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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 September 2010 (30.09.2010)

PCT

(10) International Publication Number
WO 2010/111534 A1

(51) International Patent Classification:
A01N 37/00 (2006.01) *A61K 31/21* (2006.01)

(21) International Application Number:
PCT/US2010/028730

(22) International Filing Date:
25 March 2010 (25.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/164,342 27 March 2009 (27.03.2009) US
61/214,883 28 April 2009 (28.04.2009) US

(71) Applicant *(for all designated States except US)*: **PRESIDIO PHARMACEUTICALS, INC.** [US/US]; 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LI, Leping** [US/US]; c/o Presidio Pharmaceuticals, Inc., 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US). **ZHONG, Min** [US/US]; c/o Presidio Pharmaceuticals, Inc., 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US).

(74) Agents: **FARMER-KOPPENOL, Pauline** et al.; Fenwick & West LLP, Silicon Valley Center, 801 California Street, Mountain View, CA 94041 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— *with international search report (Art. 21(3))*

WO 2010/111534 A1

(54) **Title**: FUSED RING INHIBITORS OF HEPATITIS C

(57) **Abstract**: Provided herein are compounds, pharmaceutical compositions and combination therapies for treatment of hepatitis C.

Fused Ring Inhibitors of Hepatitis C

Inventors: Leping Li and Min Zhong

Statement of Related Applications

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

Field of the Invention

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

Background of the Invention

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

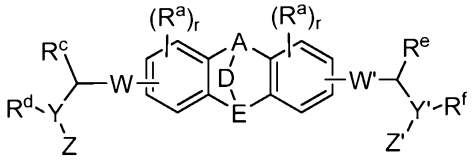
[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related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

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

Summary of the Invention

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

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



I

wherein:

D is either present or absent and if present selected from the group consisting of $-CR_2CR_2-$, $-CR_2-$, $-NR^N-$, –O– and –S– wherein:

R^N is H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently $-CR_2-$, $-CR=$, $-CR_2-CR_2-$, $-CR=CR-$, $-N=CR-$, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $-(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

two R's either both on a single C or on adjoining C's, together with the C

or C's to which they are attached, optionally form a cycle, and

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

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

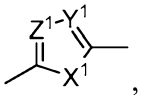
R^N and R may be replaced by a bond to D if D is present,

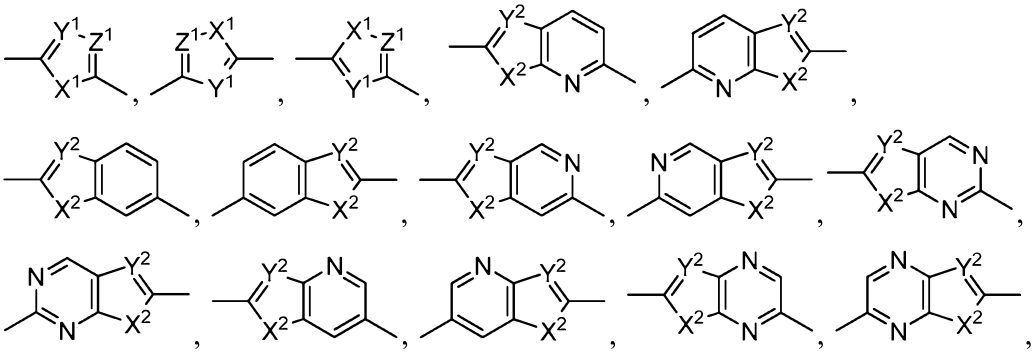
if D is absent, A and E can additionally each independently be a bond, –O–, –S–, –$S(O_2)$–, –S(O)–, –C(O)– or –N=, and

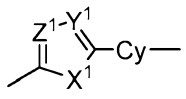
with the proviso that if W and W′ are both 5-membered rings, A and E are either both a bond or both other than a bond;

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and  , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen,

C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl,

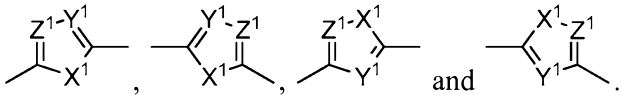
heteroaryl and aralkyl,

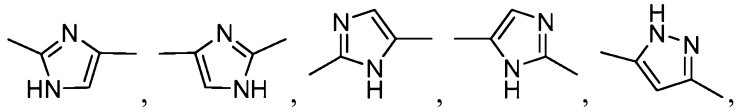
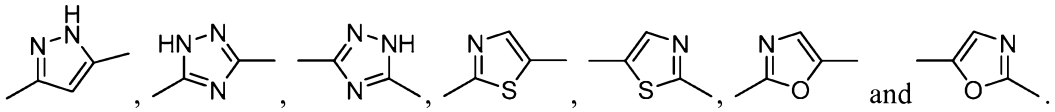
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

u is 0, 1, or 2.

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

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

[0010] In a third embodiment of the first aspect, R^c, R^d, R^e and R^f are each independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl and C_1 to C_8 heteroalkyl, wherein,

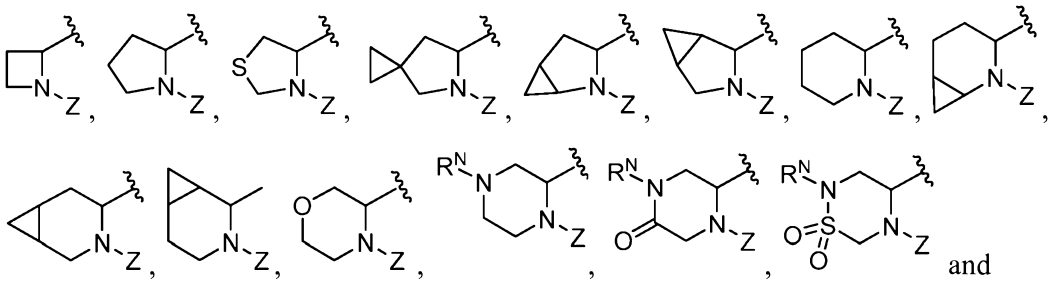
each hetero atom, if present, is independently N, O or S,

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

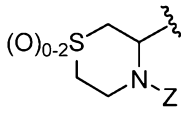
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0011] In a fourth embodiment of the first aspect, one or both of R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0012] In a fifth embodiment of the first aspect, R^c and R^d are joined and form a heterocyclic fused ring system selected from the group consisting of:

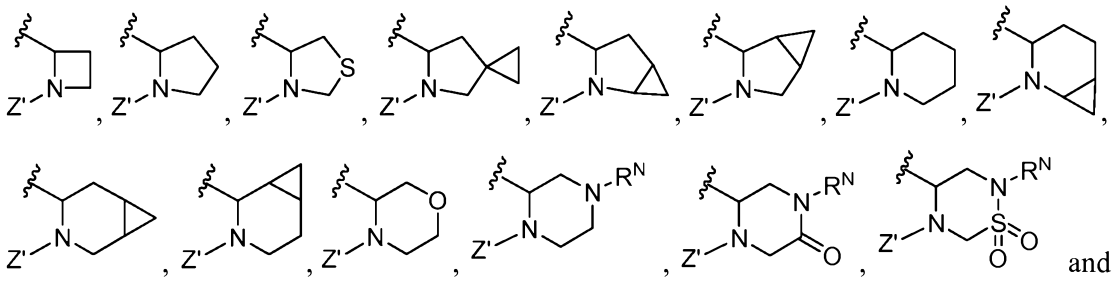


and

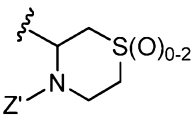


wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[0013] In a sixth embodiment of the first aspect, R^e and R^f are joined and form a heterocyclic fused ring system selected from the group consisting of:

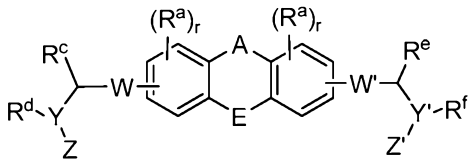


and



wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[0014] In a second aspect of the invention, compounds have formula II:



II,

wherein:

A and E are:

each independently a bond, –O–, –S–, –S(O_2)–, –S(O)–, –C(O)–, –N=,–CR_2-,

-CR=, -CR_2-CR_2-, -CR=CR-, -N=CR-, -$(CR_2)_a$-$N(R^N)$-$(CR_2)_a$-, -$(CR_2)_a$-C(O)-$N(R^N)$-$(CR_2)_a$-, -$(CR_2)_a$-$N(R^N)$-C(O)-$(CR_2)_a$- or –$(CR_2)_b$-O-$(CR_2)_b$-, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

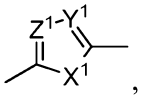
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond; and

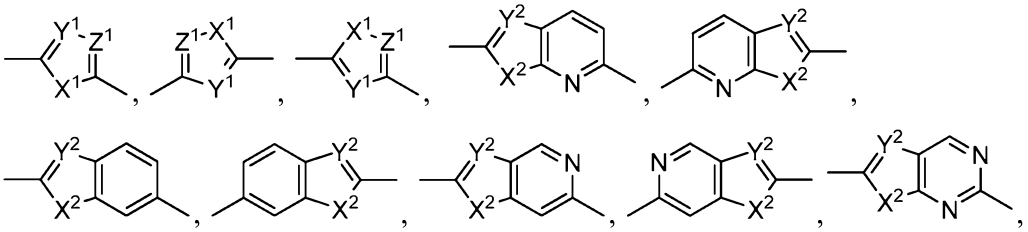
each a and b are independently 0, 1, 2, or 3; and

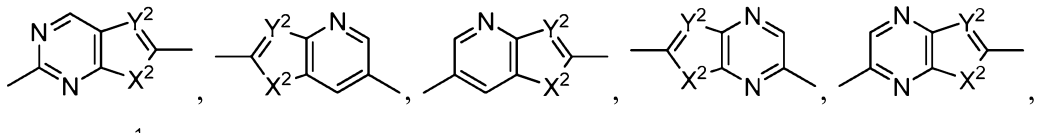
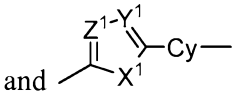
with the proviso that if W and W′ are both 5-membered rings, A and E are either both a bond or both other than a bond;

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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





and , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

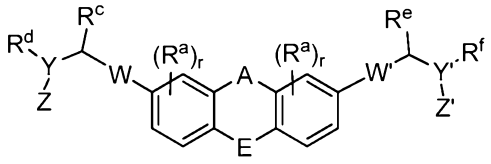
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and
$-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

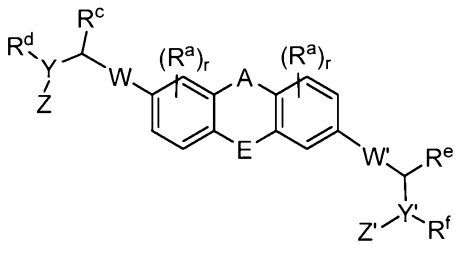
U is selected from the group consisting of –C(O)–, –C(S)– and $-S(O)_2-$,
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R^7 and R^8 together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

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



IIa.

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

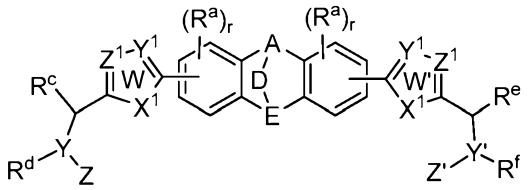


IIb.

[0017] In a third embodiment of the second aspect, both A and E are –O–.

[0018] In a fourth embodiment of the second aspect, A is –O– and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

[0019] In a third aspect of the invention, compounds of formula III are provided:



wherein:

D is either present or absent and if present selected from the group consisting of $–CR_2CR_2–$, $-CR_2-$, $–NR^N–$, –O– and –S– wherein R^N is H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently $–CR_2-$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $–(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

R^N and R may be replaced by a bond to D if D is present,

if D is absent, A and E can additionally each independently be a bond, –O–, –S–, $–S(O_2)–$, –S(O)–, –C(O)– or –N=, and

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is

optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring, and

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

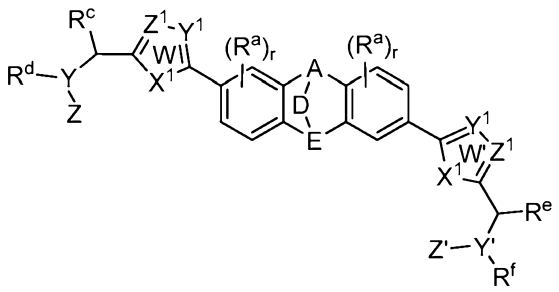
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-R^{81}_2, -$S(O)_2$-R^{81} and -$S(O)_2$-N-R^{81}_2, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

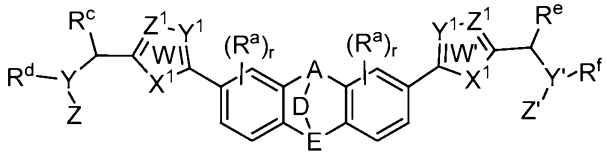
u is 0, 1, or 2.

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



IIIa.

[0021] In a second embodiment of the third aspect, compounds of formula IIIb are provided:



IIIb.

[0022] In a third embodiment of the third aspect, both A and E are –O– and D is absent.

[0023] In a fourth embodiment of the third aspect, A is –O–, D is absent and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

[0024] In a fifth embodiment of the third aspect, one or both of X^1 are –S–.

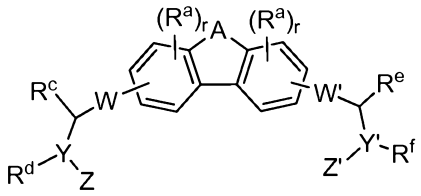
[0025] In a sixth embodiment of the third aspect, one or both of X^1 are –O–.

[0026] In a seventh embodiment of the third aspect, one or both of X^1 are –NH–.

[0027] In an eighth embodiment of the third aspect, one or both of Y^1 is –N–.

[0028] In a ninth embodiment of the third aspect, one or both of Z^1 is –N–.

[0029] In a fourth aspect of the invention, compounds of formula IV are provided:



IV

wherein:

A is a bond, $–CR_2–$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, –O–, –S–, $–S(O_2)–$, –S(O)–, –C(O)–, –N=, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $–(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino,

wherein:

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

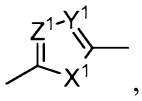
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond;

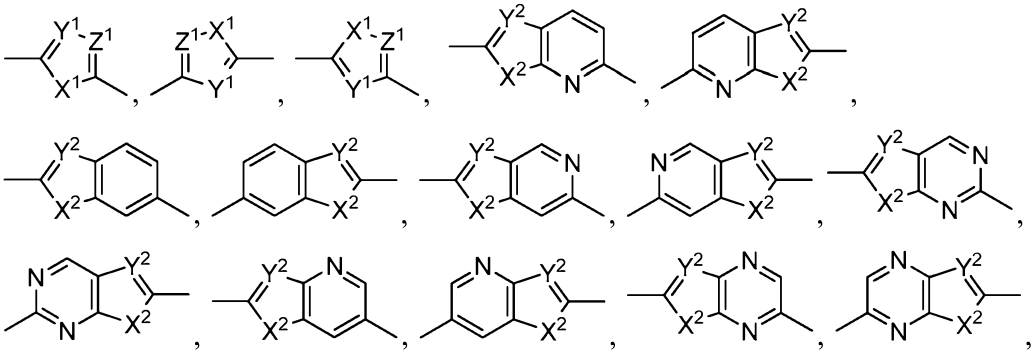
each a and b are independently 0, 1, 2, or 3; and

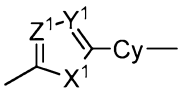
with the proviso that if W and W′ are both 5-membered rings, A is a bond;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and  , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$,

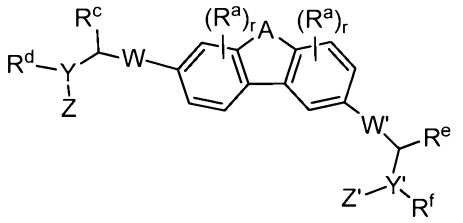
-C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

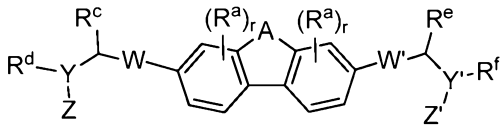
u is 0, 1, or 2.

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



IVa.

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



IVb.

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

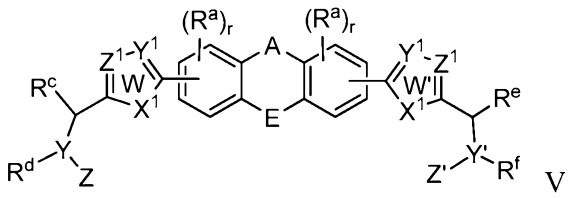
[0033] In a fourth embodiment of the fourth aspect, A is –$S(O)_2$–.

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

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

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

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



V

wherein:

A and E are:

each independently a bond, $-CR_2-$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_b-O-(CR_2)_b-$, –O–, –S–, $-S(O_2)-$, –S(O)–, –C(O)– or –N=, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

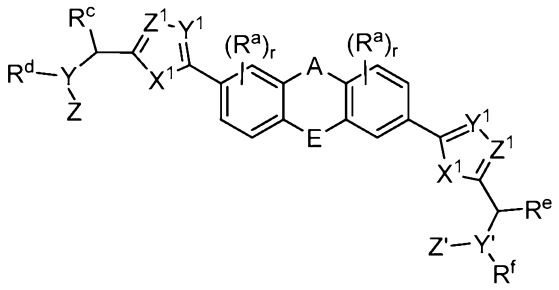
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-R^{81}_2, -$S(O)_2$-R^{81} and -$S(O)_2$-N-R^{81}_2, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

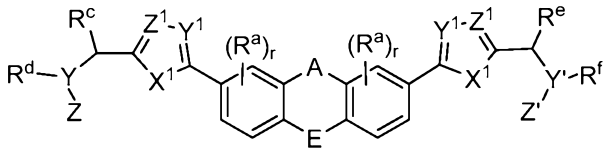
u is 0, 1, or 2.

[0038] In a first embodiment of the fifth aspect, compounds of formula Va are provided:



Va.

[0039] In a second embodiment of the fifth aspect, compounds of formula Vb are provided:



Vb.

[0040] In a third embodiment of the fifth aspect, both A and E are –O–.

[0041] In a fourth embodiment of the fifth aspect, A is –O– and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

[0042] In a fifth embodiment of the fifth aspect, one or both of X^1 are –S–.

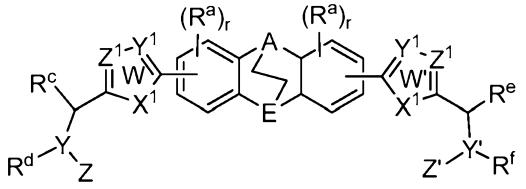
[0043] In a sixth embodiment of the fifth aspect, one or both of X^1 are –O–.

[0044] In a seventh embodiment of the fifth aspect, one or both of X^1 are –NH–.

[0045] In an eighth embodiment of the fifth aspect, one or both of Y^1 are –N–.

[0046] In a ninth embodiment of the fifth aspect, one or both of Z^1 is –N–.

[0047] In a sixth aspect, compounds of formula VI are provided:



VI

wherein:

A and E are:

each independently $–CR_2–$, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$,

$-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $-(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and

$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

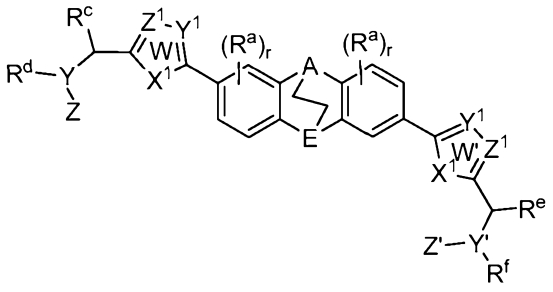
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

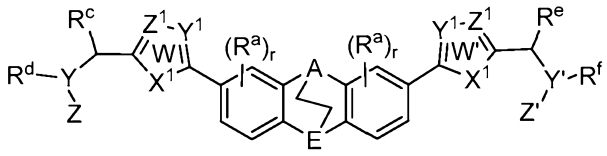
u is 0, 1, or 2.

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



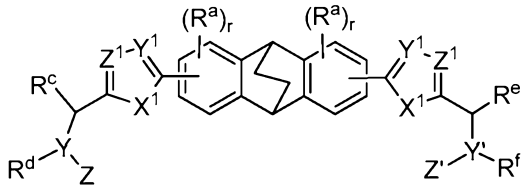
VIa.

[0049] In a second embodiment of the sixth aspect, compounds of formula VIb are provided:



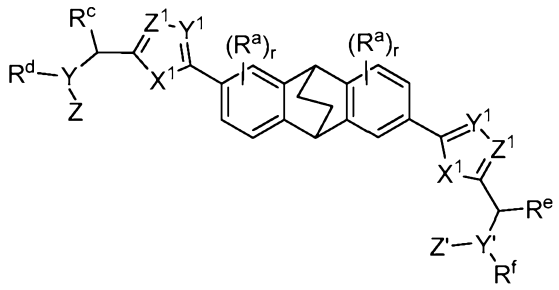
VIb.

[0050] In a third embodiment of the sixth aspect, compounds of formula VII are provided:



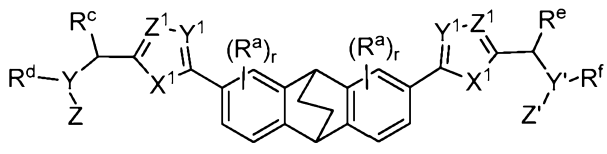
VII.

[0051] In a fourth embodiment of the sixth aspect, compounds of formula VIIa are provided:



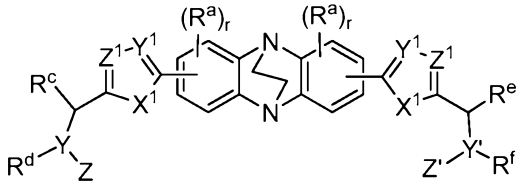
VIIa.

[0052] In a fifth embodiment of the sixth aspect, compounds of formula VIIb are provided:



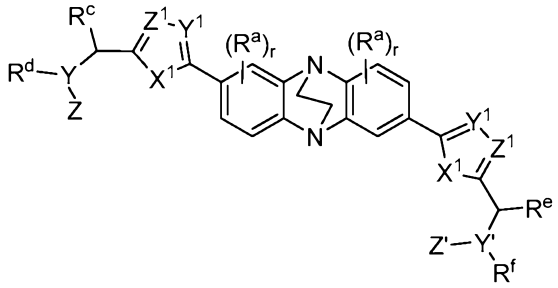
VIIb.

[0053] In a sixth embodiment of the sixth aspect, compounds of formula VIII are provided:



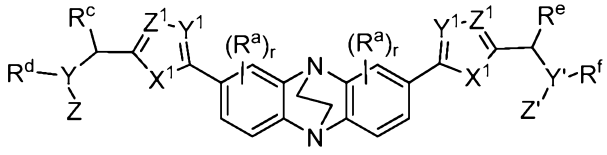
VIII.

[0054] In a seventh embodiment of the sixth aspect, compounds of formula VIIIa are provided:



VIIIa.

[0055] In an eighth embodiment of the sixth aspect, compounds of formula VIIIb are provided:



VIIIb.

[0056] In a ninth embodiment of the sixth aspect, one or both of X^1 are –O–.

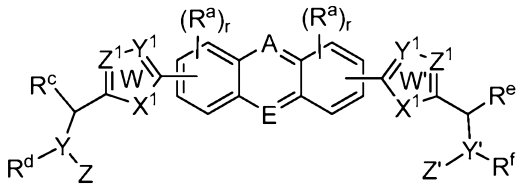
[0057] In a tenth embodiment of the sixth aspect, one or both of X^1 are –NH–.

[0058] In an eleventh embodiment of the sixth aspect, one or both of X^1 are –S–.

[0059] In a twelfth embodiment of the sixth aspect, one or both of Z^1 is –N–.

[0060] In a thirteenth embodiment of the sixth aspect, one or both of Y^1 is –N–.

[0061] In a seventh aspect of the invention, compounds of formula IX are provided:



IX

wherein:

A and E are each independently -CR= or -N= wherein R is selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

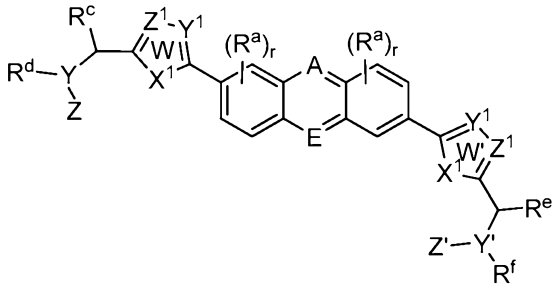
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and
$-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

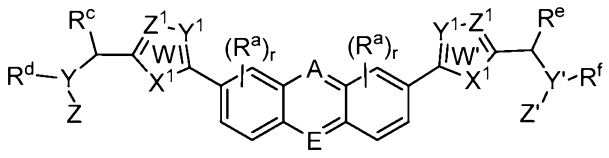
U is selected from the group consisting of –C(O)–, –C(S)– and $-S(O)_2-$,
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R^7 and R^8 together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

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



IXa.

[0063] In a second embodiment of the seventh aspect compounds of formula IXb are provided:



IXb.

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

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

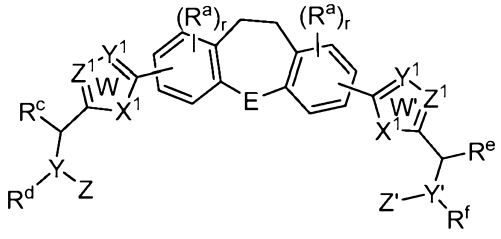
[0066] In a fifth embodiment of the seventh aspect, one or both of X^1 are –O–.

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

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

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

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



X

wherein:

E is $–CR_2$-, -CR=, $-CR_2-CR_2$-, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a$-, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a$-, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a$-, or $–(CR_2)_b-O-(CR_2)_b$-, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

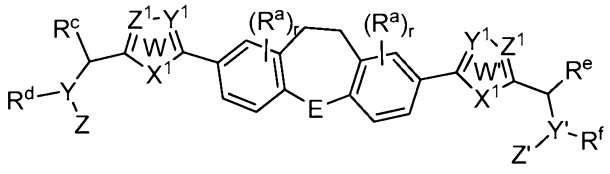
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 5- membered heterocycle or heteroaryl ring;

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and
$-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

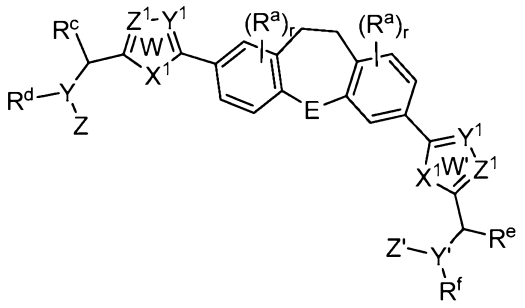
U is selected from the group consisting of –C(O)–, –C(S)– and $-S(O)_2-$,
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,
optionally, R^7 and R^8 together form a 4-7 membered ring,
each t is independently 0, 1, 2, 3, or 4, and
u is 0, 1, or 2.

[0071] In a first embodiment of the eighth aspect, compounds of formula Xa are provided:



Xa.

[0072] In a second embodiment of the eighth aspect, compounds of formula Xb are provided:



Xb.

[0073] In a third embodiment of the eighth aspect, one or both of X^1 are –S–.

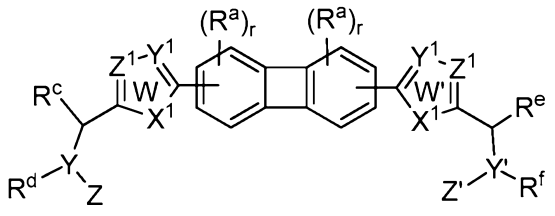
[0074] In a fourth embodiment of the eighth aspect, one or both of X^1 are –O–.

[0075] In a fifth embodiment of the eighth aspect, one or both of X^1 are –NH–.

[0076] In a sixth embodiment of the eighth aspect, one or both of Y^1 are –N–.

[0077] In a seventh embodiment of the eighth aspect, one or both of Z^1 is –N–.

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



XI

wherein:

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents

selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to

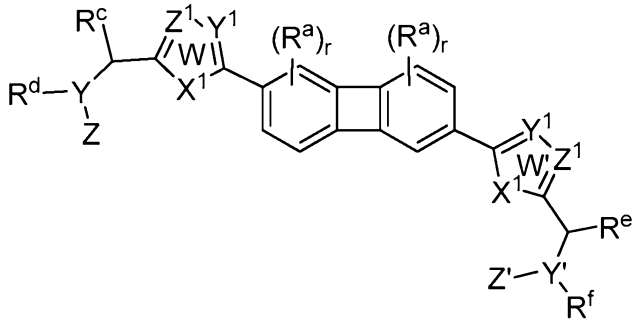
C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

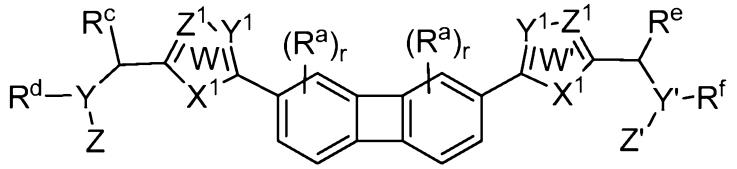
u is 0, 1, or 2.

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



XIa.

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



XIb.

[0081] In a third embodiment of the ninth aspect, one or both of X^1 are –S–.

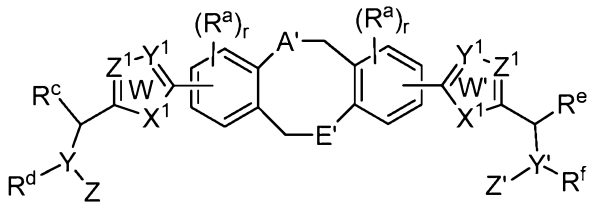
[0082] In a fourth embodiment of the ninth aspect, one or both of X^1 are –O–.

[0083] In a fifth embodiment of the ninth aspect, one or both of X^1 are –NH–.

[0084] In a sixth embodiment of the ninth aspect, one or both of Y^1 are –N–.

[0085] In a seventh embodiment of the ninth aspect, one or both of Z^1 is –N–.

[0086] In a tenth aspect of the invention, compounds of formula XII are provided:



XII, wherein:

A′ and E′ are each independently $–CR_2–$, -CR=, $–N(R^N)–$, –O–, –S–, $–S(O_2)–$, –S(O)–, or –N=, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and

R is selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and

$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

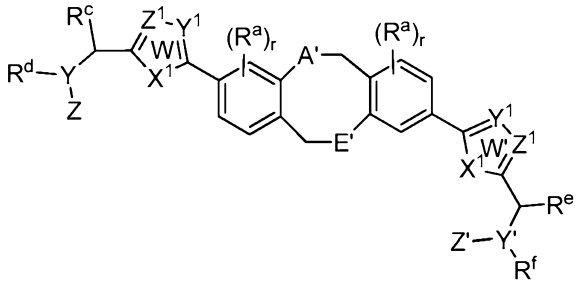
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

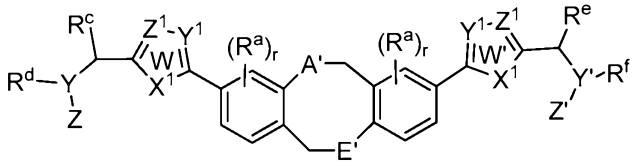
u is 0, 1, or 2.

[0087] In a first embodiment of the tenth aspect, compounds of formula XIIa are provided:



XIIa.

[0088] In a second embodiment of the tenth aspect, compounds of formula XIIb are provided:



XIIb.

[0089] In a third embodiment of the tenth aspect, one or both of X^1 are –S–.

[0090] In a fourth embodiment of the tenth aspect, one or both of X^1 are –O–.

[0091] In a fifth embodiment of the tenth aspect, one or both of X^1 are –NH–.

[0092] In a sixth embodiment of the tenth aspect, one or both of Y^1 are –N–.

[0093] In a seventh embodiment of the tenth aspect, one or both of Z^1 is –N–.

[0094] In an eleventh aspect of the invention Z and Z′ in any of the previous aspects are each 1-3 amino acids.

[0095] In a first embodiment of the eleventh aspect, the amino acids are all in the D or all in the L configuration.

[0096] In a second embodiment of the eleventh aspect, Z and Z′ are each independently selected from the group consisting of $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$, $–U–(CR^4_2)_t–R^8$ and $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–O–(CR^4_2)_t–R^8$.

[0097] In a third embodiment of the eleventh aspect, one or both of Z and Z′ are $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

[0098] In a fourth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0099] In a fifth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0100] In a sixth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0101] In a seventh embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0102] In an eighth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0103] In a ninth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0104] In a tenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0105] In an eleventh embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^{81}$.

[0106] In a twelfth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-R^{81}$.

[0107] In a thirteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-O-R^{81}$.

[0108] In a fourteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-O-R^{81}$.

[0109] In a fifteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-R^8$.

[0110] In a sixteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-R^8$.

[0111] In a seventeenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0112] In an eighteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0113] In a nineteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0114] In a twentieth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0115] In a twenty-first embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0116] In a twenty-second embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-R^8$ wherein R^7 and R^8 together form a 4-7 membered ring.

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

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

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

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

Detailed Description

[0121] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (2007) "Advanced Organic Chemistry 5th Ed." Vols. A and B, Springer Science+Business Media LLC, New York. The practice of the present invention will employ, unless otherwise indicated, conventional methods of synthetic organic chemistry, mass spectroscopy, preparative and analytical methods of chromatography, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology.

[0122] The term "alkanoyl" as used herein contemplates a carbonyl group with a lower alkyl group as a substituent.

[0123] The term "alkenyl" as used herein contemplates substituted or unsubstituted, straight and branched chain alkene radicals, including both the E- and Z-forms, containing from two to eight carbon atoms. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -S(O)R, $-SO_2R$, $-SO_3R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0124] The term "alkoxy" as used herein contemplates an oxygen with a lower alkyl group as a substituent and includes methoxy, ethoxy, butoxy, trifluromethoxy and the like. It also includes divalent substituents linked to two separated oxygen atoms such as, without limitation, $-O-(CH_2)_{1-4}-O-$, $-O-CF_2-O-$, $-O-(CH_2)_{1-4}-O-(CH_2CH_2-O)_{1-4}-$ and $-(O-CH_2CH_2-O)_{1-4}-$.

[0125] The term "alkoxycarbonyl" as used herein contemplates a carbonyl group with an alkoxy group as a substituent.

[0126] The term "alkyl" as used herein contemplates substituted or unsubstituted, straight and branched chain alkyl radicals containing from one to fifteen carbon atoms. The term "lower alkyl" as used herein contemplates both straight and branched chain alkyl radicals containing from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert-* butyl and the like. The alkyl group may be optionally substituted with one or more substituents selected from halogen, -CN, $-NO_2$, $-C(O)_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -SOR, $-SO_2R$, $-SO_3R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0127] The term "alkylene," "alkenylene" and "alkynylene" as used herein refers to the groups "alkyl," "alkenyl" and "alkynyl" respectively, when they are divalent, ie, attached to two atoms.

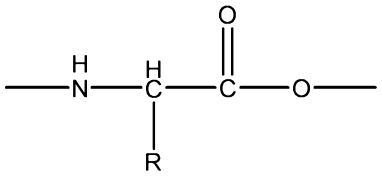
[0128] The term "alkylsulfonyl" as used herein contemplates a sulfonyl group which has a lower alkyl group as a substituent.

[0129] The term "alkynyl" as used herein contemplates substituted or unsubstituted, straight and branched carbon chain containing from two to eight carbon atoms and having at least one carbon-carbon triple bond. The term alkynyl includes, for example ethynyl,

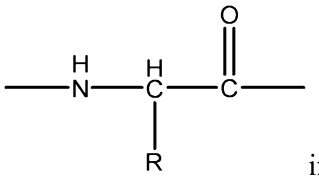
1-propynyl, 2- propynyl, 1-butynyl, 3-methyl-1-butynyl and the like. The alkynyl group may be optionally substituted with one or more substituents selected from halo, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -SOR, $-SO_2R$, $-SO_3R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0130] The term "amino" as used herein contemplates a group of the structure $-NR^N_2$.

