -(O)CO-, or -CH=CH-;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$; and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;



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each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl-, oxo, and -$P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $P^0$ is independently:



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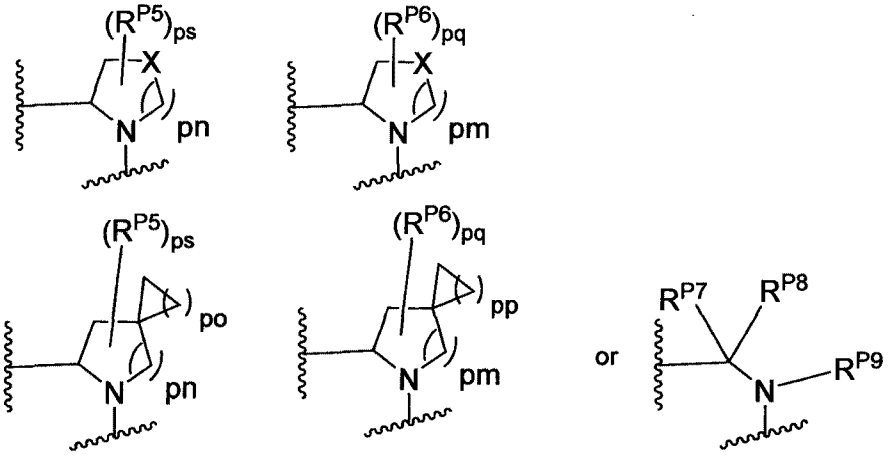

wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:



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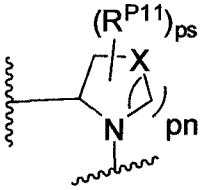


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;



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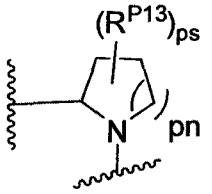
ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

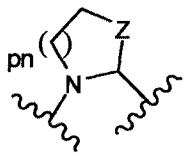
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon



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when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

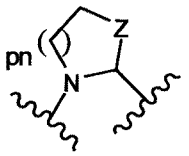
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$ ;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl,



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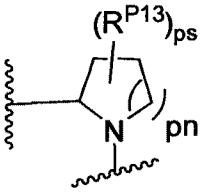
alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

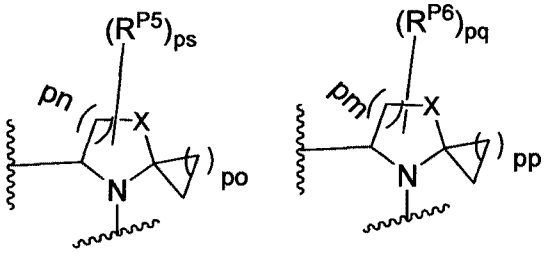
ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

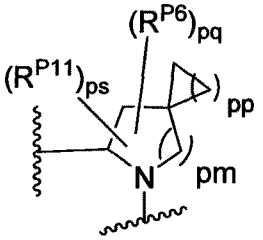
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:




wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;



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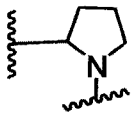
ps is 1, 2, 3, or 4;

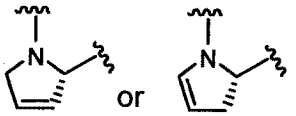
$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



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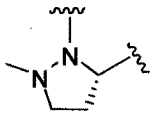
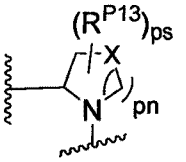
which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:



ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the



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heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;



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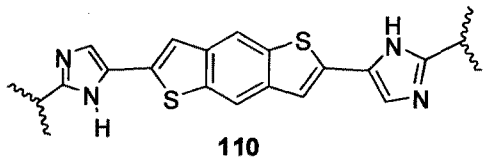
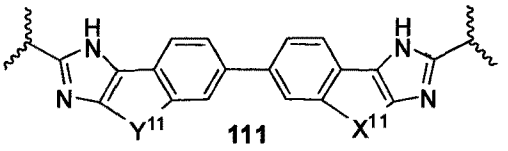
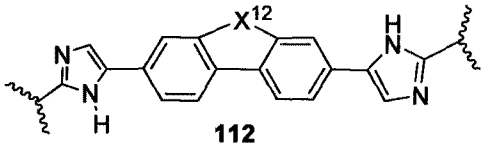
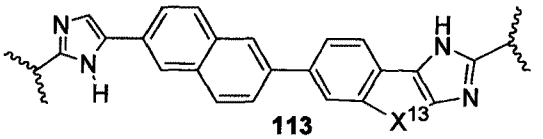
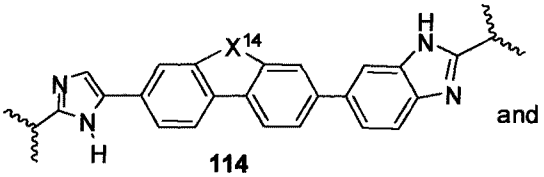
$W^{1a}$ is selected from:



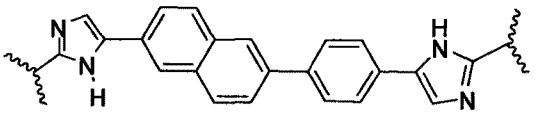



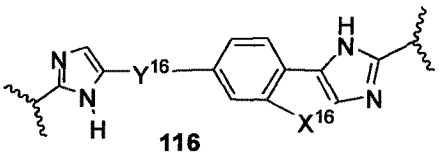



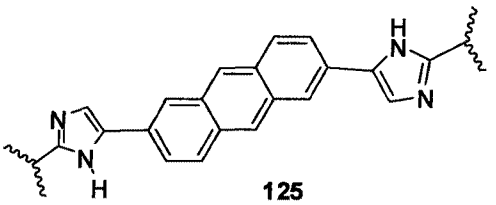



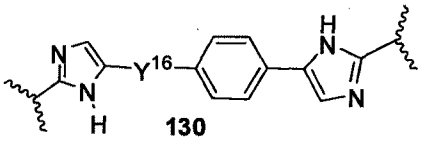

and



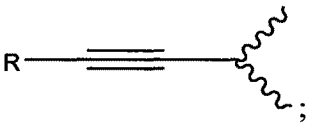




and




wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and




wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$Y^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$X^{12}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-



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$X^{13}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-O-$, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, $-CH=N-$; $-N=CH-$; or $-CH=CH-$; and

$X^{14}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-O-$, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, $-CH=N-$; $-N=CH-$; or $-CH=CH-$; and

each $Y^{16}$ is a bicyclic aromatic ring system comprising eight to 12 atoms optionally including one or more heteroatoms selected from O, S, and N, which bicyclic ring system is optionally with one or more groups independently selected from halo, haloalkyl, alkyl and oxo.

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$; and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with



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one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl-, oxo, and -$P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:



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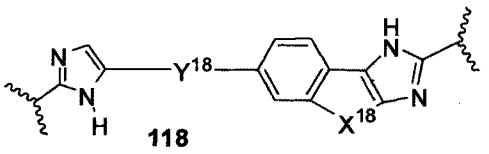

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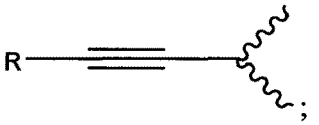
wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and

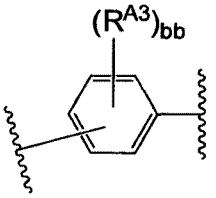


;

wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$Y^{18}$ is selected from $A^0$, $A^1$, $A^2$, $A^3$, $A^7$, $A^{15}$, $A^{16}$, and $A^{20}$;

each $A^0$ is independently:



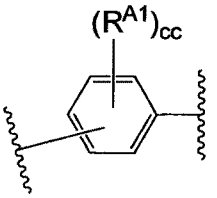
wherein:

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

bb is independently 0, 1, 2, 3, or 4; or

each $A^0$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 $R^{A3}$ groups;

each $A^1$ is independently:





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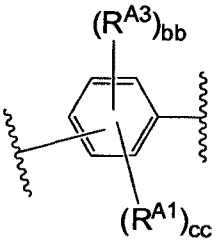
wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4;

each $A^2$ is independently:




wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, and ($NR^aR^b$)carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

$R^a$ and $R^b$ are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each $A^3$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more $R^{A1}$ groups, and which ring is optionally substituted with one or more $R^{A3}$ groups;



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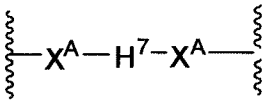
each $A^7$ is independently:

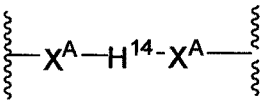


wherein:

each $H^7$ is independently a five-membered heteroaromatic ring, which $H^7$ is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; and each R is independently selected from H or alkyl;

each $A^{15}$ is independently:

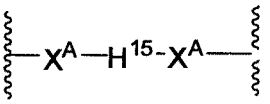


wherein:

each $H^{14}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from oxo, $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{16}$ is independently:



wherein:

each $H^{15}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and



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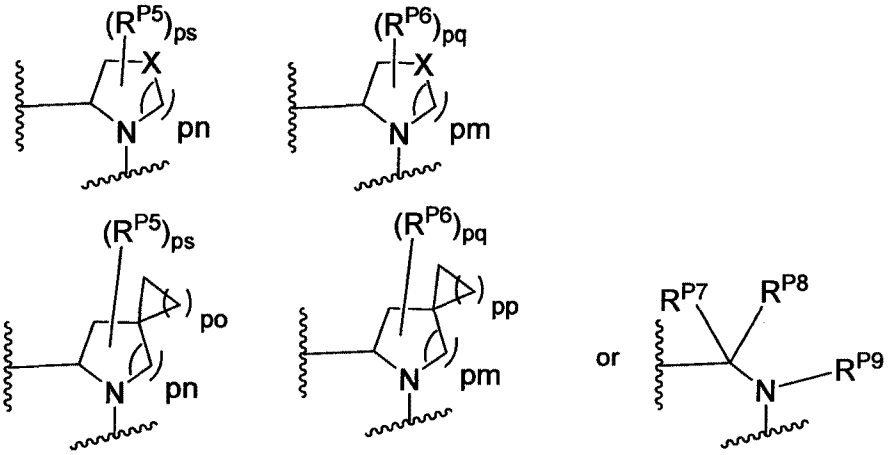
each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{20}$ is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$;

each $P^0$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are



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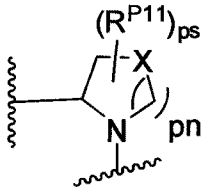
attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy,



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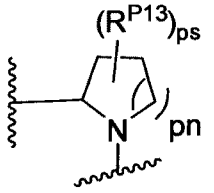
cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

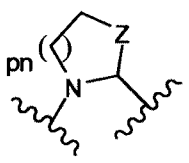
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:



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wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

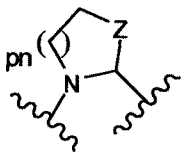
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;



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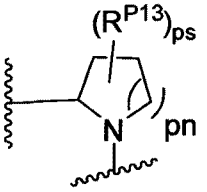
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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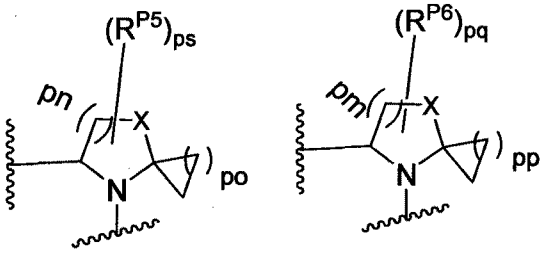


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

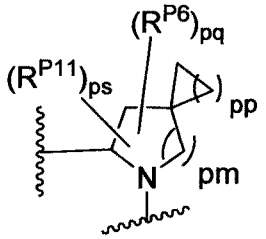
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

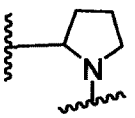
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



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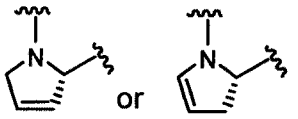
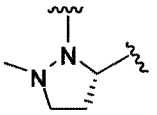


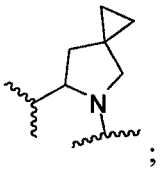
which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



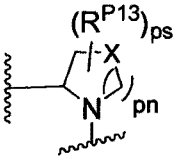
;

each $P^{20}$ is:



;

each $P^{30}$ is independently a ring of the formula:



ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl,



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alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -$(NR^XR^Y)$alkyl, and -$(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl; and

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the



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arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

$X^{18}$ is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH_2$-O-, -O-$CH_2$-, -$CH_2$-O-$CH_2$-, -S-, -S(O)$_2$-, -C(O)-, -$CF_2$-, -O-, -S-$CH_2$-, -$CH_2$-S-, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

each $E^0$ is independently -$NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the



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arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $E^2$ is independently $-NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;



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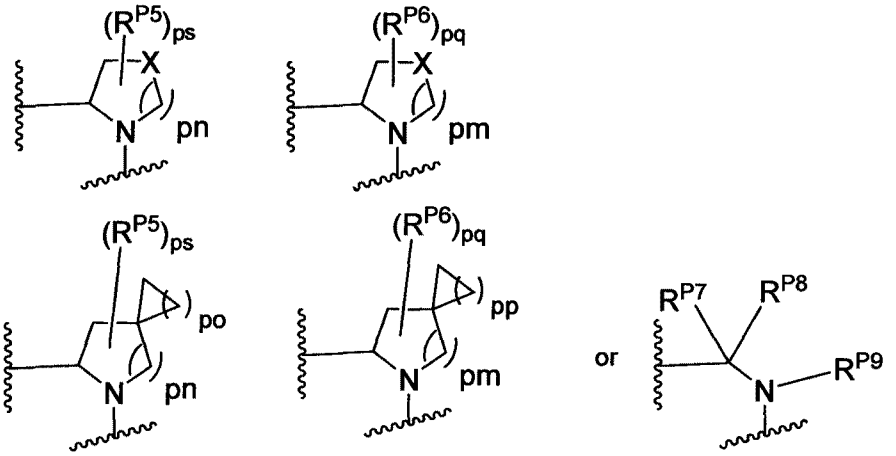
$P^{1a}$ and $P^{1b}$ are each independently selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $P^0$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:



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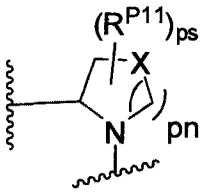


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl,



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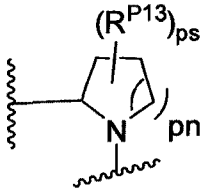
haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

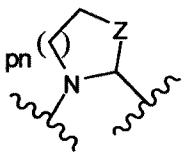
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –



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$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

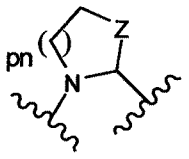
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$ ;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl,



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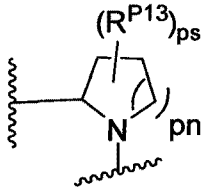
haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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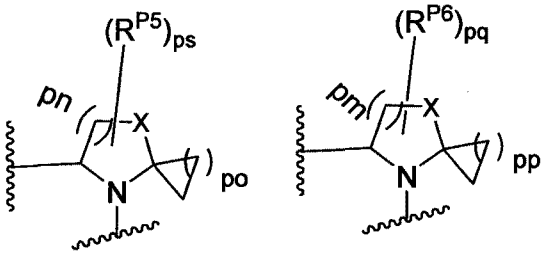


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

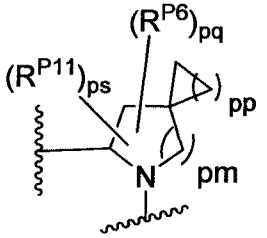
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

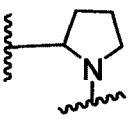
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:




which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



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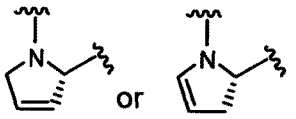
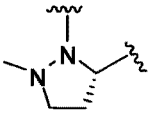


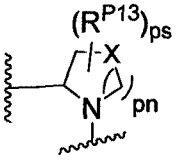
which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:



ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl,



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-C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl,



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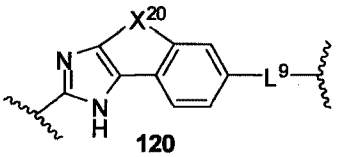
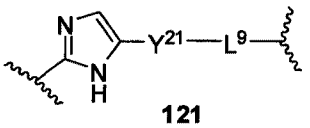
unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

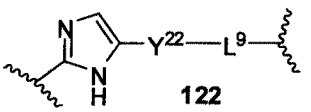
$W^{1a}$ is selected from:




120

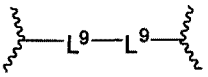



121




122

and

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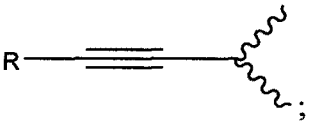
wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



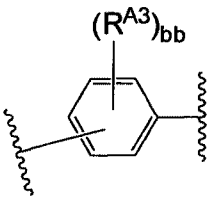

wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{20}$ is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH_2$-O-, -O-$CH_2$-, -$CH_2$-O-$CH_2$-, -S-, -$S(O)_2$-, -C(O)-, -$CF_2$-, -O-, -S-$CH_2$-, -$CH_2$-S-, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$Y^{21}$ is a bicyclic aromatic ring system comprising eight to 12 atoms optionally including one or more heteroatoms selected from O, S, and N, which bicyclic ring system is optionally with one or more groups independently selected from halo, haloalkyl, alkyl and oxo;

$Y^{22}$ is selected from $A^0$, $A^1$, $A^2$, $A^3$, $A^7$, $A^{15}$, $A^{16}$, and $A^{20}$;

each $A^0$ is independently:



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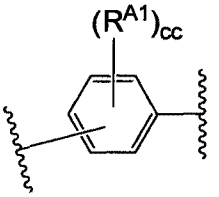
wherein:

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, and ($NR^aR^b$)carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each bb is independently 0, 1, 2, 3, or 4; or

each $A^0$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 $R^{A3}$ groups;

each $A^1$ is independently:



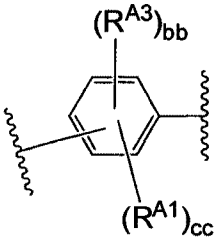

wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4;

each $A^2$ is independently:




wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl,



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(heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, and ($NR^aR^b$)carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

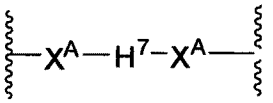
each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

$R^a$ and $R^b$ are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each $A^3$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more $R^{A1}$ groups, and which ring is optionally substituted with one or more $R^{A3}$ groups;

each $A^7$ is independently:

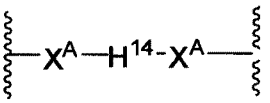


wherein:

each $H^7$ is independently a five-membered heteroaromatic ring, which $H^7$ is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; and each R is independently selected from H or alkyl;

each $A^{15}$ is independently:



wherein:

each $H^{14}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from oxo, $R^{A1}$ and $R^{A3}$; and



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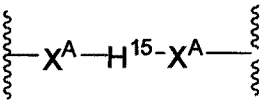
each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{16}$ is independently:



wherein:

each $H^{15}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{20}$ is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$;

each $L^9$ is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L9}$, $-OR^{L9}$, $-SR^{L9}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L9})C(=O)R^{L9}$, $-C(=O)R^{L9}$, $-OC(=O)R^{L9}$, $-C(O)OR^{L9}$, $-C(=O)NR^{L9}$, $-S(=O)R^{L9}$, $-S(=O)_2OR^{L9}$, $-S(=O)_2R^{L9}$, $-OS(=O)_2OR^{L9}$, $-S(=O)_2NR^{L9}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl;

each $R^{L9}$ is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and

$R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:



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$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

each $E^0$ is independently -$NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro,



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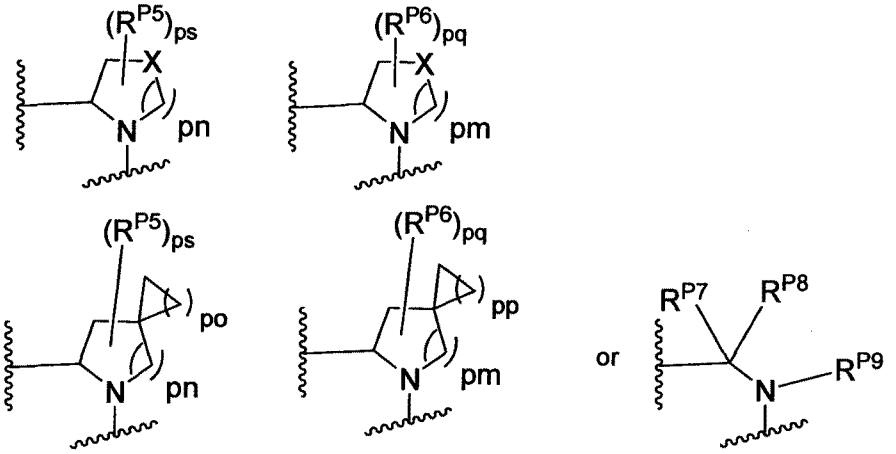
$-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$P^{1a}$ and $P^{1b}$ are each independently selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $P^0$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-



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membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

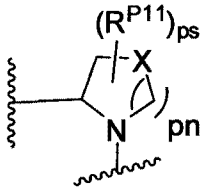
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyloxyalkyloxy, aryloxyalkyloxy,



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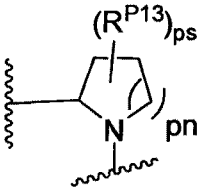
heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, -$NR^{hh}R^h$, ($NR^{hh}R^h$)alkyl, ($NR^{hh}R^h$)carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, ($NR^hR^h$)sulfonyl, heteroarylsulfonyl, -$S(=O)_2R^h$, -$C(=O)R^h$, -$C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy,



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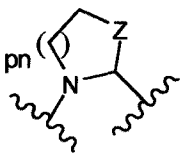
heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:



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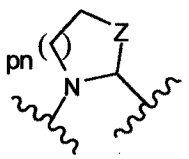



wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

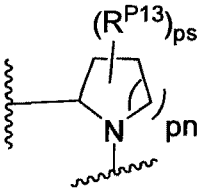
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:



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wherein:

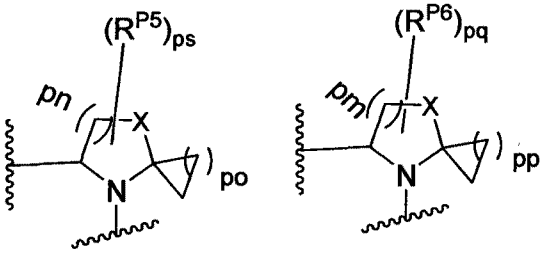
ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;



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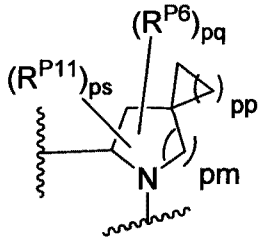
po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:




wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl,



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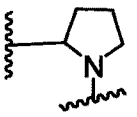
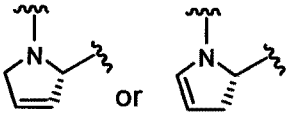
haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



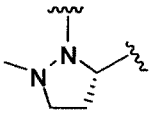
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:




which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl,



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hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -$(NR^XR^Y)$alkyl, and -$(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo,



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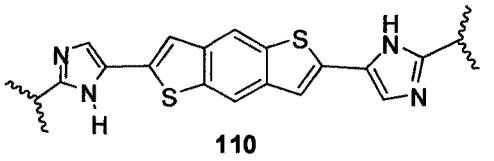
haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

$W^{1a}$ is selected from:



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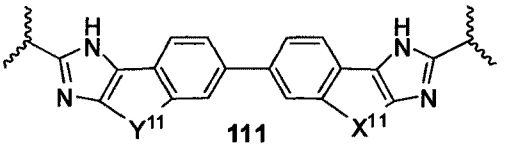
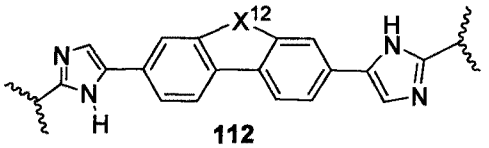
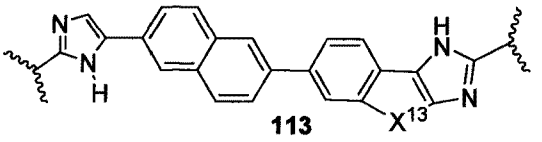


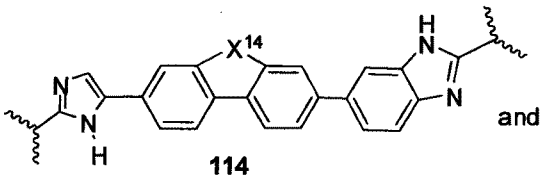
111



112



113



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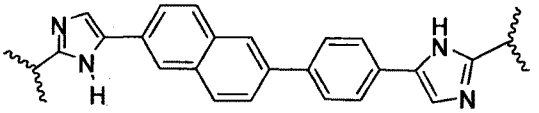
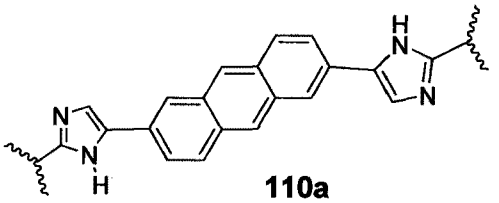
and

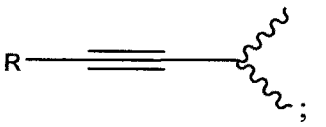


115



110a

wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and wherein each $W^{1a}$ is substituted with one or more (e.g. 1, 2, 3, or 4):



wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{11}$ is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH_2$-O-, -O-$CH_2$-, -$CH_2$-O-$CH_2$-, -S-, -$S(O)_2$-, -C(O)-, -$CF_2$-, -O-, -S-$CH_2$-, -$CH_2$-S-, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$Y^{11}$ is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH_2$-O-, -O-$CH_2$-, -$CH_2$-O-$CH_2$-, -S-, -$S(O)_2$-, -C(O)-, -$CF_2$-, -O-, -S-$CH_2$-, -$CH_2$-S-, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-



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$X^{12}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-O-$, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, $-CH=N-$; $-N=CH-$; or $-CH=CH-$

$X^{13}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-O-$, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, $-CH=N-$; $-N=CH-$; or $-CH=CH-$; and

$X^{14}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-O-$, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, $-CH=N-$; $-N=CH-$; or $-CH=CH-$;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^{0a}$ and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;



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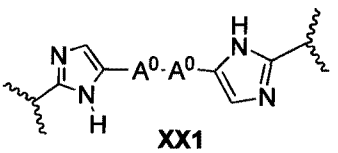
each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, -($NR^XR^Y$)alkyl, oxo, and -$P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:

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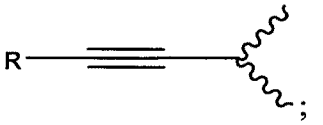
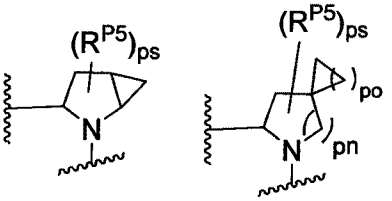
wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

each $P^{0a}$ is independently:



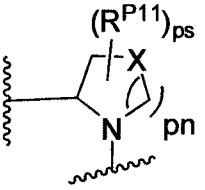
each $R^{P5}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

ps is independently 0, 1, 2, 3, or 4;

pn is independently 0, 1, or 2;

po is independently 1, 2, or 3;

each $P^1$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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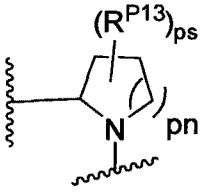
at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h$a)lkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;



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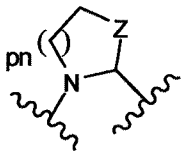
each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl,



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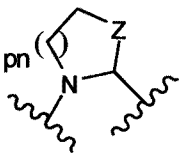
dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

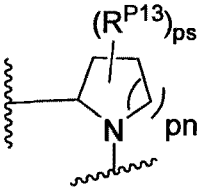
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:



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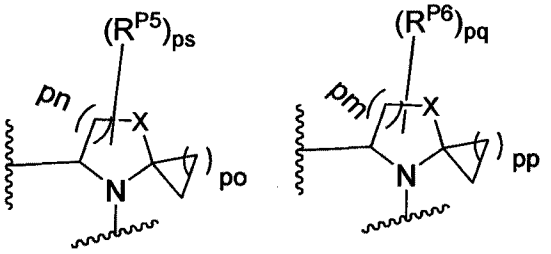
wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $P^{10}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



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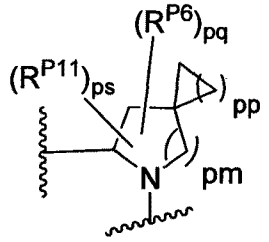


wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl,



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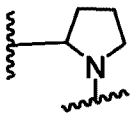
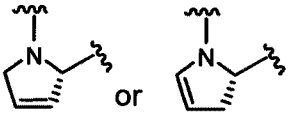
dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo,



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haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R9^b$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl,



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unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$, $E^1$, or $E^2$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$, $E^1$, or $E^2$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^{0b}$ and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^{21}$, $P^3$, $P^6$, $P^7$, $P^{28}$, $P^{12}$, $P^{15}$and $P^{38}$;

each $E^0$ is independently -$NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $E^2$ is independently -$NHR^{Ef}$ wherein $R^{Ef}$ is cycloalkylcarbonyl or cycloalkyloxycarbonyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl,



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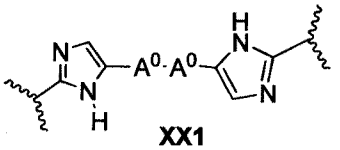
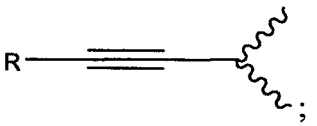
aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:



XX1

wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and





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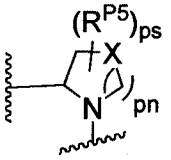
wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

each $P^{0b}$ is independently:



X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$

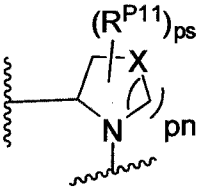
each $R^{P5}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

ps is independently 0, 1, 2, 3, or 4;

pn is independently 0, 1, or 2;

each $P^{21}$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy,



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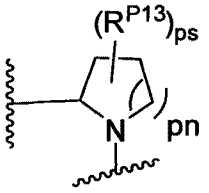
alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyalkyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, -$NR^{hh}R^h$, ($NR^{hh}R^h$)carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, ($NR^hR^h$)sulfonyl, heteroarylsulfonyl, -$S(=O)_2R^h$, -$C(=O)R^h$, -$C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl,



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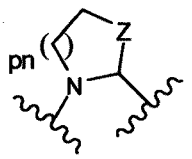
alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^{28}$ is independently a ring of the formula:



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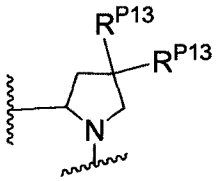
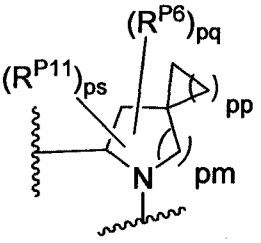



wherein:

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, where in two $R^{P13}$ groups are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $P^{12}$ is independently:




wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl,



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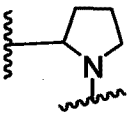
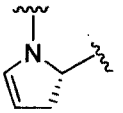
dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{38}$ is:



which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl,



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arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the



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arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is a compound of any one of formulae 1-25, 25b, 25c, and 25d as shown in Table 1, or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is a compound of any one of formulae 26-102as shown in Table 2, or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is a compound of any one of formulae 103-289 as shown in Table 3, or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides isotopically enriched compounds that are compounds of the invention that comprise an enriched isotope at one or more positions in the compound.

The present invention also provides a pharmaceutical composition comprising a compound of the invention and at least one pharmaceutically acceptable carrier.

The present invention also provides a pharmaceutical composition for use in treating disorders associated with HCV.

The present invention also provides a pharmaceutical composition further comprising an interferon or pegylated interferon.

The present invention also provides a pharmaceutical composition further comprising a nucleoside analog.



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The present invention also provides for a pharmaceutical composition wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated α-interferon.

The present invention also provides for a method of treating disorders associated with hepatitis C, said method comprising administering to an individual a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the invention.

The present invention also provides a method of inhibiting HCV, comprising administering to a mammal afflicted with a condition associated with HCV activity, an amount of a compound of the invention, effective to inhibit HCV.

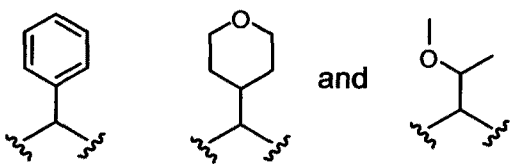
The present invention also provides a compound of the invention for use in medical therapy (e.g. for use in inhibiting HCV activity or treating a condition associated with HCV activity), as well as the use of a compound of the invention for the manufacture of a medicament useful for inhibiting HCV or the treatment of a condition associated with HCV activity in a mammal.

