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(54) **Title:**
INHIBITORS OF HCV NS5A

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

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(54) **Title**: INHIBITORS OF HCV NS5A

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

INHIBITORS OF HCV NS5A

Inventors: Leping Li and Min Zhong

Statement of Related Applications

[0001] This application claims the benefit of U.S. provisional applications 61/119,723 filed Dec. 3, 2008; 61/173,590 and 61/214,881 filed April 28, 2009; and 61/182,958 and 61/182,952 filed June 1, 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. p7, an integral membrane protein, 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 C.M. Rice, *Nature*. 436:933-938, 2005).

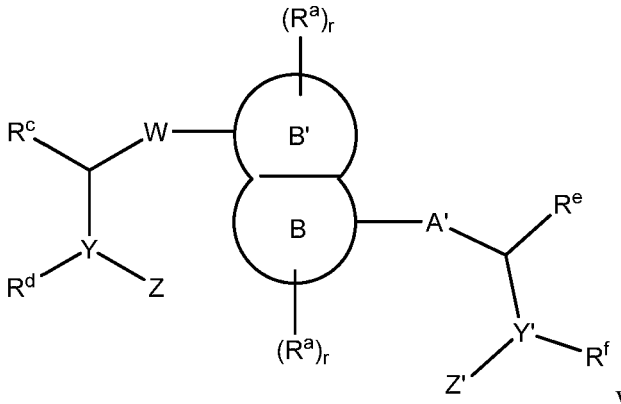
[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related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

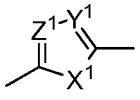
[0006] Essential features of the NS5A protein of HCV make it an ideal target for inhibitors. The present disclosure describes a class of compounds targeting the NS5A protein and methods of their use to treat HCV infection in humans.

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

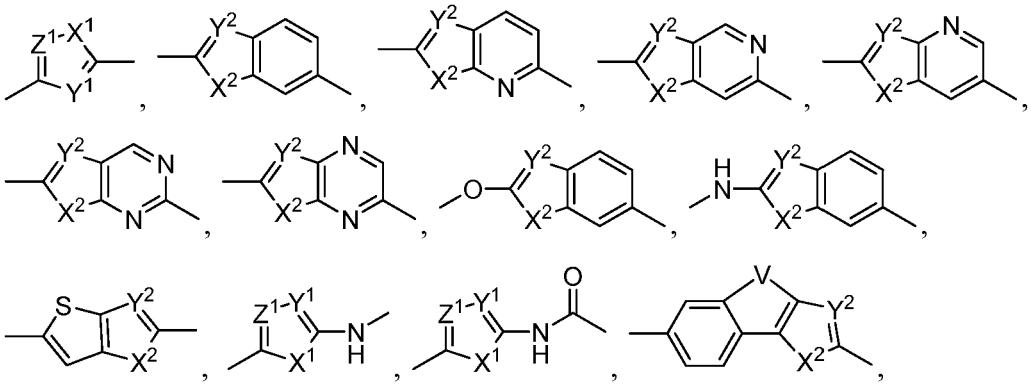


wherein:

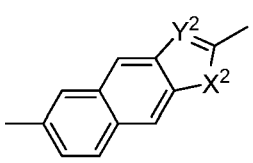
A′ is selected from the group consisting of single bond, $-(CR_2)_n-C(O)-(CR_2)_p-$, $-(CR_2)_n-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-S(O)_k-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-S(O)_k-N(R^N)-(CR_2)_p-$ and $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ and a heteroaryl group selected from the group consisting of



,



and



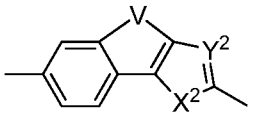
wherein:

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,

V is $-CH_2-CH_2-$, -CH=CH-, -N=CH-, $-(CH_2)_a-N(R^N)-(CH_2)_b-$ or $-(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,



optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

the carbons of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of halogen, -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,

the nitrogens, if present, of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of -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,

a and b are independently 1, 2, or 3.

c and d are independently 1 or 2,

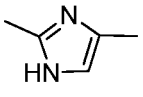
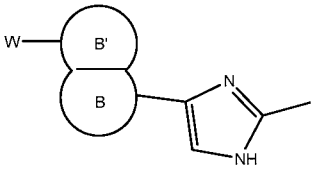
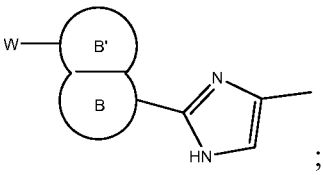
n and p are independently 0, 1, 2 or 3,

k is 0, 1, or 2,

each R is independently selected from the group consisting of hydrogen, halogen,

-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,

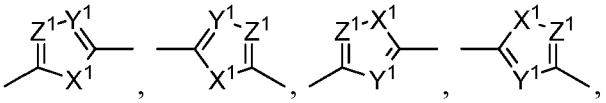
each R^N is independently selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and

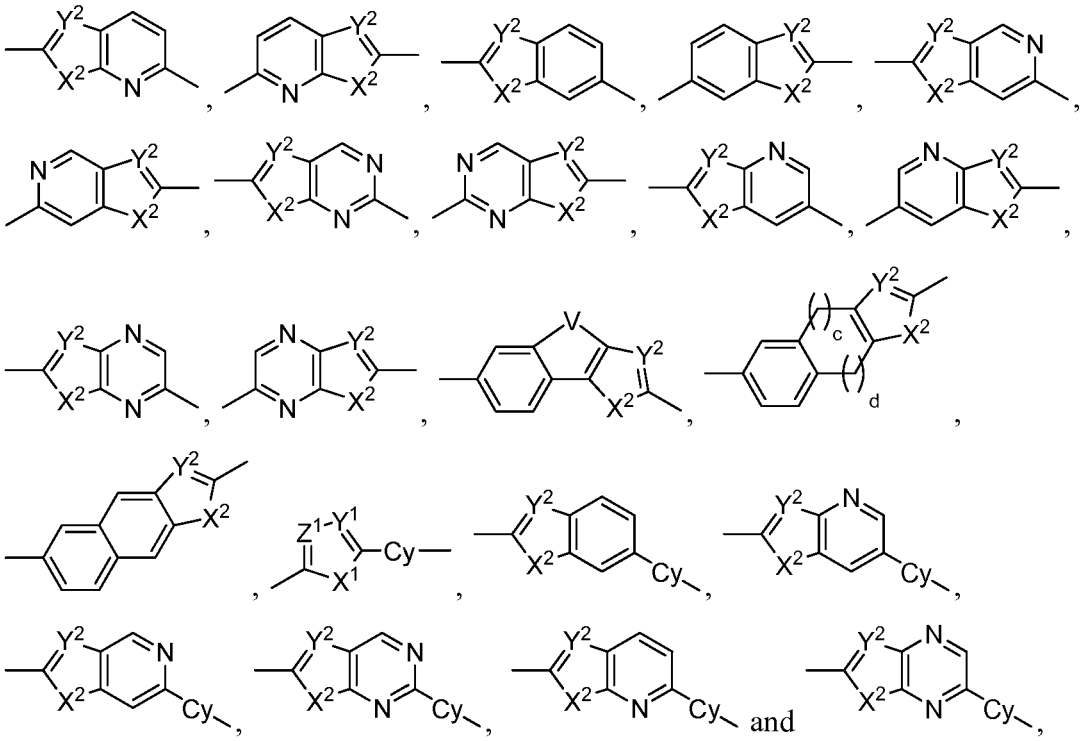
wherein B may be attached to either side of A′ so that in the example of A′ being  , the W-B-A′ can be  or  ;

B and B′ are each independently a 4- to 8-membered ring that is an aryl, heteroaryl, cycloalkyl, or heterocycle, wherein each hetero atom, if present, is independently N, O or S and wherein at least one of B or B′ is aromatic;

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; and if B or B′ is not aromatic, it may also be substituted with one or more oxo;

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

W is independently selected from  ,



and

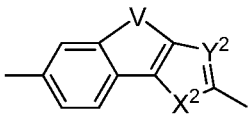
wherein:

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,

V is $–CH_2-CH_2-$, -CH=CH-, -N=CH-, $-(CH_2)_a-N(R^N)-(CH_2)_b-$ or $–(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,

 optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

W 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,

W and ring B′ can be connected through either a carbon or a nitrogen atom on B′, 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 –$S(O)_2$–,

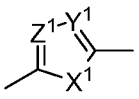
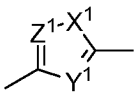
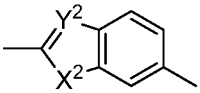
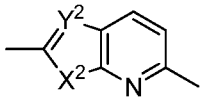
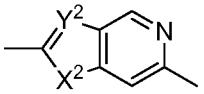
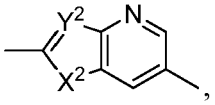
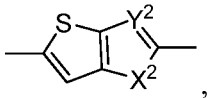
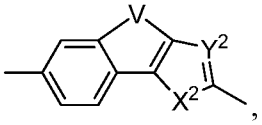
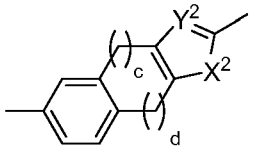
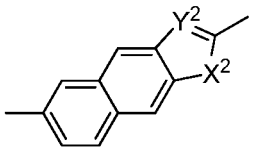
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

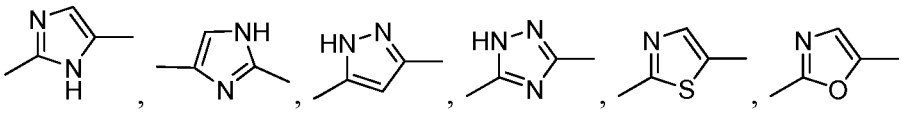
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-$R^{81}{}_2$, -$S(O)_2$-R^{81} and -$S(O)_2$-N-$R^{81}{}_2$, wherein each R^{81} is independently chosen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

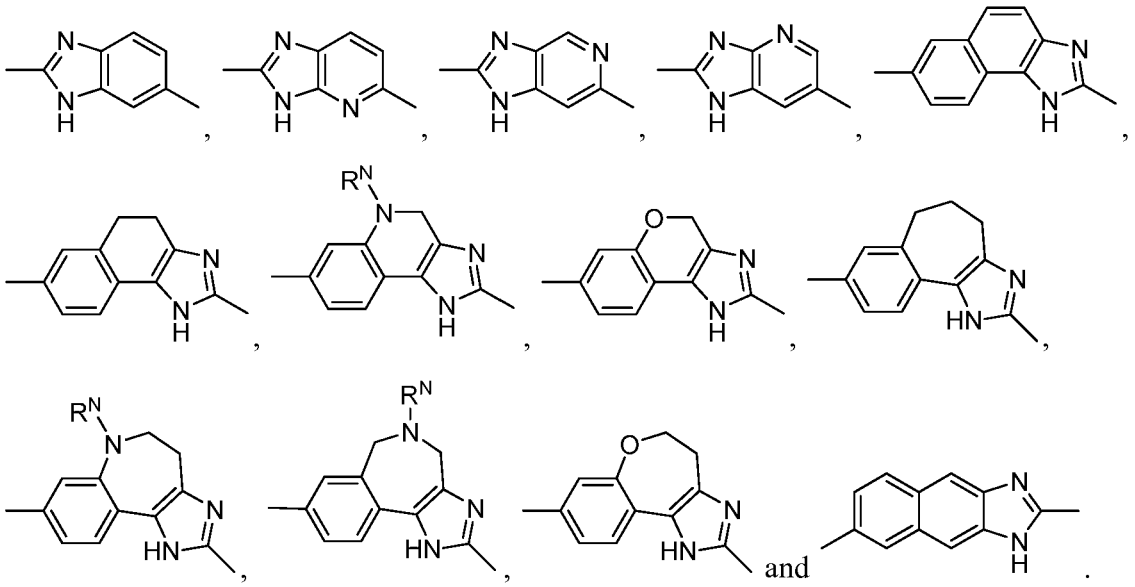
optionally, R^7 and R^8 together form a 4-7 membered ring,

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, A′ is selected from the group consisting of a single bond, –$(CR_2)_n$–O–$(CR_2)_p$–, –$(CR_2)_n$–N(R^N)–$(CR_2)_p$–, –$(CR_2)_n$–C(O)–N(R^N)–$(CR_2)_p$–, –$(CR_2)_n$–N(R^N)–C(O)–N(R^N)–$(CR_2)_p$– and –$(CR_2)_n$–N(R^N)–C(O)–O–$(CR_2)_p$– and a heteroaryl group selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  and  .

[0009] In a second embodiment of the first aspect, A′ is selected from the group consisting of a single bond, 



[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,

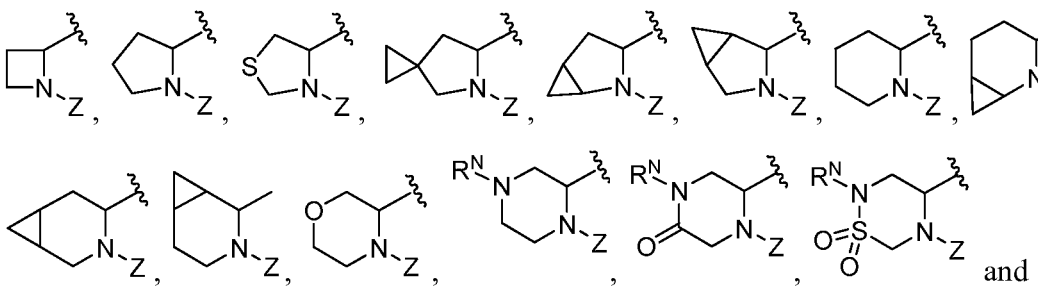
each hetero atom, if present, is independently N, O or S,

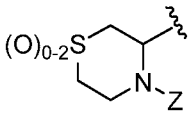
R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle, and

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.

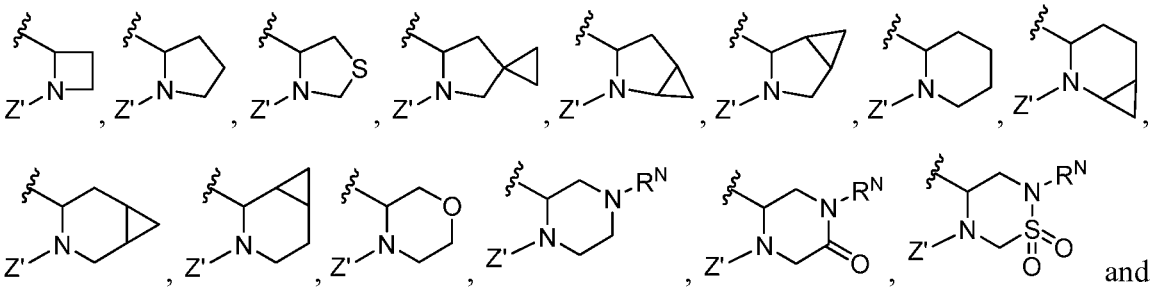
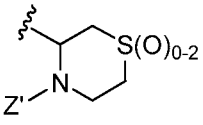
[0011] In a fourth embodiment of the first aspect, R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

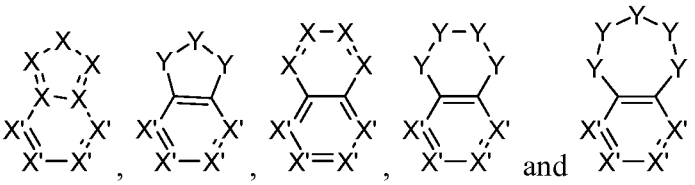
[0012] In a fifth embodiment of the first aspect, R^c and R^d are joined and form a heterocyclic fused ring system selected from the group consisting of:



 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.

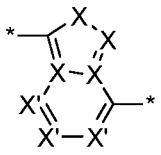
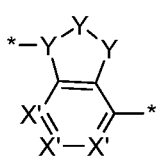
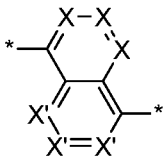
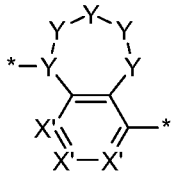
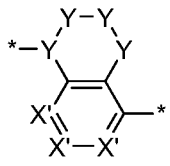
[0014] In a seventh embodiment of the first aspect, B and B′ together is selected from the group consisting of  wherein

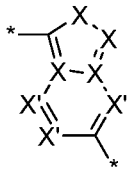
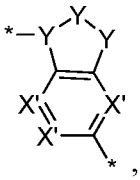
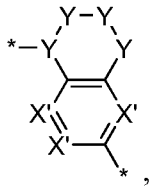
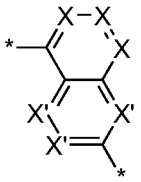
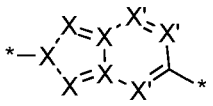
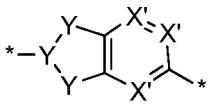
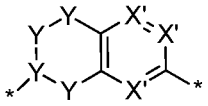
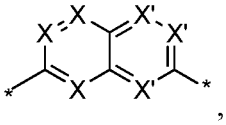
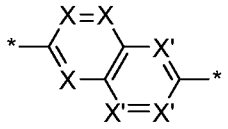
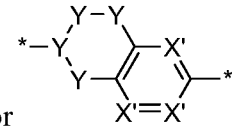
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

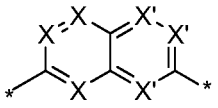
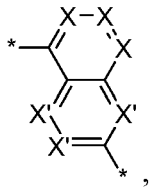
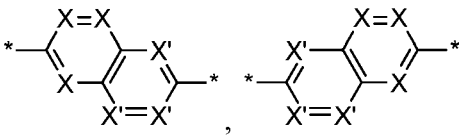
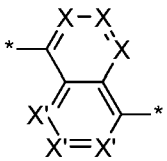
each X′ is independently –N– or –CH–, with the proviso that no more than two X′ are –N–;

each Y is independently selected from $-CH_2-$, -NH- , -O-, -S-, $-C(O)_2-$, or $-S(O)_{1-2}-$; and

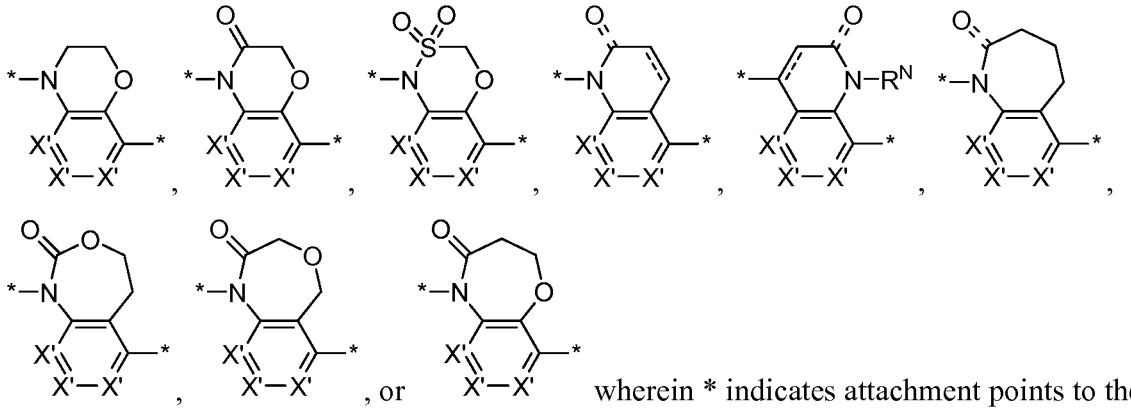
B and B′ attach to the remainder of the compound at any available attachment point on the molecule.

[0015] In an eighth embodiment of the first aspect, B and B′ together is  ,  ,  ,  or  wherein * indicates attachment points to the remainder of the compound.

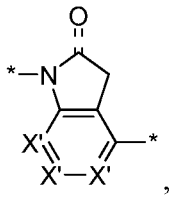
[0016] In a ninth embodiment of the first aspect, B and B′ together is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or wherein * indicates attachment points to the remainder of the compound.

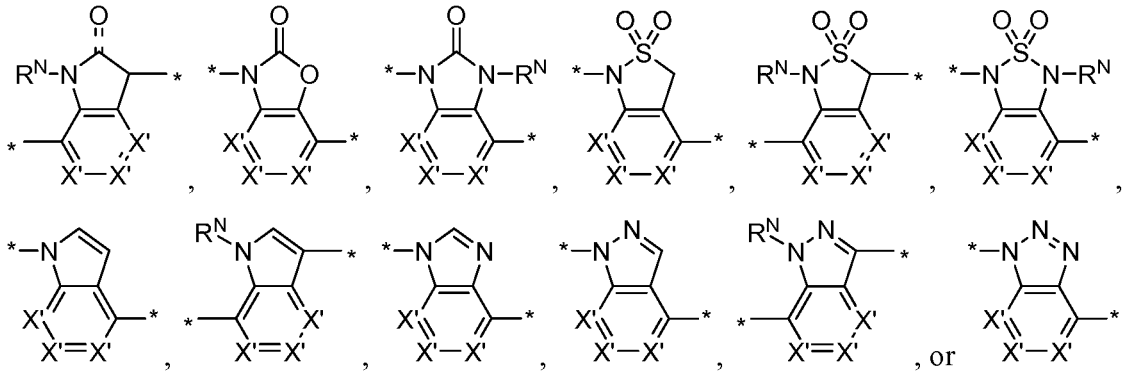
[0017] In a tenth embodiment of the first aspect, B and B′ together is  ,  ,  ,  , or wherein * indicates attachment points to the remainder of the compound wherein no more than 2 of X are nitrogen.

[0018] In an eleventh embodiment of the first aspect, B and B′ together is

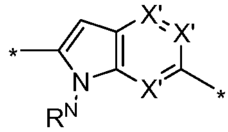


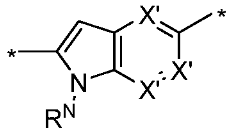
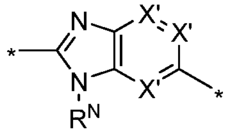
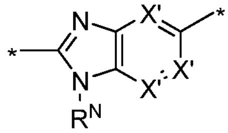
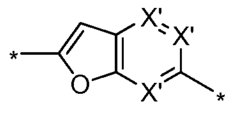
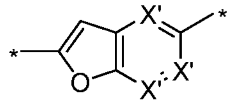
wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

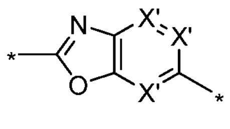
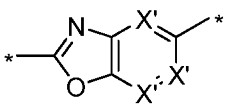
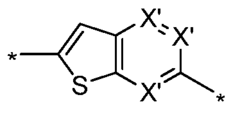
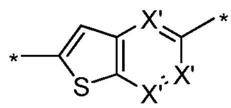
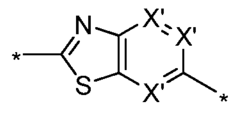
[0019] In a twelfth embodiment of the first aspect, B and B′ together is  ,

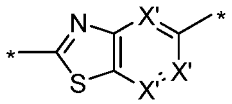


wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

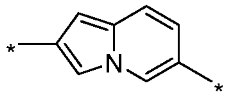
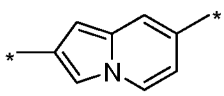
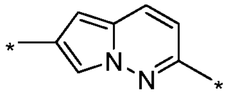
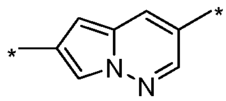
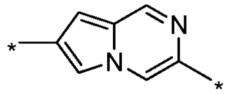
[0020] In a thirteenth embodiment of the first aspect, B and B′ together is  ,

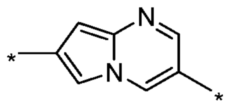
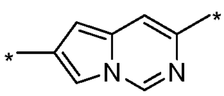
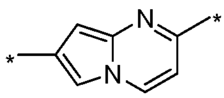
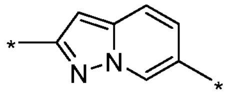
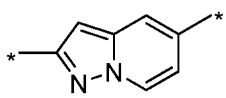
 ,  ,  ,  ,  ,

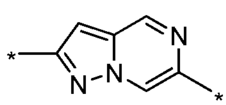
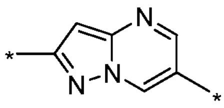
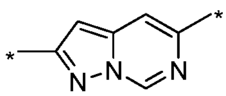
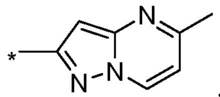
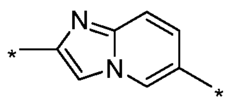
 ,  ,  ,  ,  ,

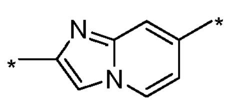
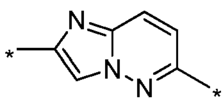
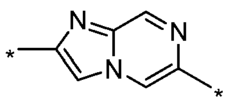
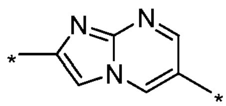
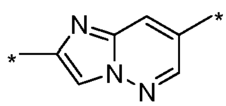
or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

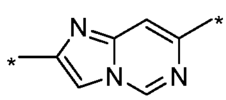
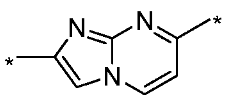
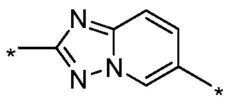
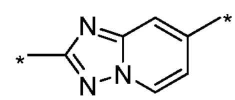
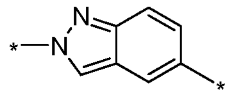
[0021] In a fourteenth embodiment of the first aspect, B and B′ together is

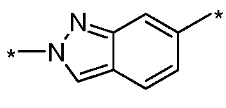
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

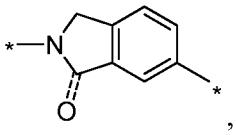
 ,  ,  ,  ,  ,

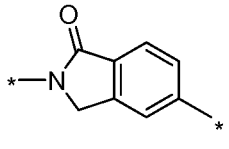
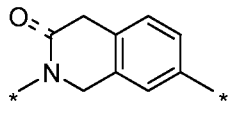
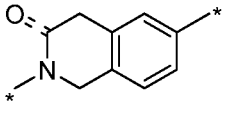
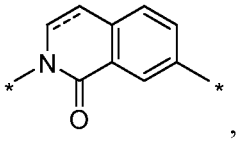
 ,  ,  ,  ,  ,

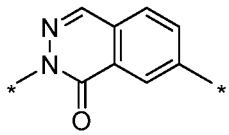
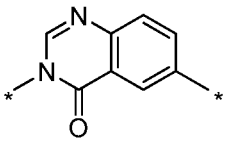
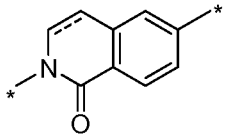
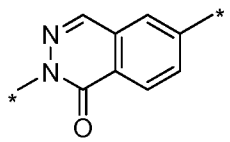
 ,  ,  ,  ,  ,

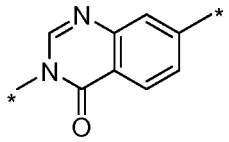
or  wherein * indicates attachment points to the remainder of the compound and the six-membered ring optionally contains one or two additional nitrogens as heteroatoms

with the proviso that the total number of nitrogens in the six-membered ring does not exceed two.

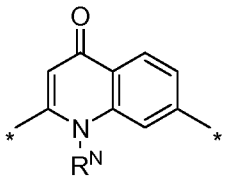
[0022] In a fifteenth embodiment of the first aspect, B and B′ together is  ,

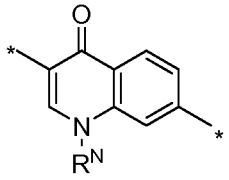
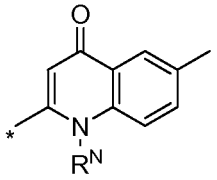
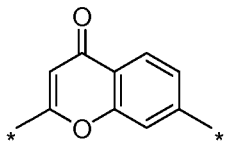
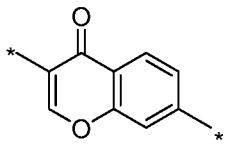
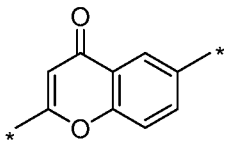
 ,  ,  ,  ,

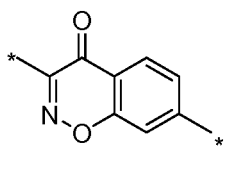
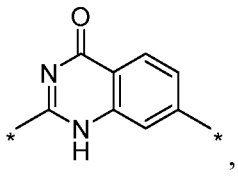
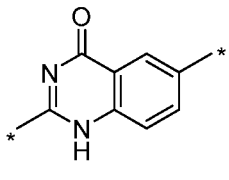
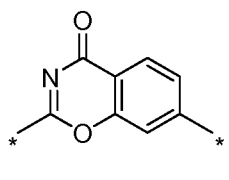
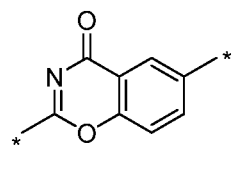
 ,  ,  ,  , or

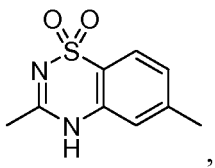
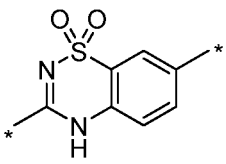


wherein * indicates attachment points to the remainder of the compound and the phenyl moiety optionally contains one or two nitrogens as heteroatoms.

[0023] In a sixteenth embodiment of the first aspect, B and B′ together is  ,

 ,  ,  ,  ,  ,

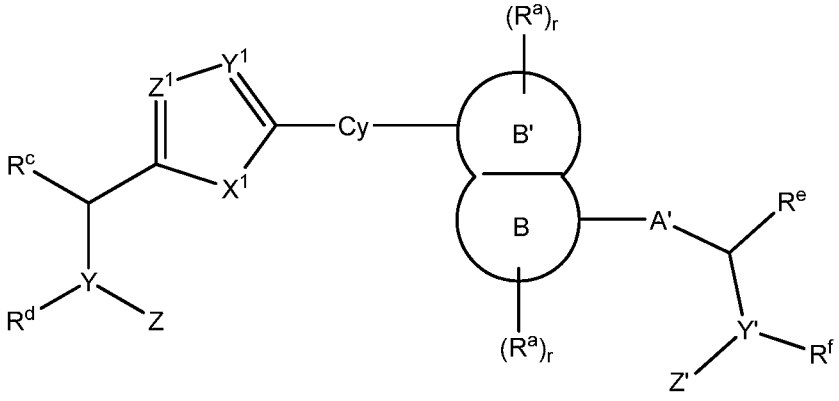
 ,  ,  ,  ,  ,

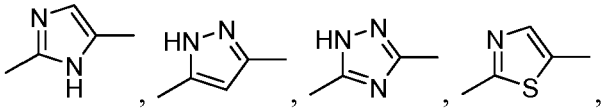
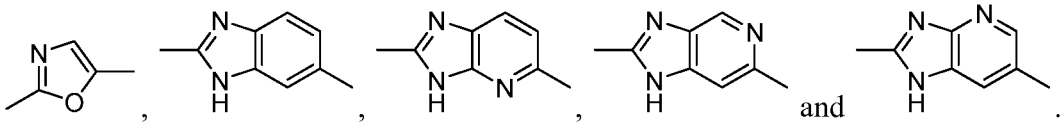
 , or 

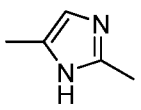
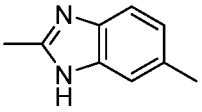
wherein * indicates attachment points to the remainder of the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and

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.

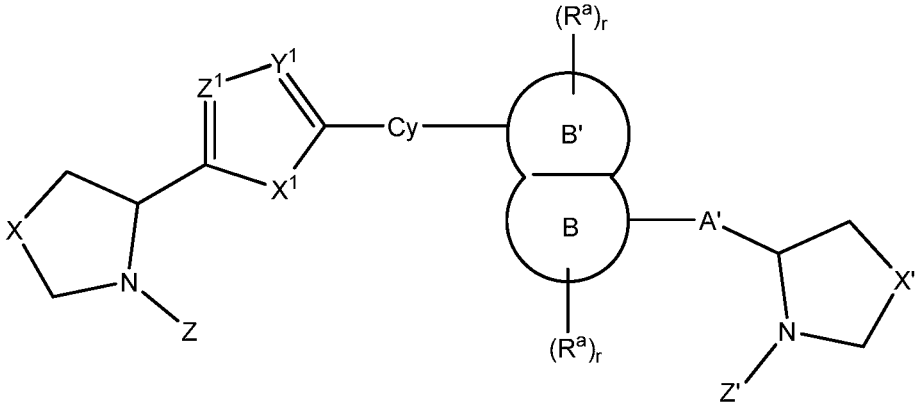
[0024] In a second aspect of the invention, compounds have formula II:



wherein A′ is selected from the group consisting of a single bond,  ,  and .

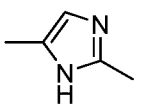
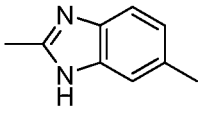
[0025] In a first embodiment of the second aspect, compounds have formula II wherein A′ is  or  .

[0026] In a second embodiment of the second aspect, compounds have formula IIa:

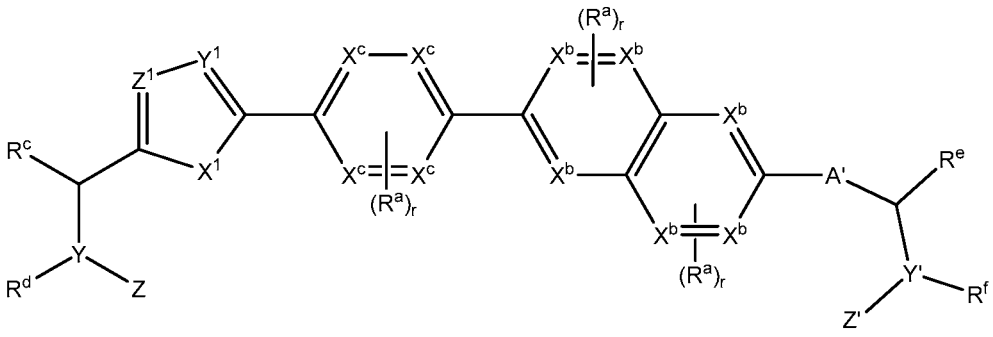


wherein X and X′ are

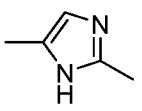
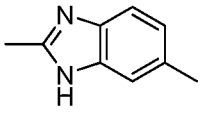
each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0027] In a third embodiment of the second aspect, compounds have formula IIa wherein A′ is  or  .

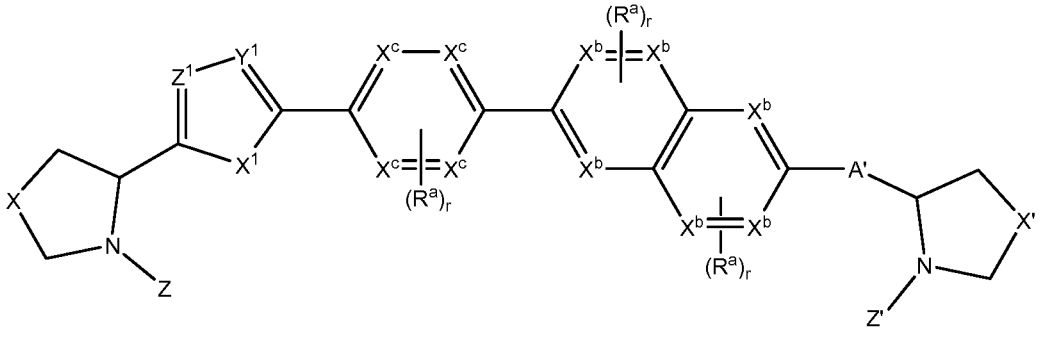
[0028] In a fourth embodiment of the second aspect, compounds have formula IIb:



wherein each X^b and X^c is independently C or N.

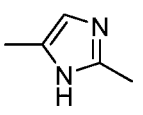
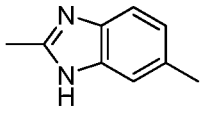
[0029] In a fifth embodiment of the second aspect, compounds have formula IIb wherein A′ is  or  .

[0030] In a sixth embodiment of the second aspect, compounds have formula IIc:

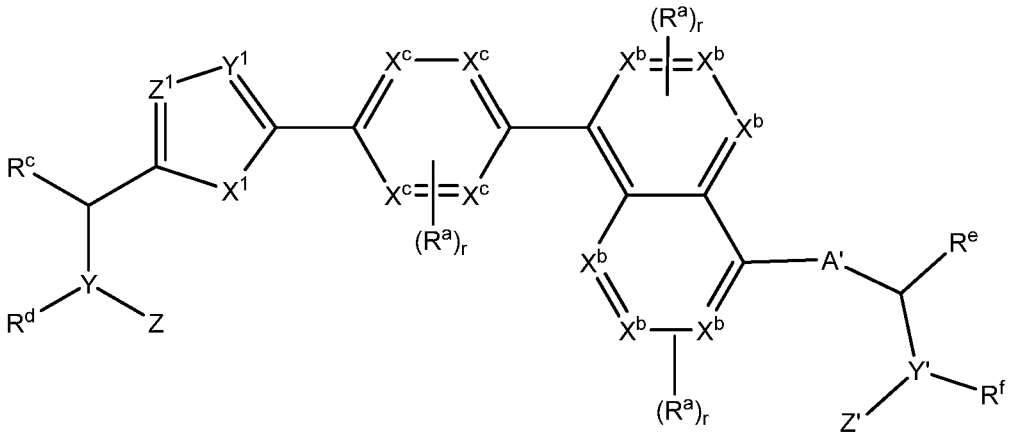


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$,

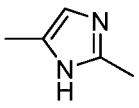
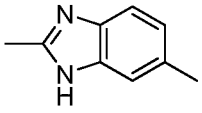
–CH_2–CH_2–, –CH=CH–, –O–, –S–, –$S(O)_{1-2}$–, –CH_2O–, –CH_2S–, –$CH_2S(O)_{1-2}$– and –$CH_2N(R^1)$–, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0031] In a seventh embodiment of the second aspect, compounds have formula IIc wherein A′ is  or  .

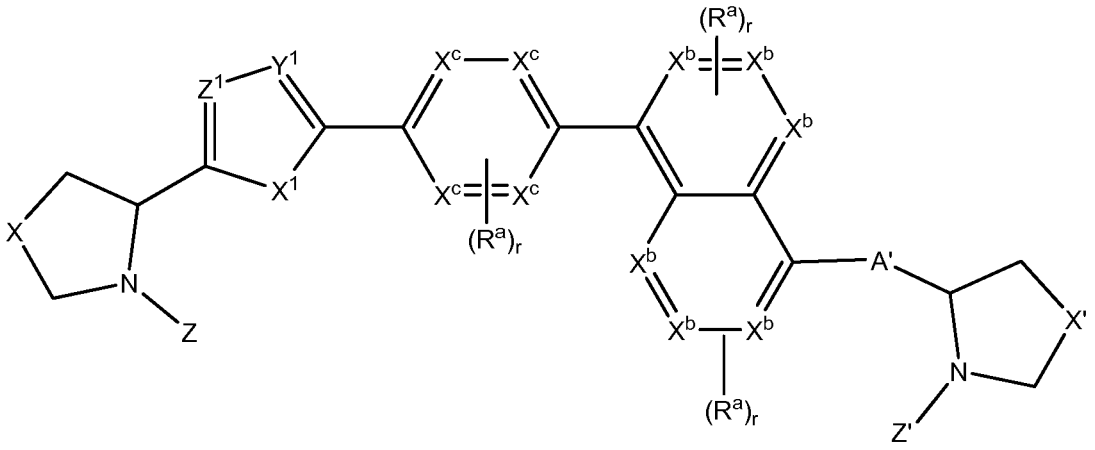
[0032] In an eighth embodiment of the second aspect, compounds have formula IId:



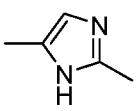
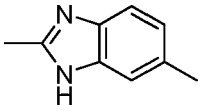
wherein each X^b and X^c is independently C or N.

[0033] In a ninth embodiment of the second aspect, compounds have formula IId wherein A′ is  or  .

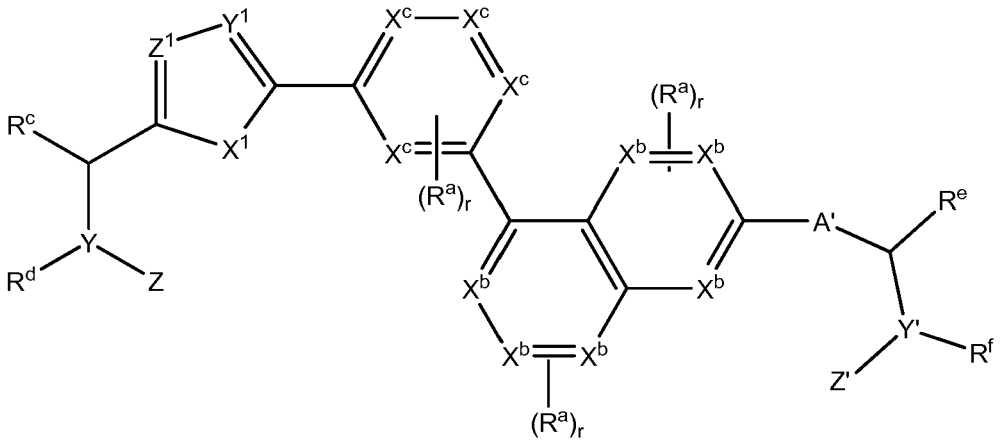
[0034] In a tenth embodiment of the second aspect, compounds have formula IIe:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

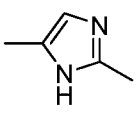
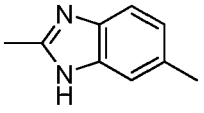
[0035] In an eleventh embodiment of the second aspect, compounds have formula IIe wherein A′ is  or  .

[0036] In a twelfth embodiment of the second aspect, compounds have formula IIf:

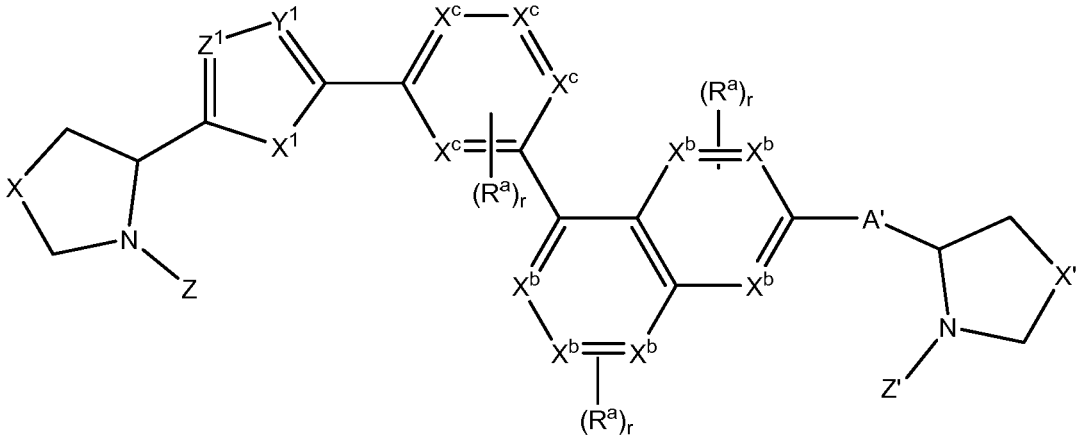


wherein each X^b and X^c is independently C or N.