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



or



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

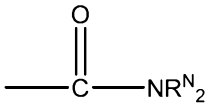
[0132] The term "aralkyl" as used herein contemplates a lower alkyl group which has as a substituent an aromatic group, which aromatic group may be substituted or unsubstituted. The aralkyl group may be optionally substituted with one or more substituents selected from halogen, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -SOR, $-SO_2R$, $-SO_3R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

[0133] The terms "aryl," "aromatic group" or "aromatic ring" as used herein contemplates substituted or unsubstituted single-ring and multiple aromatic groups (for example, phenyl, pyridyl and pyrazole, etc.) and polycyclic ring systems (naphthyl and quinolinyl, etc.). The polycyclic rings may have two or more rings in which two atoms are common to two adjoining rings (the rings are "fused") wherein at least one of the rings is aromatic, e.g., the other rings can be cycloalkyls, cycloalkenyls, aryl, heterocycles and/or heteroaryls. The aryl group may be optionally substituted with one or more substituents selected from halogen, alkyl, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -SOR, $-SO_2R$, $-SO_3R$,

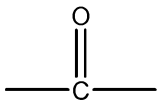
$-S(O)_2N(R^N)_2$, $-SiR_3$, -P(O)R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

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

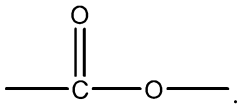
[0135] The term "carbamoyl" as used herein contemplates a group of the structure



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



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



[0138] The term "cycloalkyl" as used herein contemplates substituted or unsubstituted cyclic alkyl radicals containing from three to twelve carbon atoms and includes cyclopropyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkyl" also includes polycyclic systems having two rings in which two or more atoms are common to two adjoining rings (the rings are "fused"). The cycloalkyl group may be optionally substituted with one or more substituents selected from halo, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, -OC(O)R, $-OC(O)N(R^N)_2$, -SOR, $-SO_2R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, alkyl, cycloalkenyl, aryl and heteroaryl.

[0139] The term "cycloalkenyl" as used herein contemplates substituted or unsubstituted cyclic alkenyl radicals containing from four to twelve carbon atoms in which there is at least one double bond between two of the ring carbons and includes cyclopentenyl, cyclohexenyl and the like. The term "cycloalkenyl" also includes polycyclic systems having two rings in which two or more atoms are common to two adjoining rings (the rings are "fused"). The cycloalkenyl group may be optionally substituted with one or more substituents selected from halo, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR,

$-C(O)N(R^N)_2$, $-OC(O)R$, $-OC(O)N(R^N)_2$, $-SOR$, $-SO_2R$, $-S(O)_2N(R^N)_2$, phosphate, phosphonate, alkyl, cycloalkenyl, aryl and heteroaryl.

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

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

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

[0143] The term "heterocyclic group," "heterocycle" or "heterocyclic ring" as used herein contemplates substituted or unsubstituted aromatic and non-aromatic cyclic radicals having at least one heteroatom as a ring member. Preferred heterocyclic groups are those containing five or six ring atoms which includes at least one hetero atom and includes cyclic amines such as morpholino, piperidino, pyrrolidino and the like and cyclic ethers, such as tetrahydrofuran, tetrahydropyran and the like. Aromatic heterocyclic groups, also termed "heteroaryl" groups, contemplates single-ring hetero-aromatic groups that may include from one to three heteroatoms, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, oxodiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrimidine and the like. The term heteroaryl also includes polycyclic hetero-aromatic systems having two or more rings in which two or more atoms are common to two adjoining rings (the rings are "fused") wherein at least one of the rings is a heteroaryl, e.g., the other rings can be cycloalkyls, cycloalkenyls, aryl, heterocycles and/or heteroaryls. Examples of polycyclic heteroaromatic systems include quinoline, isoquinoline, cinnoline, tetrahydroisoquinoline, quinoxaline, quinazoline, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, indazole, purine, benzotriazole, pyrrolepyridine, pyrrazolopyridine and the like. The heterocyclic group may be optionally substituted with one or more substituents selected from the group consisting of halo, alkyl, -CN, $-NO_2$, $-CO_2R$, -C(O)R, -O-R, $-N(R^N)_2$, $-N(R^N)C(O)R$, $-N(R^N)S(O)_2R$, -SR, $-C(O)N(R^N)_2$, $-OC(O)R$, $-OC(O)N(R^N)_2$, $-SOR$, $-SO_2R$, $-SO_3R$, $-S(O)_2N(R^N)_2$, $-SiR_3$, -P(O)R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

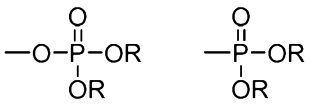
[0144] The term "oxo" as used herein contemplates an oxygen atom attached with a double bond.

[0145] By "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material which is not biologically or otherwise undesirable, i.e., the material may be

administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

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

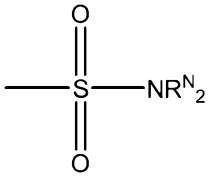
[0147] The terms "phosphate" and "phosphonate" as used herein refer to the moieties having the following structures, respectively:



[0148] The terms "salts" and "hydrates" refers to the hydrated forms of the compound that would favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which those skilled in the art may take into account in the selection

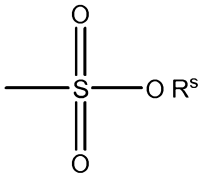
include the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity, flowability and manufacturability of the resulting bulk drug.

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



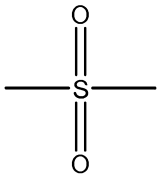
.

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



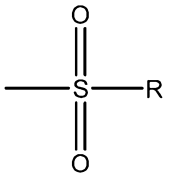
wherein R^s is selected from the group consisting of hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkanoyl or C_1-C_{10} alkoxycarbonyl.

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



.

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



including, but not limited to alkylsulfonyl and arylsulfonyl.

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

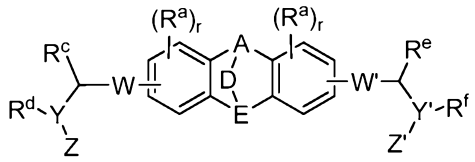
[0154] Each R is independently selected from hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, amino and oxo.

[0155] Each R^N is independently selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,

sulfonate and sulfonamide. Two R^N may be taken together with C, O, N or S to which they are attached to form a five to seven membered ring which may optionally contain a further heteroatom.

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

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



I

wherein:

D is either present or absent and if present selected from the group consisting of $-CR_2CR_2-$, $-CR_2-$, $-NR^N-$, –O– and –S– wherein:

R^N is H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently $-CR_2-$, $-CR=$, $-CR_2-CR_2-$, $-CR=CR-$, $-N=CR-$, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $-(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and

sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

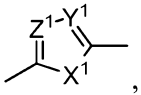
R^N and R may be replaced by a bond to D if D is present,

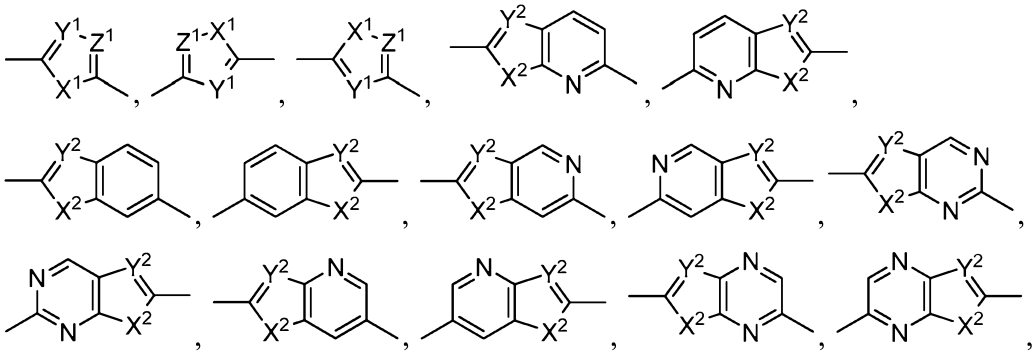
if D is absent, A and E can additionally each independently be a bond, –O–, –S–, –$S(O_2)$–, –S(O)–, –C(O)– or –N=, and

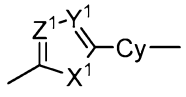
with the proviso that if W and W′ are both 5-membered rings, A and E are either both a bond or both other than a bond;

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and  , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8

alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

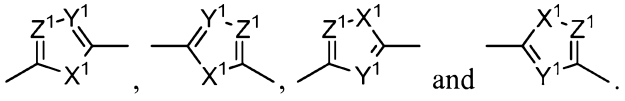
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

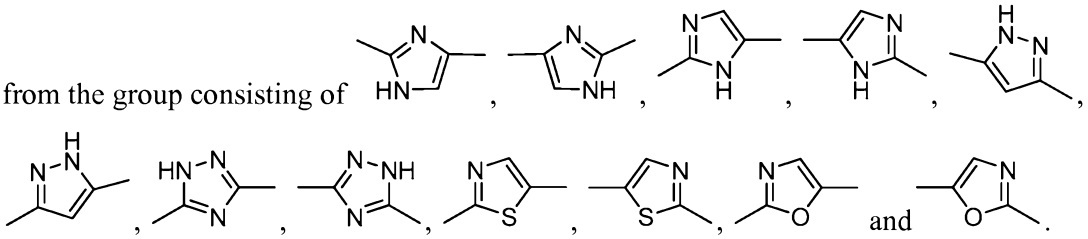
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-R^{81}_2, -$S(O)_2$-R^{81} and -$S(O)_2$-N-R^{81}_2, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

u is 0, 1, or 2.

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

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

[0160] In a third embodiment of the first aspect, R^c, R^d, R^e and R^f are each independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl and C_1 to C_8 heteroalkyl, wherein,

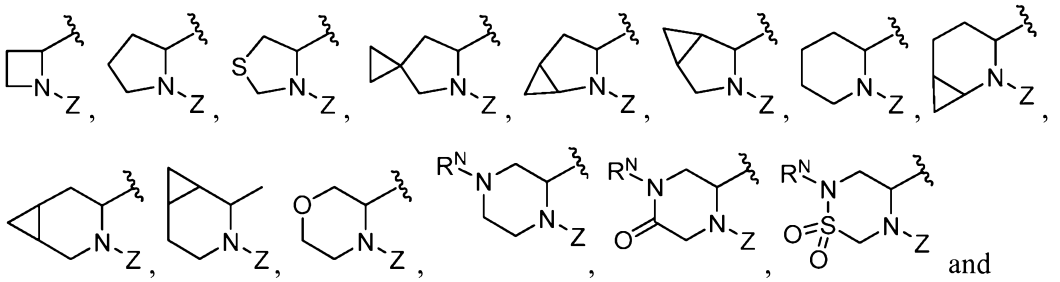
each hetero atom, if present, is independently N, O or S,

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

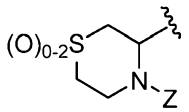
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

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

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

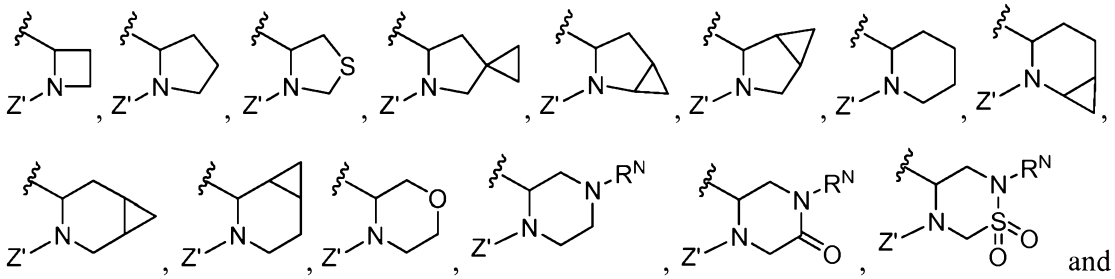


and

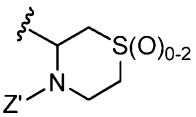


wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

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

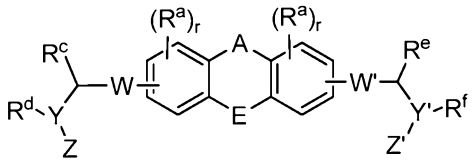


and



wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[0164] In a second aspect of the invention, compounds have formula II:



II,

wherein:

A and E are:

each independently a bond, –O–, –S–, $–S(O_2)–$, –S(O)–, –C(O)–, –N=,$–CR_2-$, $-CR=$, $-CR_2-CR_2-$, $-CR=CR-$, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $–(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

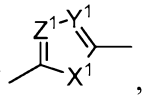
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond; and

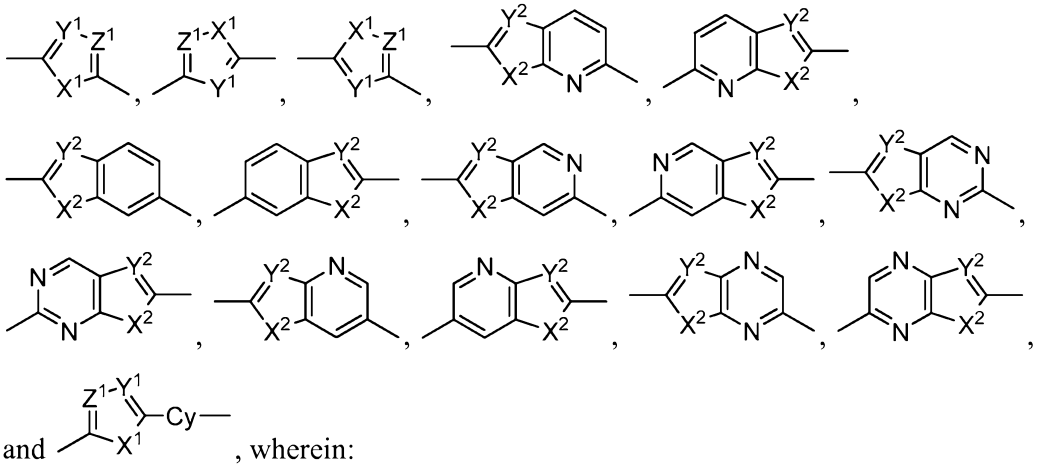
each a and b are independently 0, 1, 2, or 3; and

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl,

heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and

$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

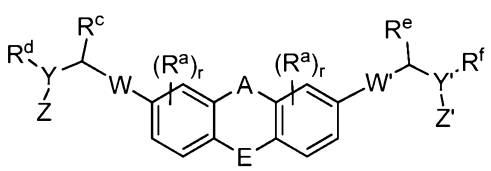
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

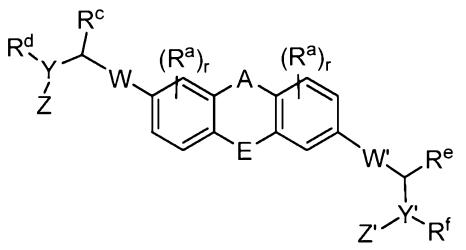
u is 0, 1, or 2.

[0165] In a first embodiment of the second aspect, compounds of formula IIa are provided:



IIa.

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

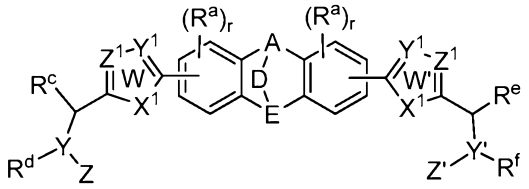


IIb.

[0167] In a first embodiment of the second aspect, both A and E are –O–.

[0168] In a second embodiment of the second aspect, A is –O– and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

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



wherein:

D is either present or absent and if present selected from the group consisting of $–CR_2CR_2–$, $-CR_2-$, $–NR^N–$, –O– and –S– wherein R^N is H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently $–CR_2-$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $–(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

R^N and R may be replaced by a bond to D if D is present,

if D is absent, A and E can additionally each independently be a bond, –O–, –S–, –S(O_2)–, –S(O)–, –C(O)– or –N=, and

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

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and

$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

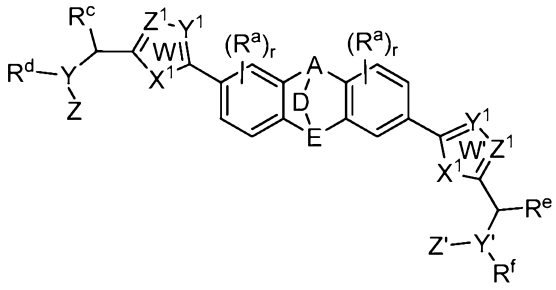
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

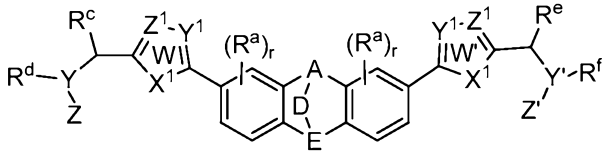
u is 0, 1, or 2.

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



IIIa.

[0171] In a second embodiment of the third aspect, compounds of formula IIIb are provided:



IIIb.

[0172] In a third embodiment of the third aspect, both A and E are –O– and D is absent.

[0173] In a fourth embodiment of the third aspect, A is –O–, D is absent and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

[0174] In a fifth embodiment of the third aspect, one or both of X^1 are –S–.

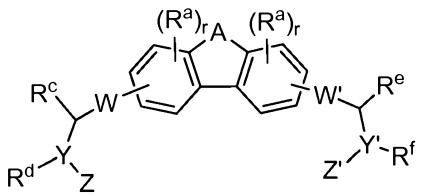
[0175] In a sixth embodiment of the third aspect, one or both of X^1 are –O–.

[0176] In a seventh embodiment of the third aspect, one or both of X^1 are –NH–.

[0177] In an eighth embodiment of the third aspect, one or both of Y^1 are –N–.

[0178] In a ninth embodiment of the third aspect, one or both of Z^1 is –N–.

[0179] In a fourth aspect of the invention, compounds of formula IV are provided:



IV

wherein:

A is a bond, $–CR_2–$, -CR=, $-CR_2-CR_2–$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a–$, –O–, –S–, $–S(O_2)–$, –S(O)–, –C(O)–, –N=, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a–$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a–$ or $–(CR_2)_b-O-(CR_2)_b–$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12}

heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

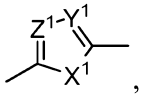
where two R's are possible on a C, the C may optionally be linked to a single R with a double bond;

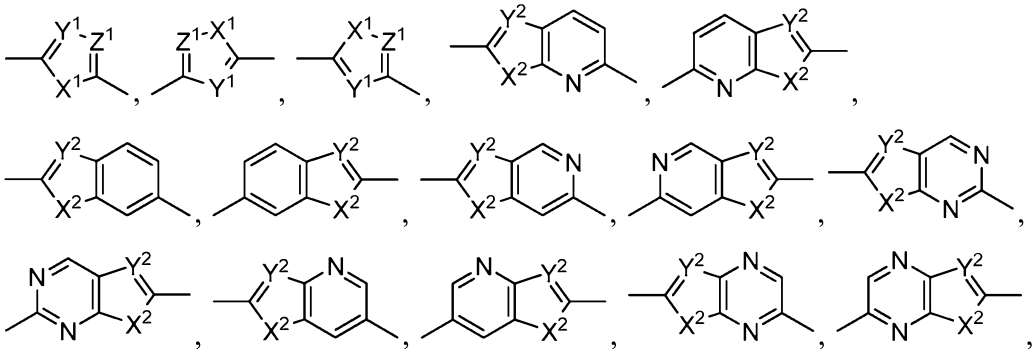
each a and b are independently 0, 1, 2, or 3; and

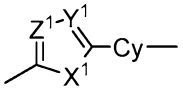
with the proviso that if W and W′ are both 5-membered rings, A is a bond;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and  , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and

$-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

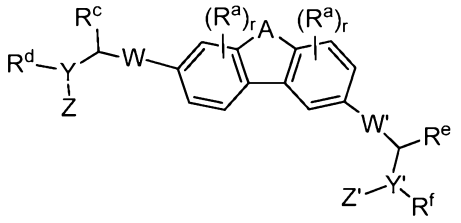
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

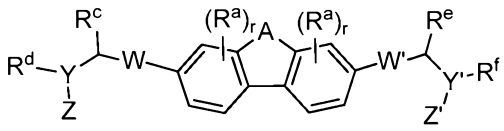
u is 0, 1, or 2.

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



IVa.

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



IVb.

[0182] In a third embodiment of the fourth aspect, A is –S–.

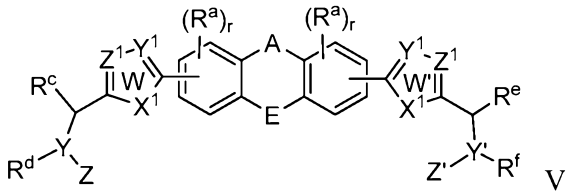
[0183] In a fourth embodiment of the fourth aspect, A is $-S(O)_2-$.

[0184] In a fifth embodiment of the fourth aspect, A is –O–.

[0185] In a sixth embodiment of the fourth aspect, A is $-CH_2-$.

[0186] In a seventh embodiment of the fourth aspect, A is $-CH_2$-CH2-.

[0187] In a fifth aspect of the embodiment, compounds of formula V are provided:



V

wherein:

A and E are:

each independently a bond, $-CR_2-$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ $-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_b-O-(CR_2)_b-$, –O–, –S–, $-S(O_2)-$, –S(O)–, –C(O)– or –N=, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and

$-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$,

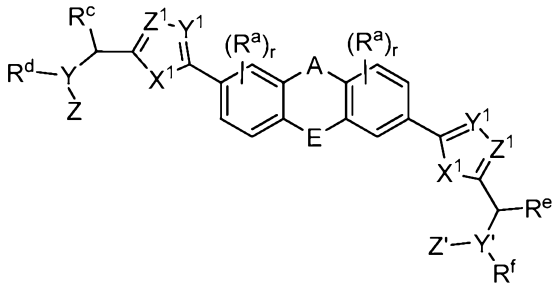
-C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

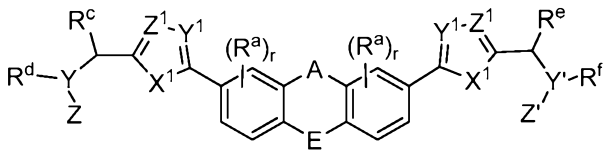
u is 0, 1, or 2.

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



Va.

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



Vb.

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

[0191] In a fourth embodiment of the fifth aspect, A is –O– and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

[0192] In a fifth embodiment of the fifth aspect, one or both of X^1 are –S–.

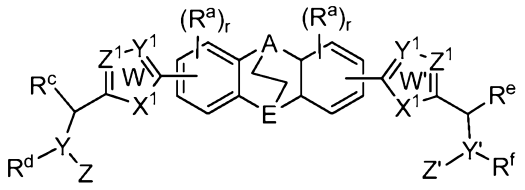
[0193] In a sixth embodiment of the fifth aspect, one or both of X^1 are –O–.

[0194] In a seventh embodiment of the fifth aspect, one or both of X^1 are –NH–.

[0195] In an eighth embodiment of the fifth aspect, one or both of Y^1 are –N–.

[0196] In a ninth embodiment of the fifth aspect, one or both of Z^1 is –N–.

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



VI

wherein:

A and E are:

each independently $-CR_2-$, $-CR_2-CR_2-$, $-CR=CR-$, $-N=CR-$,

$-(CR_2)_a-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$,

$-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$ or $-(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}{}_2$, wherein

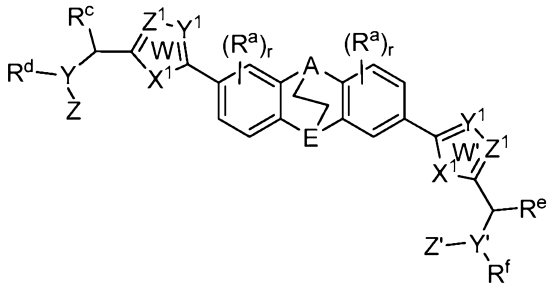
each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

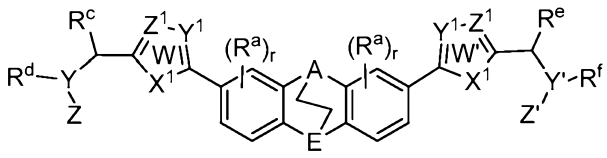
u is 0, 1, or 2.

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



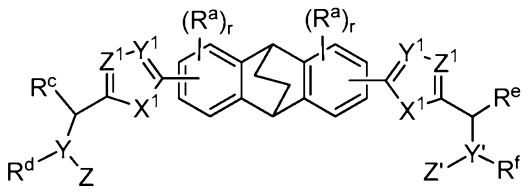
VIa.

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



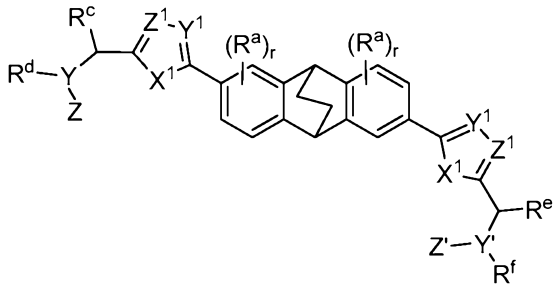
VIb.

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



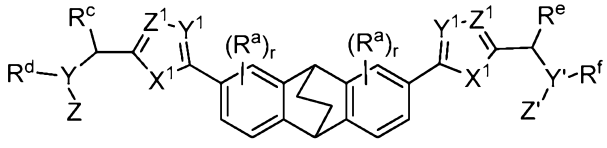
VII.

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



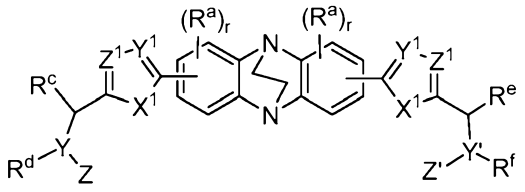
VIIa.

[0202] In a fifth embodiment of the sixth aspect, compounds of formula VIIb are provided:



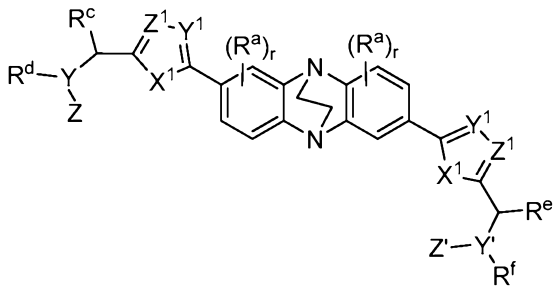
VIIb.

[0203] In a sixth embodiment of the sixth aspect, compounds of formula VIII are provided:



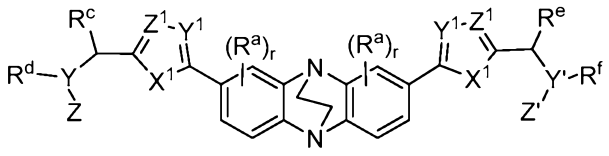
VIII.

[0204] In a seventh embodiment of the sixth aspect, compounds of formula VIIIa are provided:



VIIIa.

[0205] In an eighth embodiment of the sixth aspect, compounds of formula VIIIb are provided:



VIIIb.

[0206] In a ninth embodiment of the sixth aspect, one or both of X^1 are –O–.

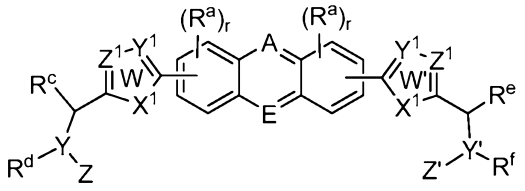
[0207] In a tenth embodiment of the sixth aspect, one or both of X^1 are –NH–.

[0208] In an eleventh embodiment of the sixth aspect, one or both of X^1 are –S–.

[0209] In a twelfth embodiment of the sixth aspect, one or both of Z^1 is –N–.

[0210] In a thirteenth embodiment of the sixth aspect, one or both of Y^1 is –N–.

[0211] In a seventh aspect of the invention, compounds of formula IX are provided:



IX

wherein:

A and E are each independently -CR= or -N= wherein R is selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}{}_2$, wherein

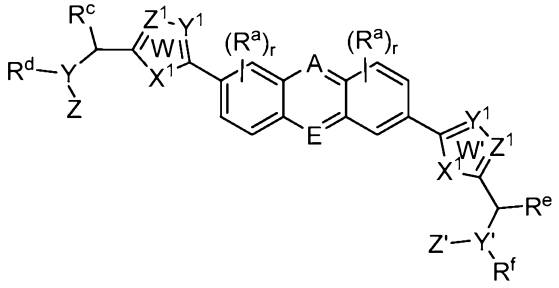
each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

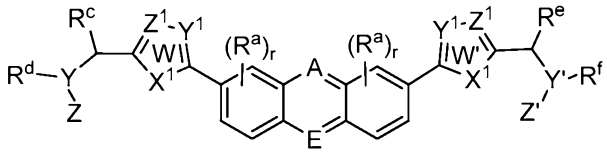
u is 0, 1, or 2.

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



IXa.

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



IXb.

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

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

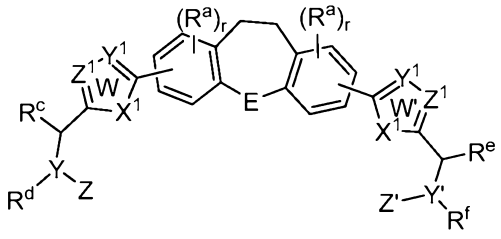
[0216] In a fifth embodiment of the seventh aspect, one or both of X^1 are –O–.

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

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

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

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



X

wherein:

E is $-CR_2-$, -CR=, $-CR_2-CR_2-$, -CR=CR-, -N=CR-, $-(CR_2)_a-N(R^N)-(CR_2)_a-$ $-(CR_2)_a-C(O)-N(R^N)-(CR_2)_a-$, $-(CR_2)_a-N(R^N)-C(O)-(CR_2)_a-$, or $-(CR_2)_b-O-(CR_2)_b-$, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide,

each R is independently selected from the group consisting of hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

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

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents

selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to

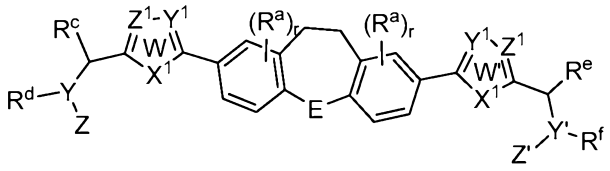
C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

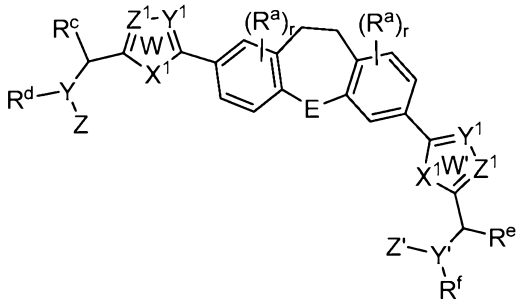
u is 0, 1, or 2.

[0221] In a first embodiment of the eighth aspect, compounds of formula Xa are provided:



Xa.

[0222] In a second embodiment of the eighth aspect, compounds of formula Xb are provided:



Xb.

[0223] In a third embodiment of the eighth aspect, one or both of X^1 are –S–.

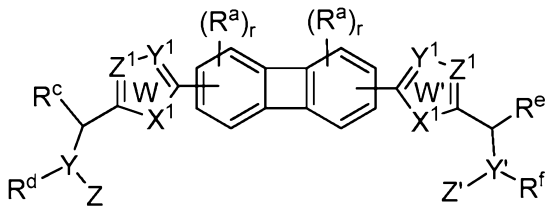
[0224] In a fourth embodiment of the eighth aspect, one or both of X^1 are –O–.

[0225] In a fifth embodiment of the eighth aspect, one or both of X^1 are –NH–.

[0226] In a sixth embodiment of the eighth aspect, one or both of Y^1 are –N–.

[0227] In a seventh embodiment of the eighth aspect, one or both of Z^1 is –N–.

[0228] In a ninth aspect of the invention, compounds of formula XI are provided:



XI

wherein:

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3

amino acids,

$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

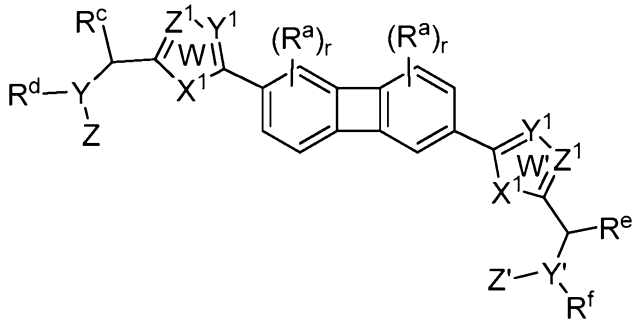
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-R^{81}_2, $-S(O)_2-R^{81}$ and $-S(O)_2$-N-R^{81}_2, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

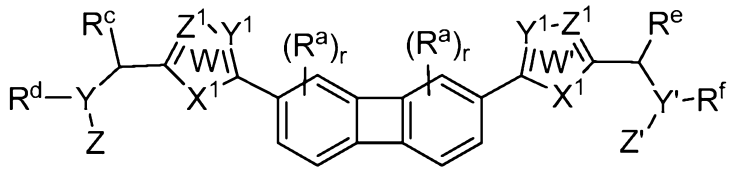
u is 0, 1, or 2.

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



XIa.

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



XIb.

[0231] In a third embodiment of the ninth aspect, one or both of X^1 are –S–.

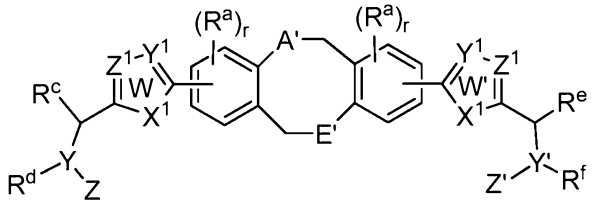
[0232] In a fourth embodiment of the ninth aspect, one or both of X^1 are –O–.

[0233] In a fifth embodiment of the ninth aspect, one or both of X^1 are –NH–.

[0234] In a sixth embodiment of the ninth aspect, one or both of Y^1 are –N–.

[0235] In a seventh embodiment of the ninth aspect, one or both of Z^1 is –N–.

[0236] In a tenth aspect of the invention, compounds of formula XII are provided:



XII, wherein:

A′ and E′ are each independently –CR_2–, -CR=, –$N(R^N)$–, –O–, –S–, –$S(O_2)$–, –S(O)–, or –N=, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and

R is selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

X^1 is CH_2, NH, O or S,

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

W and W′ are each independently optionally substituted with one or more substituents

selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, and

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,

$-[U-(CR^4{}_2)_t-NR^5-C(R^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$, $-U-(CR^4{}_2)_t-R^8$, and $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$, wherein,

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

each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}{}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to

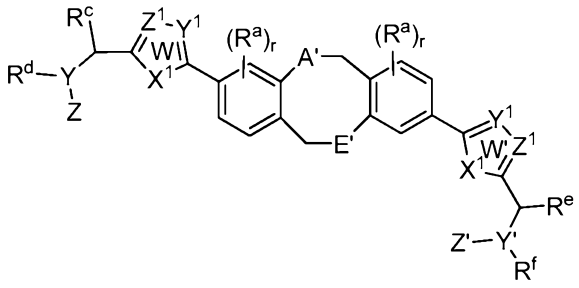
C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

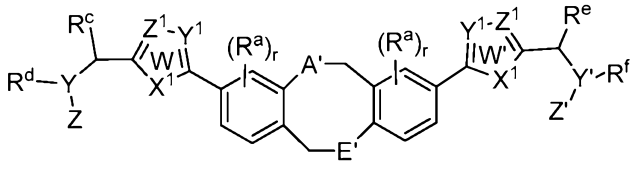
u is 0, 1, or 2.

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



XIIa.

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



XIIb.

[0239] In a third embodiment of the tenth aspect, one or both of X^1 are –S–.

[0240] In a fourth embodiment of the tenth aspect, one or both of X^1 are –O–.

[0241] In a fifth embodiment of the tenth aspect, one or both of X^1 are –NH–.

[0242] In a sixth embodiment of the tenth aspect, one or both of Y^1 are –N–.

[0243] In a seventh embodiment of the tenth aspect, one or both of Z^1 is –N–.

[0244] In an eleventh aspect of the invention Z and Z′ in any of the previous aspects are each 1-3 amino acids.

[0245] In a first embodiment of the eleventh aspect, the amino acids are all in the D or all in the L configuration.

[0246] In a second embodiment of the eleventh aspect, Z and Z′ are each independently selected from the group consisting of
$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$,
$-U-(CR^4_2)_t-R^8$ and $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0247] In a third embodiment of the eleventh aspect, one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0248] In a fourth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0249] In a fifth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0250] In a sixth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0251] In a seventh embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0252] In an eighth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0253] In a ninth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0254] In a tenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0255] In an eleventh embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)\text{-}R^{81}$.