The present invention also provides synthetic processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

In another aspect the invention provides a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

In another aspect the invention provides a method of inhibiting HCV activity in a sample comprising treating the sample with a compound of the invention.

Compounds of formula (I) have been found to possess useful activity against HCV genotypes 1 and 4. Compounds of formula (I) wherein $W^{1a}$ is selected from structures **103-109** have been found to possess useful activity against HCV genotypes 1-4. Additionally certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **101-109** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:




are improved in potency against resistant variants in GT1 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:



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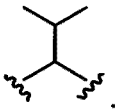
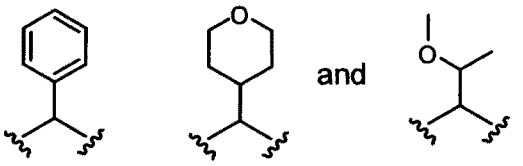
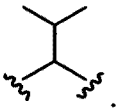


Accordingly, certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **101-102** possess beneficial pharmacokinetic properties that make them well suited to fulfil the current need for HCV agents with such beneficial properties. Additionally compounds of formula (I) wherein $W^{1a}$ is selected from structures **101, 102** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:

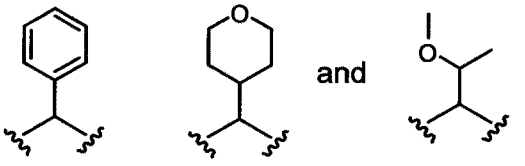



have been found to possess improved activity against HCV genotypes 2 and 3 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:

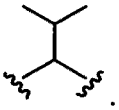


Accordingly, certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **101, 102** possess beneficial pharmacokinetic properties that make them well suited to fulfil the current need for HCV agents with such beneficial properties.

Compounds of formula (I) wherein $W^{1a}$ is selected from structures **110, 111, 112, 118 and 125** have been found to possess useful activity against HCV genotypes 1-4. Additionally certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **110, 111, 112, 118 and 125** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:




are improved in potency against resistant variants in GT1 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:



Accordingly, certain certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **113, 114, 115, 116, 130** possess beneficial pharmacokinetic properties that make them well suited to fulfil the current need for HCV agents with such beneficial properties.



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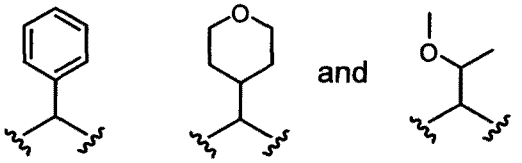
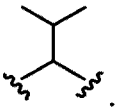
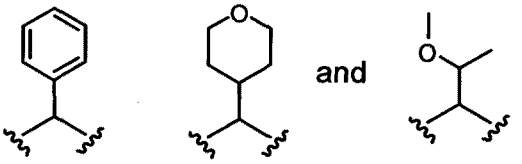
Additionally certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **113, 114, 115, 116, 130** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:



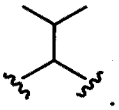

are improved in potency against resistant variants in GT1 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:



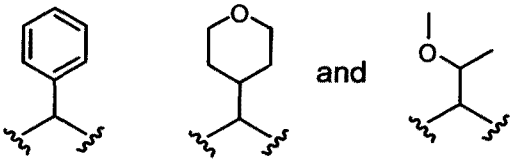
Additionally certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **120-123** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:



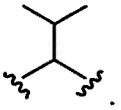

are improved in potency against resistant variants in GT1 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:



Compounds of formula (I) wherein $W^{1a}$ is selected from structure **XX1** been found to possess useful activity against HCV genotypes 1-4. Additionally certain compounds of formula (I) wherein $W^{1a}$ is selected from structures **XX1** and at least one of $V^{1a}$ and $V^{1b}$ is selected from:




are improved in potency against resistant variants in GT1 compared to the corresponding compounds wherein $V^{1a}$ and $V^{1b}$ are each selected from:





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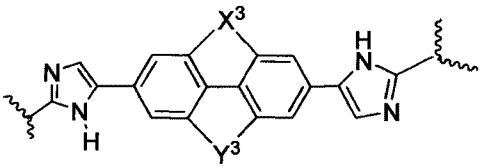
It has been further found that certain compounds of formula (I) with particular $W^{1a}$ groups have improved potency in genotypes 2, 2a and 2b ("GT2", "GT2a", and "GT2b") when a methionine is present at the residue 31 position of NS5A ("with M31 present") (in the data tables herein the GT2a J6 replicon clone and the GT2b replicon have the more resistant M31 residue present and the GT2a JFH replicon clone has the less resistant L31 residue). These certain compounds of formula (I) also can have improved potency against some resistant mutants in genotype 1 and other genotypes. One such example of a resistant mutant in genotype 1a is where residue 30 has been changed from Q to R (Q30R). This mutant is represented in the data tables. Enhanced potencies can be further improved when the particular $W^{1a}$ groups are combined with certain select P groups, or select V groups, and/or select E or $R^9$ groups independently as described below.

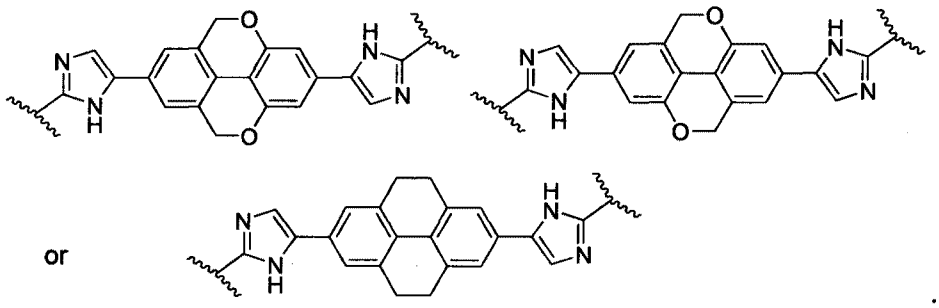
Compounds possessing enhanced potency against GT2a, GT2b (both with M31 present) and against some resistant variants in genotype 1 and other genotypes include those where $W^{1a}$ is selected from structures **103, 105, 111, and 118.**

Included are particular compounds of formula (I) wherein $W^{1a}$ is selected from structure **103** of the formula:



**103**

wherein $X^3$ is $-CH_2-CH_2-$, $-CH_2-O-$, or $-O-CH_2-$; and $Y^3$ is $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, or $-CH=CH-$. Further included are compounds where $W^{1a}$ is:



Further included are compounds where $W^{1a}$ is:



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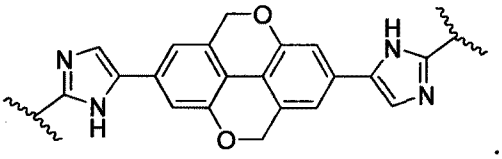
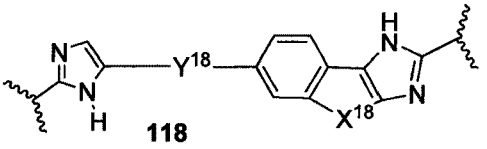
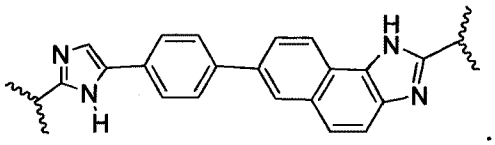


Also included are particular compounds of formula (I) wherein $W^{1a}$ is selected from structure **118** of the formula:

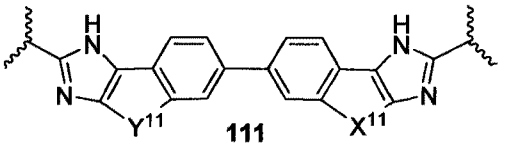


**118**

wherein $X^{18}$ is –CH=CH-, $-CH_2CH_2-$, or $-OCH_2-$; and $Y^{18}$ is phenyl. Further included are compounds where $W^{1a}$ is:

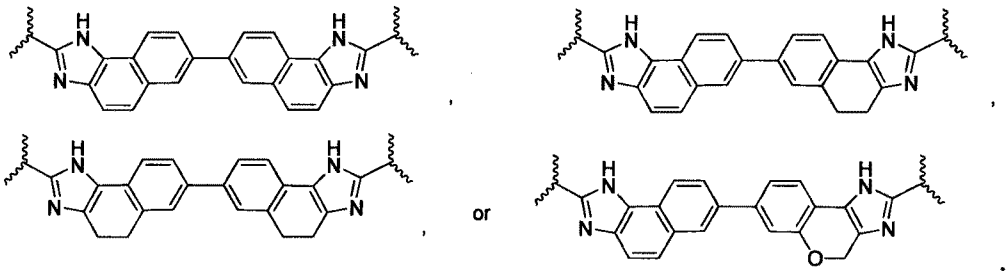


Also included are particular compounds of formula (I) wherein $W^{1a}$ is selected from structure **111** of the formula:



**111**

wherein $X^{11}$ is $-CH_2-CH_2-$, $-O-CH_2-$, or -CH=CH-; and $Y^{11}$ is -CH=CH-, $-O-CH_2-$. Further included are compounds where $W^{1a}$ is:





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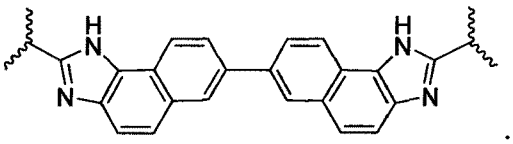
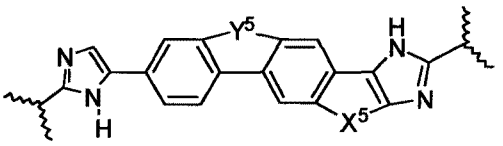
Further included are compounds where $W^{1a}$ is:

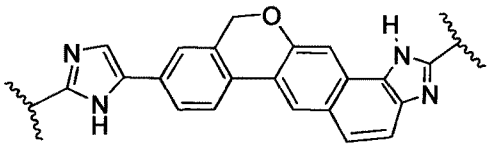


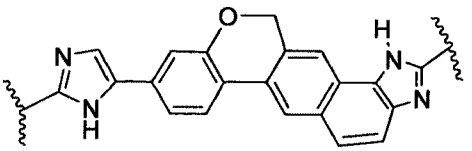
Also included are particular compounds of formula (I) wherein $W^{1a}$ is selected from structure **105** of the formula:

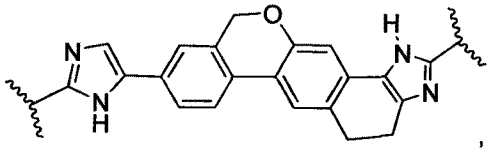


wherein $Y^5$ is -O-$CH_2$-, or -$CH_2$-O-; and $X^5$ is -$CH_2$-$CH_2$- or -CH=CH-.

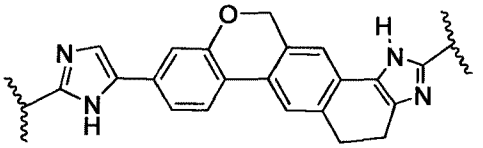
Further included are compounds where $W^{1a}$ is:



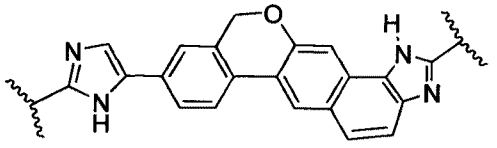




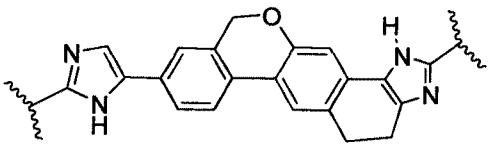
, or



Further included are compounds where $W^{1a}$ is:



or



Further included are compounds where $W^{1a}$ is:



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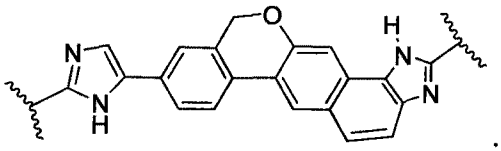
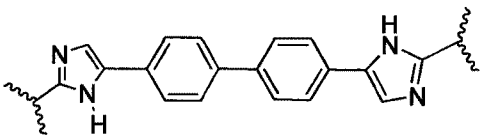


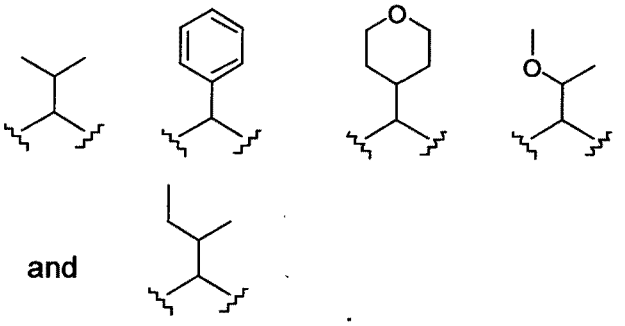
Additionally, when combined with P groups, V groups, and/or E or $R^9$ groups independently selected from groups described below, certain compounds of formula (I) wherein $W^{1a}$ is structure **130** can have improved potency in GT2a and GT2b (both with M31):



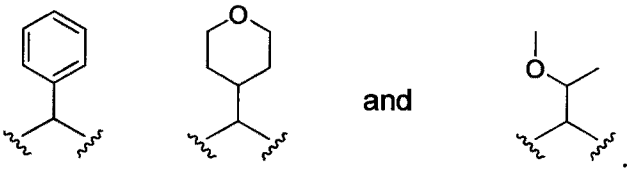
130

The observed enhanced potencies against GT2a, GT2b (both with M31 present) and against some resistant variants in genotype 1 and other genotypes can be further improved when the particular $W^{1a}$ groups described above are combined with certain select P groups, or select V groups, and/or select E or $R^9$ groups as described below.

One select combination group are those compounds wherein $V^{1a}$ is selected from:




In particular, enhanced potency is observed when at least one $V^{1a}$ is selected from:




Another select combination group are those compounds wherein $P^{1a}$ and $P^{1b}$ are selected from:



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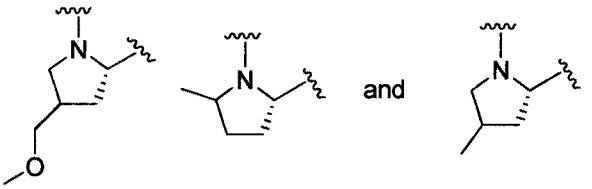
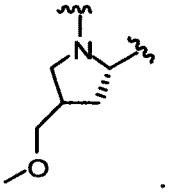
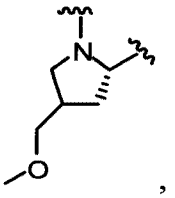


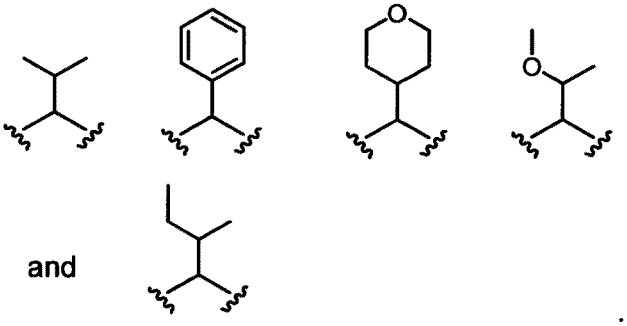

Particularly beneficial in providing enhanced potency against GT2a, GT2b (both with M31 present) and against some resistant variants in genotype 1 and other genotypes are compounds where $P^{1a}$ or $P^{1b}$ is selected from:



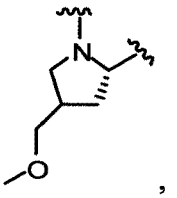
Other select combination groups include those where $P^{1a}$ is:



and $V^{1a}$ is selected from:




Other select combination groups include those where $P^{1b}$ is:



and $V^{1b}$ is selected from:



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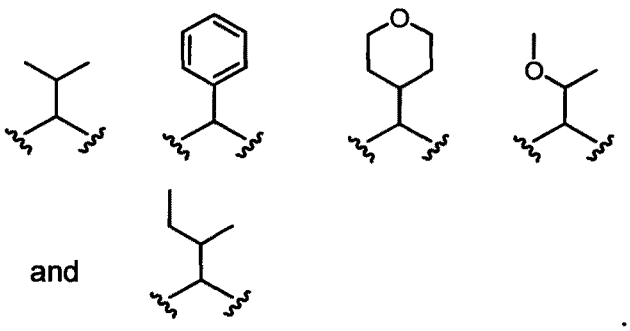
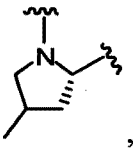
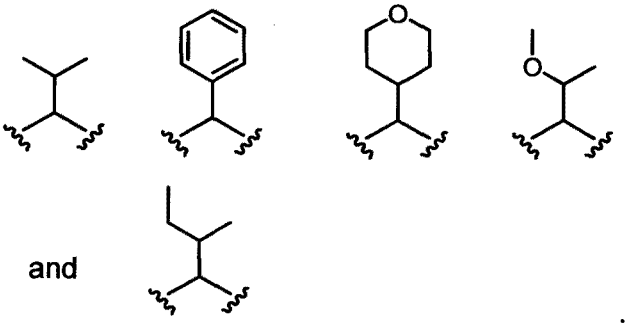


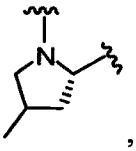

Other select combination groups include those where $P^{1a}$ is:



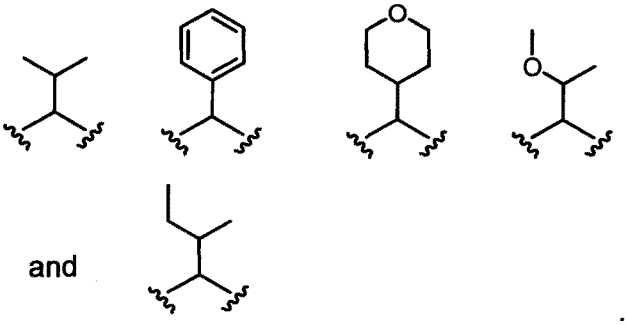

and $V^{1a}$ is selected from:




Other select combination groups include those where $P^{1b}$ is:




and the $V^{1b}$ is selected from:



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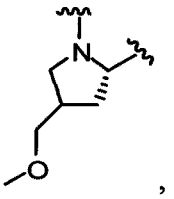
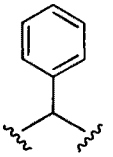
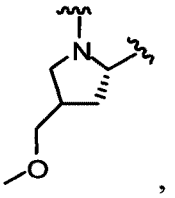
Other select combination groups include those where $P^{1a}$ is:



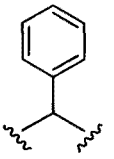
and the $V^{1a}$ is,



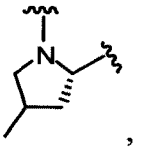
Other select combination groups include those where $P^{1b}$ is:



and the $V^{1b}$ is,



Other select combination groups include those where $P^{1a}$ is:



and $V^{1a}$ is,



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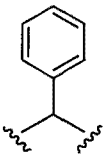
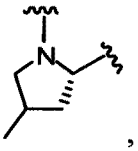
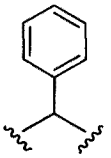


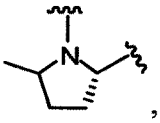
Other select combination groups include those where $P^{1b}$ is:



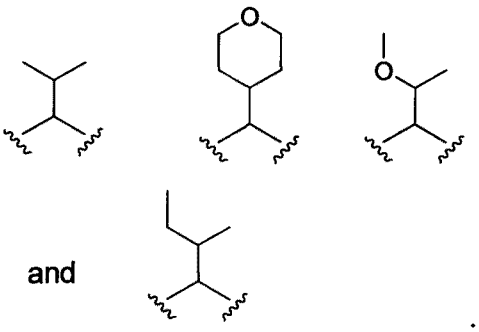
and $V^{1b}$ is,



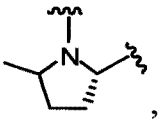
Other select combination groups include those where $P^{1a}$ is:



and $V^{1a}$ is selected from:




Other select combination groups include those where $P^{1b}$ is:



and $V^{1b}$ is selected from:



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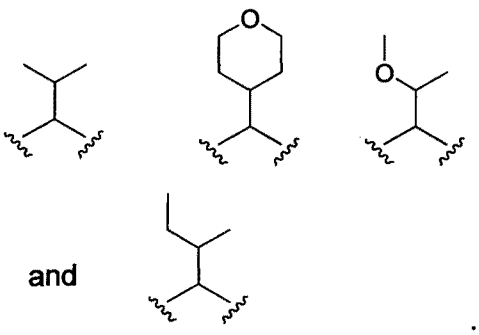
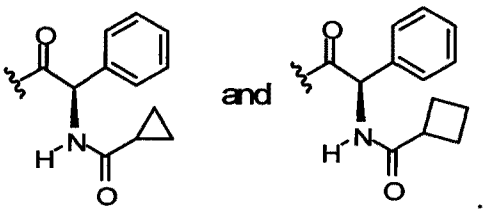



Furthermore, additional potency against GT2a, GT2b (both with M31 present) and against some resistant variants in genotype 1 and other genotypes is observed in compounds wherein $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$ or wherein $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$, wherein $R^{9a}$ or $R^{9b}$ is selected from:




Accordingly, certain compounds of formula (I) possess beneficial pharmacological properties that make them well suited to fulfil the current need for HCV agents with such beneficial properties.

In one embodiment the invention provides a compound having improved inhibitory or pharmacokinetic properties, including enhanced activity against development of viral resistance, improved oral bioavailability, greater potency (for example, in inhibiting HCV activity) or extended effective half-life *in vivo*. Certain compounds of the invention may have fewer side effects, less complicated dosing schedules, or be orally active.

## DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the embodiments.



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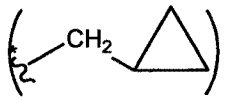
Compounds of the Invention

The compounds of the invention exclude compounds heretofore known. However, it is within the invention to use compounds that previously were not known to have antiviral properties for antiviral purposes (e.g. to produce an anti-viral effect in an animal). With respect to the United States, the compounds or compositions herein exclude compounds that are anticipated under 35 USC §102 or that are obvious under 35 USC §103.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "$R^1$" or "$A^3$", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

"Absent" – Some groups are defined such that they can be absent. When a group is absent it becomes a bond connector. The two groups that would otherwise be connected to that absent group are connected to each other through a bond. For example, when W is absent, M is bonded to M.

"Alkyl" is $C_1$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and cyclopropylmethyl




"Alkenyl" is $C_2$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, $sp^2$ double bond. Examples include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\ CH_2CH_2CH_2CH=CH_2$).



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"Alkynyl" is $C_2$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. Examples include, but are not limited to, acetylenic (-C≡CH) and propargyl (-$CH_2$C≡CH).

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to, methylene (-$CH_2$-) 1,2-ethyl (-$CH_2CH_2$-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-$CH_2$C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or $sp^3$ carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, *e.g.*, the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

The term "polycarbocycle" refers to a saturated or unsaturated polycyclic ring system having from about 6 to about 25 carbon atoms and having two or more rings (e.g. 2, 3, 4, or 5 rings). The rings can be fused and/or bridged to form the polycyclic ring system. For example, the term includes bicyclo [4,5], [5,5], [5,6] or [6,6] ring systems, as well as the following bridged ring systems:



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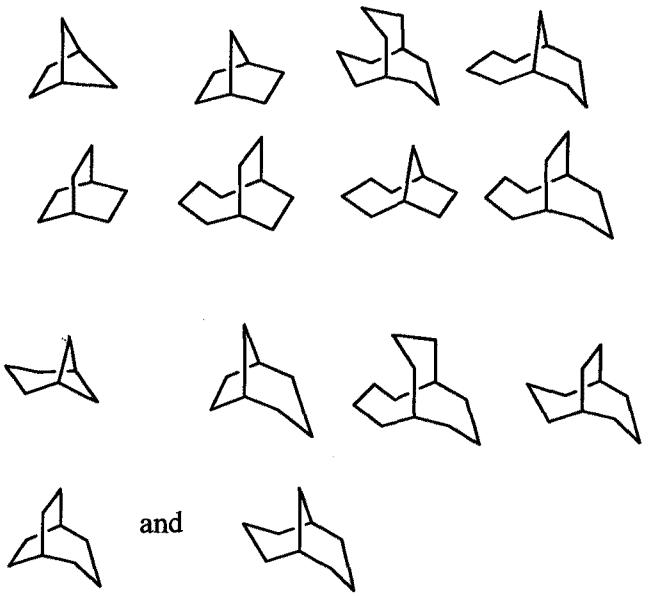


( i.e., [2.1.1], [2.2.1], [3.3.3], [4.3.1], [2.2.2], [4.2.2], [4.2.1], [4.3.2], [3.1.1], [3.2.1], [4.3.3], [3.3.2], [3.2.2] and [3.3.1] polycyclic rings, respectively) that can be linked to the remainder of the compound of formula (I) through any synthetically feasible position. Like the other polycarbocycles, these representative bicyclo and fused ring systems can optionally comprise one or more double bonds in the ring system.

The term "polyheterocycle" refers to a polycarbocycle as defined herein, wherein one or more carbon atoms is replaced with a heteroatom (e.g., O, S, S(O), $S(O)_2$, $N^+(O^-)R_x$, or $NR_x$); wherein each $R_x$ is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(O)_2NR_nR_p$, $S(O)_2R_x$, or (C1-10)alkoxy, wherein each (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, and (C1-10)alkoxy is optionally substituted with one or more halo).

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to: halo (e.g. F, Cl, Br, I), -R, -OR, -SR, $-NR_2$, $-CF_3$, $-CCl_3$, $-OCF_3$, -CN, $-NO_2$, -N(R)C(=O)R, -C(=O)R, -OC(=O)R, -C(O)OR, -C(=O)NRR, -S(=O)R, $-S(=O)_2OR$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NRR$, and each R is independently -H, alkyl, aryl, arylalkyl, or heterocycle. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

The term "optionally substituted" in reference to a particular moiety of the compound of formula I, (e.g., an optionally substituted aryl group) refers to a moiety having 0, 1, 2, or more substituents.



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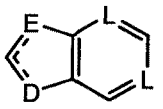
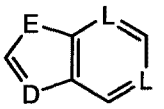
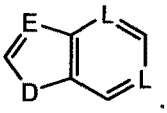
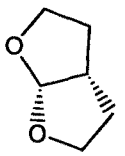
The symbol "-----" in a ring structure means that a bond is a single or double bond. In a non-limiting example,  can be  or  .

"Haloalkyl" as used herein includes an alkyl group substituted with one or more halogens (e.g. F, Cl, Br, or I). Representative examples of haloalkyl include trifluoromethyl, 2,2,2-trifluoroethyl, and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl.

"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The term heterocycle also includes "heteroaryl" which is a heterocycle wherein at least one heterocyclic rings is aromatic.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4H-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:





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By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having up to about 25 carbon atoms. Typically, a carbocycle has about 3 to 7 carbon atoms as a monocycle, about 7 to 12 carbon atoms as a bicycle, and up to about 25 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. The term carbocycle includes "cycloalkyl" which is a saturated or unsaturated carbocycle. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.



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"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. The invention includes all stereoisomers of the compounds described herein.

The term "heterocyclylsulfonyl," as used herein, refers to hetercyclyl group attached to the parent molecular moiety through a sulfonyl group.

The term "heteroarylsulfonyl," as used herein, refers to heteroaryl group attached to the parent molecular moiety through a sulfonyl group.

The term "alkyloxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three alkoxy groups.



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The term "haloalkoxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three haloalkoxy groups.

The term "cycloalkyloxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three cycloalkyloxy groups.

The term "aryloxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three aryloxy groups.

The term "heteroaryloxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three heteroaryloxy groups.

The term "heterocyclyloxyalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three heterocyclyloxy groups.

The term "cyanoalkyloxy," as used herein, refers to an alkyloxy group substituted with one, two, or three cyano groups.

The term "cyanocycloalkyloxy," as used herein, refers to a cycloalkyloxy group substituted with one, two, or three cyano groups.

The term "haloalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three haloalkoxy groups.

The term "amino," as used herein, refers to $-NH_2$.

The term "alkylamino," as used herein, refers to an amino group substituted with one alkyl group (i.e. -NH(alkyl)).

The term "dialkylamino," as used herein, refers to an amino group substituted with two alkyl groups (i.e. $-N(alkyl)_2$).

The term "aminoalkyl," as used herein, refers to an alkyl group substituted with one, two, or three amino groups.

The term "alkylaminoalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylamino groups.

The term "dialkylaminoalkyl," as used herein, refers to an alkyl group substituted with one, two, or three dialkylamino groups.

The term "alkoxyamino," as used herein, refers to an amino group substituted with one alkoxy group.

The term "sulfonylalkyl," as used herein, refers to an alkyl group substituted with at least one $SO_3H$ group.

Specific Definitions for Groups $A^0$, $P^0$, $V^0$, $Z^0$, and $E^0$

For the groups $A^0$, $P^0$, $V^0$, $Z^0$, and $E^0$ the following definitions apply. These definitions also apply for all other A, P, V, Z, and E groups unless those groups are otherwise defined herein.



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Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term 'aryl'.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxyalkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxyalkylcarbonyl groups.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "alkylsulfanylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylsulfanyl groups.



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The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxy groups.

The term "arylalkoxyalkylcarbonyl," as used herein, refers to an arylalkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkoxyalkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxyalkylcarbonyl groups.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally



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substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^XR^Y$;

The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylsulfanyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring. It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product.

The term "carbonyl," as used herein, refers to -C(=O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "carboxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three carboxy groups.

The term "cyano," as used herein, refers to -CN.

The term "cyanoalkyl" as used herein, refers to an alkyl group having at least one –CN substituent.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$ wherein the aryl and the heterocyclyl are further optionally substituted with one, two, or three



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substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-NR^cR^d$.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "cycloalkyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "formyl," as used herein, refers to -CHO.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "haloalkylsulfanyl," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through a sulfur atom.

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl,



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thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2- azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^cR^d$, wherein the aryl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^XR^Y$.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term “heterocyclylcarbonylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three heterocyclylcarbonyl groups.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyloxy groups.

The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.



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The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, $R^a$ and $R^b$, which are attached to the parent molecular moiety through a nitrogen atom. $R^a$ and $R^b$ are independently selected from hydrogen, alkenyl, and alkyl.

The term "$(NR^aR^b)$alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups.

The term "$(NR^aR^b)$carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^d$," as used herein, refers to two groups, $R^c$ and $R^d$, which are attached to the parent molecular moiety through a nitrogen atom. $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "$(NR^cR^d)$alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three $-NR^cR^d$ groups.

The term "$(NR^cR^d)$alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^d$ groups. The alkyl part of the $(NR^cR^d)$alkyl is further optionally substituted with one or two additional groups selected from alkoxy,



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alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclylcarbonyl, hydroxy, and $(NR^eR^f)$carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "$(NR^cR^d)$carbonyl," as used herein, refers to an $-NR^cR^d$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^eR^f$," as used herein, refers to two groups, $R^e$ and $R^f$, which are attached to the parent molecular moiety through a nitrogen atom. $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -$(NR^XR^Y)$alkyl, and -$(NR^XR^Y)$carbonyl.

The term "$(NR^eR^f)$alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^eR^f$ groups.

The term "$(NR^eR^f)$alkylcarbonyl," as used herein, refers to an $(NR^eR^f)$alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "$(NR^eR^f)$carbonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a carbonyl group.

The term "$(NR^eR^f)$sulfonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a sulfonyl group.

The term "$-NR^XR^Y$," as used herein, refers to two groups, $R^X$ and $R^Y$, which are attached to the parent molecular moiety through a nitrogen atom. $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl.

The term "$(NR^XR^Y)$alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^XR^Y$ groups.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

The term "trialkylsilyl," as used herein, refers to $-SiR_3$, wherein R is alkyl. The R groups may be the same or different

The term "trialkylsilylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.



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The term "trialkylsilylalkoxy," as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "trialkylsilylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

The "P" groups (eg $P^{1a}$, $P^{1b}$, $P^{0}$, etc) defined for formula (I) herein have one bond to a -C(=O)- of formula (I) and one bond to a $W^{1a}$ group. It is to be inderstood that a nitrogen of the P group is connected to the -C(=O)- group of formula (I) and that a carbon of the P group is connected to the $W^{1a}$ group.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of



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such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. The invention includes all stereoisomers of the compounds described herein.

Prodrugs

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates a compound of the invention that inhibits HCV activity ("the active inhibitory compound"). The compound may be formed from the prodrug as a result of: (i) spontaneous chemical reaction(s), (ii) enzyme catalyzed chemical reaction(s), (iii) photolysis, and/or (iv) metabolic chemical reaction(s).

"Prodrug moiety" refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^{99}$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^{99}$ where $R^{99}$ is $C_1$–$C_6$ alkyl, $C_1$–$C_6$ substituted alkyl, $C_6$–$C_{20}$ aryl or $C_6$–$C_{20}$ substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral



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bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to a phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate parent phosphonic acids. In some cases, substituents at the *ortho-* or *para-* position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate phosphoric acid and a quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958).