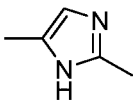
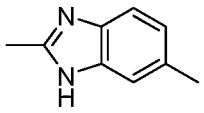
[0037] In a thirteenth embodiment of the second aspect, compounds have formula IIf

wherein A′ is  or  .

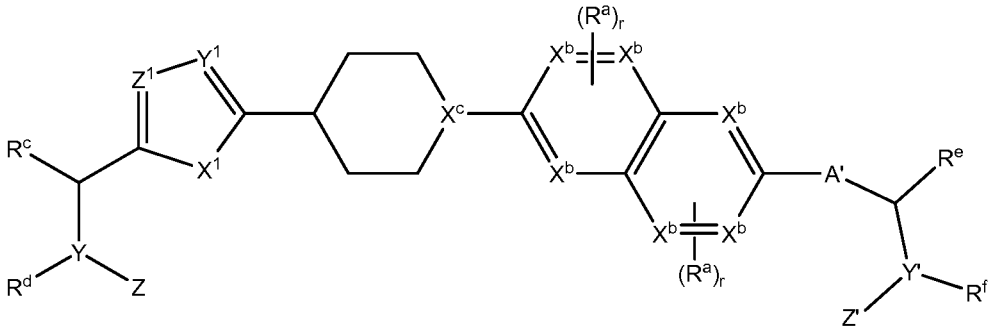
[0038] In a fourteenth embodiment of the second aspect, compounds have formula IIg:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

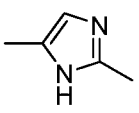
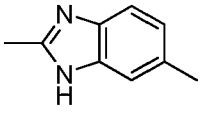
[0039] In a fifteenth embodiment of the second aspect, compounds have formula IIg wherein A′ is  or  .

[0040] In a sixteenth embodiment of the second aspect, compounds have formula IIh:

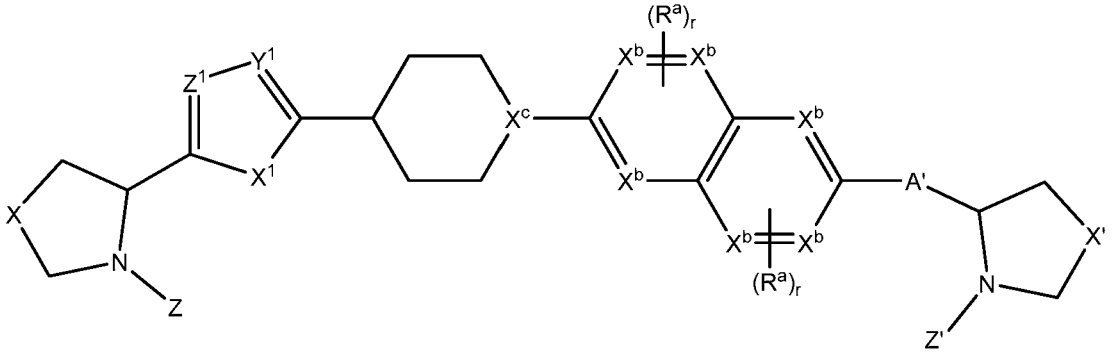


wherein X^c and each X^b is independently C or N.

[0041] In a seventeenth embodiment of the second aspect, compounds have formula IIh

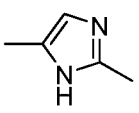
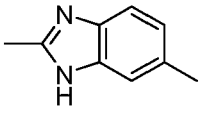
wherein A′ is  or  .

[0042] In an eighteenth embodiment of the second aspect, compounds have formula IIi:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

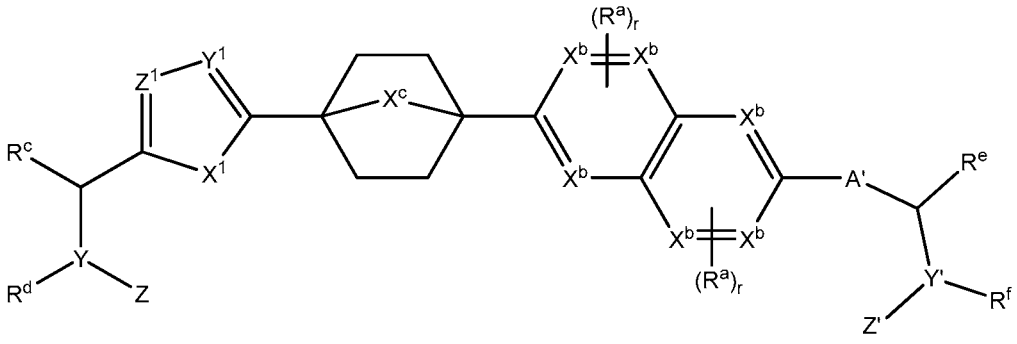
[0043] In a nineteenth embodiment of the second aspect, compounds have formula IIi

wherein A′ is  or  .

[0044] In a twentieth embodiment of the second aspect, compounds have formula IIh or IIi wherein X^c is C.

[0045] In an twenty-first embodiment of the second aspect, compounds have formula IIh or IIi wherein X^c is N.

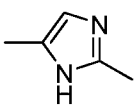
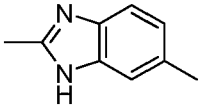
[0046] In a twenty-second embodiment of the second aspect, compounds have formula IIj:



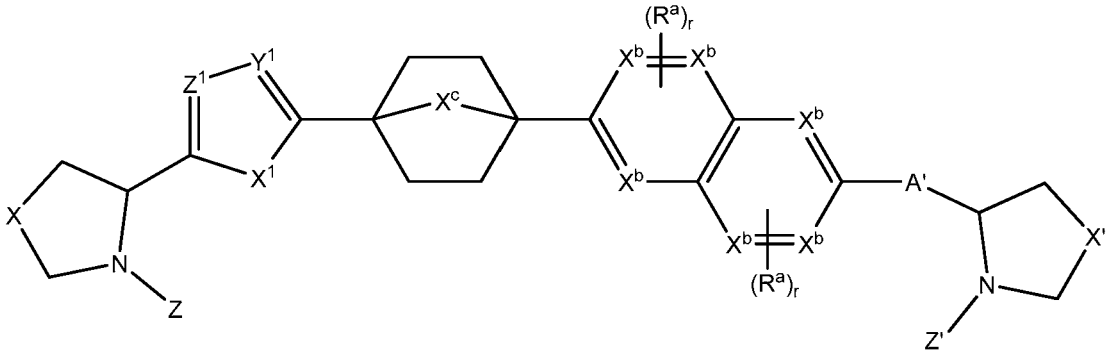
wherein

X^c is $–CH_2–$, –NH– or $–CH_2–CH_2–$; and

each X^b is independently C or N.

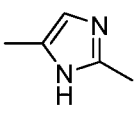
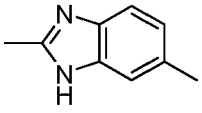
[0047] In a twenty-third embodiment of the second aspect, compounds have formula IIj wherein A′ is  or  .

[0048] In a twenty-fourth embodiment of the second aspect, compounds have formula IIk:

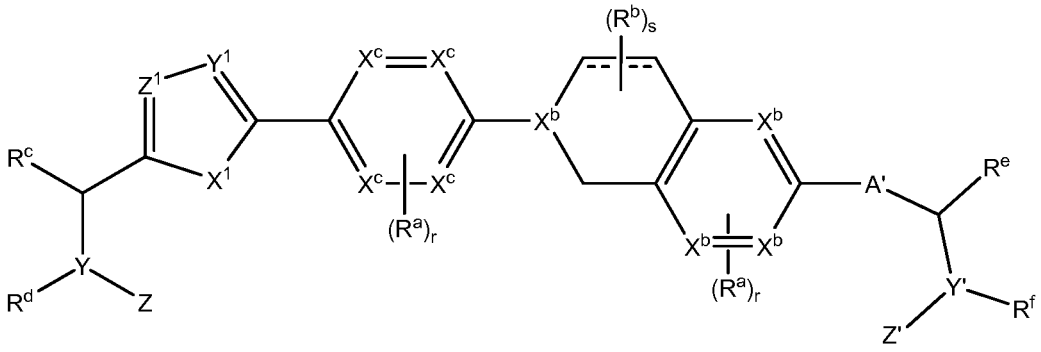


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0049] In a twenty-fifth embodiment of the second aspect, compounds have formula IIk

wherein A′ is  or  .

[0050] In a twenty-sixth embodiment of the second aspect, compounds have formula III:



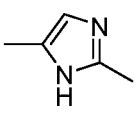
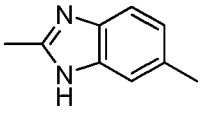
wherein:

each X^b and X^c is independently C or N;

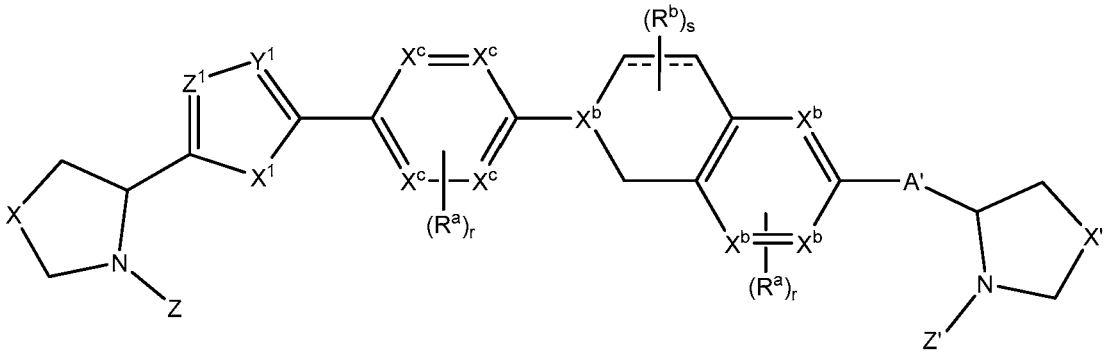
each R^b is selected from the group consisting of oxo, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; and

s is 0, 1, 2, or 3.

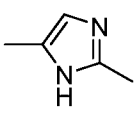
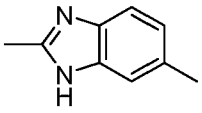
[0051] In a twenty-seventh embodiment of the second aspect, compounds have formula III

wherein A′ is  or  .

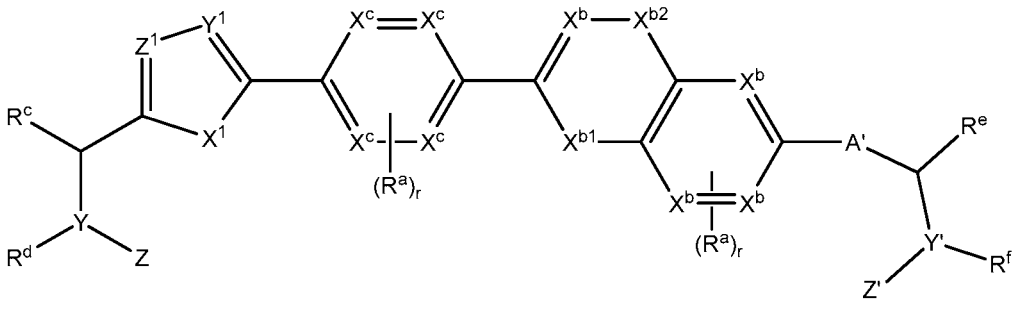
[0052] In a twenty-eighth embodiment of the second aspect, compounds have formula IIm:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0053] In a twenty-ninth embodiment of the second aspect, compounds have formula IIm wherein A′ is  or  .

[0054] In a thirtieth embodiment of the second aspect, compounds have formula IIn:



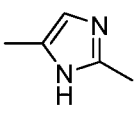
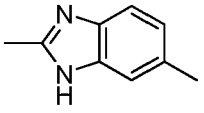
wherein:

each X^b and X^c is independently C or N;

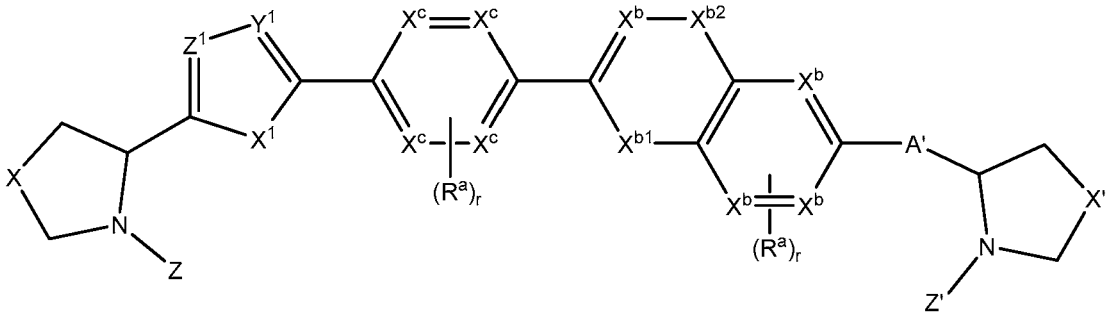
X^{b1} is N or O; and

X^{b2} is $S(O)_2$ or C(O).

[0055] In a thirty-first embodiment of the second aspect, compounds have formula IIn

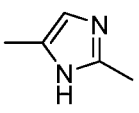
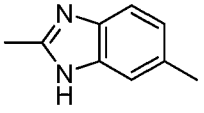
wherein A′ is  or  .

[0056] In a thirty-second embodiment of the second aspect, compounds have formula IIo:

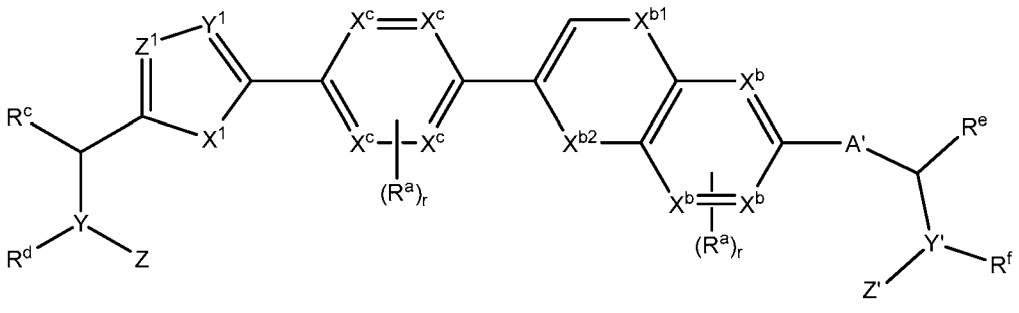


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0057] In a thirty-third embodiment of the second aspect, compounds have formula IIo

wherein A′ is  or  .

[0058] In an thirty-fourth embodiment of the second aspect, compounds have formula IIp:



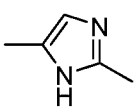
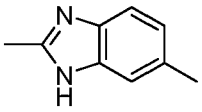
wherein:

each X^b and X^c is independently C or N;

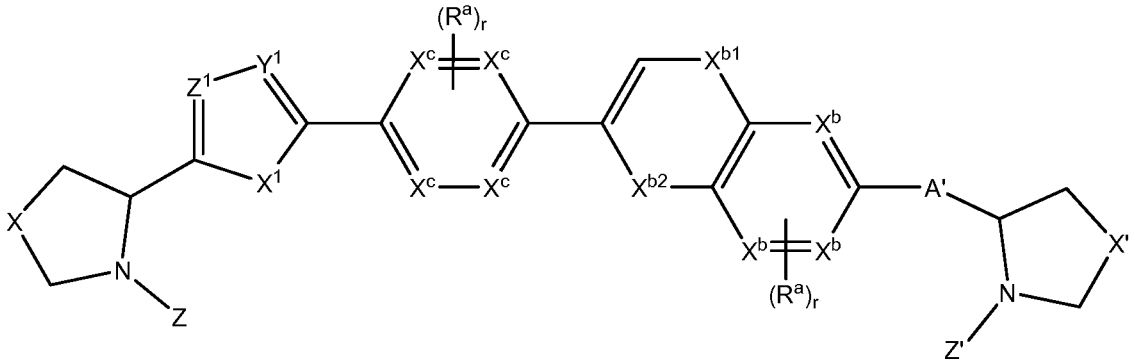
X^{b1} is N or O; and

X^{b2} is $S(O)_2$ or C(O).

[0059] In a thirty-fifth embodiment of the second aspect, compounds have formula IIp

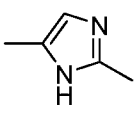
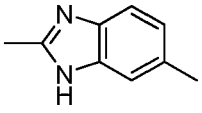
wherein A′ is  or  .

[0060] In a thirty-sixth embodiment of the second aspect, compounds have formula IIq:

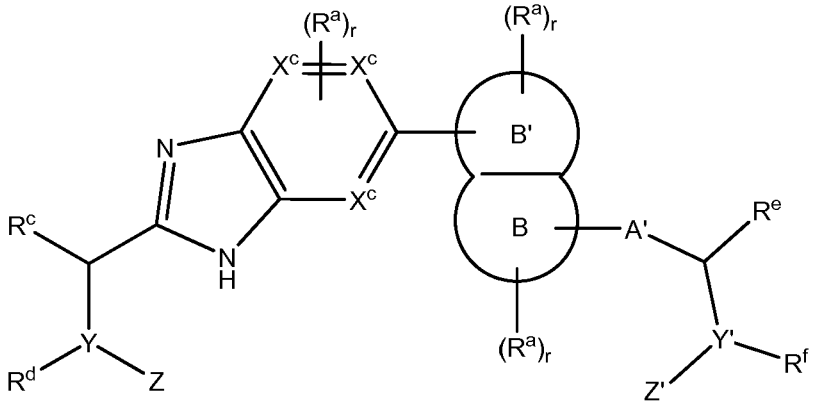


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

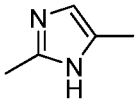
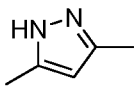
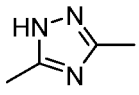
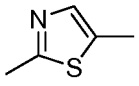
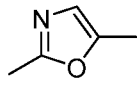
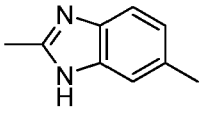
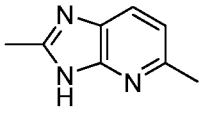
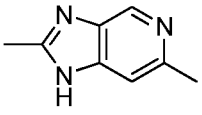
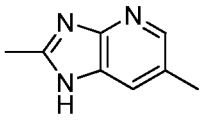
[0061] In a thirty-seventh embodiment of the second aspect, compounds have formula IIq

wherein A′ is  or  .

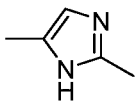
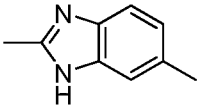
[0062] In a third aspect of the invention, compounds have formula III:



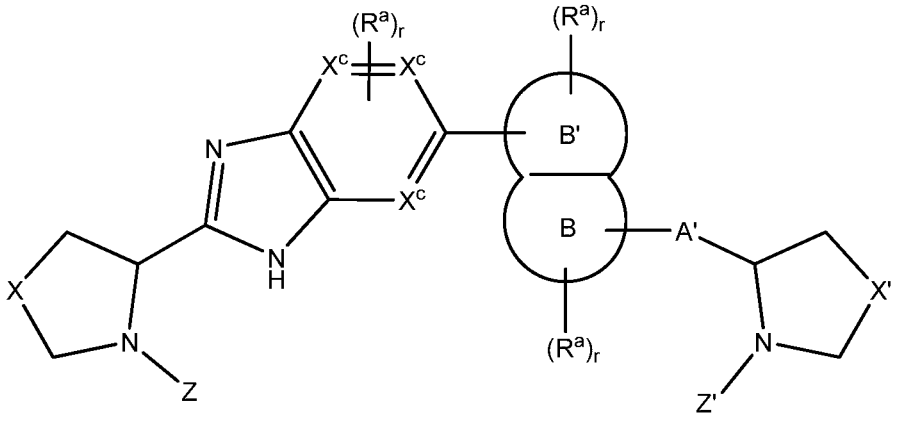
wherein

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^c is independently C or N.

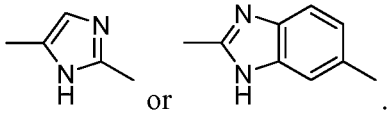
[0063] In a first embodiment of the third aspect, compounds have formula III wherein A′ is  or  .

[0064] In a second embodiment of the third aspect, compounds have formula IIIa:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

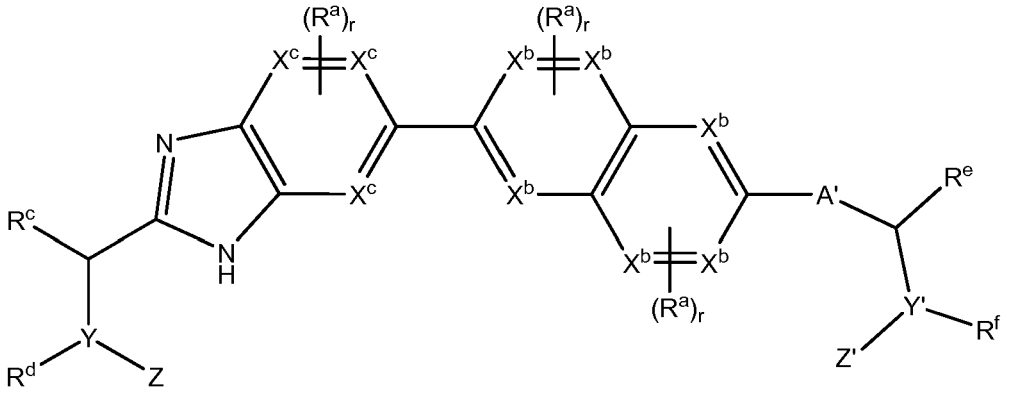
[0065] In a third embodiment of the third aspect, compounds have formula IIIa wherein A′ is



or

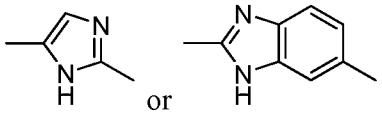
.

[0066] In a fourth embodiment of the third aspect, compounds have formula IIIb:

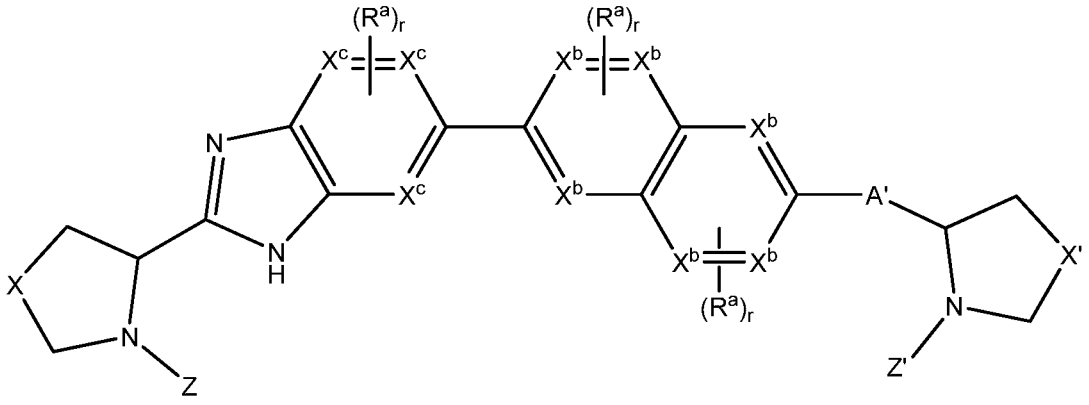


wherein each X^b is independently C or N.

[0067] In a fifth embodiment of the third aspect, compounds have formula IIIb wherein A′ is

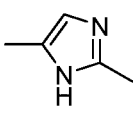
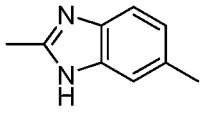
 or .

[0068] In a sixth embodiment of the third aspect, compounds have formula IIIc:

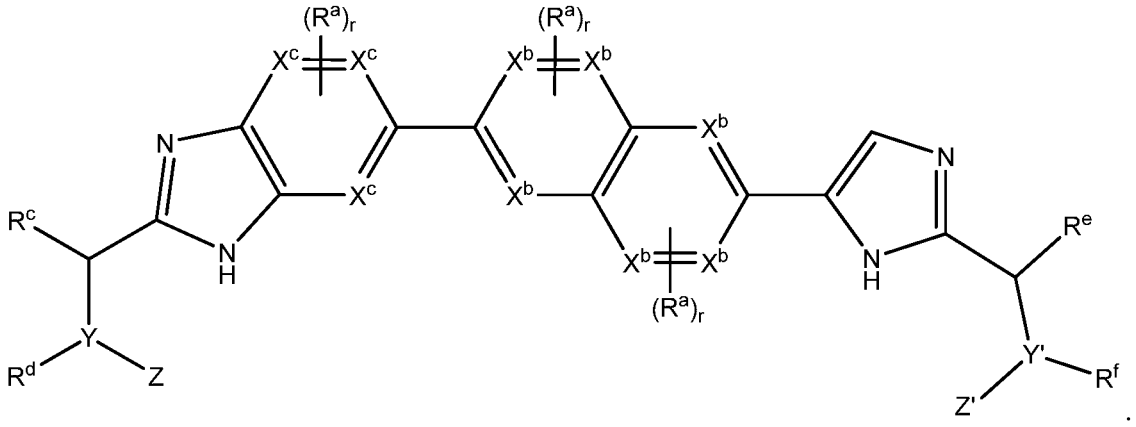


wherein

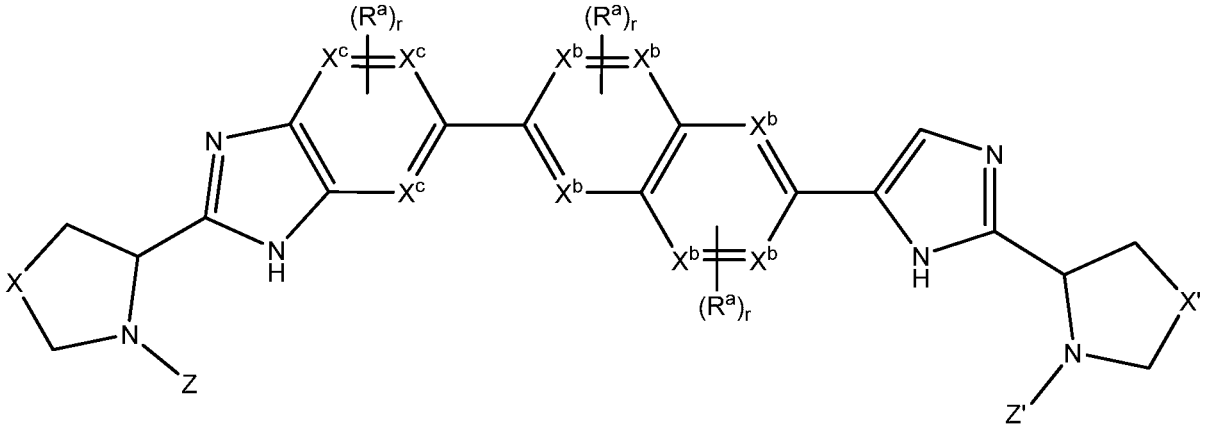
X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0069] In a seventh embodiment of the third aspect, compounds have formula IIIc wherein A′ is  or  .

[0070] In an eighth embodiment of the third aspect, compounds have formula IIId:

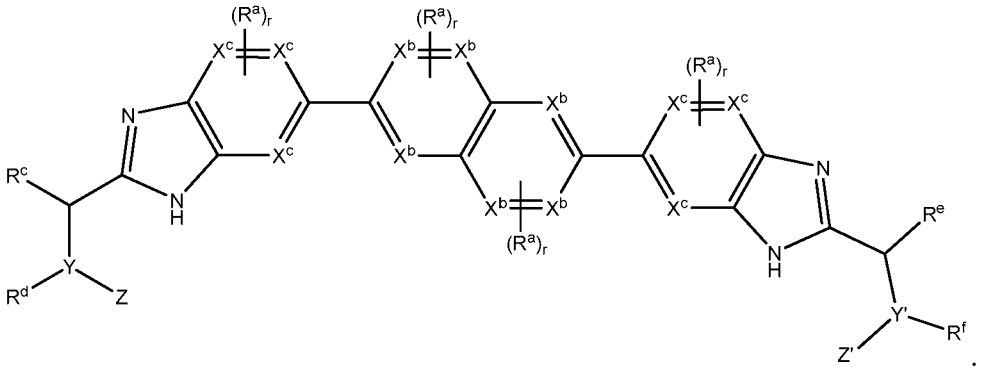
 .

[0071] In a ninth embodiment of the third aspect, compounds have formula IIIe:

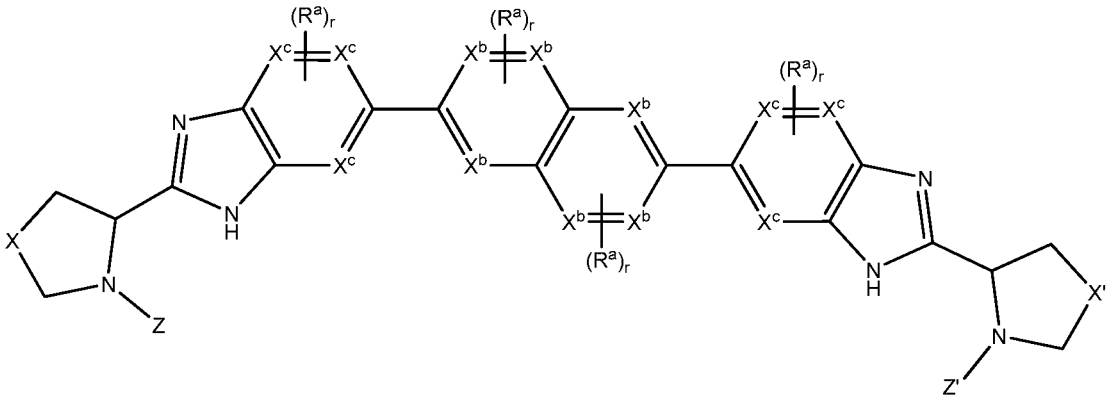


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0072] In a tenth embodiment of the third aspect, compounds have formula IIIf:

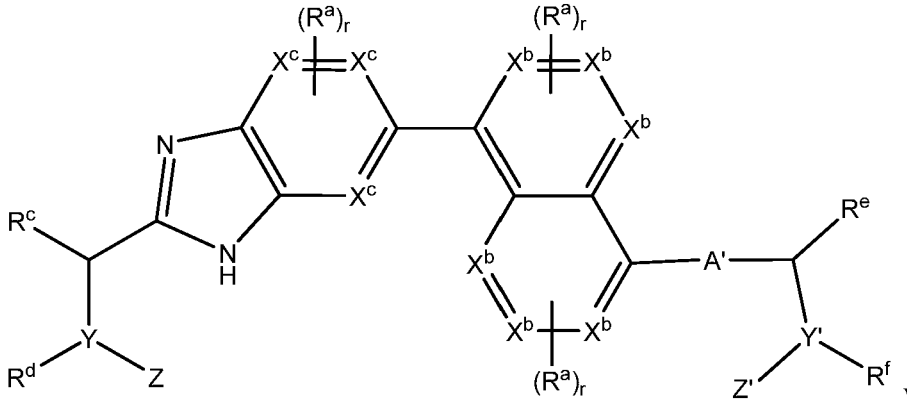


[0073] In an eleventh embodiment of the third aspect, compounds have formula IIIg:

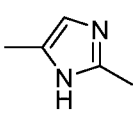
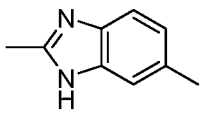


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

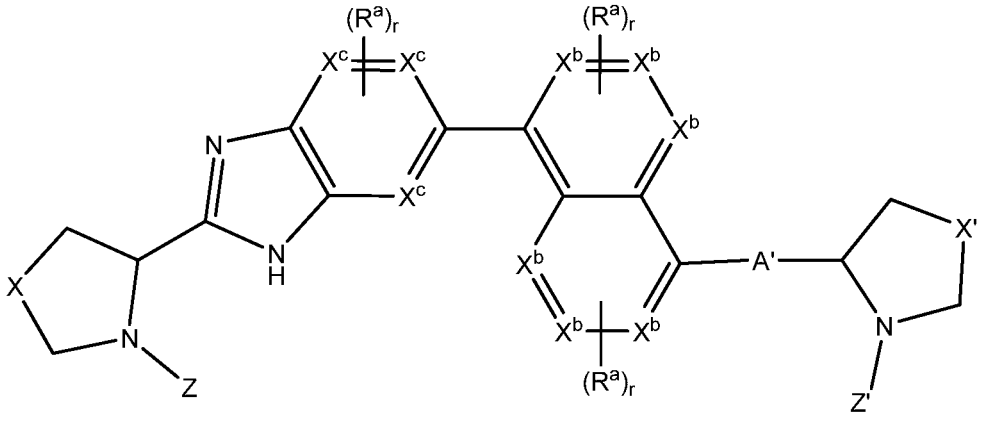
[0074] In a twelfth embodiment of the third aspect, compounds have formula IIIh:



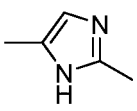
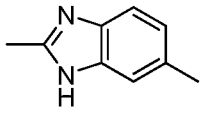
wherein each X^b is independently C or N.

[0075] In a thirteenth embodiment of the third aspect, compounds have formula IIIh wherein A′ is  or  .

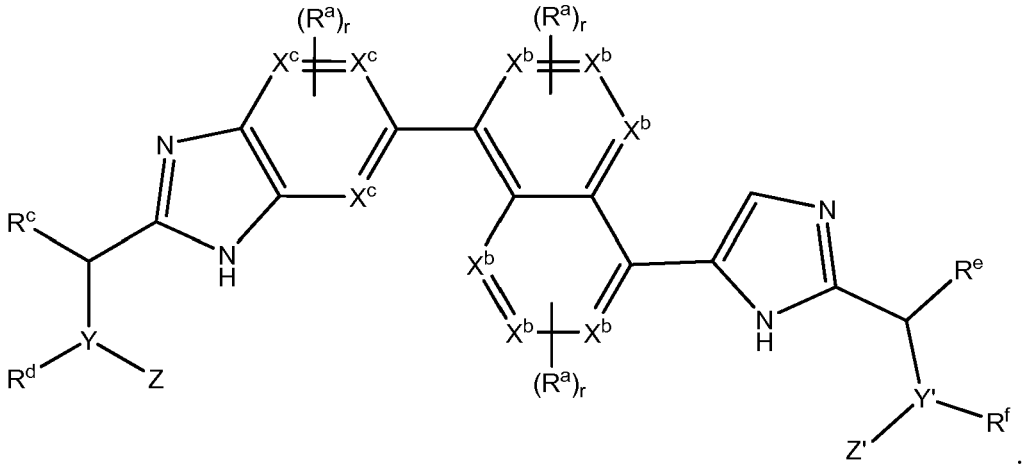
[0076] In a fourteenth embodiment of the third aspect, compounds have formula IIIi:



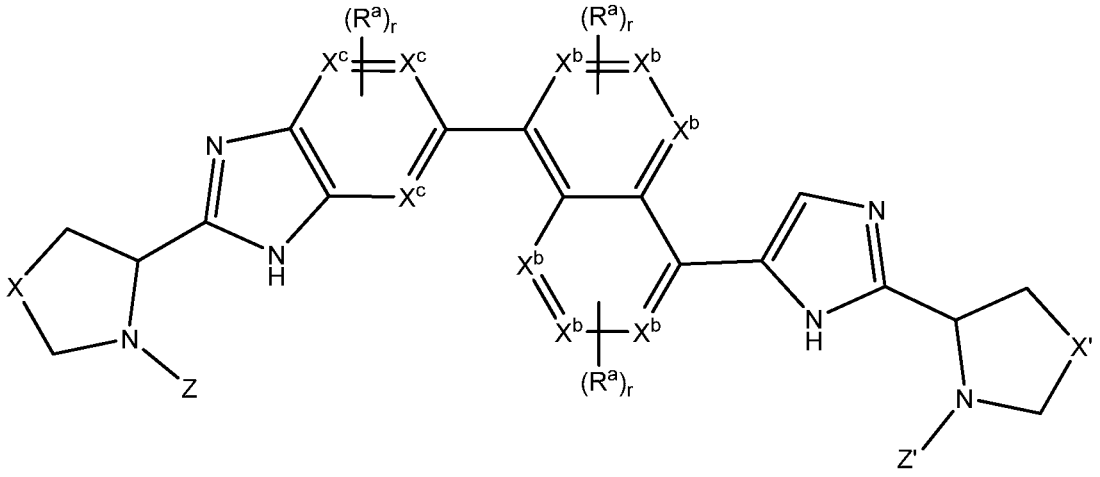
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0077] In a fifteenth embodiment of the third aspect, compounds have formula IIIi wherein A′ is  or  .

[0078] In a sixteenth embodiment of the third aspect, compounds have formula IIIj:



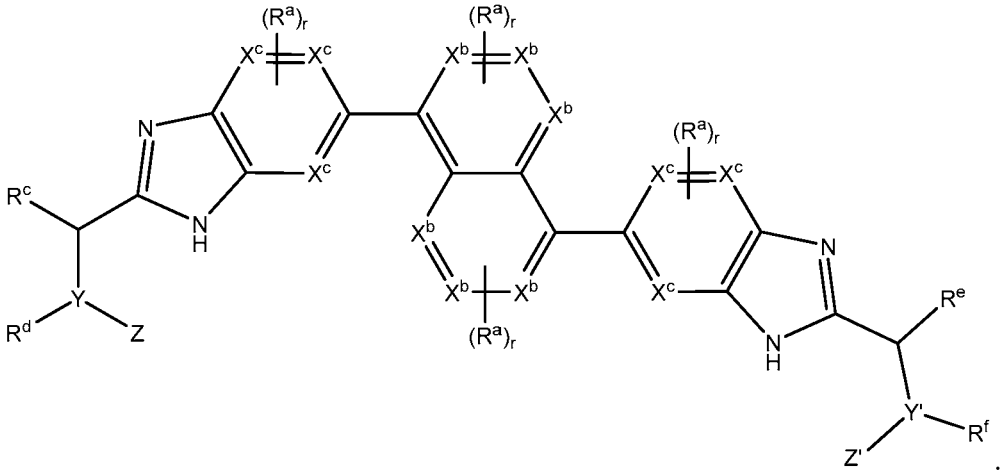
[0079] In a seventeenth embodiment of the third aspect, compounds have formula IIIk:



wherein

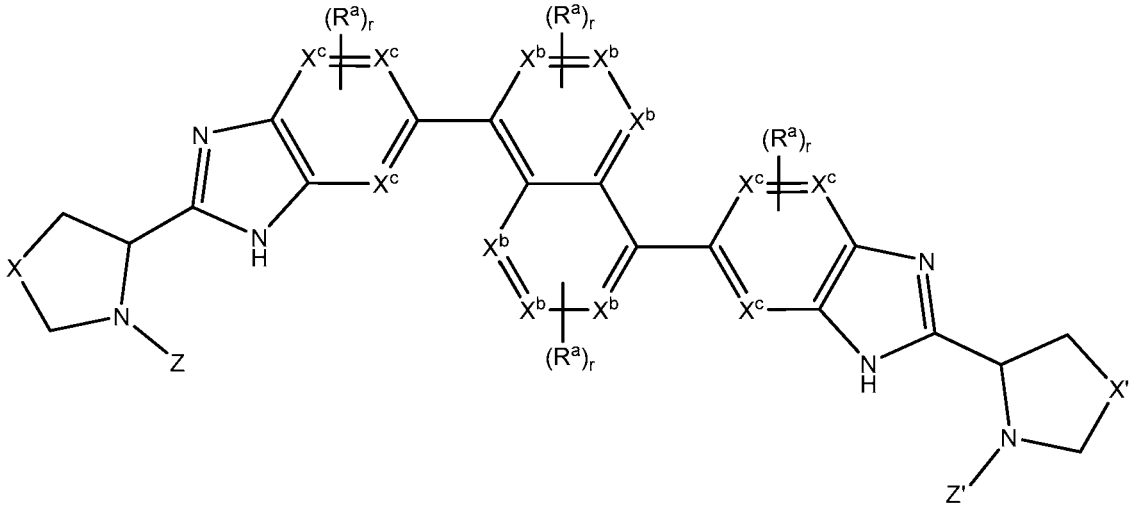
X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0080] In an eighteenth embodiment of the third aspect, compounds have formula IIIl:



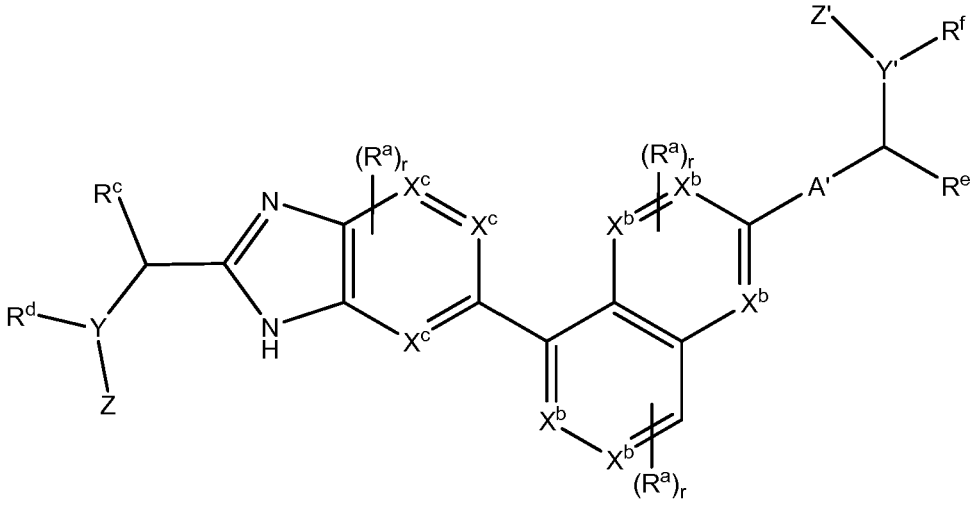
.