[0256] In a twelfth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)\text{-}R^{81}$.

[0257] In a thirteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)\text{-}O\text{-}R^{81}$.

[0258] In a fourteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)\text{-}O\text{-}R^{81}$.

[0259] In a fifteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-R^8$.

[0260] In a sixteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-R^8$.

[0261] In a seventeenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0262] In an eighteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0263] In a nineteenth embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-C(O)-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0264] In a twentieth embodiment of the eleventh aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0265] In a twenty-first embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0266] In a twenty-second embodiment of the eleventh aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_n-NR^7-R^8$ wherein R^7 and R^8 together form a 4-7 membered ring.

[0267] A twelfth aspect of the invention provides a pharmaceutical composition comprising the compounds of the invention.

[0268] A thirteenth aspect of the invention provides use of the compounds of the invention in the manufacture of a medicament.

[0269] In a first embodiment of the thirteenth aspect the medicament is for the treatment of hepatitis C.

[0270] A fourteenth aspect of the invention provides a method of treating hepatitis C comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the invention.

General Synthesis

[0271] The following abbreviations are used throughout this application:

ACN	Acetonitrile
AcOH	Acetic acid
aq	Aqueous
Bn	Benzyl
BnOH	Benzyl alcohol
Boc	*t*-Butoxycarbonyl
Cbz	Benzoxylcarbonoyl

DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPBT	3-(Diethoxy-phosphoryloxy)-3H-benzo[d][1,2,3] triazin-4-one
DIEA (DIPEA)	Diisopropylethylamine
DIBAL	Diisobutylaluminium hydride
DMA	*N,N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DPPA	Diphenylphosphoryl azide
dppp	1,3-Bis(diphenylphosphino)propane
DTT	Dithiothreitol
EDCI	1-Ethyl-3-[3-(dimethylamino) propyl]carbodiimide hydrochloride
EDTA	Ethylene diamine tetraacetic acid
EC_{50}	Effective concentration to produce 50% of the maximal effect
ESI	Electrospray Ionization
Et_3N, TEA	Triethylamine
EtOAc, EtAc	Ethyl acetate
EtOH	Ethanol
g	Gram(s)
h or hr	Hour(s)
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
IC_{50}	The concentration of an inhibitor that causes a 50 % reduction in a measured activity
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LC-MS	Liquid Chramatography Mass Spectrometry
mCPBA	m-Chloroperoxybenzoic acid
MeI	Methyl Iodide
MeOH	Methanol
min	Minute(s)
mmol	Millimole(s)
Moc	Methoxylcarbonyl
NMM	4-Methylmorpholine
NMP	N-methylpyrrolidinone
PG	Protective Group
PTT	Phenyl trimethyl tribromide
Py, Pyr	Pyridine
rt	Room temperature
TEA	Triethylamine
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

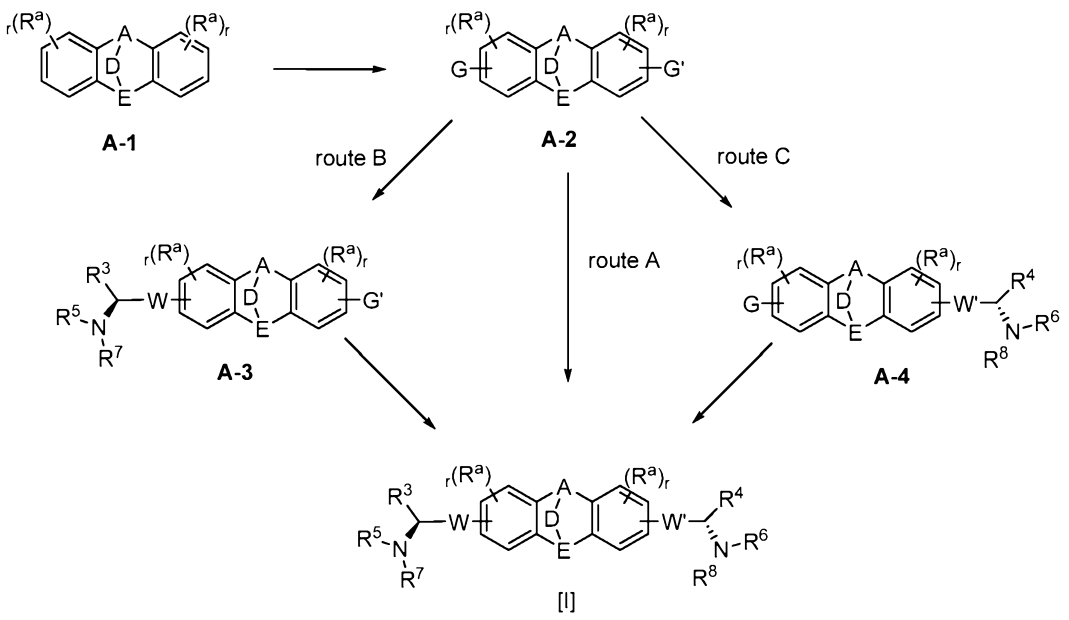
[0272] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}HNMR spectra were recorded on a Bruker 400 MHz or 500 MHz NMR spectrometer. Significant peaks are tabulated in the order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons.

[0273] The following examples are provided by way of illustration only and not by way of limitation. Those skilled in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental errors and deviations should, of course, be allowed for.

[0274] Liquid chromatography mass spectra (LC-MS) were obtained using an electrospray ionization (ESI) source in either the positive or negative mode.

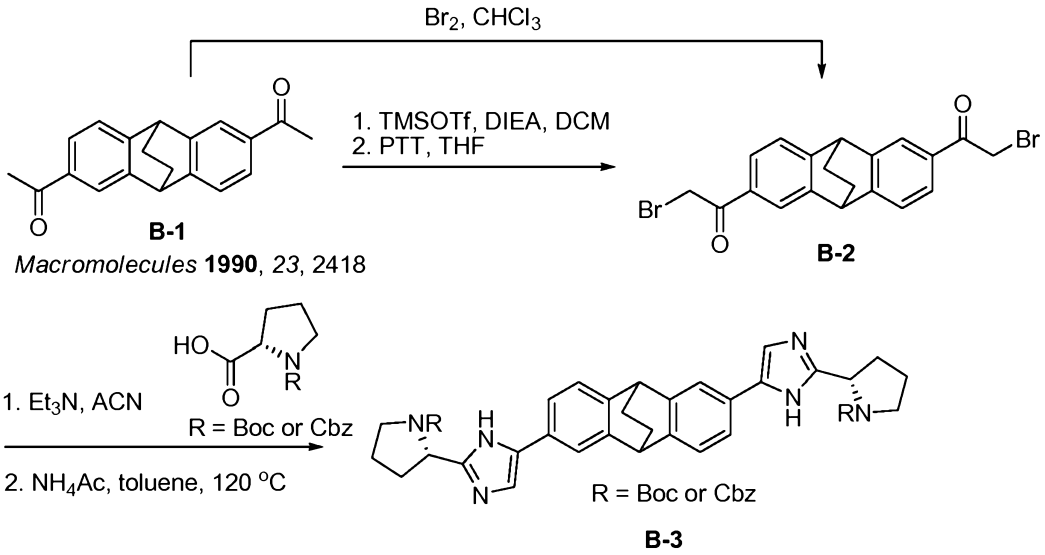
[0275] The compounds were named using ChemDraw program from Cambridge Soft Inc.

[0276] The compounds of formula I in this invention can be prepared following the synthetic strategies outlined in Scheme A. The synthesis generally starts with the tricyclic central core **A-1**, which is either available from commercial sources, prepared following literature reports or prepared as disclosed here. The cyclic core can be prepared bearing the suitable substituents. The flanking W and W' moieties, along with the groups attached to them, may be constructed through a stepwise functional group transformations of G and G' in parallel (route A) or one side at a time (route B and then route C or vice versa). The W and W' and respective moieties attached to them can be introduced through a cross coupling step. Once the central core scaffold is in place, further elaboration of the two ends yields additional compounds.



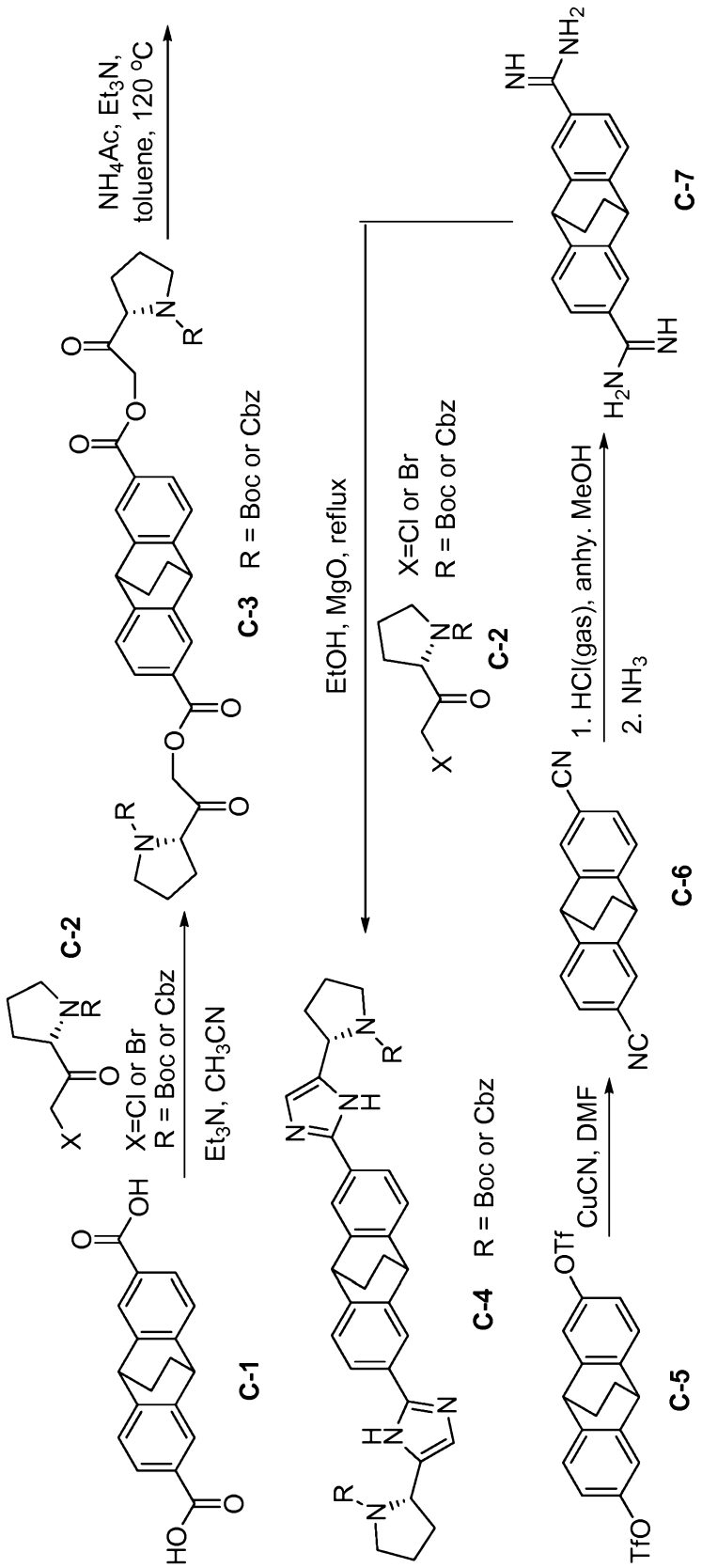
Scheme A

[0277] The preparations of the various claimed chemical series are further illustrated in the schemes outlined below and in greater details in the Example section. These reactions are often carried out using known procedures, methods or analogous methods thereof. Examples of such known methods include these described in a general reference text such as Comprehensive Organic Transformations; Volumes 1-10, 1974-2002, Wiley Interscience; Comprehensive Organic Synthesis Volumes 1-9, Ed. B. M. Trost, I. Fleming, 1991, Pergamon. Using 9,10-dihydro-9,10-ethanoanthracene, 5,10-dimethyl-5,10-dihydrophenazine, phenoxathiine and dibenzo[1,5]dioxocine systems as examples, we show some of the ways how W and W' groups are installed.



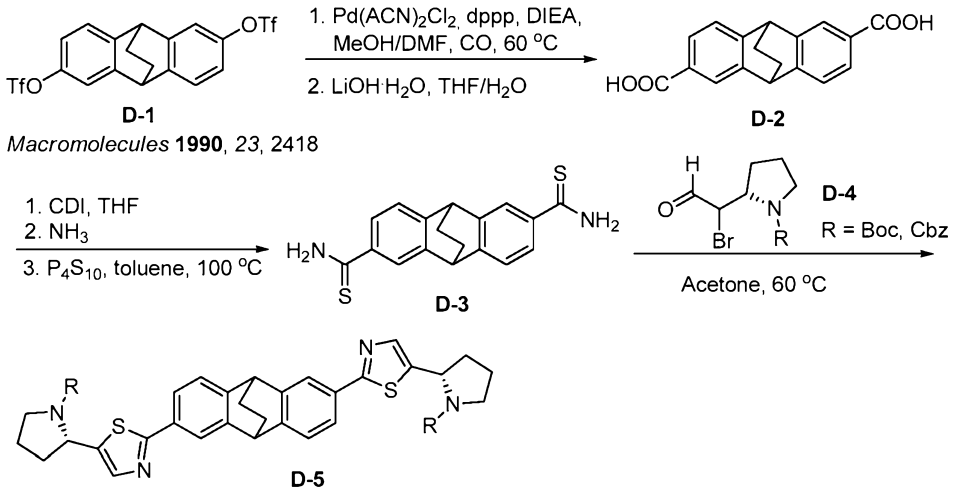
Scheme B

[0278] As shown in Scheme B, compound **B-1** is converted to the corresponding α-bromoketone **B-2**, followed by reacting with N-substituted-L-Pro-OH and ring formation, to give bis-imidazole derivative **B-3** which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-imidazole analogs of **B-3**.


C-1
C-2
X=Cl or Br
R = Boc or Cbz
Et3N, CH3CN
C-3 R = Boc or Cbz
NH4Ac, Et3N,
toluene, 120 °C
EtOH, MgO, reflux
C-4 R = Boc or Cbz
C-5
CuCN, DMF
C-6
1. HCl(gas), anhy. MeOH
2. NH3
C-7

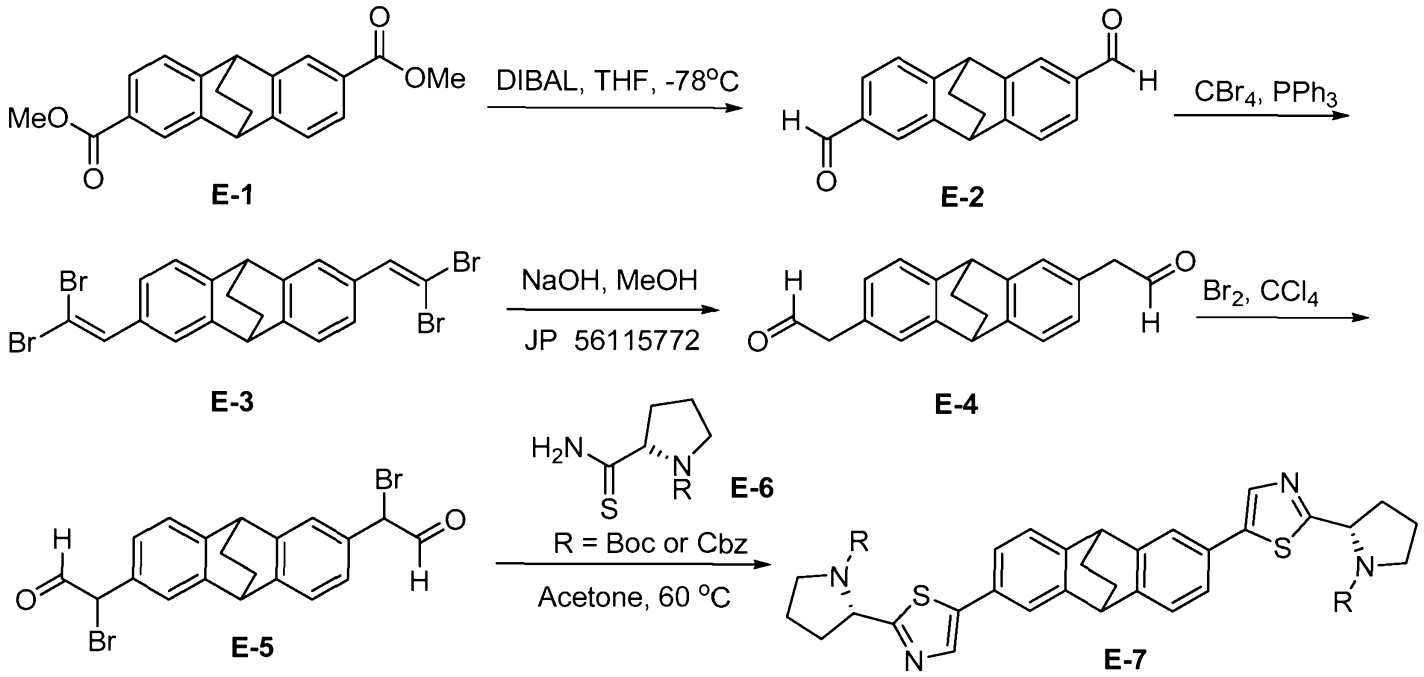
Scheme C

[0279] As described in Scheme C, the regioisomer of **B-3** with respect to the substitution pattern on the imidazole moiety is synthesized. Coupling of **C1** and (*S*)-2-halo-1-(pyrrolidin-2-yl)ethanone **C-2**, followed by ring formation, gives bis-imidazole **C-4**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Alternatively, **C-4** can be obtained by condensing **C-2** and bis-imidamide **C-7**. Moreover, (*S*)-2-halo-1-(pyrrolidin-2-yl)ethanone **C-2** can be replaced with other α-halo ketones derived from N-substituted D- or L-amino acids to generate bis-imidazole analogs of **C-4.**



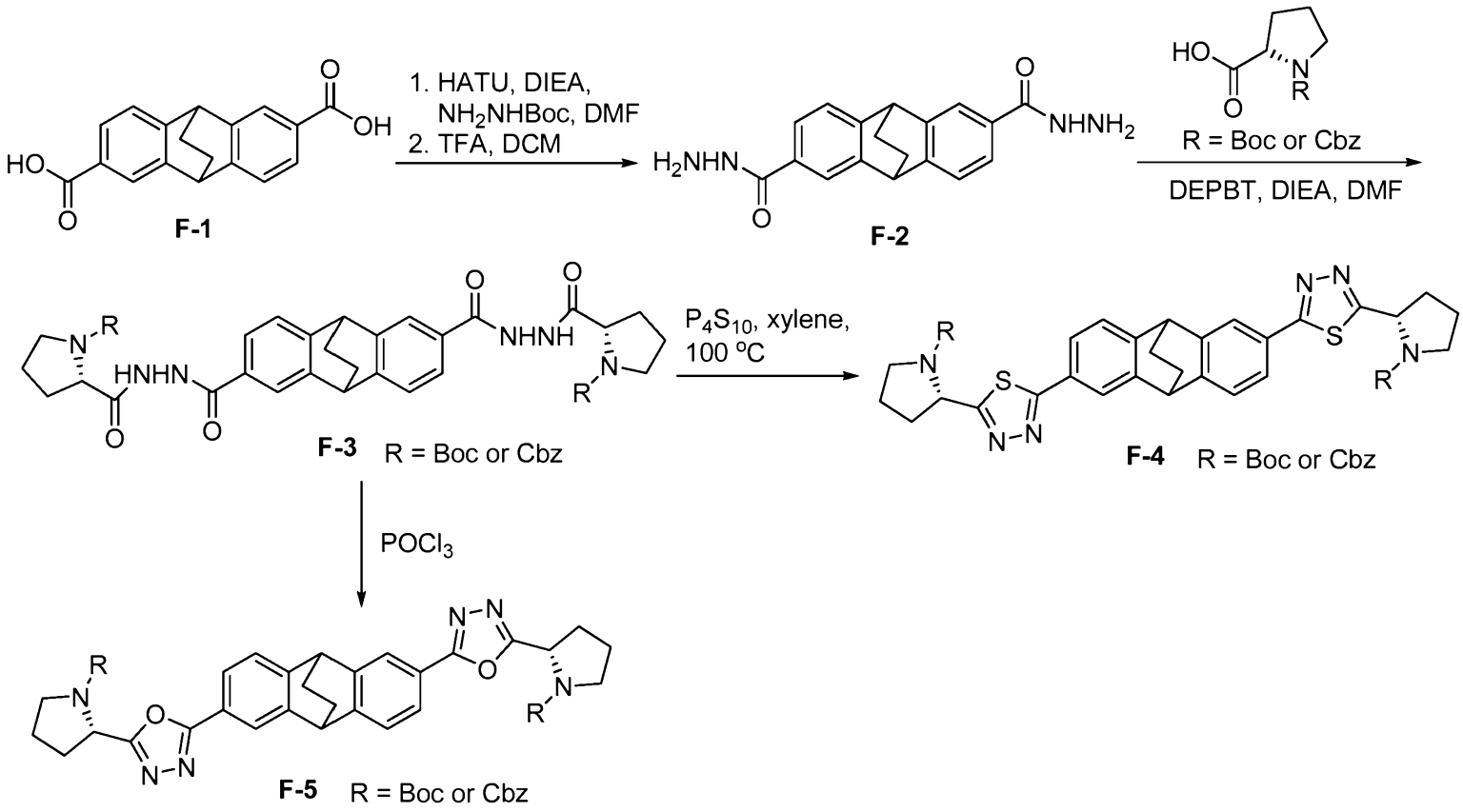
Scheme D

[0280] As illustrated in Scheme D, bis-triflate **D-1** is readily converted to the corresponding carboxylic acid **D-2** via a palladium-mediated carbonylation, followed by saponification. Subsequently, the carboxylic acid residues are converted to thio-amides **D-3**, followed by treatment with N-substituted 2-bromo-2-((*S*)-pyrrolidin-2-yl)acetaldehyde **D-4** to give bis-thiazole analog **D-5**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, 2-bromo-2-((*S*)-pyrrolidin-2-yl)acetaldehyde **D-4** can be replaced with other 2-bromo-2-substitutedacetaldehydes, derived from N-substituted D- or L-amino acids to generate bis-thiazole analogs of **D-5**.


MeO
OMe
O
O
E-1
DIBAL, THF, -78°C
H
O
O
H
E-2
CBr4, PPh3
Br
Br
Br
Br
E-3
NaOH, MeOH
JP 56115772
H
O
O
H
E-4
Br2, CCl4
H2N
N
R
S
E-6
R = Boc or Cbz
Acetone, 60 °C
H
O
Br
O
Br
H
Br
E-5
R
N
S
N
N
S
N
R
E-7

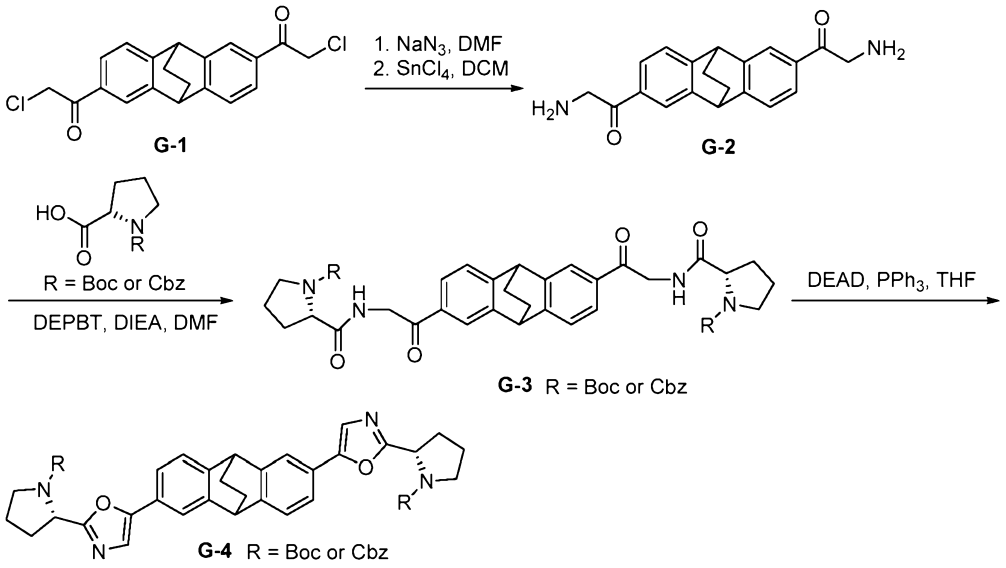
Scheme E

[0281] As depicted in Scheme E, the regio-isomer of bis-thioazole **D-5** with respect to the substitution pattern on the thiazole moiety is prepared. Reduction of **E-1**, followed by condensation and hydrolysis, gives bis-substituted acetaldehyde **E-4**. Bromination of **E-4**, followed by cyclization with N-substituted (*S*)-pyrrolidine-2-carbothioamide **E-6**, affords bis-thiazole **E-7**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted (*S*)-pyrrolidine-2-carbothioamide **E-6** can be replaced with other thio-amides derived from N-substituted D- or L- amino acids to give bis-thiazole analogs of **E-7**.


1. HATU, DIEA,
NH2NHBoc, DMF
2. TFA, DCM
F-1
F-2
R = Boc or Cbz
DEPBT, DIEA, DMF
F-3 R = Boc or Cbz
P4S10, xylene,
100 °C
F-4 R = Boc or Cbz
POCl3
F-5 R = Boc or Cbz

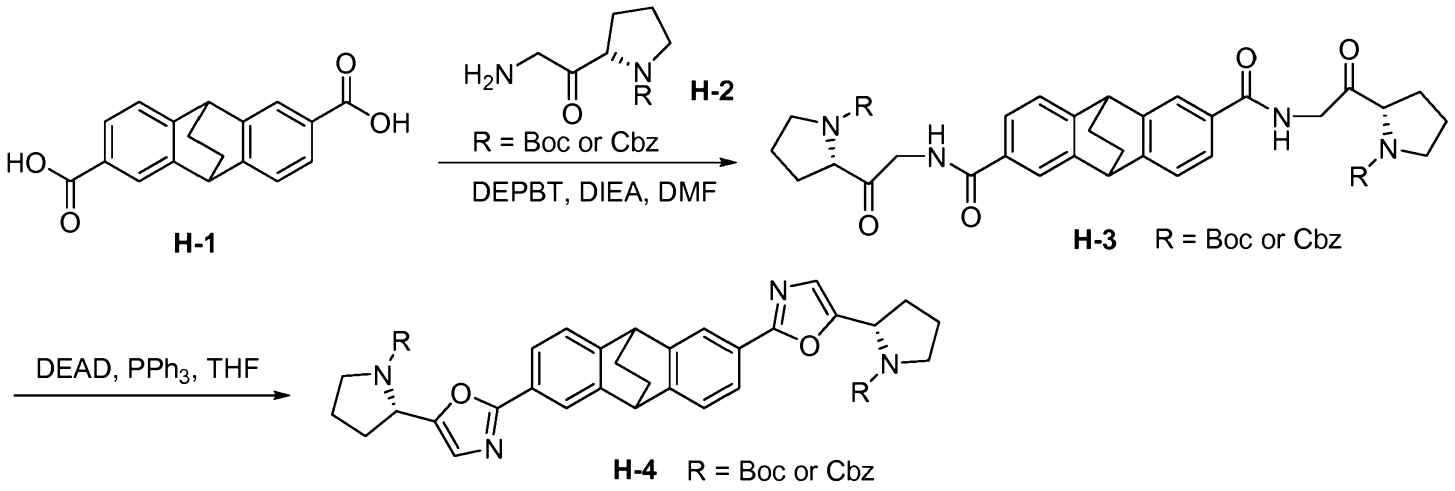
Scheme F

[0282] As outlined in Scheme F, bis-carboxylic acid **F-1** is converted to N,N'-diacylhydrazide **F-3** through a three step sequence of amide formation, de-protection and amide formation. Ring cyclization of **F-3** gives either bis-thiodiazole **F-4** or bis-oxadiazole **F-5** when the proper de-hydration reagents are used. Both **F-4** and **F-5** can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate analogs of **F-4** and **F-5**, respectively.



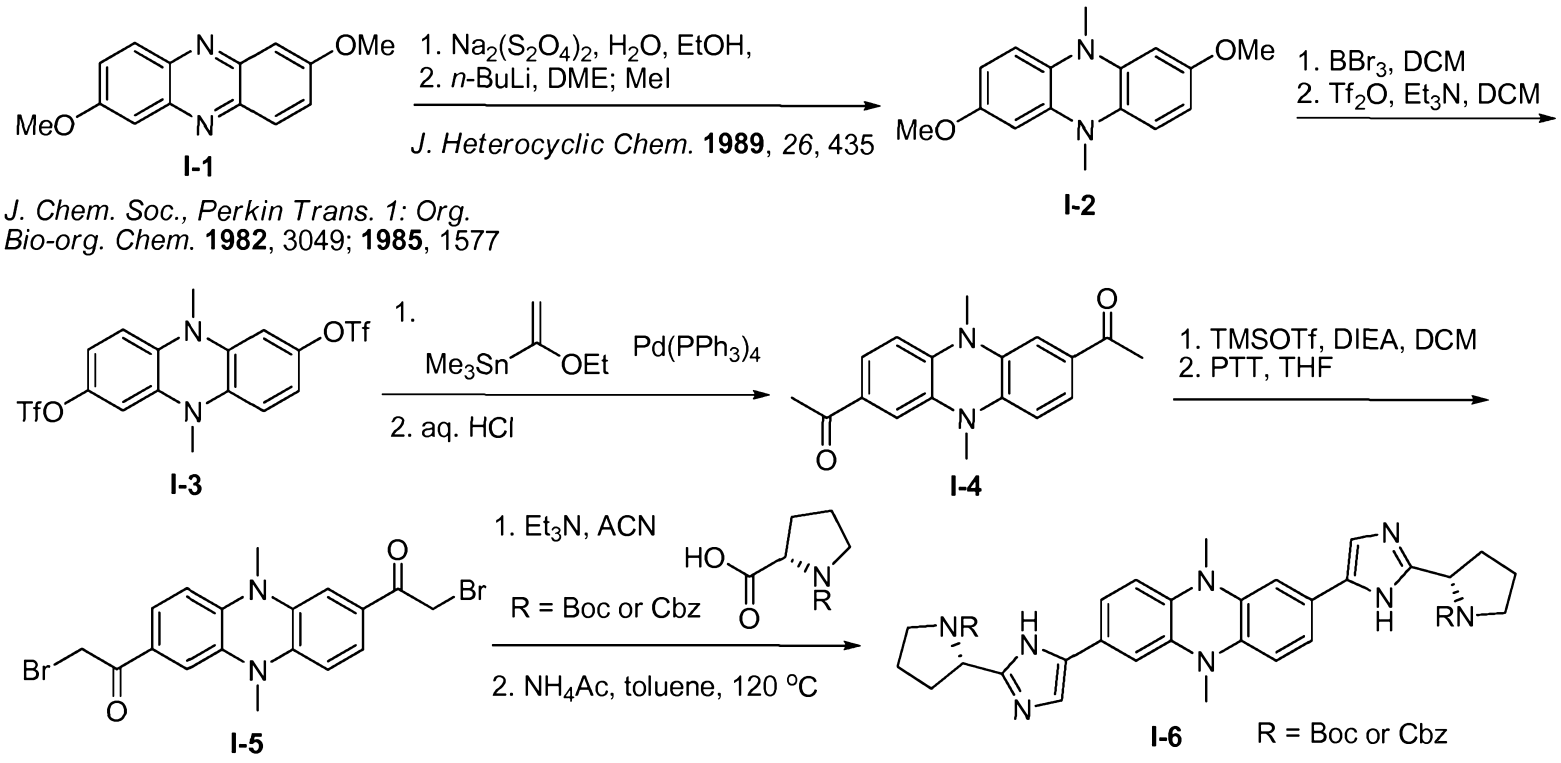
Scheme G

[0283] As shown in Scheme G, α-chloro ketone **G-1** is converted to the corresponding α-amino ketone **G-2**. Amide formation of **G-2** with N-substituted L-Pro-OH, followed by dehydration, affords bis-oxazole **G-4**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-oxazole analogs of **G-4**.


H-1
H-2
R = Boc or Cbz
DEPBT, DIEA, DMF
H-3 R = Boc or Cbz
DEAD, PPh3, THF
H-4 R = Boc or Cbz

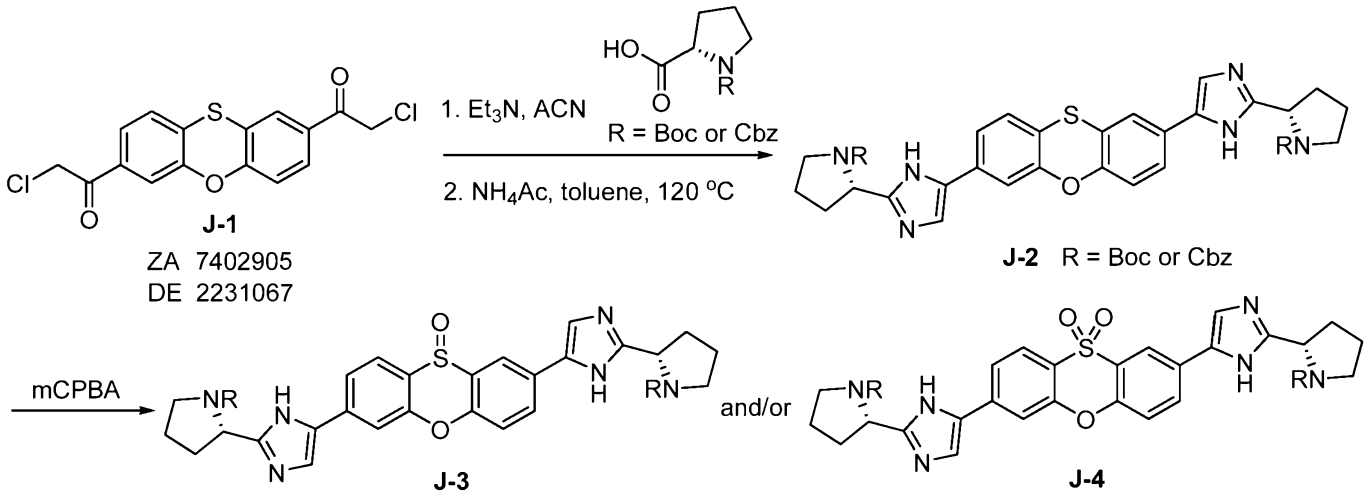
Scheme H

[0284] As outlined in Scheme H, the regioisomer of **G-4** with respect to the substitution pattern on the oxazole moiety is prepared. Amide formation of bis-carboxylic acid **H-1** with (*S*)-2-amino-1-(pyrrolidin-2-yl)ethanone **H-2**, followed by dehydration, gives bis-oxazole **H-4**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, (*S*)-2-amino-1-(pyrrolidin-2-yl)ethanone **H-2** can be replaced with other α-amino ketones derived from N-substituted D- or L-amino acids to generate bis-oxazole analogs of **H-4**.


OMe
MeO
I-1
1. $Na_2(S_2O_4)_2$, H_2O, EtOH,
2. *n*-BuLi, DME; MeI
J. Heterocyclic Chem. **1989**, *26*, 435
J. Chem. Soc., Perkin Trans. 1: Org.
Bio-org. Chem. **1982**, 3049; **1985**, 1577
I-2
1. BBr_3, DCM
2. Tf_2O, Et_3N, DCM
OTf
TfO
I-3
1.
Me_3Sn
OEt
$Pd(PPh_3)_4$
2. aq. HCl
I-4
1. TMSOTf, DIEA, DCM
2. PTT, THF
Br
I-5
1. Et_3N, ACN
R = Boc or Cbz
2. NH_4Ac, toluene, 120 °C
I-6
R = Boc or Cbz

Scheme I

[0285] As shown in Scheme I, reduction of **I-1** and the subsequent N-alkylation give **I-2**, which is readily converted to the corresponding bis-triflate **I-3**. Stille coupling of **I-3**, followed by α-bromination, *O*-alkylation and ring formation affords bis-imidazole **I-6**, which can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate bis-imidazole analogs of **I-6**.