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental



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drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. PGs do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for –OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-



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184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below.

By way of example and not limitation, $R^1$, $R^3$, $R^{A1}$, $R^{A3}$, and $X^A$ are recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.*, "$R^1$" or "$R^3$", then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

In one embodiment of the invention, the compound is in an isolated and purified form. Generally, the term "isolated and purified" means that the compound is substantially free from biological materials (e.g. blood, tissue, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 50 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 75 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 90 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 98 wt.% free from biological materials; and in another embodiment, the term means that the compound or conjugate of the invention is at least about 99 wt.% free from biological materials. In another specific embodiment, the invention provides a compound or conjugate of the invention that has been synthetically prepared (e.g., *ex vivo*).

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with



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optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and $NX_4^+$ (wherein X is $C_1$–$C_4$ alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as $Na^+$ and $NX_4^+$ (wherein X is independently selected from H or a $C_1$–$C_4$ alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will typically be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing $Li^+$, $Na^+$, and $K^+$. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, $H_2SO_4$, $H_3PO_4$ or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise



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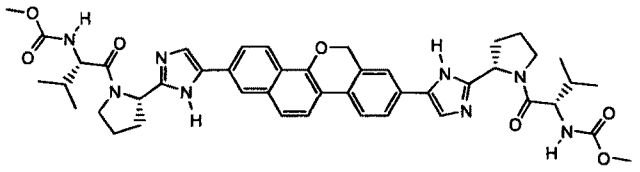
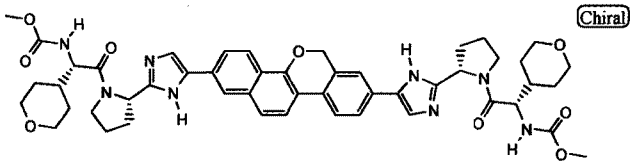
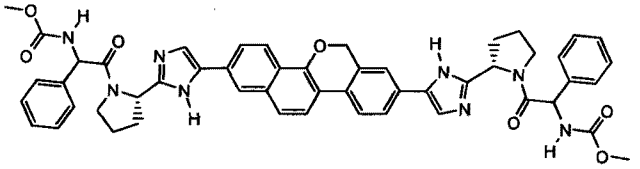
compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the natural or unnatural amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Specific Embodiments

In one specific embodiment of the invention the compound of formula (I) is not :

| Compound |
| --- |
|  |
|   |
| or  |



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In one specific embodiment of the invention the compound of formula (I) is not:

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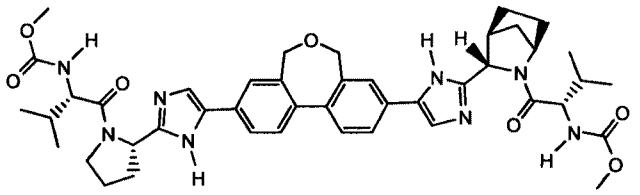
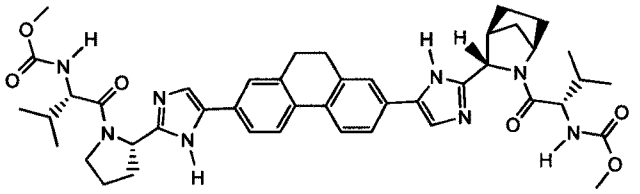
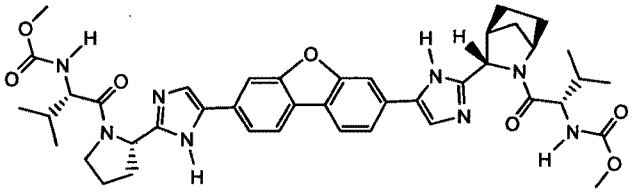
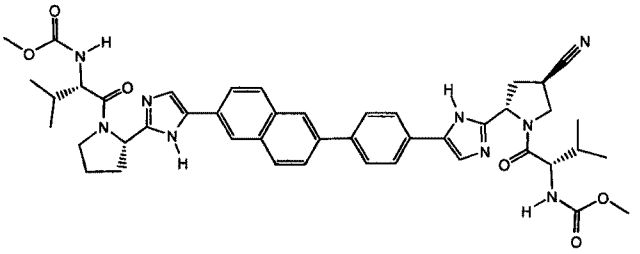
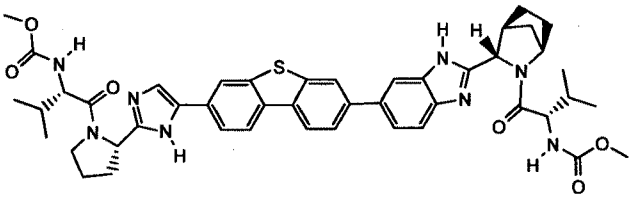
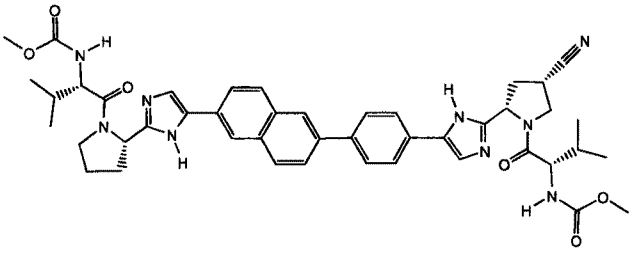
|  |
|  |
|  |
|  |
|  |
|  |



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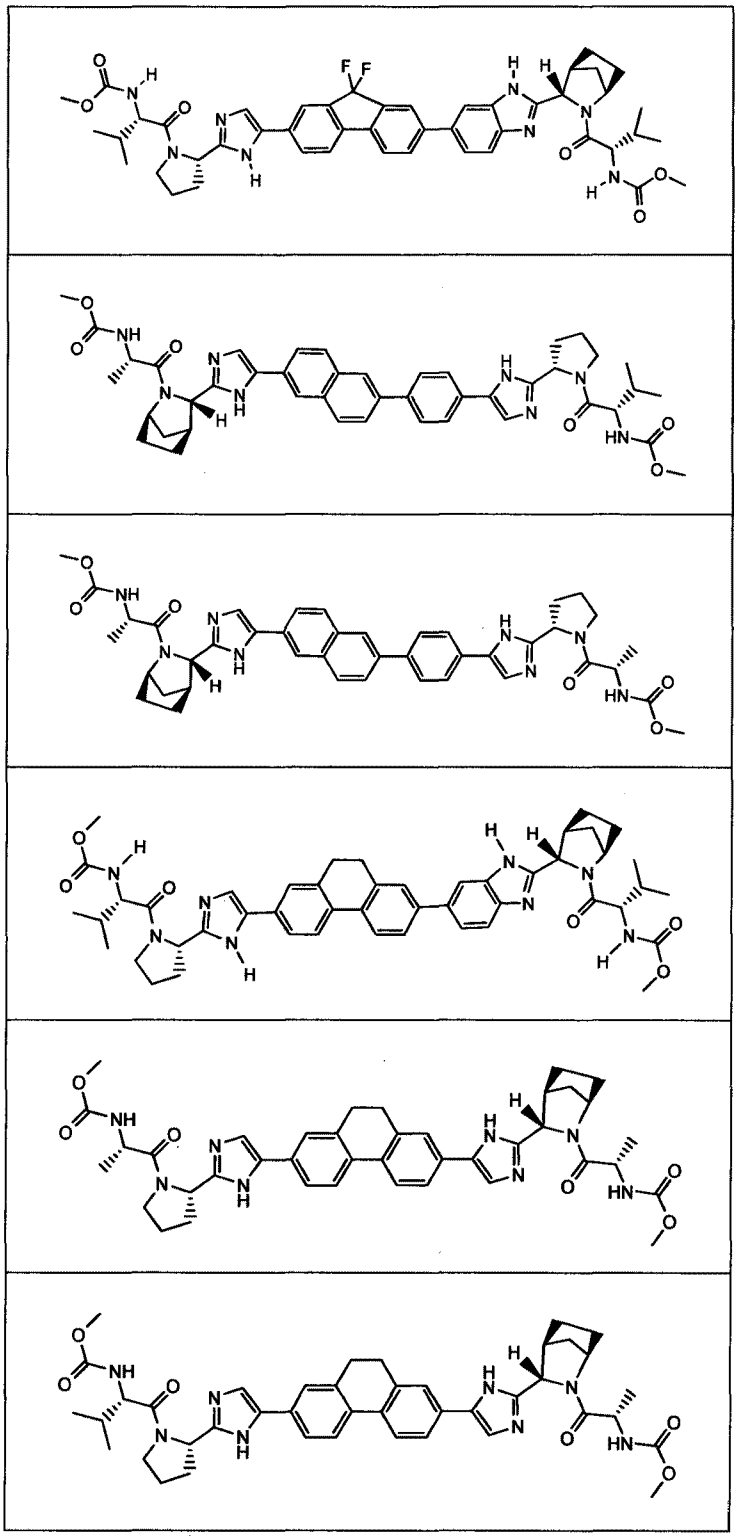



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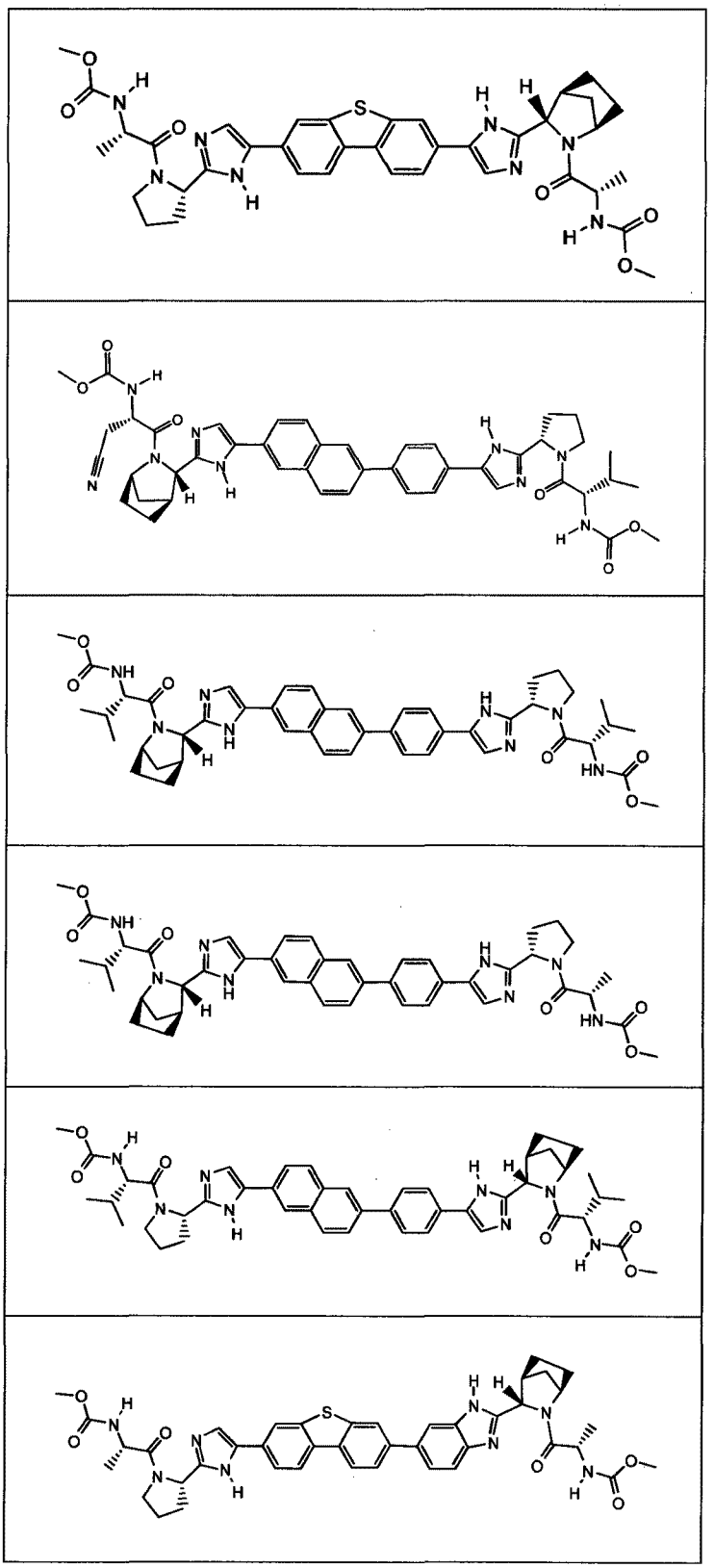



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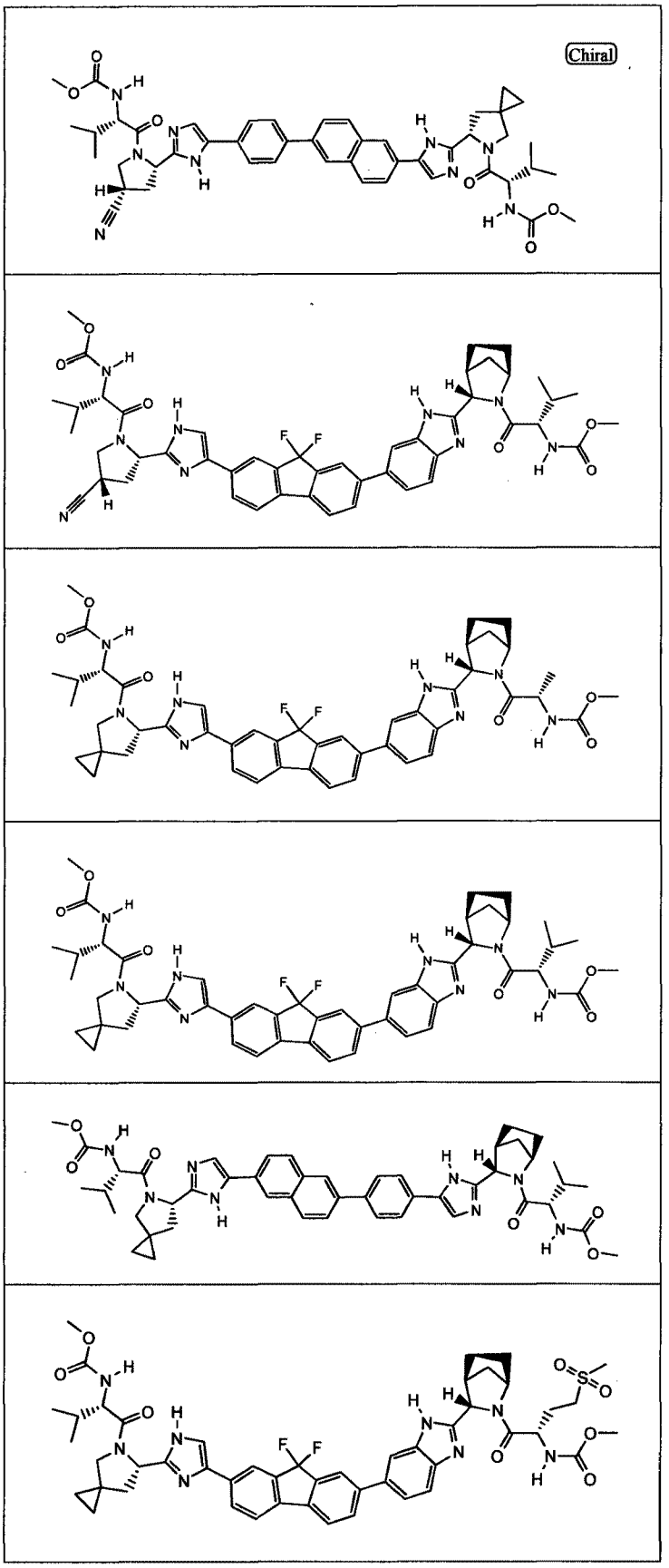




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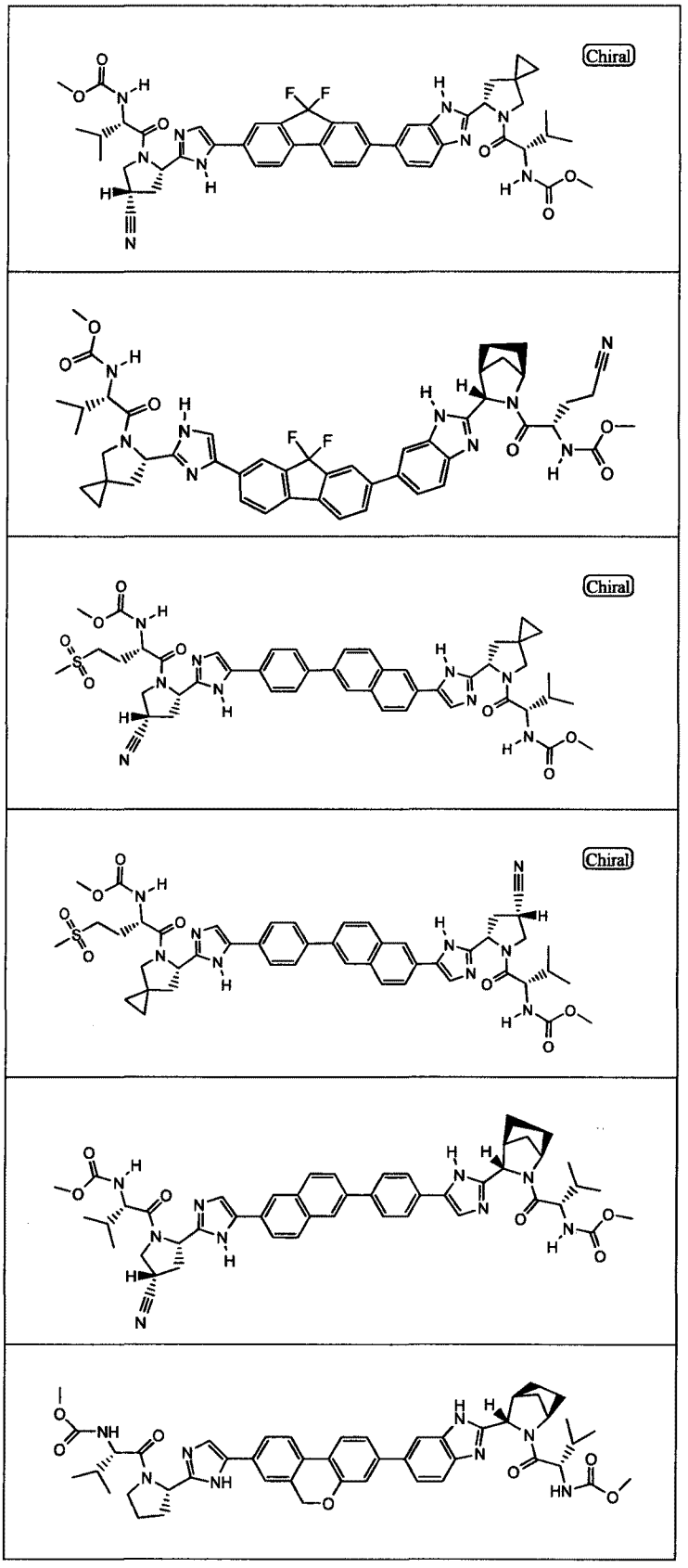




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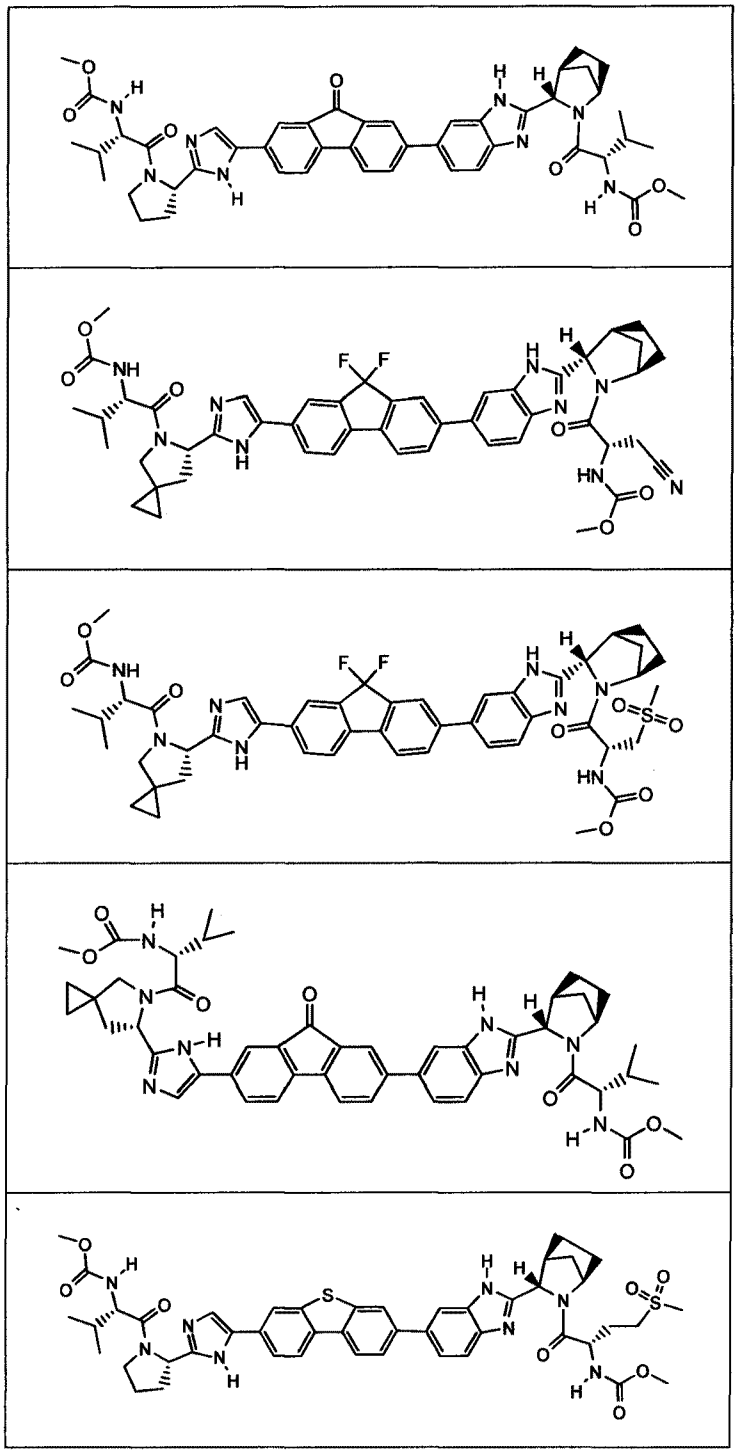



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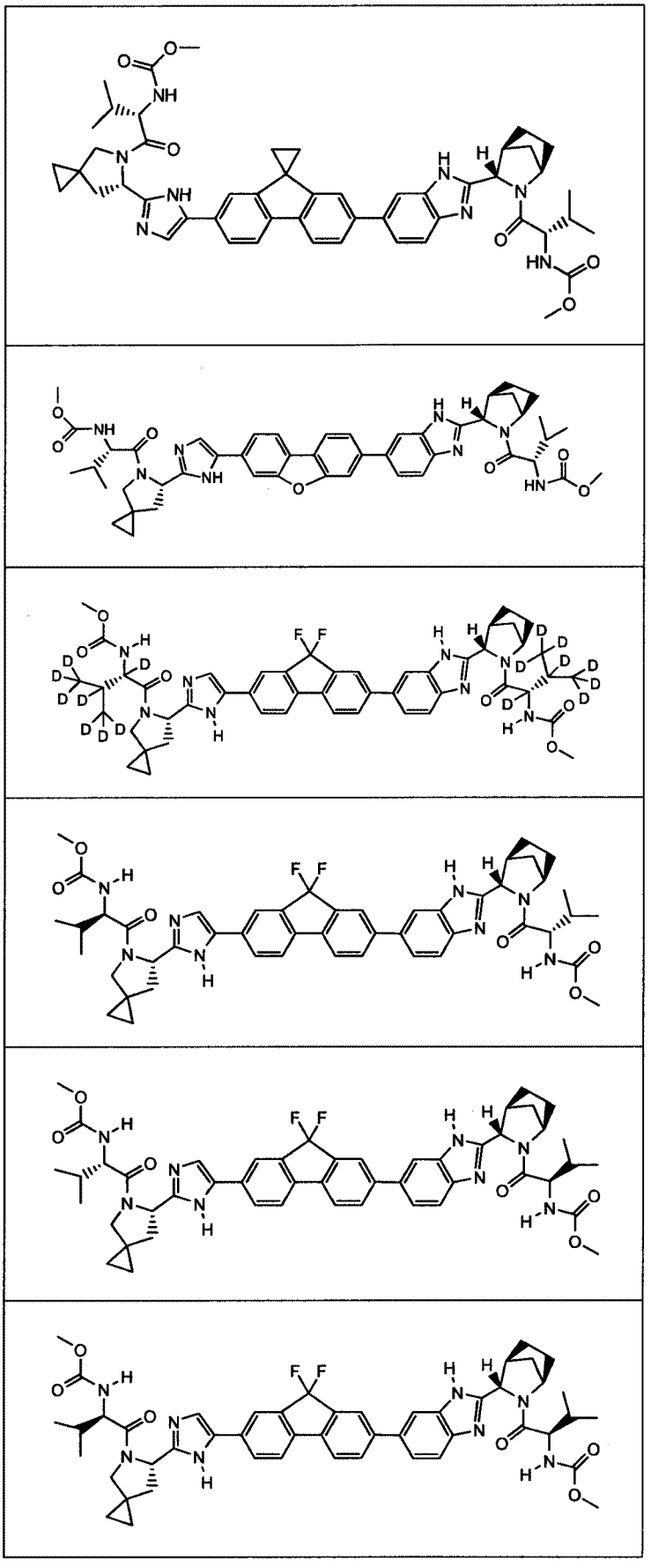



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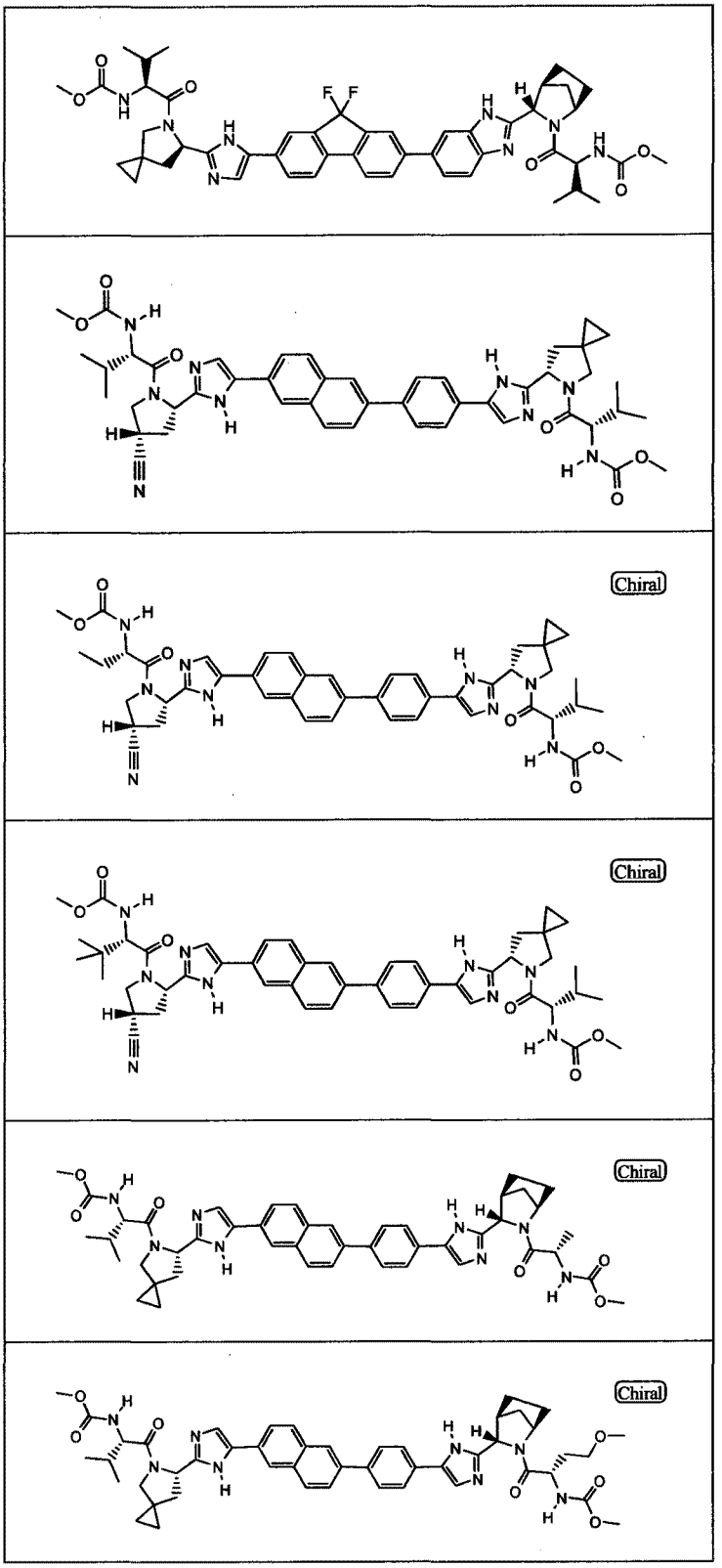



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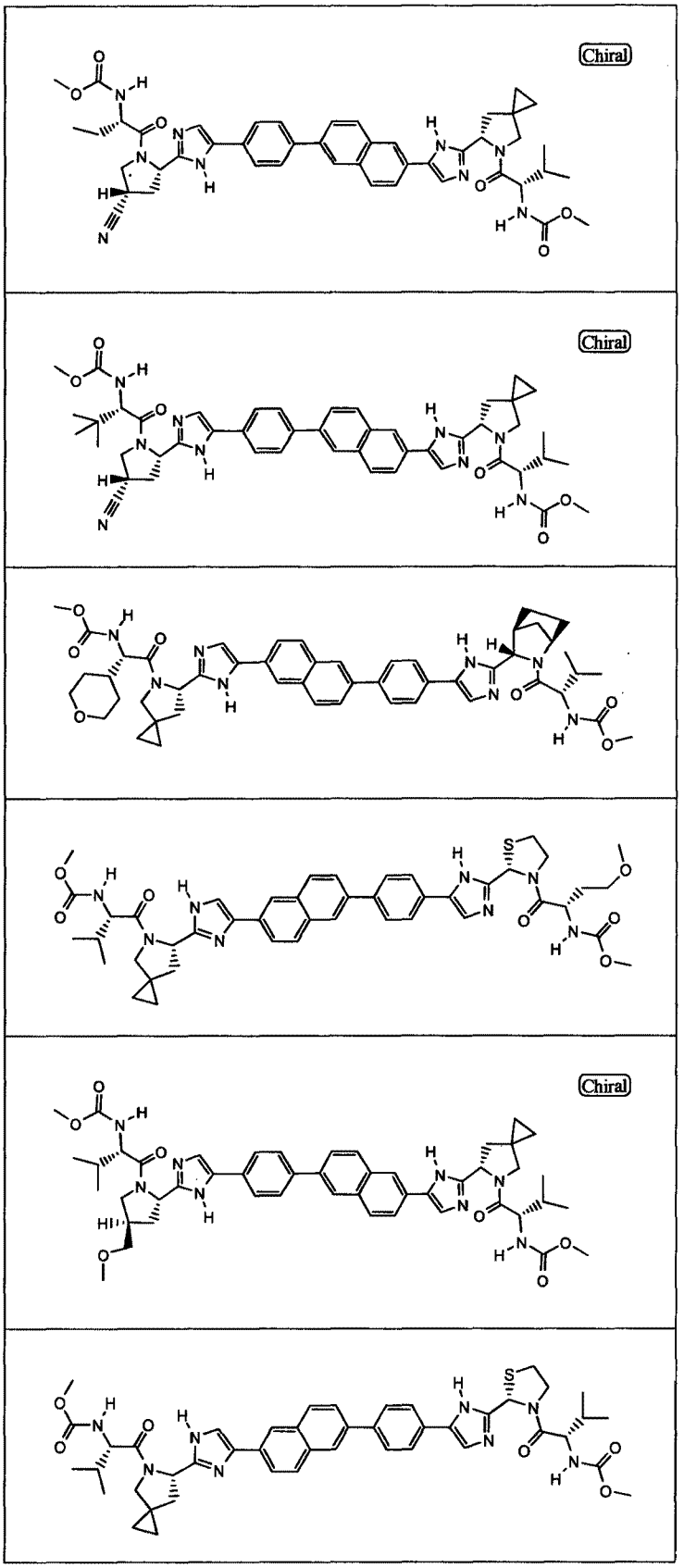