[0081] In a nineteenth embodiment of the third aspect, compounds have formula IIIm:



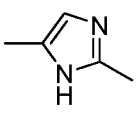
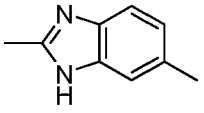
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0082] In a twentieth embodiment of the third aspect, compounds have formula IIIn:

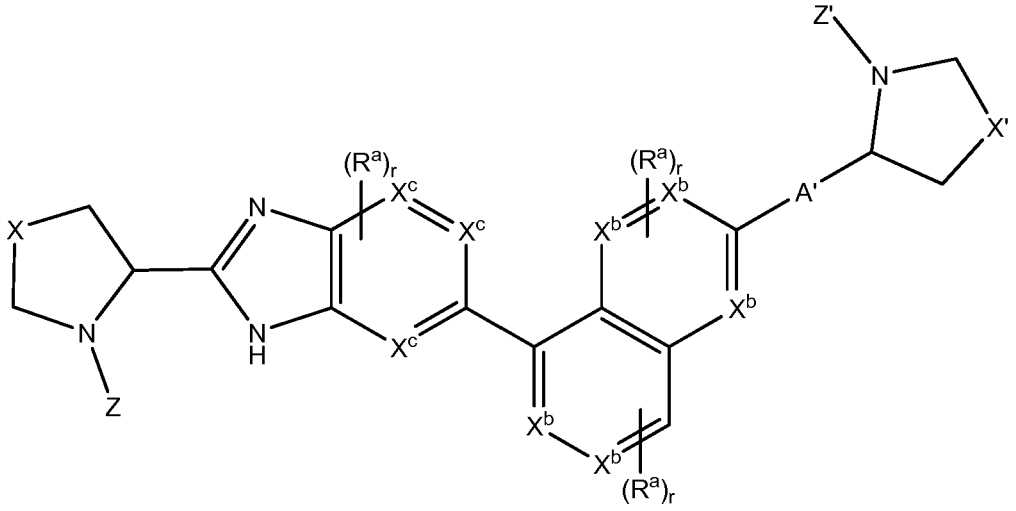


wherein each X^b is independently C or N.

[0083] In a twenty-first embodiment of the third aspect, compounds have formula IIIn

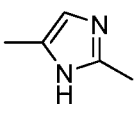
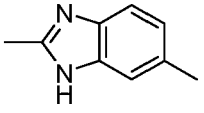
wherein A′ is  or  .

[0084] In a twenty-second embodiment of the third aspect, compounds have formula IIIo:

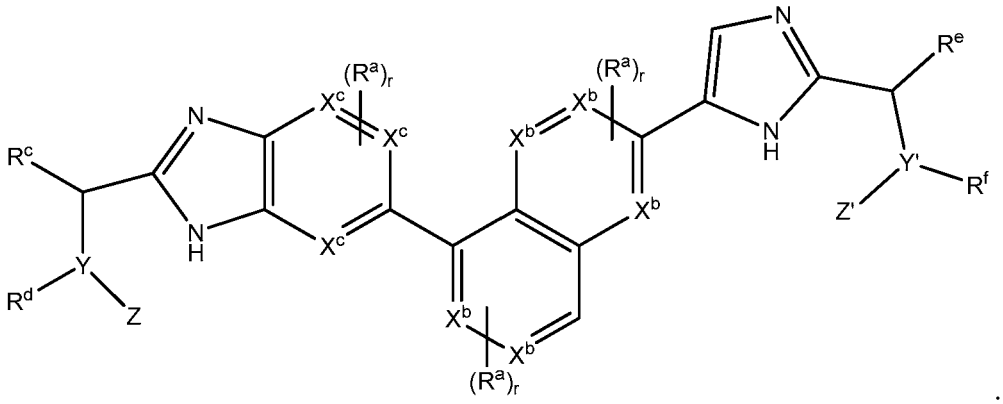


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

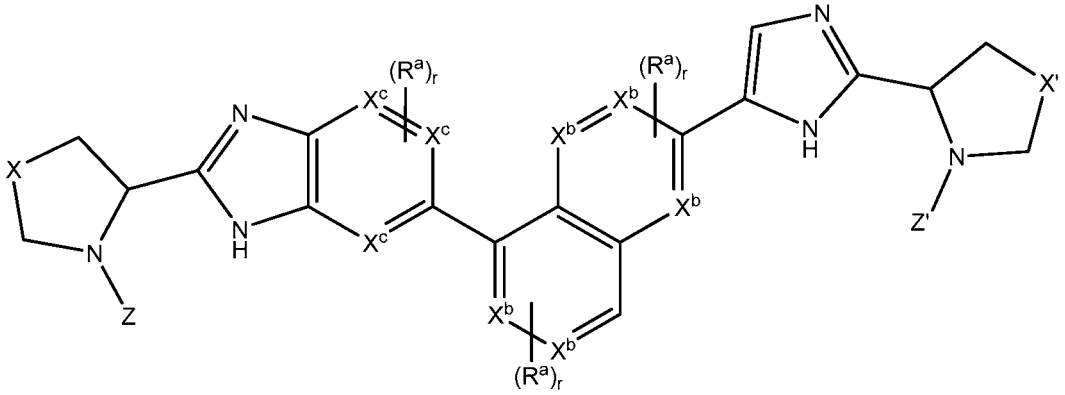
[0085] In a twenty-third embodiment of the third aspect, compounds have formula IIIo

wherein A′ is  or  .

[0086] In a twenty-fourth embodiment of the third aspect, compounds have formula IIIp:

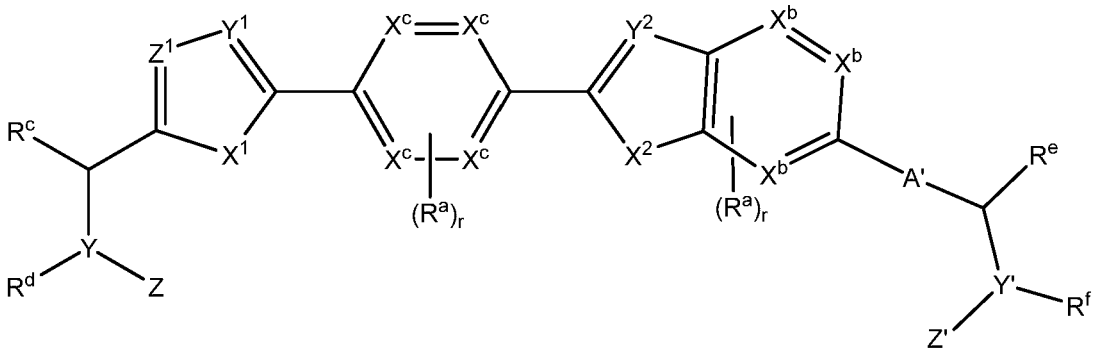


[0087] In a twenty-fifth embodiment of the third aspect, compounds have formula IIIq:

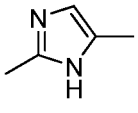
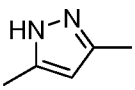
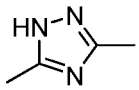
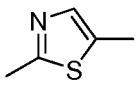
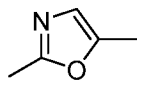
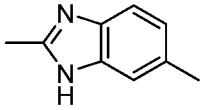
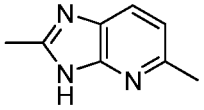
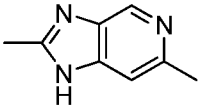
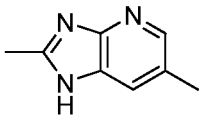


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

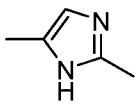
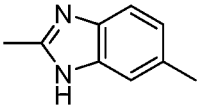
[0088] In a fourth aspect of the invention, compounds have formula IV:



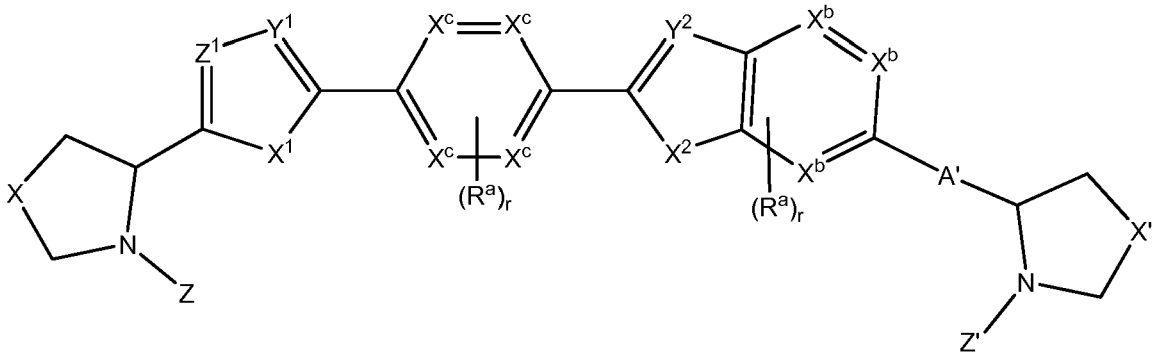
wherein:

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^b and X^c is independently C or N.

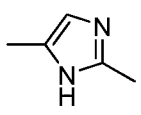
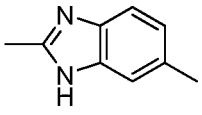
[0089] In a first embodiment of the fourth aspect, compounds have formula IV wherein A′ is  or  .

[0090] In a second embodiment of the fourth aspect, compounds have formula IVa:

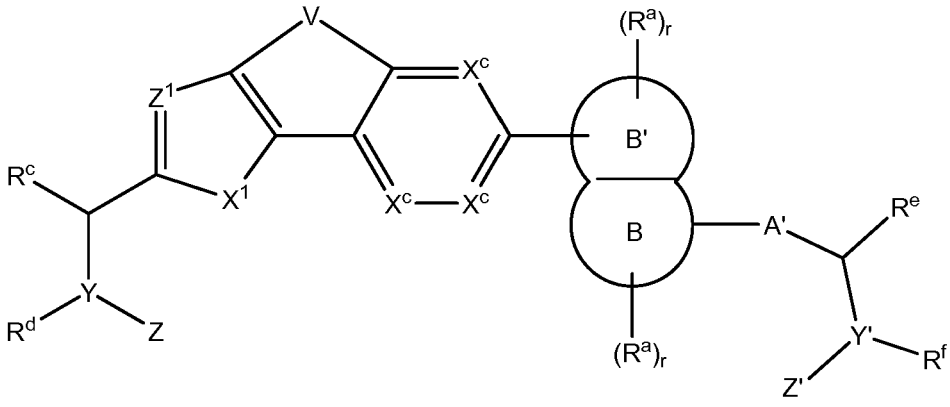


wherein X and X′ are each independently selected from the group consisting of a bond,

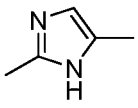
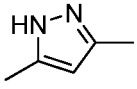
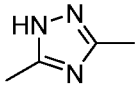
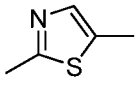
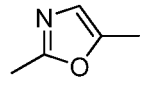
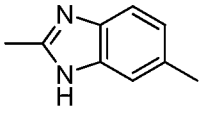
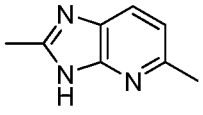
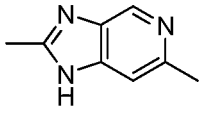
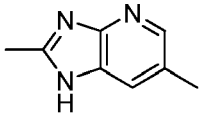
$-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0091] In a third embodiment of the fourth aspect, compounds have formula IVa wherein A′ is  or  .

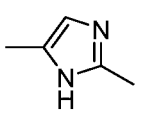
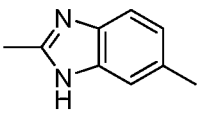
[0092] In a fifth aspect of the invention, compounds have formula V:



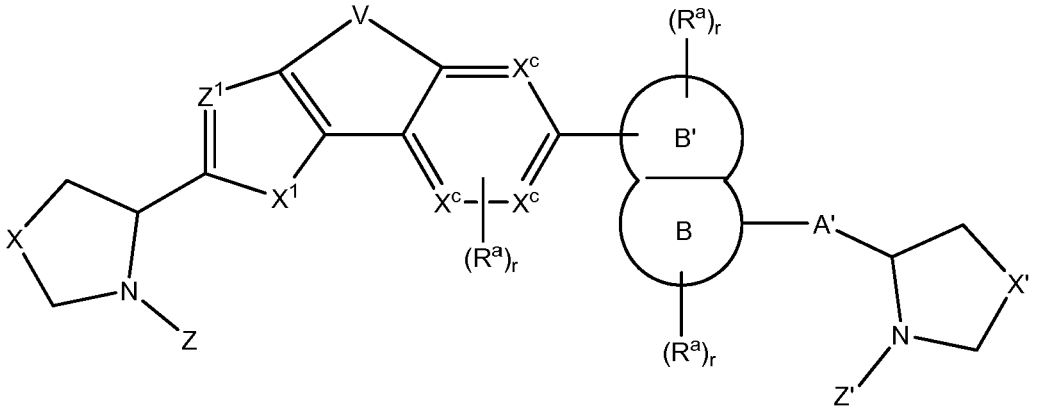
wherein:

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^c is independently C or N with the proviso that no more than two X^c are N.

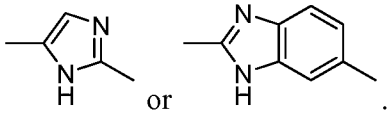
[0093] In a first embodiment of the fifth aspect, compounds have formula V wherein A′ is  or  .

[0094] In a second embodiment of the fifth aspect, compounds have formula Va:



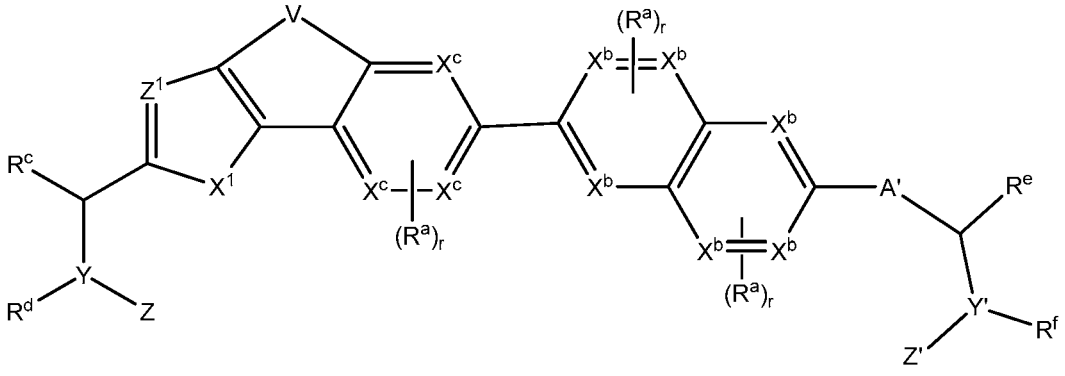
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0095] In a third embodiment of the fifth aspect, compounds have formula Va wherein A′ is



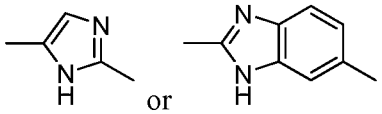
.

[0096] In a fourth embodiment of the fifth aspect, compounds have formula Vb:

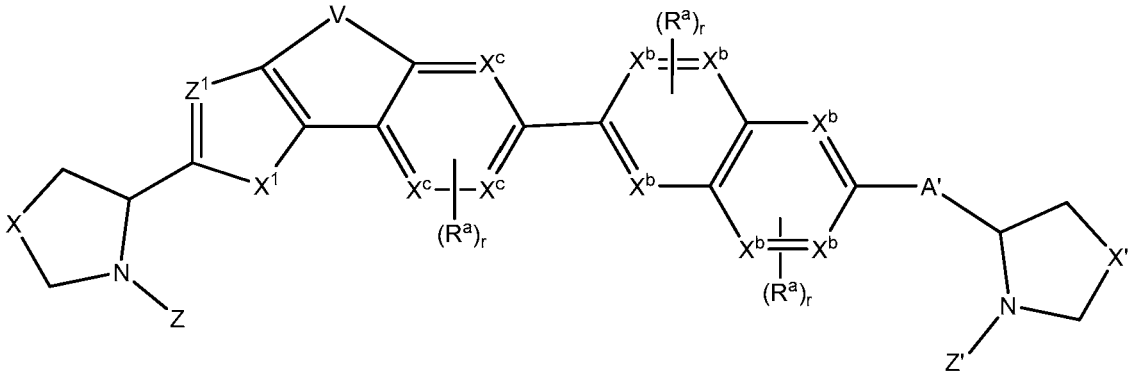


wherein each X^b is independently C or N.

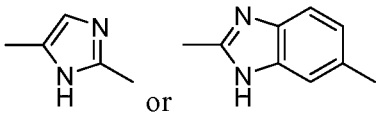
[0097] In a fifth embodiment of the fifth aspect, compounds have formula Vb wherein A′ is

 or .

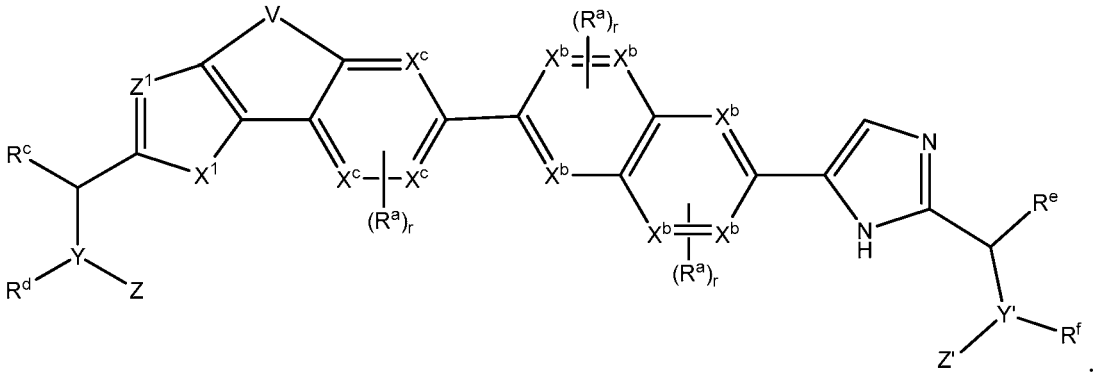
[0098] In a sixth embodiment of the fifth aspect, compounds have formula Vc:



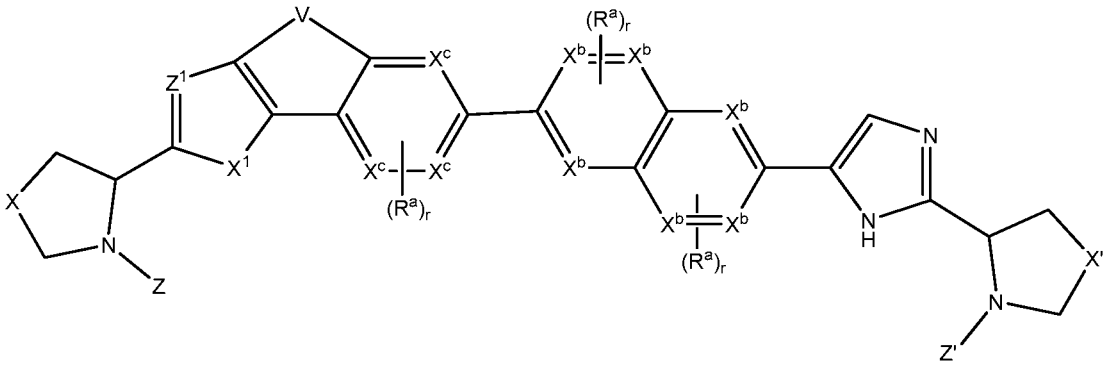
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0099] In a seventh embodiment of the fifth aspect, compounds have formula Vc wherein A′ is  or .

[0100] In an eighth embodiment of the fifth aspect, compounds have formula Vd:



[0101] In a ninth embodiment of the fifth aspect, compounds have formula Ve:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0102] In a sixth aspect of the invention, in any compound of any of the second through fifth aspects, 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.

[0103] In a first embodiment of the sixth aspect, R^c and R^d or R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0104] In a second embodiment of the sixth aspect, both of R^c and R^d and R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

[0105] In a seventh aspect of the invention, each R^a, if present in any of the other aspects of the invention, is independently –CN,–$OCHF_2$, –OCF_3, –CF_3, or –F.

[0106] In an eighth aspect of the invention, if present in any compound of any of the other aspects, one of Y and Y′ is N.

[0107] In a first embodiment of the eighth aspect, both Y and Y′ are N.

[0108] In a ninth aspect of the invention, Z and Z′ in any of the previous aspects are each 1-3 amino acids.

[0109] In a first embodiment of the ninth aspect, the amino acids are in the D configuration.

[0110] In a tenth aspect of the invention, Z and Z′ in any of the previous aspects 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 $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0111] In a first embodiment of the tenth aspect, both of Z and Z′ are $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0112] In a second embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0113] In a third embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0114] In a fourth embodiment of the tenth aspect, one or both of Z and Z′ are $-[C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0115] In a fifth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0116] In a sixth embodiment of the tenth aspect, one or both of Z and Z′ are $-[C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-C(O)-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0117] In a seventh embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-C(O)-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0118] In an eighth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

[0119] In a ninth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^{81}$.

[0120] In a tenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-R^{81}$.

[0121] In an eleventh embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-O-R^{81}$.

[0122] In a twelfth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-O-R^{81}$.

[0123] In a thirteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-R^8$.

[0124] In a fourteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-R^8$.

[0125] In a fifteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0126] In a sixteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0127] In a seventeenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0128] In an eighteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0129] An eleventh aspect of the invention provides a pharmaceutical composition comprising the compounds of the invention.

[0130] A twelfth aspect of the invention provides use of the compounds of the invention in the manufacture of a medicament.

[0131] In a first embodiment of the twelfth aspect, the medicament is for the treatment of hepatitis C.

[0132] A thirteenth aspect of the invention provides 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 the invention.

Detailed Description

[0133] 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.

[0134] The term "alkanoyl" as used herein contemplates a carbonyl group with a lower alkyl group as a substituent.

[0135] 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.

[0136] 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 $-(O-CH_2CH_2-O)_{1-4}-$.

[0137] The term "alkoxycarbonyl" as used herein contemplates a carbonyl group with an alkoxy group as a substituent.

[0138] 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.

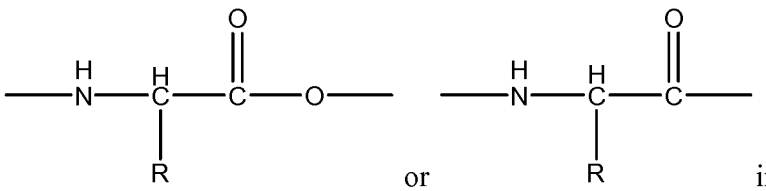
[0139] The term "alkylene," "alkenylene" and "alkynylene" as used herein refers to the groups "alkyl," "alkenyl" and "alkynyl" respectively, when they are divalent, ie, attached to two atoms.

[0140] The term "alkylsulfonyl" as used herein contemplates a sulfonyl group which has a lower alkyl group as a substituent.

[0141] 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.

[0142] The term "amino" as used herein contemplates a group of the structure $-NR^N_2$.

[0143] The term "amino acid" as used herein contemplates a group of the structure



or

in either the D or the L configuration

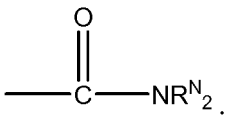
and includes but is not limited to the twenty "standard" amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine and histidine. The present invention 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.

[0144] 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.

[0145] 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.

[0146] 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).

[0147] The term "carbamoyl" as used herein contemplates a group of the structure



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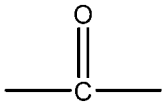
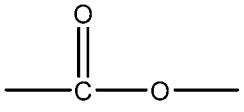
[0148] The term "carbonyl" as used herein contemplates a group of the structure



[0149] The term "carboxyl" as used herein contemplates a group of the structure



[0150] 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.

[0151] 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.

[0152] The term "halo" or "halogen" as used herein includes fluorine, chlorine, bromine and iodine.

[0153] The term "heteroalkyl" as used herein contemplates an alkyl with one or more heteroatoms.

[0154] The term "heteroatom", particularly within a ring system, refers to N, O and S.

[0155] 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.

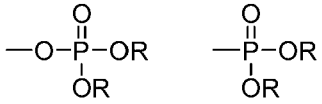
[0156] The term "oxo" as used herein contemplates an oxygen atom attached with a double bond.

[0157] 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.

[0158] "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

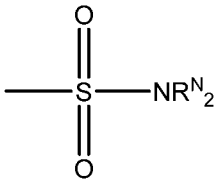
hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric 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).

[0159] The terms "phosphate" and "phosphonate" as used herein refer to the moieties having the following structures, respectively:



[0160] 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.

[0161] The term sulfonamide as used herein contemplates a group having the structure



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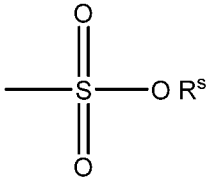
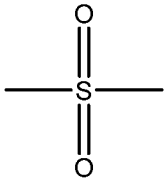
[0162] The term "sulfonate" as used herein contemplates a group having the structure



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.

[0163] The term "sulfonyl" as used herein contemplates a group having the structure



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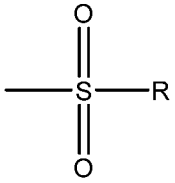
[0164] "Substituted sulfonyl" as used herein contemplates a group having the structure



including, but not limited to alkylsulfonyl and arylsulfonyl.

[0165] The term "thiocarbonyl," as used herein, means a carbonyl wherein an oxygen atom has been replaced with a sulfur.

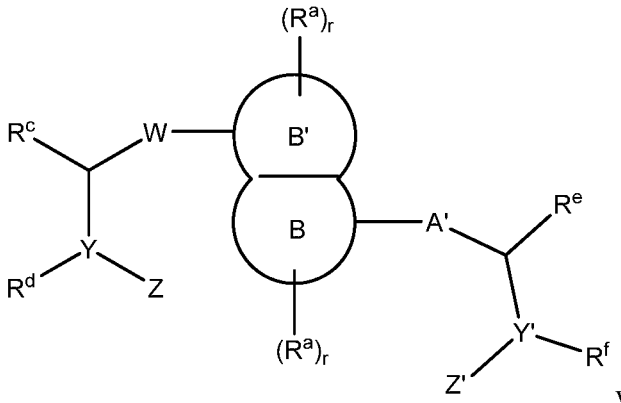
[0166] Each R is independently selected from hydrogen, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, amino, and oxo.

[0167] 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.

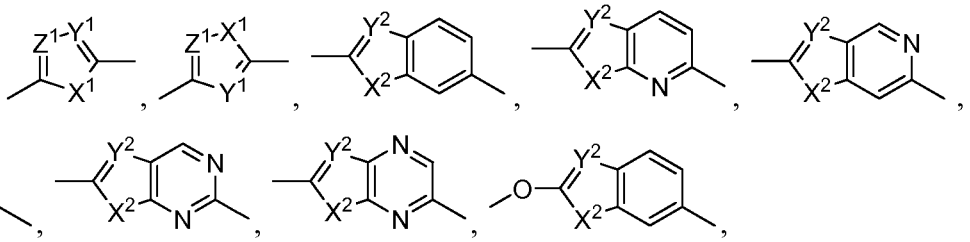
[0168] The compounds of the present invention may be used to inhibit or reduce the activity of HCV, particularly HCV's NS5A protein. In these contexts, inhibition and reduction of activity of the NS5A protein refers to a lower level of the measured activity relative to a control experiment in which the 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.

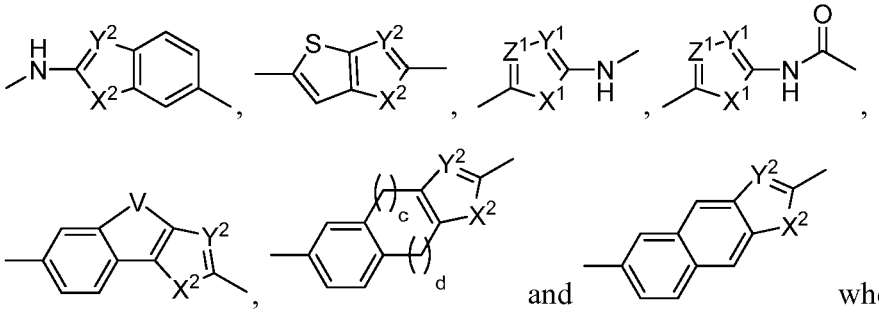
[0169] In a first aspect, compounds of formula I are provided:



wherein:

A′ is selected from the group consisting of single bond, $-(CR_2)_n-C(O)-(CR_2)_p-$, $-(CR_2)_n-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-S(O)_k-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-S(O)_k-N(R^N)-(CR_2)_p-$ and $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ and a heteroaryl group selected from the group consisting of





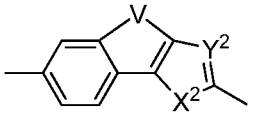
and wherein:

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,

V is $–CH_2-CH_2-$, -CH=CH-, -N=CH-, $(CH_2)_a-N(R^N)-(CH_2)_b-$ or $–(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,

 optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

the carbons of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of halogen, -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,

the nitrogens, if present, of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of -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,

a and b are independently 1, 2, or 3.

c and d are independently 1 or 2,

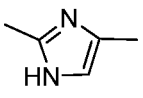
n and p are independently 0, 1, 2 or 3,

k is 0, 1, or 2,

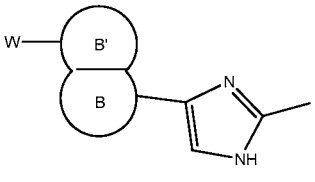
each R is independently selected from the group consisting of hydrogen, halogen, -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and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

each R^N is independently 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 and

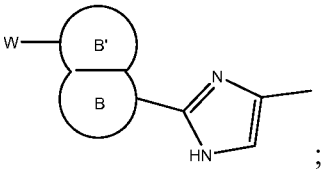
wherein B may be attached to either side of A′ so that in the example of A′ being



, the W-B-A′ can be



or

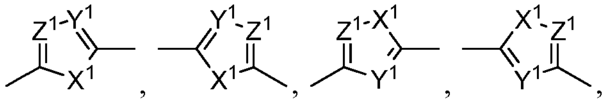


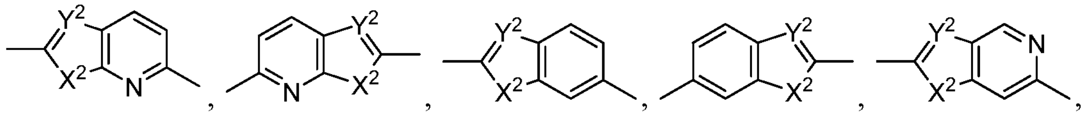
;

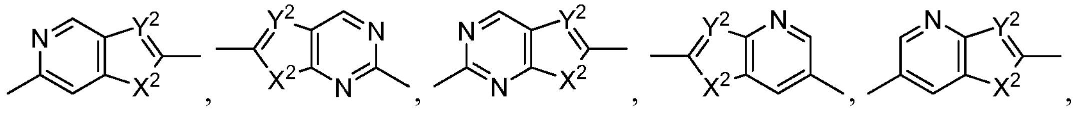
B and B′ are each independently a 4- to 8-membered ring that is an aryl, heteroaryl, cycloalkyl, or heterocycle, wherein each hetero atom, if present, is independently N, O or S and wherein at least one of B or B′ is aromatic;

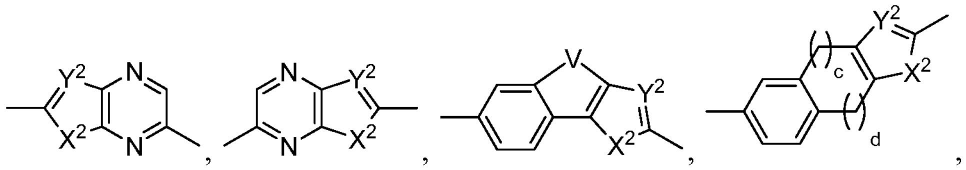
each R^a is independently selected from the group consisting of -OH, -CN, -NO_2, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; and if B or B′ is not aromatic, it may also be substituted with one or more oxo;

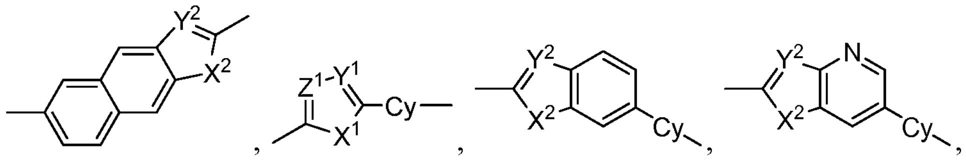
each r is independently 0, 1, 2 or 3;

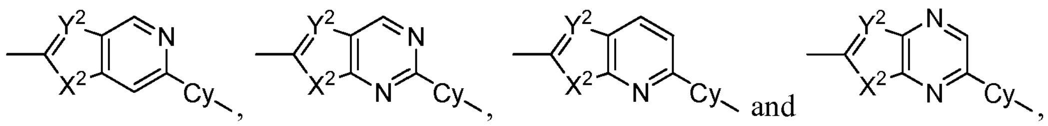
W is independently selected from 











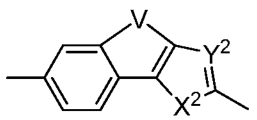
wherein:

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,

V is $-CH_2-CH_2-$, $-CH=CH-$, $-N=CH-$, $(CH_2)_a-N(R^N)-(CH_2)_b-$ or $-(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,

 optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

W 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,

W and ring B′ can be connected through either a carbon or a nitrogen atom on B′, 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,

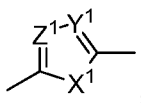
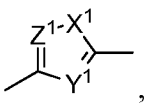
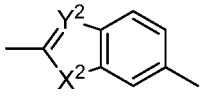
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen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

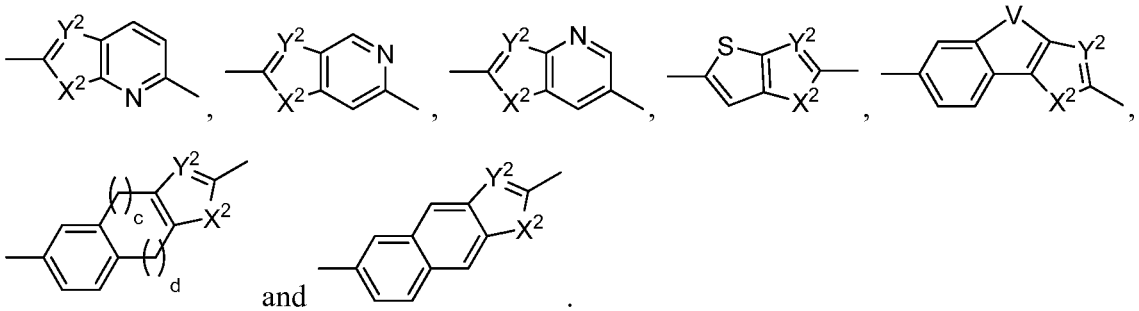
optionally, R^7 and R^8 together form a 4-7 membered ring,

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

u is 0, 1, or 2.

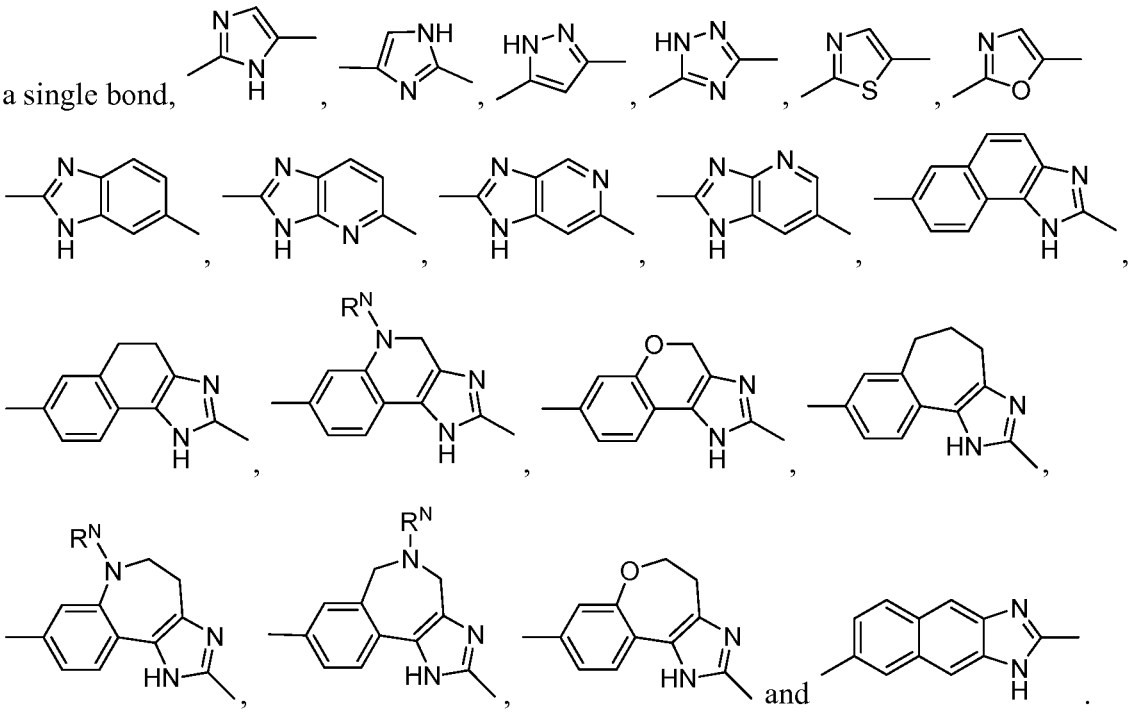
[0170] The compounds of the present invention include pharmaceutically acceptable salts of I as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0171] In a first embodiment of the first aspect, A′ is selected from the group consisting of a single bond, $-(CR_2)_n-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$ and $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ and a heteroaryl group selected from the group consisting of  ,  ,  ,



and

[0172] In a second embodiment of the first aspect, A′ is selected from the group consisting of a single bond,



and

[0173] 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,

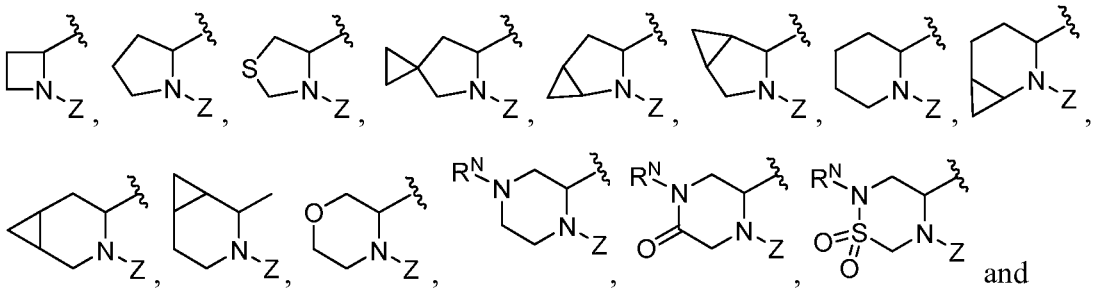
each hetero atom, if present, is independently N, O or S,

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

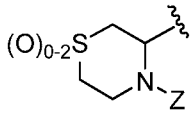
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0174] In a fourth embodiment of the first aspect, 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.

[0175] 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:

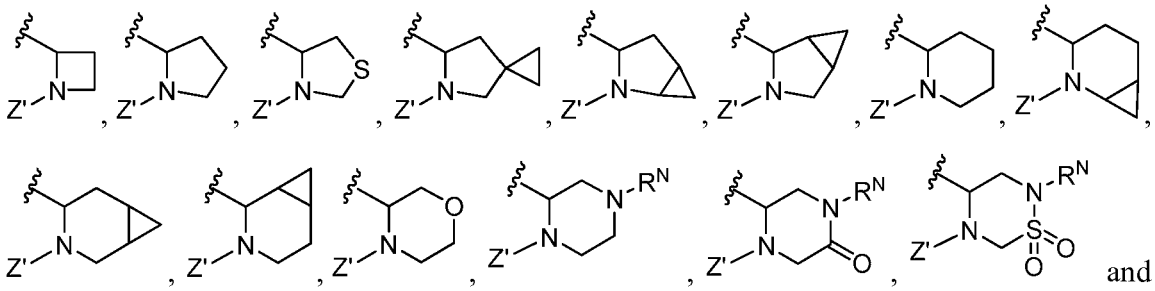


and

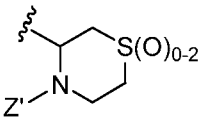


wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

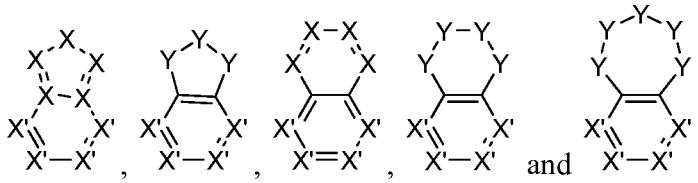
[0176] In a sixth embodiment of the first aspect, R^e and R^f are joined and form a heterocyclic fused ring system selected from the group consisting of:



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.

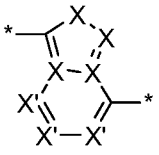
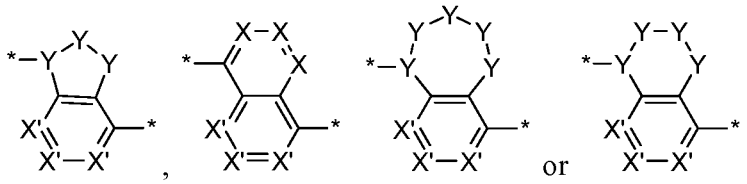
[0177] In a seventh embodiment of the first aspect, B and B′ together is selected from the group consisting of  , wherein

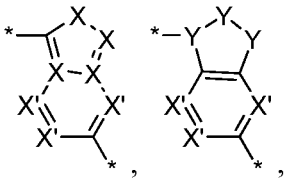
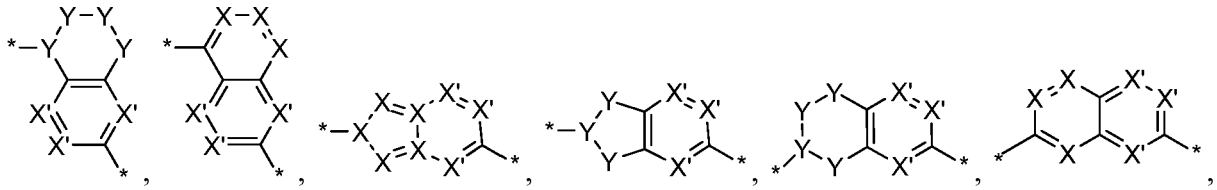
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

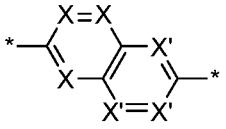
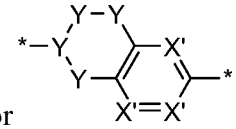
each X′ is independently –N– or –CH–, with the proviso that no more than two X′ are –N–;

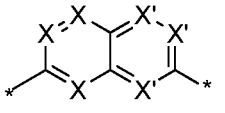
each Y is independently selected from -CH_2-, -NH- , -O-, -S-, -$C(O)_2$–, or –$S(O)_{1\text{-}2}$–; and

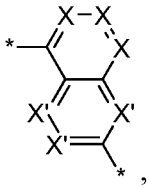
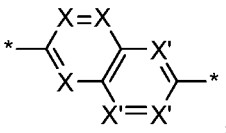
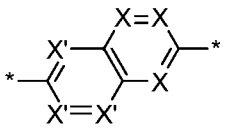
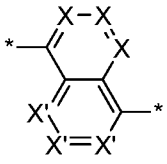
B and B′ attach to the remainder of the compound at any available attachment point on the molecule.