J-1
ZA 7402905
DE 2231067
1. Et3N, ACN
2. NH4Ac, toluene, 120 °C
R = Boc or Cbz
J-2 R = Boc or Cbz
mCPBA
J-3
and/or
J-4

Scheme J

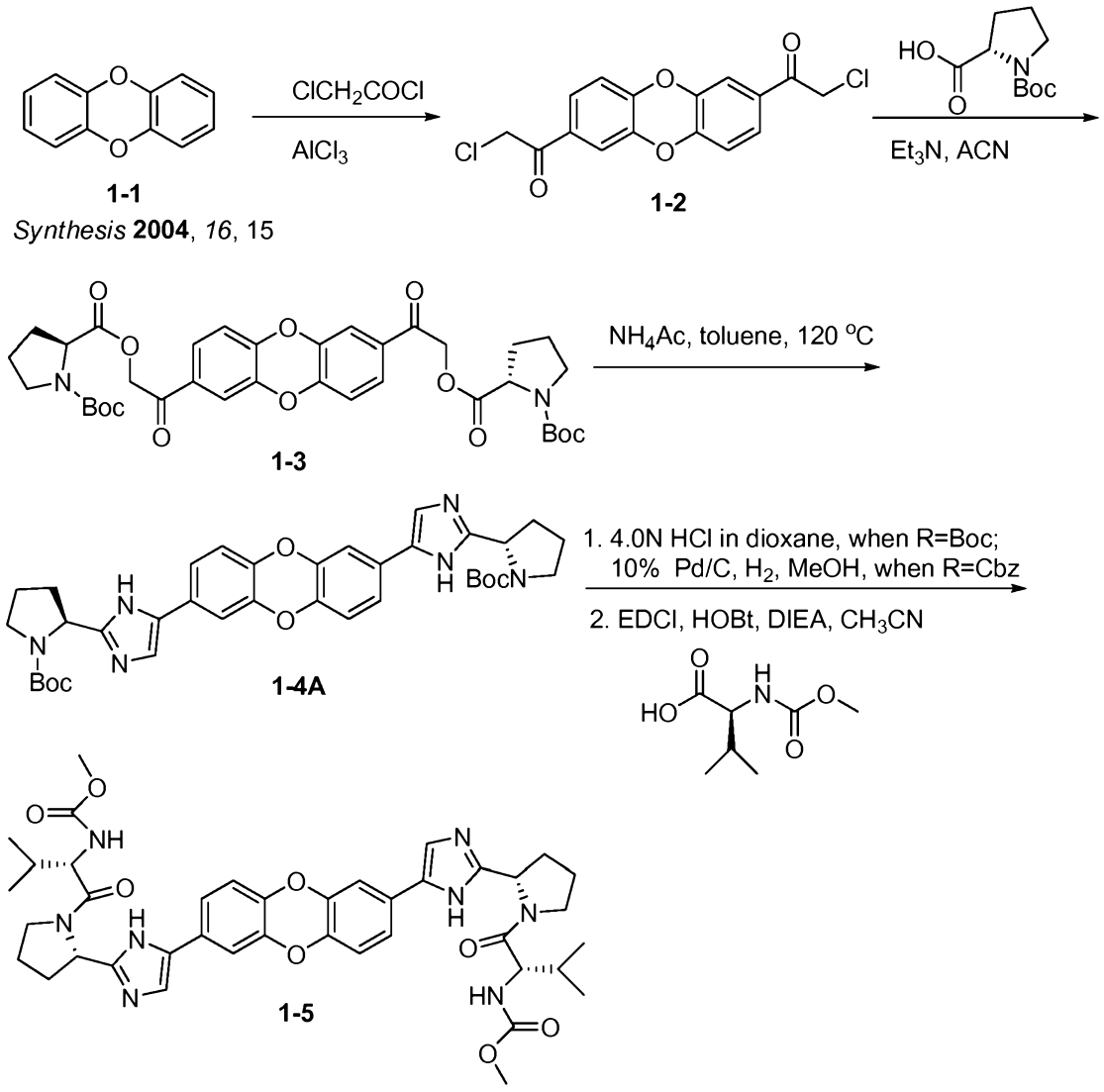
[0286] As described in Scheme J, *O*-alkylation of **J-1**, followed by ring cyclization, gives bis-imidazole **J-2**, which can be selectively oxidized to yield the corresponding sulfoxide **J-3** and sulphone **J-4**. **J-2**, **J-3** and **J-4** can be further transformed to give various analogs bearing different R groups through a sequence of typical de-protection and amide formation steps. Moreover, N-substituted L-Pro-OH can be replaced with other N-substituted D- or L-amino acids to generate analogs of **J-2**, **J-3** and **J-4**, respectively.

K-1
NaBH4
EtOH
K-2
Pd(dppf)Cl2
K3PO4
K-3
AlCl3
K-4
1. Et3N, ACN
2. NH4Ac, toluene, 120 °C
R = Boc or Cbz
K-5

Scheme K

[0287] Analogs built on a dibenzo[1,5]dioxocine scaffold are prepared by using the synthetic route outlined in Scheme K or a variation of it. A properly substituted aryl ether **K-2**, prepared from the reduction of **K-1**, is cyclized to give dioxocine compound **K-3** under the catalysis of a palladium catalyst such as Pd(dppf)Cl_2. Treatment of **K-3** with chloroacetyl chloride under the standard Friedal-Craft reaction condition yields bischloromethylketone **K-4**. Similarly to what has been described above, bis-immidazole compound **K-5** is obtained by reacting **K-4** with an N-substituted-L-Pro-OH in two steps. The N-substituted L-Pro-OH used in this Scheme K can be substituted with other N-substituted D- or L-amino acids to generate bis-imidazole analogs bearing corresponding 2-substituents off the 2-position of the imidazole.

[0288] The following schemes exemplify some of the synthetic routes that are used for the preparation of compounds and their analogs included in this invention. Those skilled in the art will understand that alternative routes may also be used to reach the same and similarly functionalized intermediates and target molecules. Alternative reagents for a given transformation are also possible.



Scheme 1

Example 1. Preparation of 1-5, dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(dibenzo[b,e][1,4]dioxine-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

[0289] **Step 1.** A solution of dibenzo-*p*-dioxine (**1-1**) (5.0 g, 27.14 mmol) and chloroacetyl chloride (4.5 mL, 57 mmol) in dichloromethane (50 mL) was added over 20 min to a stirred suspension of aluminum chloride (14.5 g, 108.6 mmol) in dichloromethane (300 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 15 min and allowed to warm up to room temperature over 30 min. The reaction mixture was then heated at 50 °C for 3 h and stirring continued at rt overnight. The reaction was cooled to 0 °C and quenched carefully with ice-cold water (250 mL). The volatiles were removed *in vacuo* and the precipitate formed was collected by vacuum filtration and washed with ethyl ether and dried at 50 °C *in*

vacuo to afford crude product **1-2** (8.85 g, 97% yield), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82-7.50 (m, 4H), 7.20 (m, 2H), 5.18(s, 4H) ppm.

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

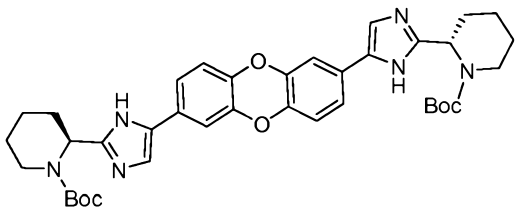
[0291] a. Diisopropylethylamine (6.85 mL, 39.58 mmol) was added to a stirred suspension of chloromethyl ketone **1-2** (5.54 g, 16.49 mmol), N-Boc-L-proline (7.80 g, 36.28 mmol), and KI (1.09 g, 6.6 mmol) in DMF (30 mL), and the mixture was stirred at 50 °C for 3 h. The cooled reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$ and then filtered. The volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography (SiO_2, 1/1 EtOAc/hexanes) to afford ketoester **1-3** (6.85 g, 60% yield) as a light yellow solid.

[0292] b. Ketoester **1-3** from above (4.85 g, 6.98 mmol) was taken up in xylene (20 mL) and placed in a 100 mL pressure vessel. Ammonium acetate (5.34 g, 69.8 mmol) and triethylamine (5 mL) were added and the reaction mixture was heated at 140 °C for 2 h. The cooled mixture was diluted with ethyl acetate (150 mL) and then washed with saturated $NaHCO_3$ aqueous solution followed by brine. The organic layer was dried over $MgSO_4$, filtered and volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc) to afford product **1-4A** (3.15 g, 69% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.40-6.60 (m, 8H), 7.44 (m, 2H), 4.98 (m, 2H), 3.60-1.85 (m, 12H), 1.47 (s, 18H) ppm. LC-MS (ESI): *m/z* 653 $[M-H]^-$.

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

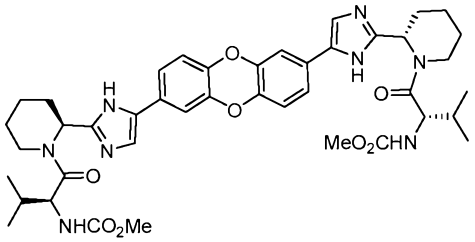
brine and dried with anhydrous $MgSO_4$. The solvent was removed and the residue was purified by preparative HPLC and to give compound **1-5**. LC-MS (ESI): *m/z* 769 $(M+H)^+$.

Example 2. Preparation of 1-4B



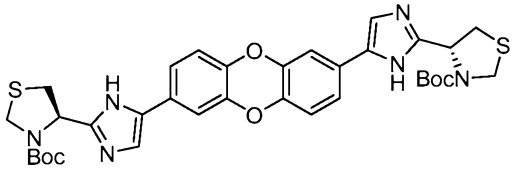
[0294] Following General Procedure A described above for the synthesis of **1-4** and substituting N-Boc-L-proline with N-Boc-L-pipecolic acid in **Step a**, compound **1-4B** (0.82 g) was obtained in 60% yield. LC-MS (ESI): *m/z* 681 $[M-H]^-$.

Example 3. Preparation of 1-5B



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

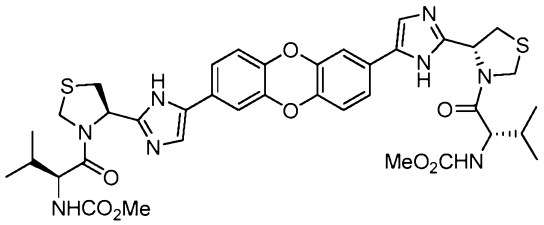
Example 4. Preparation of 1-4C



[0296] Following General Procedure A described above for synthesis of **1-4A** and replacing N-Boc-L-proline with N-Boc-L-thiaproline, the corresponding ketoester **1-3C** was obtained in 37% yield. ^1H NMR ($CDCl_3$, 300MHz) δ 7.56 (d, 2H), 7.56 (d, 2H), 7.44 (s, 2H), 5.53-5.16 (m, 4H), 4.98 (m, 1H), 4.88 (m, 1H), 4.73-4.48 (m, 4H), 3.44 (m, 4H), 1.48 (s, 18H) ppm. LC-MS (ESI): m/z 729 $[M-H]^-$.

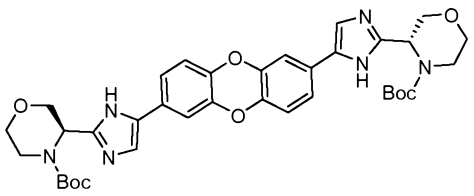
[0297] Treatment of **1-3C** with NH_4OAc under conditions as described in General Procedure A resulted in **1-4C** (0.27 g) in 35% yield. ^1H NMR ($CDCl_3$, 300MHz) δ 7.18 (m, 6H), 6.81(s, 2H), 5.48 (m, 2H), 4.68 (m, 4H), 4.44 (br s, 2H), 3.43 (m, 4H), 1.48 (s, 18H) ppm. LC-MS (ESI): *m/z* 689 $[M-H]^-$.

Example 5. Preparation of 1-5C



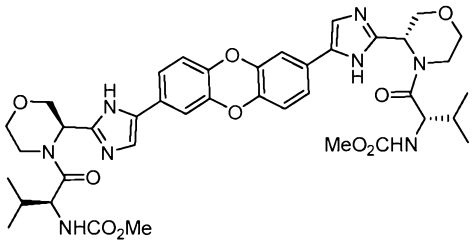
[0298] Following procedure B and substituting compound **1-4C** for **1-4A**, the title compound was obtained. LC-MS (ESI): *m/z* 805 $[M+H]^+$.

Example 6. Preparation of 1-4D



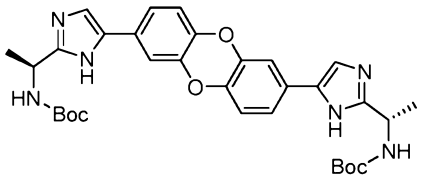
[0299] Following General Procedure A described above for synthesis of **1-4A**, and replacing N-Boc-L-proline with 4-N-Boc-3(*S*)-morphorline carboxylic acid, compound **1-4D** was obtained in 70% yield. LC-MS (ESI): *m/z* 686 $[M-H]^+$.

Example 7. Preparation of 1-5D



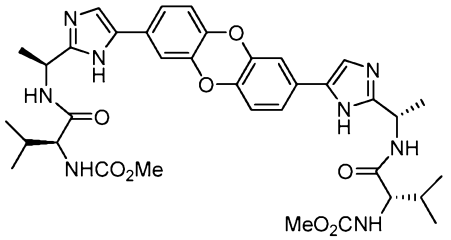
[0300] Following procedure B and substituting compound **1-4D** for **1-4A**, compound **1-5D** was obtained. LC-MS (ESI): *m/z* 801 $[M+H]^+$.

Example 8. Preparation of 1-4E

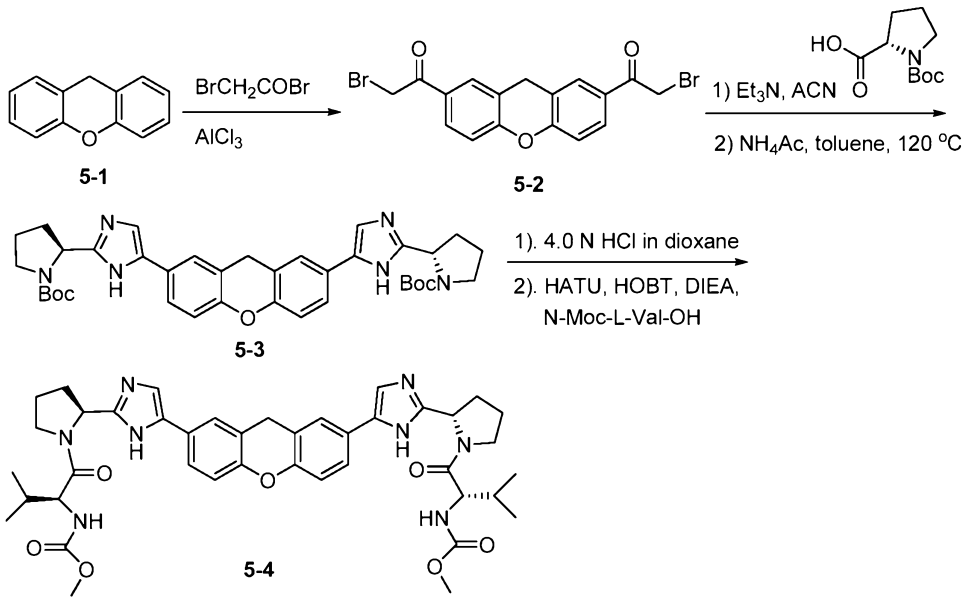


[0301] Following General Procedure A described above for synthesis of **1-4A**, and replacing N-Boc-L-proline with N-Boc-L-alanine, compound **1-4E** was obtained in 72% yield in two steps. LC-MS (ESI): *m/z* 601 $[M-H]^-$.

Example 9. Preparation of 1-5E



[0302] Following General Procedure B and substituting compound **1-4E** for **1-4A**, the title compound was obtained. LC-MS (ESI): *m/z* 717 $[M+H]^+$.



Scheme 5

Example 10. (2*S*,2*S*')-tert-butyl 2,2'(5,5'-(9*H*-xanthene-2,7-diyl)bis(1*H*-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (5-3)

[0303] **Step 1.** Referring to Scheme 5, bromoacetyl chloride (4.59 ml, 54.9 mmol) was added dropwise to a solution of 9H-xanthene (5g, 27.4 mmol) and $AlCl_3$ (8.05 g, 60.4 mmol), DCM (100 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and left to stir for 72 h. The reaction mixture was poured onto ice (400 mL), extracted with DCM (2 x 200 mL). The combined organic phase was washed with brine (400 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was precipitated in EtOAc and filtered to give 1,1'-(9H-xanthene-2,7-diyl)bis(2-bromoethanone) (**5-2**) as a white solid (4.27 g, 36.7% yield). LC-MS (ESI): *m/z* 425.9 $(M+H)^+$.

[0304] **Step 2.** Following General Procedure A as described in the synthesis of **1-4A**, and substituting 1,1'-(9H-xanthene-2,7-diyl)bis(2-bromoethanone) (**5-2**) for 1,1'-(dibenzo[b,e][1,4]dioxine-2,7-diyl)bis(2-chloroethanone) (**1-2**) in Step 2a of the procedure, compound **5-3** was obtained as a brown solid in 35% yield. LC-MS (ESI): *m/z* 653.7 $(M+H)^+$; 651.8 $(M-H)^-$.

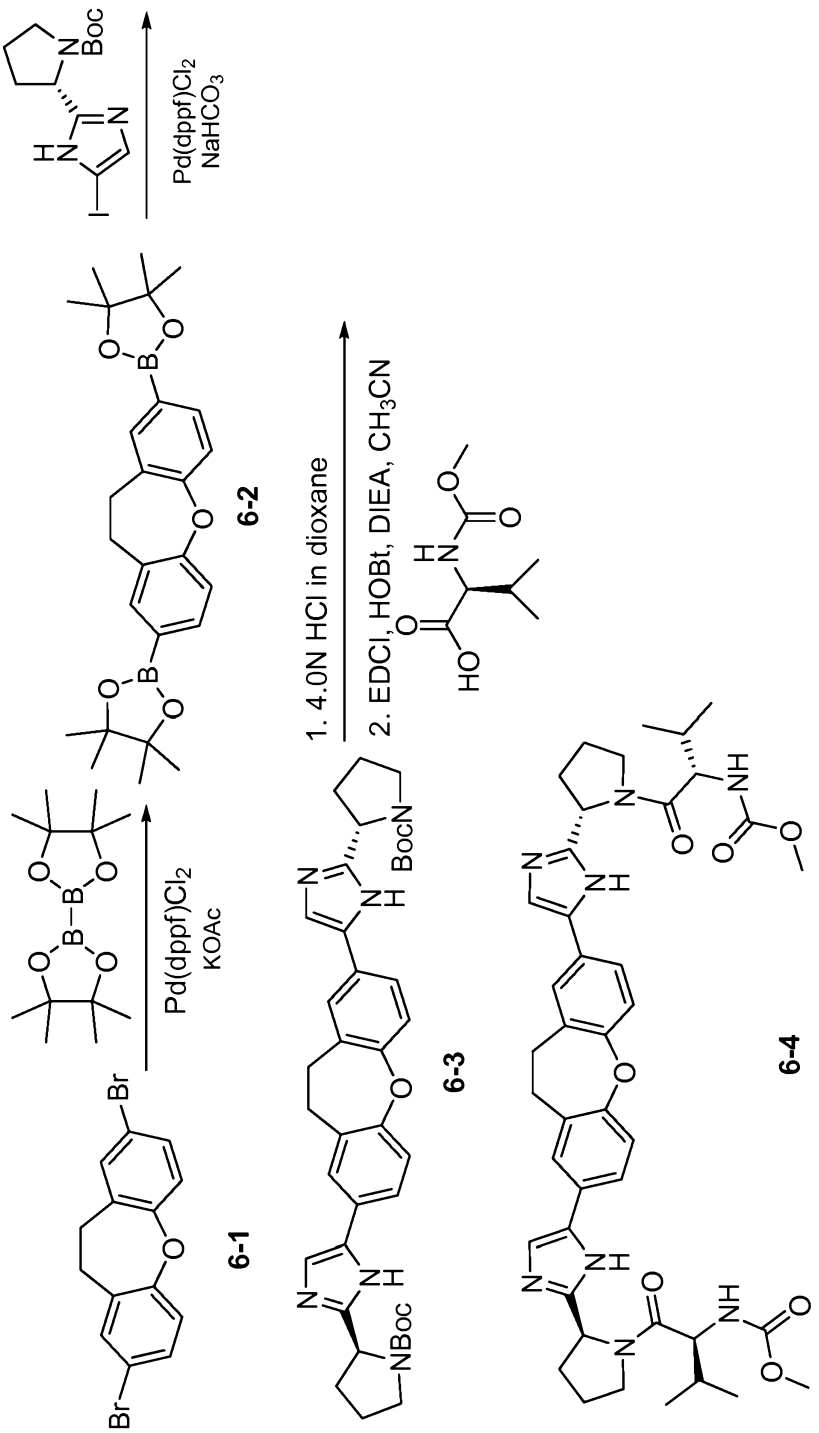
Example 11. Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(9H-xanthene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

[0305] Following General Procedure B, product **5-4** was obtained in 2 steps from **5-3** as a white solid (161 mg, 59% yield) from **5-3**. LC-MS (ESI): *m/z* 767.0 $(M+H)^+$; 765.2 $(M-H)^-$.

Example 12. Dimethyl-(1R,1'R)-2,2'-((2S,2'S)-2,2'-(5,5'-(9H-xanthene-2,7-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-phenylethane-2,1-diyl)dicarbamate (5-5)

[0306] Following General Procedure B and using N-Moc-D-phenylglycine as the coupling amino acid, product **5-5** was obtained as a white solid (209 mg, 67% yield). LC-MS (ESI): *m/z* 835.1 $(M+H)^+$; 833.0 $(M-H)^-$.

[0307] Other compounds bearing the same 2,7-disubstituted xanthenes scaffold are prepared similarly and listed in Table 1.


Pd(dppf)Cl2
KOAc
Pd(dppf)Cl2
NaHCO3
1. 4.0N HCl in dioxane
2. EDCI, HOBt, DIEA, CH3CN
6-1
6-2
6-3
6-4

Scheme 6

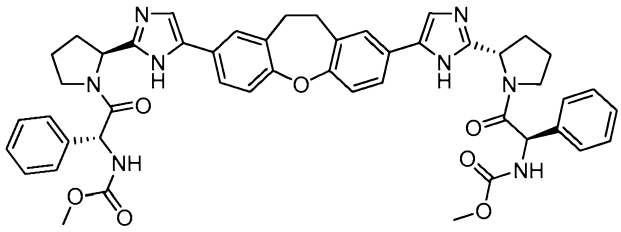
Example 13. Dimethyl-(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(10,11-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (6-4)

[0308] Step 1. General Procedure C: preparation of an arylborate from an aryl bromide, aryl iodide or aryl trifoliate. Referring to Scheme 6, a solution of 2,8-dibromo-10,11-dihydrodibenzo[b,f]oxepine (**6-1**) (prepared according procedures reported in WO2005090337) (435 mg, 1.229 mmol), potassium acetate (627 mg, 6.39 mmol), bis(pinacolato)diboron (1.31 g, 5.16 mmol) and Pd(dppf)Cl_2 (90 mg, 0.123 mmol) in dioxane (15 mL) was degassed and heated at 90 °C overnight. Reaction mixture was allowed to cool to room temperature and then filtered through celite, adsorbed on SiO_2 and then purified by column chromatography (SiO_2, 0-100% DCM/isohexanes) to give 2,8-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10,11-dihydrodibenzo[b,f]oxepine (**6-2**) (169 mg, 31 % yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.63-7.57 (4H, m), 7.17-7.13 (2H, m), 3.13 (4H, s), 1.33 (24H, s) ppm. LC-MS (ESI): *m/z* 449.0 $(M+H)^+$.

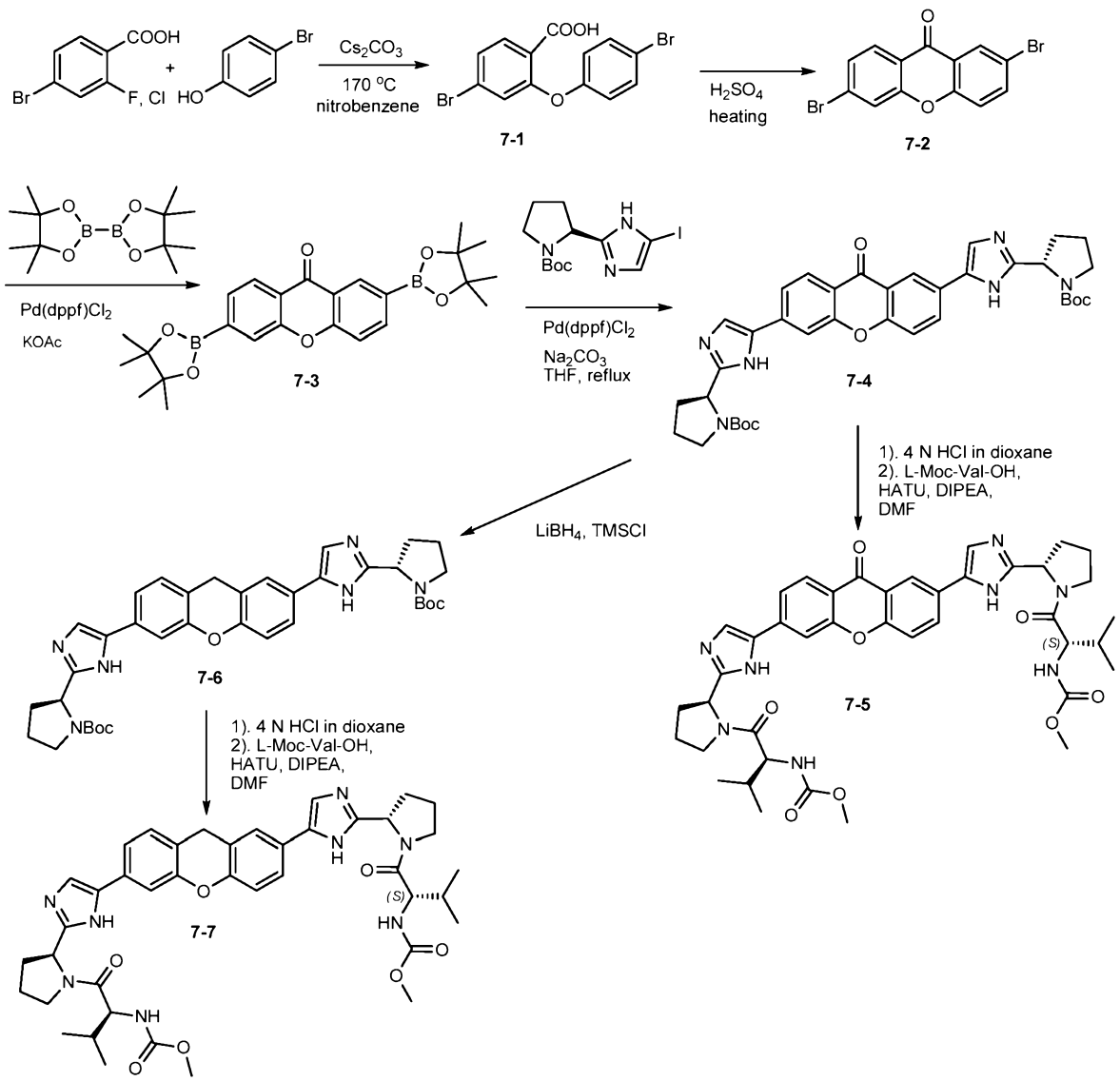
[0309] Step 2. Preparation of (*2S,2'S*)-*tert*-butyl-2,2'-(5,5'-(10,11-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (**6-3**). **General Procedure D:** A mixture of **6-2** (300 mg, 0.669 mmol), (*S*)-*tert*-butyl 2-(5-iodo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (486 mg, 1.339 mmol), $NaHCO_3$ (450 mg, 5.36 mmol) and Pd(dppf)Cl_2 (98 mg, 0.134 mmol) in DME (4.5 mL), water (1.5 mL) was degassed and then heated at 80 °C for 18 h. Water (40ml) was then added and the mixture extracted with 20% MeOH/$CHCl_3$ (3 x 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The product was purified by silica gel chromatography (Companion, 40 g cartridge, 0-10% MeOH/DCM+1% NH_3) to give ~300 mg brown oil. Further purification by silica gel chromatography eluting with 10% MeOH in DCM containing 1% NH_3 gave (*2S,2'S*)-tert-butyl-2,2'-(5,5'-(10,11-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (**6-3**) as a clear oil (210 mg, 47% yield). LC-MS (ESI): *m/z* 667.1 $(M+H)^+$; 666.2 $(M-H)^-$.

[0310] Step 3. Compound **6-4** was prepared using General Procedure B to give the product as a white solid (69 mg, 38% yield). LC-MS (ESI): *m/z* 782.0 $(M+H)^+$.

Example 14. Dimethyl-(1R,1'R)-2,2'-((2S,2'S)-2,2'-(5,5'-(10,11-dihydrodibenzo[b,f]oxepine-2,8-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-phenylethane-2,1-diyl)dicarbamate (6-5)



[0311] Prepared by using General Procedure B, the title product **6-5** was obtained as a white solid (15 mg, 9% yield). LC-MS (ESI): *m/z* 849.4 $(M+H)^+$.



Scheme 7

Example 15. Preparation of dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(9-oxo-9H-xanthene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (7-5).

[0312] Step 1. General Procedure E –synthesis of xanthen-9-one. Referring to Scheme 7, to a solution of 4-bromo-2-chlorobenzoic acid (18.4 g, 83.9 mmol) and 4-bromophenol (24 g, 109 mmol) in nitrobenzene was added cesium carbonate (82 g, 251.7 mmol). The resulting solution was heated at 170 °C with a condenser for 1 day. The reaction mixture was cooled to 70 °C and filtered at this temperature. The residue was washed with toluene. The organic layer was removed by vacuum distillation till a thick dark residue remained. To the dark residue was added aqueous HCl (1N, 400 mL) and DCM (200 mL). The resulting solution

was stirred until dark oil dispersed into DCM solution. The mixture was filtered. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. The residue was purified by column chromatography on silica gel, eluted first with DCM and then with a mixture of DCM and MeOH to give **7-1**.

[0313] **Step 2.** Compound **7-1** (16 g, 5:3 ratio, 44.3 mmol) was treated with concentrated sulfuric acid (95 mL). The solution was heated at 105 °C for 2 h. The reaction mixture was cooled and poured into ice water. The product precipitated out and was collected by filtration, washed with Et_2O and H_2O. The solid was dried and further purified by flash column chromatography on silica gel (eluents: Hex:AcOEt = 9:1 (*v/v*) to AcOEt 100% and to DCM alone) to afford **7-2** (12 g).

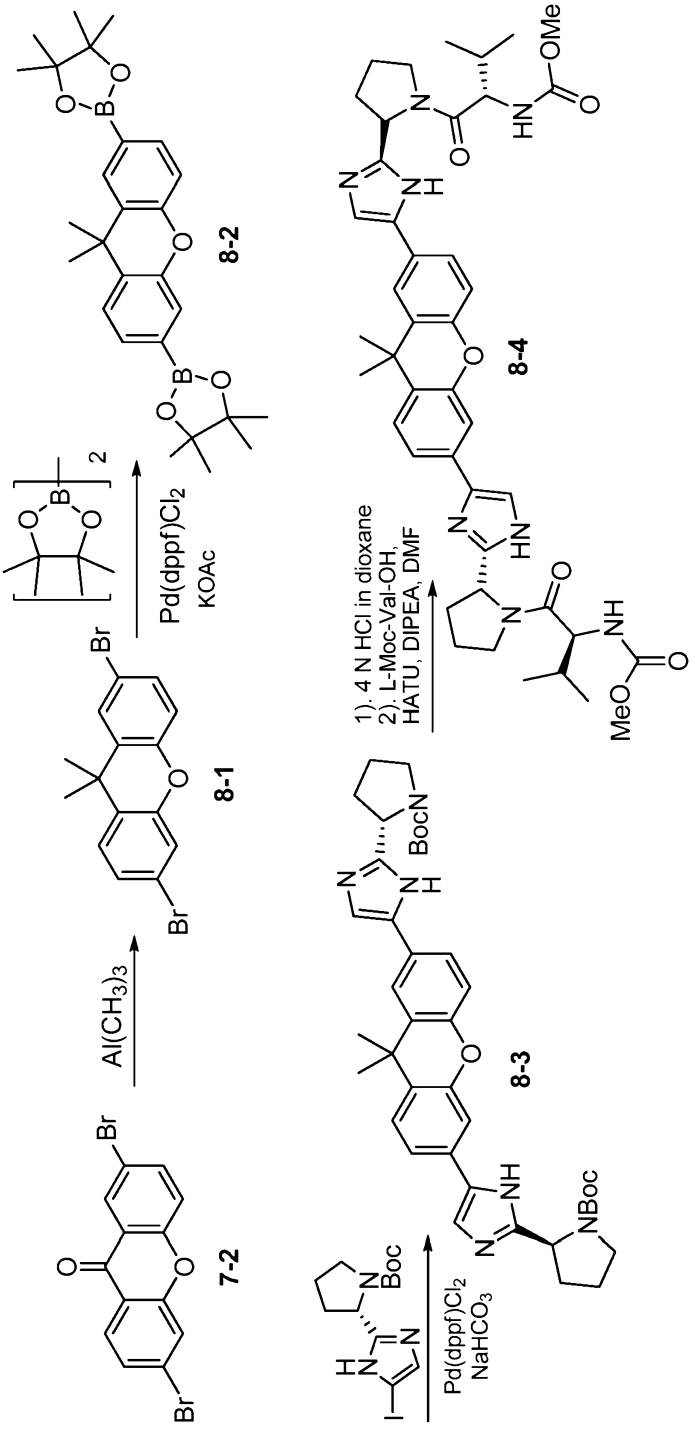
[0314] **Step 3.** Compound **7-4** was prepared according to conditions described in general procedure C. LC-MS (ESI): *m/z* 667.3 $(M+H)^+$.

[0315] **Step 4.** Compound **7-5** was prepared according to conditions described in general procedure B. LC-MS (ESI): *m/z* 781.3 $(M+H)^+$.

Example 16. Preparation of 7-7

[0316] **Step 1**. To a solution of compound **7-4** (1.6 g, 2.39 mmol) in anhydrous THF (40 mL) was added lithium borohydride (1.0 g, 45.6 mmol). The resulting solution was warmed up to 60 °C. After stirring for 3 h, the reaction was cooled to room temperature and slowly transferred to another bottle that was charged with chlorotrimethylsilane (3.0 mL, 23.6 mmol) in THF (100 mL). The mixture was stirred for an additional 20 mins at rt, and quenched by addition of methanol (10 mL). After removal of all the solvents by *vacuum*, **7-6** was obtained. LC-MS (ESI): *m/z* 667.3 $(M+H)^+$.

[0317] **Step 2**. Treatment of **7-6** under the conditions of general procedure B afforded compound **7-7**. LC-MS (ESI): *m/z* 767 $(M+H)^+$.