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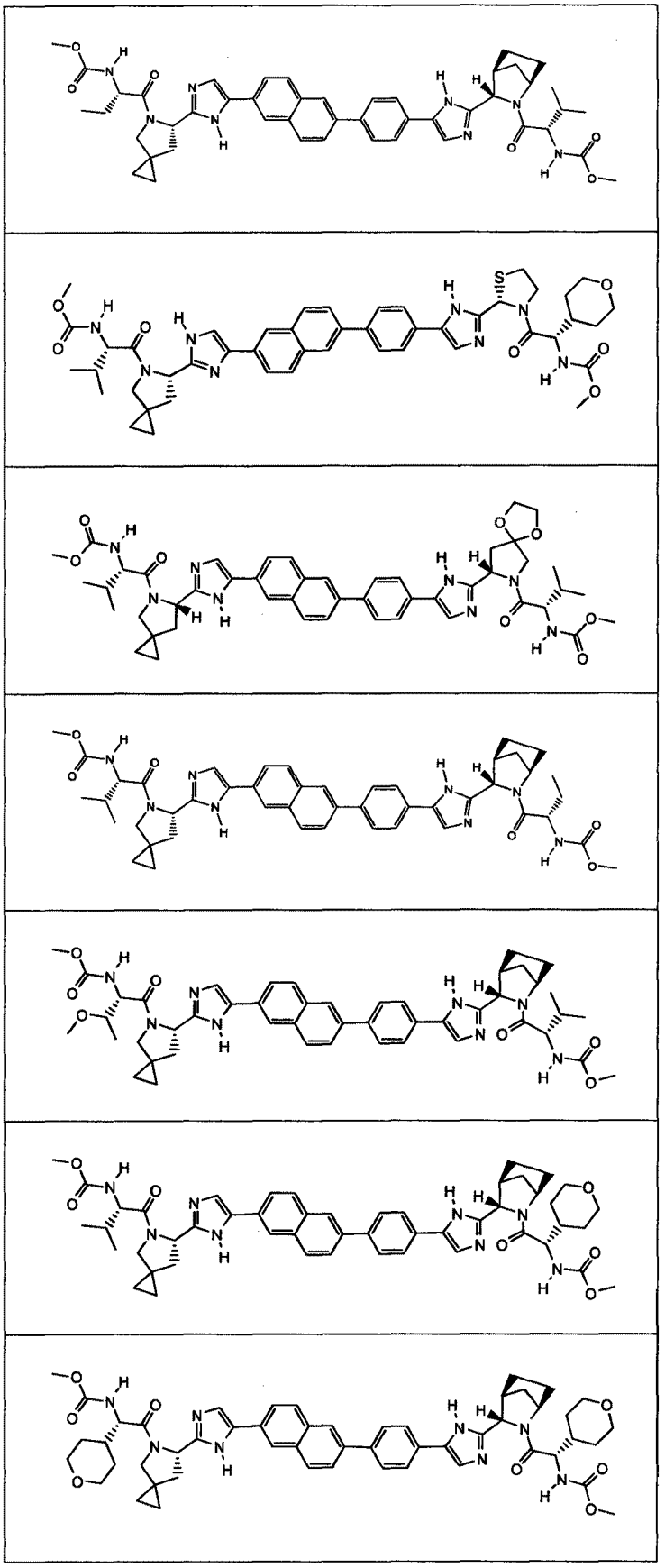



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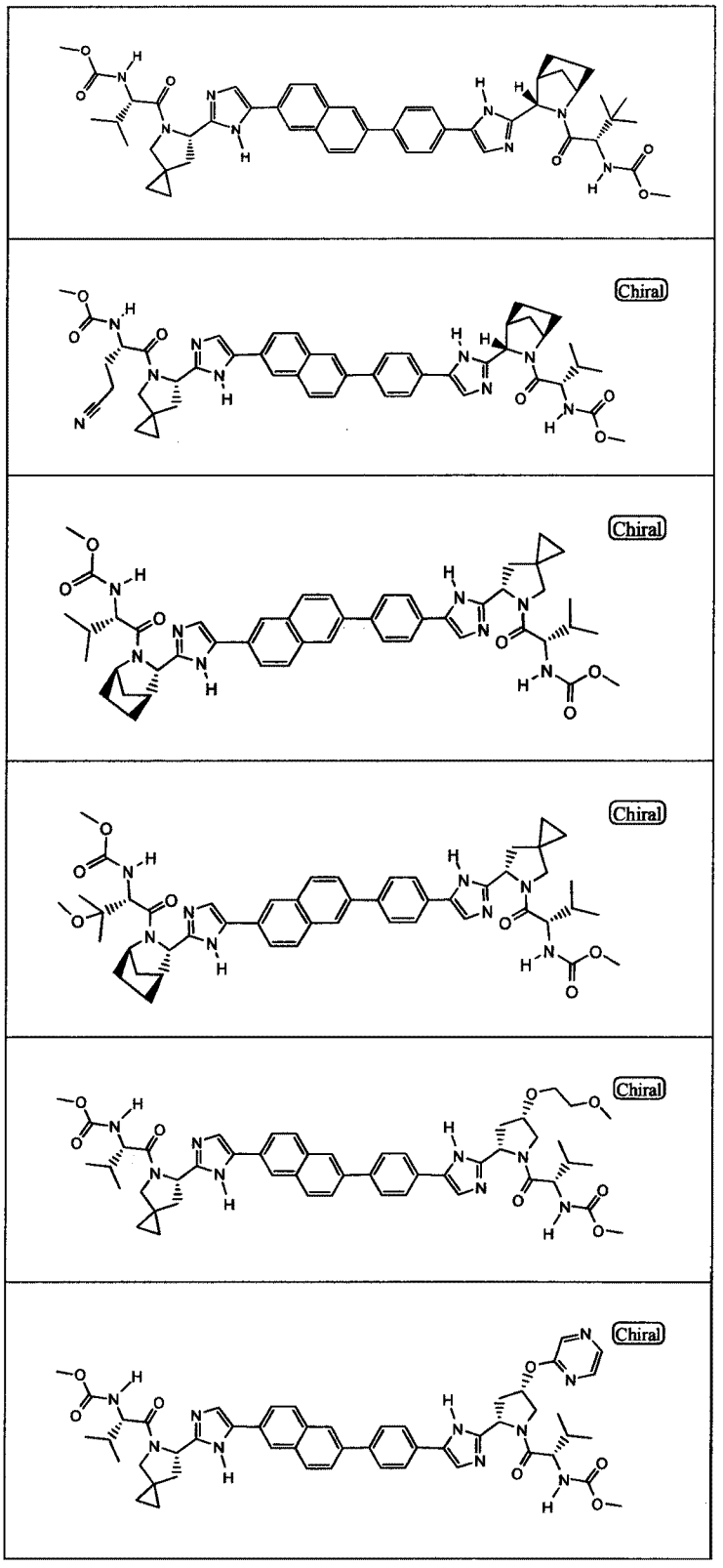



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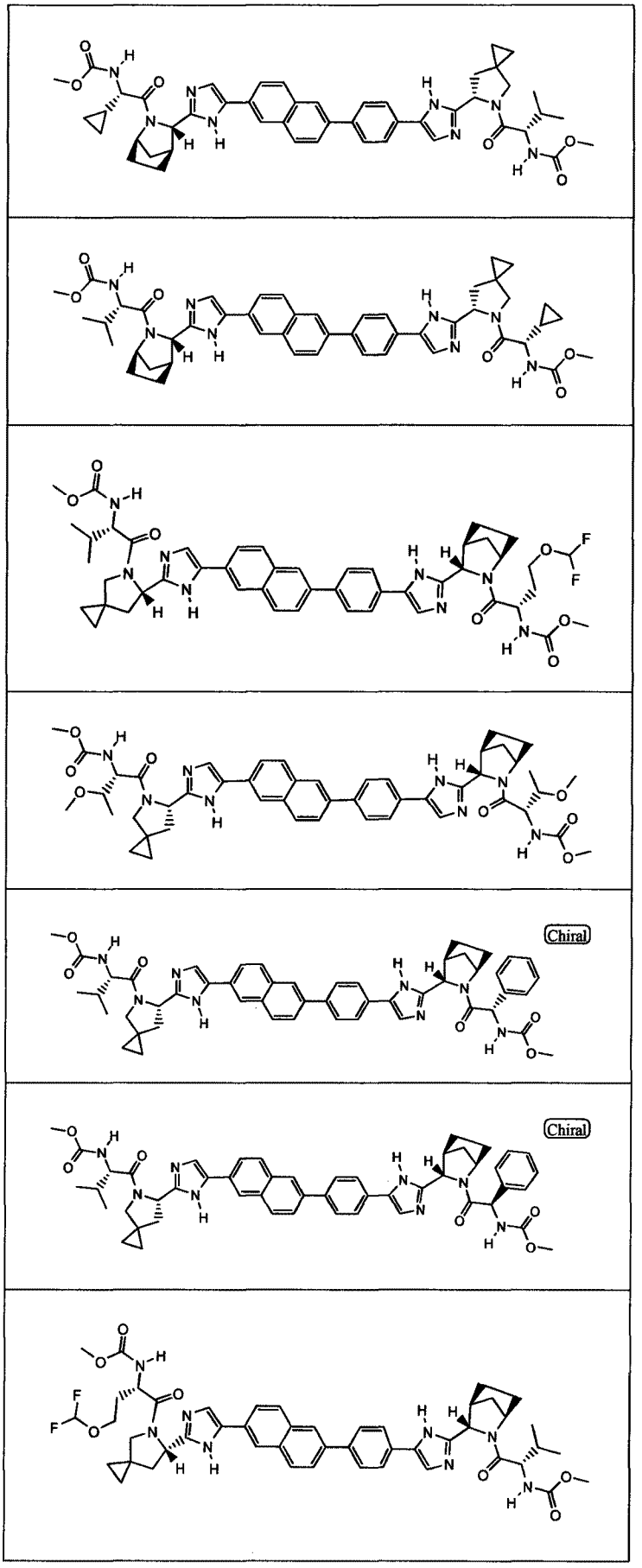




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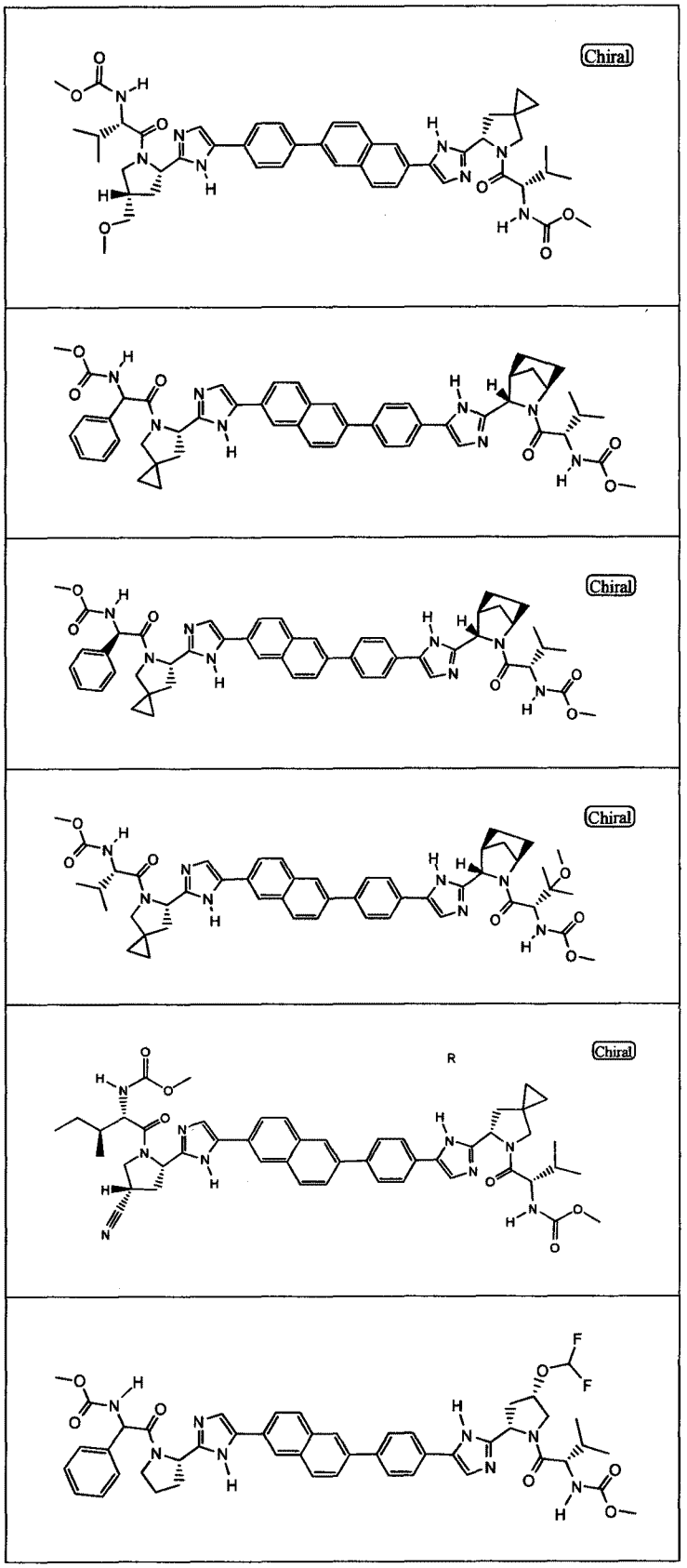




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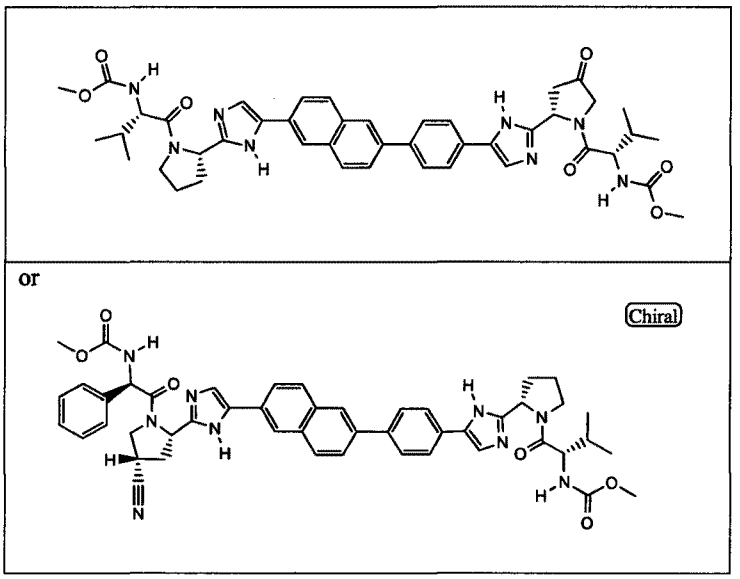


In one specific embodiment of the invention the compound of formula (I) is not:

| Compound |
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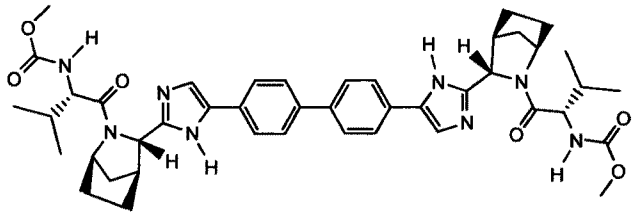
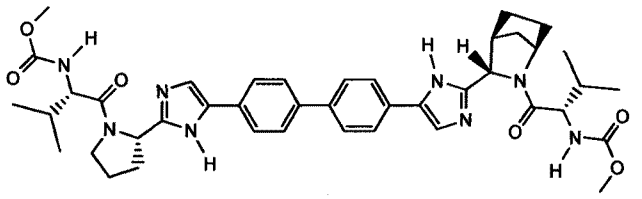
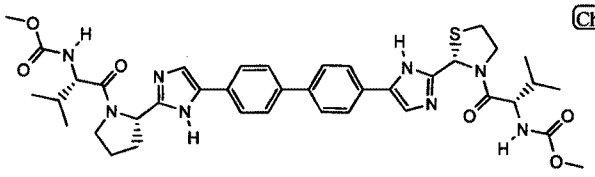
|  |
|  |
|  Chiral |



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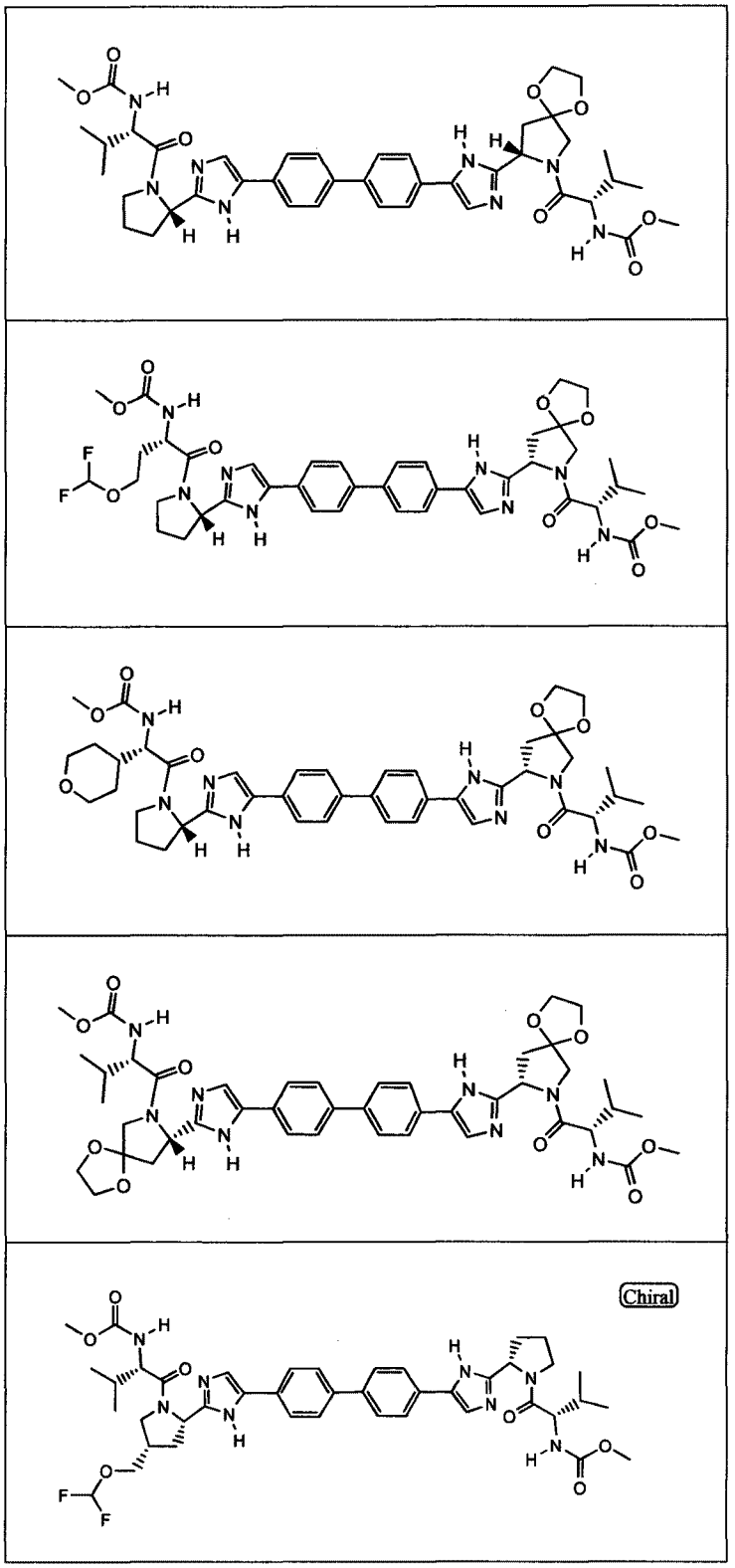




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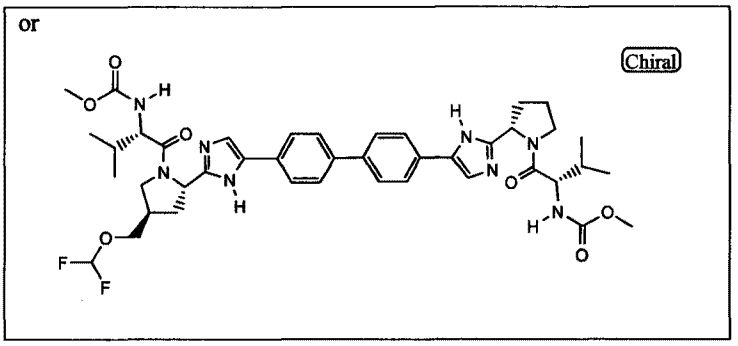


Methods of Inhibition of HCV

Another aspect of the invention relates to methods of inhibiting the activity of HCV comprising the step of treating a sample suspected of containing HCV with a compound or composition of the invention.

Compounds of the invention may act as inhibitors of HCV, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will generally bind to locations on the surface or in a cavity of the liver. Compounds binding in the liver may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compounds are useful as probes for the detection of HCV. Accordingly, the invention relates to methods of detecting NS3 in a sample suspected of containing HCV comprising the steps of: treating a sample suspected of containing HCV with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino. In one embodiment the invention provides a compound of any one of formulae (I)-(XIII) that comprises or that is bound or linked to one or more detectable labels. Within the context of the invention samples suspected of containing HCV include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.



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The treating step of the invention comprises adding the compound of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HCV after application of the compound can be observed by any method including direct and indirect methods of detecting HCV activity. Quantitative, qualitative, and semiquantitative methods of determining HCV activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Many organisms contain HCV. The compounds of this invention are useful in the treatment or prophylaxis of conditions associated with HCV activation in animals or in man.

However, in screening compounds capable of inhibiting HCV activity it should be kept in mind that the results of enzyme assays may not always correlate with cell culture assays. Thus, a cell based assay should typically be the primary screening tool.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which



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constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with



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a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a



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sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial



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esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable



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base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of conditions associated with HCV activity.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the



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active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provides compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

HCV Combination Therapy

In another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of

1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha-2b XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda-1 (PEGylated IL-29), and belerofon,



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2) ribavirin and its analogs, *e.g.*, ribavirin (Rebetol, Copegus), and taribavirin (Viramidine),

3) HCV NS3 protease inhibitors, *e.g.*, boceprevir (SCH-503034, SCH-7), telaprevir (VX-950), TMC435350, BI-1335, BI-1230, MK-7009, VBY-376, VX-500, GS-9256, GS-9451, BMS-790052, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, and ITMN-191,

4) alpha-glucosidase 1 inhibitors, *e.g.*, celgosivir (MX-3253), Miglitol, and UT-231B,

5) hepatoprotectants, *e.g.*, emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ,

6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.*, R1626, R7128 (R4048), IDX184, IDX-102, BCX-4678, valopicitabine (NM-283), and MK-0608,

7) non-nucleoside inhibitors of HCV NS5B polymerase, *e.g.*, PF-868554, VCH-759, VCH-916, JTK-652, MK-3281, GS-9190, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, and GS-9190,

8) HCV NS5A inhibitors, *e.g.*, AZD-2836 (A-831), BMS-790052, and A-689,

9) TLR-7 agonists, *e.g.*, imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), and SM-360320,

10) cyclophillin inhibitors, *e.g.*, DEBIO-025, SCY-635, and NIM811,

11) HCV IRES inhibitors, *e.g.*, MCI-067,

12) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin,

13) other drugs for treating HCV, *e.g.*, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, and VX-497 (merimepodib).

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin



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analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, levovirin, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of formula I and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of formula I may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, non-nucleoside inhibitors of HIV reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors,



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gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.,* capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.,* zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.,* tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.,* aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, levovirin, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689, and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626,



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PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating Hepatitis C, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20) RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, $C^{14}$ or $H^3$) compound of the invention, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV –inhibitory activity of their own.

Methods for determining stability of compounds in surrogate gastrointestinal secretions are known.



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Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing). Other methods suitable for preparing compounds of the invention are described in International Patent Application Publication Number WO 2006/020276.

A number of exemplary methods for the preparation of the compositions of the invention are provided in the schemes and examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and



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will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the Examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent



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selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113, 3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched substrate. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl



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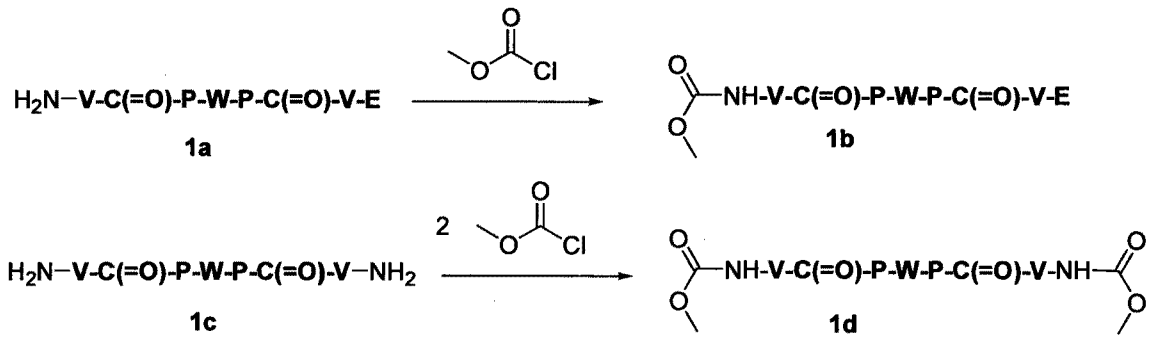
chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention. In the exemplary methods described herein, the fragment **E-V-** can also be written as **R9-**. PG represents a protecting group common for the given functional group that it is attached. The installation and removal of the protecting group can be accomplished using standard techniques, such as those described in Wuts, P. G. M., Greene, T. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2007.

**Scheme 1. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



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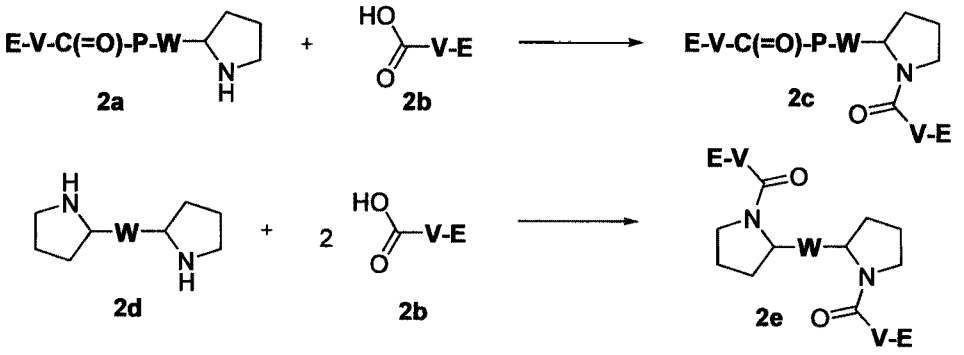
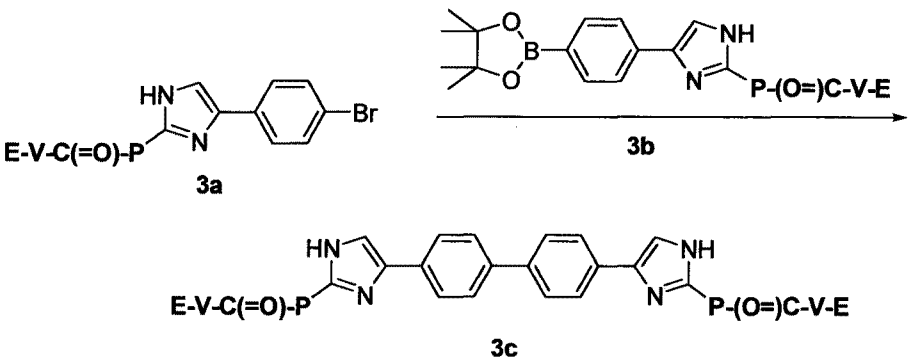
Scheme 1 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **1a** or **1c** with one or two equivalents respectively of methyl chloroformate under basic conditions (e.g. sodium hydroxide) provides the molecule **1b** or **1d**.

**Scheme 2. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**




Scheme 2 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine. Coupling of amine **2a** with acid **2b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **2c**. Alternatively, amine **2d** is coupled with two equivalents of **2b** under similar conditions to provide **2e**.

**Scheme 3. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**




Scheme 3 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **W** is a four aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **3b**



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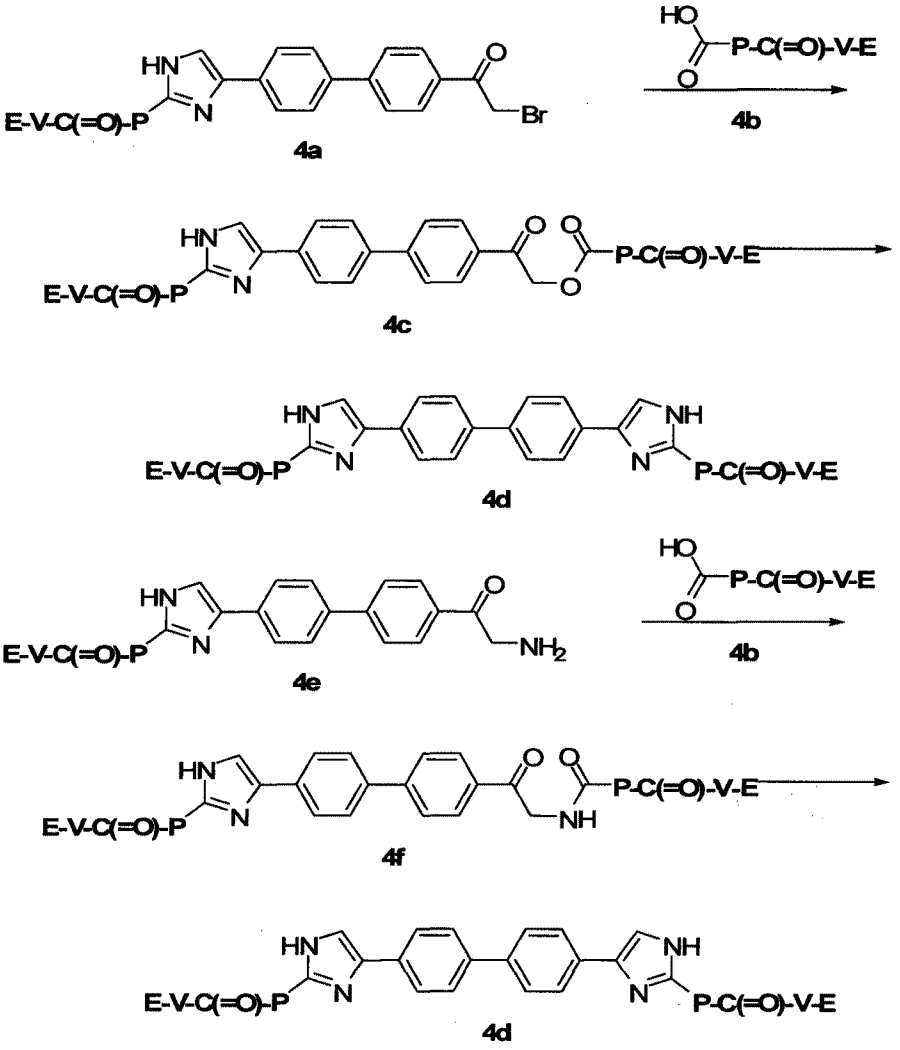
is coupled with an appropriate coupling partner (e.g. **3a**) using a palladium catalyst, such as Pd(PPh3)4, to afford **3c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings.

**Scheme 4. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



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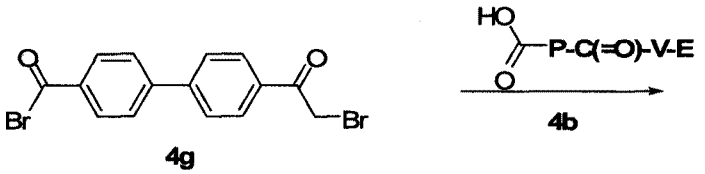
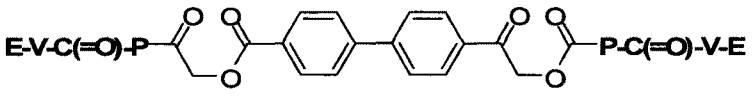
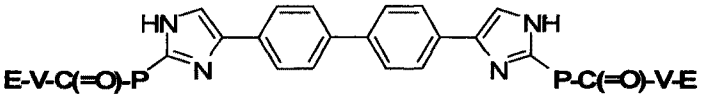



4g 4b




4h

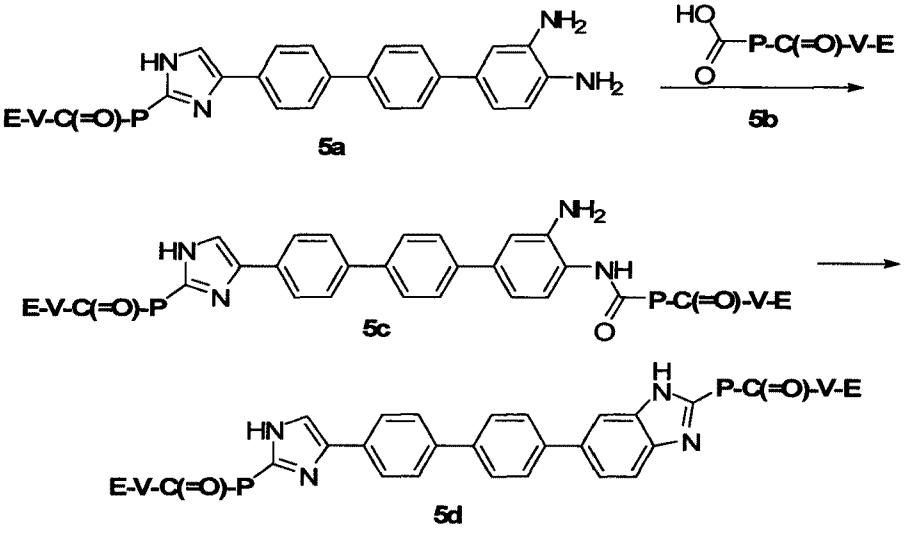



4d

Scheme 4 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **W** is a four aromatic ring unit constructed by the formation of a substituted imidazole ring. The formation of the imidazole is accomplished by coupling the acid **4b** with an α-haloketone, such as α-bromoketone **4a,** under basic conditions (e.g. $Et_3N$) to afford **4c**. Alternatively, the acid **4b** is coupled with an α-aminoketone **4e,** under amide formation conditions (e.g. EDC, $Et_3N$) to afford **4f**. Reaction of **4c** or **4f** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **4d**.