[0178] In an eighth embodiment of the first aspect, B and B′ together is  ,  wherein * indicates attachment points to the remainder of the compound.

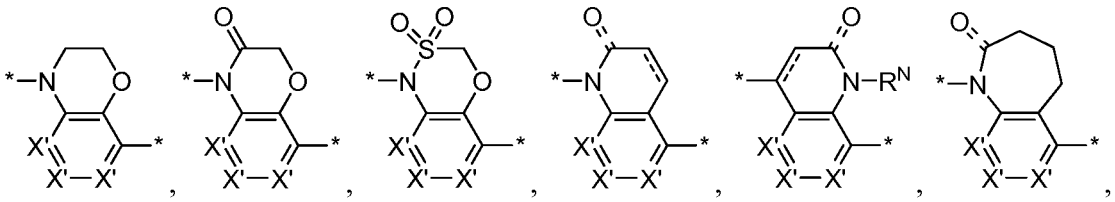
[0179] In a ninth embodiment of the first aspect, B and B′ together is  , 

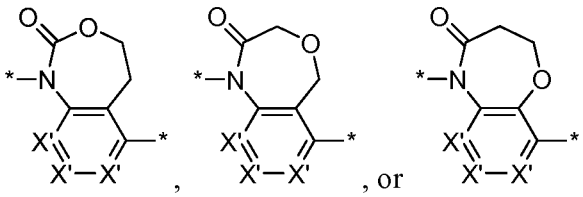

, or  wherein * indicates attachment points to the remainder of the compound.

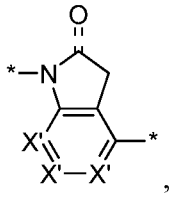
[0180] In a tenth embodiment of the first aspect, B and B′ together is  ,

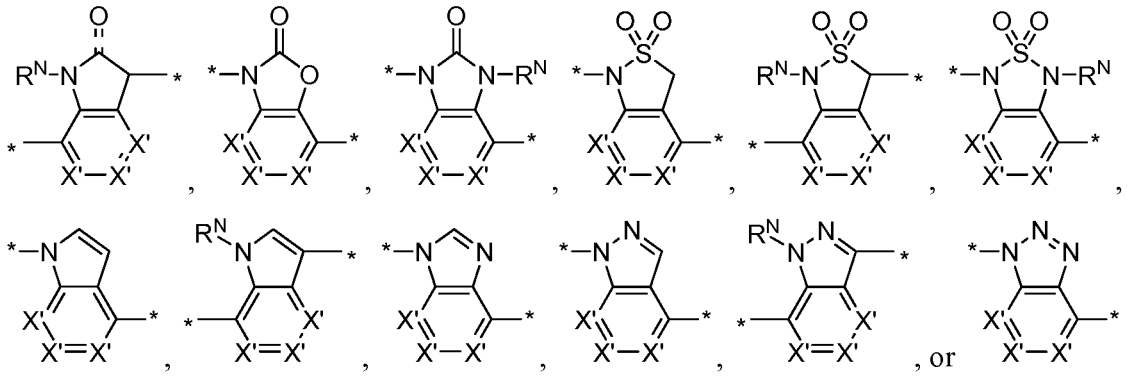
 ,  ,  , or  wherein * indicates attachment points to the remainder of the compound wherein no more than 2 of X are nitrogen.

[0181] In an eleventh embodiment of the first aspect, B and B′ together is

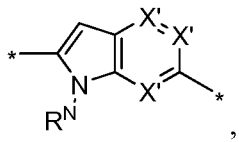


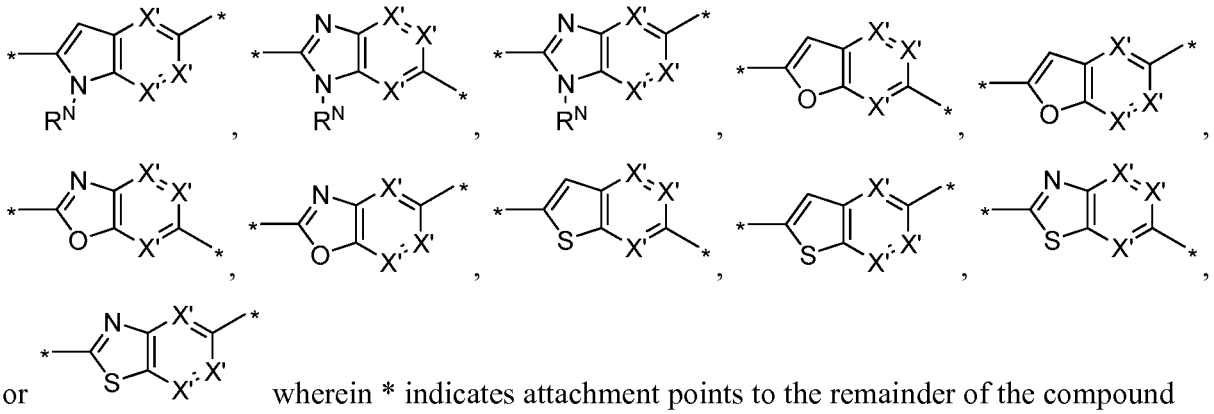
 , or wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

[0182] In a twelfth embodiment of the first aspect, B and B′ together is  ,



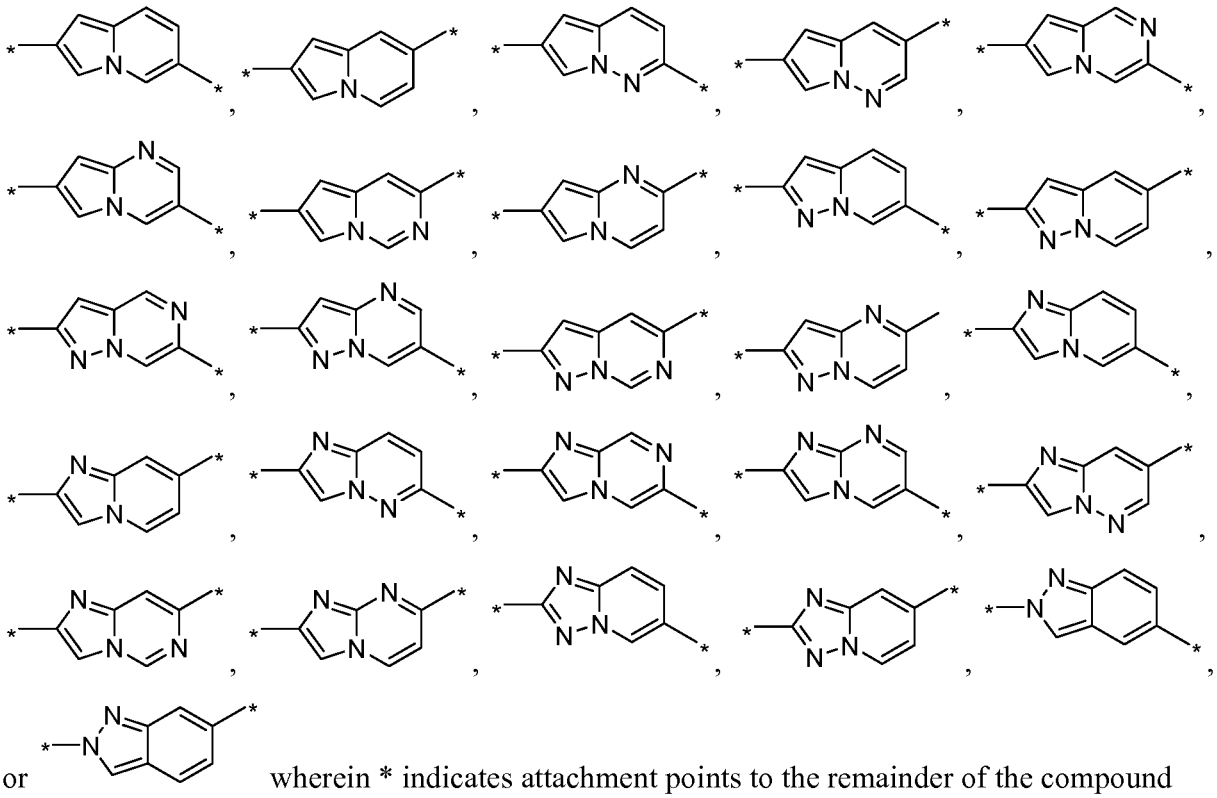
wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

[0183] In a thirteenth embodiment of the first aspect, B and B′ together is  ,

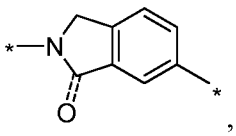


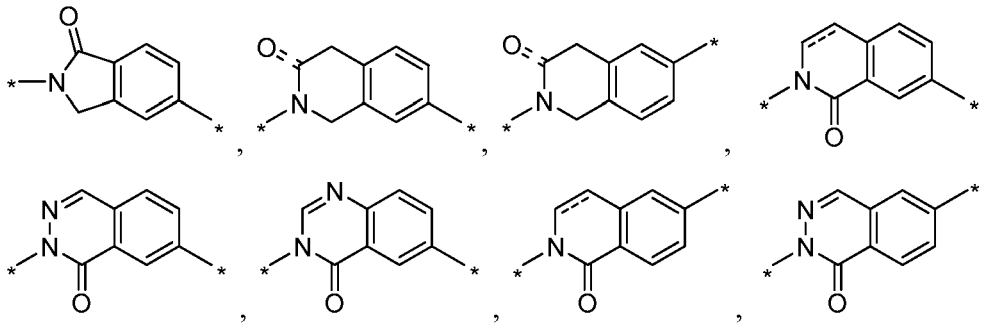
or wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

[0184] In a fourteenth embodiment of the first aspect, B and B′ together is

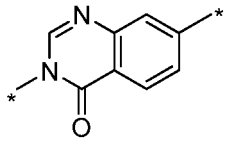


wherein * indicates attachment points to the remainder of the compound and the six-membered ring optionally contains one or two additional nitrogens as heteroatoms with the proviso that the total number of nitrogens in the six-membered ring does not exceed two.

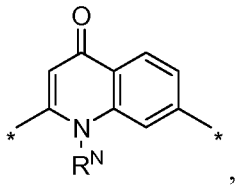
[0185] In a fifteenth embodiment of the first aspect, B and B′ together is  ,

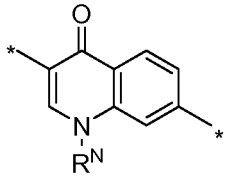
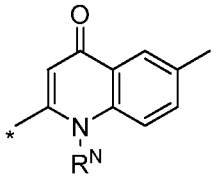
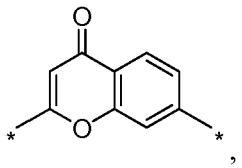
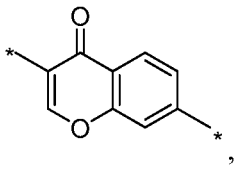
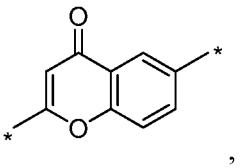


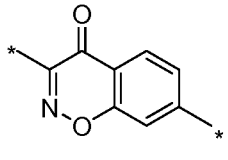
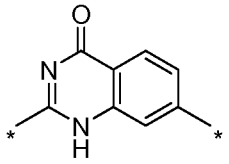
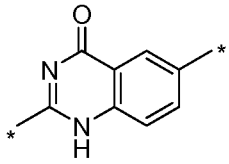
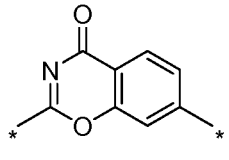
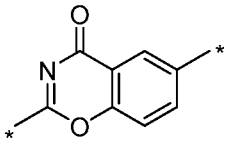
, or

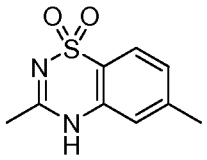
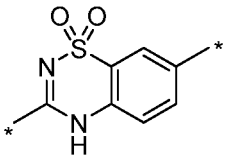


wherein * indicates attachment points to the remainder of the compound and the phenyl moiety optionally contains one or two nitrogens as heteroatoms.

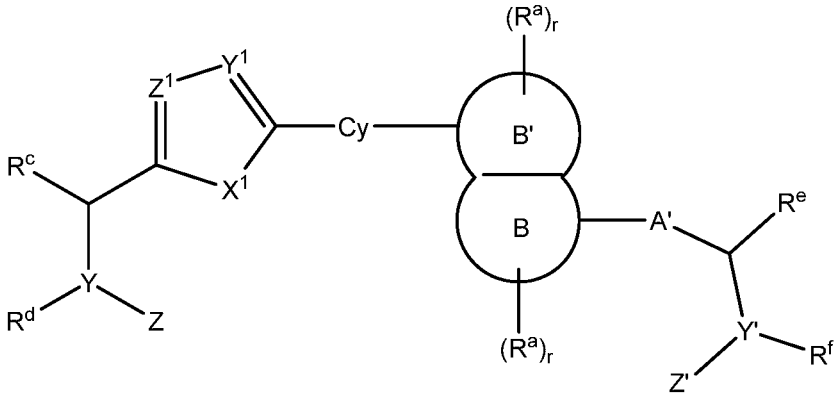
[0186] In a sixteenth embodiment of the first aspect, B and B′ together is  ,

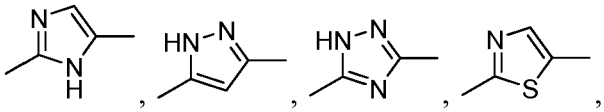
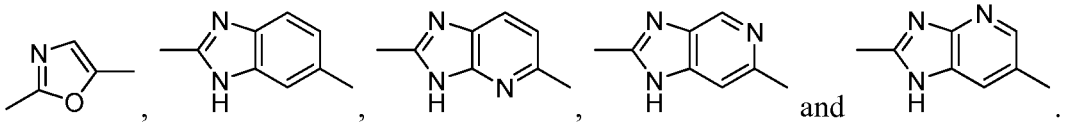
 ,  ,  ,  ,  ,

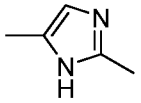
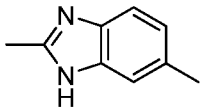
 ,  ,  ,  ,  ,

 , or  wherein * indicates attachment points to the remainder of the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and 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.

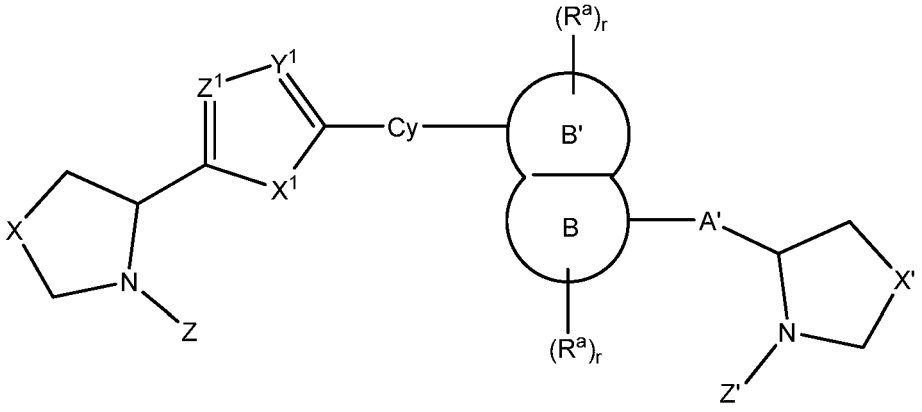
[0187] In a second aspect of the invention, compounds have formula II:



wherein A′ is selected from the group consisting of a single bond,  and  .

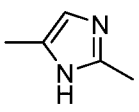
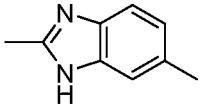
[0188] In a first embodiment of the second aspect, compounds have formula II wherein A′ is  or  .

[0189] In a second embodiment of the second aspect, compounds have formula IIa:

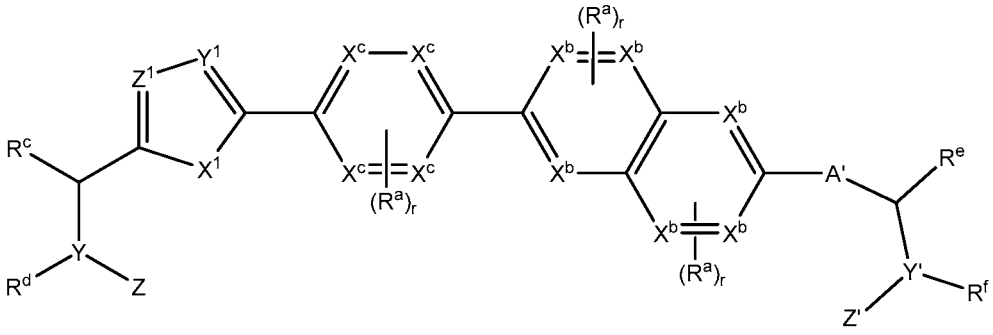


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, $–CH=CH–$, $–O–$, $–S–$, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0190] The compounds of the present invention include pharmaceutically acceptable salts of IIa as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

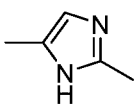
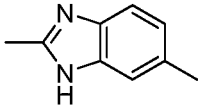
[0191] In a third embodiment of the second aspect, compounds have formula IIa wherein A′ is  or  .

[0192] In a fourth embodiment of the second aspect, compounds have formula IIb:

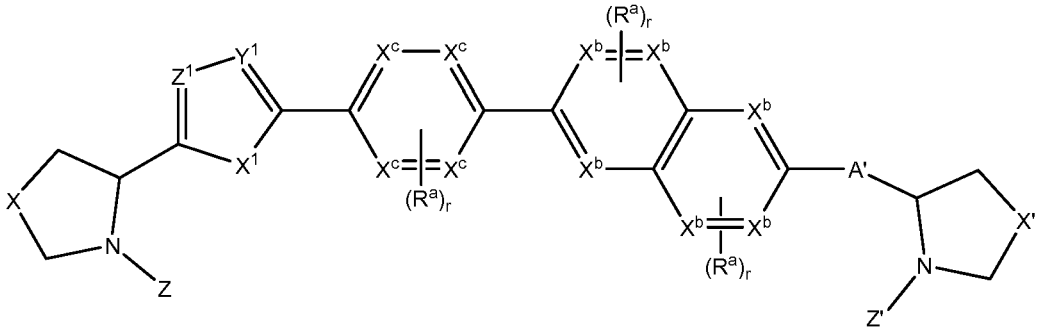


wherein each X^b and X^c is independently C or N.

[0193] The compounds of the present invention include pharmaceutically acceptable salts of IIb as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0194] In a fifth embodiment of the second aspect, compounds have formula IIb wherein A′ is  or  .

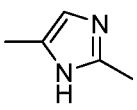
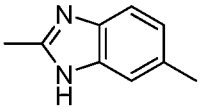
[0195] In a sixth embodiment of the second aspect, compounds have formula IIc:



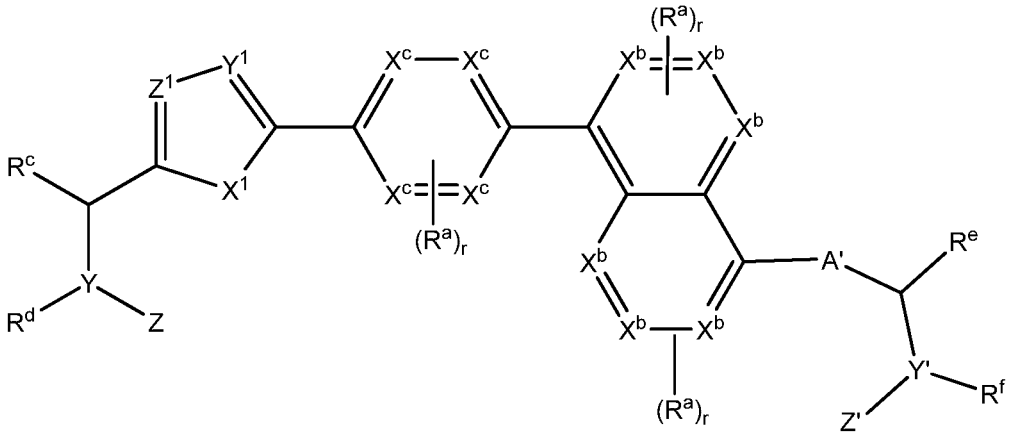
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and

–$CH_2N(R^1)$–, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0196] The compounds of the present invention include pharmaceutically acceptable salts of IIc as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

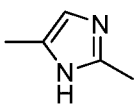
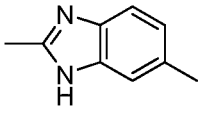
[0197] In a seventh embodiment of the second aspect, compounds have formula IIc wherein A′ is  or  .

[0198] In an eighth embodiment of the second aspect, compounds have formula IId:

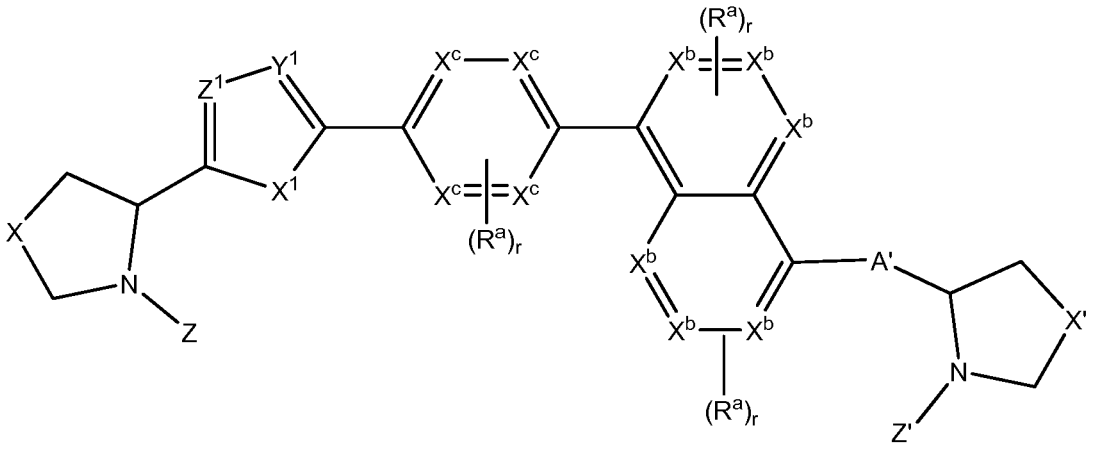


wherein each X^b and X^c is independently C or N.

[0199] The compounds of the present invention include pharmaceutically acceptable salts of IId as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0200] In a ninth embodiment of the second aspect, compounds have formula IId wherein A′ is  or  .

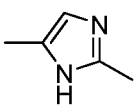
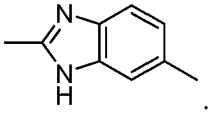
[0201] In a tenth embodiment of the second aspect, compounds have formula IIe:



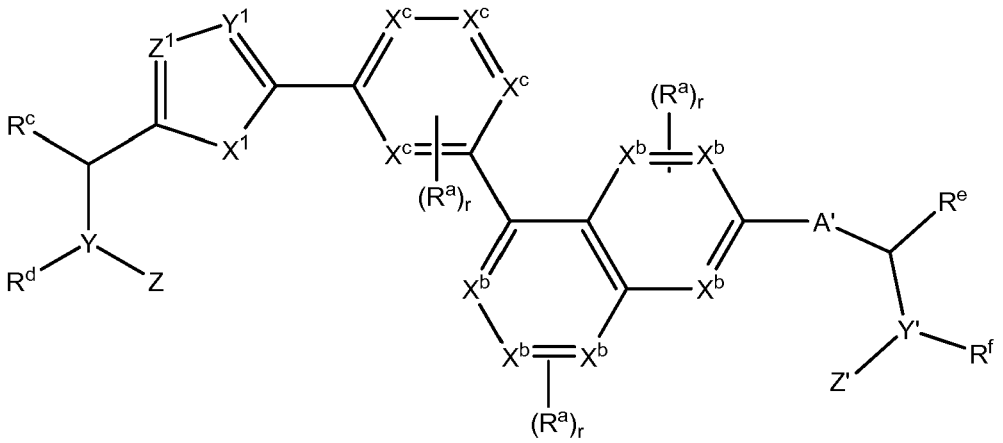
wherein

X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0202] The compounds of the present invention include pharmaceutically acceptable salts of IIe as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0203] In an eleventh embodiment of the second aspect, compounds have formula IIe wherein A′ is  or  .

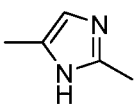
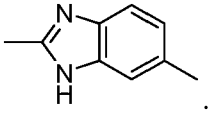
[0204] In a twelfth embodiment of the second aspect, compounds have formula IIf:



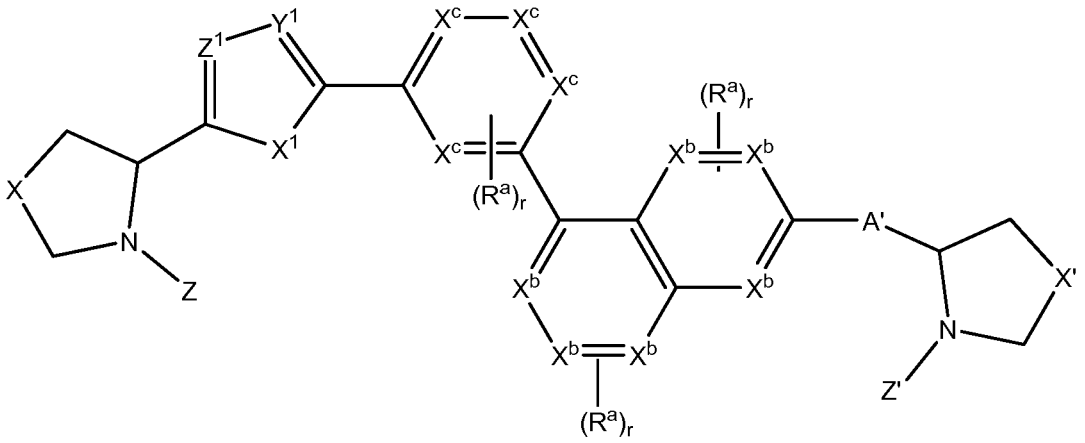
wherein each X^b and X^c is independently C or N.

[0205] The compounds of the present invention include pharmaceutically acceptable salts of IIf as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0206] In a thirteenth embodiment of the second aspect, compounds have formula IIf

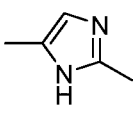
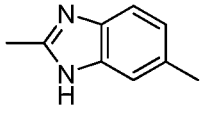
wherein A′ is  or  .

[0207] In a fourteenth embodiment of the second aspect, compounds have formula IIg:

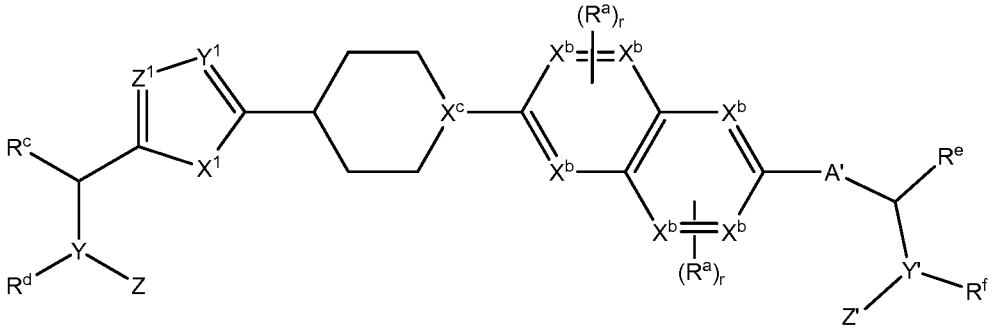


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0208] The compounds of the present invention include pharmaceutically acceptable salts of IIg as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

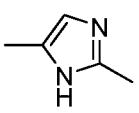
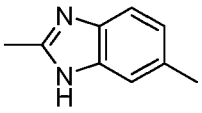
[0209] In a fifteenth embodiment of the second aspect, compounds have formula IIg wherein A′ is  or  .

[0210] In a sixteenth embodiment of the second aspect, compounds have formula IIh:

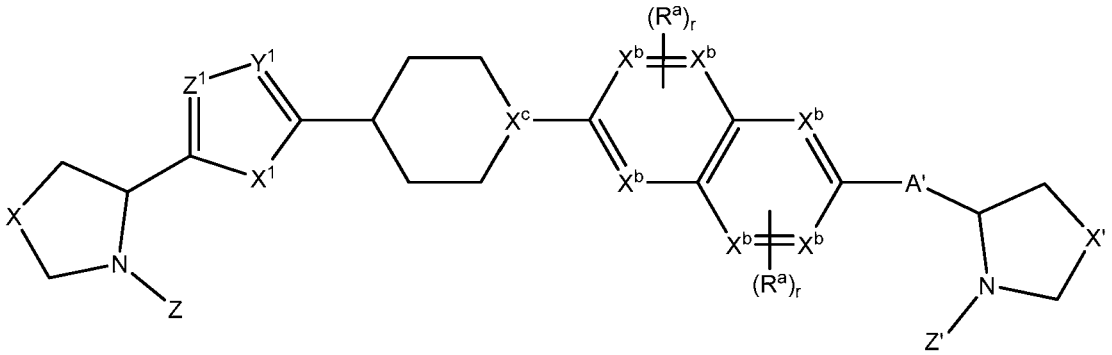


wherein X^c and each X^b is independently C or N.

[0211] The compounds of the present invention include pharmaceutically acceptable salts of IIh as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0212] In a seventeenth embodiment of the second aspect, compounds have formula IIh wherein A′ is  or  .

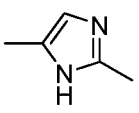
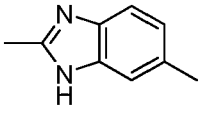
[0213] In an eighteenth embodiment of the second aspect, compounds have formula IIi:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0214] The compounds of the present invention include pharmaceutically acceptable salts of IIi as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

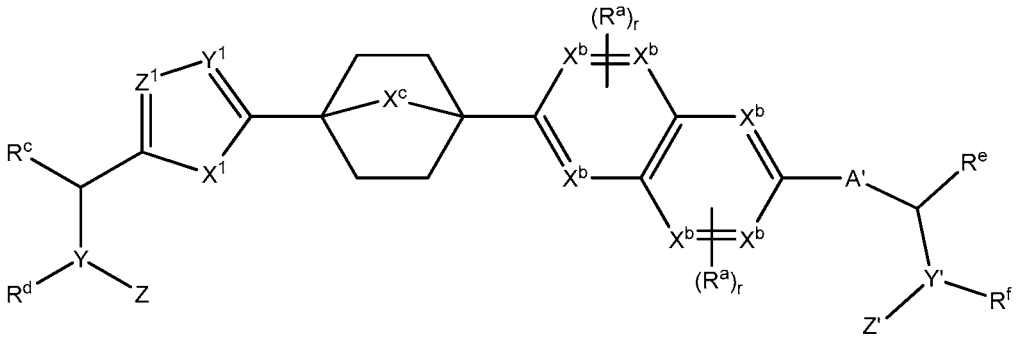
[0215] In a nineteenth embodiment of the second aspect, compounds have formula IIi

wherein A′ is  or  .

[0216] In a twentieth embodiment of the second aspect, compounds have formula IIh or IIi wherein X^c is C.

[0217] In an twenty-first embodiment of the second aspect, compounds have formula IIh or IIi wherein X^c is N.

[0218] In a twenty-second embodiment of the second aspect, compounds have formula IIj:



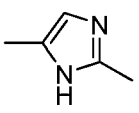
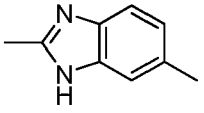
wherein

X^c is $–CH_2–$, –NH– or $–CH_2–CH_2–$; and

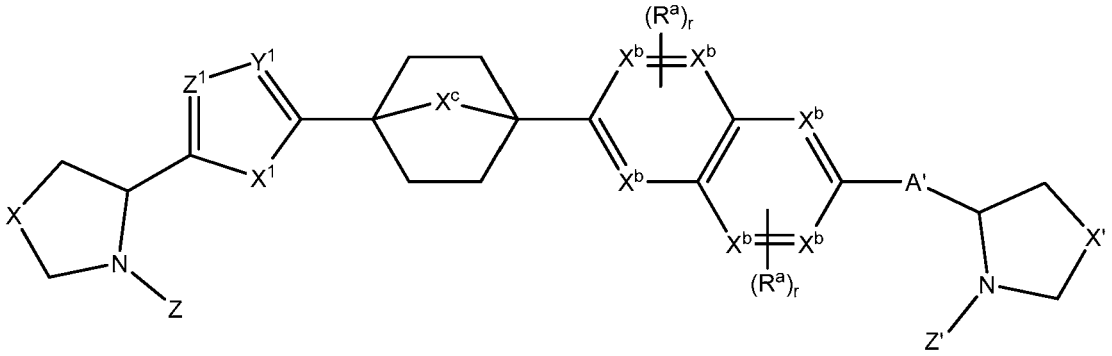
each X^b is independently C or N.

[0219] The compounds of the present invention include pharmaceutically acceptable salts of IIj as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0220] In a twenty-third embodiment of the second aspect, compounds have formula IIj

wherein A′ is  or  .

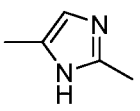
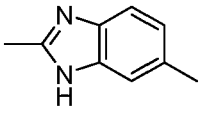
[0221] In a twenty-fourth embodiment of the second aspect, compounds have formula IIk:



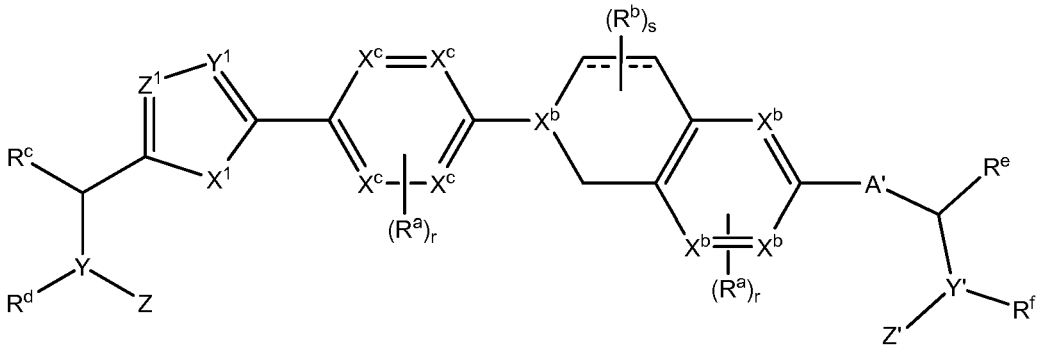
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0222] The compounds of the present invention include pharmaceutically acceptable salts of IIk as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0223] In a twenty-fifth embodiment of the second aspect, compounds have formula IIk

wherein A′ is  or  .

[0224] In a twenty-sixth embodiment of the second aspect, compounds have formula III:



wherein:

each X^b and X^c is independently C or N;

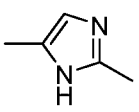
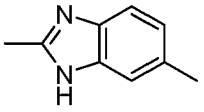
each R^b is selected from the group consisting of oxo, -OH, -CN, $-NO_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy,

alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; and

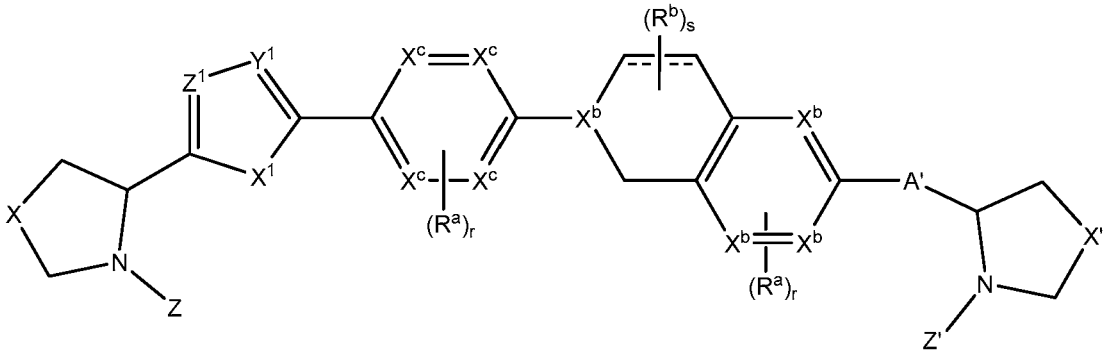
s is 0, 1, 2, or 3.

[0225] The compounds of the present invention include pharmaceutically acceptable salts of III as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0226] In a twenty-seventh embodiment of the second aspect, compounds have formula III

wherein A′ is  or  .

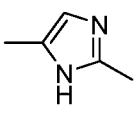
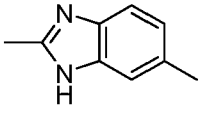
[0227] In a twenty-eighth embodiment of the second aspect, compounds have formula IIm:



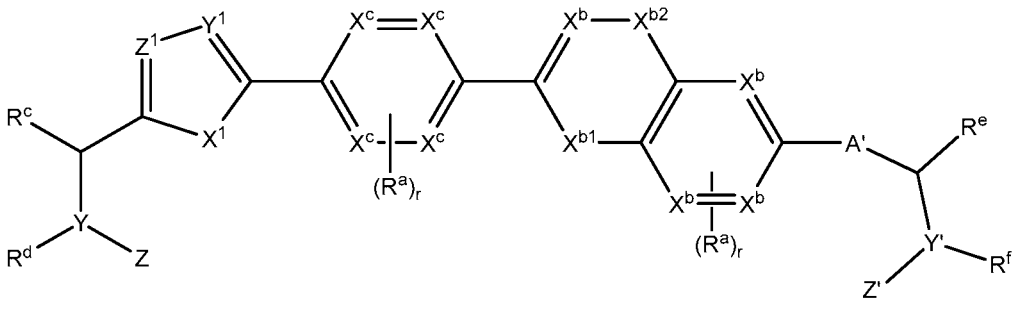
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0228] The compounds of the present invention include pharmaceutically acceptable salts of IIm as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0229] In a twenty-ninth embodiment of the second aspect, compounds have formula IIm

wherein A′ is  or  .

[0230] In a thirtieth embodiment of the second aspect, compounds have formula IIn:



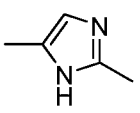
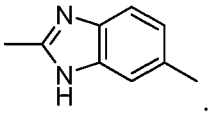
wherein:

each X^b and X^c is independently C or N;

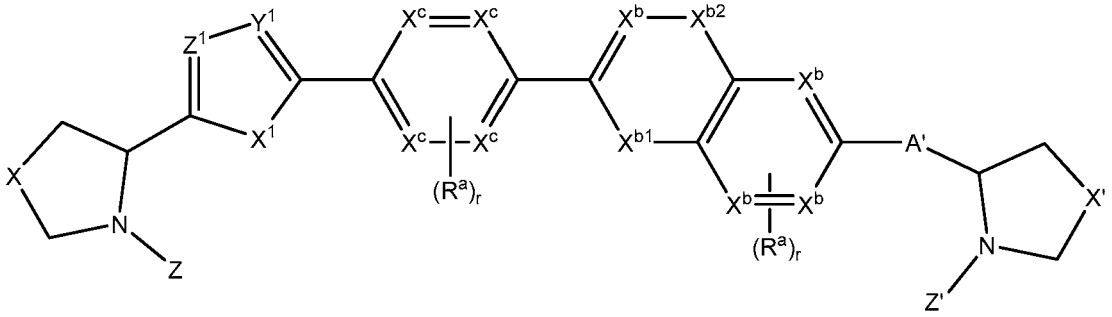
X^{b1} is N or O; and

X^{b2} is $S(O)_2$ or C(O).

[0231] The compounds of the present invention include pharmaceutically acceptable salts of IIn as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0232] In a thirty-first embodiment of the second aspect, compounds have formula IIn wherein A′ is  or  .

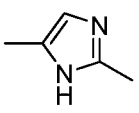
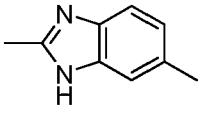
[0233] In a thirty-second embodiment of the second aspect, compounds have formula IIo:



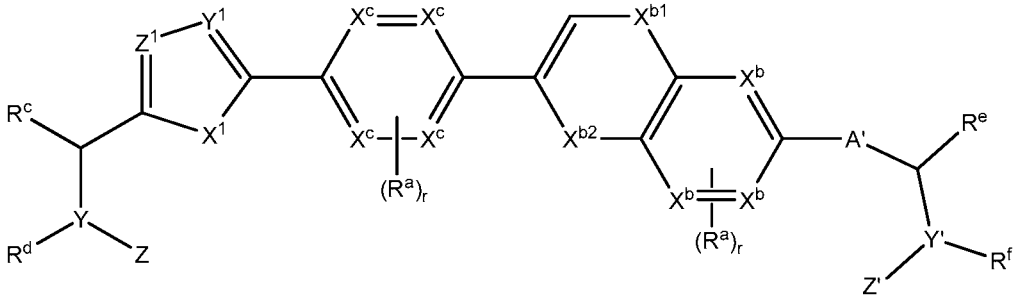
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0234] The compounds of the present invention include pharmaceutically acceptable salts of IIo as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0235] In a thirty-third embodiment of the second aspect, compounds have formula IIo

wherein A′ is  or  .

[0236] In an thirty-fourth embodiment of the second aspect, compounds have formula IIp:



wherein:

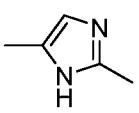
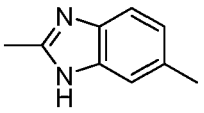
each X^b and X^c is independently C or N;

X^{b1} is N or O; and

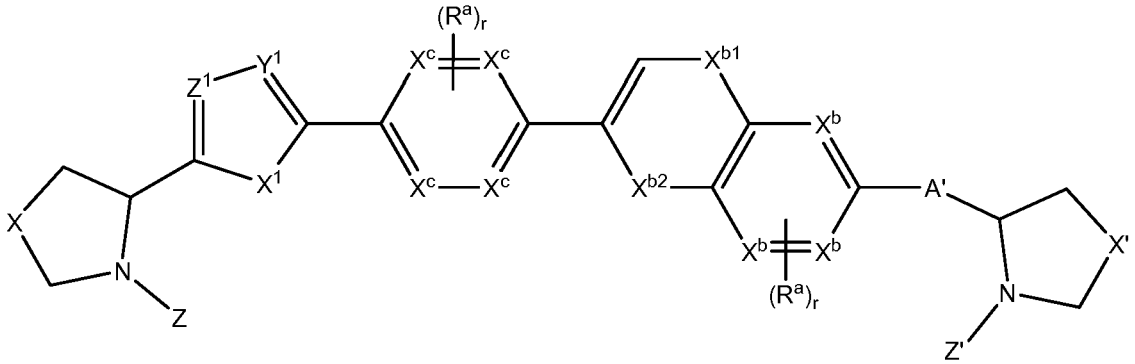
X^{b2} is $S(O)_2$ or C(O).