Br
O
Br
7-2
Al(CH3)3
Br
Br
8-1
Pd(dppf)Cl2
KOAc
8-2
Pd(dppf)Cl2
NaHCO3
8-3
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA, DMF
8-4
MeO

Scheme 8

Example 17. Preparation of 8-3

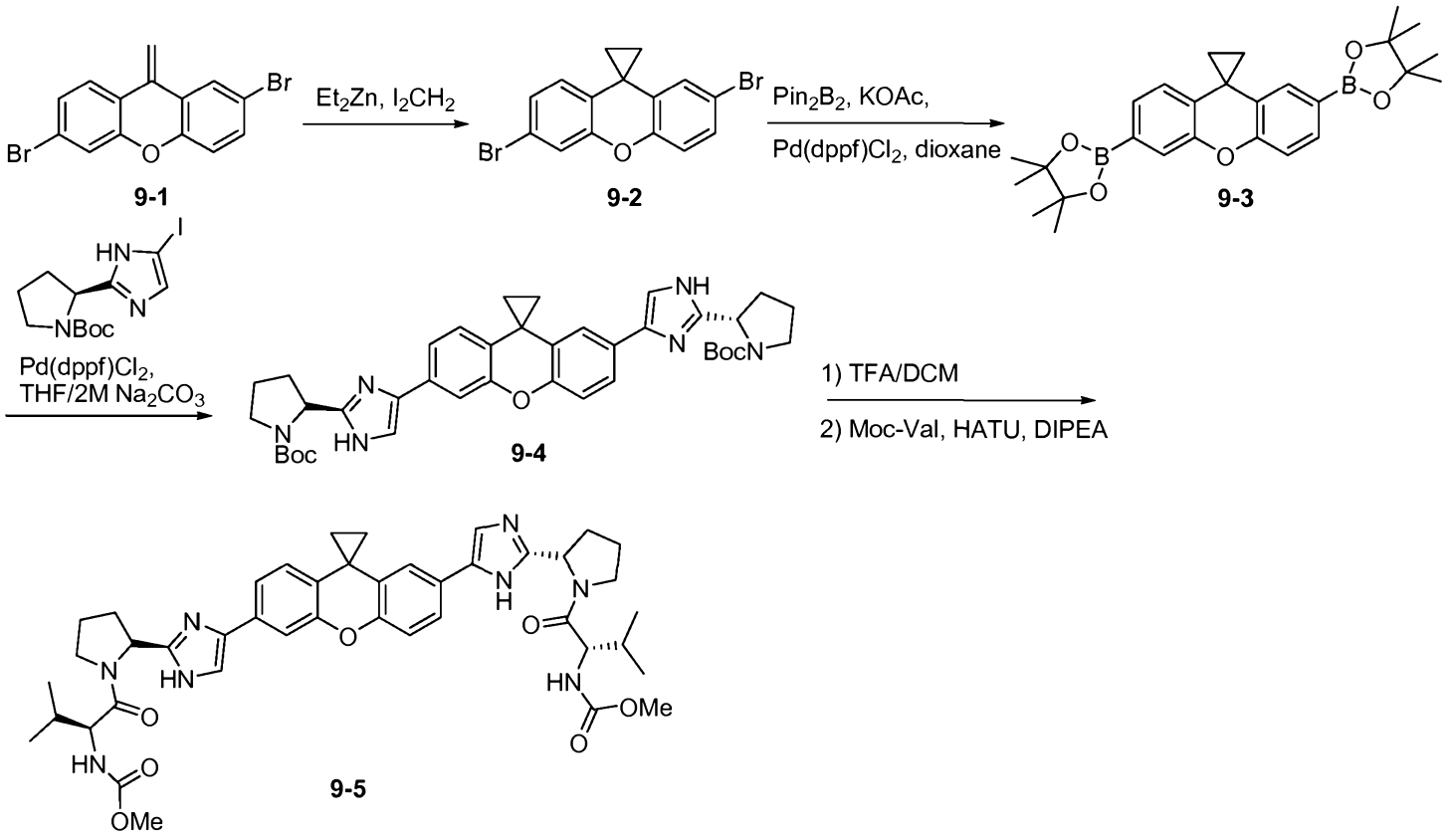
[0318] **Step 1.** Referring to Scheme 8, trimethylaluminum (2.4 mL, 2 M in hexanes, 4.80 mmol) was added dropwise to a degassed stirred solution of 2,6-dibromo-9H-xanthen-9-one **7-2** (500 mg, 1.412 mmol) in toluene (8 mL) at 0 °C. The resulting solution was allowed to warm up to rt and left to stir for 16 h. The crude reaction mixture was poured into ice-cold 1M HCl aq (200 mL), and the aqueous layer was washed with DCM (2 x 150 mL), dried over $MgSO_4$, filtered and solvents were removed *in vacuo* to give 2,6-dibromo-9,9-dimethyl-9H-xanthene **8-1** (482 mg, 93 % yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.77-7.74 (1H, m), 7.55-7.51 (1H, m), 7.44-7.40 (1H, m), 7.33-7.29 (2H, m), 7.06-7.02 (1H, m), 1.58 (6H, s) ppm.

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

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

Example 18. Preparation of 8-4

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


Br
Br
9-1
Et2Zn, I2CH2
Br
Br
9-2
Pin2B2, KOAc,
Pd(dppf)Cl2, dioxane
O
B
O
O
B
O
9-3
HN
I
N
NBoc
Pd(dppf)Cl2,
THF/2M Na2CO3
N
HN
N
Boc
NH
N
BocN
O
9-4
1) TFA/DCM
2) Moc-Val, HATU, DIPEA
N
N
H
N
O
HN
OMe
O
N
HN
O
HN
O
OMe
9-5

Scheme 9

Example 19. Preparation of 9-4

[0322] **Step 1.** To a solution of **9-1** (1.3 g, 3.70 mmol) in anhydrous DCM (40 mL) was added Et_2Zn (1.0 M in heptane, 18.5 mL) at rt. Diiodomethane (2.97 mL, 37 mmol) was then added drop-wisely. The reaction mixture was heated up to reflux. After stirring overnight, the reaction was cooled to rt and diluted with DCM, washed with brine, saturated NH_4Cl and water and dried over sodium sulfate. After removing the solvents, the crude mixture was purified by flash column chromatography (Hexane: Ethyl acetate = 30:1 (*v/v*)) to afford compound **9-2** (0.50 g).

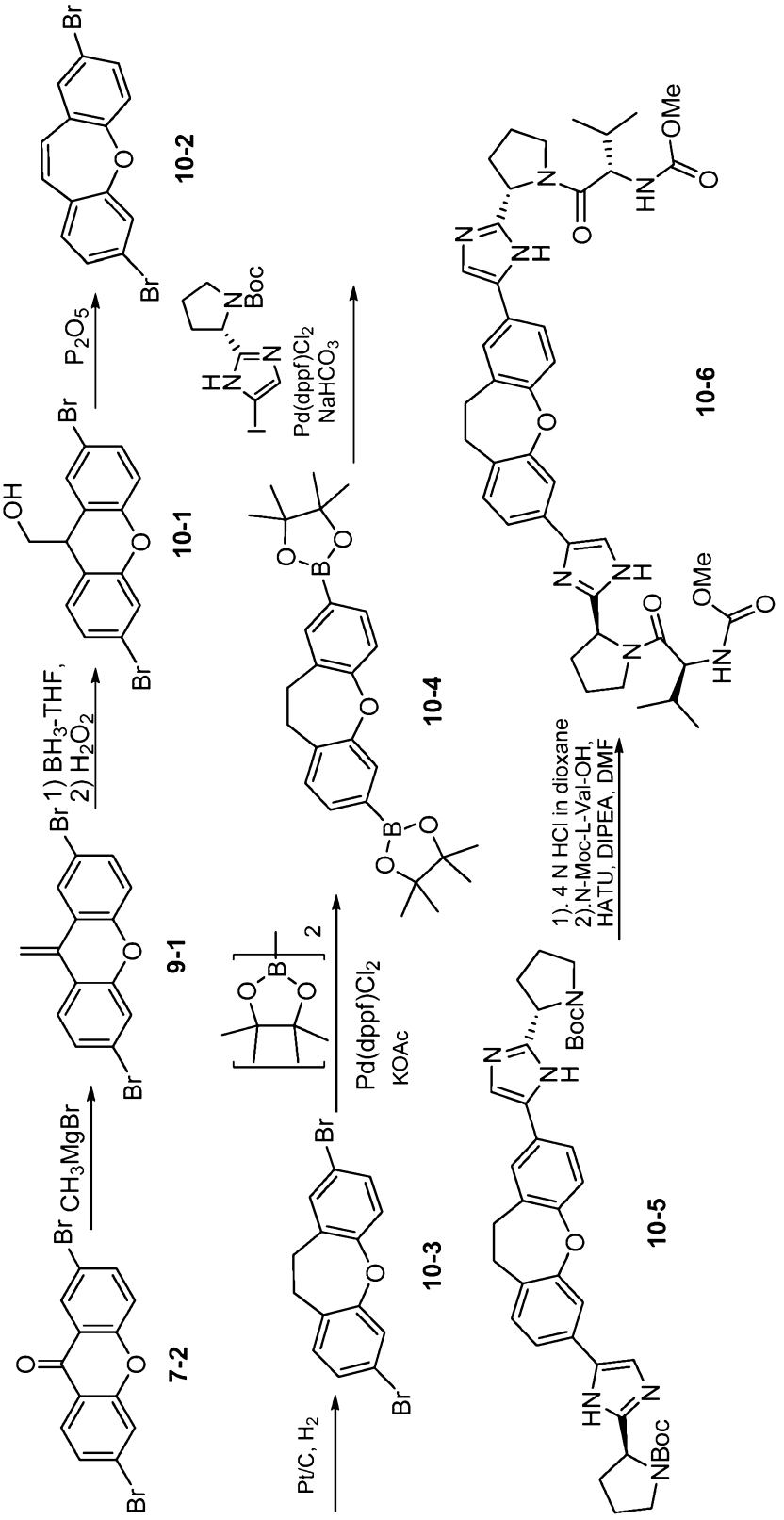
[0323] **Step 2.** General Procedure D. To a solution of **9-2** (350 mg, 0.959 mmol) in dioxane (20 mL) was added bis(pinacolato)diboron (584 mg, 2.3 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II)·DCM (39 mg, 0.048 mmol) and potassium acetate (565 mg, 5.75 mmol). The resulting solution was bubbled with N_2 for 15 minutes, then heated at 85°C overnight. The solvent was removed *in vacuo* and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phases were washed with brine, water and dried over Na_2SO_4. The solvents were removed by vacuum to afford t crude **9-3** (450 mg). LC-MS (ESI): *m/z* 461 $(M+H)^+$.

[0324] **Step 3.** To a solution of the crude **9-3** (0.959 mmol) in THF (10 mL) was added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (766 mg, 2.11 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (40 mg, 0.049 mmol) and 2 M sodium carbonate (4 mL). The resulting solution was bubbled with N_2 for 15 mins, then heated at 85 °C overnight. The solvent was removed *in vacuo*, and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM:Methanol = 20:1 (*v/v*)) to afford compound **9-4** (110 mg). LC-MS (ESI): *m/z* 340 $(M+2H)^{2+}$.

Example 20. Preparation of 9-5

[0325] To a solution of the **9-4** (20 mg, 0.0295 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.3 mL). The reaction was stirred for 3 h at rt. The reaction was concentrated to afford compound **de-Boc-9-4** (20 mg). LCMS (ESI): *m/z* 240 1/2$(M+2H)^{2+}$ To a solution of **de-Boc-9-4** (20 mg) in DMF (2 mL), DIPEA (24 μL, 0.138 mmol), N-Moc-L-Val-OH (12 mg, 0.068 mmol) and HATU (26 mg, 0.068 mmol) was added. After one h stirring, the reaction was diluted with methanol and directly subject to prep-HPLC

(Phenomenex, C18-Luna column, H_2O-MeCN, 0.1% HCO_2H) to provide **9-5** (12.0 mg). LC-MS (ESI): *m/z* 397 $(M + 2H)^{2+}$. ^1H NMR (300 MHz, CD_3OD) δ 7.87 (s, 1H), 7.80 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 7.22 (s, 1H), 7.08 (d, *J* = 9.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 5.23-5.20 (m, 2H), 4.23 (d, J = 7.1 Hz, 2H), 4.10-4.07 (m, 2H), 3.94-3.88 (m, 2H), 3.65 (s, 6H), 2.60-2.55 (m, 2H), 2.38-2.05 (m, 8 H), 1.68-1.50 (m, 4H), 0.98-0.88 (m, 12H) ppm.


7-2
9-1
10-1
10-2
10-3
10-4
10-5
10-6
CH3MgBr
1) BH3-THF,
2) H2O2
P2O5
Pt/C, H2
Pd(dppf)Cl2
KOAc
Pd(dppf)Cl2
NaHCO3
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF

Scheme 10

Example 21. Preparation of 10-6

[0326] **Step 1.** Referring to Scheme 10, methylmagnesium iodide (14.12 mL, 3 M in Et_2O, 42.4 mmol) was added to a stirred solution of 2,6-dibromo-9H-xanthen-9-one (**7-2**) (10 g, 28.2 mmol) in THF (30 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (250 mL) and stirred for 30 min. The volatiles were removed *in vacuo*. The residue was taken up in $CHCl_3$ (200 mL), and the organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (2 x 200 mL) and combined organics was dried over $MgSO_4$, filtered and solvents removed *in vacuo* to crude product (9.46 g). The crude reaction was taken up in EtOAc (200 mL) and AcOH was added (20 mL) and the reaction mixture was stirred at room temperature for 3 h, the volatiles removed *in vacuo* and the residue was precipitated from isohexanes to give 2,6-dibromo-9-methylene-9H-xanthene (**9-1**) (6.43 g, 64.7% yield).

[0327] **Step 2.** Borane-THF complex (36.5 mL, 1M THF, 36.5 mmol) was added to a stirred solution of 2,6-dibromo-9-methylene-9H-xanthene (**9-1**) (6.43 g, 18.27 mmol) in THF (75 mL) at 0 °C. The mixture was allowed to warm up to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C and a mixture of hydrogen peroxide (35 wt% in water) (5.76 mL, 65.8 mmol) and NaOH (25.6 mL, 2 M aq, 51.1 mmol) was added cautiously. The mixture was allowed to warm up to rt over 30 min. The reaction mixture was then poured into water (200 mL) and extracted with DCM (3 x 150 mL). The combined organics were washed with water (2 x 200 mL), brine (200 mL), dried over $MgSO_4$, filtered and volatiles removed *in vacuo* to give a yellow solid. The crude product was purified by column chromatography (SiO_2, 0-100% EtOAc/isohexanes) to afford (2,6-dibromo-9H-xanthen-9-yl)methanol (**10-1**) (2.5 g, 37.0% yield) as a yellow solid. ^1H NMR ($CDCl_3$) δ 7.42-7.39 (1H, m), 7.37-7.35 (1H, m), 7.28-7.27 (1H, m), 7.25-7.21 (1H, m), 7.16-7.12 (1H, m), 7.00-6.97 (1H, m), 4.00 (1H, t, J = 5.9 Hz), 1.46 (2H, d, J = 5.9 Hz) ppm.

[0328] **Step 3.** Phosphorus pentoxide (5.04 g, 35.5 mmol) was added portion-wisely to a stirred solution of (2,6-dibromo-9H-xanthen-9-yl)methanol (**10-1**) (1.01 g, 2.73 mmol) in toluene (100 mL) and the suspension was heated under reflux for 20 min. The mixture was allowed to cool to rt and toluene was removed by decantation. The residual solid was washed with toluene (2 x 100 mL) by further decantation. The combined organics were cooled in an ice bath and brine (400 mL) was added slowly. The layers were separated and the organic washed with water (300 mL), brine (300 mL), dried over $MgSO_4$ and evaporated to dryness,

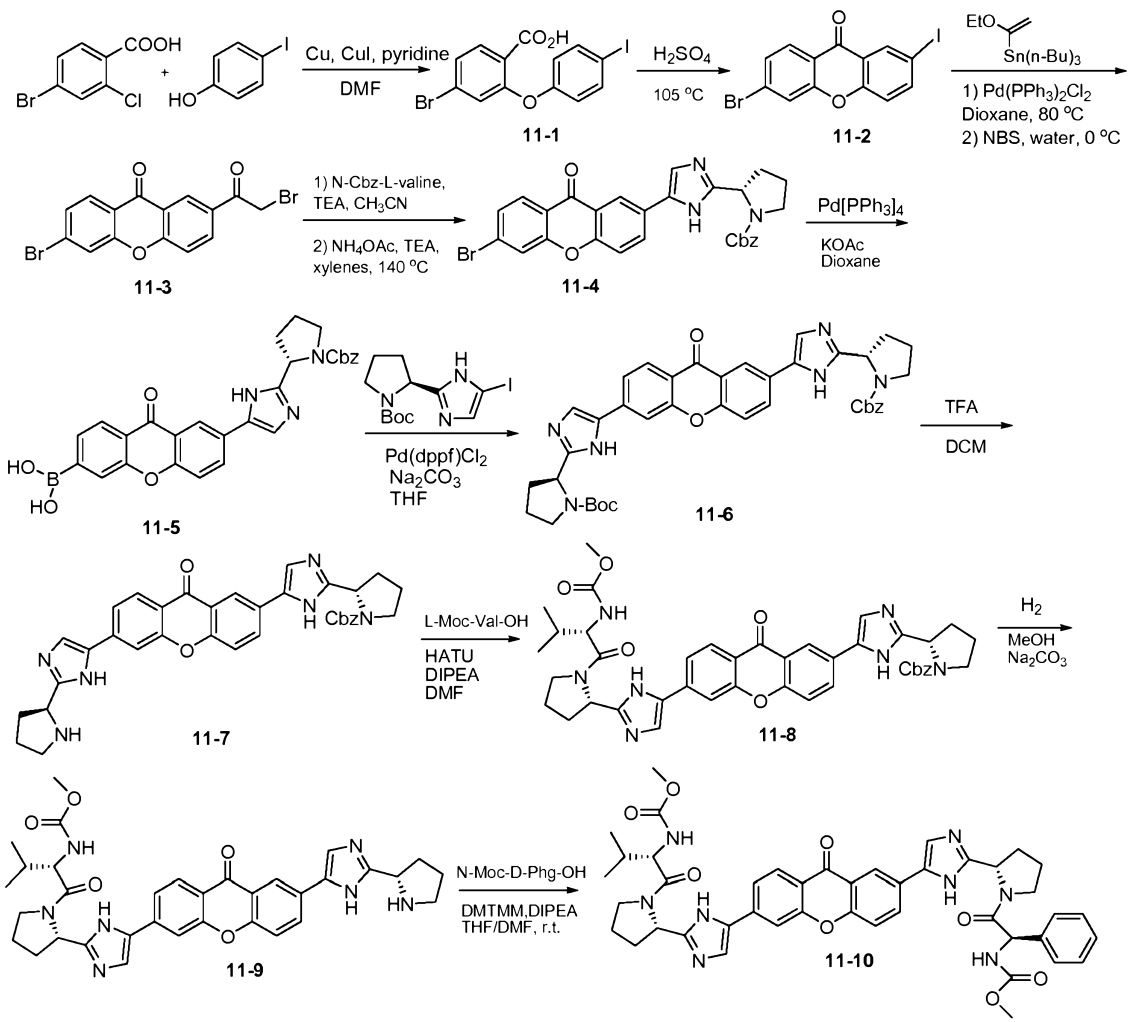
to give a yellow oily solid. The product was purified by column chromatography (SiO_2, 0-10% EtOAc/isohexanes) to give 2,7-dibromodibenzo[b,f]oxepine (**10-2**) (763 mg, 79% yield) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.41-7.36 (1H, m), 7.33-7.31 (1H, m), 7.29-7.24 (2H, m), 7.04-6.99 (2H, m), 6.68-6.57 (2H, m) ppm.

[0329] **Step 4.** A solution of 2,7-dibromodibenzo[b,f]oxepine (**10-2**) (663 mg, 1.88 mmol) in EtOAc (40 mL) was degassed under N_2. Pt/C 10% by wt (200 mg) was added and the reaction was evacuated and placed under H_2 gas. After 2 h reaction mixture was degassed and filtered through Celite®545 (eluant EtOAc) and solvent was removed *in vacuo* to give a yellow oil. The compound was dissolved in petroleum ether and passed through a short pad of SiO_2, eluting with isohexanes 400 mL. Solvent was removed *in vacuo*, to give 2,7-dibromo-10,11-dihydrodibenzo[b,f]oxepine (**10-3**) (542 mg, 81% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.32 (1H, m), 7.29-7.24 (2H, m), 7.18-7.14 (1H, m), 7.04-6.96 (2H, m), 3.08 (4H, s) ppm.

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

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

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



Scheme 11

Example 22. Preparation of 11-8

[0333] **Step 1.** Referring to Scheme 11, to a solution of 4-bromo-2-chlorobenzoic acid (18.4 g, 83.9 mmol) and 4-bromophenol (24 g, 109 mmol) in nitrobenzene was added cesium carbonate (82 g, 251.7 mmol). The resulting solution was heated at 170 °C with condenser for 1 day. The reaction mixture was cooled to 70 °C and filtrated at this temperature. The residue was washed with toluene. The organic layer was removed by vacuum distillation till a thick dark residue remained. The dark residue was added to aqueous HCl (1N, 400 mL) and DCM (200 mL). The resulting solution was stirred until the dark oil dispersed into DCM solution. The mixture was filtered. The organic layer was dried (Na_2SO_4) and concentrated to afford the crude product. The residue was purified by column chromatography on silica gel, eluted first with DCM and then with a mixture of DCM and MeOH in 10:1 (*v/v*) ratio to give **11-1** along with the

corresponding des- iodo compound **11-1′**(16 g, 5:3 ratio). LC-MS (ESI): *m/z* 419 $(M+H)^+$ for **11-1**, *m/z* 293 $(M+H)^+$ for **11-1′**. The mixture was used in the next step.

[0334] **Step 2.** The mixture of **11-1** and **11-1′** (16 g, 5:3 ratio, 44.3 mmol) was treated with concentrated sulfuric acid (95 mL). The solution was heated at 105 °C for 2 h. The reaction mixture was cooled down and poured into ice water. The product was precipitated out and was collected by filtration, washed with Et_2O and H_2O. The solid was dried and further purified by flash column chromatography on silica gel (eluents: Hex:AcOEt = 9:1(*v/v*) to AcOEt 100%, and then to DCM) to afford **11-2** (7 g) and **11-2′** (5 g). LC-MS (ESI): *m/z* 401 $(M+H)^+$ for **11-2**, *m/z* 275 $(M+H)^+$ for **11-2′**.

[0335] **Step 3.** To a solution of iodide **11-2** (6.5 g, 16.2 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (6.02 mL, 17.8 mmol) in dioxane (70 mL) was added $Pd(PPh_3)_2Cl_2$ (0.57g, 0.81 mmol). The resulting solution was bubbled with N_2 for 15 min and heated at 80 °C for 17 h. The reaction mixture was treated with H_2O (24 mL) and cooled to 0 °C. To the solution was added NBS (3.17 g, 17.8 mmol) in portions over 15 min. After about 30 min stirring, the volatiles were removed *in vacuo* and the residue was partitioned between DCM and water. The aqueous layer was back extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography (Hex:AcOEt = 5:1 (*v/v*) to 1:1 (*v/v*) and DCM:MeOH = 10:1(*v/v*)) to afford a mixture of **11-3** (4.6 g pure). ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.76 (s, 1H), 7.59 (m, 2H), 4.58 (s, 0.5H), 4. 44 (s, 1.5H) ppm.

[0336] **Step 4.** A solution of **11-3** (3.3 g, 8.33 mmol) in CH_3CN (15 mL) was added drop-wisely over 5 minutes to a solution of N-Cbz-L-proline (2.26 g, 9.16 mmol) and triethylamine (1.74 mL, 12.5 mmol) in CH_3CN (30 mL). The resulting mixture was stirred for 90 min. The volatiles were removed *in vacuo* and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM to DCM:MeOH = 10:1(*v/v*)) to afford the ketoester intermediate (3.4 g). LC-MS (ESI): *m/z* 564 $(M+H)^+$.

The solution of ketoester from above (3.4 g, 6.03 mmol), ammonium acetate (6.97 g, 90.5 mmol) and triethylamine (12.6 mL, 90.5 mml) in xylene (70 mL) was placed in a sealed tube and heated at 140 °C with stir for 2 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and AcOEt. The aqueous layer was extracted with AcOEt. The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The crude mixture

was purified by flash column chromatography (DCM:MeOH = 10:1 (*v/v*)) to afford compound **11-4** (2.0 g). LC-MS (ESI): *m/z* 544 $(M+H)^+$.

[0337] **Step 5.** To a solution of **11-4** (1.9 g, 3.5 mmol) in dioxane (35 mL) was added bis(pinacolato)diboron (2.22 g, 8.75 mmol), tetrakis(triphenylphosphine)palladium (202 mg, 0.175 mmol) and potassium acetate (1.03 g, 10.5 mmol). The resulting solution was degassed by bubbling with N_2 for 15 min, and then heated at 95 ^oC for 5 h. The reaction mixture was filtered through a pad of Celite. The organic solvent was removed *in vacuo*. The residue was purified by flash column chromatography (DCM:MeOH = 10:1 (*v/v*)) to afford compound **11-5** (1.5 g). LC-MS (ESI): *m/z* 510 $(M+H)^+$.

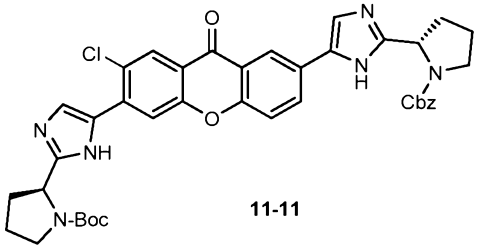
[0338] **Step 6.** To a solution of **11-5** (1.5 g, 2.5 mmol) in THF (30 mL) was added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.78 mmol), dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium(II) (102 mg, 0.125 mmol) and sodium carbonate (2 M, 12 mL). The resulting solution was bubbled with N_2 for 15 min, then refluxed overnight. The solvent was removed *in vacuo* and the residue was partitioned between water and DCM. The aqueous layer was extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography (DCM:MeOH = 9:1(*v/v*)) to afford compound **11-6** (1.3 g). LC-MS (ESI): *m/z* 351 $(M+2H)^{2+}$.

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

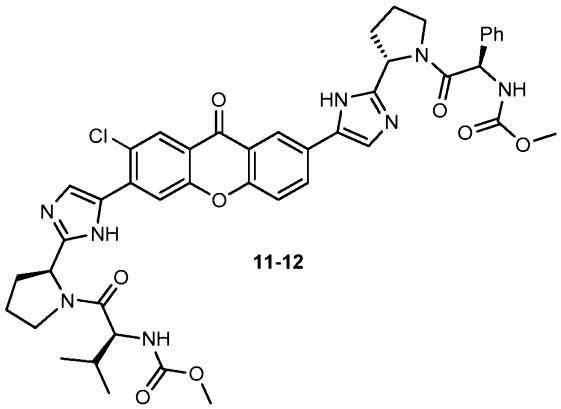
Example 23. Preparation of 11-10

[0340] **Step 1**. Compound **11-8** was treated with H_2 in the presence of Pd/C for the removal of Cbz protecting group to give **11-9**. LC-MS (ESI): *m/z* 624.3 $(M+H)^+$.

[0341] **Step 2.** Following conditions in General Procedure B, **11-9** was converted to compound **11-10**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (bs, 2H), 8.20 (s, 1H), 8.05 (d, 1H), 7.82 (m, 2H), 7.42-7.32 (m, 5H), 7.20 (m, 2H), 6.36 (bs, 1H), 5.60 (d, 1H), 5.52 (m, 1H), 5.32 (m, 2H), 4. 40 (t, 1H), 4.03 - 3.85 (m, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 3.32 (m, 1H), 2.60 (m, 1H), 2.42 - 2.08 (m, 7H), 1.92 (m, 1H), 1.09 - 0.90 (m, 6H) ppm; LC-MS (ESI): *m/z* 815.8 $(M+H)^+$.



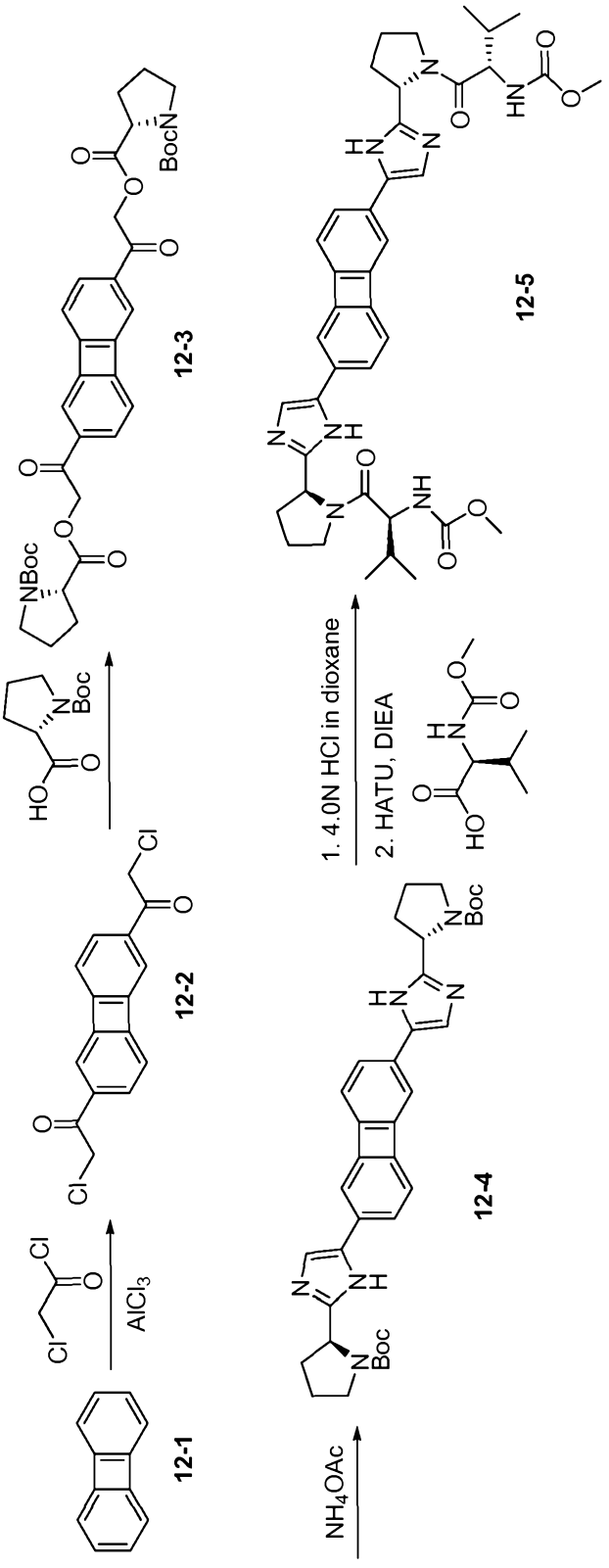
11-11



11-12

Example 24. Preparation of 11-12

[0342] Following the procedures described for steps in Scheme 11 and substituting 4-bromo-2,5-dichloro-5-nitrobenzoic acid for 4-bromo-2chloro-5-nitrobenzoic acid in step 1. Compounds **11-11** and **11-12** were obtained. LC-MS (ESI): *m/z* 735.3 $(M+H)^+$ for **11-11** and LC-MS (ESI): *m/z* 850.3 $(M+H)^+$ for **11-12**.


12-1
AlCl3
12-2
12-3
12-4
NH4OAc
1. 4.0N HCl in dioxane
2. HATU, DIEA
12-5

Scheme 12

Example 25. Preparation of 12-5

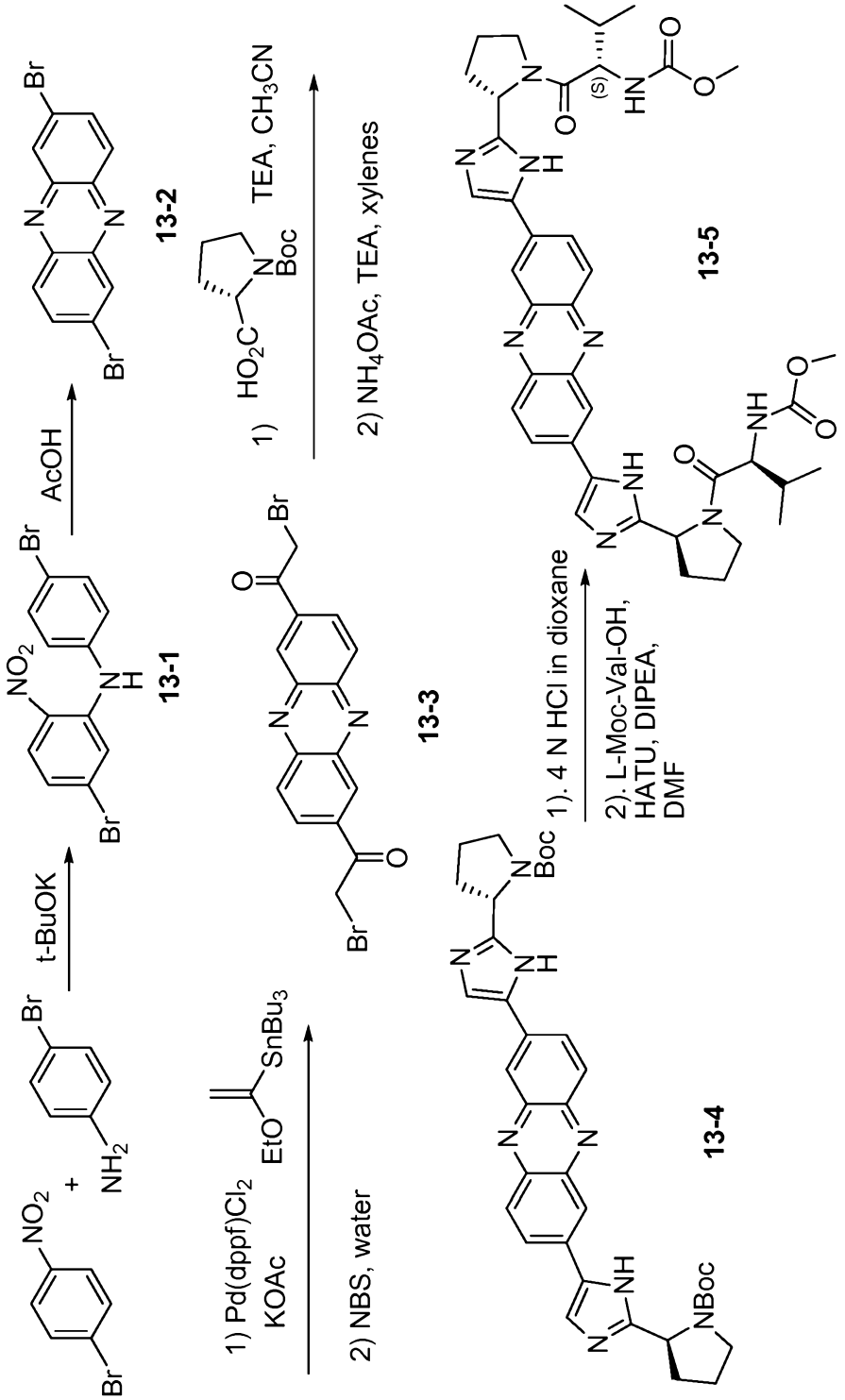
[0343] **Step 1**. Referring to Scheme 12, to a solution of **12-1** (200 mg, 1.31 mmol) in CS_2 (20 mL), $AlCl_3$ (876 mg, 6.57 mmol) and 2-chloroacetyl chloride (964 mg, 8.54 mmol) were added at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was added to H_2O (50 mL). The mixture was extracted with EtOAc for several times (3 x 50 mL) and the extracts were combined and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 10:1 (*v/v*)) to give **12-2** (140 mg, 35% yield). LC-MS (ESI): *m/z* 305 $(M+H)^+$.

[0344] **Step 2.** To a solution of **12-2** (140 mg, 0.459 mmol) in DCM (10 mL), (*S*)-N-Boc-Pro- OH (197 g, 0.917 mmol) and Et_3N (0.26 mL, 1.84 mmol) were added at rt. After stirring at rt overnight, the reaction mixture was concentrated and the residue was dried *in vacuo* to give crude **12-3** (100 mg), which was used for the next step without further purification. LC-MS (ESI): *m/z* 663 $(M+H)^+$.

[0345] **Step 3.** To a solution of crude **12-3** (100 mg, 0.124 mmol) in toluene (20 mL) was added NH_4OAc (95.0 mg, 1.24 mmol). After refluxing overnight, the reaction micture was concentrated and the residue was purified by silica gel column chromatography (Petroleum Ether/EtOAc = 3:1 (*v/v*)) to give **12-4** (34 mg, 45% yield) as a yellow solid. LC-MS (ESI): *m/z* 623 $(M+H)^+$.