The formation of multiple imidazoles is performed in the same manner, starting with a bis- α-haloketone such as α-bromoketone **4g,** to provide molecule **4d**.

**Scheme 5. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



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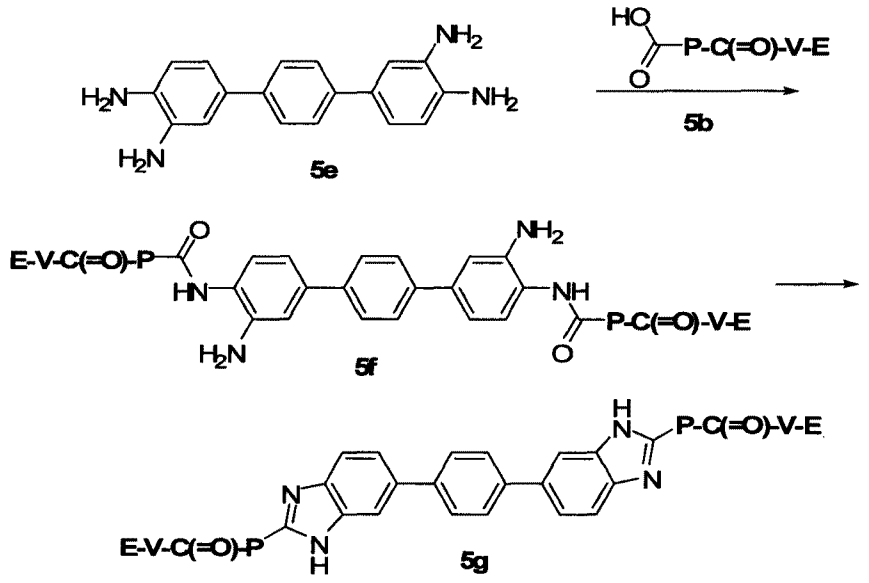
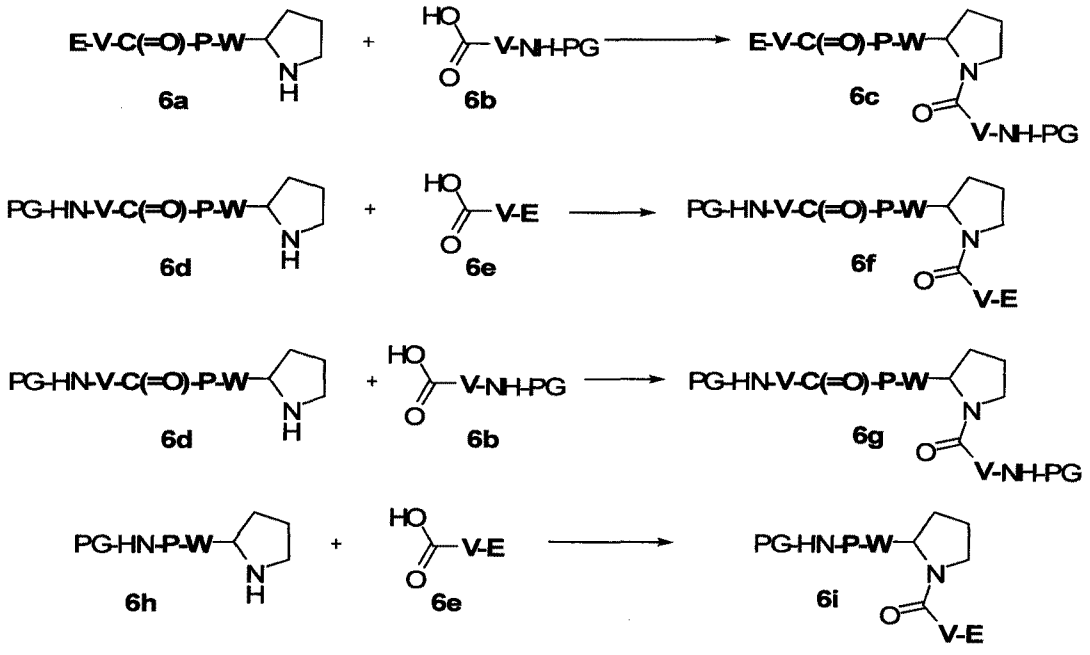



Scheme 5 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **W** is a three or four aromatic ring unit constructed by the formation of a substituted benzimidazole ring. The formation of the benzimidazole is accomplished by coupling the acid **5b** with an arylamine **5a**, using a peptide coupling reagent such as HATU, to afford **5c**. Cyclization of the amide **5c** in the presence an acid (such as acetic acid) affords the benzimidazole containing molecule **5d**.

The formation of multiple benzimidazoles is performed in the same manner, starting with a bis-diamine such as **5f**, to provide molecule **5g**.

**Scheme 6. Representative synthesis of $R^1$-V-C(=O)-P-$R^2$**



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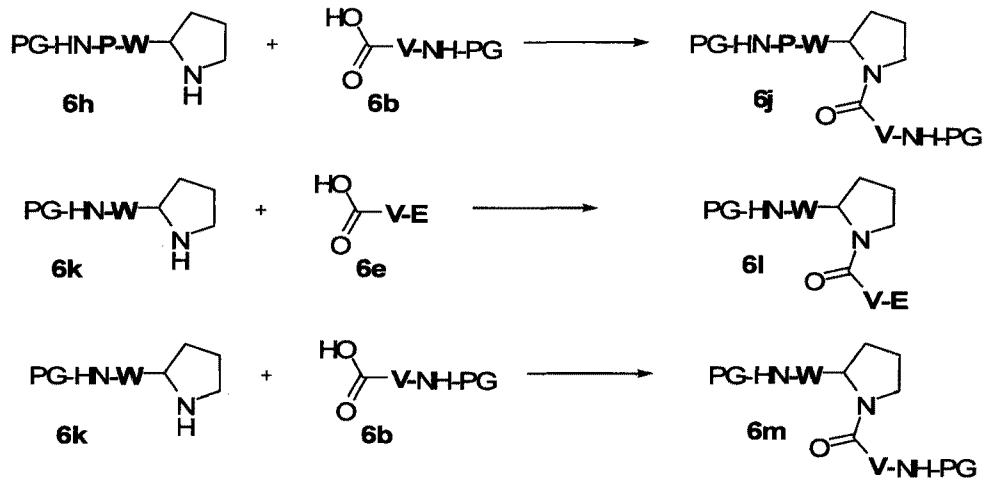
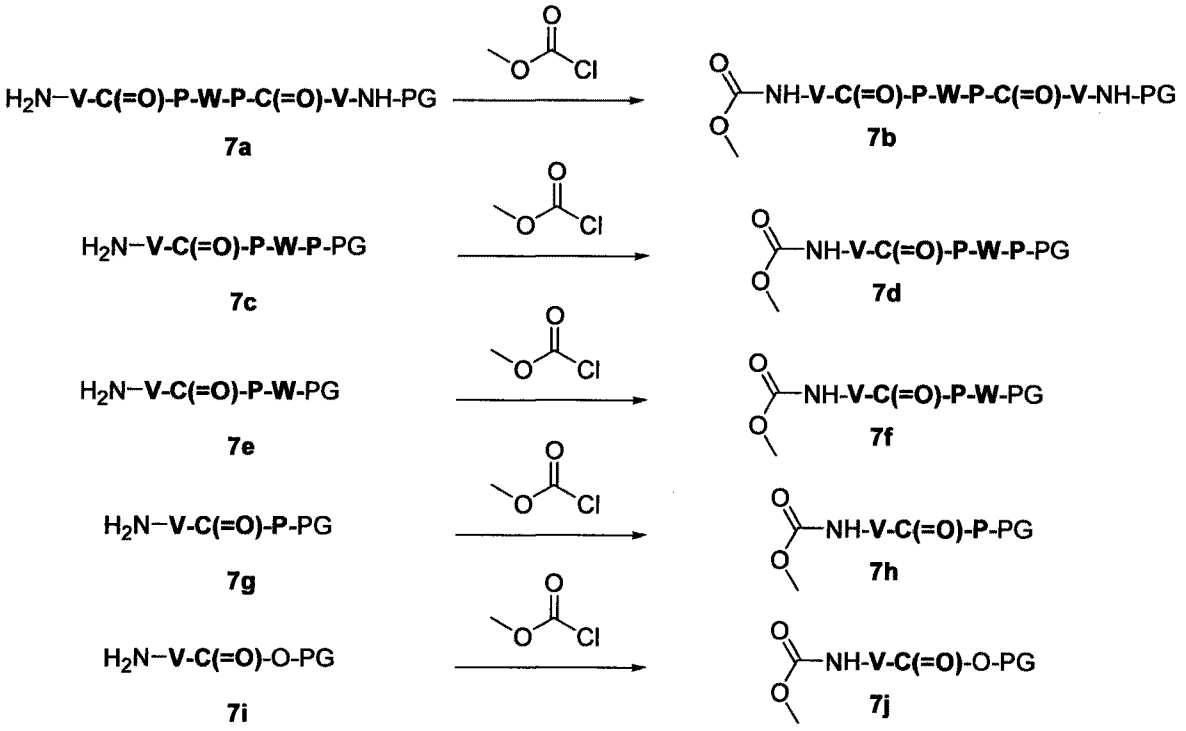



Scheme 6 shows a general synthesis of an $R^1$-**V-C(=O)-P-**$R^2$ intermediate wherein, for illustrative purposes, **P** is pyrrolidine, $R^1$ is a generic group that is depicted as either -**E** or a amino protecting group, and $R^2$ is a generic group that is depicted as -**W-P-C(=O)-V-E**, -**W-P-C(=O)-V**-NH-PG, -**W-P**-NH-PG, or -**W**-NH-PG. Coupling of amine **6a** (or **6d**, **6h**, **6k**) with acid **6b** or **6e** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **6c** (or **6f**, **6g**, **6i**, **6j**, **6l**, **6m**) respectively.

**Scheme 7. Representative synthesis of E-V-C(=O)-$R^1$**



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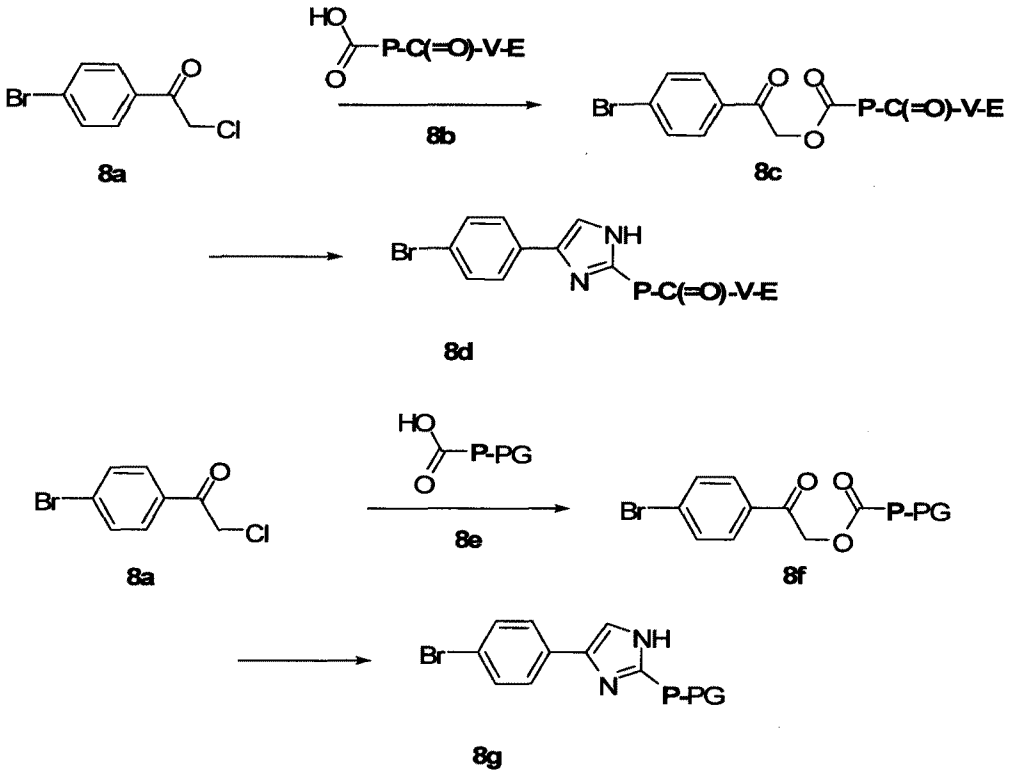
Scheme 7 shows a general synthesis of an **E-V-C(=O)-**$R^1$ intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and $R^1$ is a generic group that is depicted as either **-P-W-P-C(=O)-V**-NH-PG, **-P-W-P**-PG, **-P-W**-PG, **-P**-PG, or -O-PG. Treatment of **7a** (or **7c**, **7e**, **7g**, **7i**) with methyl chloroformate under basic conditions (e.g. sodium hydroxide) provides the molecule **7b** (or **7d**, **7f**, **7h**, **7j**).

**Scheme 8. Representative synthesis of** $R^1$**-P-**$R^2$



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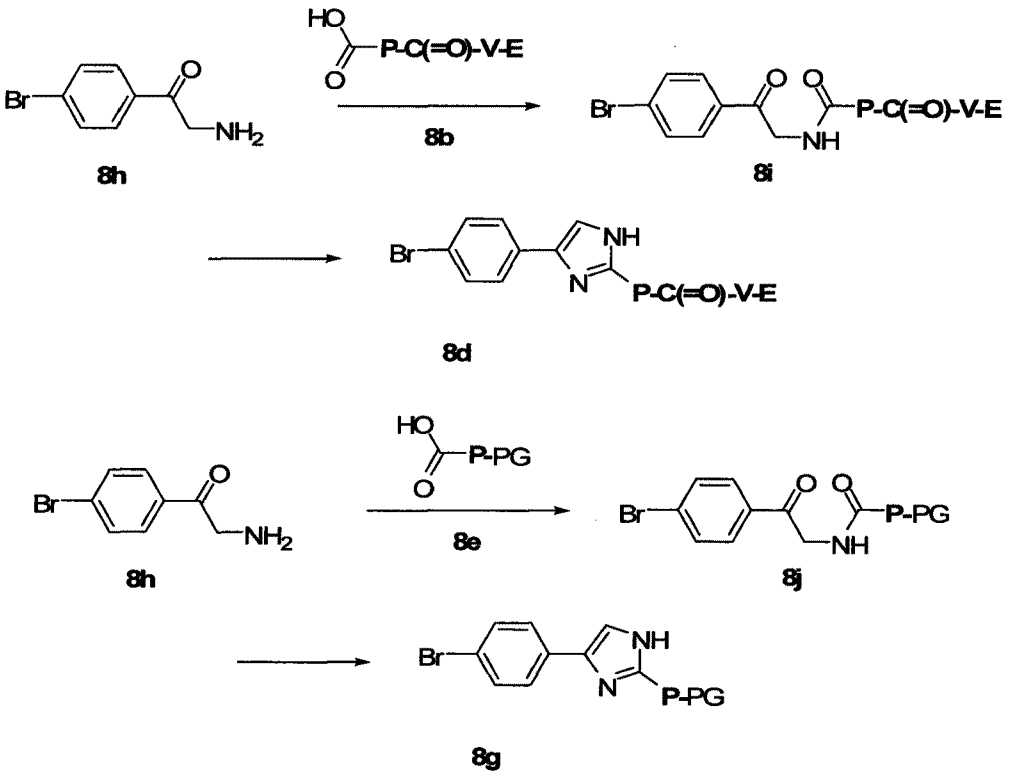


Scheme 8 shows a general synthesis of an $R^1$-**P**-$R^2$ intermediate wherein, for illustrative purposes, $R^1$ is **-C(=O)-V-E** or a protecting group and $R^2$ is a substituted imidazole. The formation of the imidazole is accomplished by coupling the acid **8b** or **8e** with an α-haloketone, such as α-chloroketone **8a,** under basic conditions (e.g. $Et_3N$) to afford **8c** or **8f**. Alternatively, the acid **8b** or **8e** is coupled with an α-aminoketone **8h,** under amide formation conditions (e.g. EDC, $Et_3N$) to afford **8i** or **8j**. Reaction of **8c** (or **8f**, **8i**, **8j**) with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **8d** or **8g**.

The formation of multiple imidazoles is performed in the same manner, starting with a bis-α-haloketone to provide the corresponding bis-imidazole.



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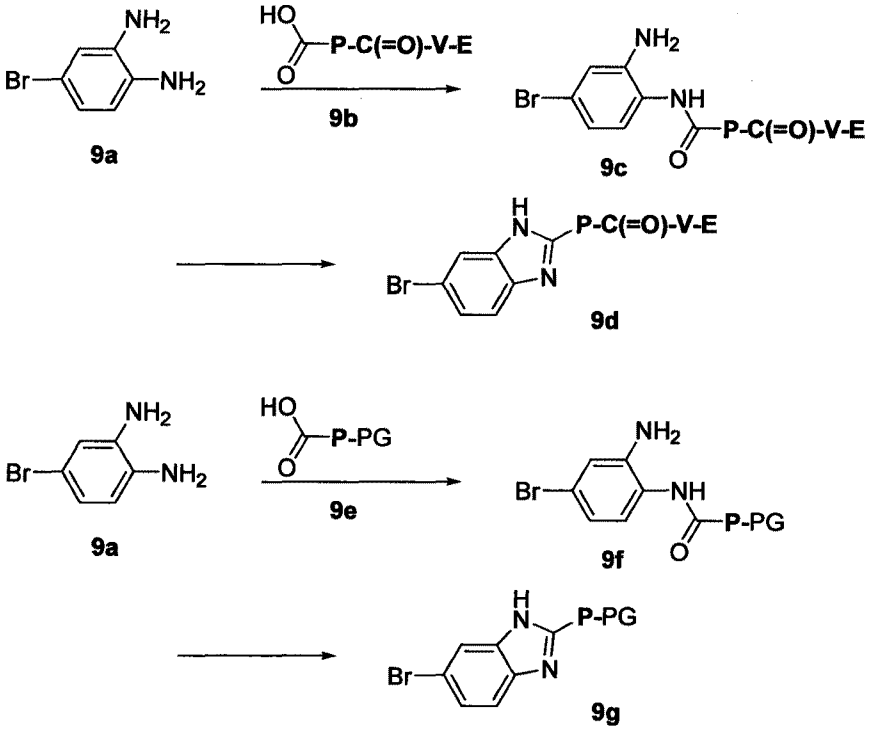
**Scheme 9. Representative synthesis of $R^1$-P-$R^2$**




Scheme 9 shows a general synthesis of an $R^1$-**P**-$R^2$ intermediate wherein, for illustrative purposes, $R^1$ is -**C(=O)-V-E** or a protecting group and $R^2$ is a substituted benzamidazole. The formation of the benzimidazole is accomplished by coupling the acid **9b** or **9e** with an arylamine **9a**, using a peptide coupling reagent such as HATU, to afford **9c** or **9d**. Cyclization of the amide in the presence an acid (such as acetic acid) affords the benzimidazole containing molecule **9d** or **9g**.

The formation of multiple benzimidazoles is performed in the same manner, starting with a bis-diamine to provide the corresponding bis-benzamidazole.



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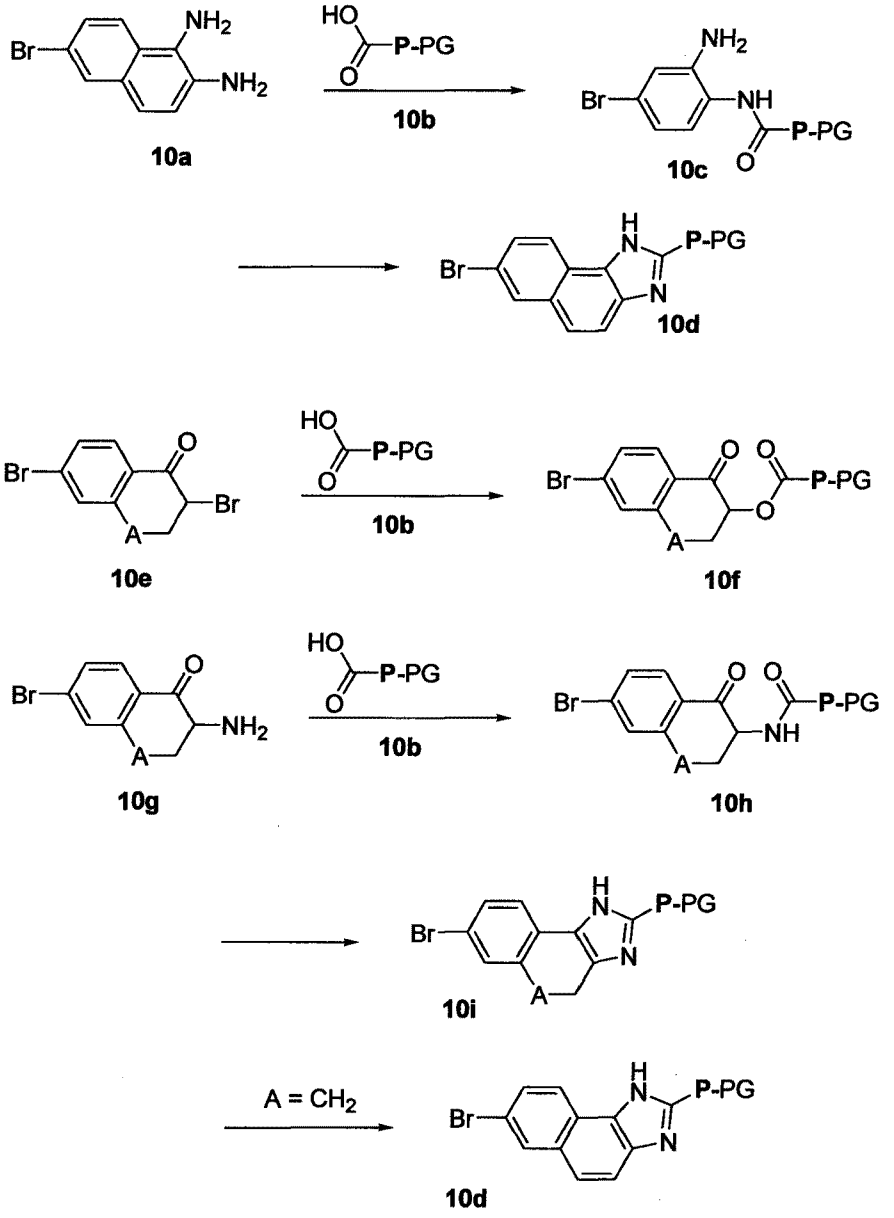
**Scheme 10. Representative synthesis of $R^1$-P-$R^2$**




Scheme 10 shows a general synthesis of an $R^1$-**P**-$R^2$ intermediate wherein, for illustrative purposes, $R^1$ is a protecting group and $R^2$ is a substituted naphthamidazole. The formation of the naphthamidazole is accomplished by coupling the acid **10b** with an arylamine **10a**, using a peptide coupling reagent such as HATU, to afford **10c**. Cyclization of the amide in the presence an acid (such as acetic acid) affords the benzimidazole containing molecule **10d**.

The naphthamidazole can also be accomplished by coupling the acid **10b**, where A represents O or $CH_2$, with an α-haloketone, such as α-bromoketone **10e,** under basic conditions (e.g. $Et_3N$) to afford **10f**. Alternatively, the acid **8b** is coupled with an α-aminoketone **10g,**



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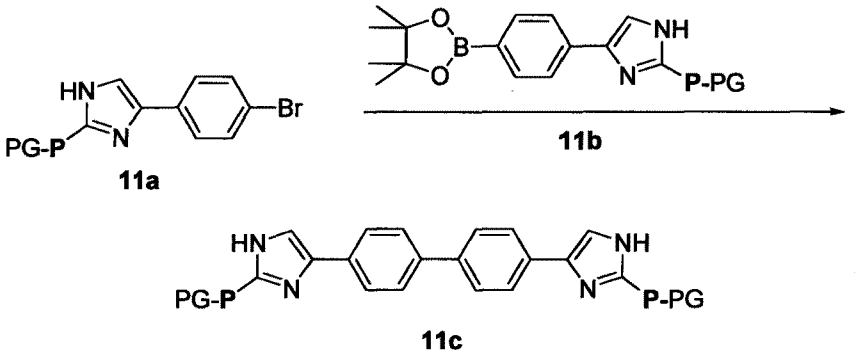
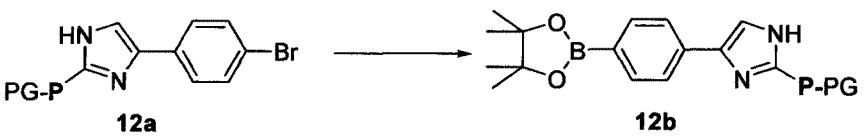
under amide formation conditions (e.g. EDC, $Et_3N$) to afford **10h**. Reaction of **10f** or **10h** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **10i**. When A is $CH_2$, oxidation of **10i** to **10d** can be accomplished by heating in the presence of $MnO_2$.

**Scheme 11. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 11 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a four aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **11b** is coupled with an appropriate coupling partner (e.g. **11a**) using a palladium catalyst, such as Pd(PPh3)4, to afford **11c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings.

**Scheme 12. Representative synthesis of $R^1$-P-$R^2$**




Scheme 12 shows a general synthesis of an $R^1$-**P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ is a generic group that is depicted as a protecting group and $R^2$ is a generic group that is depicted as an aryl boronic ester. A transition metal-mediated



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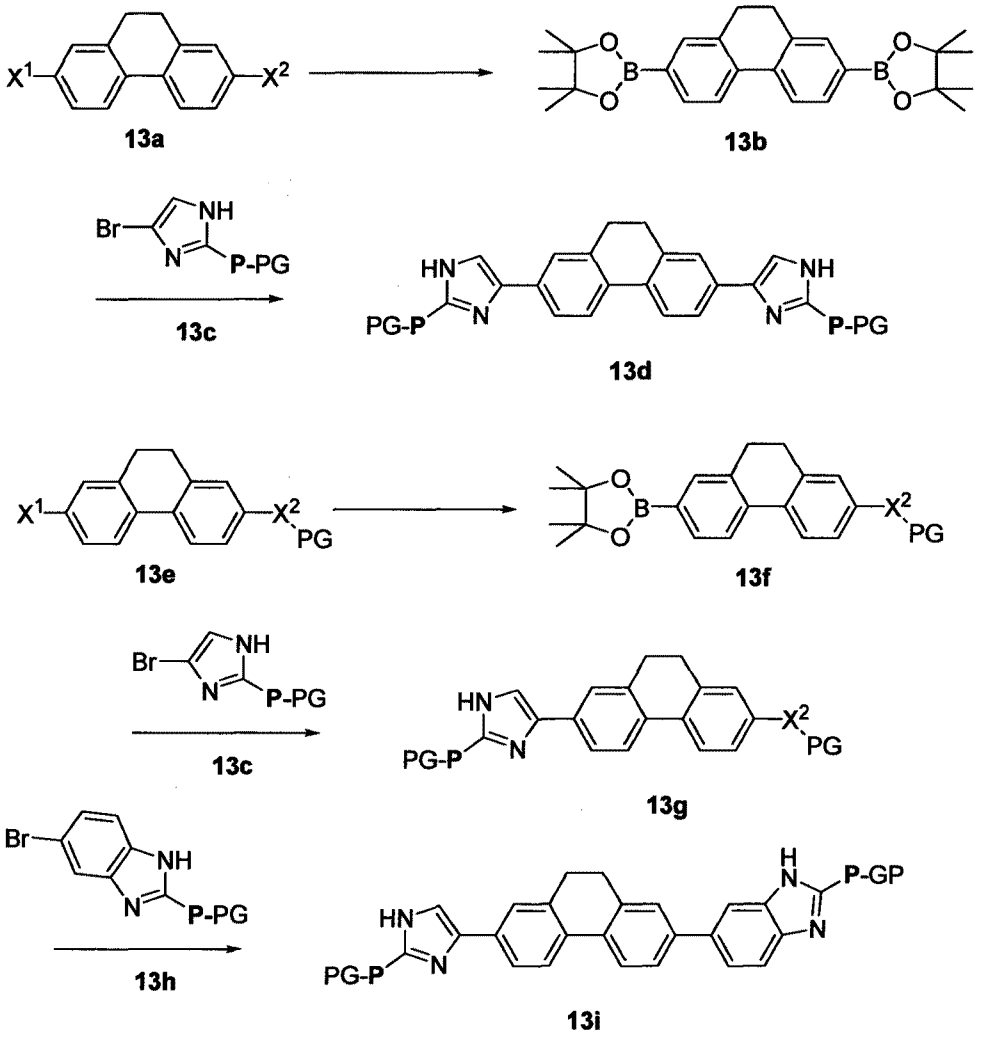
cross-coupling reaction is utilized to install the boronic ester. Treatment of the corresponding aryl bromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diboron provides the boronic ester **12b**.

**Scheme 13. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 13 shows a general synthesis of an $R^1$-P-W-P-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a three aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, **W** is constructed from a tricyclic aromatic ring, wherein $X^1$ and $X^2$ are independent halogens or halogen equivalents that may be suitably protected. For illustrative purposes, a transition metal-mediated cross-coupling reaction is utilized to install the boronic ester and the Suzuki reaction is employed to couple the boronic ester to a heteroarylbromide. Treatment of the **13a** or **13e** with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source



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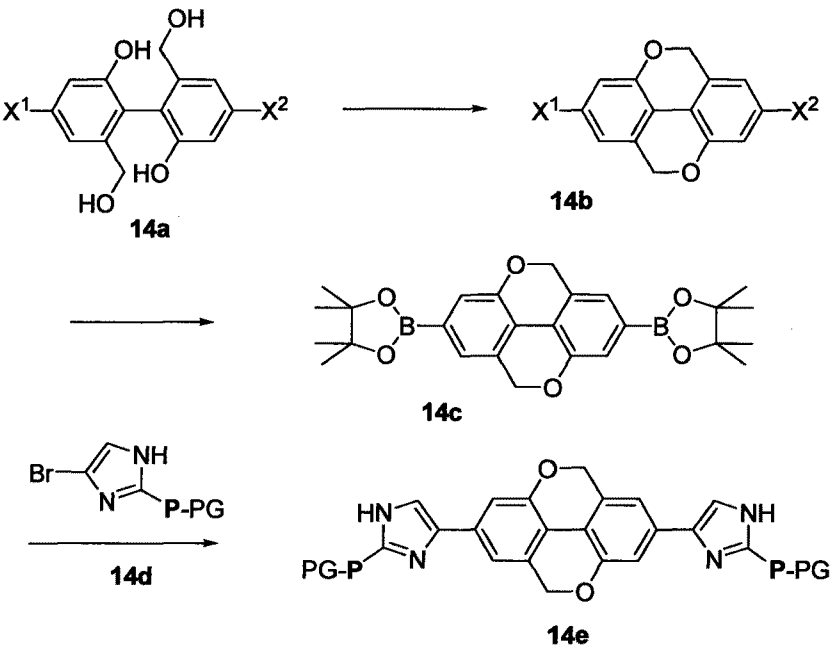
such as bis(pinacolato)diboron provides the boronic ester **13b** or **13f**. The boronic ester is coupled with an appropriate coupling partner (e.g. **13c** or **13h**) using a palladium catalyst, such as Pd(PPh3)4, to afford **13d** or **13i**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings.

**Scheme 14. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 14 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a three aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, **W** is constructed from a tetracyclic aromatic ring, wherein $X^1$ and $X^2$ are independent halogens or halogen equivalents that may be suitably protected. The construction of the tetracyclic compound **14b** can be accomplished from a suitably functionalized biphenyl intermediate (e.g. **14a**) by activation with $PBr_3$ followed by treatment with a base, such as cesium carbonate. For illustrative purposes, a transition metal-mediated cross-coupling reaction is utilized to install the boronic ester and the Suzuki reaction is employed to couple the boronic ester to a heteroarylbromide. Treatment of the **14b** with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diboron provides the boronic ester **14c**.