[0237] The compounds of the present invention include pharmaceutically acceptable salts of IIp as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0238] In a thirty-fifth embodiment of the second aspect, compounds have formula IIp

wherein A′ is  or  .

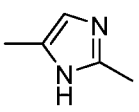
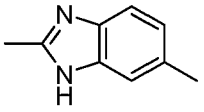
[0239] In a thirty-sixth embodiment of the second aspect, compounds have formula IIq:



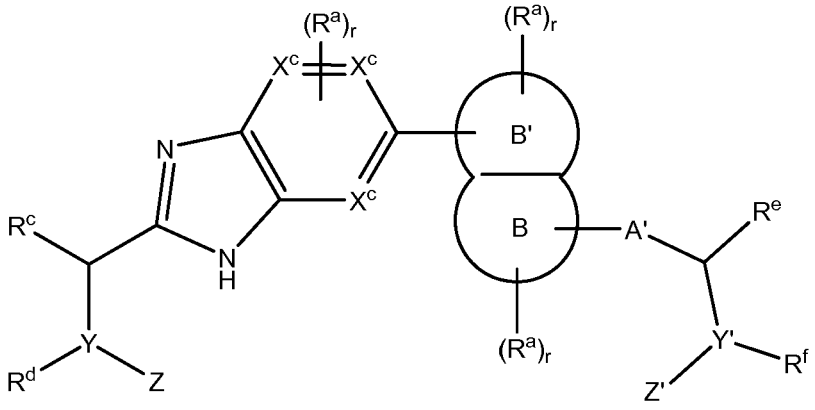
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and

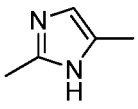
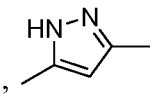
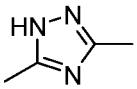
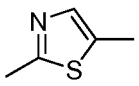
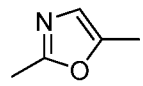
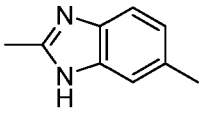
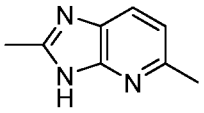
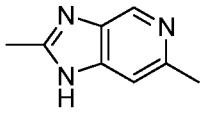
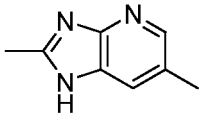
–$CH_2N(R^1)$–, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0240] The compounds of the present invention include pharmaceutically acceptable salts of IIq as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0241] In a thirty-seventh embodiment of the second aspect, compounds have formula IIq wherein A′ is  or  .

[0242] In a third aspect of the invention, compounds have formula III:

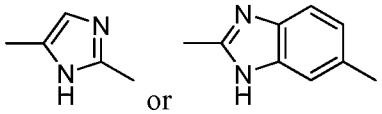


wherein A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^c is independently C or N.

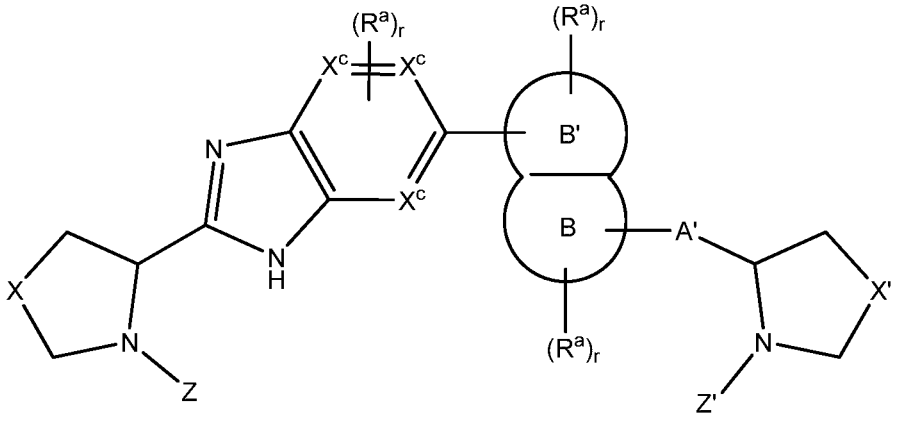
[0243] The compounds of the present invention include pharmaceutically acceptable salts of III as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0244] In a first embodiment of the third aspect, compounds have formula III wherein A′ is



.

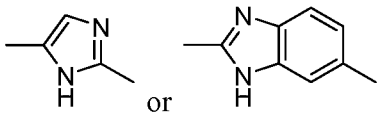
[0245] In a second embodiment of the third aspect, compounds have formula IIIa:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, $–CH=CH–$, $–O–$, $–S–$, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

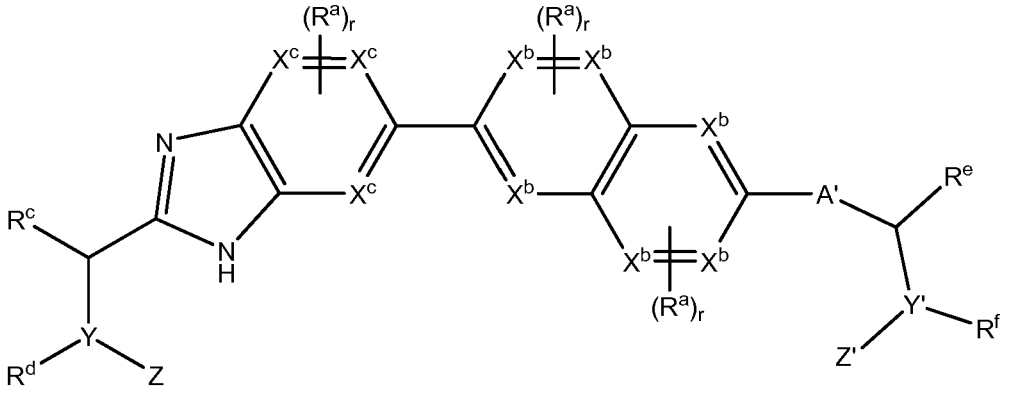
[0246] The compounds of the present invention include pharmaceutically acceptable salts of IIIa as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0247] In a third embodiment of the third aspect, compounds have formula IIIa wherein A′ is



.

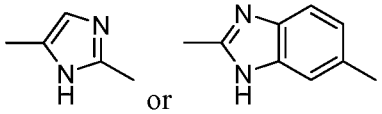
[0248] In a fourth embodiment of the third aspect, compounds have formula IIIb:



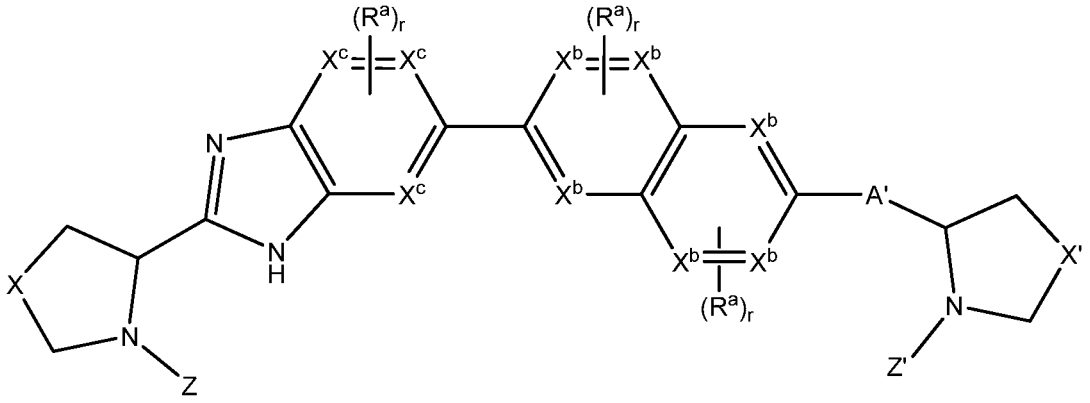
wherein each X^b is independently C or N.

[0249] The compounds of the present invention include pharmaceutically acceptable salts of IIIb as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0250] In a fifth embodiment of the third aspect, compounds have formula IIIb wherein A′ is



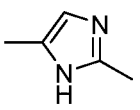
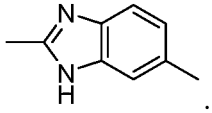
[0251] In a sixth embodiment of the third aspect, compounds have formula IIIc:



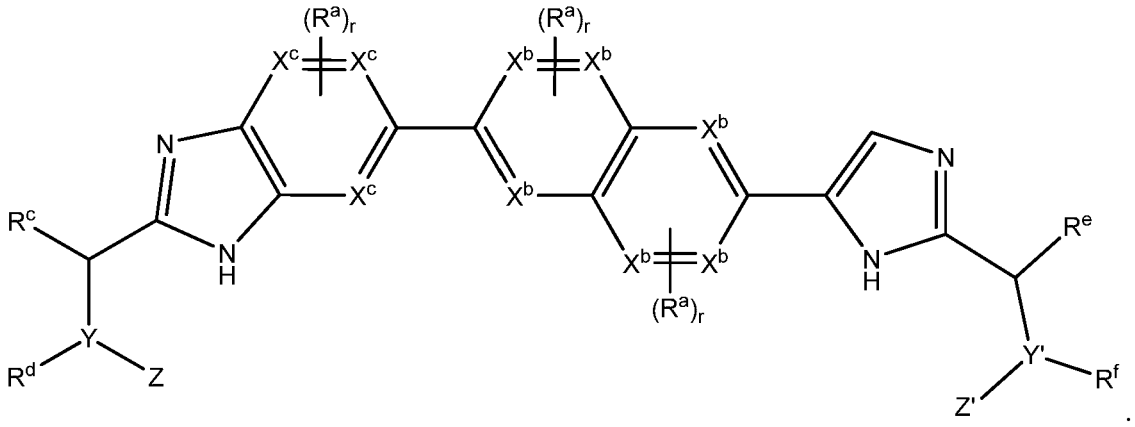
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0252] The compounds of the present invention include pharmaceutically acceptable salts of IIIc as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0253] In a seventh embodiment of the third aspect, compounds have formula IIIc wherein

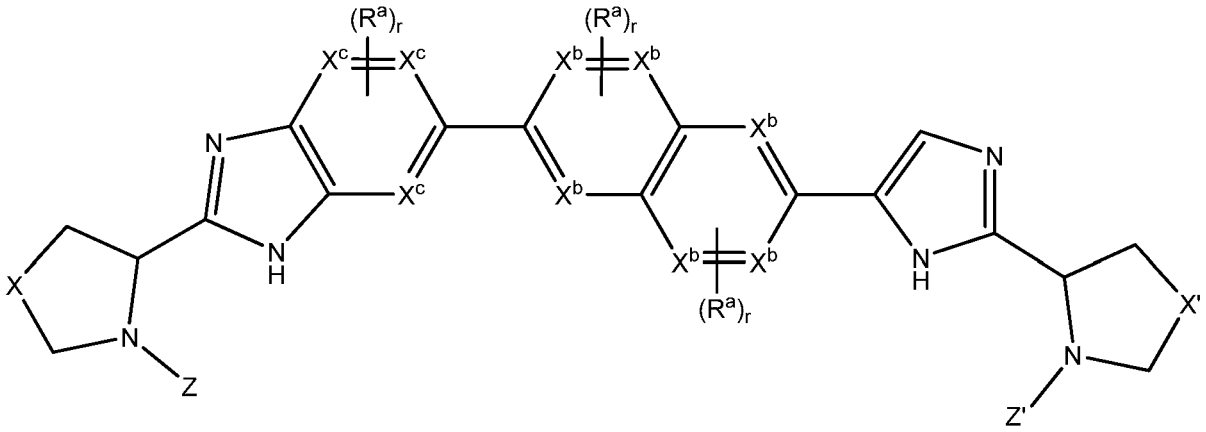
A′ is  or  .

[0254] In an eighth embodiment of the third aspect, compounds have formula IIId:



[0255] The compounds of the present invention include pharmaceutically acceptable salts of IIId as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0256] In a ninth embodiment of the third aspect, compounds have formula IIIe:

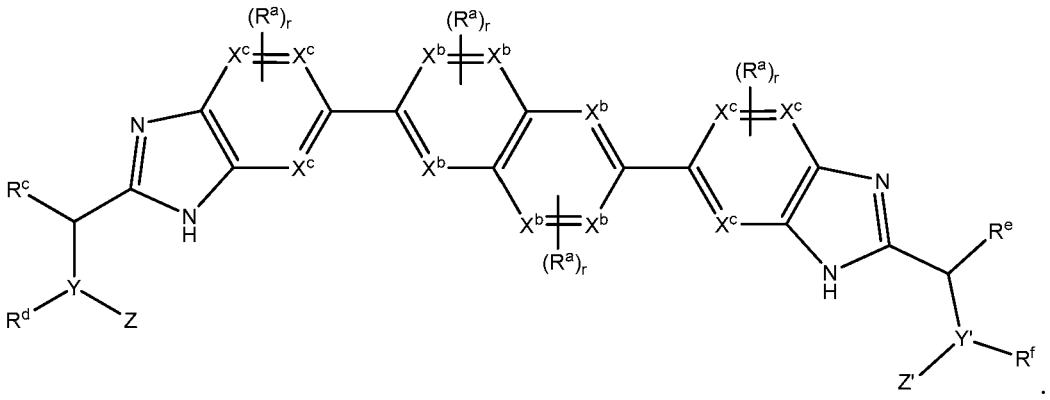


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl,

carbamoyl and substituted sulfonyl.

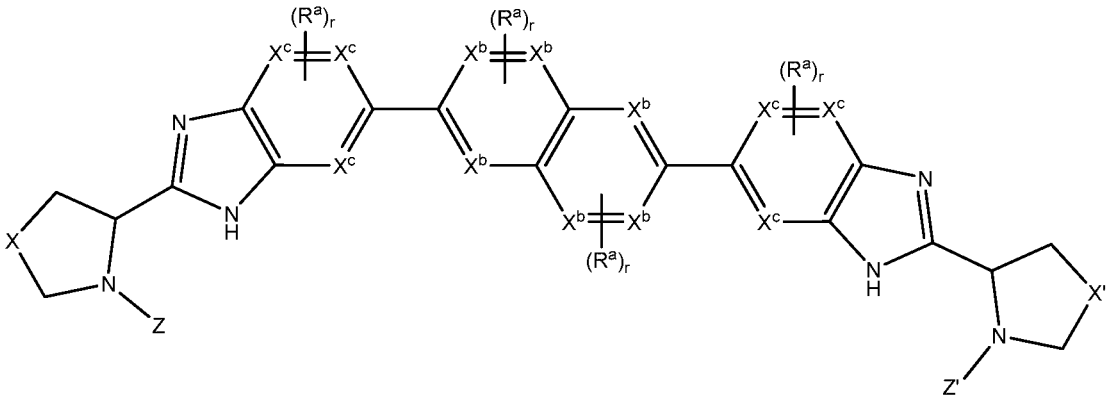
[0257] The compounds of the present invention include pharmaceutically acceptable salts of IIIe as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0258] In a tenth embodiment of the third aspect, compounds have formula IIIf:



[0259] The compounds of the present invention include pharmaceutically acceptable salts of IIIf as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

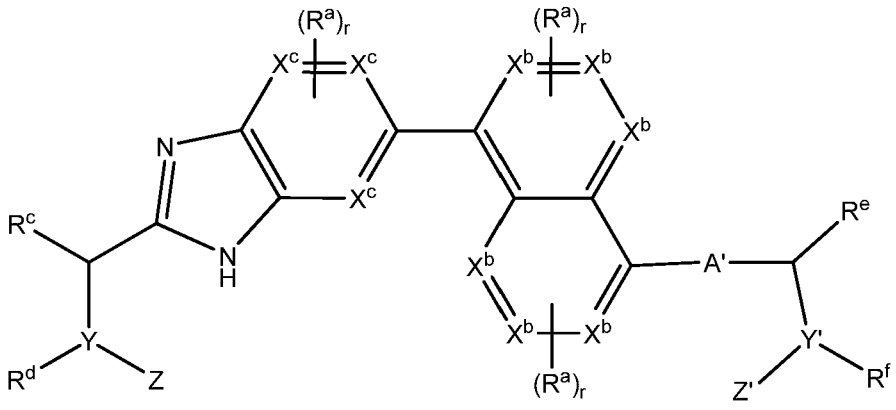
[0260] In an eleventh embodiment of the third aspect, compounds have formula IIIg:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

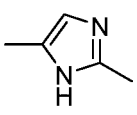
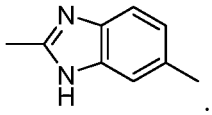
[0261] The compounds of the present invention include pharmaceutically acceptable salts of IIIg as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0262] In a twelfth embodiment of the third aspect, compounds have formula IIIh:

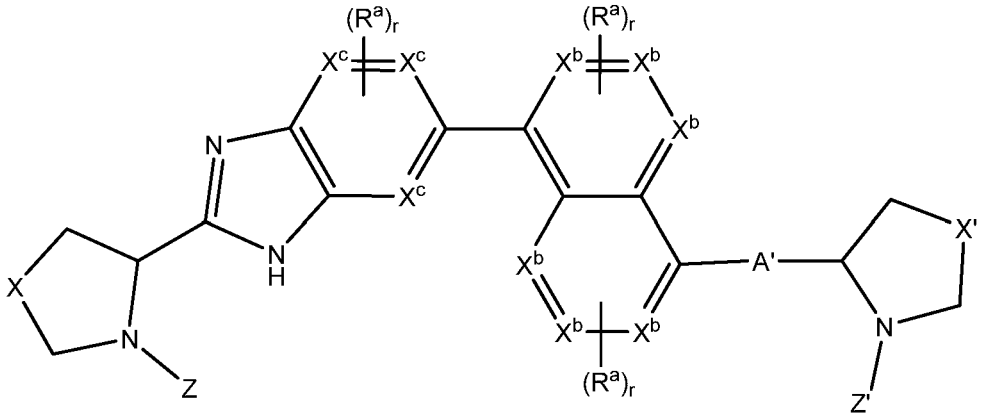


wherein each X^b is independently C or N.

[0263] The compounds of the present invention include pharmaceutically acceptable salts of IIIh as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0264] In a thirteenth embodiment of the third aspect, compounds have formula IIIh wherein A′ is  or  .

[0265] In a fourteenth embodiment of the third aspect, compounds have formula IIIi:

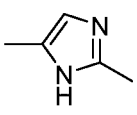
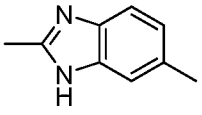


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to

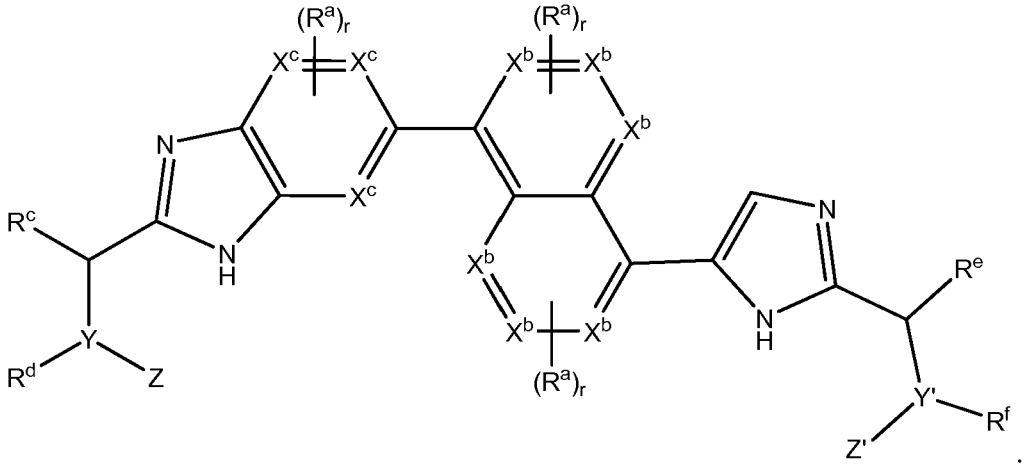
C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0266] The compounds of the present invention include pharmaceutically acceptable salts of IIIi as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0267] In a fifteenth embodiment of the third aspect, compounds have formula IIIi wherein

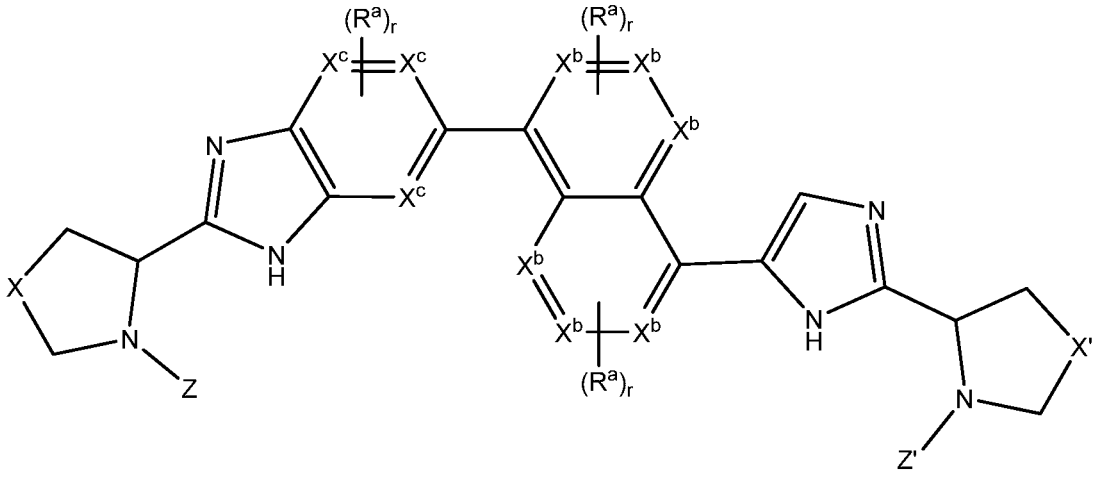
A′ is  or  .

[0268] In a sixteenth embodiment of the third aspect, compounds have formula IIIj:



[0269] The compounds of the present invention include pharmaceutically acceptable salts of IIIj as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0270] In a seventeenth embodiment of the third aspect, compounds have formula IIIk:

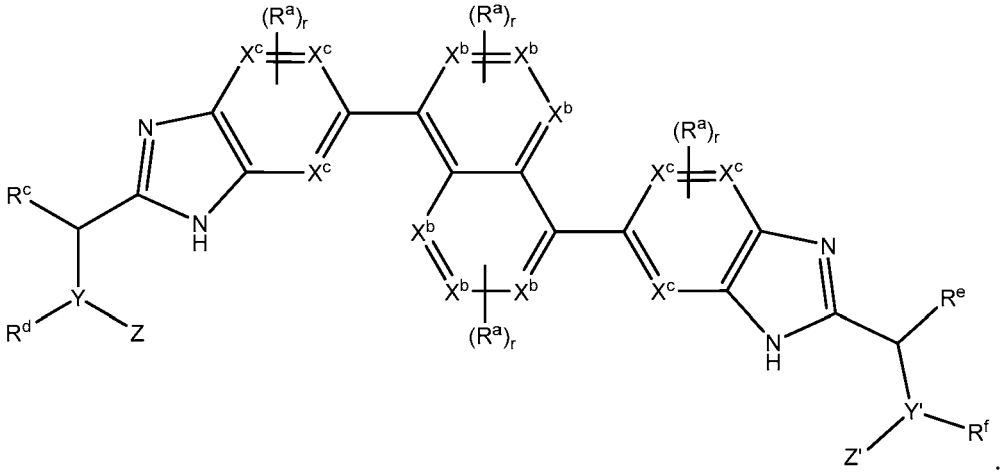


wherein

X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0271] The compounds of the present invention include pharmaceutically acceptable salts of IIIk as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

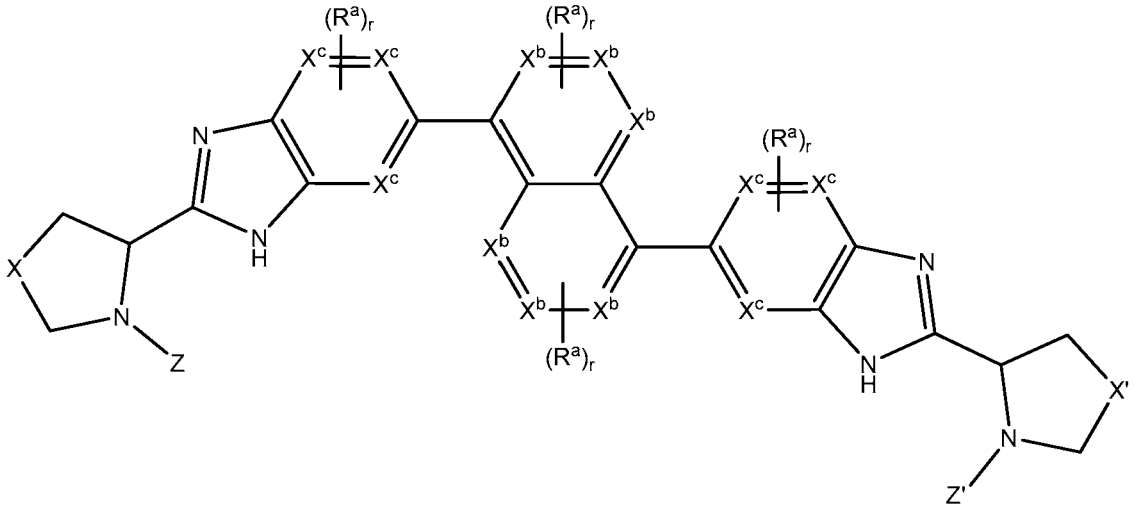
[0272] In an eighteenth embodiment of the third aspect, compounds have formula IIIl:



.

[0273] The compounds of the present invention include pharmaceutically acceptable salts of IIIl as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

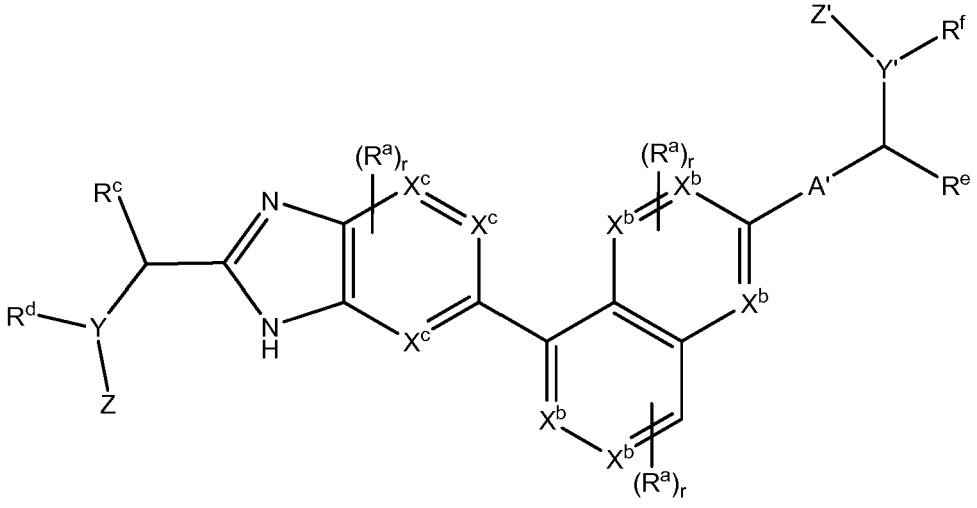
[0274] In a nineteenth embodiment of the third aspect, compounds have formula IIIm:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0275] The compounds of the present invention include pharmaceutically acceptable salts of IIIm as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

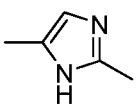
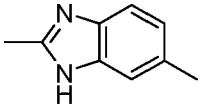
[0276] In a twentieth embodiment of the third aspect, compounds have formula IIIn:



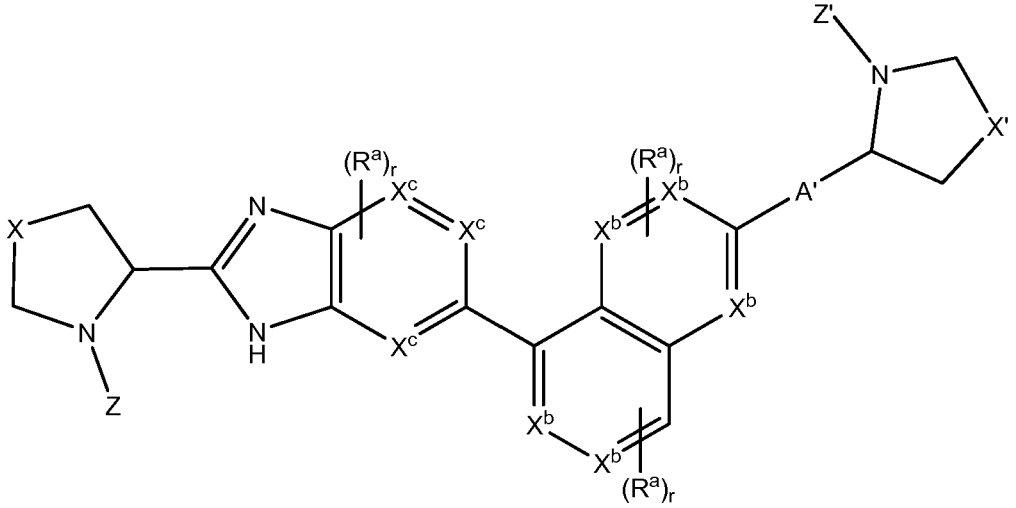
wherein each X^b is independently C or N.

[0277] The compounds of the present invention include pharmaceutically acceptable salts of IIIn as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0278] In a twenty-first embodiment of the third aspect, compounds have formula IIIn

wherein A′ is  or  .

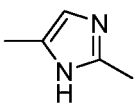
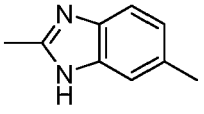
[0279] In a twenty-second embodiment of the third aspect, compounds have formula IIIo:



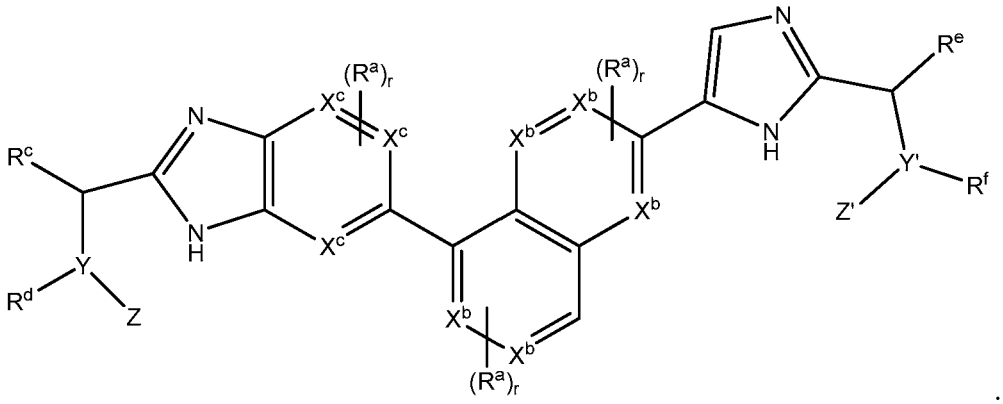
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0280] The compounds of the present invention include pharmaceutically acceptable salts of IIIo as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0281] In a twenty-third embodiment of the third aspect, compounds have formula IIIo

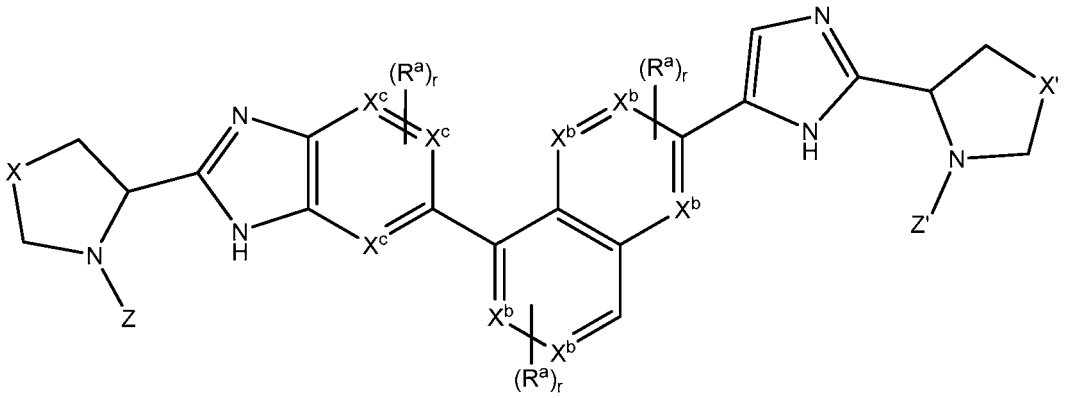
wherein A′ is  or  .

[0282] In a twenty-fourth embodiment of the third aspect, compounds have formula IIIp:



[0283] The compounds of the present invention include pharmaceutically acceptable salts of IIIp as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

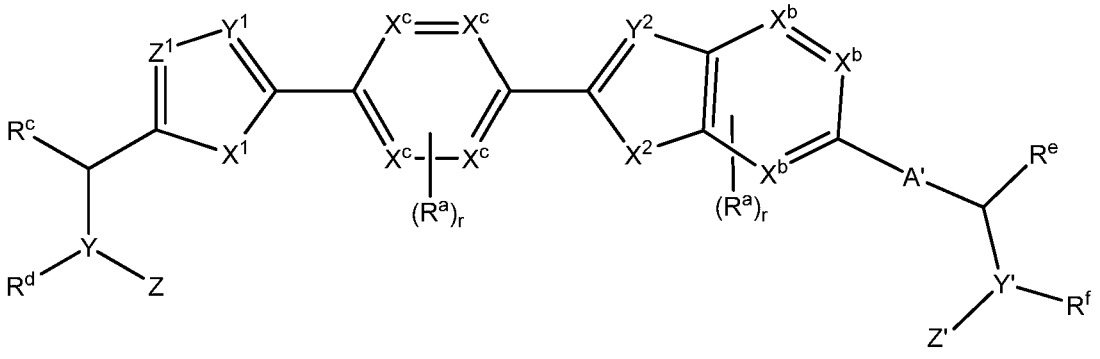
[0284] In a twenty-fifth embodiment of the third aspect, compounds have formula IIIq:



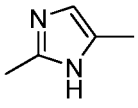
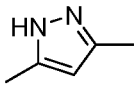
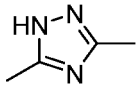
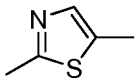
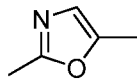
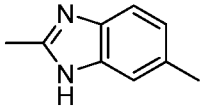
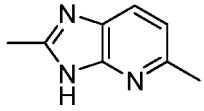
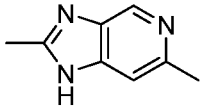
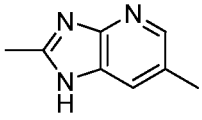
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0285] The compounds of the present invention include pharmaceutically acceptable salts of IIIq as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0286] In a fourth aspect of the invention, compounds have formula IV:

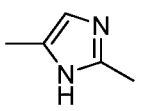
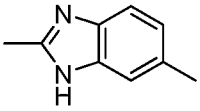


wherein:

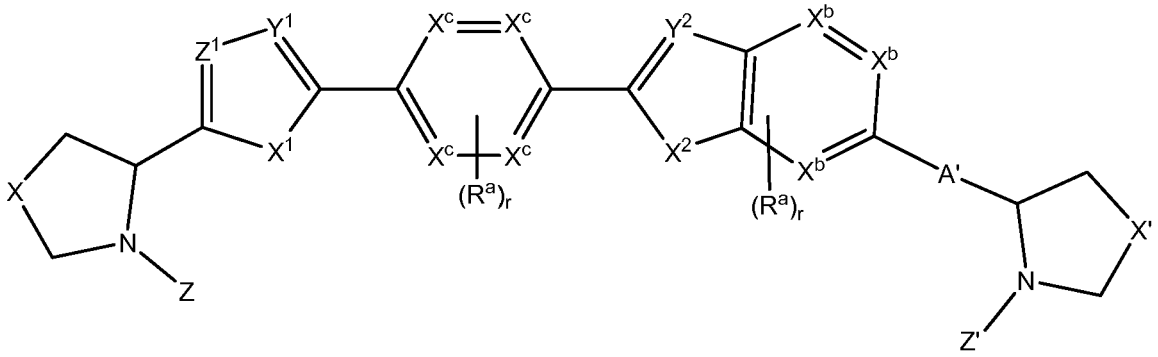
A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^b and X^c is independently C or N.

[0287] The compounds of the present invention include pharmaceutically acceptable salts of IV as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

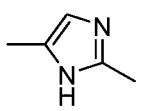
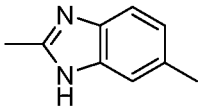
[0288] In a first embodiment of the fourth aspect, compounds have formula IV wherein A′ is  or  .

[0289] In a second embodiment of the fourth aspect, compounds have formula IVa:

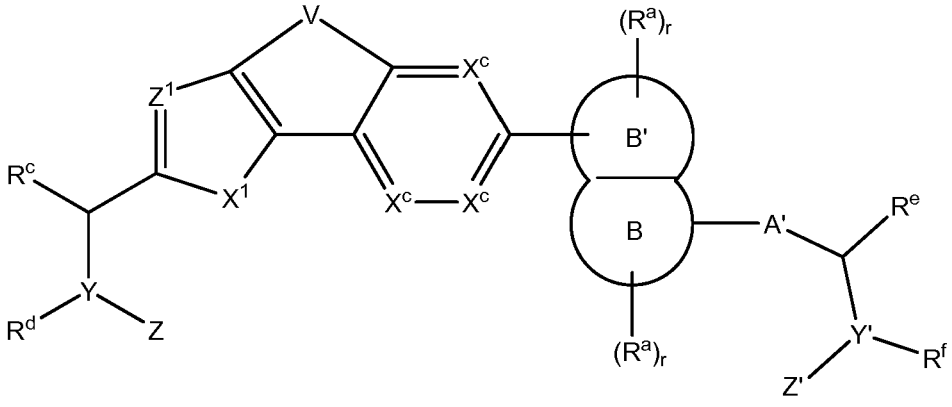


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

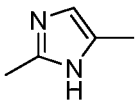
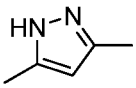
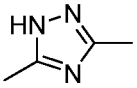
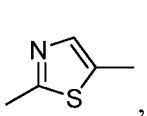
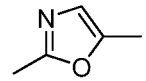
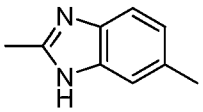
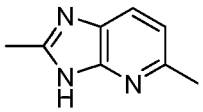
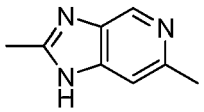
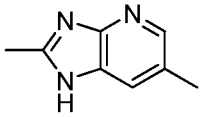
[0290] The compounds of the present invention include pharmaceutically acceptable salts of IVa as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0291] In a third embodiment of the fourth aspect, compounds have formula IVa wherein A′ is  or  .

[0292] In a fifth aspect of the invention, compounds have formula V:



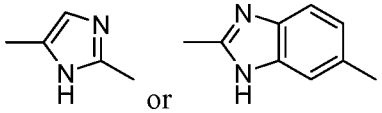
wherein:

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

each X^c is independently C or N with the proviso that no more than two X^c are N.

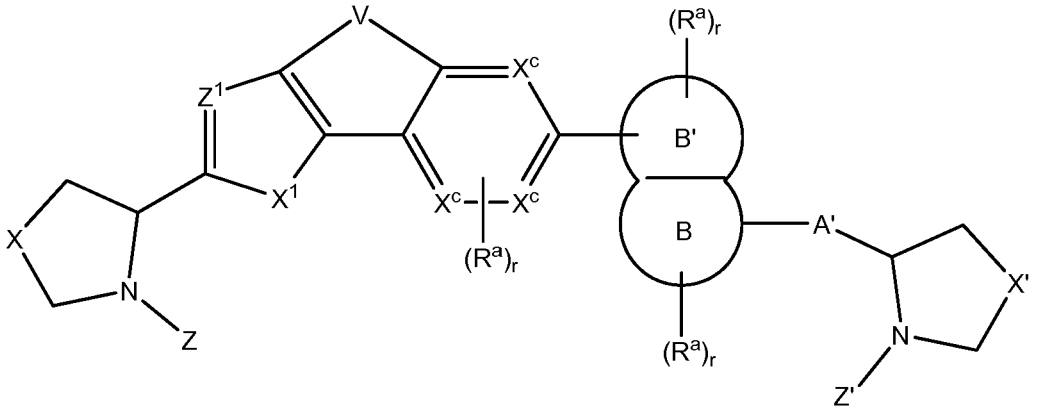
[0293] The compounds of the present invention include pharmaceutically acceptable salts of V as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0294] In a first embodiment of the fifth aspect, compounds have formula V wherein A′ is



.

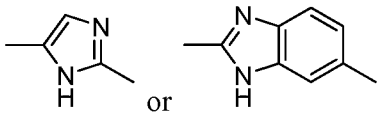
[0295] In a second embodiment of the fifth aspect, compounds have formula Va:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

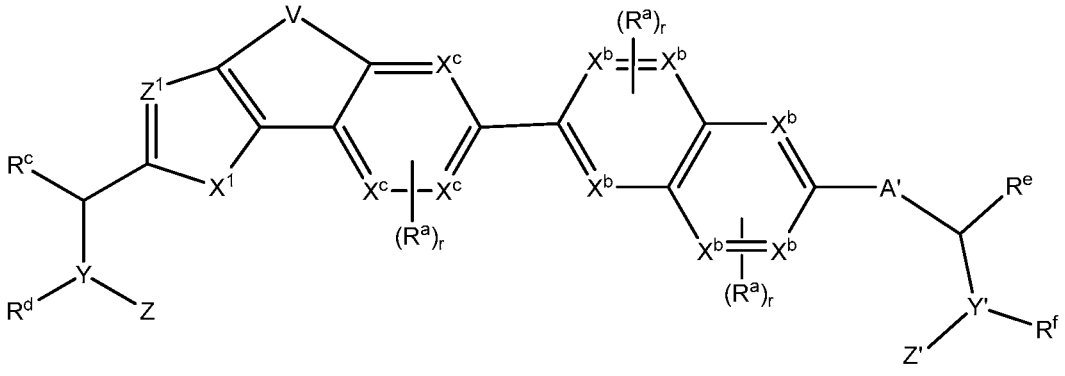
[0296] The compounds of the present invention include pharmaceutically acceptable salts of Va as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0297] In a third embodiment of the fifth aspect, compounds have formula Va wherein A′ is



.

[0298] In a fourth embodiment of the fifth aspect, compounds have formula Vb:

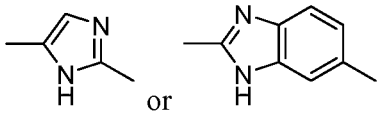


wherein

each X^b is independently C or N.