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

[0347] To a mixture of the HCl salt in DMF (2 mL) was added DIPEA (0.1 mL, 0.5 mmol), followed by N-Moc-L-Val-OH (22 mg, 0.13 mmol) and HATU (50 mg, 0.13 mmol). After stirred at rt for 30 min, the reaction mixture was poured into water. The solid was filtrated and purified by preparative HPLC to give **12-5** (10 mg, 27%) as an off-white solid. ^1H NMR (500 MHz, CD_3OD) δ 7.92 (s, 2H), 7.25 (d, *J* = 7.0, 2H), 7.16 (s, 2H), 6.91 (d, *J* = 6.5, 2H), 5.21 (s, 2H), 4.22 (d, *J* = 6.5, 2H), 4.09 (s, 2H), 3.91 (s, 2H), 3.65 (s, 6H), 2.55 (s, 2H), 2.28 (s, 2H), 2.17 (s, 2H), 2.07 (d, *J* = 6.0, 2H), 1.00 - 0.88 (m, 12H) ppm; LC-MS (ESI): *m/z* 737 $(M+H)^+$.


t-BuOK
AcOH
13-1
13-2
1) Pd(dppf)Cl2
KOAc
2) NBS, water
13-3
1) TEA, CH3CN
2) NH4OAc, TEA, xylenes
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA,
DMF
13-4
13-5

Scheme 13

Example 26. Preparation of 13-5

[0348] **Step 1.** Referring to Scheme 13, a solution of 4-bromoaniline (10 g, 58.1 mmol) in DMF (30 mL) was added dropwise to a solution of potassium *t*-butoxide (19.57 g, 174 mmol) in DMF (60 mL) at - 60 °C, followed immediately by a solution of 1-bromo-4-nitrobenzene (11.74 g, 58.1 mmol) in DMF (45 mL). The mixture was stirred for 5 min, and then a cooled mixture of AcOH (45 mL) and DMF (45 mL) was added in one portion. The mixture was allowed to warm to room temperature, and poured into water (500 mL) and extracted with EtOAc (3 x 300 mL), the organics were combined and washed with water (3 x 500 mL), brine (500 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude brown solid. The product was purified by silica gel chromatography (SiO_2, 0-10% EtOAc/isohexane) to afford **13-1** as brown solid (10 g, 48.3 % yield).

[0349] **Step 2.** 5-bromo-N-(4-bromophenyl)-2-nitrosoaniline (**13-1**) (10 g, 28.1 mmol) in AcOH (300 mL) was heated under reflux for 1.5 h. Water (400 mL) was then added and the brown precipitate formed was collected by filtration after washing with water (2 x 200 mL). The product was purified by silica gel chromatography (SiO_2, hexanes/DCM = 1/1(*v/v*)) to afford a brown solid, 2,7-dibromophenazine **13-2** (1.52 g, 16 % yield).
^{1}H NMR ($CDCl_3$) δ 8.43 (2H, dd, *J* 2.2, 0.4 Hz), 8.10 (2H, dd, *J* 9.2, 0.4 Hz), 7.91 (2H, dd, *J* 9.2, 2.2 Hz) ppm. LC-MS (ESI): *m/z* 338.6 $(M+H)^+$.

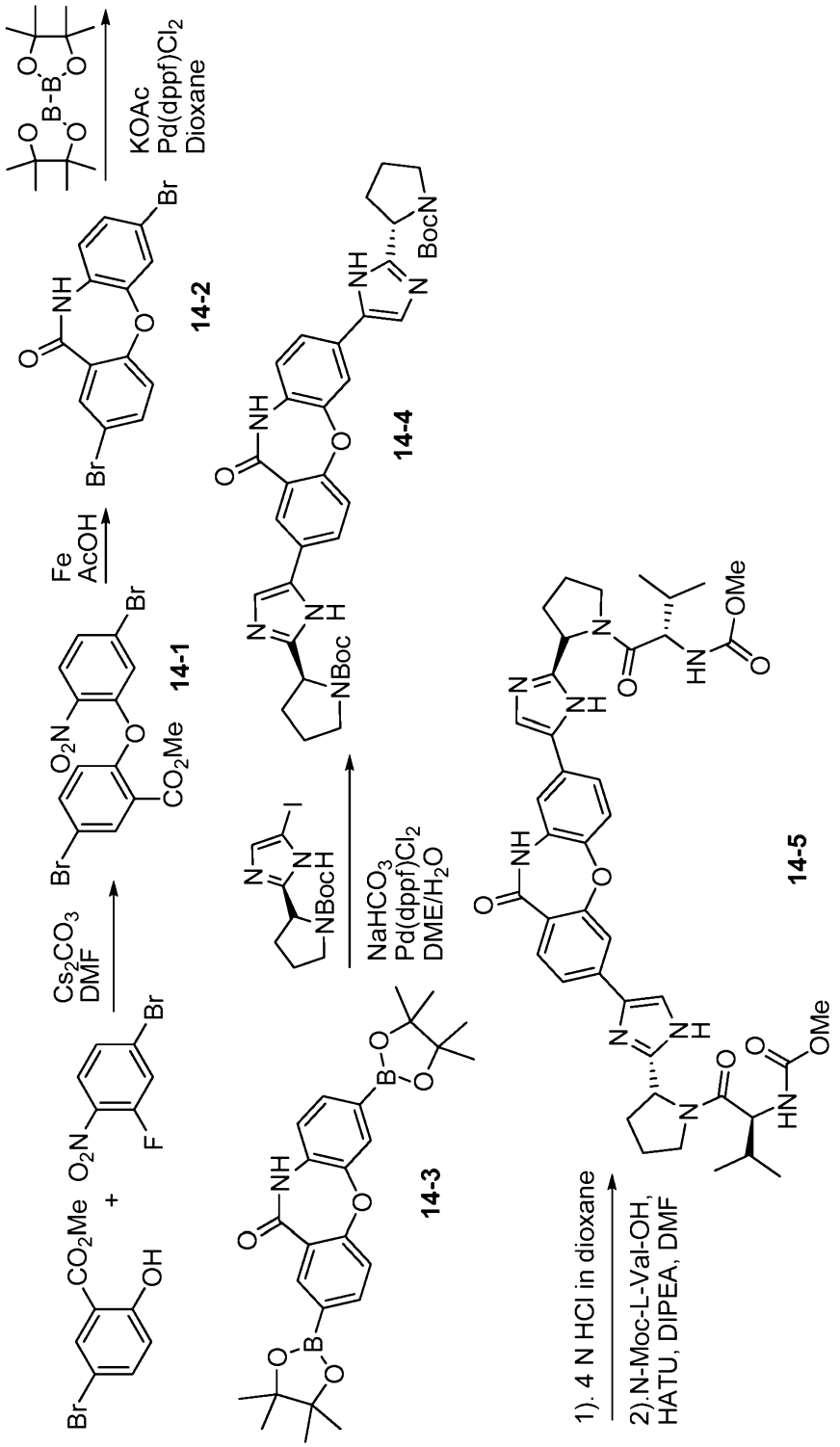
[0350] **Step 3.** To a solution of 2,7-dibromophenazine (**13-2**) (1.52 g, 4.50 mmol) in dry dioxane (75 mL) under N_2 was added tributyl(1-ethoxyvinyl)stannane (3.34 ml, 9.89 mmol) and Pd(dppf)Cl_2 (0.316 g, 0.450 mmol). The resultant mixture was heated at 100°C for 4h in a sealed tube. The crude reaction mixture was filtered through CELITE^{TM}545, and the volatiles were removed *in vacuo*. The crude brown solid was triturated with isohexanes and filtered to give 2,7-bis(1-ethoxyvinyl)phenazine as a brown solid (1.27 g, 88 % yield).
^{1}H NMR ($CDCl_3$) δ 8.55-8.53 (2H, m), 8.19-8.15 (2H, m), 8.11-8.07 (2H, m), 4.98 (2H, d, *J* = 3 Hz), 4.49 (2H, d, *J* = 3 Hz), 4.03 (4H, q, *J* = 7 Hz), 1.50 (6H, t, *J* = 7 Hz) ppm. LC-MS (ESI): *m/z* 322.1 $(M+H)^+$.

[0351] *N*-Bromosuccinimide (1.411 g, 7.93 mmol) was added to a stirred solution of 2,7-bis(1-ethoxyvinyl)phenazine (1.27 g, 3.96 mmol) in THF (95 mL) and water (20 mL) and left to stir at rt for 1 h. The reaction mixture was filtered and the yellow solid collected was washed with water and dried under vacuum to afford 1,1'-(phenazine-2,7-diyl)bis(2-bromoethanone) (**13-3**) (991 mg, 59.2 % yield) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 8.93-8.91 (2H, m), 8.47-8.46 (2H, m), 8.41-8.37 (2H, m), 4.66 (4H, s) ppm. LC-MS (ESI): *m/z* 423.8 $(M+H)^+$.

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

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


Cs2CO3
DMF
Fe
AcOH
KOAc
Pd(dppf)Cl2
Dioxane
14-1
14-2
NaHCO3
Pd(dppf)Cl2
DME/H2O
14-3
14-4
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF
14-5

Scheme 14

Example 27. Preparation of 14-5

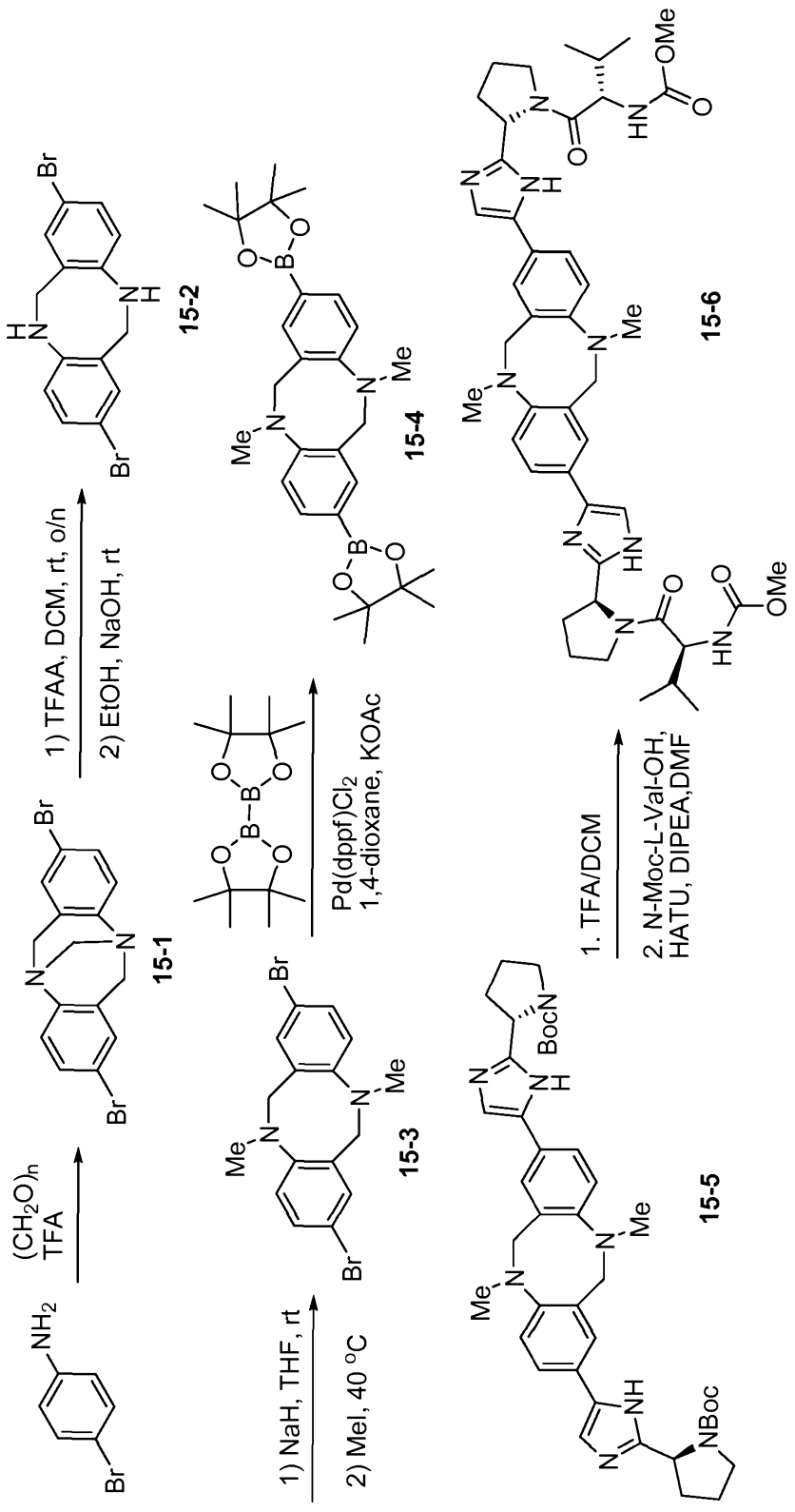
[0354] **Step 1.** Referring to Scheme 14, cesium carbonate (6.20 g, 19.0 mmol) was added to a solution of methyl 5-bromo-2-hydroxybenzoate (4.0 g, 17.3 mmol) in DMF (20 mL) and the mixture was stirred for 30 mins. 4-bromo-2-fluoro-1-nitrobenzene (3.81 g, 17.3 mmol) was then added and the mixture was heated at 60 ^{o}C for 3 h. After cooling at the completion of the reaction, the mixture was poured into water (500 mL) and extracted with ether (2 x 250 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude **14-1** as brown oil (5.85 g, 78% yield).

[0355] **Step 2.** The crude product from above was dissolved in AcOH (12 mL) and treated with iron powder (320 mesh, 4.55 g, 81 mmol) at 115 ^{o}C for 40 mins. The reaction mixture was cooled to rt, poured into water (300 mL) and extracted with EtOAc (2x200 mL). The combined organic extracts were sequentially washed with water (300 mL), aq. $NaHCO_3$ (300 mL) and brine (200 mL) and concentrated *in vacuo*. The residue was taken up in minimal amount of Et_2O and precipitated with addition of hexanes. Precipitate was collected by filtration to give **14-2** as a white solid in 72% yield. LC-MS (ESI): *m/z* 368.2 $(M-H)^-$.

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

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

[0358] **Step 5.** Compound **14-5** was obtained in 45% yield by treating **14-4** under General Procedure B. LC-MS (ESI): *m/z* 796 $(M+H)^+$.


(CH2O)n
TFA
1) TFAA, DCM, rt, o/n
2) EtOH, NaOH, rt
15-1
15-2
1) NaH, THF, rt
2) MeI, 40 °C
15-3
Pd(dppf)Cl2
1,4-dioxane, KOAc
15-4
1. TFA/DCM
2. N-Moc-L-Val-OH,
HATU, DIPEA,DMF
15-5
15-6

Scheme 15

Example 28. Preparation of 15-6

[0359] **Step 1**. Referring to Scheme 15, 4-Bromoaniline and paraformaldehyde were added to TFA (23 mL) at -15 °C. After stirred at rt for 24 h, the reaction mixture was slowly added to a stirred mixture of ice and 30% aqueous NH_3 (40 mL). The entire mixture (solid and solution) was extracted with DCM (3 x 10 mL), the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **15-1** (2.35 g, 57%, yellow solid).

[0360] **Step 2**. Compound **15-1** was suspended in a mixture of TFAA (4 mL) and DCM (8 mL) and stirred at rt in a sealed vessel overnight. LC-MS indicated the presence of trifluoracetylated product and the absence of starting **15-1**. The reaction was then quenched with H_2O and basified with aqueous $NaHCO_3$. The mixture was extracted with DCM (3x100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in EtOH (40 mL) with sodium hydroxide (800 mg) and stirred at rt for 2 h. The reaction was concentrated under reduced pressure and the residue dissolved in a mixture of water and DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give product **15-2** in 57% yield.

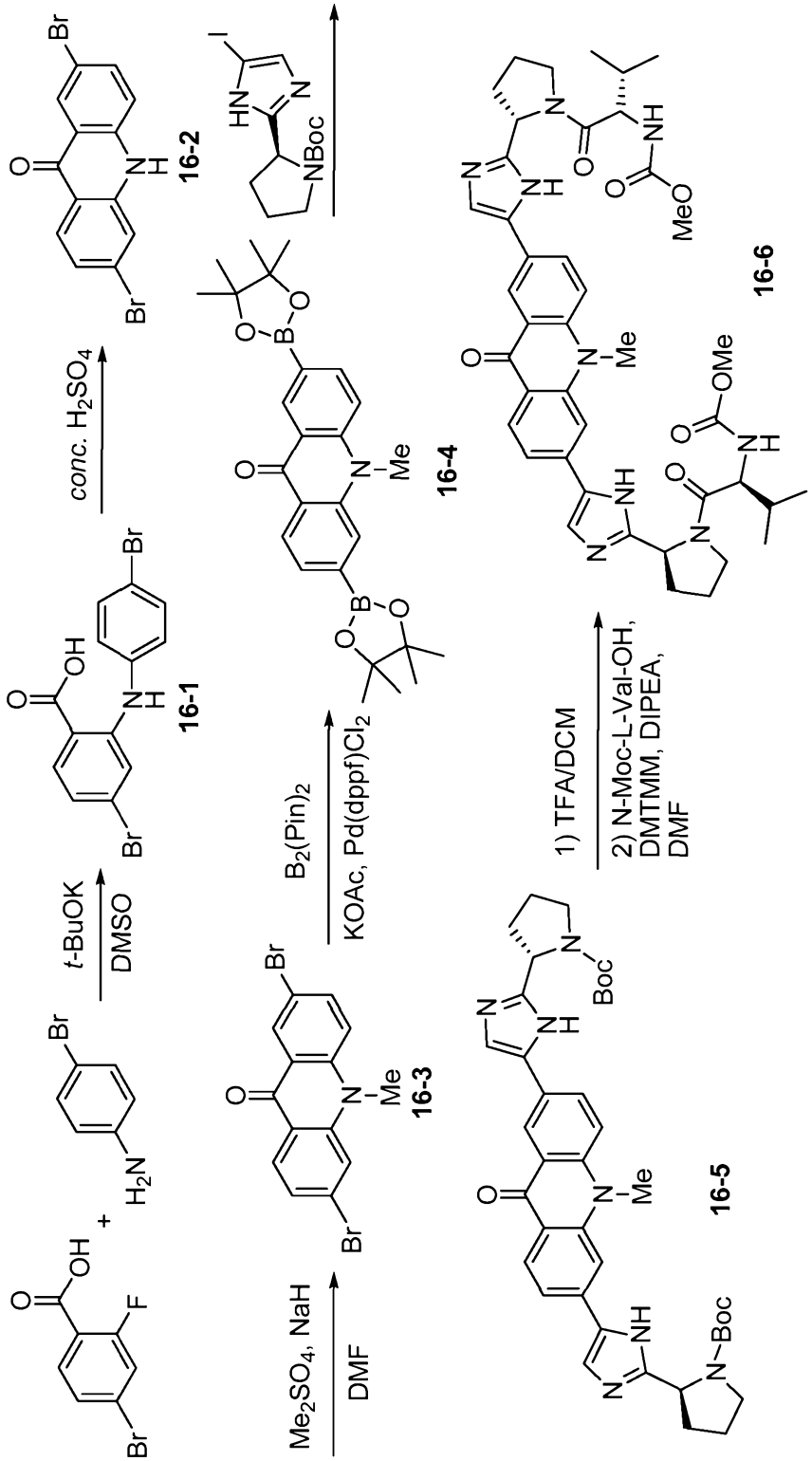
[0361] **Step 3**. NaH (60% mineral oil dispersion, 0.103 g, 4.29 mmol) was added to a solution of **15-2** (0.75 g, 2.04 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 45 mins at rt. MeI (0.638 g, 4.50 mmol) was added at 0 °C, and the reaction mixture stirred at rt overnight. The reaction was cooled down to rt and quenched with water. The aqueous layer was extracted with DCM (3 x 50 mL) and Et_2O (2 x 50 mL), respectively. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluted with mixed solvents of hexanes and DCM in 9:1 (*v/v*) ratio to give **15-3** (0.634 g, 78% yield). LC-MS (ESI): *m/z* 397.1 $(M+H)^+$.

[0362] **Step 4.** Compound **15-4** was prepared in 66% by treating **15-3** under general procedure C.

[0363] **Step 5.** Compound **15-5** was obtained in 54% yield by treating **15-4** under general procedure D. LC-MS (ESI): *m/z* 709.6 $(M+H)^+$.

[0364] **Step 6.** Compound **15-6** was obtained in 32% yield by treating **15-5** under general procedure B. LC-MS (ESI): *m/z* 823.5 $(M+H)^+$.

[0365]



Scheme 16

Example 29. Preparation of 16-6

[0366] **Step 1.** Referring to Scheme 16, to a solution of acid 4-bromo-4-fluorobenzoic acid (6 g) and 4-bromoaniline (7 g) in DMSO (75 mL) was added potassium *tert*-butoxide (1.3 g) at rt. After stirring for three days, the reaction was diluted with water (300 mL) and extracted with diethyl ether (3x100 mL). The aqueous layer was acidified by 2 M HCl to pH 1, extracted by ethyl acetate (with 10% MeOH). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide the crude product, which was recrystallized in MeOH to provide **16-1** (1.2 g, red solid, 12% yield). LC-MS (ESI): *m/z* 372 $(M+H)^+$.

[0367] **Step 2.** Compound **16-1** (1.2 g) was dissolved in *conc.* H_2SO_4 (6 mL) and the solution was warmed up to 110 °C. After stirring for one h, the reaction was cooled to rt and slowly transferred to ice-water (100 mL). The yellow precipitation from ice-water solution was filtered to afford **16-2** (900 mg), which was used without further purification. LC-MS (ESI): *m/z* 352 $(M+H)^+$.

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

[0369] **Step 4**. To a solution of **16-3** (100 mg, 0.272 mmol) in 24 mL of dioxane was added bis(pinacolato)diboron (166 mg, 0.653 mmol), dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium(II) (11 mg, 0.014 mmol) and potassium acetate (160 mg, 1.63 mmol) under N_2 atmosphere. The reaction mixture was stirred at 80 °C overnight, and then cooled to rt and diluted with dichloromethane (150 mL) and then aq. phase was extracted with dichloromethane. The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo* to give crude **16-4** (140 mg). LC-MS (ESI): *m/z* 462 $(M+H)^+$.

[0370] **Step 5.** To a solution of **16-4** (140 mg, 0.272 mmol) in 3.2 mL of THF and 2M Na_2CO_3 (3/1(*v/v*) was added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.598 mmol), dichloro [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (11 mg, 0.014 mmol) and sodium bicarbonate (2.7 g, 32 mmol) under N_2 atmosphere. The reaction mixture was stirred at 80 °C overnight and diluted with dichloromethane (120 mL). The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue was further purified

by silica gel column chromatography (Hexane / acetone = 1:1 (*v/v*)) to give **16-5** (110 mg, 43%) as a yellow solid. LC-MS (ESI): *m/z* 680 $(M+H)^+$.

[0371] **Step 6**. To a stirred solution of **16-5** (55 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL). After 3 h, the reaction was concentrated to dryness to provide de-Boc- -**16-5**. de-Boc- **16-5** was dissolved in DMF (2 mL) and DIPEA (100 μL), N-Moc-L-Val-OH (18 mg) and DMTMM (20 mg) were added subsequently. After one h stirring, the reaction was diluted with water. The reaction was extracted with dichloromethane. The combined extracts were washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by prep-HPLC (Phenomenex, C18-Luna column, H_2O-MeCN, 0.1% HCO_2H) to provide **16-6** (6.0 mg, 6.5% yield). ^1H NMR (300 MHz, CD_3OD) δ8.77-8.69 (m, 1H), 8.56 - 8.45 (m, 1H), 8.31 - 8.18 (m, 3H), 8.06 - 8.01 (m, 1H), 7.96 (s, 1H), 7.74 - 7.71 (m, 1H), 5.33 - 5.26 (m, 2H), 4.27-4.24 (m, 2H), 4.17 - 4.04 (m, 3H), 3.99 - 3.80 (m, 2H), 3.70 – 3.60 (m, 6H), 2.62 - 2.55 (m, 2H), 2.38 - 2.05 (m, 8H), 1.03 - 0.86 (m, 12H) ppm; LC-MS (ESI): *m/z* 794 $(M+H)^+$.

Biological Activity

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

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

% Control = (Compound Luciferase Level/Control Luciferase Level)*100

[0374] The EC_{50} value was determined using GraphPad Prism and the following equation:

Y = Bottom asymptote + (Top asymptote-Bottom asymptote)/ (1+10^ ((LogEC_{50}-X)*HillSlope))

[0375] EC_{50} values of compounds are determined several times in the replicon assay to generate average EC_{50} values.

[0376] Example compounds of the disclosed invention are illustrated in Table 1. The table shows inhibitory activity of many of the example compounds with respect to HCV 1b. The biological activity is indicated as being *, **, *** or ****, which corresponds to EC_{50} ranges of >1000 nM, 999 nM to 10 nM, 9.9 nM to 1 nM, or <1 nM respectively. The tables further provide mass spectrometry results for the synthesized example compounds.

Pharmaceutical Compositions

[0377] A twelfth aspect of the invention provides a pharmaceutical composition comprising the compounds of the invention. In a first embodiment, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients or vehicles, and optionally other therapeutic and/or prophylactic ingredients. Such excipients are known to those of skill in the art. The compounds of the present invention include, without limitation, basic compounds such as free bases and pharmaceutically acceptable salts of these compounds. A thorough discussion of pharmaceutically acceptable excipients and salts is available in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990).

[0378] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc.

[0379] The invention includes a pharmaceutical composition comprising a compound of the present invention including isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic and/or prophylactic ingredients.

[0380] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate and the like.

[0381] For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule nonaqueous solution, suspension or syrup. Tablets and capsules are

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

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

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

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

Combination Therapy

[0385] The compounds of the present invention and their isomeric forms and pharmaceutically acceptable salts thereof are useful in treating and preventing HCV infection alone or when used in combination with other compounds targeting viral or cellular elements or functions involved in the HCV lifecycle. Classes of compounds useful in the invention may include, without limitation, all classes of HCV antivirals. For combination therapies, mechanistic classes of agents that may be useful when combined with the compounds of the

present invention include, for example, nucleoside and non-nucleoside inhibitors of the HCV polymerase, protease inhibitors, helicase inhibitors, NS4B inhibitors and medicinal agents that functionally inhibit the internal ribosomal entry site (IRES) and other medicaments that inhibit HCV cell attachment or virus entry, HCV RNA translation, HCV RNA transcription, replication or HCV maturation, assembly or virus release. Specific compounds in these classes and useful in the invention include, but are not limited to, macrocyclic, heterocyclic and linear HCV protease inhibitors such as telaprevir (VX-950), boceprevir (SCH-503034), narlaprevir (SCH-900518), ITMN-191 (R-7227), TMC-435350 (a.k.a. TMC-435), MK-7009, BI-201335, BI-2061 (ciluprevir), BMS-650032, ACH-1625, ACH-1095 (HCV NS4A protease co-factor inhibitor), VX-500, VX-813, PHX-1766, PHX2054, IDX-136, IDX-316, ABT-450 EP-013420 (and congeners) and VBY-376; the Nucleosidic HCV polymerase (replicase) inhibitors useful in the invention include, but are not limited to, R7128, PSI-7851, IDX-184, IDX-102, R1479, UNX-08189, PSI-6130, PSI-938 and PSI-879 and various other nucleoside and nucleotide analogs and HCV inhibitors including (but not limited to) those derived as 2'-C-methyl modified nucleos(t)ides, 4'-aza modified nucleos(t)ides, and 7'-deaza modified nucleos(t)ides. Non-nuclosidic HCV polymerase (replicase) inhibitors useful in the invention, include, but are not limited to , HCV-796, HCV-371, VCH-759, VCH-916, VCH-222, ANA-598, MK-3281, ABT-333, ABT-072, PF-00868554, BI-207127, GS-9190, A-837093, JKT-109, GL-59728 and GL-60667.

[0386] In addition, NS5A inhibitors of the present invention may be used in combination with cyclophyllin and immunophyllin antagonists (eg, without limitation, DEBIO compounds, NM-811 as well as cyclosporine and its derivatives), kinase inhibitors, inhibitors of heat shock proteins (e.g., HSP90 and HSP70), other immunomodulatory agents that may include, without limitation, interferons (-alpha, -beta, -omega, -gamma, -lambda or synthetic) such as Intron A™, Roferon-A™, Canferon-A300™, Advaferon™, Infergen™, Humoferon™, Sumiferon MP™, Alfaferone™, IFN-β™, Feron™ and the like; polyethylene glycol derivatized (pegylated) interferon compounds, such as PEG interferon-α-2a (Pegasys™), PEG interferon-α-2b (PEGIntron™), pegylated IFN-α-con1 and the like; long acting formulations and derivatizations of interferon compounds such as the albumin-fused interferon, Albuferon™, Locteron ™ and the like; interferons with various types of controlled delivery systems (e.g. ITCA-638, omega-interferon delivered by the DUROS ™ subcutaneous delivery system); compounds that stimulate the synthesis of interferon in cells, such as resiquimod and the like; interleukins; compounds that enhance the development of

type 1 helper T cell response, such as SCV-07 and the like; TOLL-like receptor agonists such as CpG-10101 (actilon), isotorabine, ANA773 and the like; thymosin α -1; ANA-245 and ANA-246; histamine dihydrochloride; propagermanium; tetrachlorodecaoxide; ampligen; IMP-321; KRN-7000; antibodies, such as civacir, XTL-6865 and the like and prophylactic and therapeutic vaccines such as InnoVac C, HCV E1E2/MF59 and the like. In addition, any of the above-described methods involving administering an NS5A inhibitor, a Type I interferon receptor agonist (e.g., an IFN-α) and a Type II interferon receptor agonist (e.g., an IFN-γ) can be augmented by administration of an effective amount of a TNF-α antagonist. Exemplary, non-limiting TNF-α antagonists that are suitable for use in such combination therapies include ENBREL ™, REMICADE™ and HUMIRA ™.

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

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

WO00/056331; WO 98/22496; WO 99/07734; WO 05/073216, WO 05/073195 and WO 08/021927.

[0389] Additionally, combinations of, for example, ribavirin and interferon, may be administered as multiple combination therapy with at least one of the compounds of the present invention. The present invention is not limited to the aforementioned classes or compounds and contemplates known and new compounds and combinations of biologically active agents (*see*, Strader, D.B., Wright, T., Thomas, D.L. and Seeff, L.B., *AASLD Practice Guidelines*. 1-22, 2009 and Manns, M.P., Foster, G.R., Rockstroh, J.K., Zeuzem, S., Zoulim, F. and Houghton, M., *Nature Reviews Drug Discovery*. 6:991-1000, 2007, Pawlotsky, J-M., Chevaliez, S. and McHutchinson, J.G., *Gastroenterology*. 132:179-1998, 2007 , Lindenbach, B.D. and Rice, C.M., *Nature* 436:933-938, 2005, Klebl, B.M., Kurtenbach, A., Salassidis, K., Daub, H. and Herget, T., *Antiviral Chemistry & Chemotherapy*. 16:69-90, 2005, Beaulieu, P.L., *Current Opinion in Investigational Drugs*. 8:614-634, 2007, Kim, S-J., Kim, J-H., Kim, Y-G., Lim, H-S. and Oh, W-J., *The Journal of Biological Chemistry*. 48:50031-50041, 2004, Okamoto, T., Nishimura, Y., Ichimura, T., Suzuki, K., Miyamura, T., Suzuki, T., Moriishi, K. and Matsuura, Y., *The EMBO Journal*. 1-11, 2006, Soriano, V., Peters, M.G. and Zeuzem, S. *Clinical Infectious Diseases*. 48:313-320, 2009, Huang, Z., Murray, M.G. and Secrist, J.A., *Antiviral Research*. 71:351-362, 2006 and Neyts, J., *Antiviral Research*. 71:363-371, 2006, each of which is incorporated by reference in their entirety herein). It is intended that combination therapies of the present invention include any chemically compatible combination of a compound of this inventive group with other compounds of the inventive group or other compounds outside of the inventive group, as long as the combination does not eliminate the anti-viral activity of the compound of this inventive group or the anti-viral activity of the pharmaceutical composition itself.

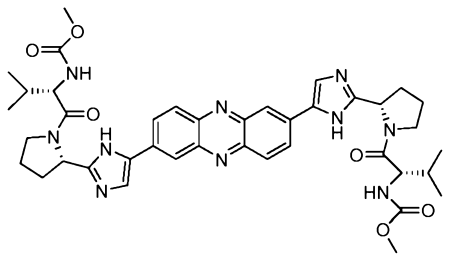
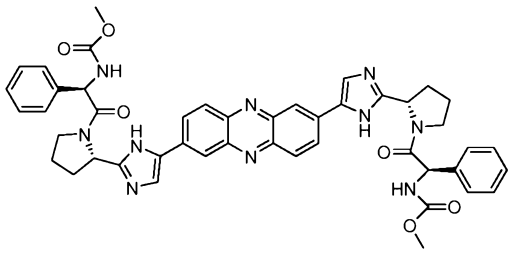
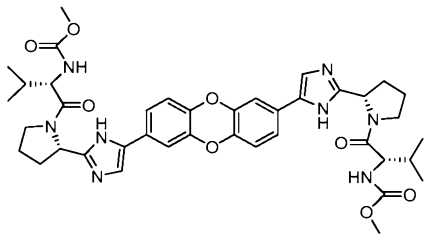
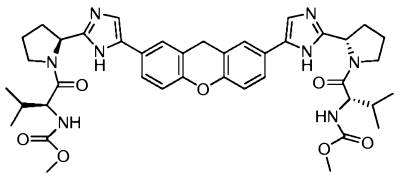
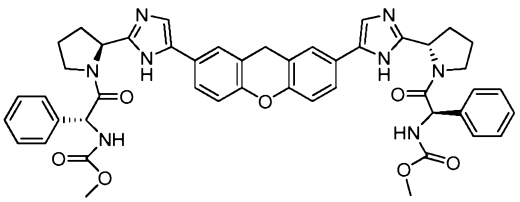
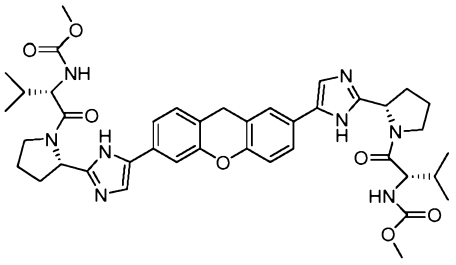
[0390] Combination therapy can be sequential, that is treatment with one agent first and then a second agent (for example, where each treatment comprises a different compound of the invention or where one treatment comprises a compound of the invention and the other comprises one or more biologically active agents) or it can be treatment with both agents at the same time (concurrently). Sequential therapy can include a reasonable time after the completion of the first therapy before beginning the second therapy. Treatment with both agents at the same time can be in the same daily dose or in separate doses. Combination therapy need not be limited to two agents and may include three or more agents. The dosages for both concurrent and sequential combination therapy will depend on absorption,

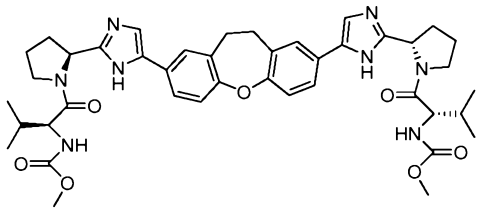
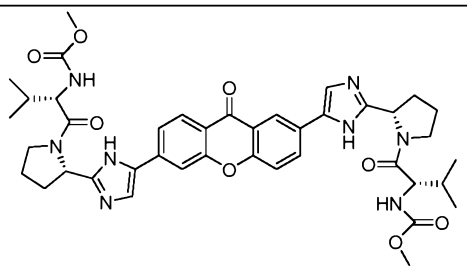
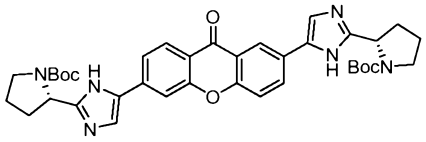
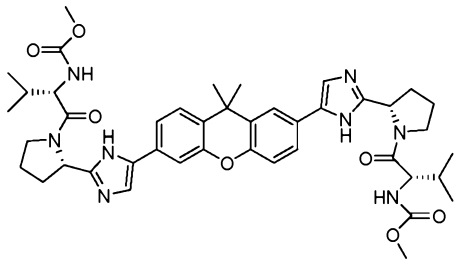
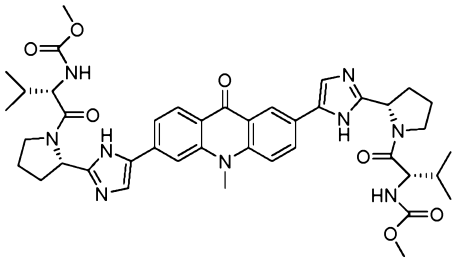
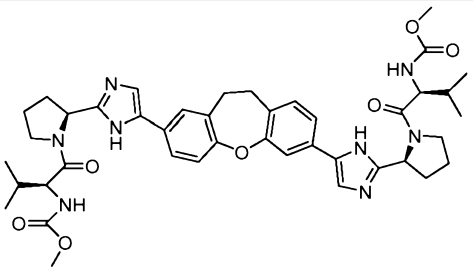
distribution, metabolism and excretion rates of the components of the combination therapy as well as other factors known to one of skill in the art. Dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules may be adjusted over time according to the individual's need and the professional judgment of the person administering or supervising the administration of the combination therapy.