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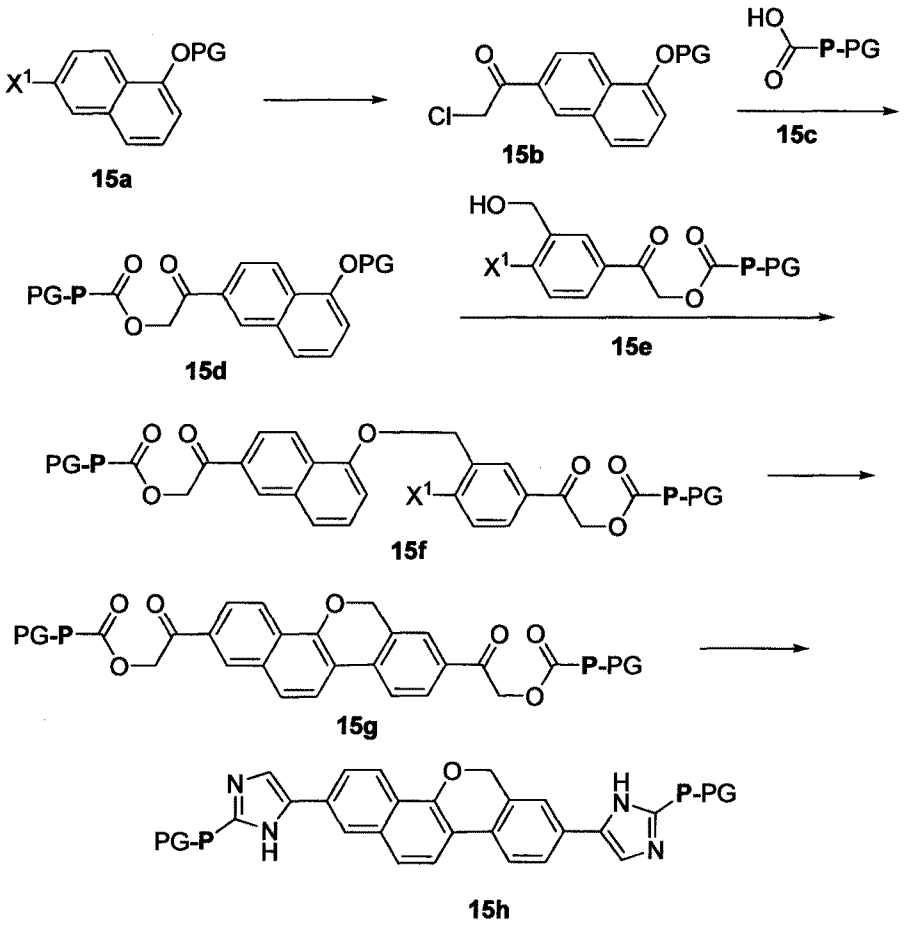
The boronic ester is coupled with an appropriate coupling partner (e.g. **14d**) using a palladium catalyst, such as Pd(PPh3)4, to afford **14e**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings.

**Scheme 15. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 15 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a three aromatic ring unit constructed via a transition metal mediated cyclization. For illustrative purposes, **W** includes a tetracyclic aromatic ring. Metalation of **15a** with either *n*-BuLi or *i*-PrMgCl, followed by treatment with 2-Chloro-N-methoxy-N-methyl-acetamide provides the α-haloketone **15b**. Treatment with an acid, such as **15c**, under basic conditions (e.g. $Et_3N$) provides the ester **15d**. Activation of **15e**, and treatment with **15d**, under basic conditions



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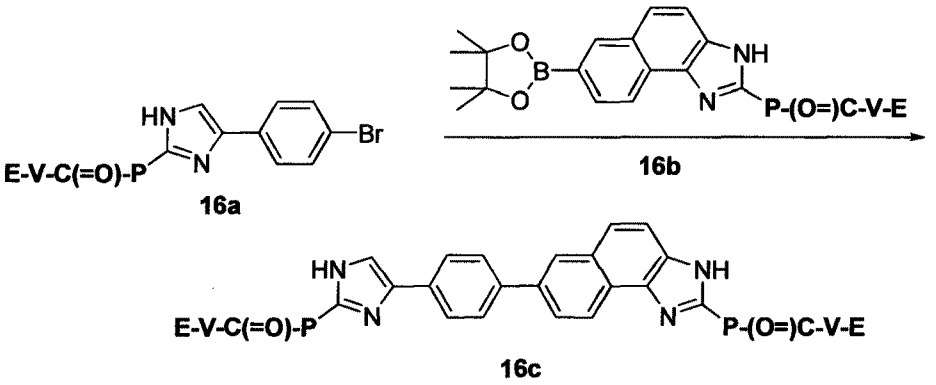
provides the ether **15f**. Cyclization in the presence of a transition metal catalyst, such as $Pd(OAc)_2$ provides **15g**. Reaction of **15g** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **15h**.

**Scheme 16. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**




Scheme 16 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **W** is a three aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **16b** is coupled with an appropriate coupling partner (e.g. **16a**) using a palladium catalyst, such as Pd(PPh3)4, to afford **16c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate three aromatic ring containing **W** groups, this general scheme can be applied through the choice of the appropriate cross coupling partners and reagents.



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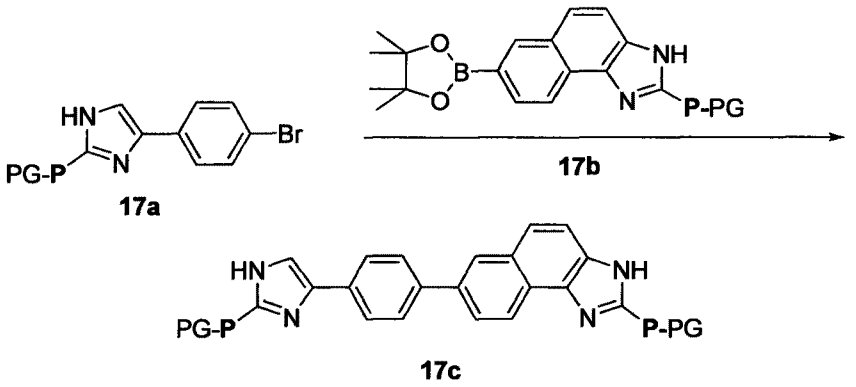
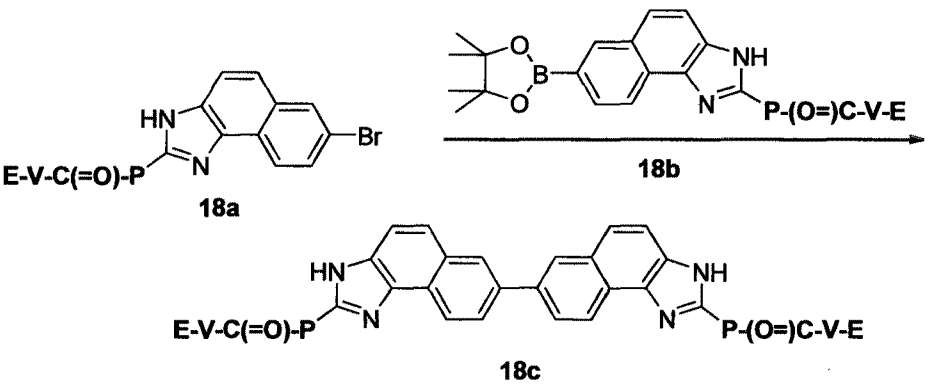
**Scheme 17. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 17 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a three aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **17b** is coupled with an appropriate coupling partner (e.g. **17a**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **17c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate three aromatic ring containing **W** groups, this general scheme can be applied through the choice of the appropriate cross coupling partners and reagents.

**Scheme 18. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



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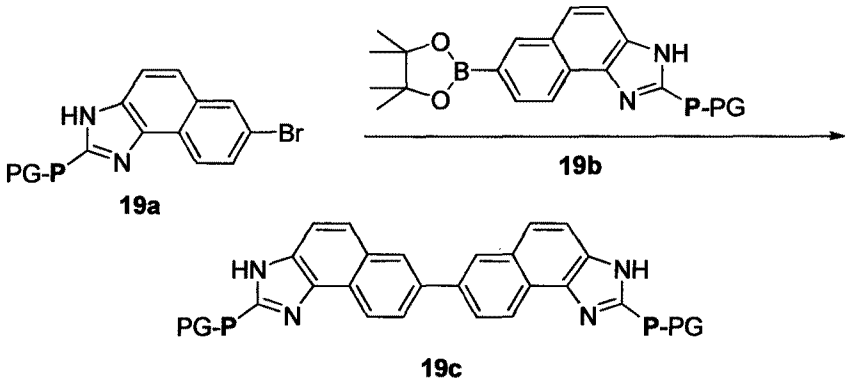
Scheme 18 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **W** is a two aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **18b** is coupled with an appropriate coupling partner (e.g. **18a**) using a palladium catalyst, such as Pd(PPh3)4, to afford **18c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate two aromatic ring containing **W** groups, this general scheme can be applied through the choice of the appropriate cross coupling partners and reagents.

**Scheme 19. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 19 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to either an aryl- or heteroarylbromide. Boronic ester **19b** is coupled with an appropriate coupling partner (e.g. **19a**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **19c**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate two aromatic ring containing **W** groups, this general scheme can be applied through the choice of the appropriate cross coupling partners and reagents.



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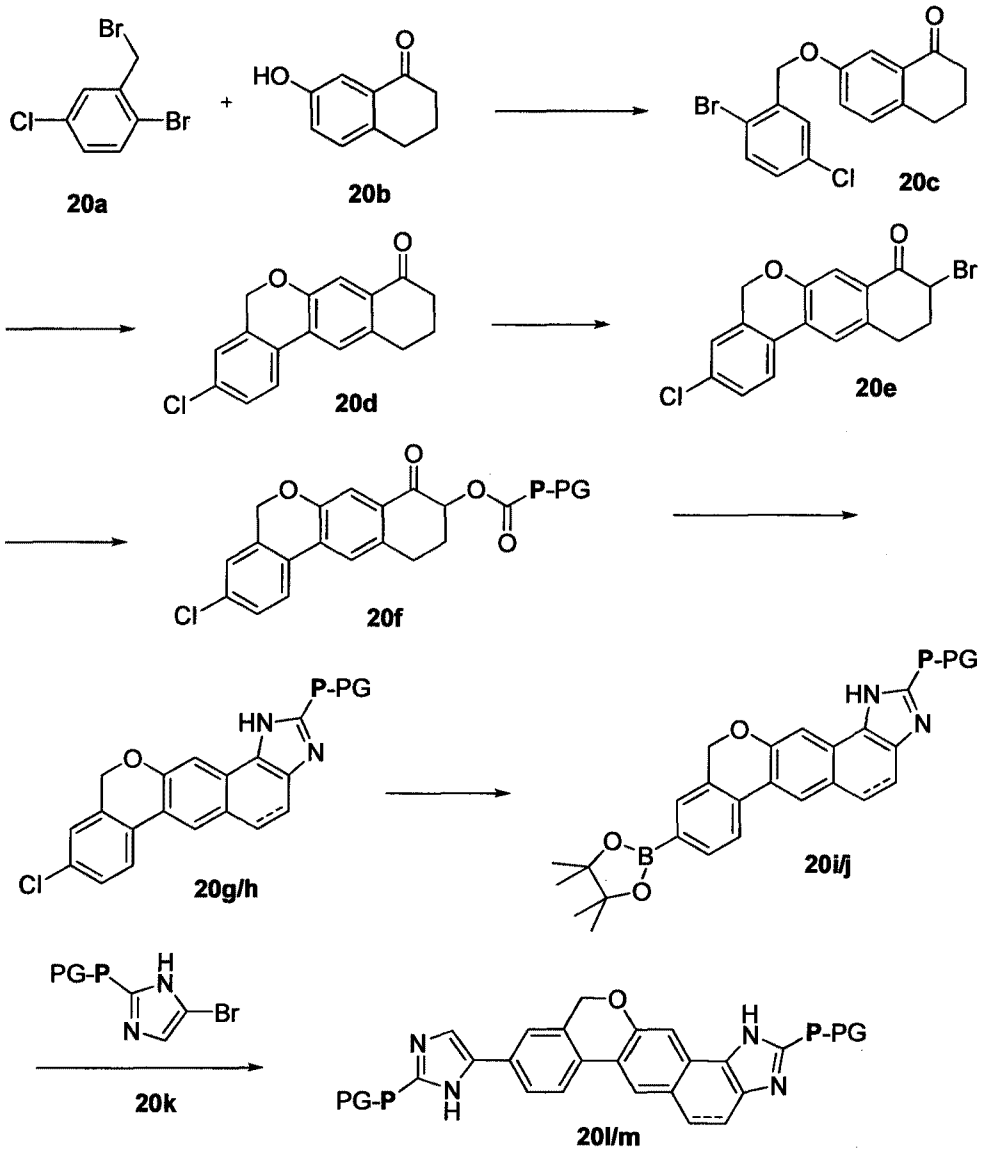
**Scheme 20. Representative synthesis of $R^1$-P-W-P-$R^2$**




Scheme 20 shows a general synthesis of an $R^1$-**P-W-P-**$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cyclization. Alkylation of phenol **20b** with an alkyl bromide, such as **20a**, provides the ether **20c**. Cyclization of the aromatic rings in the presence of a palladium catalyst provides the compound **20d**. Treatment of **20d** with $CuBr_2$ provides the α-haloketone **20e**, which provides **20f** upon addition of an acid under basic conditions (e.g. $Et_3N$). Reaction of **20f** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **20g**. Oxidation of **20g**, **20i**, or **20l** can be



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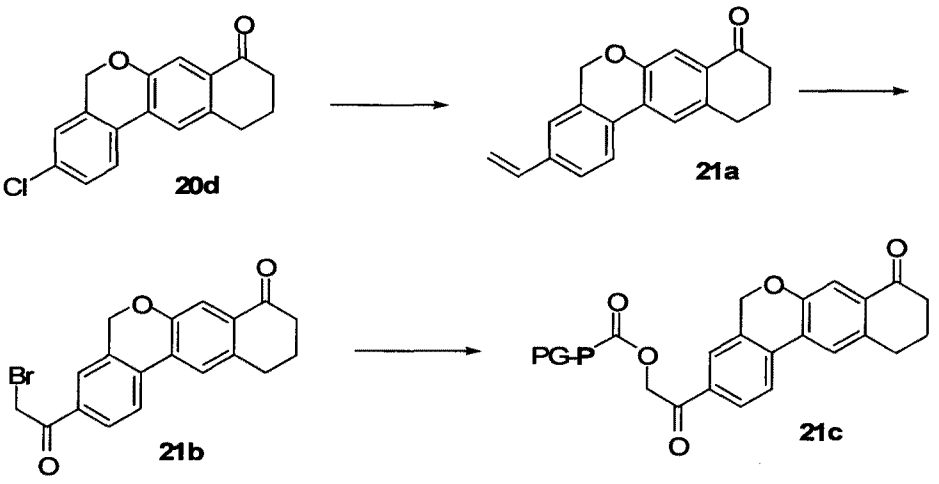
accomplished by heating in the presence of $MnO_2$ to provide **20h**, **20j**, or **20m**, respectively. Conversion of **20g** or **20h** with a palladium catalyst, such as $Pd_2dba_3$ and X-Phos, and a boron source such as bis(pinacolato)diboron provides the boronic ester **20i** or **20j**. The boronic ester is coupled with an appropriate coupling partner (e.g. **20k**) using a palladium catalyst, such as $Pd(PPh_3)_4$ or $PdCl_2(dppf)$, to afford **20l** or **20m**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate two aromatic ring containing **W** groups, this general scheme can be applied through the appropriate choice of the starting reagents.

**Scheme 21. Representative synthesis of $R^1$-P-W-P-$R^2$**



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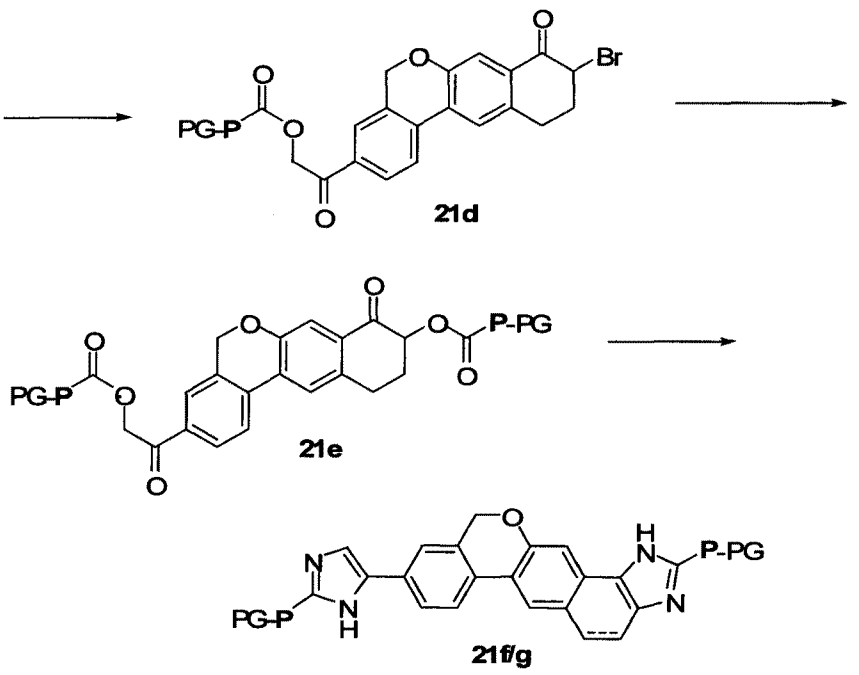


Scheme 21 shows a general synthesis of an $R^1$-**P**-**W**-**P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cyclization. Treatment of **20d** with an activated vinyl reagent (e.g. potassium vinyltrifluoroborate) in the presence of a palladium catalyst (e.g. palladium acetate and S-Phos) provides the vinyl compound **21a**. Conversion to the corresponding α-halo ketone can be accomplished by bromination with N-bromosuccinimide, followed by oxidation with $MnO_2$. Displacement of the α-halo ketone proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Bromination of **21d** proceeds upon treatment with pyridinium tribromide, and is followed by the addition of a second acid under basic conditions to provide the diester **21e**. Reaction of **21e** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **21f**. Oxidation of **21f** can be accomplished in the presence of $MnO_2$ to provide **21g**.



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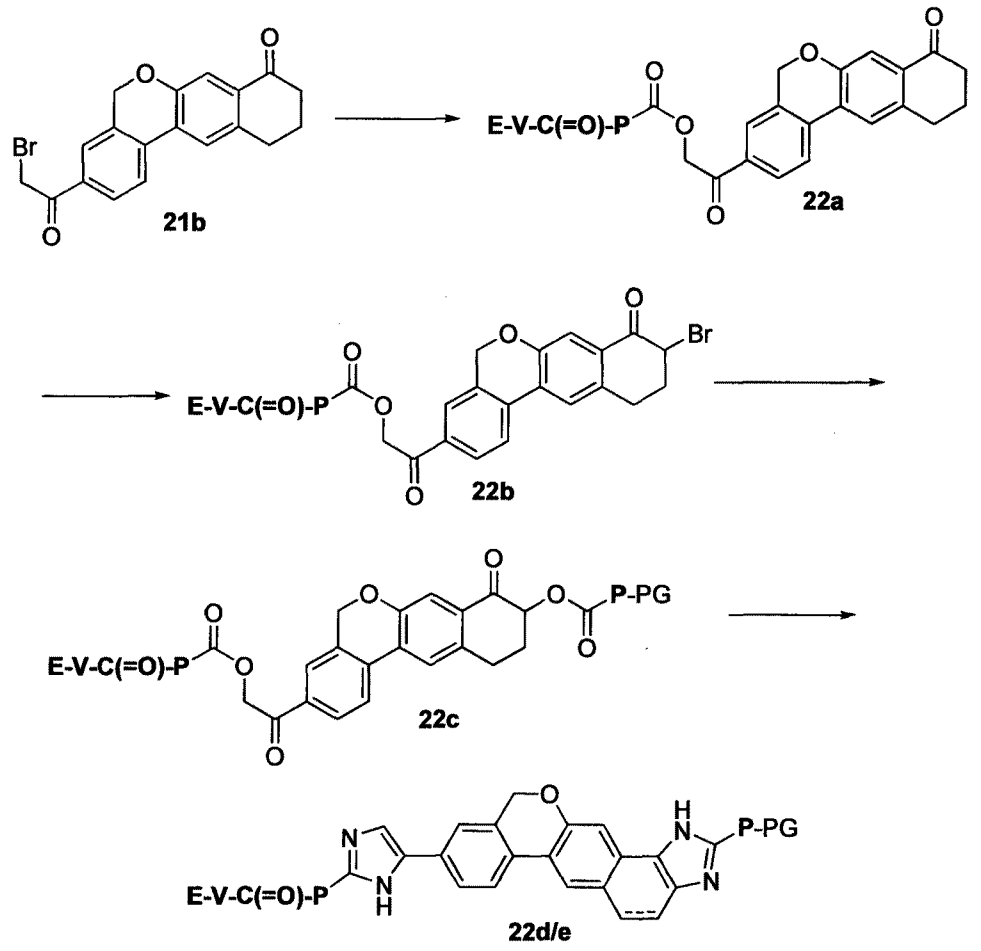
**Scheme 22. Representative synthesis of E-V-C(=O)-P-W-P-R**




Scheme 22 shows a general synthesis of an **E-V-C(=O)-P-W-P-R** intermediate of the invention wherein, for illustrative purposes, R is a protecting group and **W** is a two aromatic ring unit. Displacement of the α-halo ketone **21b** proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Bromination of **22b** proceeds upon treatment with pyridinium tribromide, and is followed by the addition of a second acid under basic conditions to provide the diester **22c**. Reaction of **22c** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **22d**. Oxidation of **22d** can be accomplished in the presence of $MnO_2$ to provide **22e**.



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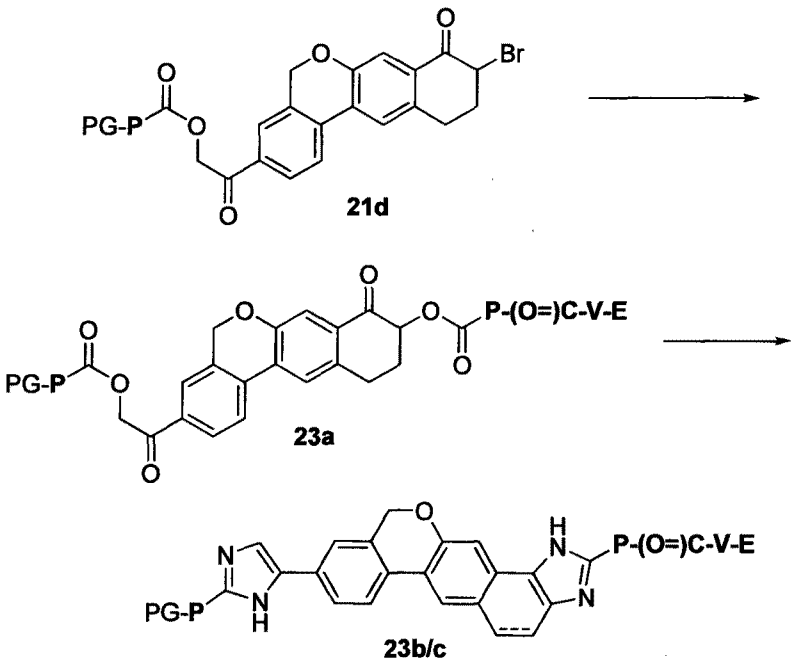
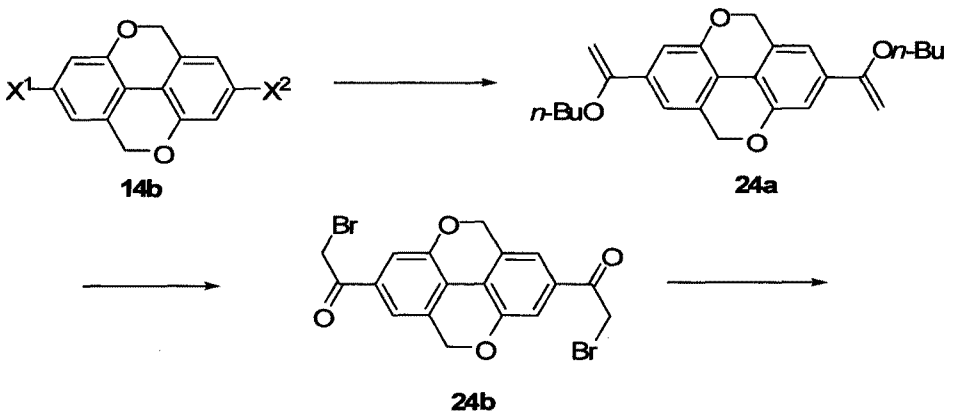
**Scheme 23. Representative synthesis of R-P-W-P-C(=O)-V-E**




Scheme 23 shows a general synthesis of an **E-V-C(=O)-P-W-P-**R intermediate of the invention wherein, for illustrative purposes, R is a protecting group and **W** is a two aromatic ring unit. Displacement of the α-halo ketone **21d** proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Reaction of **23a** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **23b**. Oxidation of **23b** can be accomplished in the presence of $MnO_2$ to provide **23c**.

**Scheme 24. Representative synthesis of $R^1$-P-W-P-$R^2$**



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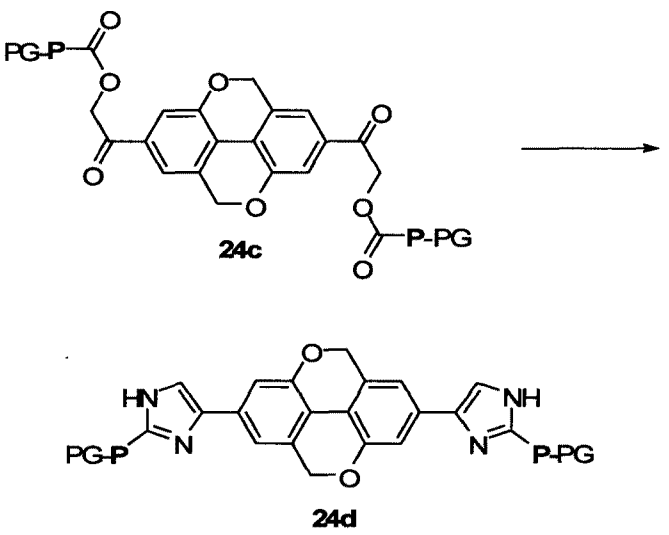


Scheme 24 shows a general synthesis of an $R^1$-**P**-**W**-**P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a three aromatic ring unit constructed via a transition metal mediated cross-coupling reaction. For illustrative purposes, **W** is constructed from a tetracyclic aromatic ring, wherein $X^1$ and $X^2$ are independent halogens or halogen equivalents that may be suitably protected. A transition metal-mediated cross-coupling reaction with butylvinylether, in the presence of palladium acetate and dppp, provides the divinyl compound **24a**. Treatment of **24a** with N-bromosuccinimide installs the corresponding a-halo ketone. Displacement of the α-halo ketone **24b** proceeds by the addition of two equivalents of acid under basic conditions (e.g. $Et_3N$). Reaction of **24c** with an amine or amine salt (e.g. ammonium acetate) affords the bis-imidazole containing molecule **24d**.



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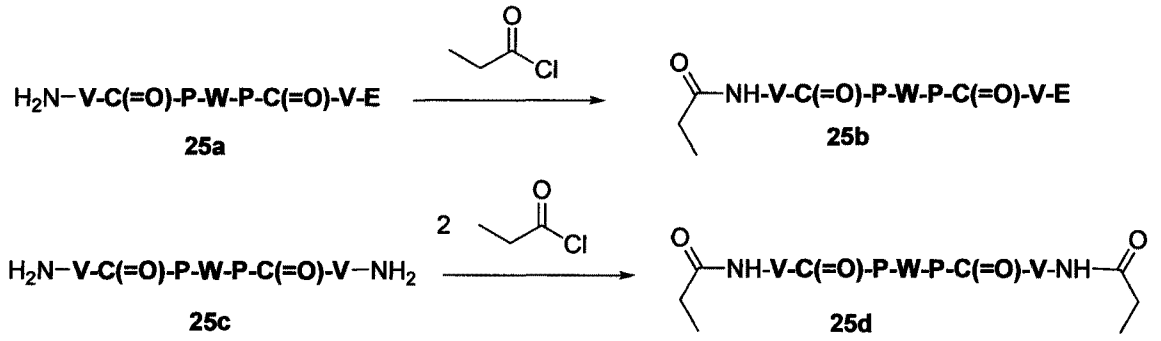
**Scheme 25. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**




Scheme 25 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **E** is ethylcarbonylamino. The treatment of either **25a** or **25c** with one or two equivalents respectively of propionyl chloride under basic conditions (e.g. sodium hydroxide) provides the molecule **25b** or **25d**.



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In one embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$P^{1a}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

$P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, (cycloalkyl)alkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, arylalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl,



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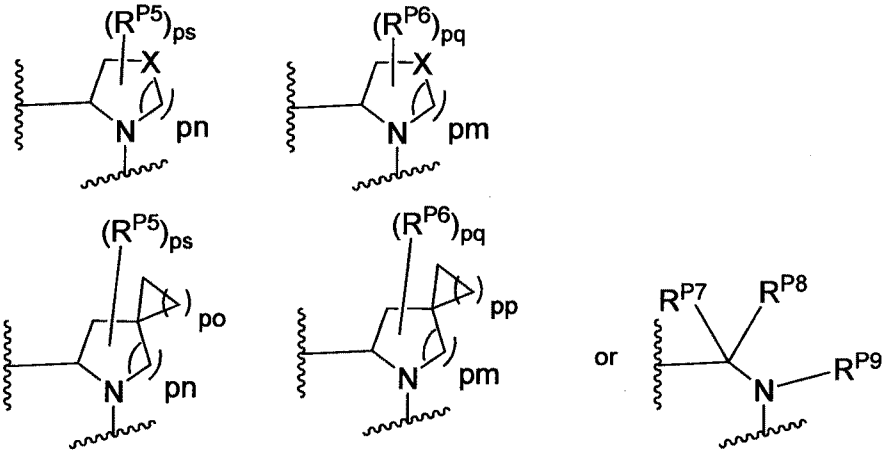
heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $P^0$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;



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each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

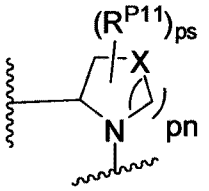
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy,



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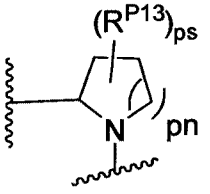
heteroaryloxyalkyloxy, heterocyclyloxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, -$NR^{hh}R^h$, ($NR^{hh}R^h$)alkyl, ($NR^{hh}R^h$)carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, ($NR^hR^h$)sulfonyl, heteroarylsulfonyl, -$S(=O)_2R^h$, -$C(=O)R^h$, -$C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy,



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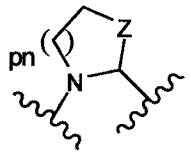
heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:



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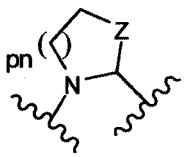


wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

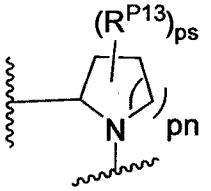
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and $R^{P11}$;

each $P^8$ is independently a ring of the formula:





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wherein:

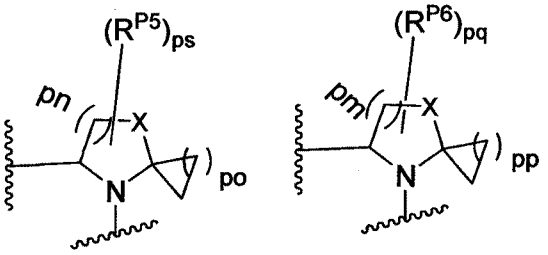
ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;



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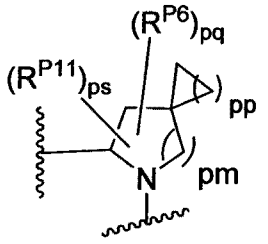
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:




wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano,



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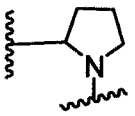
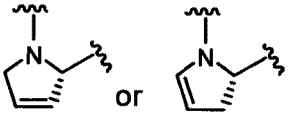
alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



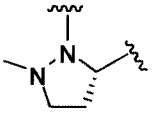
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



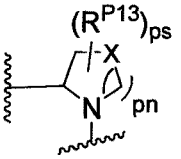

which is optionally substituted, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonylwith one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:




ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.