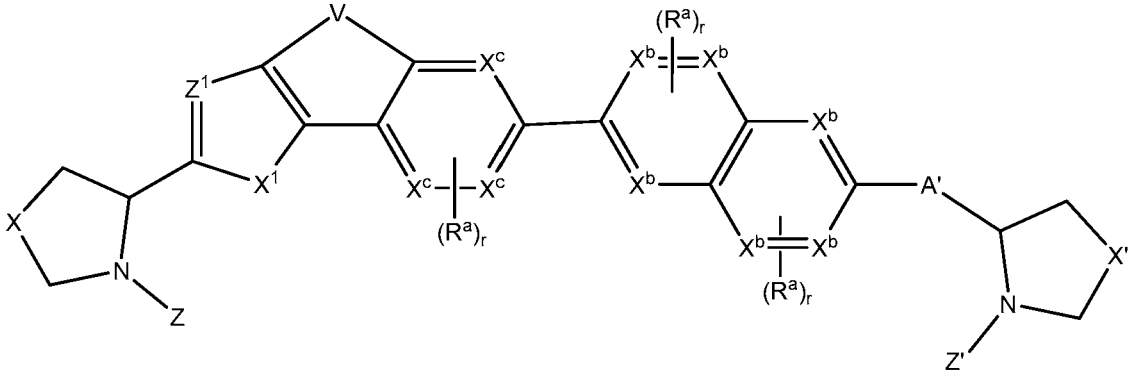
[0299] The compounds of the present invention include pharmaceutically acceptable salts of Vb as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0300] In a fifth embodiment of the fifth aspect, compounds have formula Vb wherein A′ is



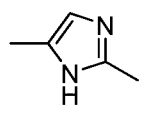
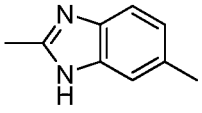
.

[0301] In a sixth embodiment of the fifth aspect, compounds have formula Vc:

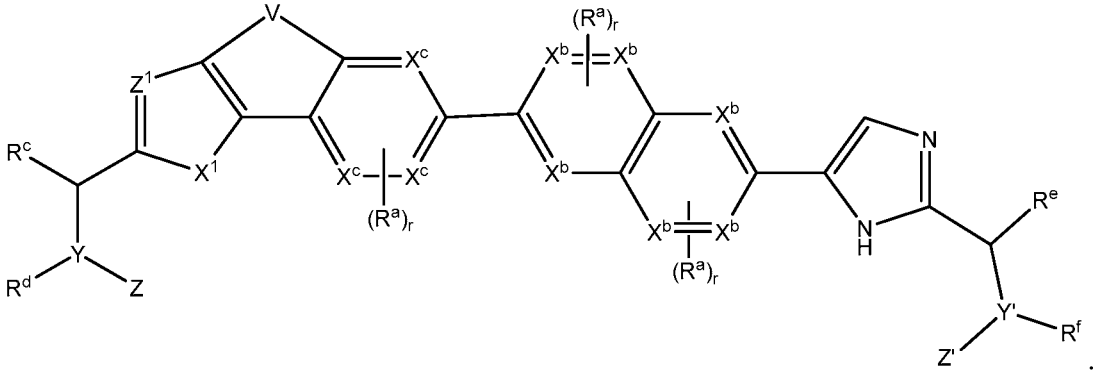


wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0302] The compounds of the present invention include pharmaceutically acceptable salts of Vc as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

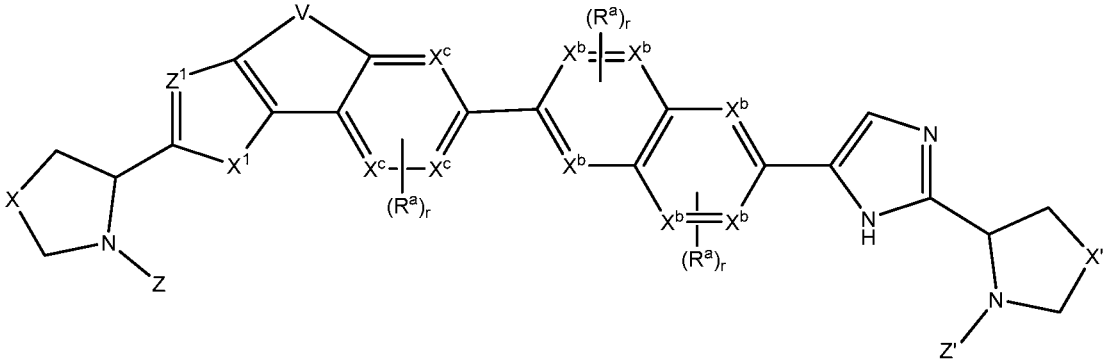
[0303] In a seventh embodiment of the fifth aspect, compounds have formula Vc wherein A′ is  or  .

[0304] In an eighth embodiment of the fifth aspect, compounds have formula Vd:



[0305] The compounds of the present invention include pharmaceutically acceptable salts of Vd as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0306] In a ninth embodiment of the fifth aspect, compounds have formula Ve:



wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[0307] The compounds of the present invention include pharmaceutically acceptable salts of Ve as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0308] In a sixth aspect of the invention, in any compound of any of the second through fifth aspects, 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.

[0309] In a first embodiment of the sixth aspect, R^c and R^d or R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

[0310] In a second embodiment of the sixth aspect, both of R^c and R^d and R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

[0311] In a seventh aspect of the invention, each R^a, if present in any of the other aspects of the invention, is independently –CN,–$OCHF_2$, –OCF_3, –CF_3, or –F.

[0312] In an eighth aspect of the invention, if present in any compound of any of the other aspects, one of Y and Y′ is N.

[0313] In a first embodiment of the eighth aspect, both Y and Y′ are N.

[0314] In a ninth aspect of the invention, Z and Z′ in any of the previous aspects are each 1-3 amino acids.

[0315] In a first embodiment of the ninth aspect, the amino acids are in the D configuration.

[0316] In a tenth aspect of the invention, Z and Z′ in any of the previous aspects 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 $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-O-(CR^4{}_2)_t-R^8$.

[0317] In a first embodiment of the tenth aspect, both of Z and Z′ are $-[U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0318] In a second embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0319] In a third embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0320] In a fourth embodiment of the tenth aspect, one or both of Z and Z′ are $-[C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0321] In a fifth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-U-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0322] In a sixth embodiment of the tenth aspect, one or both of Z and Z′ are $-[C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t]_u-C(O)-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0323] In a seventh embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^5-(CR^4{}_2)_t-C(O)-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0324] In an eighth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-NR^7-(CR^4{}_2)_t-R^8$.

[0325] In a ninth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_n-NR^7-(CR^4{}_2)_n-C(O)\text{-}R^{81}$.

[0326] In a tenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_n-NR^7-C(O)\text{-}R^{81}$.

[0327] In an eleventh embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_n-NR^7-(CR^4{}_2)_n-C(O)\text{-}O\text{-}R^{81}$.

[0328] In a twelfth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_n-NR^7-C(O)\text{-}O\text{-}R^{81}$.

[0329] In a thirteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4{}_2)_t-R^8$.

[0330] In a fourteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4{}_2)_t-R^8$.

[0331] In a fifteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0332] In a sixteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0333] In a seventeenth embodiment of the tenth aspect, one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

[0334] In an eighteenth embodiment of the tenth aspect, one or both of Z and Z′ are $-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

General Synthesis

[0335] The following schemes exemplify some of the synthetic routes that are used for the preparations of compounds and their analogs included in this invention. These 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.

[0336] The following abbreviations are used throughout this application:

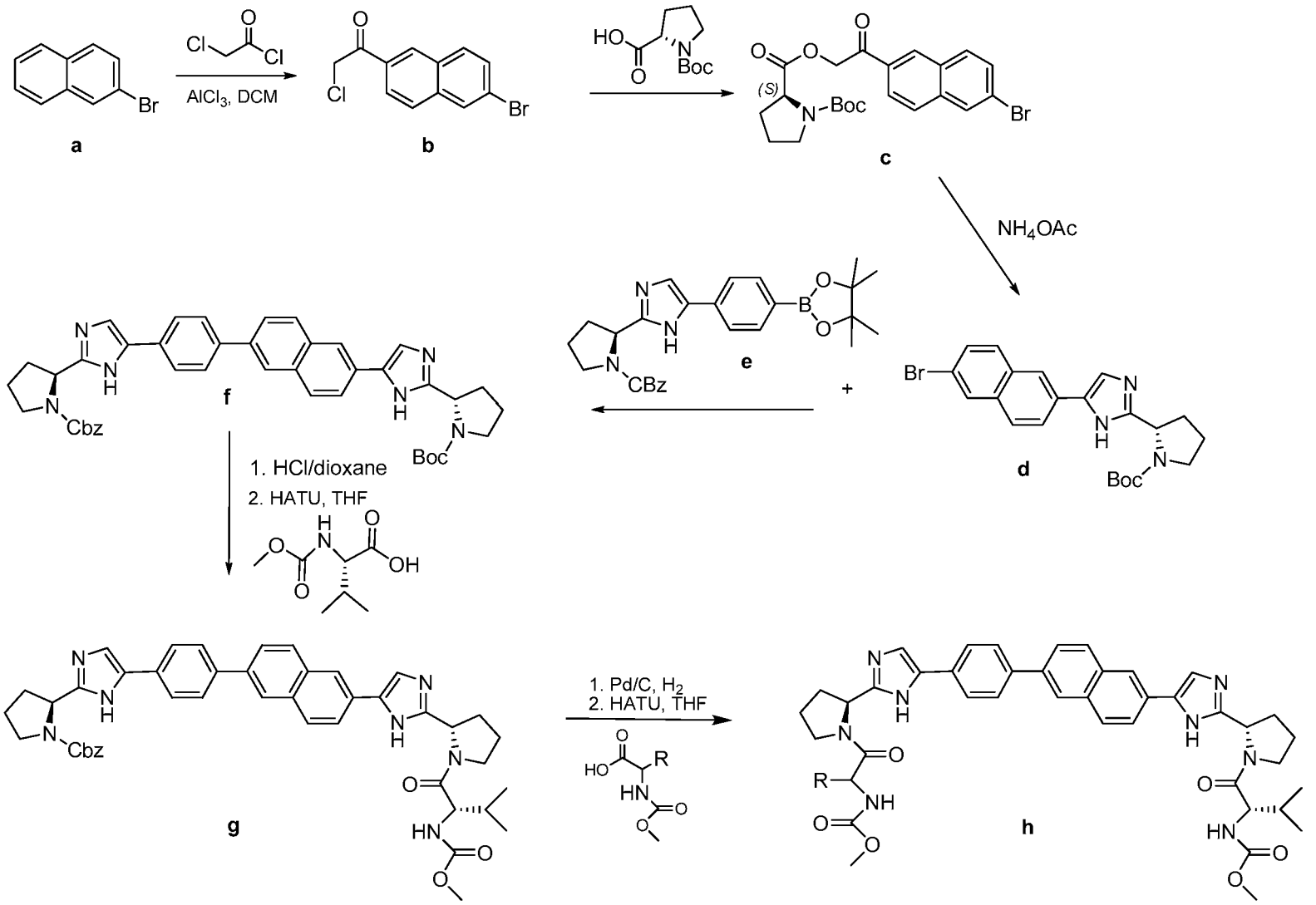
ACN	Acetonitrile
aq	Aqueous
Bn	Benzyl
BnOH	Benzyl alcohol
Boc	*t*-butoxycarbonyl
DCE	Dichloroethane
DCM	Dichloromethane
DIEA(DIPEA)	Diisopropylethylamine
DMA	*N,N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DPPA	Diphenylphosphoryl azide

DTT	Dithiothreitol
EDC	Ethylcarbodiimide hydrochloride
EDCl	1-Ethyl-3-[3-(dimethylamino) propyl]carbodiimide hydrochloride
EDTA	Ethylene diamine tetraacetic acid
ESI	Electrospray Ionization
Et_3N, TEA	Triethylamine
EtOAc, EtAc	Ethyl acetate
EtOH	Ethanol
g	Gram(s)
h	Hour(s)
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
LCMS	Liquid Chramatography Mass Spectrometry
MeI	Methyl Iodide
MeOH	Methanol
min	Minute(s)
mmol	Millimole(s)
NMM	4-Methylmorpholine
NMP	N-methylpyrrolidinone
PG	Protective Group
PTT	Phenyl trimethyl tribromide
Py	Pyridine
rt	Room temperature
TEA	Triethylamine
Tf	Trifluoromethanesulfonate

TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

[0337] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). 1H-NMR spectra were recorded on a Bruker 400 MHz or 500 MHz NMR spectrometer. Significant peaks are tabulated in the order: 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. Electrospray spray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard 1100 MSD electrospray mass spectrometer using the HP1 100 HPLC for sample delivery. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses) or a single m/z value for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Normally the analyte was dissolved in methanol at 0.l mg/mL and 5 microliter was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using an acetonitrile/ H_2O gradient (10%-90%) acetonitrile in H_2O with 0.1% formic acid as delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2 mM NH_4OAc in acetonitrile/ H_2O as delivery solvent. Enantiomeric purity was determined using a Hewlett-Packard Series 1050 system equipped with a chiral HLPC column (ChiralPak AD, 4.6 mm x 150mm) and isocratic elution using 5:95 isopropanol-hexane as a mobile phase.

[0338] The compounds were named using ChemDraw program from Cambridge Soft Inc.


Br
a
Cl
Cl
O
AlCl3, DCM
Cl
O
Br
b
HO
O
N
Boc
O
O
O
(S)
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Boc
Br
c
NH4OAc
N
N
H
B
O
O
N
CBz
e
+
Br
N
N
H
N
Boc
d
N
N
H
N
Cbz
f
N
Boc
1. HCl/dioxane
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O
O
O
OH
O
N
N
H
N
Cbz
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N
O
HN
O
O
1. Pd/C, H2
2. HATU, THF
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R
HN
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Scheme 1-1

EXAMPLE 1 – Synthesis of compounds of Formula IIc

[0339] Scheme 1-1 describes preparation of target molecules and their analogs with symmetrical and non-symmetrical functionalized ends.

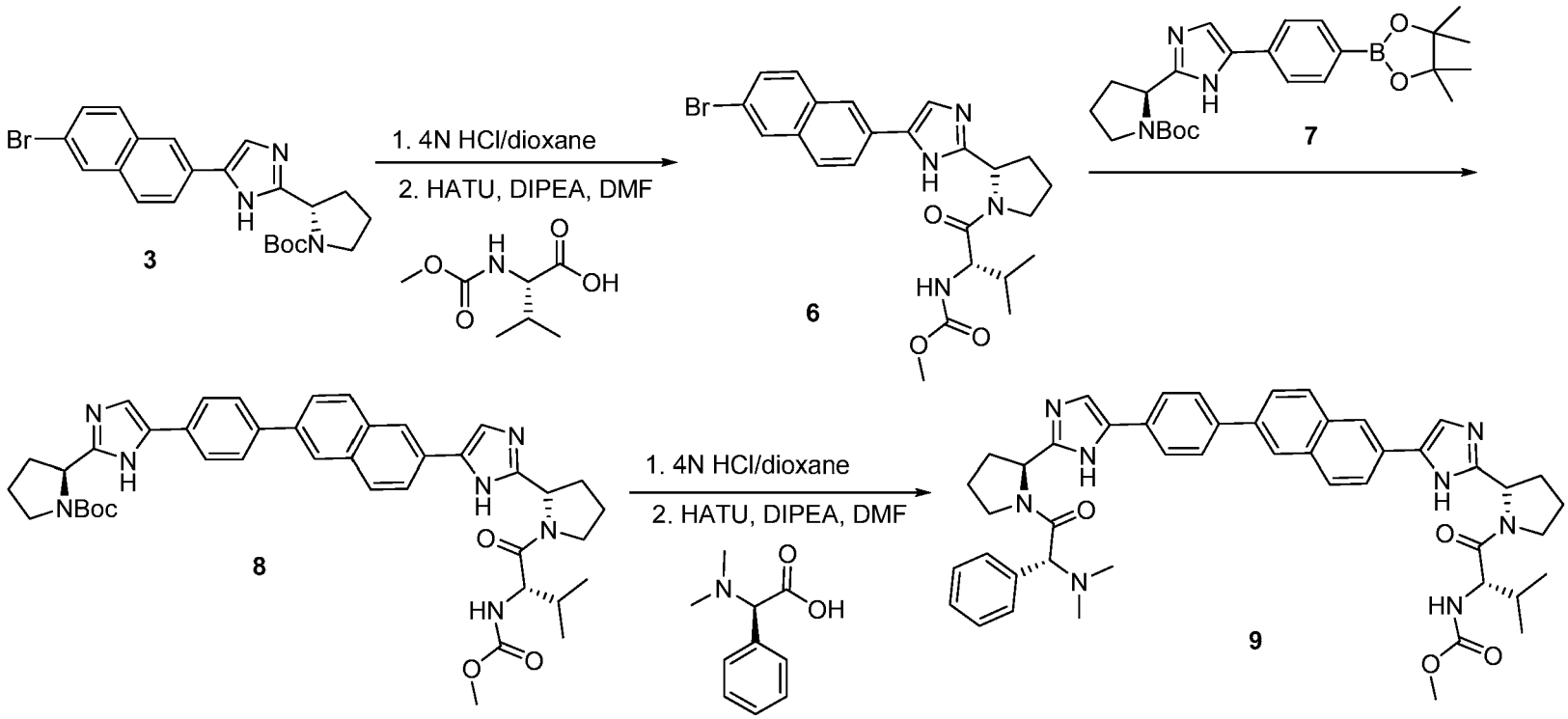
[0340] **Step a**. To a solution of 2-bromonaphthane **a** (62.0 g, 300 mmol) in DCM (1 L) was added $AlCl_3$ (44.0 g, 330 mmol) and 2-chloroacetyl chloride (34.0 g, 330 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then H_2O added (500 mL) and extracted. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give 80 g crude product, which was purified by re-crystallization from 10% EtOAc-hexane (*v/v*) to yield **b** (28 g, 36% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.07 (s, 1H), 8.04 (d, J = 11.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 1H), 4.81 (s, 2H) ppm; LCMS (ESI) *m/z* 282.9 $(M + H)^+$.

[0341] **Step b**. To a solution of **b** (28.0 g, 100 mmol) in DCM (500 mL) was added N-Boc-L-Pro-OH (24.7 g, 115 mmol) and Et_3N (70.0 mL, 500 mmol) and the mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure to afford crude **c** which was used for the next step without further purification. LC-MS (ESI) *m/z* 462.1 $(M + H)^+$.

[0342] **Step c**. To a solution of **c** (46.0 g, 100 mmol) in toluene (500 mL) was added NH_4OAc (77 g, 1.0 mol) and the mixture was stirred at 110 °C overnight, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc 1:1(*v/v*)) to afford **d** (30 g, 68% yield) as a yellow solid: LC-MS (ESI) *m/z* 442.1 $(M + H)^+$.

[0343] **Step d**. To a solution of **d** (10.0 g, 23.0 mmol) in anhydrous DME (200 mL) and equal molar of boronate **e** was added PPh_3 (1.2 g, 4.6 mmol), $Pd(PPh_3)_4$ (1.6 g, 2.3 mmol), and 2.0 M Na_2CO_3 solution. The mixture was refluxed under argon overnight. The organic solvent was removed under reduced pressure and the residue was treated with H_2O, extracted with EtOAc (2 x 200 mL). The combined organic phase was dried, filtered, and concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc 3:1(*v/v*)) to afford **f** (10 g, 96% yield) as a yellow solid. LC-MS (ESI): *m/z* 709.3 $(M+H)^+$.

[0344] **Step e.** To a stirred solution of **f** (150 mg, 0.29 mmol) in dioxane (3 mL) was added 4.0 N HCl in dioxane (3 mL) dropwise. The mixture was stirred at rt for 4 h, and then concentrated to yield a yellowish solid (134 mg), which was used directly for the next step. The residue (134 mg, 0.290 mmol) was suspended in THF (5 mL) and DIPEA (0.32 mL) was added and followed by addition of N-methoxycarbonyl-L-Val-OH (151 mg, 0.860 mmol). After stirring for 15 min, HATU (328 mg, 0.860 mmol) was added and the mixture was stirred at rt for another 2 h and then concentrated. The residue was purified by prep-HPLC to obtain **g** (40 mg, 19% yield).


Br
3
1. 4N HCl/dioxane
2. HATU, DIPEA, DMF
6
NBoc
7
8
1. 4N HCl/dioxane
2. HATU, DIPEA, DMF
9

Scheme 1-2

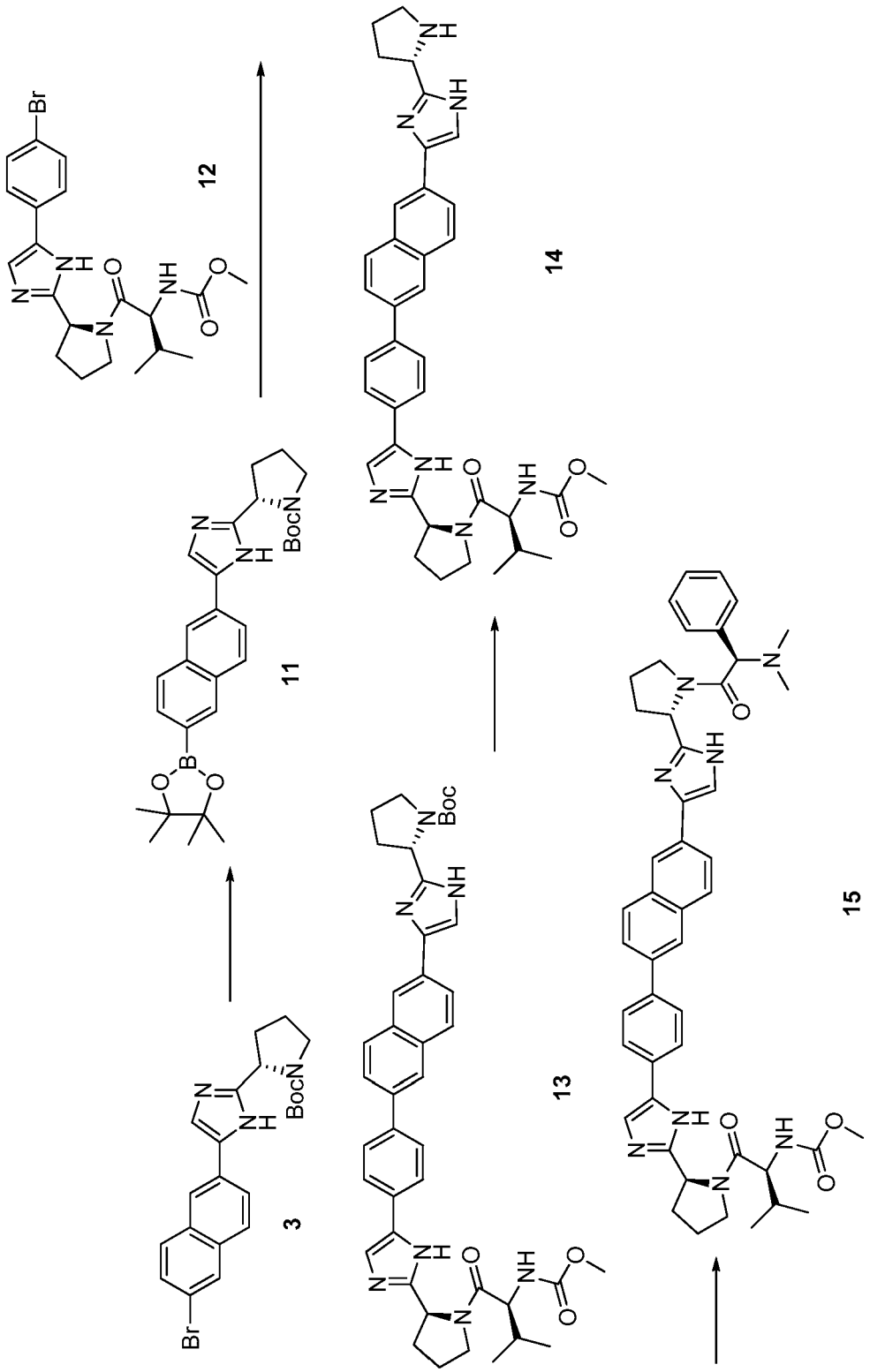
[0345] **Step a**. Referring to Scheme 1-2, to a solution of compound **3** (2.0 g, 4.5 mmol) in dioxane (25 mL) was added 4.0 N HCl in dioxane (25 mL). After stirring at rt for 4 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give a yellowish solid (2.1 g), which was used directly for the next step without further purification.

[0346] **Step b**. To the residue of step a (4.5mmol) was added DMF (25 mL), followed by adding DIPEA (3.7 mL, 22.5 mmol) and N-methyl carbamate-L-valine (945 mg, 5.4 mmol). After stirring at rt for 15 min, the reaction mixture was added slowly to H_2O (400 mL). A white solid precipitated was filtered and dried to give compound **6** (2.2 g, 98% yield). LC-MS (ESI): *m/z* 499.1 $(M+H)^+$.

[0347] **Step c**. To a mixture of compound **6** (800 mg, 1.6 mmol), compound **7** (718 mg, 1.6 mmol), and $NaHCO_3$ (480 mg, 5.7 mmol) in 1,2-dimethoxyethane (15mL) and H_2O (5mL) was added $Pd(dppf)Cl_2$ (59 mg, 0.08 mmol). After stirring at 80°C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/$CHCl_3$ (100 mL) and H_2O (100 mL). The organic phase was separated and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc=15:1(*v/v*)) to give compound **8** (1.0 g, 85% yield) as a yellow solid. LC-MS (ESI): *m/z* 732.4 $(M+H)^+$.

[0348] **Step d**. To a solution of compound **8** (200 mg, 0.27 mmol) in dioxane (3.0 mL) was added 4 N HCl in dioxane (3.0 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 in quantitative yield, which was used directly for the next step without further purification.

[0349] **Step e**. To a solution of the salt (0.27 mmol) in DMF (5.0 mL) was added DIPEA (0.47mL, 2.7 mmol), followed by adding N,N-dimethyl-D-phenyl glycine (59 mg, 0.33 mmol) and HATU (125 mg, 0.33 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H_2O and DCM. The organic phase was washed successively with H_2O and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **9**. LC-MS (ESI): *m/z* 793.4 $(M+H)^+$.



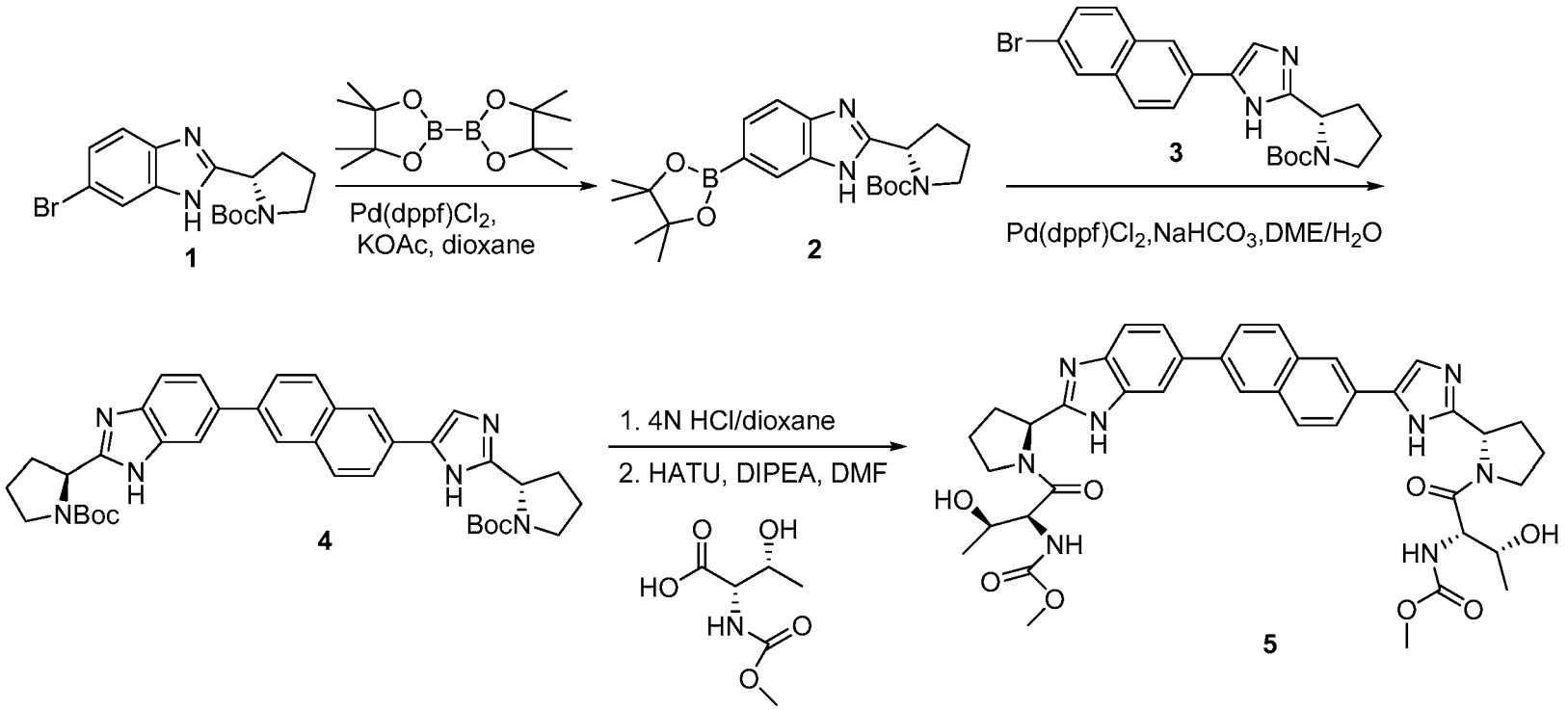
Scheme 1-3

[0350] **Step a**. To a mixture of compound **3** (3.2 g, 7.2 mmol), bis(pinacolato)diboron (3.86 g, 15.2 mmol), and KOAc (1.85g, 18.8mmol) in 1,4-dioxane (100 mL) was added $Pd(dppf)Cl_2$ (440 mg, 0.6 mmol). After stirring at 80 °C for 3 h under an atmosphere of N_2, the reaction mixture was concentrated. The residue was purified with silica gel column chromatography (Petroleum ether/EtOAc=2/1(*v/v*)) to give compound **11** (2.8 g, 80% yield) as a white solid. LC-MS (ESI): *m/z* 490.3 $(M+H)^+$.

[0351] **Step b**. To a mixture of compound **11** (626 mg, 1.27 mmol), compound **12** (570 mg, 1.27 mmol), and $NaHCO_3$ (420 mg, 4.99 mmol) in 1, 2-dimethoxyethane (30 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (139 mg, 0.19 mmol). After stirring at 80°C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/$CHCl_3$ (100 mL) and H_2O (100 mL). The aqueous phase was extracted with 20% methanol/$CHCl_3$ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc=2/1(*v/v*)) to give compound **13** (635 mg, 68% yield) as a yellow solid. LC-MS (ESI): *m/z* 732.4 $(M+H)^+$.

[0352] **Step c**. To a solution of compound **13** (200 mg, 0.27 mmol) in dioxane (3.0 mL) was added 4 N HCl in dioxane (3.0 mL). After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to yield the HCl salt of compound **14** in quantitative yield, which was used directly for the next step without further purification.

[0353] **Step d**. To a solution of the salt (0.27 mmol) in DMF (5.0 mL) was added DIPEA (0.47 mL, 2.7 mmol), followed by adding N,N-dimethyl-D-phenyl glycine (59 mg, 0.33 mmol) and HATU (125 mg, 0.33 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H_2O and DCM. The organic phase was consequently washed with H_2O and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **15**. LC-MS (ESI): *m/z* 793.4 $(M+H)^+$.


Br
N
N
H
BocN
1
Pd(dppf)Cl2,
KOAc, dioxane
2
3
Pd(dppf)Cl2,NaHCO3,DME/H2O
NBoc
4
1. 4N HCl/dioxane
2. HATU, DIPEA, DMF
HO
OH
HN
O
5

Scheme 2-1

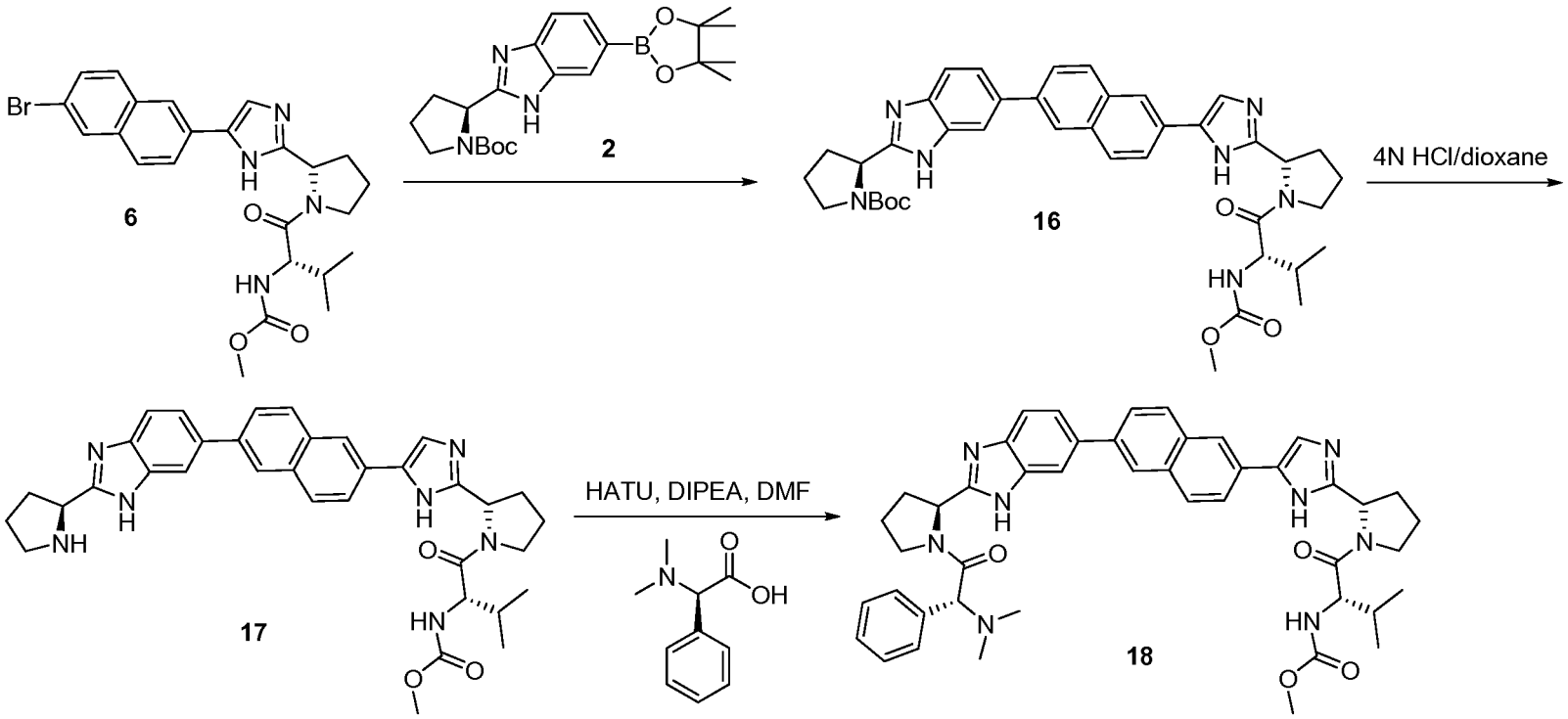
EXAMPLE 2 – Synthesis of compounds of Formula IIIe

[0354] **Step a**. Referring to Scheme 2-1, to a mixture of compound **1** (5.05 g, 13.8 mmol), bis(pinacolato)diboron (7.1 g, 27.9 mmol), and KOAc (3.2 g, 32.5 mmol) in 1,4-dioxane (100 mL) was added $Pd(dppf)Cl_2$ (400 mg, 0.5 mmol). After stirring at 80 °C for 3 h under an atmosphere of N_2, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc=2/1(*v/v*)) to give compound 2 (3.0 g, 53% yield) as a gray solid. LC-MS (ESI): *m/z* 414.2 $(M+H)^+$.

[0355] **Step b**. To a mixture of compound **2** (522 mg, 1.26 mmol), compound **3** (500 mg, 1.13 mmol), and $NaHCO_3$ (333 mg, 3.96 mmol) in 1, 2-dimethoxyethane (30 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (74 mg, 0.1 mmol). After stirring at 80°C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/$CHCl_3$ (100 mL) and H_2O (100 mL). The organic phase was separated and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH=50:1 (*v/v*)) to give compound **4** (450 mg, 55% yield) as a yellow solid. LC-MS (ESI): *m/z* 649.3 $(M+H)^+$.

[0356] **Step c**. To a stirred solution of compound **4** (160 mg, 0.25 mmol) in dioxane (2.0 mL) was added 4N HCl in dioxane (2.0 mL). After stirring at rt for 3h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give an HCl salt in quantitative yield, which was used directly for the next step without further purification.

[0357] **Step d**. To a solution of above salt (0.25 mmol) in DMF (4.0 mL) was added DIPEA (0.44 mL, 2.5mmol), followed by adding N-methyl carbamate-L-Threonine (110 mg, 0.62 mmol) and HATU (240 mg, 0.63 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H_2O and DCM. The organic phase was consequently washed with H_2O and brine, dried with anhydrous Na_2SO_4, filtrated, and concentrated. The residue was purified by prep-HPLC to give compound **5** as a white powder. LC-MS (ESI): *m/z* 767.3 $(M+H)^+$.

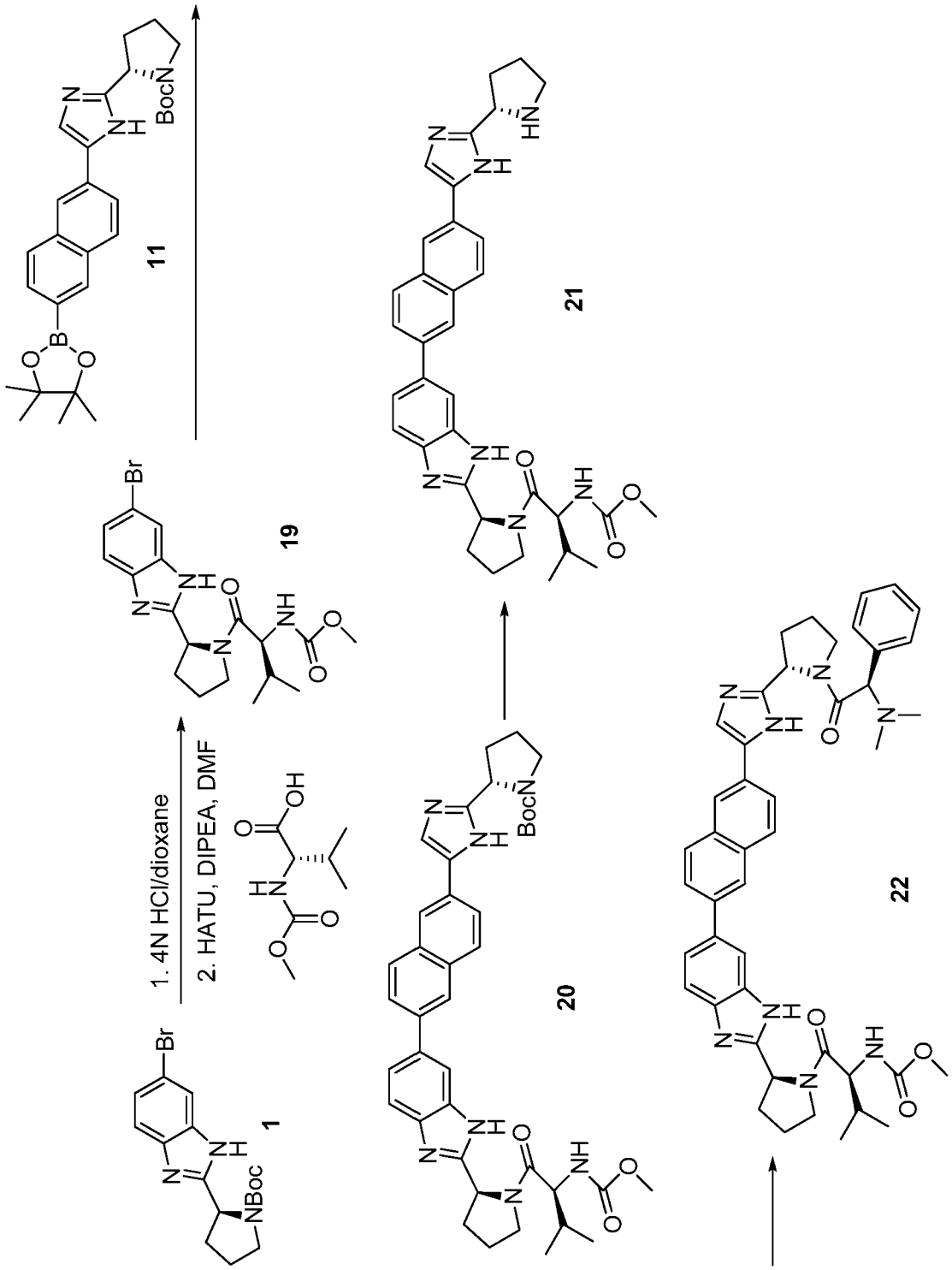


Scheme 2-2

[0358] **Step a**. Referring to Scheme 2-2, to a mixture of compound **2** (1.16 g, 2.32 mmol), compound **6** (1.40 g, 3.39 mmol), and $NaHCO_3$ (823 mg, 9.8 mmol) in 1, 2-dimethoxyethane (30 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (103 mg, 0.14 mmol). After stirring at 80 °C over night under an atmosphere of N_2, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/$CHCl_3$ (150 mL) and H_2O (150 mL). The aqueous phase was extracted with 20% methanol/$CHCl_3$ (150 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/acetone=1.5/1 (*v/v*)) to give compound **16** (1.32g, 80% yield) as a yellow solid. LC-MS (ESI): *m/z* 706.4 $(M + H)^+$.

[0359] **Step b**. To a solution of compound **16** (200 mg, 0.28 mmol) in dioxane (3.0 mL) was added 4 N HCl in dioxane (3.0 mL). After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give the HCl salt of compound **17** in quantitative yield, which was used directly for the next step.

[0360] **Step c**. To a solution of the salt (0.28 mmol) in DMF (5.0 mL) was added DIPEA (0.49 mL, 2.8 mmol), followed by adding N,N-dimethyl-D-phenyl glycine (61 mg, 0.34 mmol) and HATU (129 mg, 0.34 mmol). After stirring for 1h at rt, the reaction mixture was partitioned between H_2O and DCM. The organic phase was consequently washed with H_2O and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **18**. LC-MS (ESI): *m/z* 767.4 $(M+H)^+$.



Scheme 2-3

[0361] **Step a**. Referring to Scheme 2-3, to a solution of compound **1** (4.0 g, 10.9 mmol) in dioxane (40 mL) was added 4 N HCl in dioxane (40 mL). After stirring at rt overnight, the reaction mixture was concentrated. The residue was washed with DCM, filtered, and dried *in vacuo* to afford a hydrochloride salt in quantitative yield, which was used for the next step without further purification.