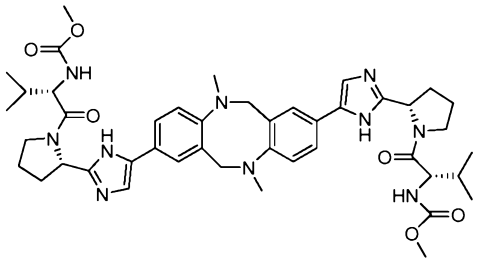
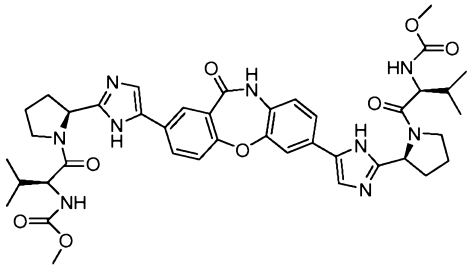
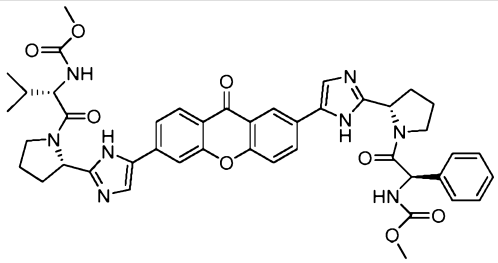
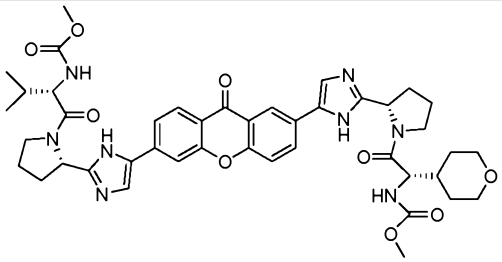
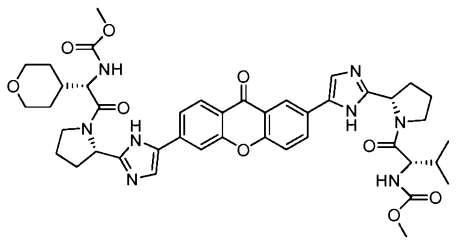
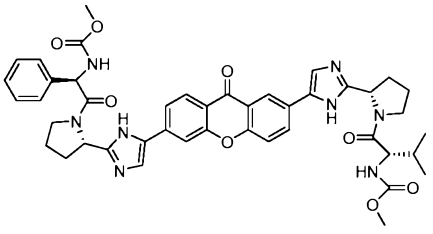
[0391] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

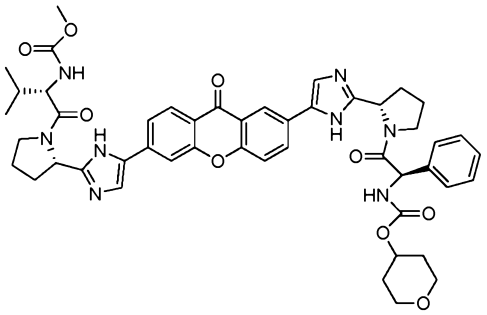
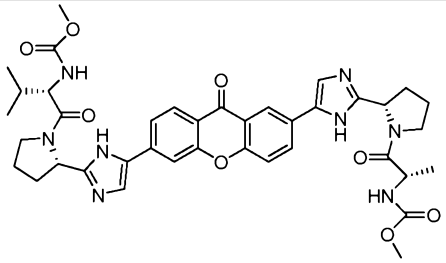
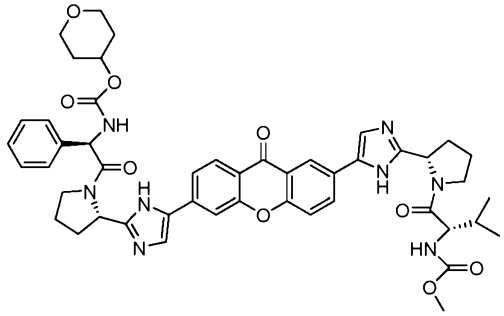
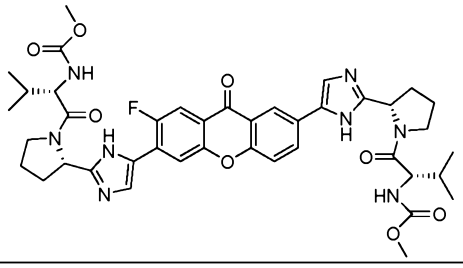
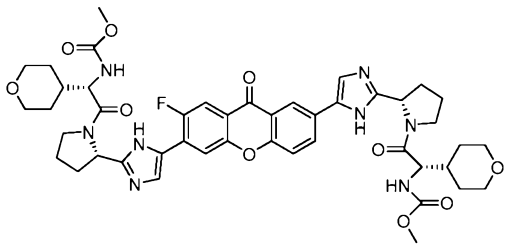
[0392] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may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

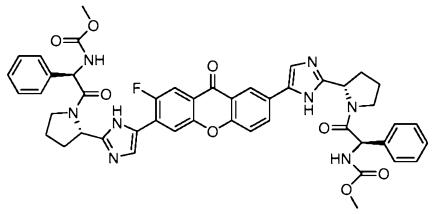
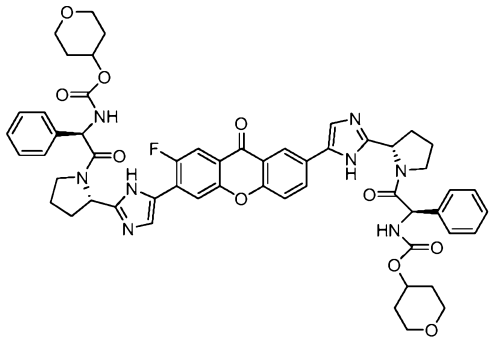
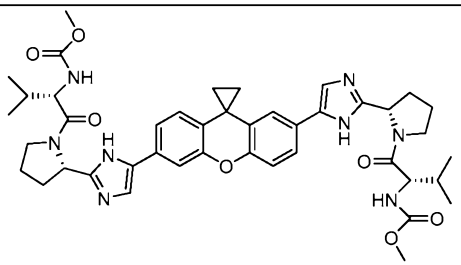
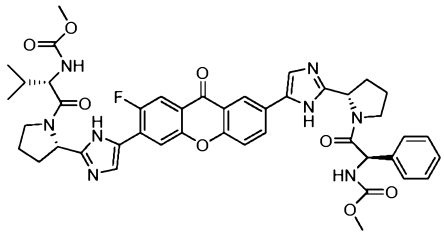
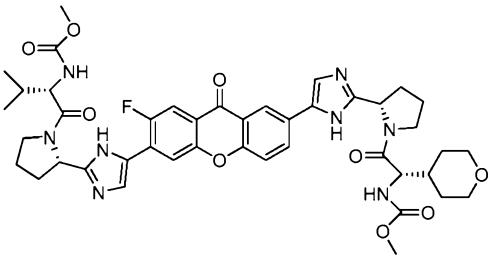
Table 1. Example Compounds and Assay Data

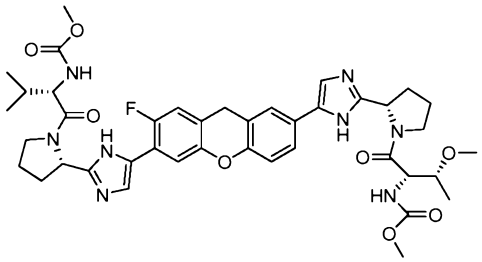
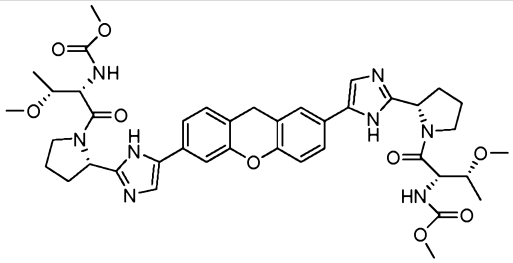
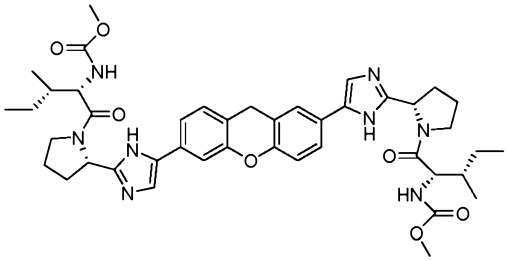
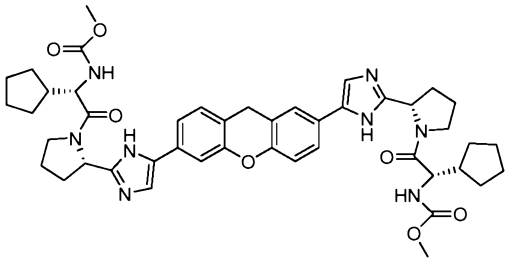
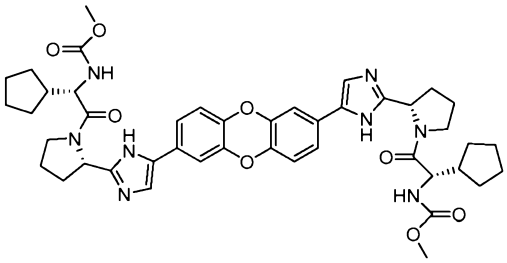
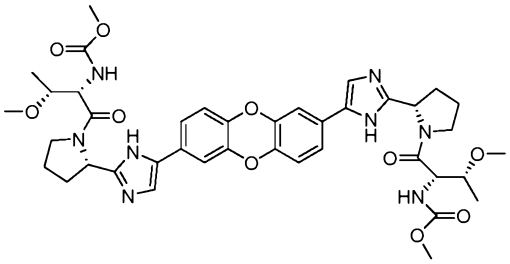
Compound #	Structure	Inhibition of HCV genotype 1b	MS (M+H)$^+$
1		****	765.4
2		****	833.3
3		****	769.4
4		**	767.4
5		****	835.3
6		****	767.4

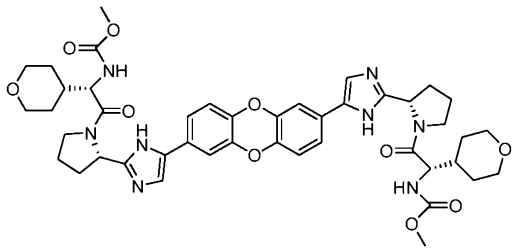
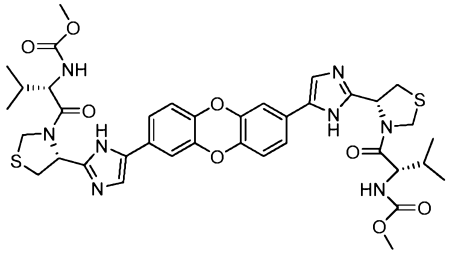
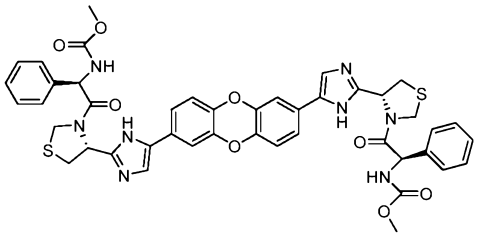
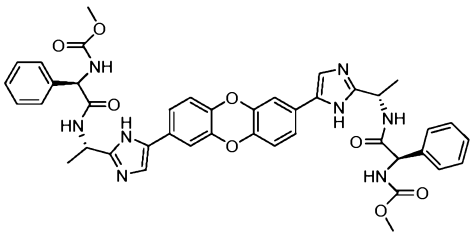
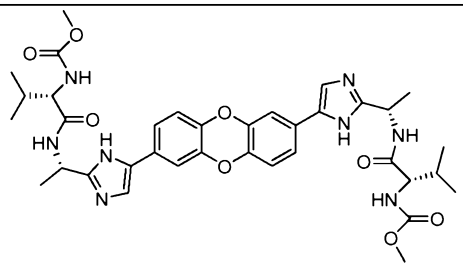
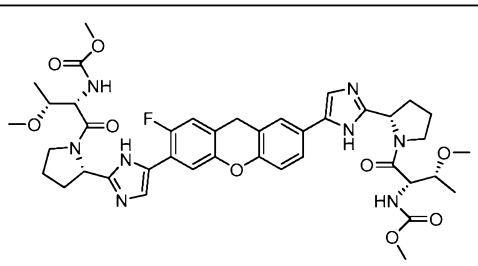
Compound #	Structure	Inhibition of HCV genotype 1b	MS (M+H)$^+$
7		****	781.4
8		****	781.4
9		**	667.3
10		****	795.4
11		****	794.4
12		****	781.4

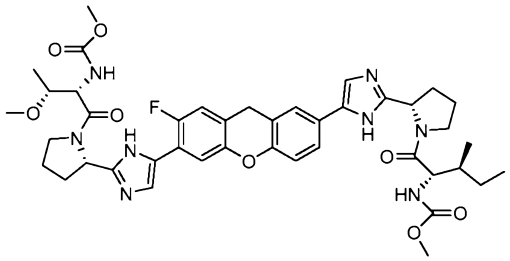
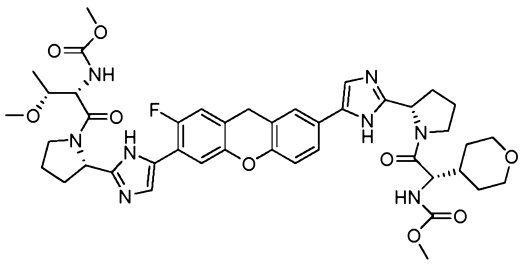
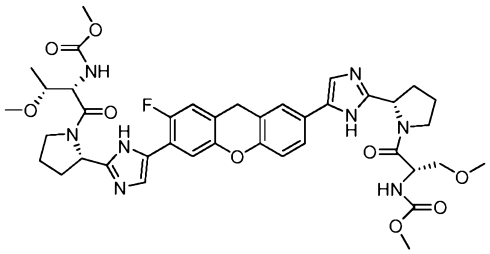
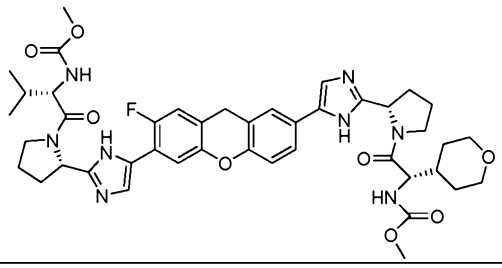
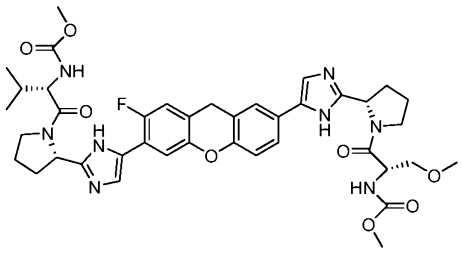
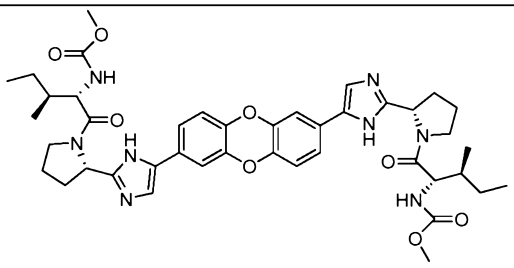
Compound #	Structure	Inhibition of HCV genotype 1b	MS (M+H)$^+$
13		****	823.5
14		**	796.4
15		****	815.3
16		****	823.4
17		****	823.4
18		****	815.3

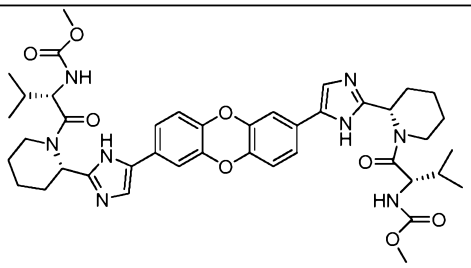
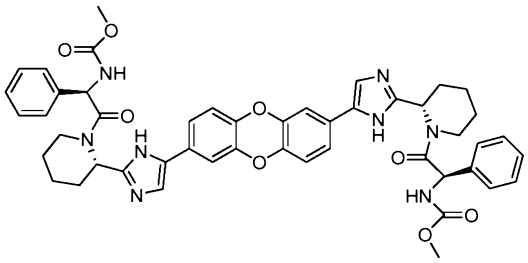
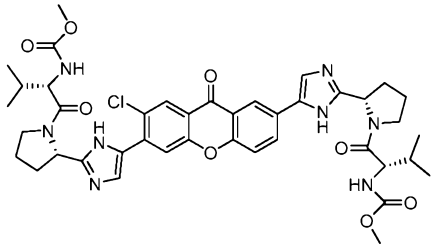
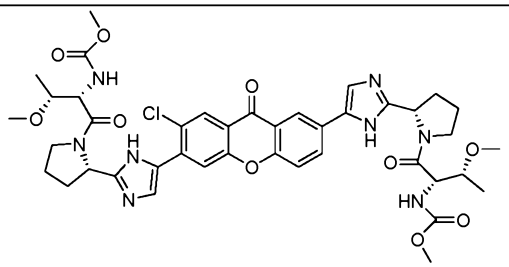
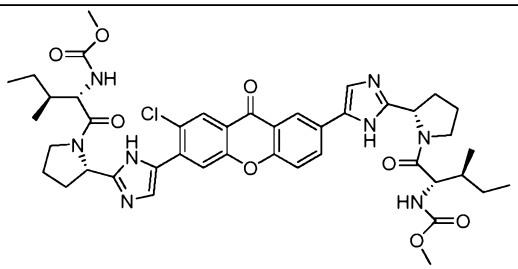
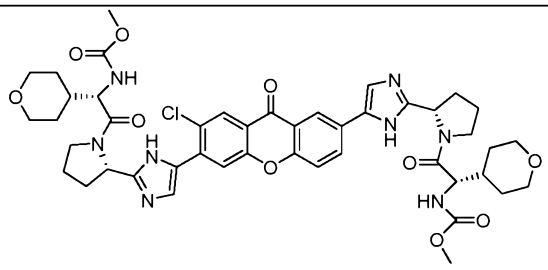
Compound #	Structure	Inhibition of HCV genotype 1b	MS (M+H)$^+$
19		****	885.4
20		****	753.3
21		****	885.4
22		****	799.4
23		****	883.4

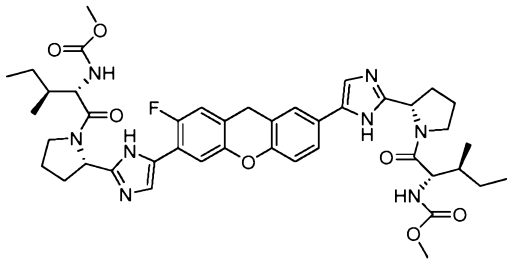
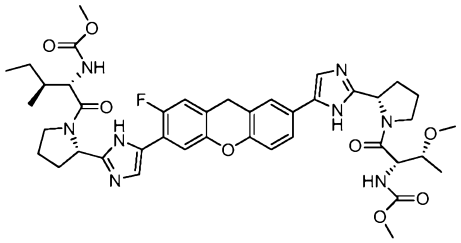
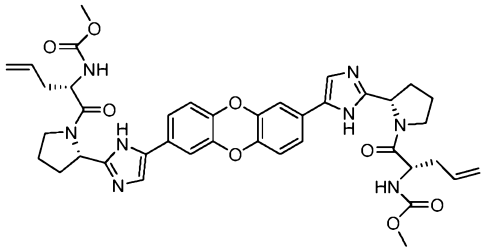
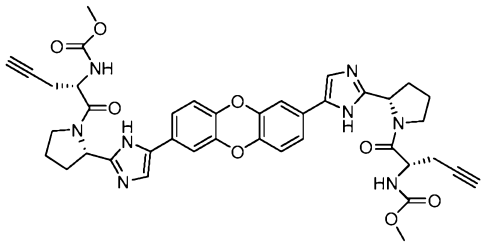
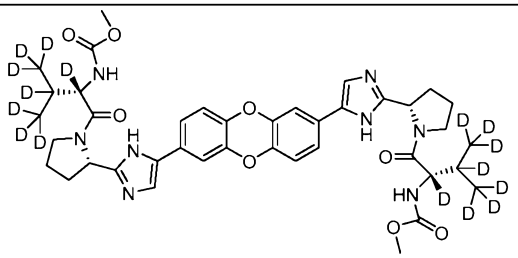
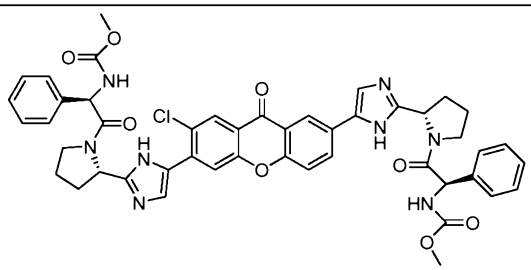
Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
24		****	867.3
25		****	1007.4
26		****	793.4
27		****	833.3
28		****	841.4

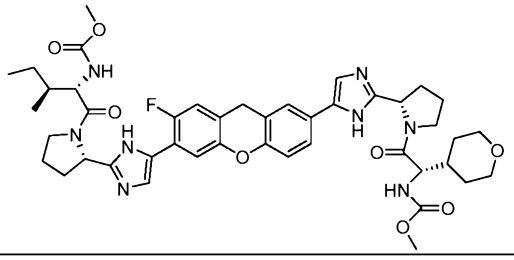
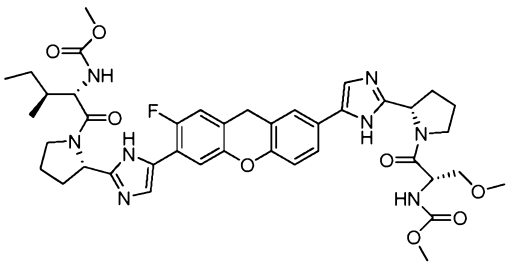
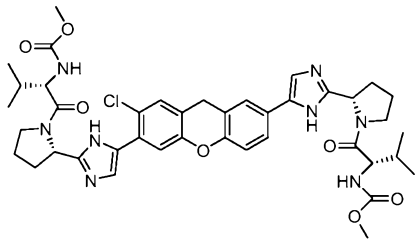
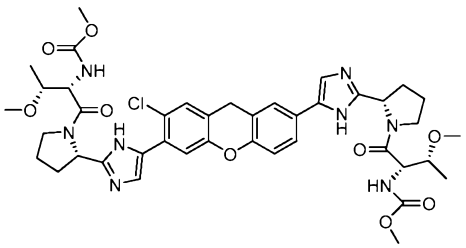
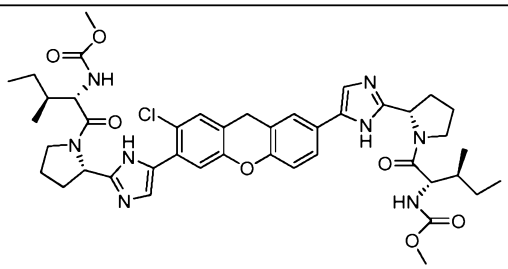
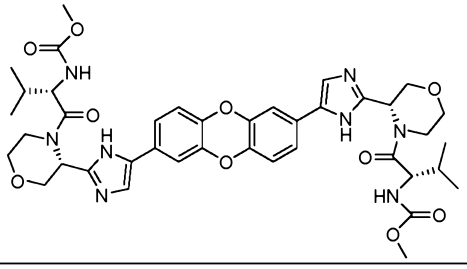
Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
29		****	801.4
30		****	799.4
31		****	795.4
32		****	819.4
33		****	821.4
34		****	801.3

Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
35		****	853.4
36		****	805.3
37		****	873.2
38		****	785.3
39		****	717.3
40		****	817.4

Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
41		****	815.4
42		****	843.4
43		****	803.3
44		****	827.4
45		****	787.4
46		****	797.4

Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
47		****	797.4
48		****	865.4
49		****	815.3
50		****	847.3
51		****	843.4
52		****	899.3

Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
53		****	813.4
54		****	815.4
55		****	765.3
56		****	761.3
57		****	785.5
58		****	883.3

Compound #	Structure	Inhibition of HCV genotype 1b	MS (M+H)$^+$
59		****	841.4
60		****	801.4
61		****	801.3
62		****	833.3
63		****	829.4
64		****	801.3

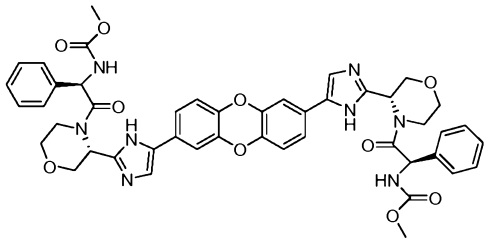
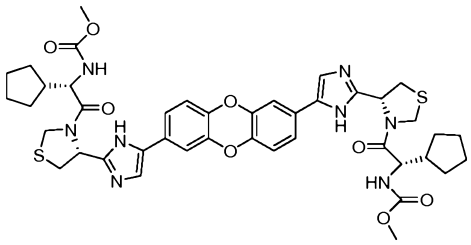
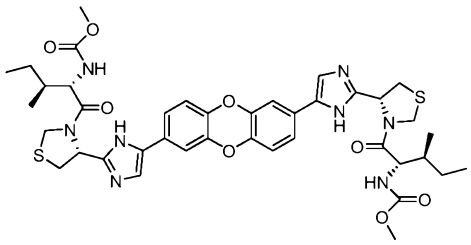
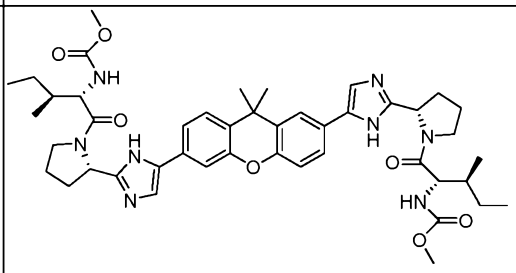
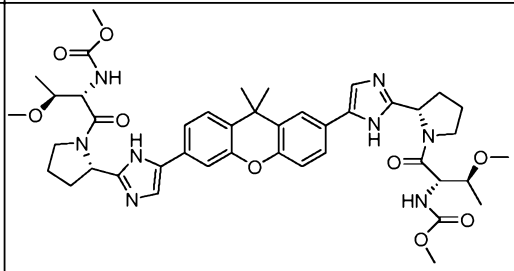
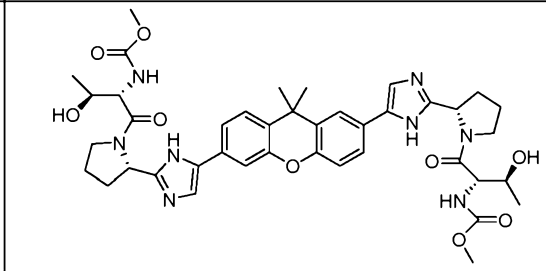
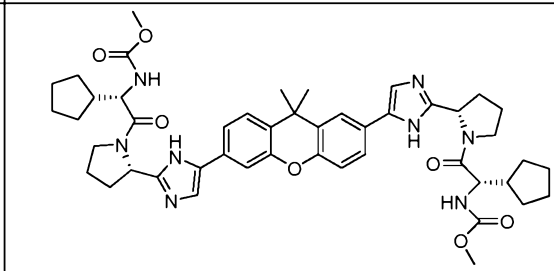
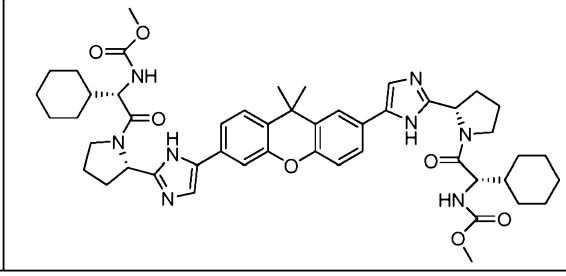
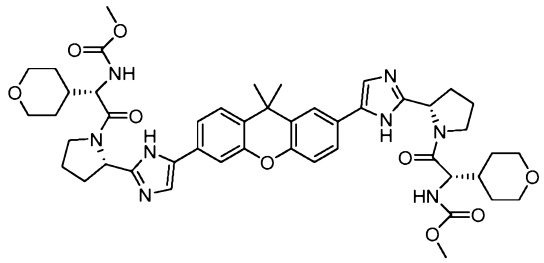
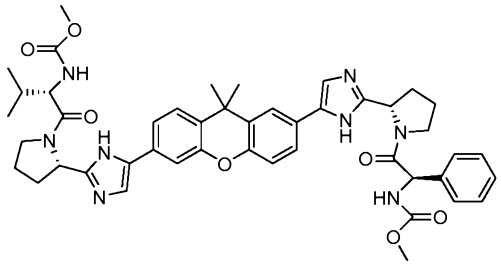
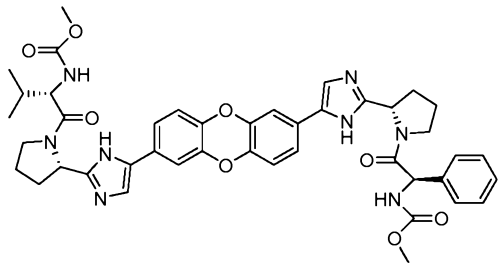
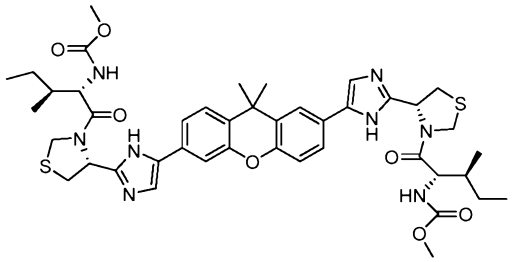
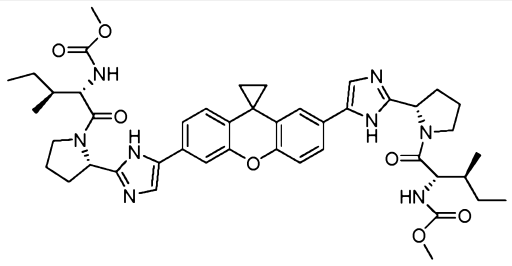
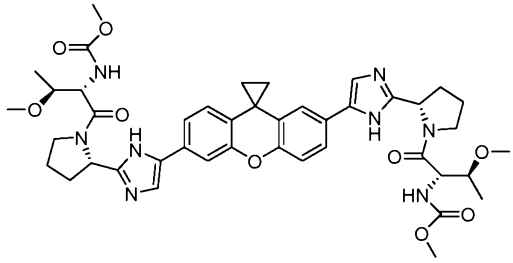
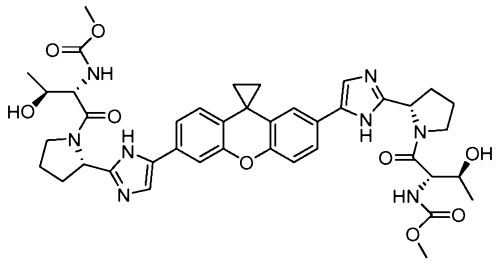
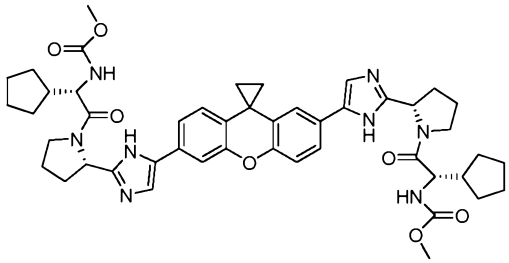
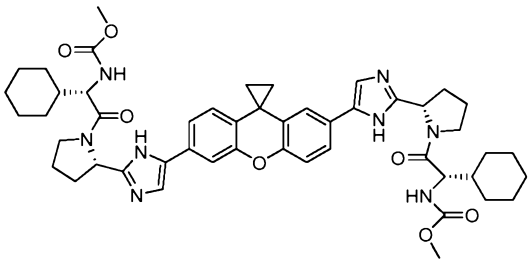
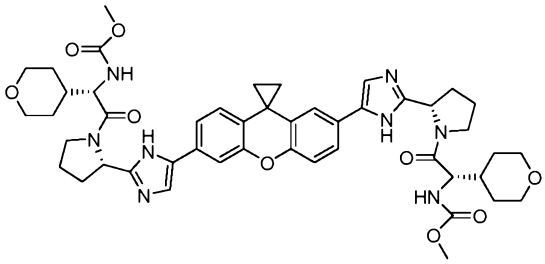
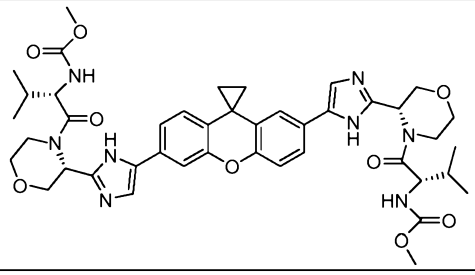
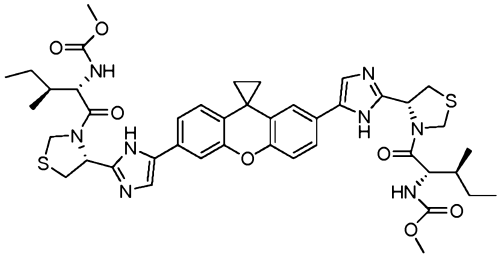
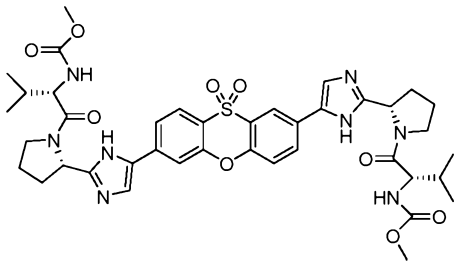
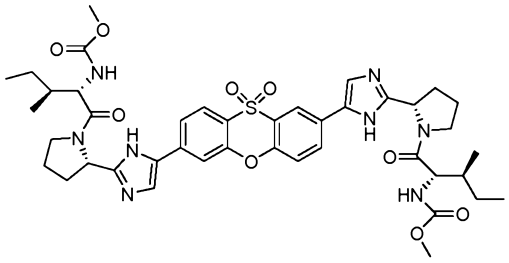
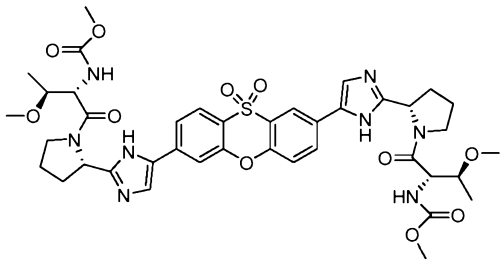
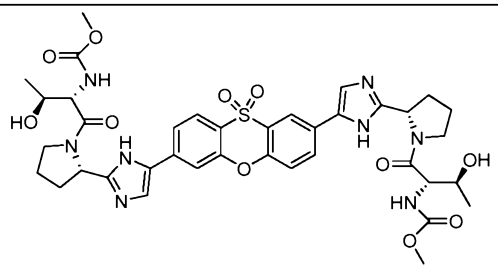
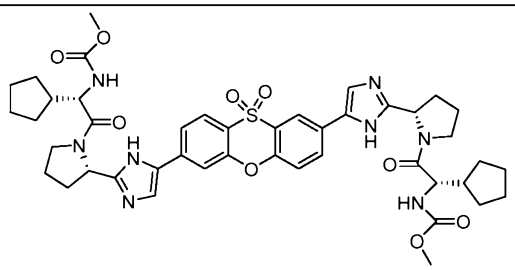
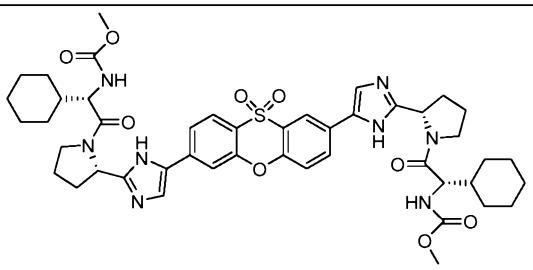
Compound #	Structure	Inhibition of HCV genotype 1b	MS $(M+H)^+$
65		****	869.3
66		****	857.3
67		****	833.3