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each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl,



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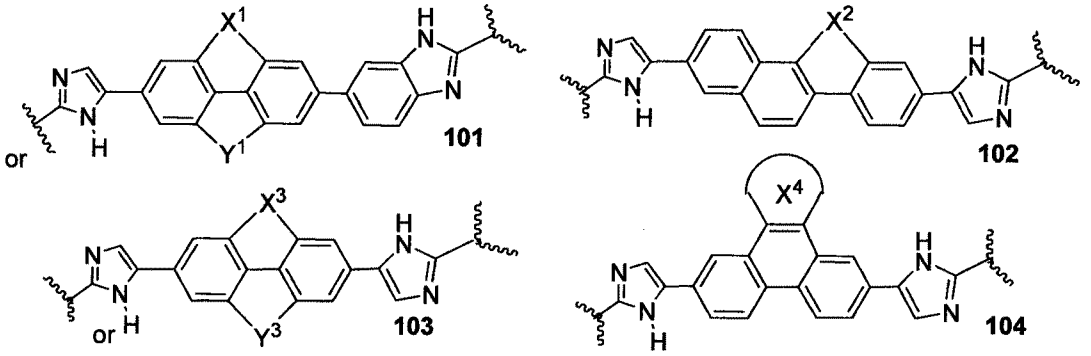
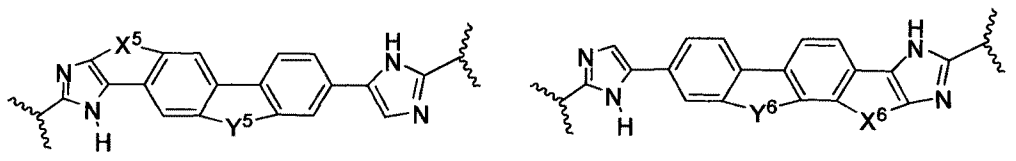
hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl; and

$W^{1a}$ is selected from:



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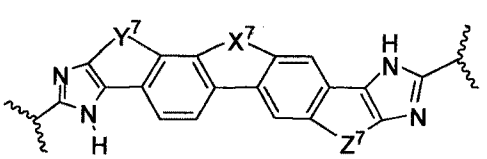

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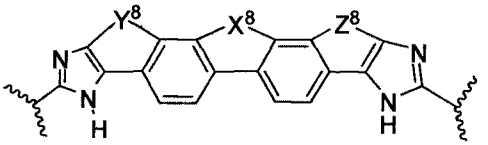

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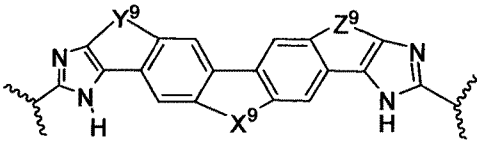
and



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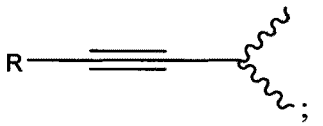
wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



;

wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^1$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^1$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^2$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^3$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^3$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^4$ is a six membered aromatic or heteroaromatic or five membered heteroraromatic ring;

$X^5$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^5$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^6$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$Y^6$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;

$X^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, -S- $CH_2-$, - $CH_2$-S-, -OC(O)-, -(O)CO-, or -CH=CH-;



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$Y^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$Z^7$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$X^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$Y^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$Z^8$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$X^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

$Y^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$; and

$Z^9$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-CF_2-$, -$-O-$, $-S-$ $CH_2-$, - $CH_2-S-$, $-OC(O)-$, $-(O)CO-$, or $-CH=CH-$;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$; and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl,



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heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are



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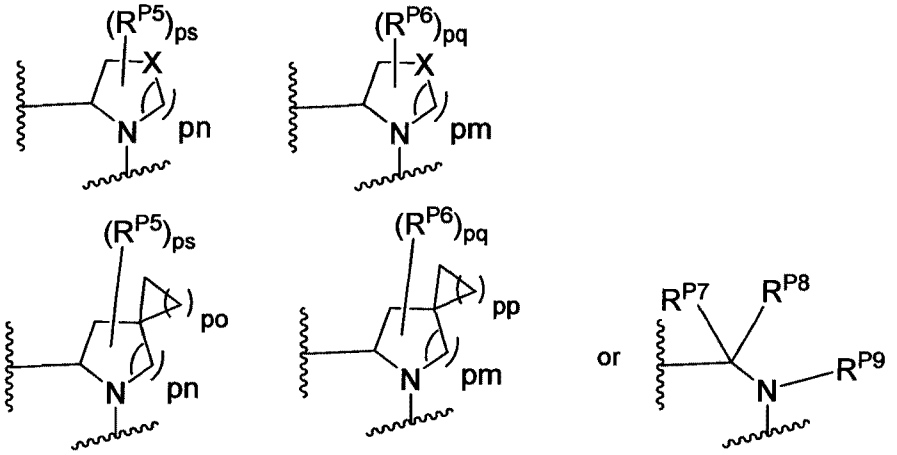
unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $P^0$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are



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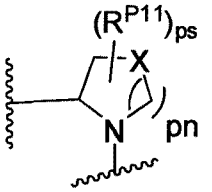
attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl;



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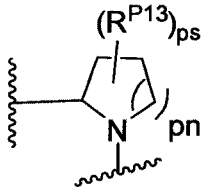
wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

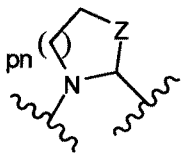
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:



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the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

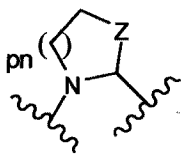
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$ ;

pn is 0, 1, or 2;



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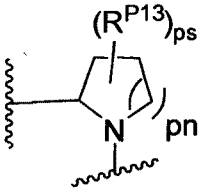
each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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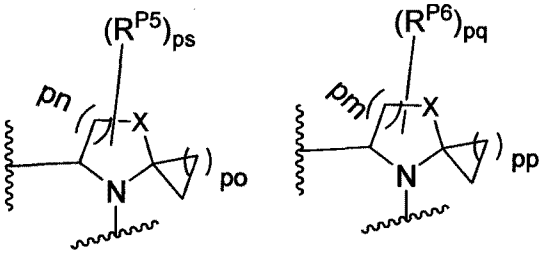


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

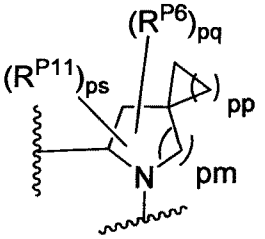
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to



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six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

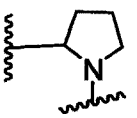
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



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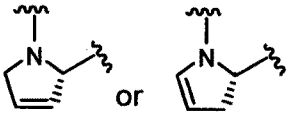
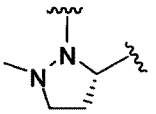
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



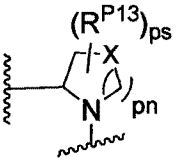
which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:



ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl,



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hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo,



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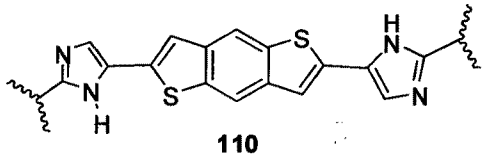
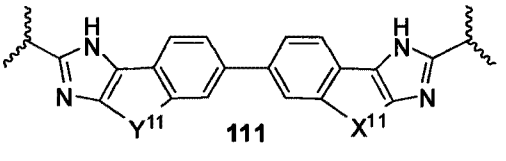
haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

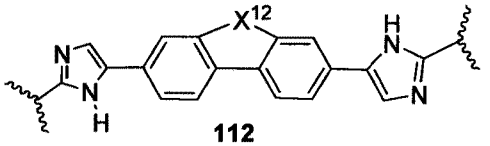
$W^{1a}$ is selected from:



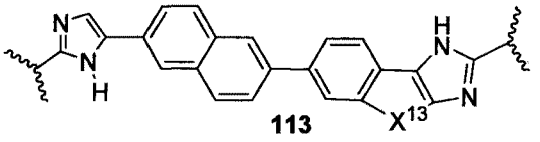
**110**



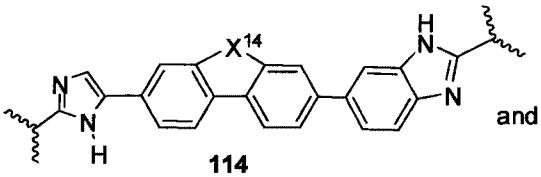
**111**



**112**

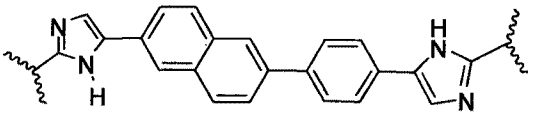


**113**

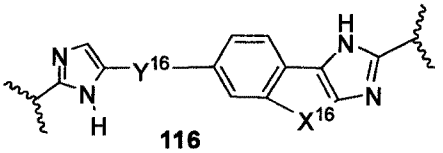


**114**

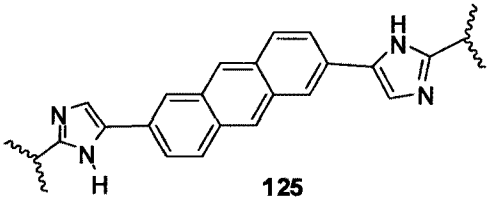
and



**115**

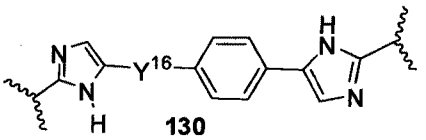


**116**



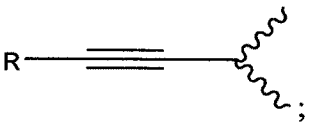
**125**

and



**130**

wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and





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wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$Y^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$X^{12}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-

$X^{13}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-; and

$X^{14}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-; and

each $Y^{16}$ is a bicyclic aromatic ring system comprising eight to 12 atoms optionally including one or more heteroatoms selected from O, S, and N, which bicyclic ring system is optionally with one or more groups independently selected from halo, haloalkyl, alkyl and oxo.

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$; and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$ and $P^{30}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl,



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-C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl-, oxo, and -$P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -$NR^XR^Y$, ($NR^XR^Y$)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one,



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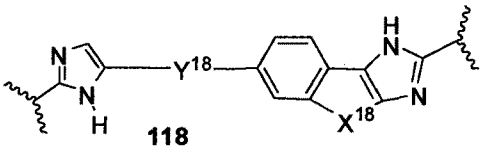
two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:



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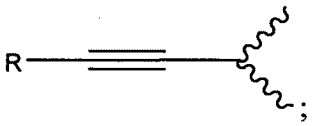
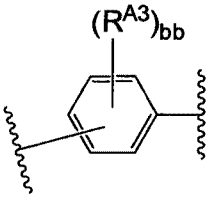
wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$Y^{18}$ is selected from $A^0$, $A^1$, $A^2$, $A^3$, $A^7$, $A^{15}$, $A^{16}$, and $A^{20}$;

each $A^0$ is independently:



wherein:

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

bb is independently 0, 1, 2, 3, or 4; or

each $A^0$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 $R^{A3}$ groups;

each $A^1$ is independently:



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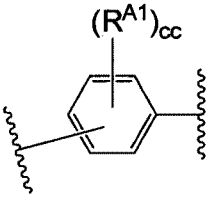


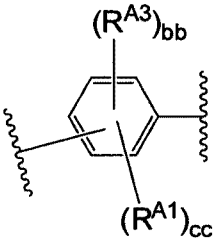
wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4;

each $A^2$ is independently:



wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, and ($NR^aR^b$)carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

$R^a$ and $R^b$ are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;



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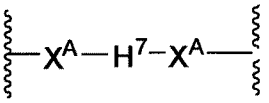
each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each $A^3$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more $R^{A1}$ groups, and which ring is optionally substituted with one or more $R^{A3}$ groups;

each $A^7$ is independently:

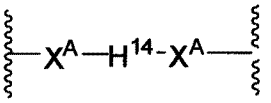


wherein:

each $H^7$ is independently a five-membered heteroaromatic ring, which $H^7$ is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; and each R is independently selected from H or alkyl;

each $A^{15}$ is independently:



wherein:

each $H^{14}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from oxo, $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{16}$ is independently:



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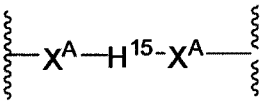


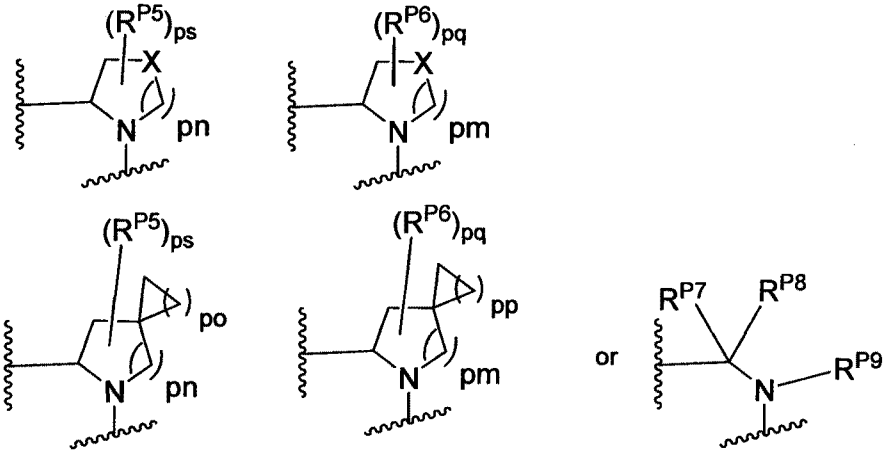
wherein:

each $H^{15}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{20}$ is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$;

each $P^0$ is independently:



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

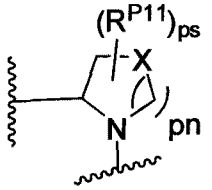
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and ($NR^{Pa}R^{Pb}$)alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, ($NR^{hh}R^h$)alkyl, ($NR^{hh}R^h$)carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the



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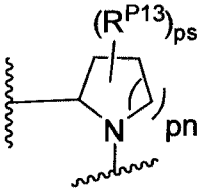
atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;



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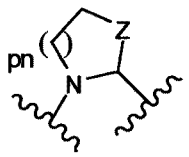
ps is 0, 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

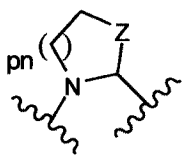
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:



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wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

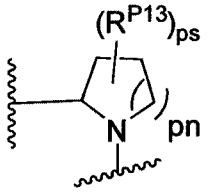
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to



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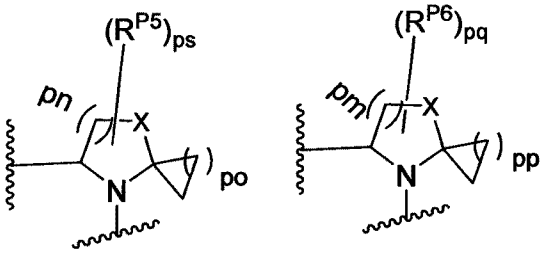
six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



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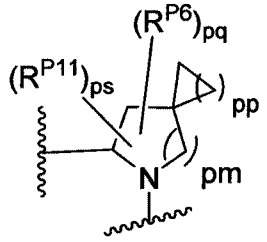


wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl,



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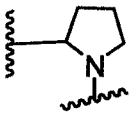
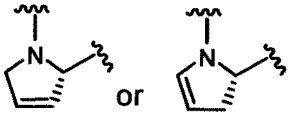
alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



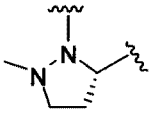
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



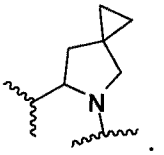

which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



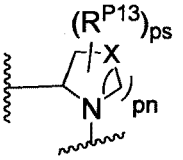
;

each $P^{20}$ is:



;

each $P^{30}$ is independently a ring of the formula:




ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.



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each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl; and

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl,



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hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and -C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

$X^{18}$ is -$CH_2$-, -$CH_2$-$CH_2$-, -$CH_2$-O-, -O-$CH_2$-, -$CH_2$-O-$CH_2$-, -S-, -$S(O)_2$-, -C(O)-, -$CF_2$-, -O-, -S-$CH_2$-, -$CH_2$-S-, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;



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each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;



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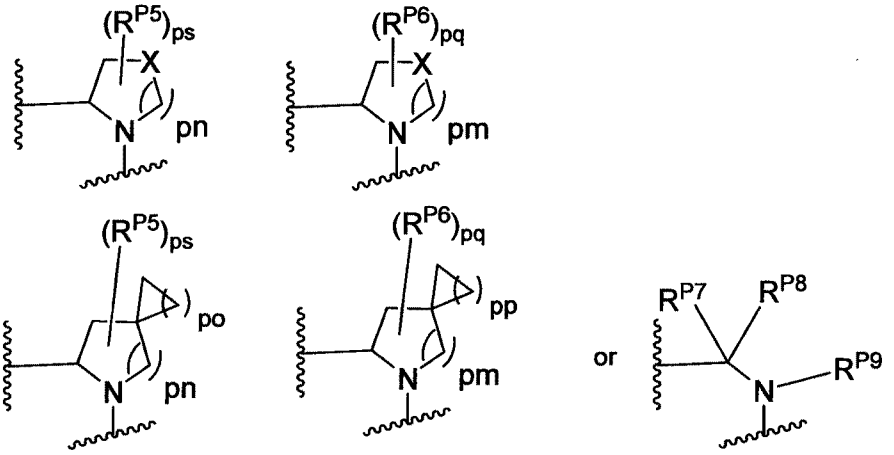
and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$P^{1a}$ and $P^{1b}$ are each independently selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $P^0$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

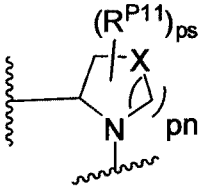
pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and ($NR^{Pa}R^{Pb}$)alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, ($NR^{hh}R^h$)alkyl, ($NR^{hh}R^h$)carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the



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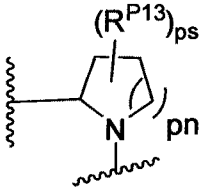
atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;



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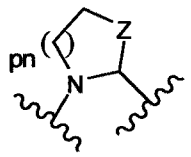
ps is 0, 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:



wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

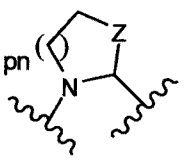
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:





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wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

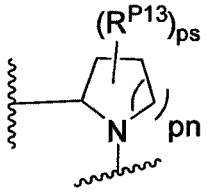
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to



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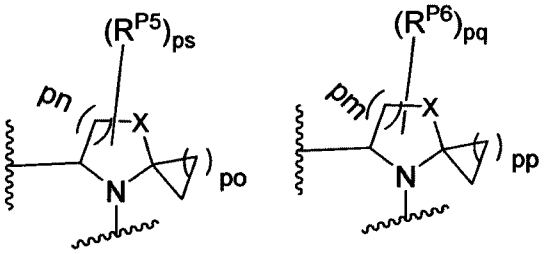
six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



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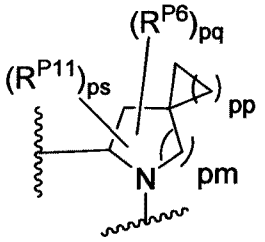


wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl,



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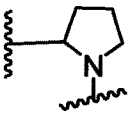
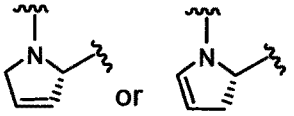
alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



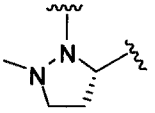
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



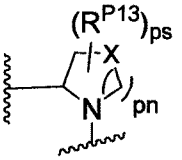

which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $P^{30}$ is independently a ring of the formula:




ps is 2

pn is 0, 1 or 2;

X is selected from O, S, S(O), $SO_2$, or $CH_2$; provided that when pn is 0, X is $CH_2$.

each $R^{P13}$ is independently selected from alkyl-, alkoxyalkyl-, hydroxyalkyl-, alkyl-S-alkyl-, sulfanylalkyl-, aminoalkyl-, alkylaminoalkyl-, dialkylaminoalkyl-, alkyl-SO2-alkyl where two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;



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each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl,



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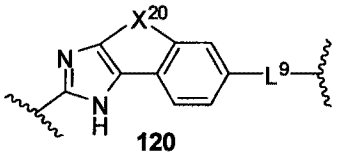
heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -$(NR^XR^Y)$alkyl, and -$(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

$W^{1a}$ is selected from:



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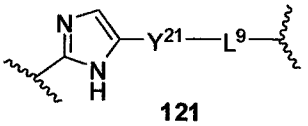

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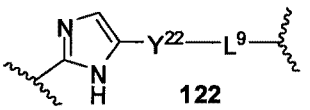

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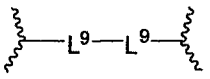
and



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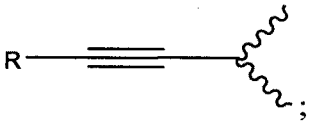
wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{20}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, -O-C(O)-, -C(O)-O-, -CH=N-; -N=CH-; or -CH=CH-



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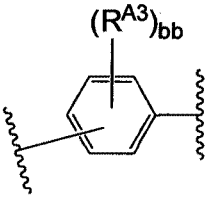
$Y^{21}$ is a bicyclic aromatic ring system comprising eight to 12 atoms optionally including one or more heteroatoms selected from O, S, and N, which bicyclic ring system is optionally with one or more groups independently selected from halo, haloalkyl, alkyl and oxo;

$Y^{22}$ is selected from $A^0$, $A^1$, $A^2$, $A^3$, $A^7$, $A^{15}$, $A^{16}$, and $A^{20}$;

each $A^0$ is independently:



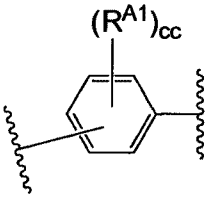

wherein:

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

bb is independently 0, 1, 2, 3, or 4; or

each $A^0$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is optionally substituted with 1, 2, 3, or 4 $R^{A3}$ groups;

each $A^1$ is independently:




wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, $-alkylSO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

each cc is independently 1, 2, 3, or 4;



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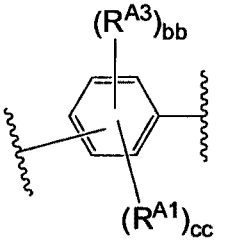
each $A^2$ is independently:




wherein:

each $R^{A1}$ is independently selected from cyano, nitro, $SOR^4$, $SO_2R^4$, -alkyl$SO_2R^4$, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each $R^{A3}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl; $R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

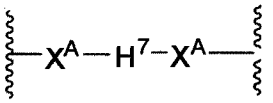
each $R^4$ is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

$R^a$ and $R^b$ are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each bb is 0, 1, 2, 3, or 4; each cc is 1, 2, 3, or 4; and the sum of bb and cc is 1, 2, 3, or 4;

each $A^3$ is independently a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms, which ring is substituted with one or more $R^{A1}$ groups, and which ring is optionally substituted with one or more $R^{A3}$ groups;

each $A^7$ is independently:




wherein:

each $H^7$ is independently a five-membered heteroaromatic ring, which $H^7$ is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and



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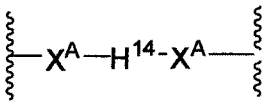
each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; and each R is independently selected from H or alkyl;

each $A^{15}$ is independently:

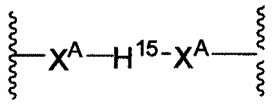


wherein:

each $H^{14}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle which is optionally substituted with one or more groups independently selected from oxo, $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{16}$ is independently:



wherein:

each $H^{15}$ is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$; and

each $X^A$ is independently O, NR, SO, $SO_2$, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each $A^{20}$ is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from $R^{A1}$ and $R^{A3}$;

each $L^9$ is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L9}$, $-OR^{L9}$, $-SR^{L9}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L9})C(=O)R^{L9}$, $-C(=O)R^{L9}$, $-OC(=O)R^{L9}$, $-C(O)OR^{L9}$, $-C(=O)NR^{L9}$, $-S(=O)R^{L9}$, $-S(=O)_2OR^{L9}$, $-S(=O)_2R^{L9}$, $-OS(=O)_2OR^{L9}$, $-S(=O)_2NR^{L9}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, and $(NR^aR^b)$carbonyl;

each $R^{L9}$ is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and



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$R^a$ and $R^b$ are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, haloalkyl, -NHhaloalkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl,



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hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl-, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$P^{1a}$ and $P^{1b}$ are each independently selected from $P^0$, $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $P^0$ is independently:



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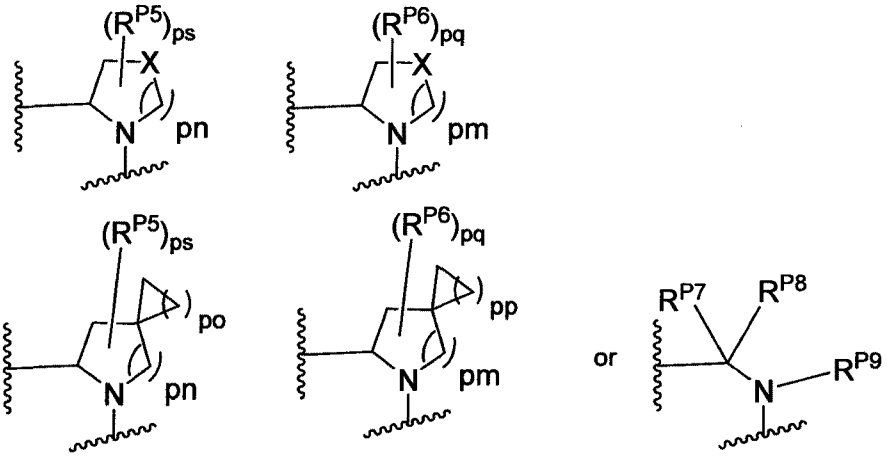

wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

$R^{P7}$ and $R^{P8}$ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or $R^{P7}$ and $R^{P8}$, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from $NR^{Pz}$, O, and S; wherein $R^{Pz}$ is selected from hydrogen and alkyl;

$R^{P9}$ is selected from hydrogen and alkyl;

each $P^1$ is independently:



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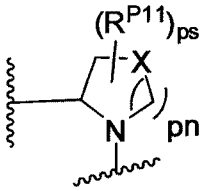

wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyloxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclyloxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo and heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when



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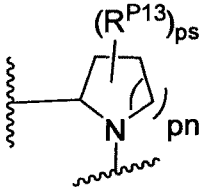
two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

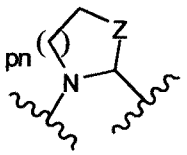
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, ($NR^hR^h$)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, ($NR^hR^h$)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:




wherein:

the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an



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adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

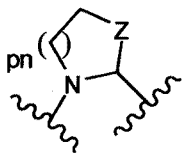
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$ ;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$,



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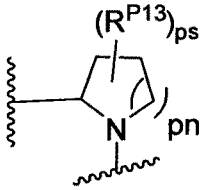
$-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

each $P^{10}$ is independently:



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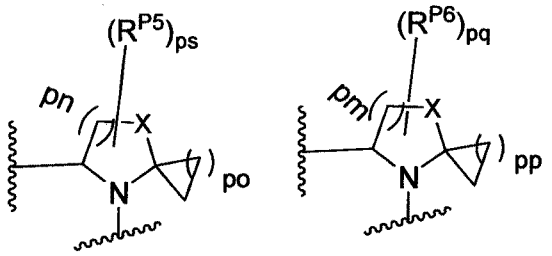


wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

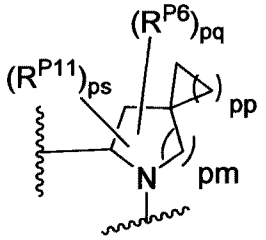
each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:



wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to



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six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

pq is independently 0, 1, 2, 3, or 4;

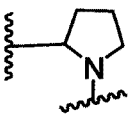
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



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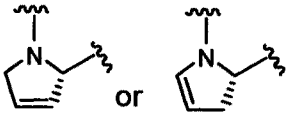
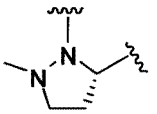
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $P^{19}$ is:



;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, $(NR^cR^d)$alkenyl, $(NR^cR^d)$alkyl, and $(NR^cR^d)$carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and $-C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl,



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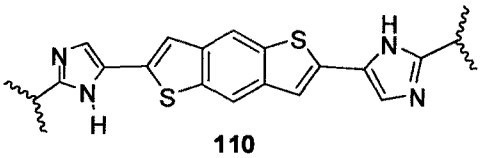
and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R^{9b}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

$W^{1a}$ is selected from:



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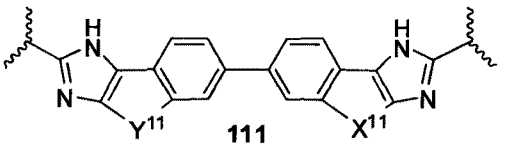

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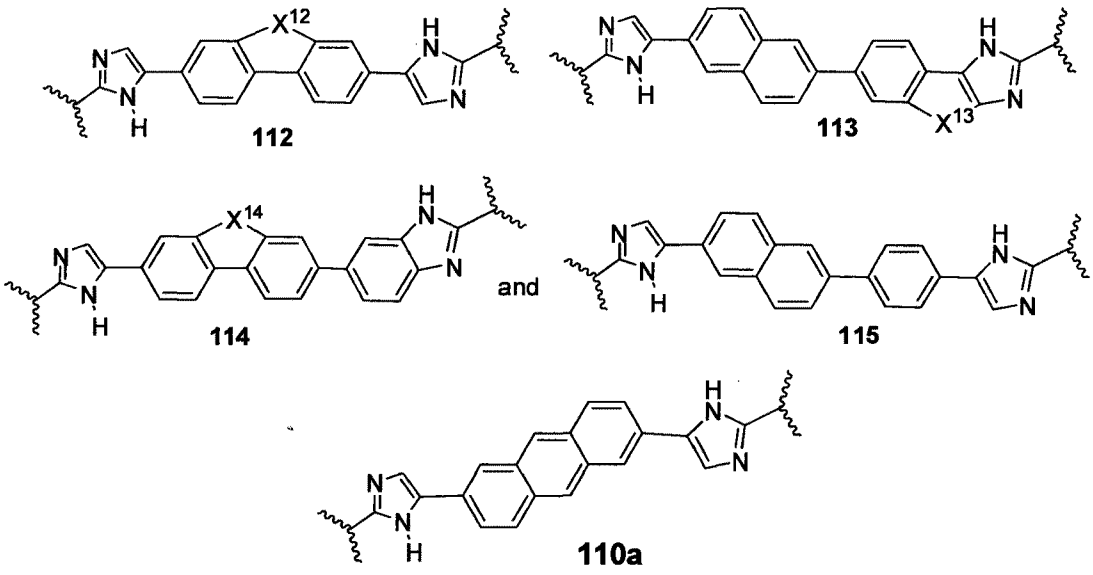
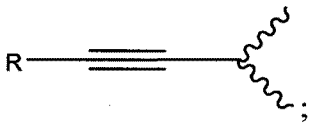



wherein each $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and wherein each $W^{1a}$ is substituted with one or more (e.g. 1, 2, 3, or 4):




wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

$X^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, -CH=N-; -N=CH-; or -CH=CH-

$Y^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, -CH=N-; -N=CH-; or -CH=CH-

$X^{12}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, -CH=N-; -N=CH-; or -CH=CH-

$X^{13}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, -CH=N-; -N=CH-; or -CH=CH-; and

$X^{14}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-CH_2-$, -S-, $-S(O)_2-$, -C(O)-, $-CF_2-$, -O-, $-S-CH_2-$, $-CH_2-S-$, $-O-C(O)-$, $-C(O)-O-$, -CH=N-; -N=CH-; or -CH=CH-;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:



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$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^{0a}$ and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^1$, $P^3$, $P^5$, $P^6$, $P^7$, $P^8$, $P^{10}$, $P^{12}$, $P^{15}$, $P^{18}$, $P^{19}$, and $P^{30}$;

each $E^0$ is independently -$NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro,



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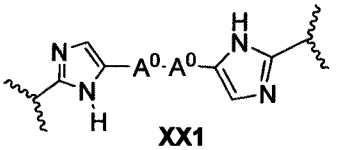
$-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:



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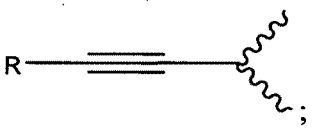
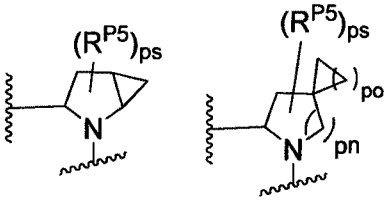
wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and



wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

each $P^{0a}$ is independently:





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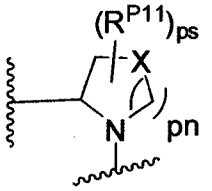
each $R^{P5}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

ps is independently 0, 1, 2, 3, or 4;

pn is independently 0, 1, or 2;

po is independently 1, 2, or 3;

each $P^1$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h$a)lkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from