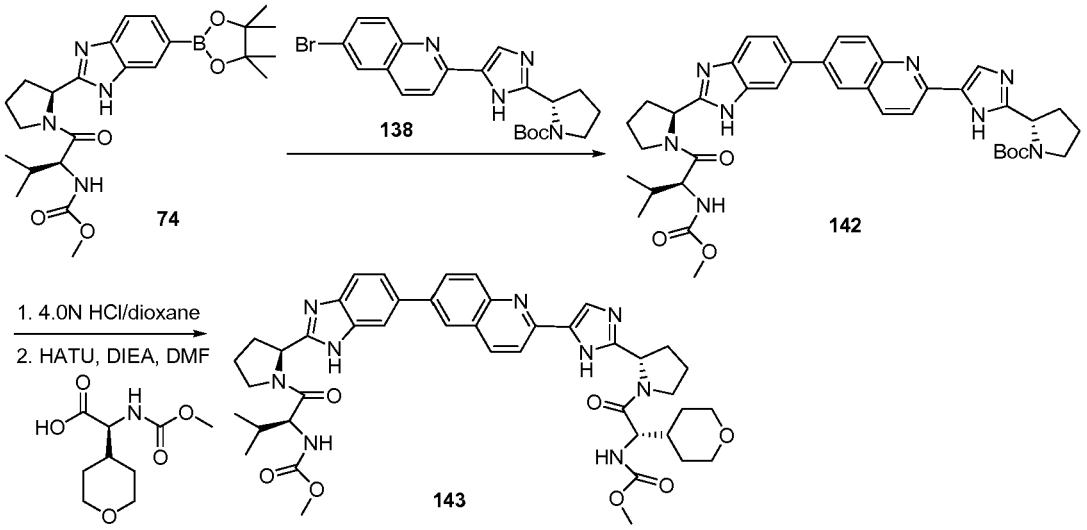
[0362] **Step b**. To a solution of the salt (10.9 mmol) in DMF (30 mL) was added DIPEA (5.8 mL, 33.0 mmol), followed by adding N-methoxycarbonyl-L-valine (2.1 g, 12.1 mmol) and HATU (4.6 g, 12.1 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H_2O and DCM. The organic phase was consequently washed with H_2O and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (DCM/Petroleum ether=4/1 (*v/v*)) to give compound **19** (3.0 g, 65% yield). LC-MS (ESI): *m/z* 423.1 $(M+H)^+$.

[0363] **Step c**. To a mixture of compound **11** (800 mg, 1.9 mmol), compound **19** (700 mg, 1.7 mmol), and $NaHCO_3$ (561 mg, 6.6 mmol) in 1, 2-dimethoxyethane (60 mL) and H_2O (20 mL) was added $Pd(dppf)Cl_2$ (183 mg, 0.25 mmol). After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was then partitioned between 20% methanol/$CHCl_3$ (100 mL) and H_2O (100 mL). The aqueous phase was extracted with 20% methanol/$CHCl_3$ (100 mL) again. The combined organic phase was consequently washed with brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc=2/1(*v/v*)) to give compound **20** (600 mg, 52% yield) as a yellow solid. LC-MS (ESI): *m/z* 706.4 $(M+H)^+$.

[0364] **Step d.** To a solution of compound **20** (200 mg, 0.28 mmol) in dioxane (3.0 mL) was added 4N HCl in dioxane (3.0 mL). After stirring at rt for 2h, the reaction mixture was concentrated and the residue was dried *in vacuo* to yield the HCl salt of compound **21** in quantitative yield, which was used directly for the next step without further purification.

[0365] **Step e**. To a solution of compound **21** (0.28 mmol) in DMF (5.0 mL) was added DIPEA (0.49 mL, 2.8 mmol), followed by N,N-dimethyl-D-phenyl glycine (64 mg, 0.36 mmol) and HATU (129 mg, 0.34 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H_2O and DCM. The organic phase was washed successively with H_2O and brine, dried

with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **22**. LC-MS (ESI): m/z 767.4 $(M+H)^+$.



Scheme 2-4

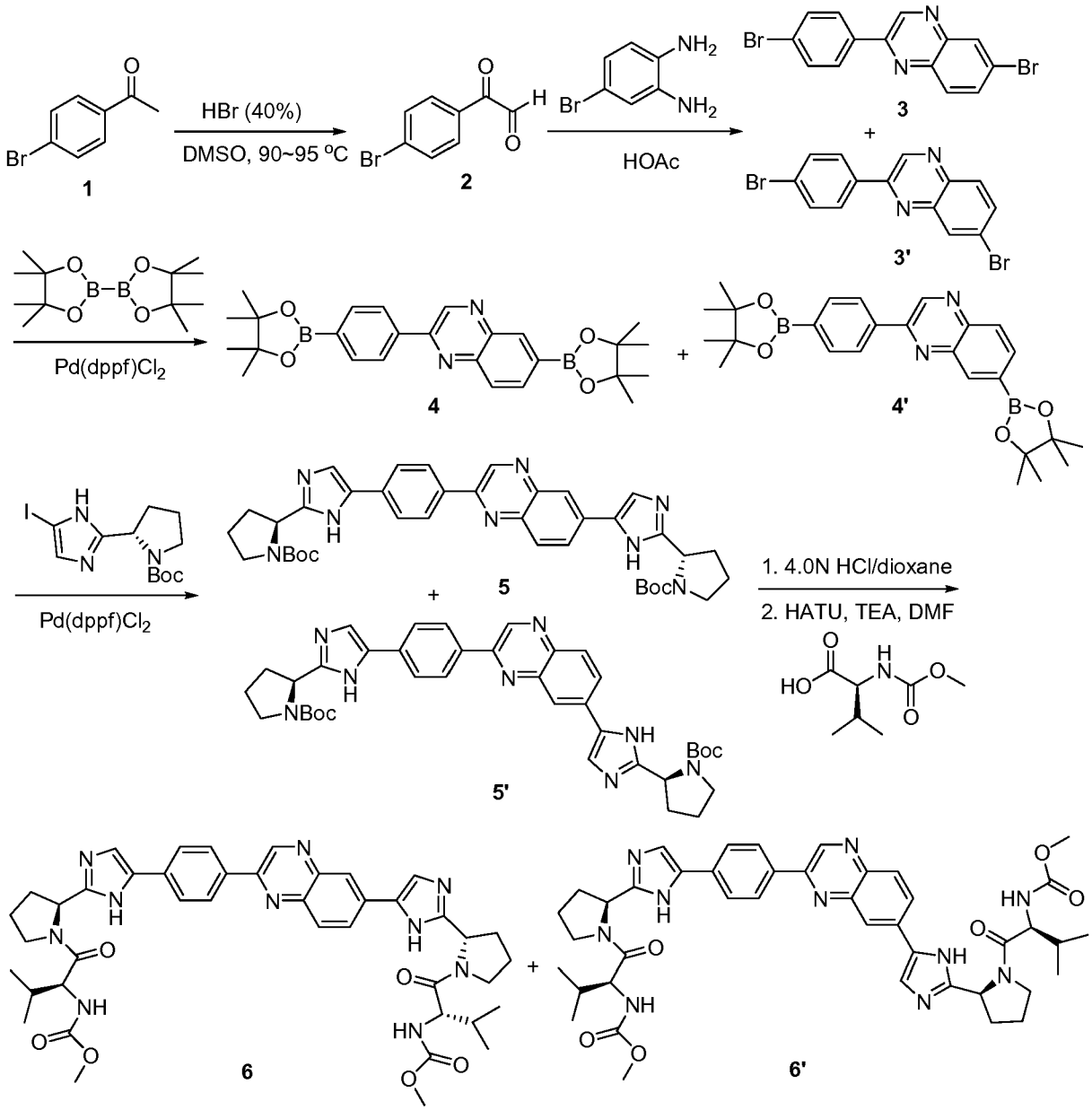
[0366] **Step a**. To a mixture of compound **74** (510 mg, 1.09 mmol), compound **138** (300 mg, 0.68 mmol), $NaHCO_3$ (228 mg, 2.72 mmol) in 1, 2-dimethoxyethane (20 mL) and H_2O (5 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (111 mg, 0.140 mmol) at rt under an atmosphere of N_2. After stirring at 80°C overnight under an atmosphere of N_2, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL) and H_2O (25 mL). The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/2 (*v/v*)) to give compound **142** (360 mg, 75% yield) as a yellow solid. LC-MS (ESI): *m/z* 707.4 $(M+H)^+$.

[0367] **Step b**. To a solution of compound **142** (115 mg, 0.16 mmol) in dioxane (2.0 mL) was added 4 N HCl in dioxane (2.0 mL) at rt. After stirring at rt overnight, 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 607.3 $(M + H)^+$.

[0368] **Step c**. Subsequently, the HCl salt was dissolved in DMF (2 mL) and the resulting mixture was added DIEA (0.28 mL, 1.6 mmol), N-Moc-L-(tetrahydro-2*H*-pyran-4-yi)glycine (41 mg, 0.19 mmol), and HATU (73 mg, 0.19 mmol). After stirring at rt for 15 min, the reaction

mixture was concentrated and the residue was purified by preparative HPLC to give compound **143**. LC-MS: (ESI) *m/z* 806.4 $(M+H)^+$.

EXAMPLE 3 – Synthesis of additional compounds of Formula IIc



Scheme 3-1

[0369] **Step a**. Referring to Scheme 3-1, to a solution of compound **1** (49.7 g, 0.25 mol) in DMSO was added 40% aq. HBr (0.50 mol) drop wise at rt. After stirring at 90 °C for 3 h, the

reaction mixture was poured into $H_2O$and the resulting mixture was kept at 50~60 °C. The yellow solid was collected by filtration and re-crystallized in acetone/H_2O (1/19 (*v/v*) two times to give compound **2** (50 g, 87% yield). LC-MS (ESI): *m/z* 212.9 $(M+H)^+$.

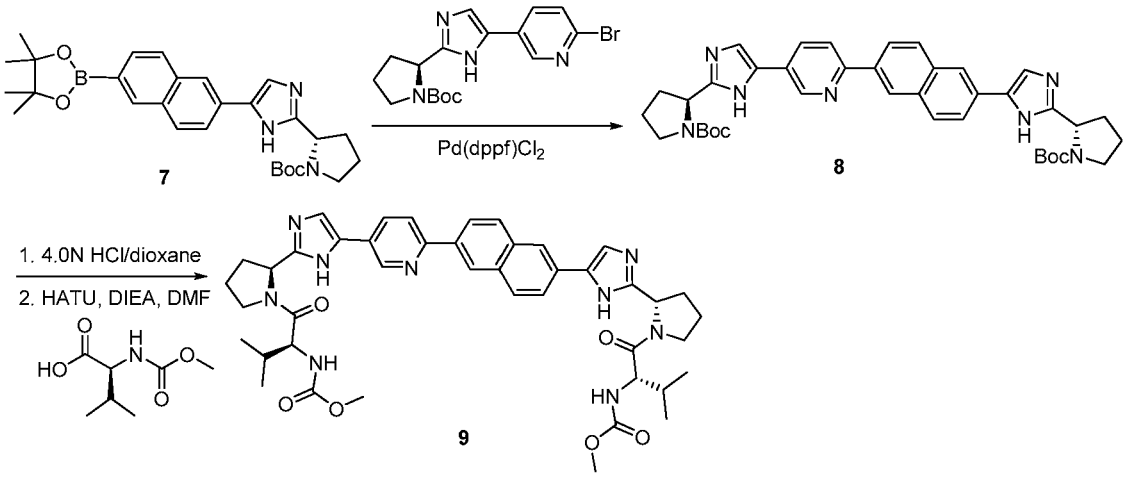
[0370] **Step b**. A mixture of **2** (19.0 g, 80.0 mmol) and 4-bromobenzene-1, 2-diamine (15.0 g, 80.0 mmol) in HOAc (180 mL) was refluxed overnight. Subsequently, the reaction mixture was poured into ice H_2O. The solid was collected by filtration and purified by silica gel column chromatography to give compounds **3** and **3′** (2.8 g, 10% yield) as a pair of regioisomers. LC-MS (ESI): *m/z* 362.9 $(M+H)^+$.

[0371] **Step c**. A mixture of compound **3** (4.8 g, 5.4 mmol), bis(pinacolato)diboron (9.6 g, 38 mmol), potassium acetate (3.8 g, 38 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (524 mg, 0.54 mmol) in dioxane (100 mL) was stirred at 80°C for 17 h under an atmosphere of Ar. Subsequently, the reaction mixture was filtered. The filtered cake was washed with EtOAc (50 mL × 3) several times. The filtrate was washed with H_2O and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (PE/acetone = 10: 1 (*v/v*)) to give compounds **4** and **4′** (2.2 g, 89% yield) as a pair of regio-isomers. LC-MS (ESI): *m/z* 459.3 $(M+H)^+$. (The corresponding boronic acid was also isolated and used as an active intermediate for the next step).

[0372] **Step d**. A mixture of compounds **4** and **4′** (1.0 g, 2.2 mmol), (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.0 g, 5.4 mmol), sodium bicarbonate (1.5 g, 18 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (427 mg, 0.44 mmol) in DME/H_2O (3/1 (*v/v*) (80 mL) was stirred at 80 °C for 17 h under an atmosphere of Ar. Subsequently, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (PE/acetone = 10: 1 (*v/v*)) to give compounds **5** and **5′** (590 mg, 40% yield) as a pair of regio-isomers. LC-MS (ESI): *m/z* 677.3 $(M+H)^+$.

[0373] **Step e**. A mixture of compounds **5** and **5′** (200 mg, 0.3 mmol) in 4.0 N HCl in dioxane (10 mL) was stirred at rt overnight. The solvent was removed 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* 477.2 $(M+H)^+$.

[0374] **Step f**. Subsequently, the HCl salt was dissolved in DMF (3 mL) and the resulting mixture was sequentially added Et_3N (304 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 H_2O (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 compounds **6** and **6′** as a pair of regio-isomers. LC-MS (ESI): *m/z* 791.4 $(M+H)^+$.



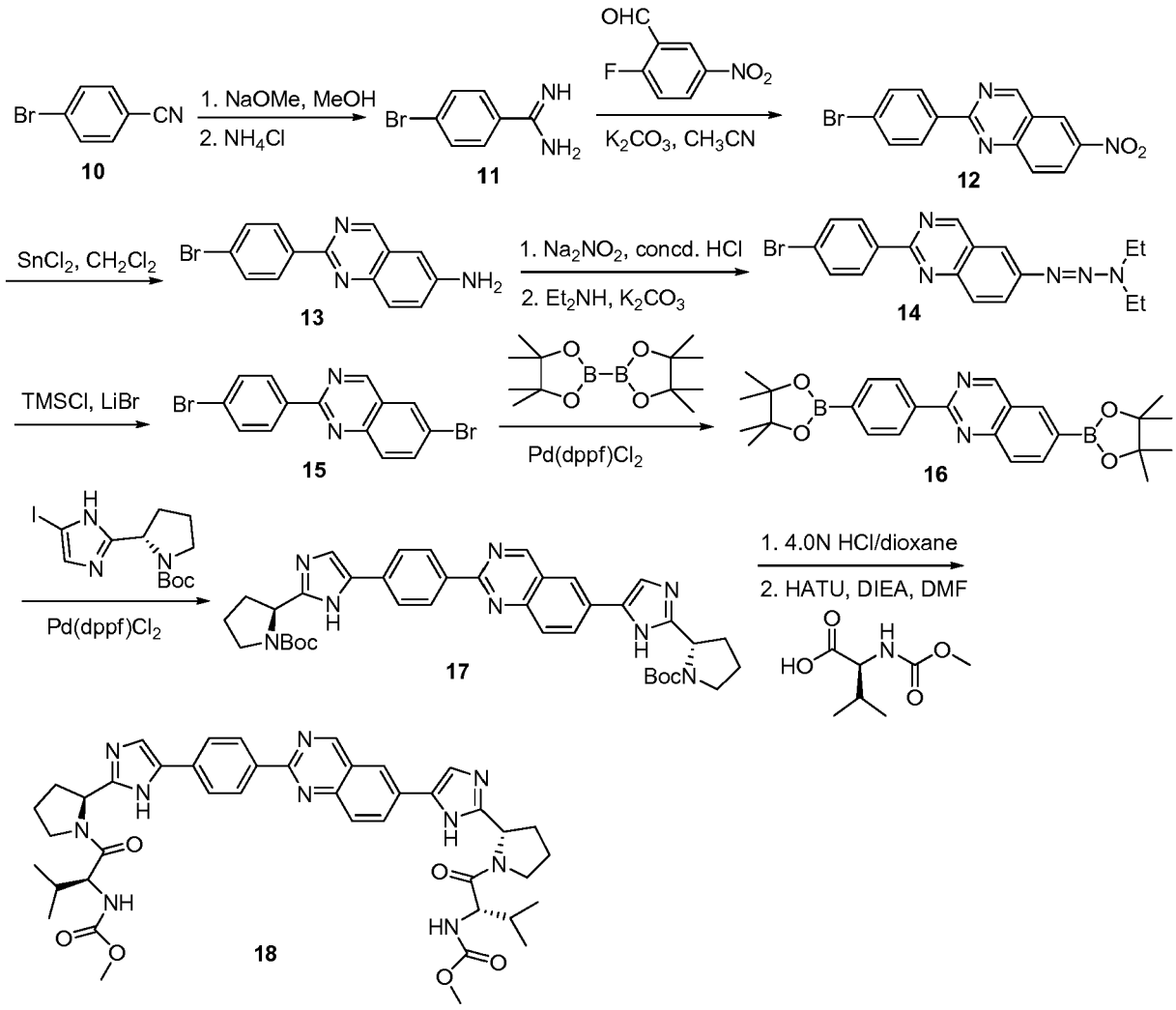
Scheme 3-2

[0375] **Step a**. Referring to Scheme 3-2, to a solution of compound **7** (909 mg, 1.86 mmol), (*S*)-tert-butyl- 2-(5-(6-bromopyridin-3-yl)pyrrolidine-1-carboxylate (800 mg, 2.04 mmol), and $NaHCO_3$ (625 mg, 7.44 mmol) in 1, 2-dimethoxyethane (100 mL) and H_2O (30 mL) was added $Pd(dppf)Cl_2$ (152 mg, 0.186 mmol)at rt under an atmosphere of Ar. After stirring at 80 °C overnight under an atmosphere of Ar, the reaction mixture was concentrated. The residue was diluted with CH_2Cl_2 (200 mL). The organic layer was washed with H_2O and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 50:1 (*v/v*)) to give compound **8** (700 mg, 55% yield). LC-MS (ESI) *m/z*: 676.4 $(M+H)^+$.

[0376] **Step b**. To a stirred solution of compound **8** (200 mg, 0.296 mmol) in dioxane (3 mL) was added 4 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*: 476.2 $(M+H)^+$.

[0377] **Step c**. Subsequently, the HCl salt was dissolved in DMF (3 mL) and the resulting mixture was 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 H_2O (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 **9**. ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.67 (s, 1H), 8.31-8.34 (m, 3H), 8.27-8.29 (m, 1H), 8.17-8.19 (m, 1H), 8.11-8.13 (m, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.90-7.91 (m, 1H), 5.29-5.31 (m, 2H), 4.26-4.27 (m, 2H), 4.13 (s, 2H), 3.93-3.95 (m, 2H), 3.68 (s, 6H), 2.60-2.62 (m, 3H), 2.32-2.33 (m, 2H), 2.15-2.28 (m, 5H), 2.10-2.11 (m, 3H), 1.00-1.02 (m, 2H), 0.96-0.98 (m, 6H), 0.92-0.93 (m, 6H) ppm. LC-MS (ESI): *m/z* 790.4 $(M+H)^+$.



Scheme 3-3

[0378] **Step a**. Referring to Scheme 3-3, to a solution of **10** (45.0 g, 247 mmol) in MeOH (500 mL) was added NaOMe (1.4 g, 25 mmol) at rt. After stirring at rt for 48 h, the reaction mixture was added NH_4Cl (13.4 g, 250 mmol) and the resulting mixture was stirred from another 24 h. The solvent was removed and the residue was dried *in vacuo* to give compound **11**, which was used for the next step without further purification. LC-MS: (ESI) *m/z* = 199.0 $(M+H)^+$.

[0379] **Step b**. To a solution of **11** (15 g, 75 mmol) in CH_3CN (500 mL) was added K_2CO_3 (11.4 g, 83.0 mmol), followed by 2-fluoro-5-nitrobenzaldehyde (12.7 g, 75.0 mmol). After refluxing for 12 h, the reaction mixture was concentrated and the residue was washed with MeOH to give crude compound **12** (12 g), which was used for the next step without further purification. LC-MS: (ESI) *m/z* = 330.0 $(M+H)^+$.

[0380] **Step c**. A solution of **12** (5.0 g, 15 mmol) in MeOH (500 mL) was added tin (II) chloride (14.3 g, 75.0 mmol) and concentrated hydrochloric acid (17 mL). After stirring at rt for 3.5 h, the reaction mixture was carefully added saturated aqueous $NaHCO_3$ solution (470 mL). The resulting mixture was extracted with ethyl acetate (100 mL × 3). The extracts were combined and washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **13** (2.5 g). LC-MS: (ESI) m/z = 300.0 $(M+H)^+$.

[0381] **Step d**. To a solution of **13** (300 mg, 1.0 mmol) in concentrated HCl (0.25 mL) was added a solution of $NaNO_2$ (76 mg, 1.1 mmol) in H_2O (1 mL) drop wise at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was added to a solution of K_2CO_3 (207 mg, 1.5 mmol) and Et_2NH (0.11 g, 1.5 mmol) in ice H_2O (1 mL). Subsequently, ether (100 mL) was added to the mixure. The organic layer was separated, washed with H_2O (15 mL) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **14** (350 mg), which was used for the next step without further purification. LC-MS (ESI): *m/z* 384.1 $(M+H)^+$.

[0382] **Step e**. To a solution of compound **14** (1.8 g, 4.7 mmol) and LiBr (834 mg, 9.6 mmol) in acetonitrile (10 mL) was added TMSCl (782 mg, 7.2 mmol) at rt. After stirring at 60 °C for 15 min, the reaction mixture was cooled to rt and treated with 5% aqueous $NaHCO_3$ solution (30 mL). The mixture was concentrated and the residue was extracted with CH_2Cl_2 (50 mL × 3). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Pentane/ether = 1/19 (*v/v*)) to give compound **15** (1.0 g, 59% yield). LC-MS: (ESI) m/z = 362.9 $(M+H)^+$.

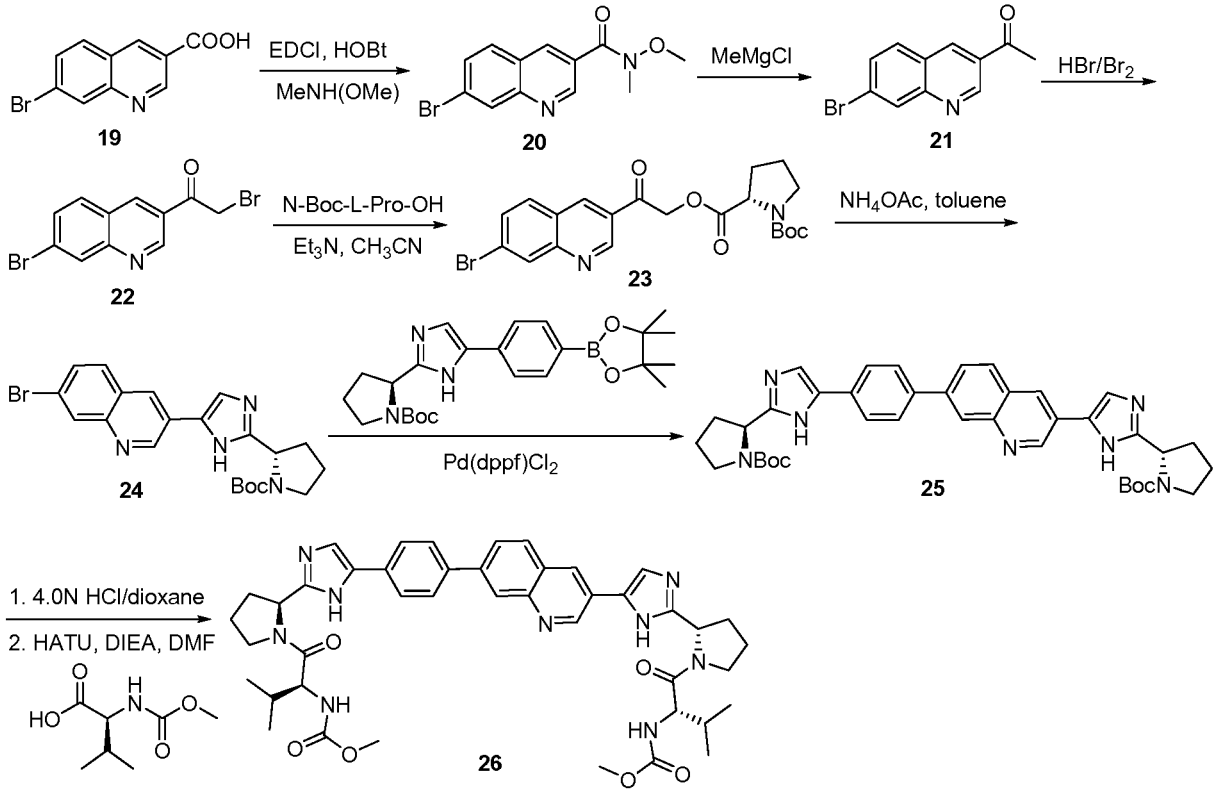
[0383] **Step f**. To a solution of **15** (300 mg, 0.82 mmol) in dioxane (20 mL) was sequentially added bis(pinacolato)diboron (915 mg, 3.63 mmol), potassium acetate (403 mg, 4.12 mmol), and $Pd(dppf)Cl_2$ (134 mg, 0.160 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C for 17 h under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with $H_2O$and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (PE/acetone = 3/1 (*v/v*)) to give compound **16** (227 mg, 60% yield) LC-MS (ESI): m/z 459.3 $(M+H)^+$. (The

corresponding boronic acid was also isolated and used as an active intermediate for the next step).

[0384] **Step g**. A solution of **16** (300 mg, 0.65 mmol) in DME/H_2O (3/1(*v/v*); 30 mL) was sequentially added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (595 mg, 1.64 mmol), $NaHCO_3$ (443 mg, 5.28 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (126 mg, 0.13 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C for 17 h under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (150 mL). The organic layer was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (PE/acetone = 2/1(*v/v*)) to give compound **17** (151 mg, 34% yield) as a yellowish solid. LC-MS (ESI): m/z 677.3 $(M+H)^+$.

[0385] **Step h**. To a solution of compound **17** (100 mg, 0.15 mmol) in dioxane (2 mL) was added 4 N HCl in dioxane (2 mL) at rt. After stirring at rt overnight, the solvent was removed 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 477.2 $(M+H)^+$.

[0386] **Step i**. To a solution of the HCl salt in DMF (2 mL) was added DIPEA (0.24 mL, 1.5 mmol), followed by N-Moc-L-Val-OH (65 mg, 0.37 mmol), and HATU (141 mg, 0.37 mmol). After stirring at rt for 30 min, the reaction solution was poured into H_2O (50 mL). The suspension was filtered and the solid was purified by preparative HPLC to give compound **18**. ^1H NMR (500 MHz, CD_3OD) δ 9.69 (s, 1H), 8.80 (d, 2H, J = 7.5), 8.49 (s, 1H), 8.35 (d, 2H, J = 8.0), 8.24 (d, 2H, J = 8.5), 8.15 (s, 1H), 8.12 (s, 1H), 8.01 (s, 2H), 7.93 (d, 2H, J = 8.5), 5.30–5.26 (m, 2H), 4.25 (d, 2H, J = 6.5), 4.12 (s, 2H), 3.91 (s, 2H), 3.67 (s, 6H), 2.61–2.60 (m, 2H), 2.31–2.17 (m, 6H), 2.08–2.05 (m, 2H), 1.02–0.91 (m, 12H) ppm; LC-MS (ESI) *m/z*: 791.4 $(M + H)^+$.



Scheme 3-4

[0387] **Step a**. Referring to Scheme 3-4, a solution of **19** (5.00 g, 19.8 mmol) in CH_3CN (200 mL) was respectively added EDCI (9.10 g, 47.6 mmol), HOBt (1.34 g, 5.95 mmol), MeNH(OMe)·HCl (2.93 g, 30 mmol), and Et_3N (6.6 g, 65.3 mmol) at rt. After stirring at rt for 3 h, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 5/1 (*v/v*)) to give compound **20** (5.1 g, 87% yield) as a white solid. LC-MS (ESI): *m/z* 295.0 $(M + H)^+$.

[0388] **Step b**. To a solution of compound **20** (2.0 g, 6.8 mmol) in THF (200 mL) was slowly added 3M MeMgCl in THF (4.5 mL) at 0°C under an atmosphere of N_2. After stirring at 0°C for 1 h and then at rt for 1 h, the reaction was quenched by adding several drops of aqueous NH_4Cl. The reaction mixture was concentrated and the residue was diluted with aqueous $NaHCO_3$ (5 mL) and EtOAc (100 mL). The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/AcOEt = 10:1(*v/v*)) to give compound **21** (1.0 g, 59%) as a white solid. LC-MS (ESI): *m/z* 250.0 $(M + H)^+$.

[0389] **Step c**. A solution of compound **21** (500 mg, 2.0 mmol) in HOAc (20 mL) and 48% aqueous HBr (0.5 mL) was slowly added Br_2 (320 mg, 2.0 mmol) in 48% aqueous HBr (0.5 mL) at rt. After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was diluted with H_2O (100 mL). The mixture was extracted with EtOAc (100 mL × 3). The extracts were combined and washed with saturated $NaHCO_3$ (30 mL × 3) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **22** (440 mg) as a white solid, which was used for the next step without further purification. LC-MS (ESI): *m/z* 327.9 $(M + H)^+$.

[0390] **Step d**. A solution of compound **22** (415 mg, 1.26 mmol) in CH_3CN (15 mL) was respectively added N-Boc-L-Pro-OH (300 mg, 1.36 mol) and Et_3N (382 mg, 3.78 mmol) at rt. After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give crude compound **23** (580 mg), which was used for the next step without further purification; LC-MS (ESI): *m/z* 463.1 $(M + H)^+$.

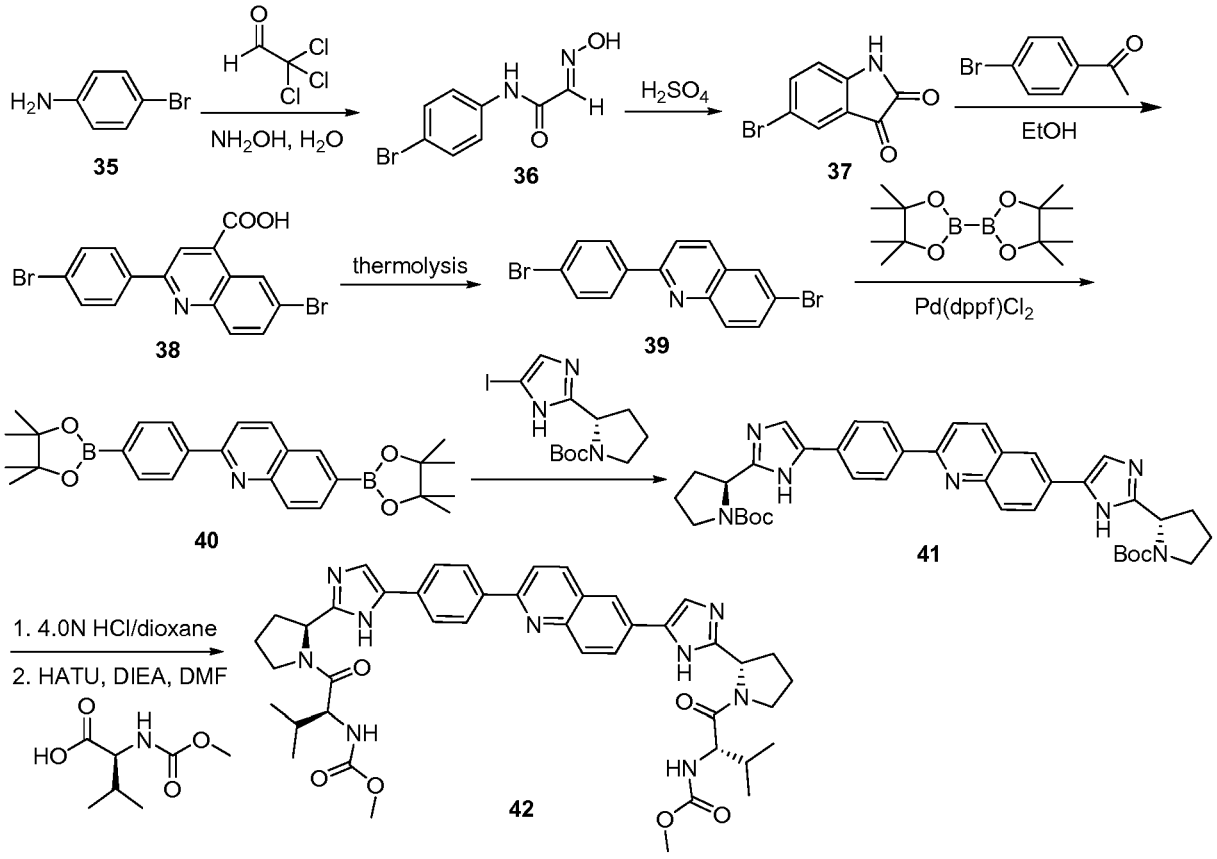
[0391] **Step e**. A mixture of compound **23** (580 mg, 1.25 mmol) and NH_4OAc (962 mg, 12.5 mmol) in toluene (25 mL) was stirred at 110 °C overnight. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 9/1(*v/v*)) to give compound **24** (400 mg, 72%) as a white solid. LC-MS (ESI): *m/z* 443.1 $(M + H)^+$.

[0392] **Step f**. To a mixture of compound **24** (380 mg, 0.86 mmol), (*S*)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazol-2-yl)pyrolidine-1-carboxylate (378 mg, 0.860 mmol), and $NaHCO_3$ (253 mg, 3.01 mmol) in 1, 2-dimethoxyethane (15 mL) and H_2O (5 mL) was added $Pd(dppf)Cl_2$ (35 mg, 0.04 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL × 3). The extracts were combined and washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether /EtOAc = 5/2 (*v/v*)) to give compound **25** (550 mg, 95% yield) as a yellow solid. LC-MS (ESI): *m/z* 676.4 $(M + H)^+$.

[0393] **Step g**. To a solution of compound **26** (150 mg, 0.22 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL) at rt. After stirring at rt overnight, the solvent was removed 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 476.2 $(M+H)^+$.

[0394] **Step h**. To a mixture of the HCl salt in DMF (2 mL) was added DIPEA (0.37 mL, 2.3 mmol), followed by N-Moc-L-Val-OH (101 mg, 0.58 mmol) and HATU (218 mg, 0.58 mmol). After stirring at rt for 30 min, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **26**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, 2H, *J* =11.5), 7.83 - 7.78 (m, 4H), 7.72 (d, 2H, *J* =8.0) , 5.56 (m, 1H), 5.38 - 5.32 (m, 2H), 4.46 - 4.42 (m, 1H), 4.27 - 4.26 (m, 1H), 4.21 - 4.13 (m, 2H), 3.97 - 3.94 (m, 1H), 3.66 (s, 6H), 2.89 - 2.86 (m, 1H), 2.64 - 2.62 (m, 2H), 2.34 - 2.25 (m, 3H), 2.01 - 1.96 (m, 2H) , 0.94 - 0.87 (m, 12H) ppm; LC-MS (ESI): *m/z* 790.4 $(M + H)^+$..



Scheme 3-5

[0395] **Step a**. Referring to Scheme 3-5, a mixture of trichloroacetealdehyde (7.2 g, 48 mmol) in water (120 mL) was added Na_2SO_4 (104 g), followed by 4-bromobenzenamine (**35**) in concd. aq. HCl (10 mL) and $NH_2OH{\cdot}HCl$ (8.8 g, 0.13 mol) in H_2O (100 mL). After refluxing for

1 h, the reaction mixture was cooled to rt. The solid was collected by filtration and dried *in vacuo* to give compound **36** (8.0 g, 91%) as a yellow solid. LC-MS (ESI) *m/z*: 243.0 $(M + H)^+$.

[0396] **Step b**. To a round-bottomed flask was charged with 20 mL of H_2SO_4 (98%) and the solution was warmed to 50 °C. Subsequently, compound **36** (4.8 g, 20 mmol) was added at such a rate as to keep the temperature between 60 and 70 °C. After the completion of adding compound **36**, the resulting mixture was warmed to 80 °C and stirred for another 10 min. The mixture was cooled to rt and poured into ice (200 g). The solid was collected by filtration, washed with water for several times, and dried *in vacuo* to give compound **37** (3.6 g, 80% yield) as an orange solid. LC-MS (ESI) *m/z*: 225.9 $(M + H)^+$.

[0397] **Step c**. A mixture of compound **37** (1.35 g, 6.0 mmol), 1- (4-bromophenyl) ethanone (1.14 g, 5.7 mmol), and potassium hydroxide (1.02 g, 18.3 mmol) in ethanol (50 mL) was refluxed overnight. The reaction mixture was concentrated and the residue was diluted with petroleum ether (100 mL) and water (200 mL). The aqueous phase was isolated, acidified by adding 1N HCl, and then extracted with ethyl acetate (50 mL× 3). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **38** (1.2 g) as a red solid, which was used for the next step without further purification. LC-MS (ESI) *m/z*: 405.9 $(M + H)^+$.

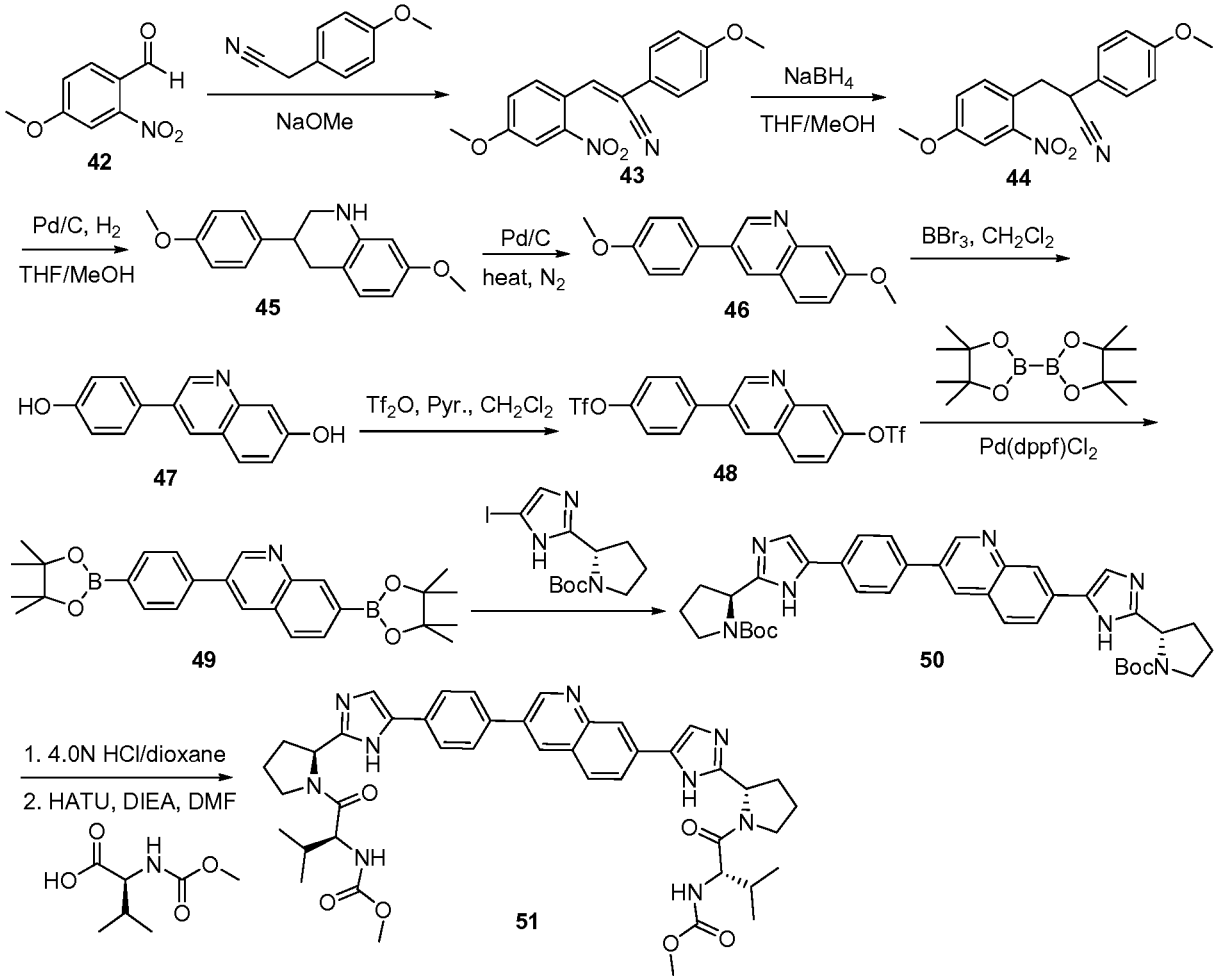
[0398] **Step d**. A flask that charged with compound **5** (1.2 g, 2.95 mmol) was heated to 300 °C for 30 min under an atmosphere of Ar. The solid was then purified by silica gel column chromatography (Petroleum ether/EtOAc = 19:1 (*v/v*)) to give compound **39** (160 mg, 15% yield) as a yellow solid. LC-MS (ESI) *m/z*: 361.9 $(M + H)^+$.

[0399] **Step e**. A mixture of compound **39** (0.11 g, 0.30 mmol), bis(pinacolato)diboron (0.34 g, 1.3 mmol), potassium acetate (0.15 g, 1.5 mmol), and $Pd(dppf)Cl_2$ (50 mg, 0.06 mmol) and dioxane (20 mL) was stirred at 80 °C overnight under an atmosphere of Ar. Subsequently, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with H_2O (50 mL) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 10/1 (*v/v*)) to give compound **40** (0.12 g, 86% yield). LC-MS (ESI) *m/z*: 458.3 $(M + H)^+$. (The corresponding boronic acid was also isolated and used as an active intermediate for the next step).

[0400] **Step f**. A solution of compound **40** (120 mg, 0.26 mmol) in DME/H_2O (3/1(*v/v*); 24 mL) was sequentially added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (290 mg, 0.80 mmol), $NaHCO_3$ (220 mg, 2.6 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (62 mg, 0.064 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C overnight under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (100 mL). The organic layer was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (PE/acetone = 2/1(*v/v*)) to give compound **17** (151 mg, 86% yield) as a yellow solid. LC-MS (ESI): m/z 676.4 $(M+H)^+$.