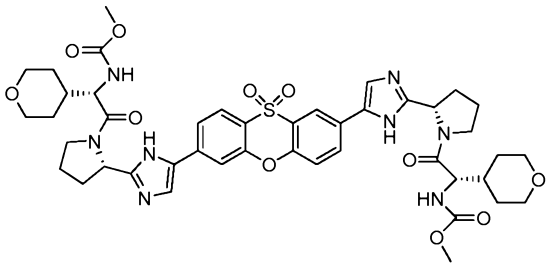
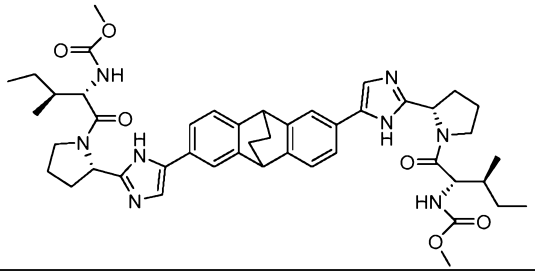
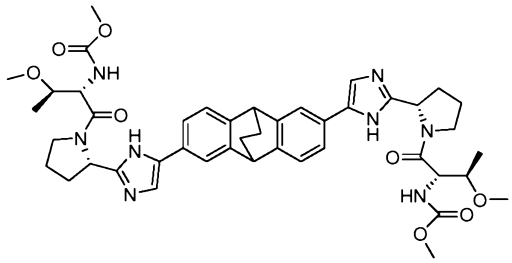
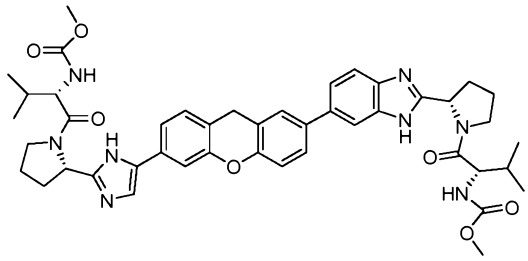
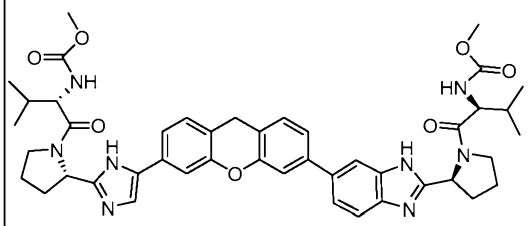
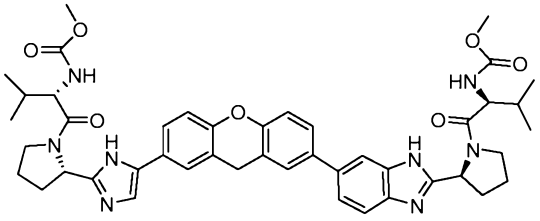
Table 2. Additional Example Compounds

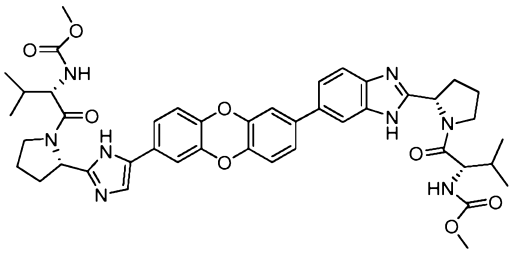
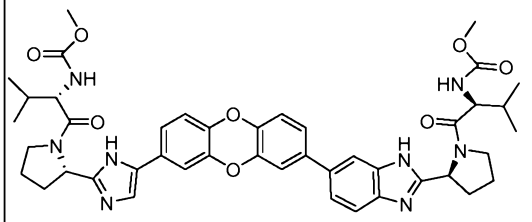
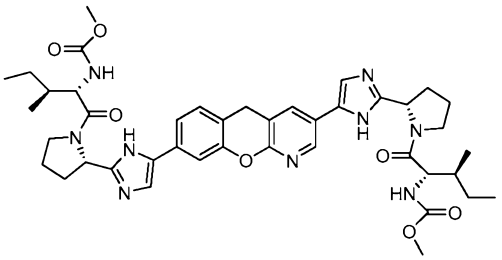
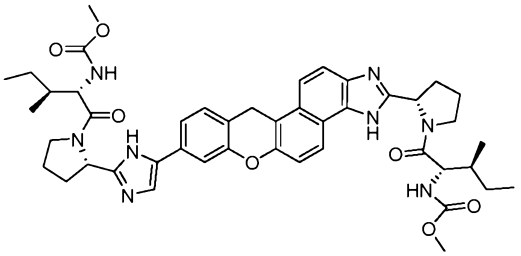
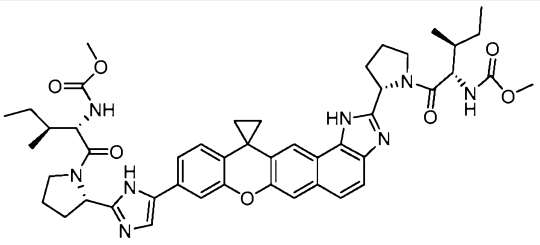
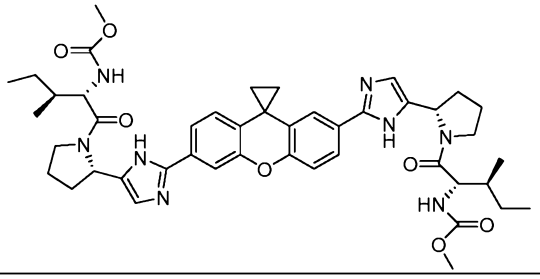
Compound #	Structure
70	
71	
72	
73	
74	

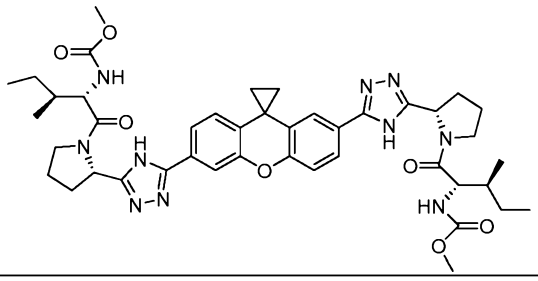
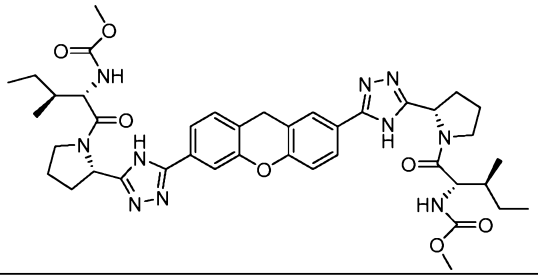
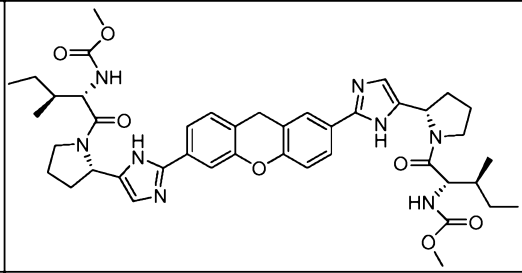
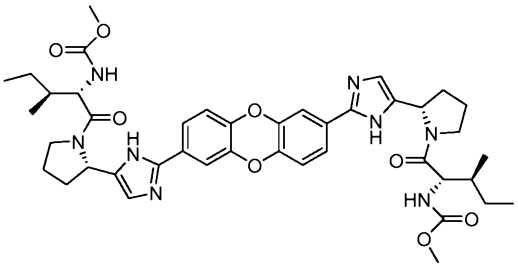
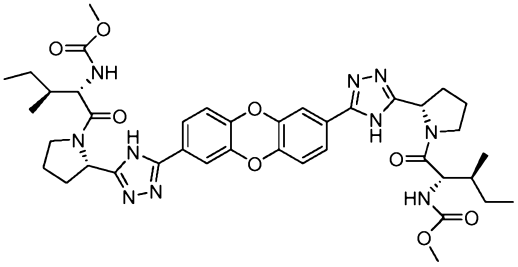
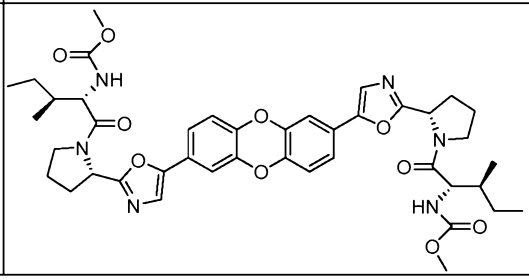
Compound #	Structure
75	
76	
77	
78	
79	
80	

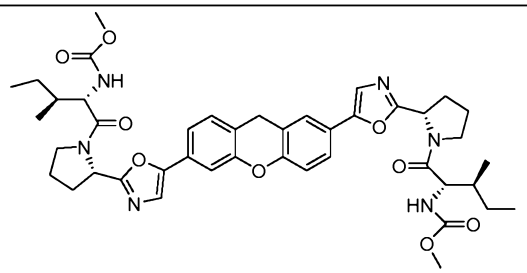
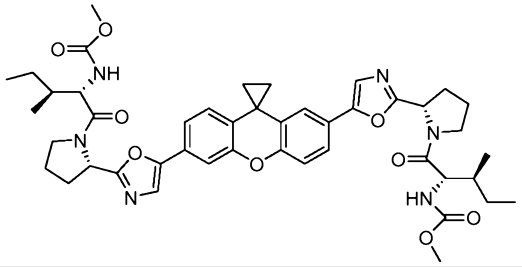
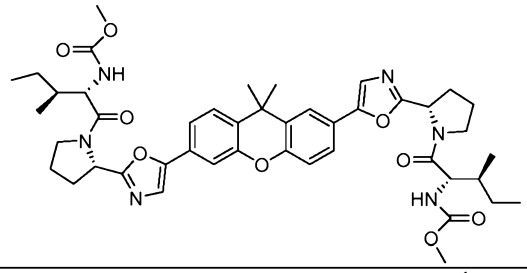
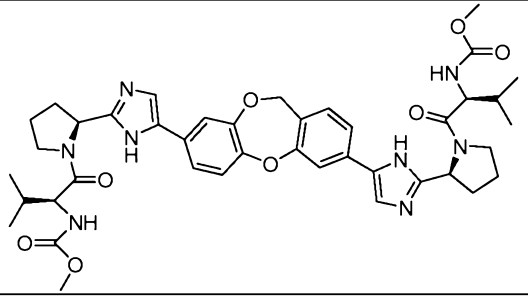
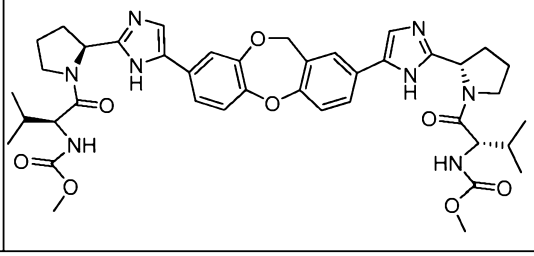
Compound #	Structure
81	
82	
83	
84	
85	
86	

Compound #	Structure
87	
88	
89	
90	
91	
92	

Compound #	Structure
93	
94	
95	
96	
97	
98	

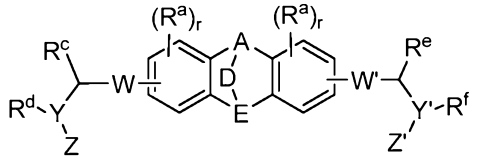
Compound #	Structure
99	
100	
101	
102	
103	
104	

Compound #	Structure
105	
106	
107	
108	
109	
110	

Compound #	Structure
111	
112	
113	
114	
115	

We claim:

1. A compound having formula I:



I

wherein:

D is either present or absent and if present selected from the group consisting of –CR_2CR_2–, -CR_2-, –NR^N–, –O– and –S– wherein R^N is H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

A and E are:

each independently –CR_2-, -CR=, -CR_2-CR_2-, -CR=CR-, -N=CR-, -$(CR_2)_a$-$N(R^N)$-$(CR_2)_a$-, -$(CR_2)_a$-C(O)-$N(R^N)$-$(CR_2)_a$-, -$(CR_2)_a$-$N(R^N)$-C(O)-$(CR_2)_a$- or –$(CR_2)_b$-O-$(CR_2)_b$-, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide;

each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino, wherein:

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

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

each a and b are independently 0, 1, 2, or 3 with the proviso that if D is present

both b's are not 0; and

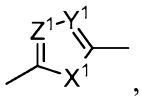
R^N and R may be replaced by a bond to D if D is present,

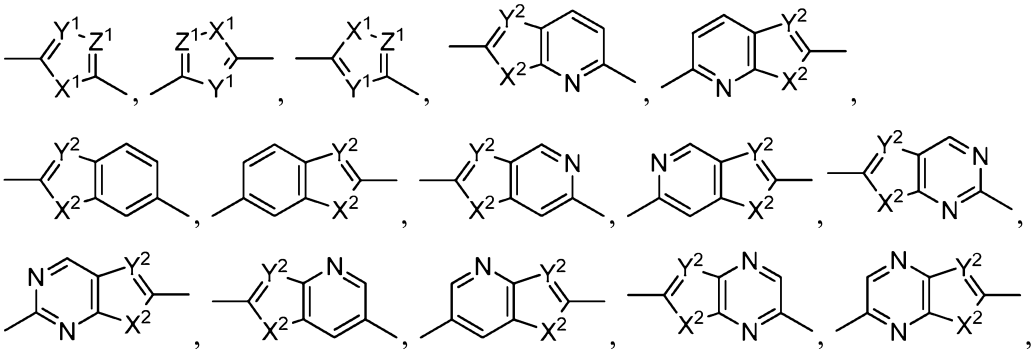
if D is absent, A and E can additionally each independently be a bond, –O–, –S–, $–S(O_2)–$, –S(O)–, –C(O)– or –N=, and

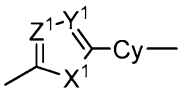
with the proviso that if W and W′ are both 5-membered rings, A and E are either both a bond or both other than a bond;

each R^a is independently selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

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

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



and  , wherein:

X^1 is CH_2, NH, O or S,

Y^1, Y^2 and Z^1 are each independently CH or N,

X^2 is NH, O or S,

W and W′ are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate,

sulfonamide and amino, and

Cy is a monocyclic, bicyclic or tricyclic 5- to 12-membered cycloalkyl, heterocycle, aryl group or heteroaryl group wherein up to three heteroatoms are independently N, S or O and which is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino;

each R^c, R^d, R^e and R^f is independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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

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

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

Z and Z′ are independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids,
$-[U-(CR^4_2)_t-NR^5-C(R^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$, $-U-(CR^4_2)_t-R^8$, and
$-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$, wherein,

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

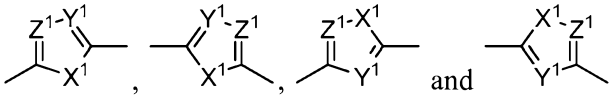
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

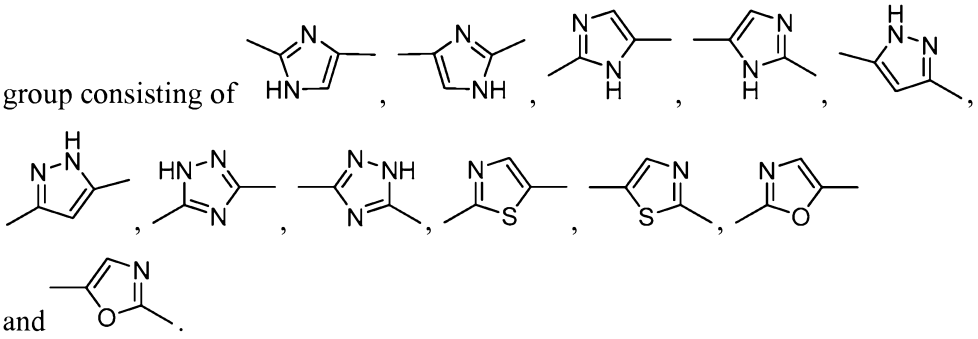
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

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

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

u is 0, 1, or 2.

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

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

4. The compound of any of the preceding claims wherein

R^c, R^d, R^e and R^f are each independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl and C_1 to C_8 heteroalkyl, wherein,

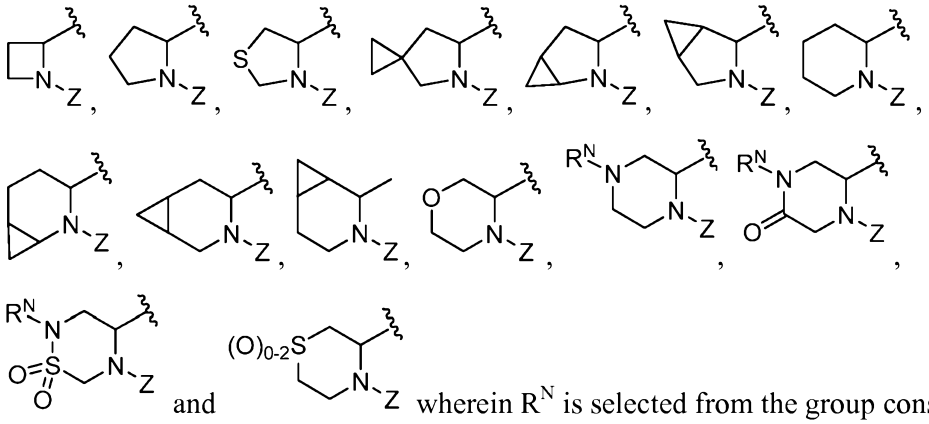
each hetero atom, if present, is independently N, O or S,

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

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

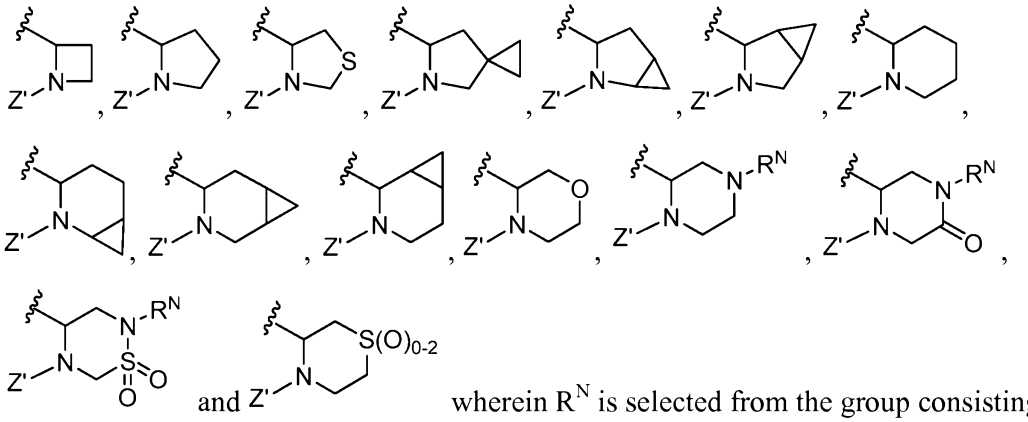
5. The compound of claim 4 wherein one or both of R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

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



and wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

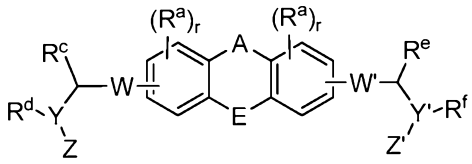
7. The compound of claim 4 or claim 6 wherein R^e and R^f are joined and form a heterocyclic fused ring system selected from the group consisting of:



and wherein R^N is selected from the group consisting

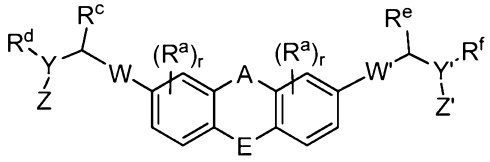
of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

8. The compound of claim 1 having formula II:



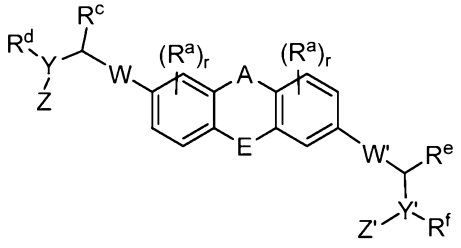
II.

9. The compound of claim 8 having formula IIa:



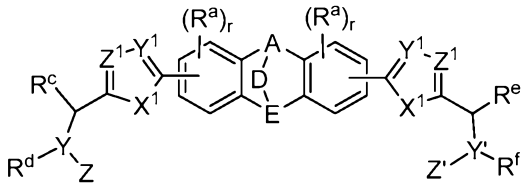
IIa.

10. The compound of claim 8 having formula IIb:



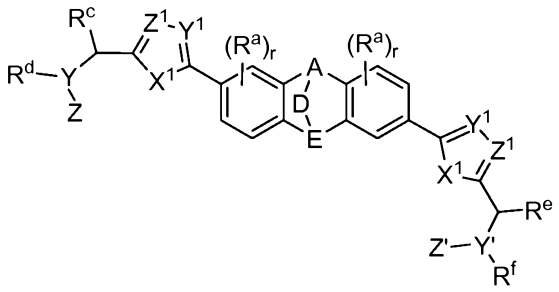
IIb.

11. The compound of claim 1 having formula III:



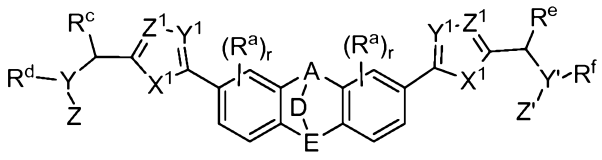
III.

12. The compound of claim 11 having formula IIIa:



IIIa.

13. The compound of claim 11 having formula IIIb:

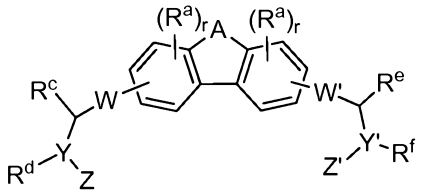


IIIb.

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

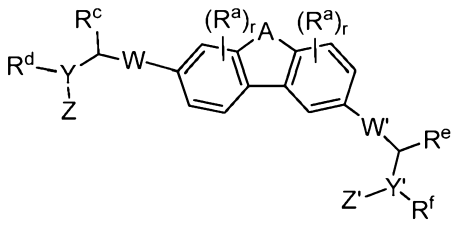
15. The compound of any one of claims 1-7, 11-13 wherein A is –O–, D is absent and E is $–CH_2–$, $–C(CH_3)_2–$, $–C(CH_2CH_2)–$ or –C(O)–.

16. The compound of claim 1 having formula IV:



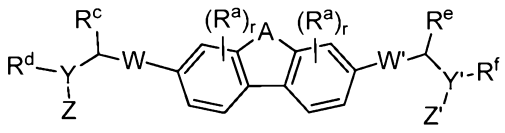
IV.

17. The compound of claim 14 having formula IVa:



IVa.

18. The compound of claim 14 having formula IVb:



IVb.

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

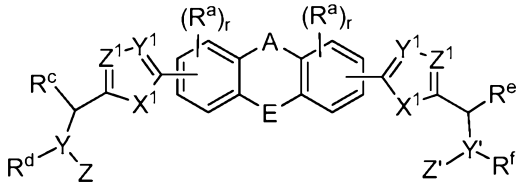
20. The compound of any one of claims 16, 17 or 18 wherein A is $–S(O)_2–$.

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

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

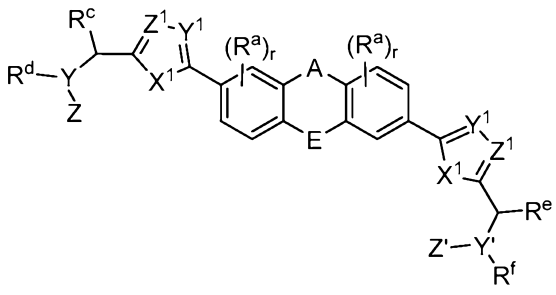
23. The compound of any one of claims 16, 17 or18 wherein A is $-CH_2–CH_2–$.

24. The compound of claim 1 having formula V:



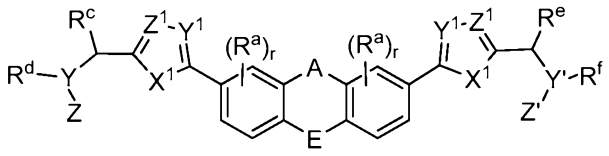
V.

25. The compound of claim 24 having formula Va:



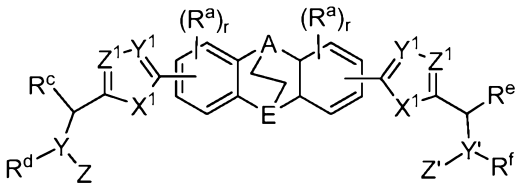
Va.

26. The compound of claim 24 having formula Vb:



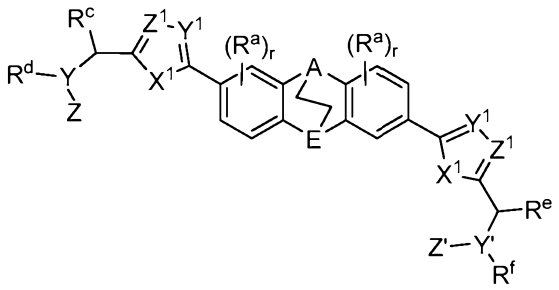
Vb.

27. The compound of claim 1 having formula VI:



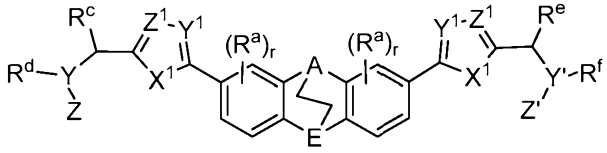
VI.

28. The compound of claim 27 having formula VIa:



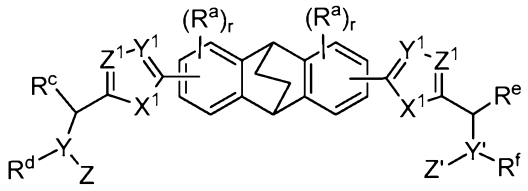
VIa.

29. The compound of claim 27 having formula VIb:



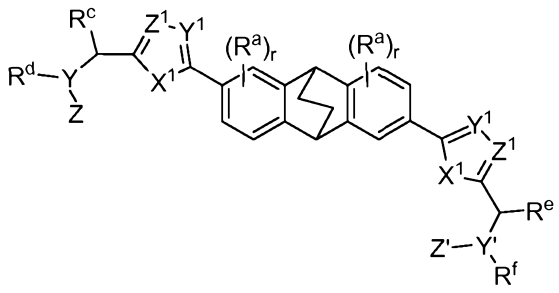
VIb.

30. The compound of claim 1 having formula VII:



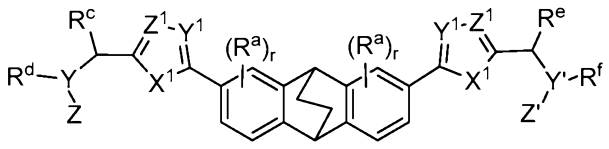
VII.

31. The compound of claim 30 having formula VIIa:



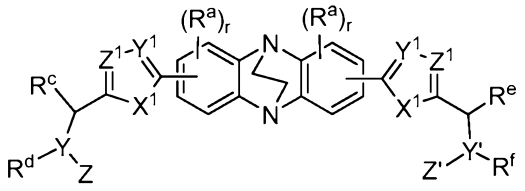
VIIa.

32. The compound of claim 30 having formula VIIb:



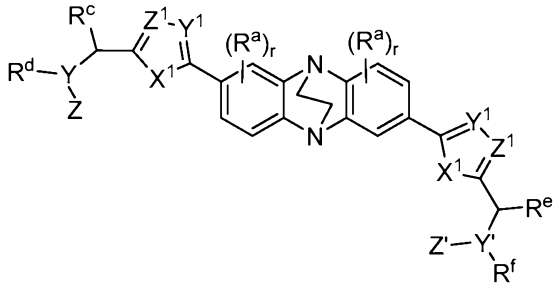
VIIb.

33. The compound of claim 1 having formula VIII:



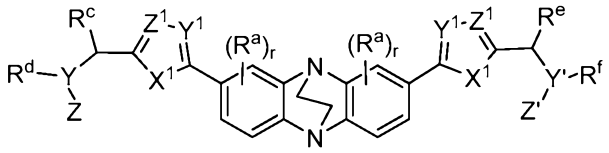
VIII.

34. The compound of claim 33 having formula VIIIa:



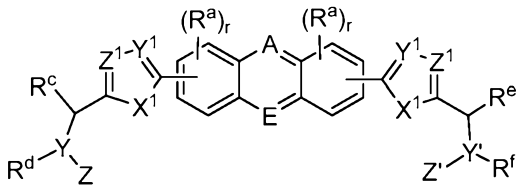
VIIIa.

35. The compound of claim 33 having formula VIIIb:



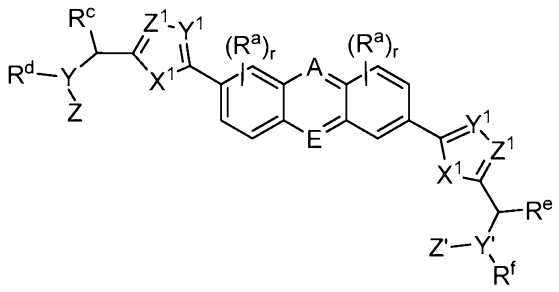
VIIIb.

36. The compound of claim 1 having formula IX:



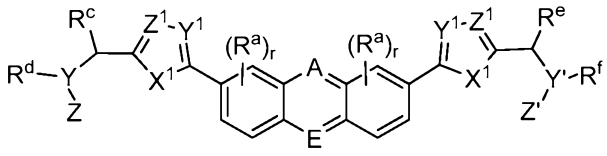
IX.

37. The compound of claim 36 having formula IXa:



IXa.

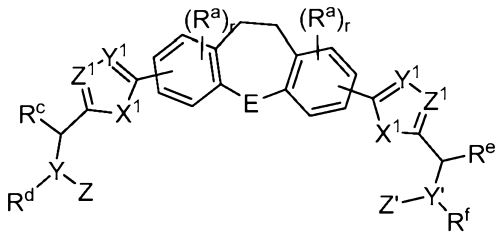
38. The compound of claim 36 having formula IXb:



IXb.

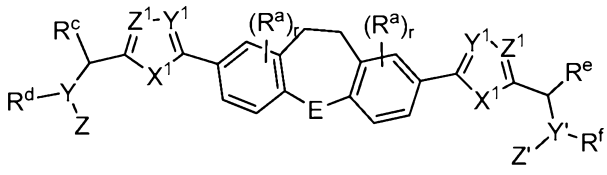
39. The compound of any one of claims 36, 37 or 38 wherein A and E are N.

40. The compound of claim 1 having formula X:



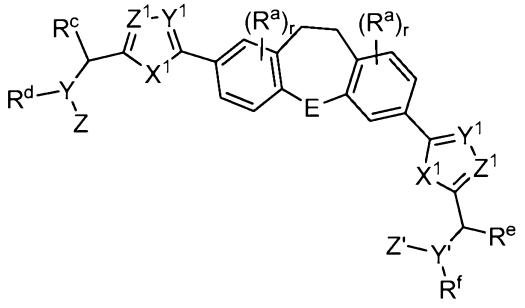
X.

41. The compound of claim 40 having formula Xa:



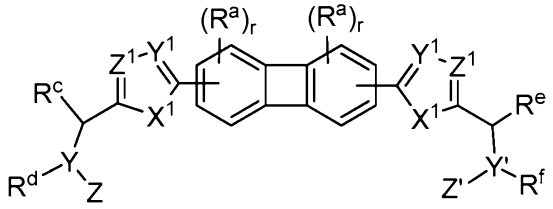
Xa.

42. The compound of claim 40 having formula Xb:



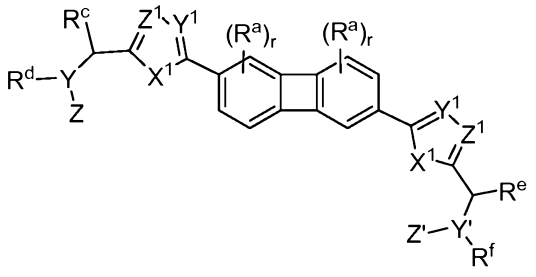
Xb.

43. The compound of claim 1 having formula XI:



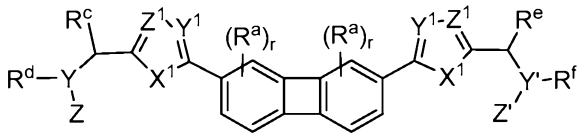
XI.

44. The compound of claim 43 having formula XIa:



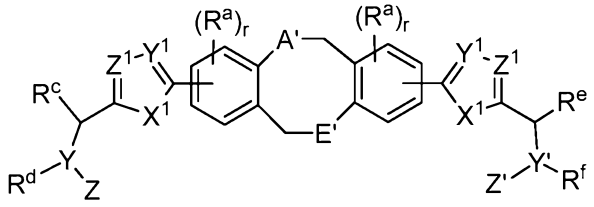
XIa.

45. The compound of claim 43 having formula XIb:



XIb.

46. The compound of claim 1 having formula XII:



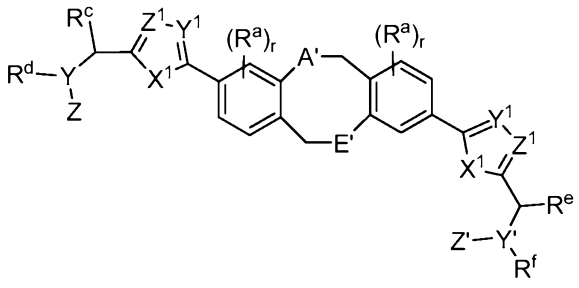
XII, wherein:

A′ and E′ are each independently –CR_2–, -CR=, –$N(R^N)$–, –O–, –S–, –$S(O_2)$–, –S(O)–, or –N=, wherein:

R^N is selected from the group consisting of H, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide; and

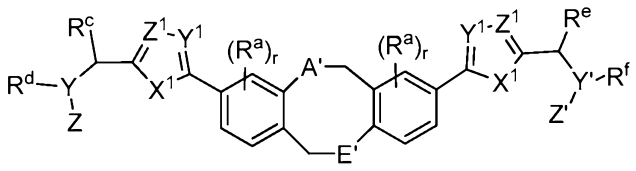
each R is independently selected from the group consisting of hydrogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino.

47. The compound of claim 46 having formula XIIa:



XIIa.

48. The compound of claim 46 having formula XIIb:



XIIb.

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

50. The compound of any one of claims 9-48 wherein both of Y and Y′ are N.

51. The compound of any one of claims 11-13 or 24-48 wherein one or both of X^1 are –S–.

52. The compound of any one of claims 11-13 or 24-48 wherein one or both of X^1 are –O–.

53. The compound of any one of claims 11-13 or 24-48 wherein one or both of X^1 are –NH–.

54. The compound of any one of claims 11-13 or 24-48 wherein one or both of Z^1 is –N–.

55. The compound of any one of claims 11-13 or 24-48 wherein one or both of Y^1 is –N–.

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

57. The compound of any one of claims 1-55 wherein Z and Z′ are each independently selected from the group consisting of $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$, $–U–(CR^4_2)_t–R^8$ and $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–O–(CR^4_2)_t–R^8$.

58. The compound of claim 57 wherein one or both of Z and Z′ are $–[U–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

59. The compound of claim 58 wherein one or both of Z and Z′ are $–U–(CR^4_2)_t–NR^5–(CR^4_2)_t–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

60. The compound of claim 58 wherein one or both of Z and Z′ are $–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

61. The compound of claim 58 wherein either one or both of Z and Z′ are $–[C(O)–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

62. The compound of claim 61 wherein one or both of Z and Z′ are $–C(O)–(CR^4_2)_t–NR^5–(CR^4_2)_t–U–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

63. The compound of claim 58 wherein one or both of Z and Z′ are $–[C(O)–(CR^4_2)_t–NR^5–(CR^4_2)_t]_u–C(O)–(CR^4_2)_t–NR^7–(CR^4_2)_t–R^8$.

64. The compound of claim 63 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

65. The compound of claim 63 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

66. The compound of claim 65 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^{81}$.

67. The compound of claim 66 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-R^{81}$.

68. The compound of claim 65 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-O-R^{81}$.

69. The compound of claim 68 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-O-R^{81}$.

70. The compound of claim 57 wherein one or both of Z and Z′ are $-U-(CR^4_2)_t-R^8$.

71. The compound of claim 70 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-R^8$.

72. The compound of claim 57 wherein one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

73. The compound of claim 72 wherein one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

74. The compound of claim 73 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

75. The compound of claim 72 wherein one or both of Z and Z′ are $-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

76. The compound of claim 75 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

77. The compound of claim 57 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-R^8$ wherein R^7 and R^8 together form a 4-7 membered ring.

78. A pharmaceutical composition comprising any one of the compounds of claims 1-77.

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

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

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