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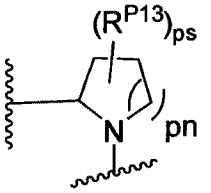
$R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^5$ is independently a ring of the formula:



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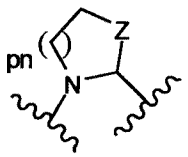


wherein:

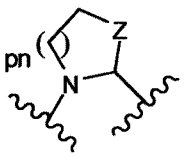
the ring is optionally substituted with one or more groups $R^{P15}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups $R^{P15}$ that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^6$ is independently a ring of the formula:



wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and –$NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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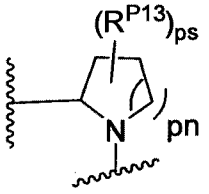
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

each $P^8$ is independently a ring of the formula:




wherein:

ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups $R^{P13}$ that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $P^{10}$ is independently:



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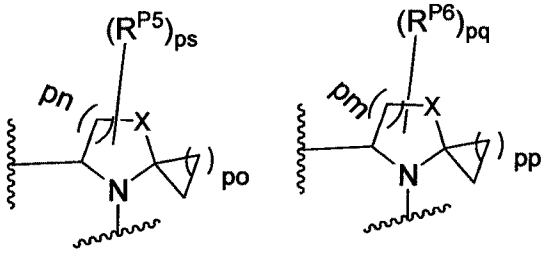



wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn or pm is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

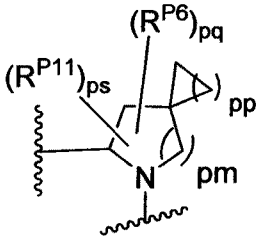
each $R^{P5}$ and $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq and ps are independently 0, 1, 2, 3, or 4;

pm and pn are independently 0, 1, or 2;

po and pp are independently 1, 2, or 3;

each $P^{12}$ is independently:




wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;



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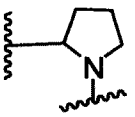
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

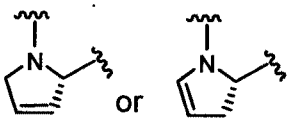
$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl;

each $P^{18}$ is:



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which is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, and cycloalkylalkyl;

each $R^{9a}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, ($NR^eR^f$)alkyl, ($NR^eR^f$)alkylcarbonyl, ($NR^eR^f$)carbonyl, ($NR^eR^f$)sulfonyl, -C(NCN)OR', and - C(NCN)$NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -$NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, -($NR^XR^Y$)alkyl, and -($NR^XR^Y$)carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{X'}R^{Y'}$)carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

each $R9^b$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -$NR^cR^d$, ($NR^cR^d$)alkenyl, ($NR^cR^d$)alkyl, and ($NR^cR^d$)carbonyl; $R^c$ and $R^d$ are independently selected from hydrogen,



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alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; $R^e$ and $R^f$ are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, $-(NR^XR^Y)$alkyl, and $-(NR^XR^Y)$carbonyl; $R^X$ and $R^Y$ are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{X'}R^{Y'})$carbonyl, wherein $R^{X'}$ and $R^{Y'}$ are independently selected from hydrogen and alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides a compound of the invention which is compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$E^{1a}$ is $E^0$ or $E^1$, or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is $E^0$ or $E^1$, or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ is $V^0$ or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$V^{1b}$ is $V^0$ or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

one of $P^{1a}$ and $P^{1b}$ is selected from $P^{0b}$ and the other of $P^{1a}$ and $P^{1b}$ is selected from $P^{21}$, $P^3$, $P^6$, $P^7$, $P^{28}$, $P^{12}$, $P^{15}$and $P^{38}$;



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each $E^0$ is independently $-NR^{Ec}R^{Ed}$ wherein $R^{Ec}$ and $R^{Ed}$ are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, $(NR^eR^f)$alkyl, $(NR^eR^f)$alkylcarbonyl, $(NR^eR^f)$carbonyl, $(NR^eR^f)$sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each $E^1$ is independently selected from hydrogen, hydroxy, alkyl, aryl, and heterocyclyl;

each $V^0$ is independently alkyl, arylalkyl, alkenyl, CO, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;



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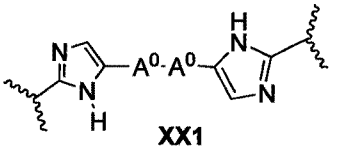
and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

$W^{1a}$ is:

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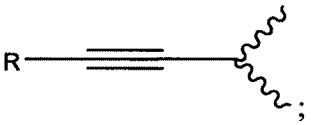
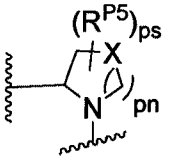
wherein $W^{1a}$ is optionally substituted with one or more (e.g. 1, 2, 3, or 4) groups independently selected from halo, alkyl, haloalkyl, cyano, and




;

wherein each R is independently H, alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

each $P^{0b}$ is independently:




X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$

each $R^{P5}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;



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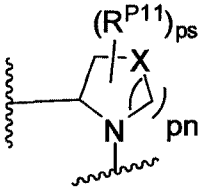
$R^{Pa}$ and $R^{Pb}$ are each independently H, alkyl, aryl, or arylalkyl; or $R^{Pa}$ and $R^{Pb}$ taken together with the atom to which they are attached form a heterocycle;

ps is independently 0, 1, 2, 3, or 4;

pn is independently 0, 1, or 2;

each $P^{21}$ is independently:




wherein:

X is selected from O, S, S(O), $SO_2$, $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$; provided that when pn is 0, X is selected from $CH_2$, $CHR^{P10}$, and $C(R^{P10})_2$;

each $R^{P10}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

at least one $R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyalkyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, $-NR^{hh}R^h$, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle,



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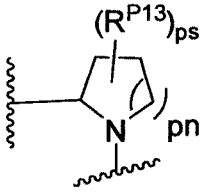
heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each $P^3$ is independently a ring of the formula:




wherein:

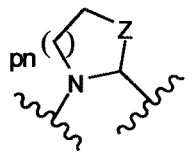
the ring is substituted with one or more oxo group;

each $R^{P13}$ is independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

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

pn is 0, 1, or 2;

each $P^6$ is independently a ring of the formula:




wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups $R^{P16}$ that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to



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six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

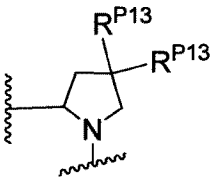
Z is O, S, S(=O), $S(=O)_2$, or $NR^f$;

pn is 0, 1, or 2;

each $R^f$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $-S(=O)_2NR^hR^h$, $-S(=O)_2R^h$, $C(=O)R^h$, $C(=O)OR^h$, $-C(=O)NR^hR^h$ ; each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; or when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^7$ is a bridged 5-15 membered bicyclic heterocyclic ring that is attached to the remainder of the compound of formula I through one N-link and through one C-link; wherein the ring is optionally substituted with one or more groups independently selected from $R^{P6}$ and $R^{P11}$;

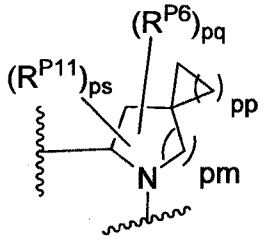
each $P^{28}$ is independently a ring of the formula:




wherein:

each $R^{P13}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, where in two $R^{P13}$ groups are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each $P^{12}$ is independently:



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wherein:

each $R^{P6}$ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

pq is independently 0, 1, 2, 3, or 4;

pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

$R^{P11}$ is independently selected from cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl, $-NR^{hh}R^h$, $(NR^{hh}R^h)$alkyl, $(NR^{hh}R^h)$carbonyl, wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring; wherein each $R^{hh}$ is independently aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl, $(NR^hR^h)$sulfonyl, heteroarylsulfonyl, $-S(=O)_2R^h$, $-C(=O)R^h$, $-C(=O)NR^hR^h$; and the remaining $R^{P11}$ are independently selected from $R^{P5}$, cyano, alkylsulfonyl, arylsulfonyl, $(NR^hR^h)$sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, $(NR^hR^h)$alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each $R^h$ is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two $R^h$ groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each $P^{15}$ is:



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# DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 5
CONTENANT LES PAGES 1 À 252

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

# JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 5
CONTAINING PAGES 1 TO 252

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

## CLAIMS

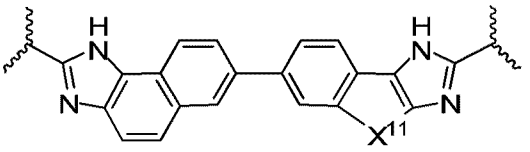
What is claimed is:

1. A compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$W^{1a}$ is :



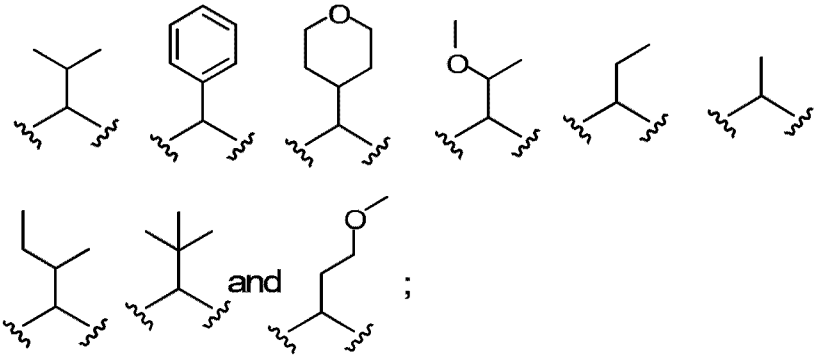
optionally substituted with one or more groups independently selected from the group consisting of halo, alkyl, haloalkyl, and cyano;

$X^{11}$ is $-CH_2-CH_2-$, $-O-CH_2-$, or -CH=CH-;

$E^{1a}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ and $V^{1b}$ are each independently selected from the group consisting of:




;

one of $P^{1a}$ and $P^{1b}$ is



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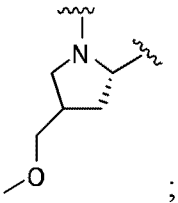
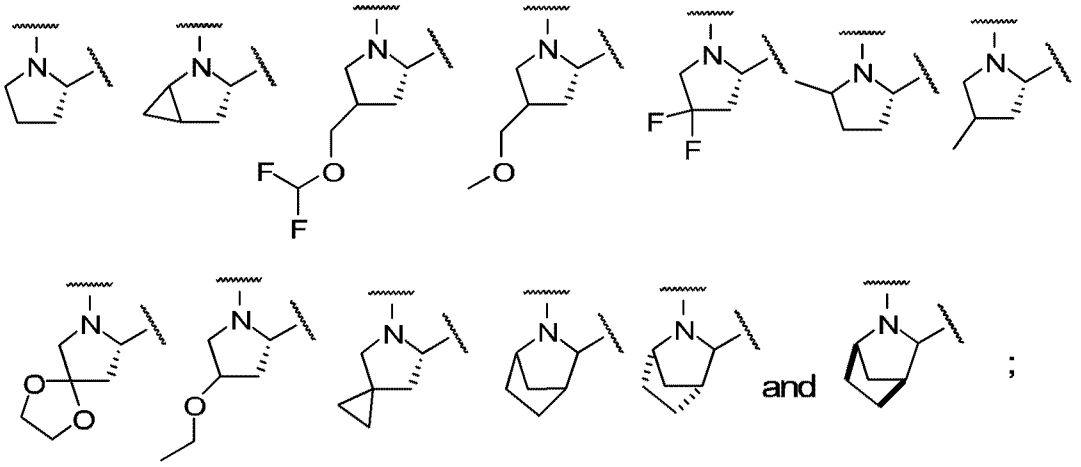


;

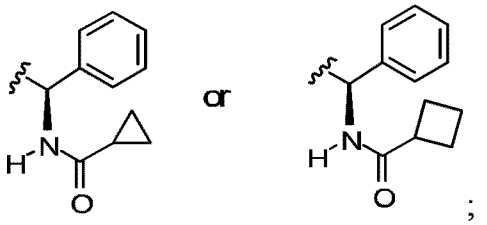
and the other of $P^{1a}$ and $P^{1b}$ is selected from the group consisting of:



and

;

$R^{9a}$ and $R^{9b}$ are each independently:



or

;

or a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of claim 1, wherein at least one of $E^{1a}$ and $E^{1b}$ is -N(H)C(=O)$OCH_3$.

3. The compound of claim 1 or 2, wherein both of $E^{1a}$ and $E^{1b}$ is -N(H)C(=O) $OCH_3$.

4. The compound of any one of claims 1-3, wherein at least one of $V^{1a}$ and $V^{1b}$ is selected from the group consisting of:



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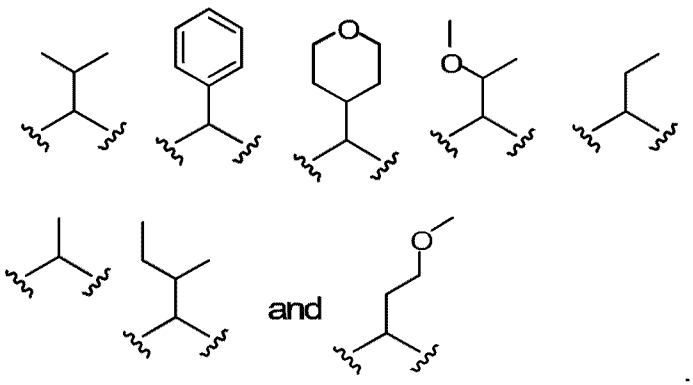
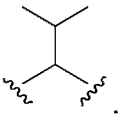
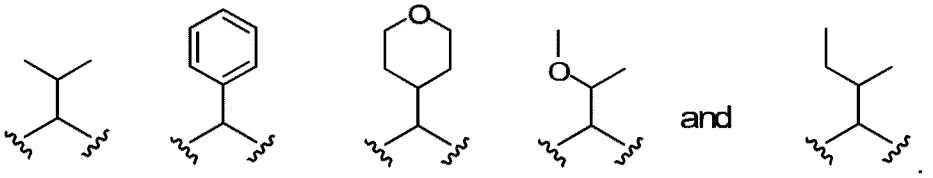


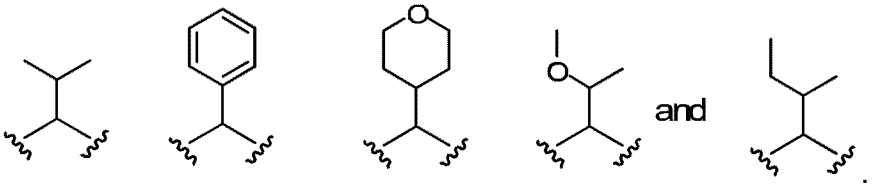

5. The compound of any one of claims 1-4, wherein at least one of $V^{1a}$ and $V^{1b}$ is:



6. The compound of any one of claims 1-4, wherein at least one of $V^{1a}$ and $V^{1b}$ is selected from the group consisting of:




7. The compound of any one of claims 1-3, wherein $V^{1a}$ and $V^{1b}$ are each independently selected from the group consisting of:




8. The compound of any one of claims 1-7, wherein the other of $P^{1a}$ and $P^{1b}$ is selected from the group consisting of:



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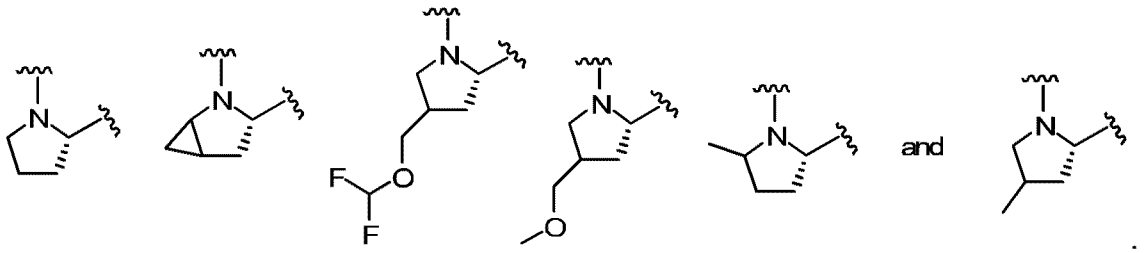
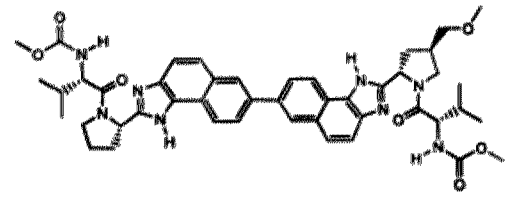
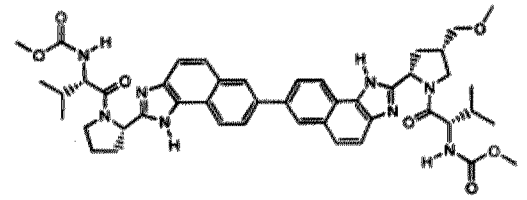
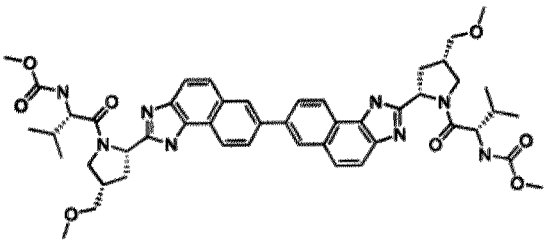



9. A compound selected from the group consisting of:









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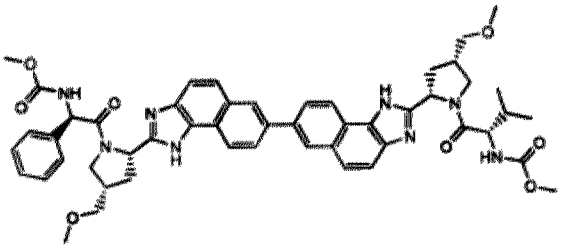

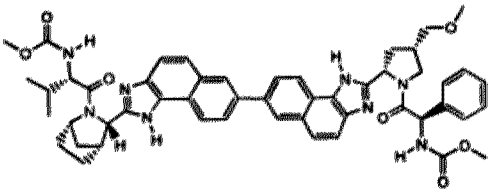

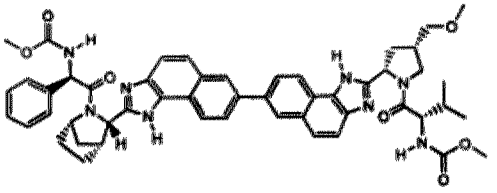

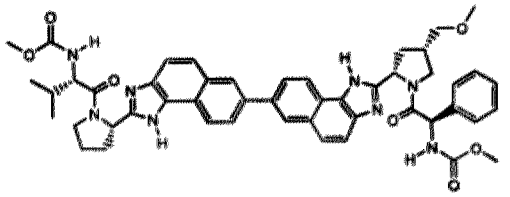

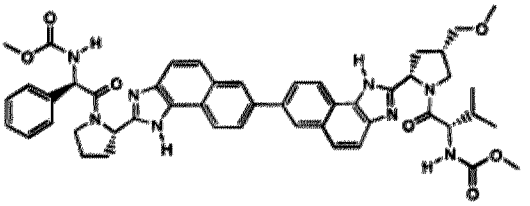



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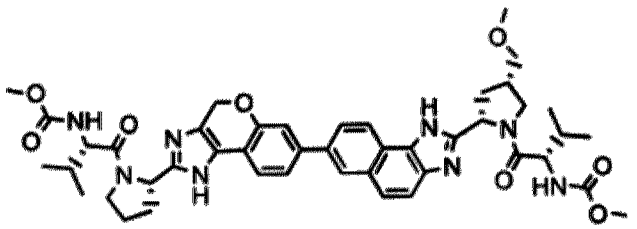

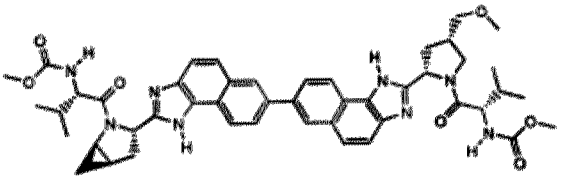

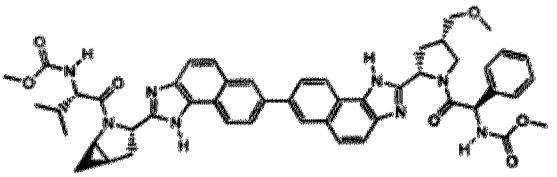

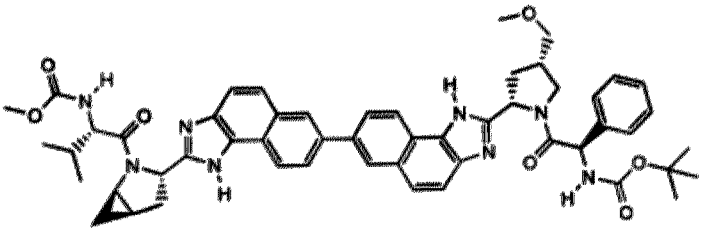

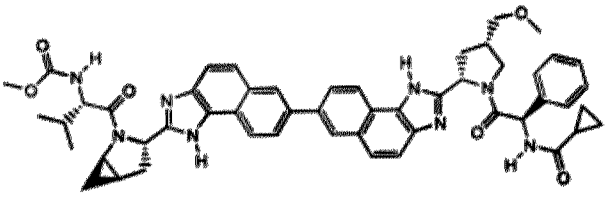



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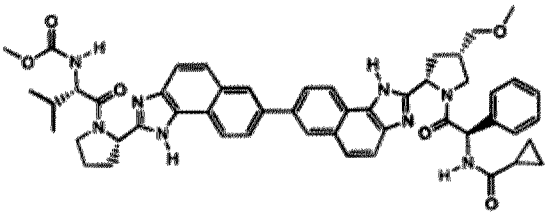

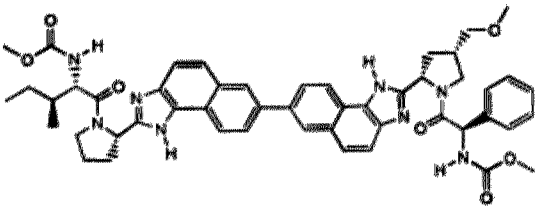

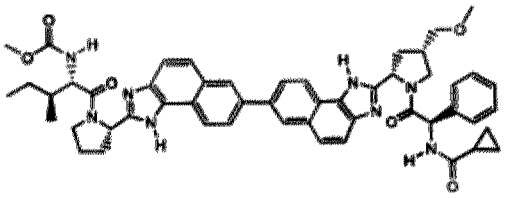

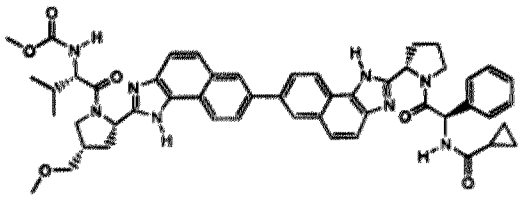

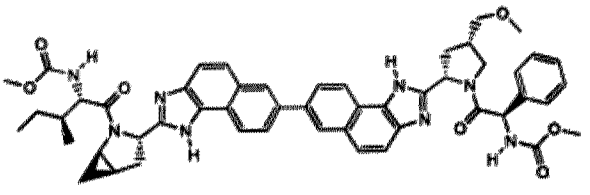



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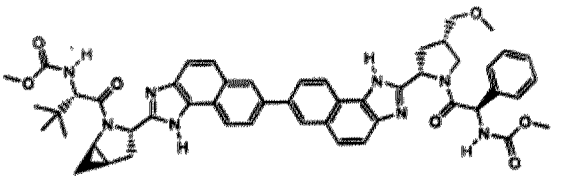

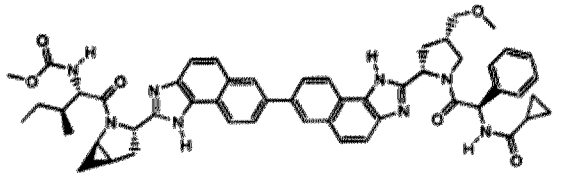

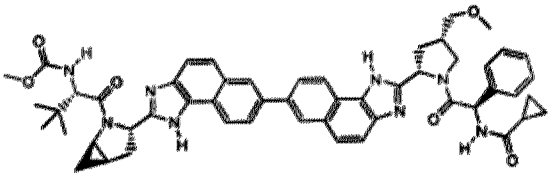

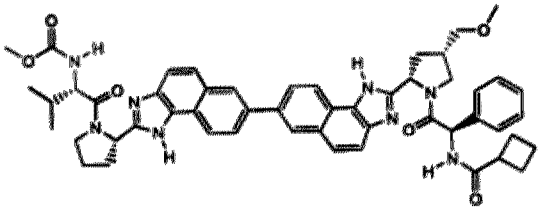

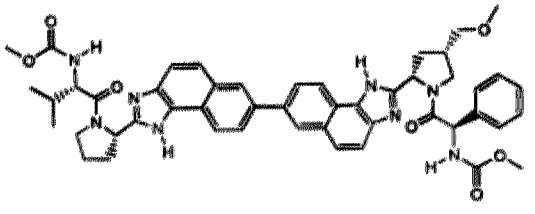



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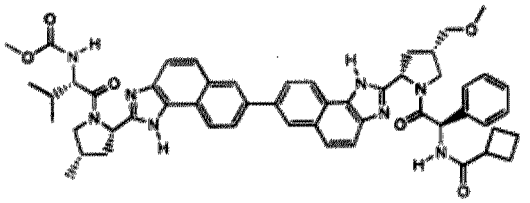

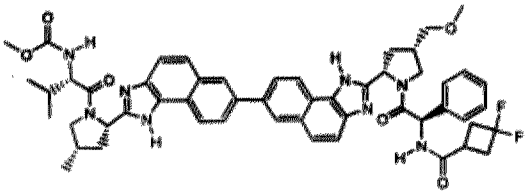

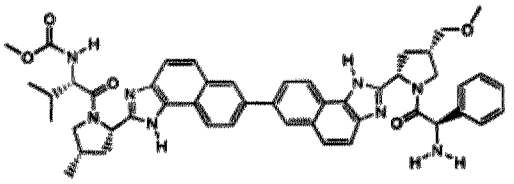

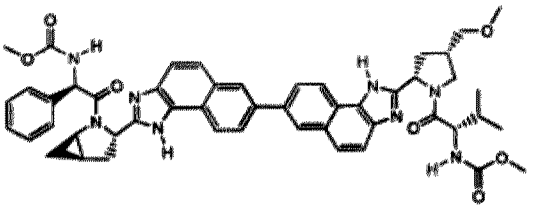

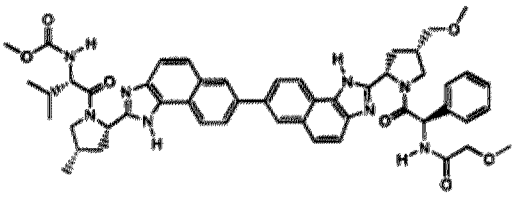



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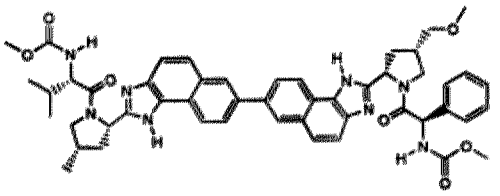

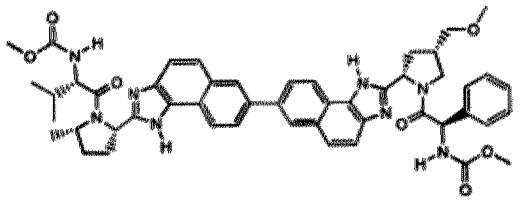

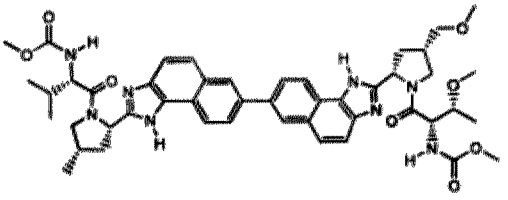

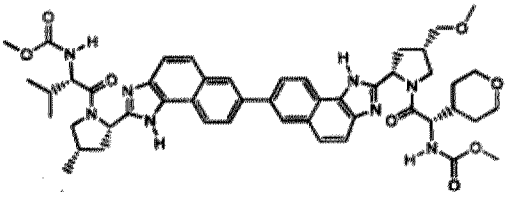

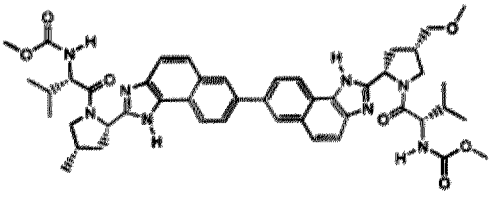



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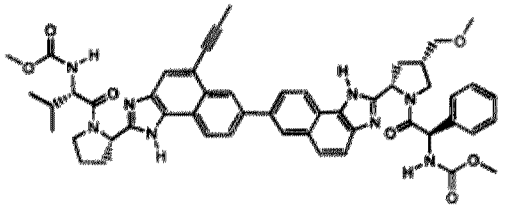

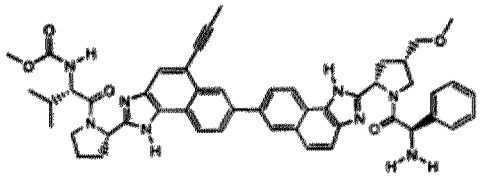

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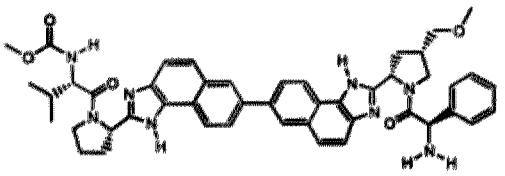

10. A pharmaceutical composition comprising the compound of any one of claims 1-9 or a pharmaceutically acceptable thereof; and pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising at least one additional therapeutic agent, wherein said additional therapeutic agent is selected from the group consisting of a ribavirin analog, a NS3 protease inhibitor, a NS5b polymerase inhibitor, an alpha-glucosidase 1 inhibitors, a hepatoprotectant, and a non-nucleoside inhibitors of HCV.

12. The pharmaceutical composition of claim 10, further comprising a nucleoside analogue, wherein said nucleoside analogue is selected from the group consisting of ribavirin, viramidine, levovirin, a L-nucleoside, and isatoribine.



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13. Use of the compound of any one of claims 1-9 or a pharmaceutically acceptable salt for preparing a medicament for treating hepatitis C or a hepatitis C associated disorder in an animal.

14. The compound of any one of claims 1-9 or a pharmaceutically acceptable salt for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.



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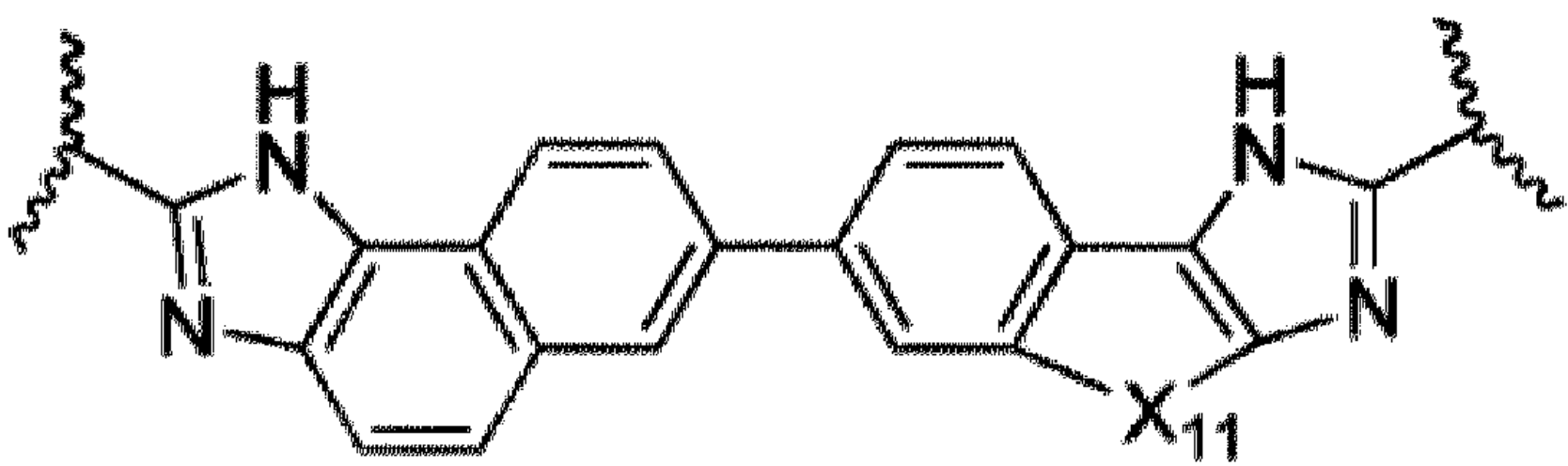
$$E^{1a}\text{-}V^{1a}\text{–}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b}$$

**(I)**




**($W^{1a}$)**