[0401] **Step g**. To a stirred solution of compound **41** (120 mg, 0.18 mmol) in dioxane (2 mL) was added 4N HCl/dioxane (2 mL). After stirring at rt overnight, 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 476.2 $(M+H)^+$.

[0402] **Step h**. To a mixture of the HCl salt in DMF (2 mL) was added DIPEA (0.3 mL, 1.8 mmol), followed by N-Moc-L-Val-OH (79 mg, 0.45 mmol) and HATU (169 mg, 0.45 mmol). After stirring at rt for 30 min, the reaction mixture was slowly poured into H_2O. The solid was collected by filtration and purified by preparative HPLC to give compound **42**. ^1H NMR (500 MHz, CD_3OD) δ 8.96 (d, 2H, J = 9.5 Hz), 8.63 (s, 1H), 8.53 (d, 2H, J = 10.0 Hz) , 8.40–8.39 (m, 3H), 8.18 (s, 1H), 8.08 (d, 2H, J = 13 Hz), 5.29–5.28 (m, 2H), 4.26–4.24 (m, 2H), 4.11–4.10 (m, 2H), 3.99–3.97 (m, 2H), 3.66 (s, 6H), 2.60 (m, 2H), 2.30–2.24 (m, 3H), 2.21–2.19 (m, 3H), 2.14–2.09 (m, 2H) , 1.00–0.83 (m, 12H) ppm; LC-MS (ESI) *m/z*: 790.4 $(M + H)^+$.



Scheme 3-6

[0403] **Step a**. Referring to Scheme 3-6, a mixture of 4-methoxy-2-nitrobenzaldehyde (**42**) (1.4 g, 7.7 mmol) and 4-methoxyphenyl acetonitrile (1.13 g, 7.7 mmol) was added to a solution of sodium methylate (0.4 g, 7.7 mmol) in methanol (10 mL) at rt. After stirring at rt for 5 h, the reaction mixture was filtered. The solid was washed with water and 95% ethanol, respectively, and dried *in vacuo* to give compound **43** (1.82 g, 77% yield) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.28 (m, 1H), 6.98 (d, J = 9.0 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H) ppm.LC-MS (ESI): *m/z* 311.1 $(M + H)^+$.

[0404] **Step b**. A solution of compound **43** (15.5 g, 50 mmol) in THF/methanol (5/1 (*v/v*), 240 mL) was added $NaBH_4$ (2.8 g, 75 mmol) at rt. After stirring at rt for 4 h, the reaction mixture was poured into ice water and treated with 1 N aq. HCl. The resulting mixture was extracted with

EtOAc (50 mL × 2). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **44** (9.8 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 335.1 $(M + Na)^+$.

[0405] **Step c**. A mixture of compound **44** (9.0 g, 29 mmol) and 10% Pd/C (4.5 g) in THF (240 mL) and MeOH (60 mL) was stirred at 45 °C for 48 h under an atmosphere of H_2. The resulting mixture was filtered through CELITE™545; the filtered cake was washed with MeOH (50 mL × 3). The filtrate was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether / Ethyl acetate 9:1) to give compound **45** (5.5 g, 71 % yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.5 Hz, 2H), 6.91-6.87 (m, 3H), 6.25 (d, *J* = 8.5 Hz, 1H), 6.12 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.41 (d, *J* = 11.0 Hz, 1H), 3.27 (t, *J* = 11.0 Hz, 1H), 3.11-3.05 (m, 1H), 2.90 (d, *J* = 8.0 Hz, 2H) ppm; LC-MS (ESI): *m/z* 270.1 $(M + H)^+$.

[0406] **Step d**. A mixture of compound **45** (2.7 g, 10 mmol) and 10% Pd/C (1.4 g) was stirred at 270~280 °C for 30 min under an atmosphere of Ar. The mixture was purified by silica gel column chromatography (Petroleum ether/EtOAc = 6/1 (*v/v*)) to give compound **46** (1.8 g, 68%) as a white solid. LC-MS (ESI): *m/z* 266.1 $(M + H)^+$.

[0407] **Step e**. To a solution of compound **46** (0.80 g, 3.0 mmol) in CH_2Cl_2 (30 mL) was added 4 N BBr_3/CH_2Cl_2 (4.5 mL, 18 mmol) at -40 °C. After stirring at rt overnight, the reaction mixture was diluted with water (30 mL). The resulting mixture was treated with 1 N aq. NaOH solution to adjust the pH to 8, and extracted with EtOAc (60 mL × 2). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (Petroleum ether/EtOAc = 2/1 (*v/v*)) to give compound **47** (0.7 g, 99%) as a white solid. LC-MS (ESI): *m/z* 238.1 $(M + H)^+$.

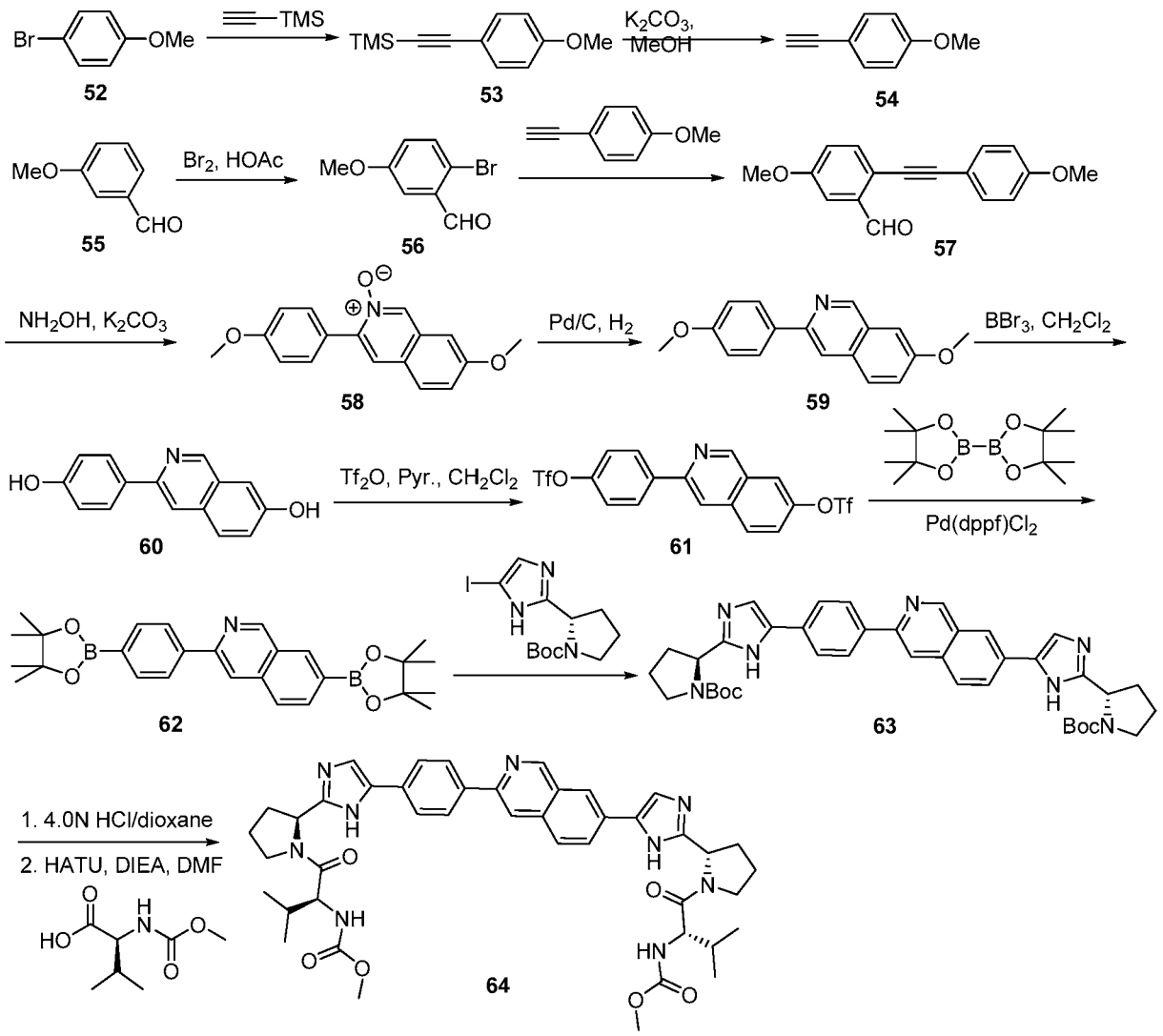
[0408] **Step f**. To a solution of compound **47** (0.82 g, 3.5 mmol) and pyridine (1.3 g, 16 mmol) in CH_2Cl_2 (45 mL) was added and Tf_2O (3.6 g, 13 mmol) at 0 °C. After stirring at rt for 30 min, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (Petroleum ether/EtOAc = 10/1 (*v/v*)) to give compound **48** (0.40 g, 23%) as a yellow solid. LC-MS (ESI): *m/z* 502.1 $(M + H)^+$.

[0409] **Step g**. A mixture of compound **48** (0.40 g, 0.80 mmol), bis(pinacolato)diboron (1.0 g, 4.0 mmol), potassium acetate (0.55 g, 5.6 mmol), and Pd(dppf)Cl_2 (200 mg, 0.24 mmol) and dioxane (20 mL) was stirred at 80 °C overnight under an atmosphere of Ar. Subsequently, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with H_2O (50 mL) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 10/1 (*v/v*)) to give compound **49** (0.20 g, 54% yield). LC-MS (ESI) *m/z*: 458.3 $(M + H)^+$. (The corresponding boronic acid was also isolated and used as an active intermediate for the next step).

[0410] **Step h**. A solution of compound **49** (160 mg, 0.35 mmol) in DME/H_2O (3/1(*v/v*); 40 mL) was sequentially added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (388 mg, 1.07 mmol), $NaHCO_3$ (289 mg, 3.44 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (71 mg, 0.090 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C overnight under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (100 mL). The organic layer was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 2/1(*v/v*)) to give compound **50** (151 mg, 64% yield) as a yellow solid. LC-MS (ESI): *m/z* 676.4 $(M+H)^+$.

[0411] **Step i**. To a stirred solution of compound **50** (140 mg, 0.21 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL) at rt. After stirring at rt overnight, 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* 476.2 $(M+H)^+$.

[0412] **Step j**. To a mixture of the HCl salt in DMF (2 mL) was added DIPEA (0.35 mL, 2.1 mmol), followed by N-Boc-L-Val-OH (92 mg, 0.53 mmol), and HATU (200 mg, 0.530 mmol). After stirring at rt for 30 min, the reaction mixture was poured into water. The solid was collected by filtration and purified by preparative HPLC to give compound **51**. ^1H NMR (500 MHz, CD_3OD) δ 9.29 (br, 1H), 8.67–8.63 (m, 1H), 8.44–8.41 (m, 1H), 8.29–8.21 (m, 2H), 8.13 (s, 2H), 8.01 (s, 2H), 5.31–5.25(m, 2H), 4.26–4.23 (m, 2H), 4.12 (s, 2H), 4.05–3.91 (m, 2H), 3.66 (s, 3H), 3.62 (s, 3H), 2.60 (m, 2H), 2.31–1.95 (m, 7H), 1.01–0.86 (m, 12H) ppm; LC-MS (ESI): *m/z* 790.4 $(M + H)^+$.



Scheme 3-7

[0413] **Step a**. Referring to Scheme 3-7, a mixture of compound **52** (9.35 g, 50 mmol), TMS-acetylene (7.35 g, 75 mmol), DIEA (21.0 mL, 150 mmol), CuI (475 mg, 2.50 mmol), $Pd(PPh_3)_2Cl_2$ (3.51 g, 5.0 mmol), and PPh_3 (2.62 g, 10.0 mmol) in anhydrous THF (100 mL) was refluxed overnight under an atmosphere of Ar. The reaction mixture was concentrated and the residue was diluted with water (50mL) and EtOAc (150 mL). The organic layer was washed with brine 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 compound **53** (10.0 g, 98%) as a yellow oil. LC-MS (ESI): *m/z* 205.1 $(M+H)^+$.

[0414] **Step b**. A mixture of compound **53** (2.4 g, 11.7 mmol) and K_2CO_3 (4.9 g, 35.3 mmol) in THF (20 mL) and MeOH (20 mL) was stirred at rt for 3 h. The solvent was removed and the residue was diluted with EtOAc (150 mL), washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 10/1 (*v/v*)) to give compound **54** (1.3 g, 84%) as a yellow oil. LC-MS (ESI): *m/z* 133.1 $(M+H)^+$.

[0415] **Step c**. To a solution of compound **55** (25.0 g, 184 mmol) in AcOH (125 mL) was added Br_2 (11.0 mL, 220 mmol). After stirring at rt for 4 h, the reaction mixture was filtered. The solid was washed with $H_2O$and dried *in vacuo* to give compound **56** (38 g, 96%) as a white solid. LC-MS (ESI): *m/z* 215.0 $(M+H)^+$.

[0416] **Step d**. A mixture of compound **54** (17.9 g, 83.3 mmol), compound **56** (11.0 g, 83.3 mmol), CuI (1.59 g, 0.25 mmol), Et_3N (23.00 mL, 166.6 mmol), $Pd(PPh_3)_2Cl_2$ (2.95 g, 4.20 mmol), and PPh_3 (4.40 g, 16.7 mmol) in DMF (100mL) was stirred at 40 °C overnight under an atmosphere of N_2. The reaction mixture was concentrated and the residue was diluted with EtOAc (500 mL). The resulting mixture was washed with brine 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 compound **57** (9.8 g, 45%). LC-MS (ESI): *m/z* 267.1 $(M+H)^+$.

[0417] **Step e**. A solution of compound **57** (5.5 g, 21 mmol) in EtOH (100 mL) was added hydroxylamine hydrochloride (1.73 g, 25.0 mmol) and NaOAc (2.05 g, 25.0 mmol), respectively. After stirring at 60 °C for 2 h, the reaction mixture was added K_2CO_3 (4.3 g, 31 mmol) and H_2O (15 mL). The resulting mixture was refluxed for 12 h and then concentrated. The residue was dissolved in EtOAc and the resulting mixture was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **58** (5.8 g). LC-MS (ESI): *m/z* 282.1 $(M+H)^+$.

[0418] **Step f**. A mixture of compound **58** (100 mg, 0.36 mmol) and 5% Pd/C (75 mg) in EtOH (25 mL) was stirred at rt overnight under an atmosphere of H_2. The reaction mixture was filtered through CELITE™545. The filtered cake was washed MeOH (25 mL × 3). The filtrate was concentrated and the residue was purified by silica gel column chromatography to give compound **59** (50 mg, 53%). LC-MS (ESI): *m/z* 266.1 $(M+H)^+$.

[0419] **Step g**. To a solution of compound **59** (2.0 g, 7.5 mmol) in CH_2Cl_2 (75 mL) was added 4N BBr_3 in CH_2Cl_2 (12 mL, 45 mmol) at -40 °C under an atmosphere of N_2. After stirring at rt overnight, the reaction was quenched by adding water (10 mL). Subsequently, the mixture was treated with saturated aqueous $NaHCO_3$ to adjust the pH value to 8. The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 2/1 (*v/v*)) to give compound **60** (1.36 g, 76%) as a white solid. LC-MS (ESI): *m/z* 238.1 $(M+H)^+$.

[0420] **Step h**. To a solution of substrate **7** (1.36 g, 5.7 mmol) and pyridine (2.03 g, 25.7 mmol) in CH_2Cl_2 (120 mL) was added Tf_2O (5.84 g, 20.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 10/1 (*v/v*)) to give compound **61** (2.4 g, 84%) as a yellow solid. LC-MS (ESI): *m/z* 502.0 $(M+H)^+$.

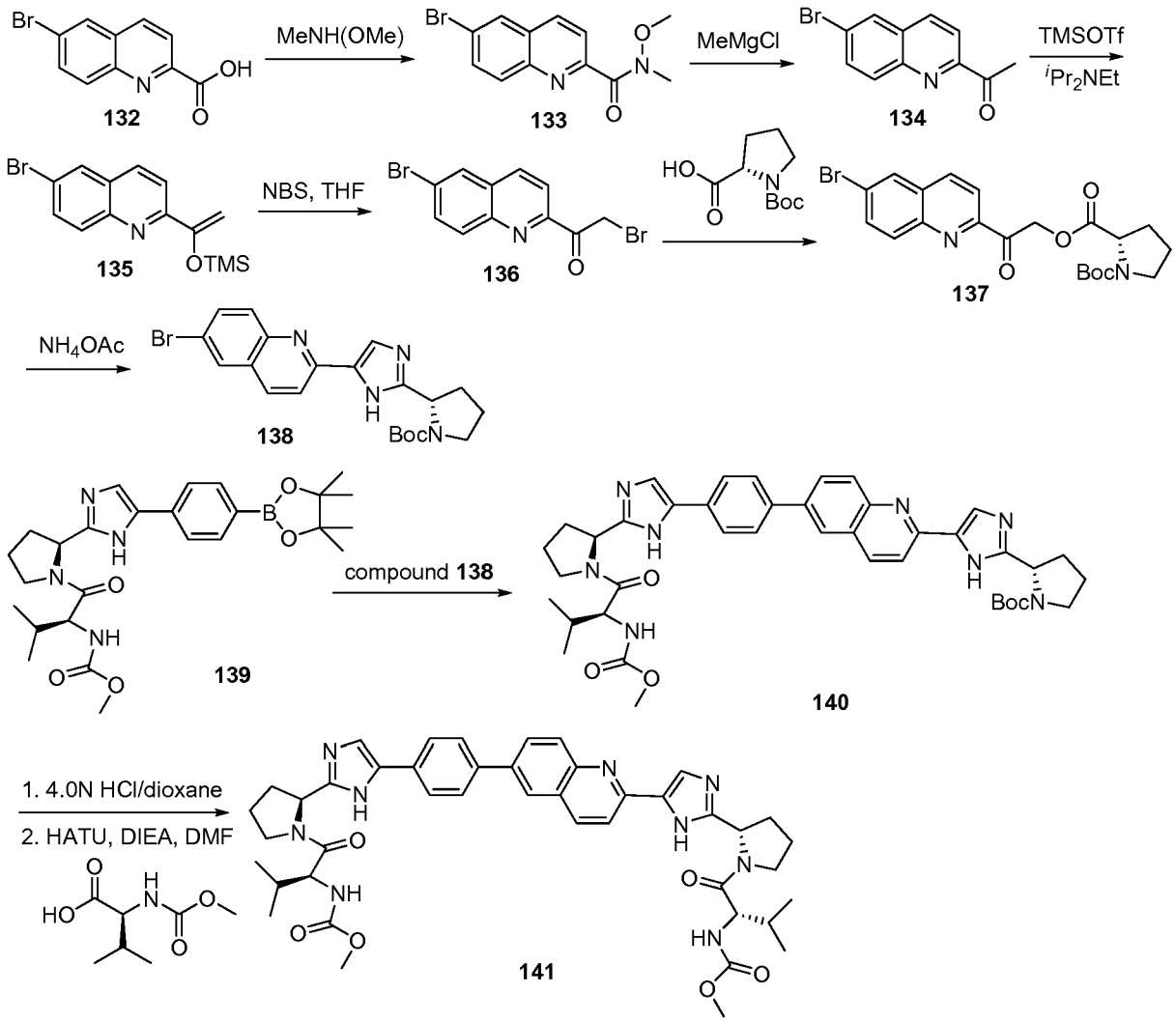
[0421] **Step i**. A mixture of compound **61** (2.0 g, 4.0 mmol), bis(pinacolato)diboron (5.1 g, 20 mmol), potassium acetate (2.7 g, 28 mmol), and Pd(dppf)Cl_2 (0.98 g, 1.2 mmol) and dioxane (80 mL) was stirred at 80 °C overnight under an atmosphere of Ar. Subsequently, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with H_2O (50 mL) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 10/1 (*v/v*)) to give compound **62** (986 mg, 54% yield). LC-MS (ESI) *m/z*: 458.3 $(M + H)^+$. (The corresponding boronic acid was also isolated and used as an active intermediate for the next step).

[0422] **Step j**. A solution of compound **62** (1.7 g, 3.7 mmol) in DME/H_2O (3/1(*v/v*); 40 mL) was sequentially added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (3.70 g, 10.0 mmol), $NaHCO_3$ (2.7 g, 32 mmol), and Pd(dppf)Cl_2 (0.65 mg, 0.80 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C overnight under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (150 mL). The organic layer was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 2/1(*v/v*)) to give compound **63** (650 mg, 26%) as a yellow solid. LC-MS (ESI): *m/z* 676.4 $(M+H)^+$.

[0423] **Step k**. To a stirred solution of compound **63** (200 mg, 0.3 mmol) in dioxane (3 mL) was added 4N HCl in dioxane (3 mL) at rt. After stirring at rt overnight, the reaction mixture was

concentrated and the residue was dried *in vacuo* to give an HCl salt, which was used for the next without further purification. LC-MS (ESI): *m/z* 476.2 $(M+H)^+$.

[0424] **Step l**. Subsequently, a mixture of the HCl salt in DMF (3 mL) was added DIPEA (0.5 mL, 3.0 mmol), followed by N-Moc-L-Val-OH (130 mg, 0.740 mmol), and HATU (281 mg, 0.740 mmol). After stirring at rt for 30 min, the reaction mixture was poured into H_2O. The solid was collected by filtration and purified by preparative HPLC to give compound **64**. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.80 (s, 1H), 8.87-8.71 (m, 2H), 8.41-8.18 (m, 6H), 8.05-7.80 (m, 3H), 5.30-5.27 (m, 2H), 4.25 (s, 2H), 4.12 (s, 2H), 4.03-3.90 (m, 2H), 3.66 (s, 6H), 2.61 (s, 2H), 2.31-2.08 (m, 8H), 1.09-0.90 (m, 12H); LCMS (ESI): *m/z* 790.4 $(M + H)^+$.



Scheme 3-8

[0425] **Step a**.Referring to Scheme 3-8, to a solution of **132** (3.70 g, 14.7 mmol) in DMF (50 mL) at rt, *N*,*O*-Dimethylhydroxylamine hydrochloride (1.46 g, 15.0 mmol), HATU (6.15 g, 16.2 mmol), and Et_3N (2.22 g, 22.0 mmol) were added. After stirring at rt for 24 h, the reaction mixture was concentrated and the residue was diluted with DCM (150 mL). The mixture was washed with saturated aqueous NH_4Cl and brine, respectively, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 4/1 (*v/v*)) to give compound **133** (3.78 g, 87% yield) as a yellow solid. LC-MS (ESI): *m/z* 295.0 $(M + H)^+$.

[0426] **Step b**. To a solution of compound **133** (3.53 g, 12.0 mmol) in THF (80 mL) was slowly added 3M MeMgCl in THF (6 mL) at 0 °C. After stirring at 0°C for 1 h and then at rt for another 1 h, the reaction was quenched by adding saturated aqueous NH_4Cl. The reaction mixture was concentrated and the residue was added saturated aqueous $NaHCO_3$ (25 mL) and EtOAc (100 mL). The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give compound **134** (3.0 g, 100%) as a white solid. LC-MS (ESI): *m/z* 250.0 $(M+H)^+$.

[0427] **Step c**. To a solution of compound **134** (2.80 g, 11.2 mmol) in DCM (80 mL) was added $^{i}Pr_2NEt$ (5.79 g, 44.8 mmol). The mixture was cooled to 0 °C and TMSOTf (7.47 g, 33.6 mmol) was drop-wisely added. After stirring at 0 °C for 30 min and then at rt for another 1 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, respectively, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **135** (3.6 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 322.0 $(M+H)^+$.

[0428] **Step d**. To a solution of compound **135** (3.60 g, 11.2 mmol) in THF (60 mL) was drop-wisely added solution of NBS (1.79 g, 10.1 mmol) in THF (20 mL) at 0 °C. After stirring at 10 °C for 1 h, the reaction mixture was concentrated and the residue was diluted with DCM (150 mL). The mixture was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **136** (3.6 g), which was used of the next step without further purification. LC-MS (ESI): *m/z* 327.9 $(M+H)^+$.

[0429] **Step e**. To a solution of compound **136** (3.6 g, 10.9 mmol) in EtOAc (100 mL) at rt, (*S*)-N-Boc-Pro-OH (2.47 g, 11.5 mmol) and Et_3N (3.31 g, 32.7 mmol) were added. After stirring

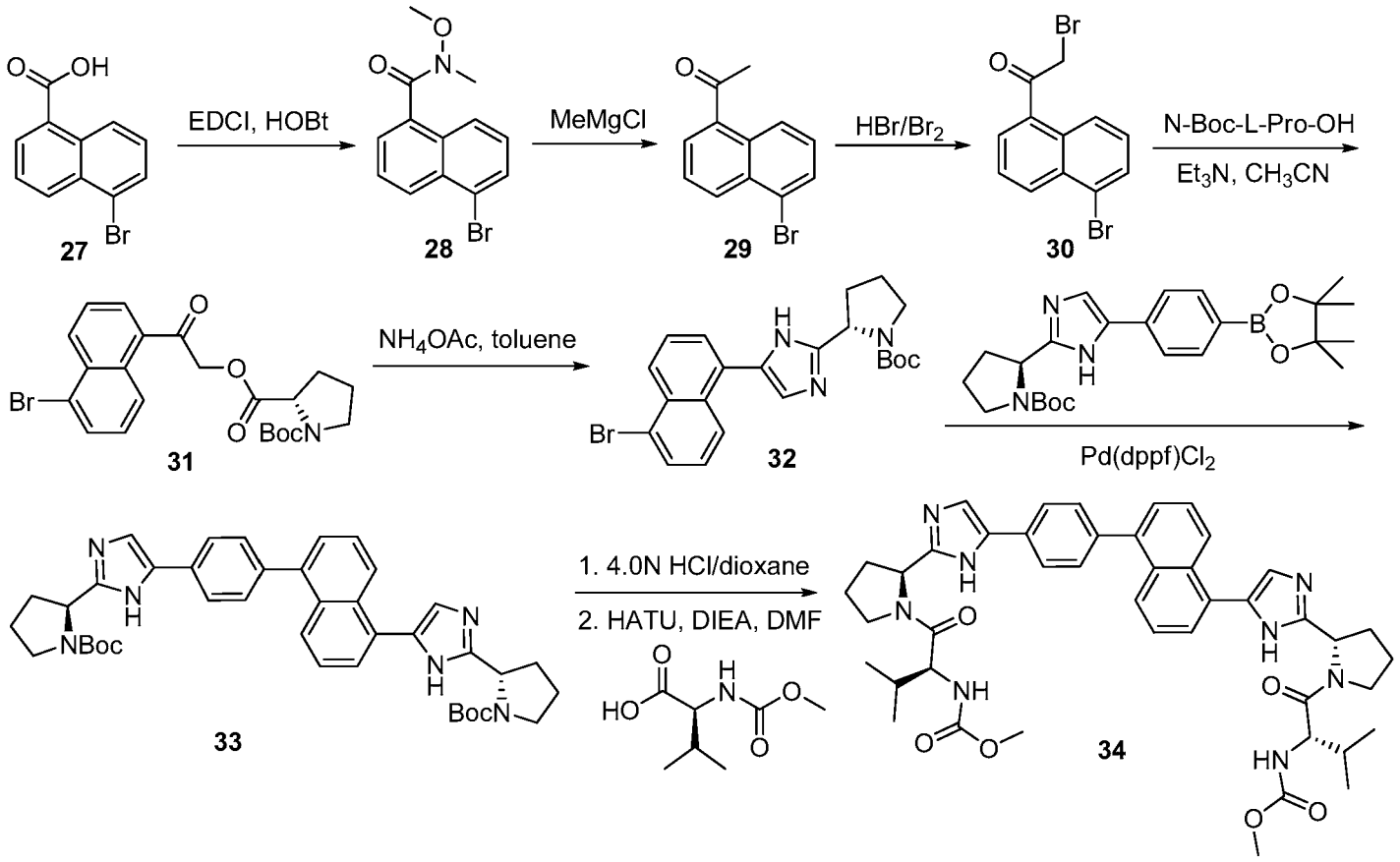
at rt for 5 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, respectively, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **137** (5.0 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 463.1 $(M+H)^+$.

[0430] **Step f**. A mixture of crude compound **137** (5.0 g) and NH_4OAc (8.39 g, 109 mmol) in toluene (100 mL) was stirred at 115 °C overnight. The solvent was removed and the residue was diluted with EtOAc (200 mL). The mixture was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 3/1 (*v/v*)) to give compound **138** (1.2 g, 25%) as a white solid. LC-MS (ESI): *m/z* 443.1 $(M+H)^+$.

[0431] **Step g**. To a mixture of compound **138** (442 mg, 1.00 mmol), compound **139** (546 mg, 1.10 mmol), and $NaHCO_3$ (336 mg, 4.00 mmol) in 1, 2-dimethoxyethane (8 mL) and H_2O (2 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163 mg, 0.20 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight, the reaction mixture was concentrated and the residue was diluted with EtOAc (50 mL) and H_2O (10 mL).The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/2 (*v/v*)) to give compound **140** (500 mg, 68% yield) as a yellow solid. LC-MS (ESI): *m/z* 733.4 $(M+H)^+$.

[0432] **Step h**. To a solution of compound **140** (139 mg, 0.19 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2.0 mL). After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was dissolved in water (5 mL) and added saturated aqueous $NaHCO_3$ to adjust pH value to 8. The resulting mixture was saturated with NaCl and extracted with DCM (15 mL x 5). The extracts were combined and dried with dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give a free base, which was used for the next step without further purification. LC-MS (ESI): *m/z* 633.3 $(M + H)^+$.

[0433] **Step i**. Subsequently, the free base was dissolved in DCM (5 mL) and the mixture was added N-Moc-L-Val-OH (40 mg, 0.23 mmol) and DIC (29 mg, 0.23 mmol). After stirring at rt for 20 min, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **141**. LC-MS (ESI): *m/z* 790.4 $(M+H)^+$.


EDCI, HOBt
MeMgCl
HBr/Br2
N-Boc-L-Pro-OH
Et3N, CH3CN
NH4OAc, toluene
Pd(dppf)Cl2
1. 4.0N HCl/dioxane
2. HATU, DIEA, DMF
27
28
29
30
31
32
33
34

Scheme 4-1

EXAMPLE 4 – Synthesis of compounds of Formula IIe

[0434] **Step a**.Referring to Scheme 4-1, a solution of compound **27** (5.0 g, 20 mmol) in CH_3CN (200 mL) was added EDCI (5.8 g, 30 mmol), HOBt (675 mg, 30 mmol), MeNH(OMe)·HCl (2.93 g, 30 mmol), and Et_3N (6.1 g, 60 mmol) at rt. After stirring at rt for 3 h, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 5/1 (*v/v*)) to give compound **28** (5.4 g, 92% yield) as a white solid. LC-MS (ESI): *m/z* 294.0 $(M + H)^+$.

[0435] **Step b**. To a solution of compound **28** (2.9 g, 10 mmol) in THF (100 mL) was slowly added 3M MeMgCl in THF (20 mmol) at 0°C under an atmosphere of N_2. After stirring at 0°C for 1 h and then at rt for 1 h, the reaction was quenched by adding several drops of aq. NH_4Cl. The reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL). The organic phase was washed with sat. aq. $NaHCO_3$ and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/AcOEt = 10:1(*v/v*)) to give compound **29** (2.3 g, 92% yield). LC-MS (ESI): *m/z* 249.0 $(M + H)^+$.

[0436] **Step c**. To a solution of **29** (1.84 g, 7.4 mmol) in DCM (100mL) was drop-wisely added Br_2 (l8.8 g, 14.7 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was warmed to rt with stirring for another 2 h. Subsequently, the reaction mixture was respectively washed with water, and saturated aqueous $NaHCO_3$, and the organic phase was dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **30** (2.0 g) as a yellow solid, which was used for the next step without further purification. LC-MS (ESI): *m/z* 326.9 $(M+H)^+$.

[0437] **Step d**. A solution of compound **30** (1.95 g, 5.9 mmol) in DCM (50 mL) was added N-Boc-L-Pro-OH (1.6 g, 7.3 mmol) and Et_3N (1.7 mL, 12.2 mmol) at rt. After stirring st rt for 2 h, the reaction mixture was washed with saturated NH_4Cl, and brine, respectively; the organic phase was dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **31** (2.4 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 462.1 $(M+H)^+$.

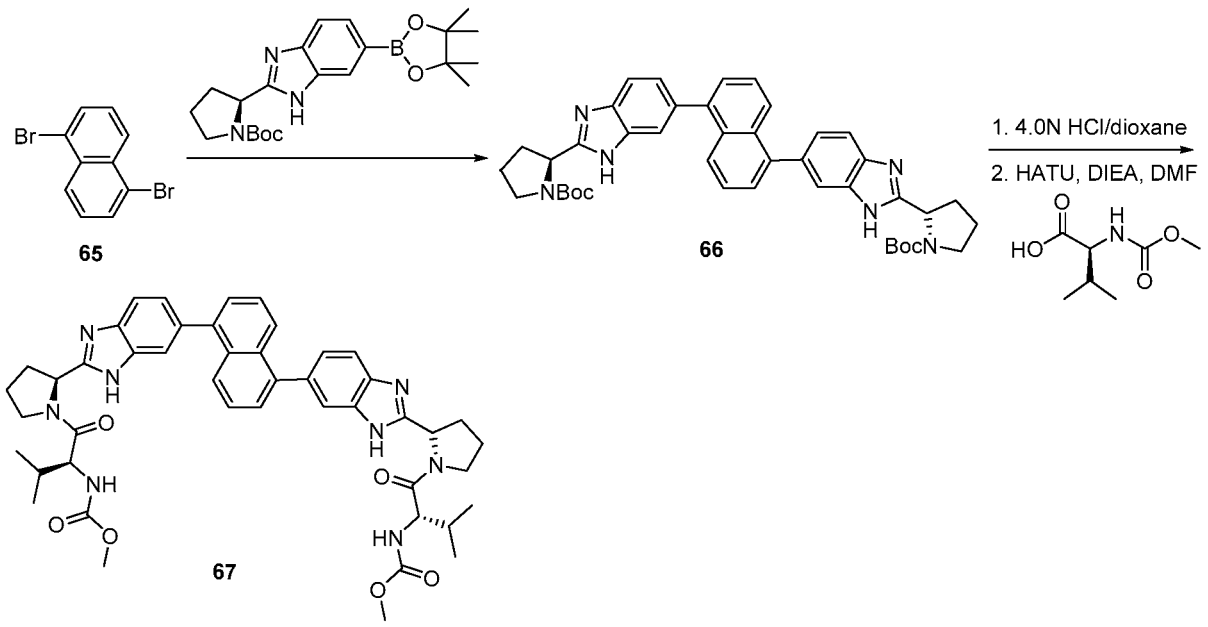
[0438] **Step e**. A mixture of compound **31** (2.4 g, 5.2 mmol) and NH_4OAc (4.0 g, 52 mmol) in toluene (52 mL) stirred at 110 °C overnight. Subsequently, the reaction mixture was cooled to rt and diluted with EtOAc (100 mL). The mixture was washed with saturated aqueous Na_2CO_3 (50 mL × 2), and brine, respectively; the organic phase was dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/1(*v/v*)) to give compound **32** (1.4 g, 62%) as a yellow solid. LC-MS (ESI): *m/z* 442.1 $(M+H)^+$.

[0439] **Step f**. To a mixture of compound **32** (1.0 g, 2.3 mmol), (*S*)-*tert*-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazol-2-yl)pyrolidine-1-carboxylate (1.0 g, 2.3 mmol), and $NaHCO_3$ (0.76 g, 9.0 mmol) in 1, 2-dimethoxyethane (30 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (277 mg, 0.34 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was diluted with H_2O (50 mL) and the aqueous phase was extracted with EtOAc (50 mL × 3). The extracts were combined and washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether /EtOAc = 5/2 (*v/v*)) to give compound **33** (1.0 g, 78% yield) as a yellow solid. LC-MS (ESI): *m/z* 675.4 $(M + H)^+$.

[0440] **Step g**. To a stirred solution of compound 33 (250 mg, 0.37 mmol) in dioxane (3 mL) was drop-wisely added 4.0N HCl in dioxane (3mL) at rt. 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* 475.3 $(M + H)^+$.

[0441] **Step h**. Subsequently, the HCl salt was suspended in THF (5 mL) and DIPEA (0.35 mL) and N-Moc-L-Val-OH (130 mg, 0.74 mmol) at rt. After stirring at rt for 15 min, HATU (340 mg, 0.89 mmol) was added and the resulting reaction mixture was stirred at rt for another 2 h. The solvent was removed and the residue was purified by preparative HPLC to give compound **34**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.04-8.06 (m, 1H), 7.96-7.99 (m, 2H), 7.91-7.92 (m, 2H), 7.79 (s, 1H), 7.70-7.71 (m, 2H), 7.66-7.67 (m, 2H), 7.60-7.61 (m, 2H), 5.29-5.31 (m, 2H), 4.27 (s, 2H), 4.13 (s, 2H), 3.92 (s, 2H), 3.68 (s, 6H), 2.63 (s, 2H), 2.17-2.32 (m, 6H), 2.12 (s, 2H), 0.93 - 0.97 (m, 12H) ppm; LC-MS (ESI): *m/z* 789.4 $(M+H)^+$.

EXAMPLE 5 – Synthesis of compounds of Formula IIII



Scheme 5-1

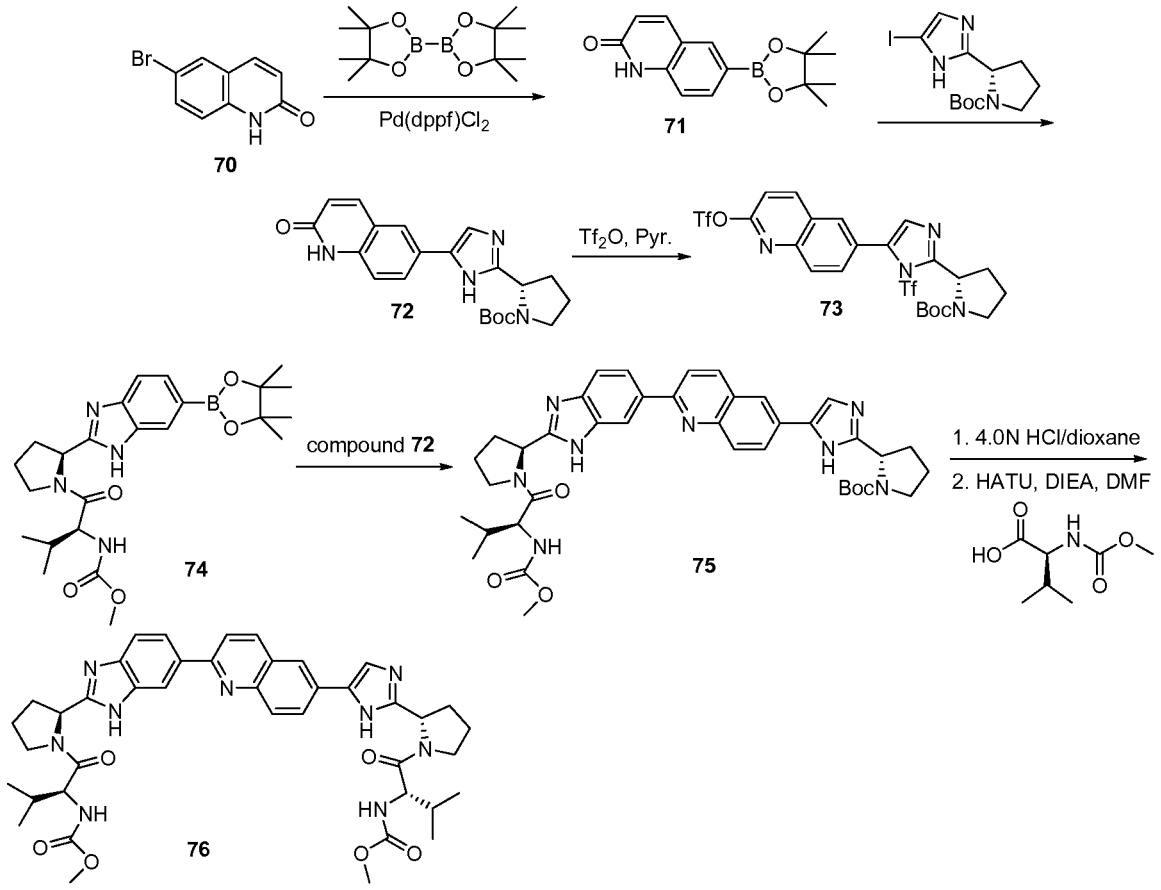
[0442] **Step a**. Referring to Scheme 5-1, a mixture of compound **65** (300 mg, 1.05 mmol), (*S*)-tert-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (1.14 g, 2.75 mmol), and $NaHCO_3$ (740 mg, 8.80 mmol) in 1, 2-dimethoxyethane (30 mL) and water (10 mL) were added $Pd(dppf)Cl_2$ (179 mg, 0.220 mmol) at rt under an atmosphere of N_2. After stirring at 80 ^{0}C overnight, the reaction mixture was concentrated. The residue was diluted with DCM (100 mL) and water (25 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 2/1 (*v/v*)) to give compound **66** (650 mg, 86%). LC-MS (ESI): *m/z* 699.4 $(M+H)^+$.

[0443] **Step b**. To a solution of compound **66** (110 mg, 0.16 mmol) in dioxane (2 mL) was added 4.0 N HCl in dioxane (2 mL) at rt. After stirring at rt for 3 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give an HCl salt, which was used directly for the next step without further purification. LC-MS (ESI): *m/z* 499.3 $(M+H)^+$.

[0444] **Step c**. Subsequently, the HCl salt was dissolved in DMF (2 mL), followed by adding DIPEA (207 mg, 16 mmol), N-Moc-L-Val-OH (68 mg, 0.39 mmol), and HATU (148 mg, 0.39 mmol) at rt. After stirring at rt for 15 min, the reaction mixture was added into water. The

solid was collected by filtration and purified by preparative HPLC to give compound **67**. LC-MS (ESI) *m/z* 813.4 $(M + H)^+$.

EXAMPLE 6 – Synthesis of compounds of Formula IIId



Scheme 6-1

[0445] **Step a**. Referring to Scheme 6-1, a mixture of compound **70** (8.00 g, 35.7 mmol, purchased from Aldrich Chemicals, Milwaukee, Wisconsin, USA), bis(pinacolato)diboron (10.9 g, 42.8 mmol), K_2CO_3 (10.50 g, 107.1 mmol) in 1,4-dioxane (600 mL) was added $Pd(dppf)Cl_2$ (2.9 g, 3.6 mmol) at rt under an atmosphere of N_2. After stirring at 80 °C for 3 h under an atmosphere of N_2, the reaction mixture was cooled to rt and filtered through Celiirt®545. The filtered cake was washed with EtOAct (100 mL × 3). The filtrate was concentrated and the residue was diluted with EtOAc (500 mL). The resulting mixture was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica

gel column chromatography (Petroleum ether/Acetone = 1/1 (*v/v*)) to give compound **71** (8.28 g, 86% yield) as a light brown solid. LC-MS (ESI) *m/z* 272.1 $(M + H)^+$.

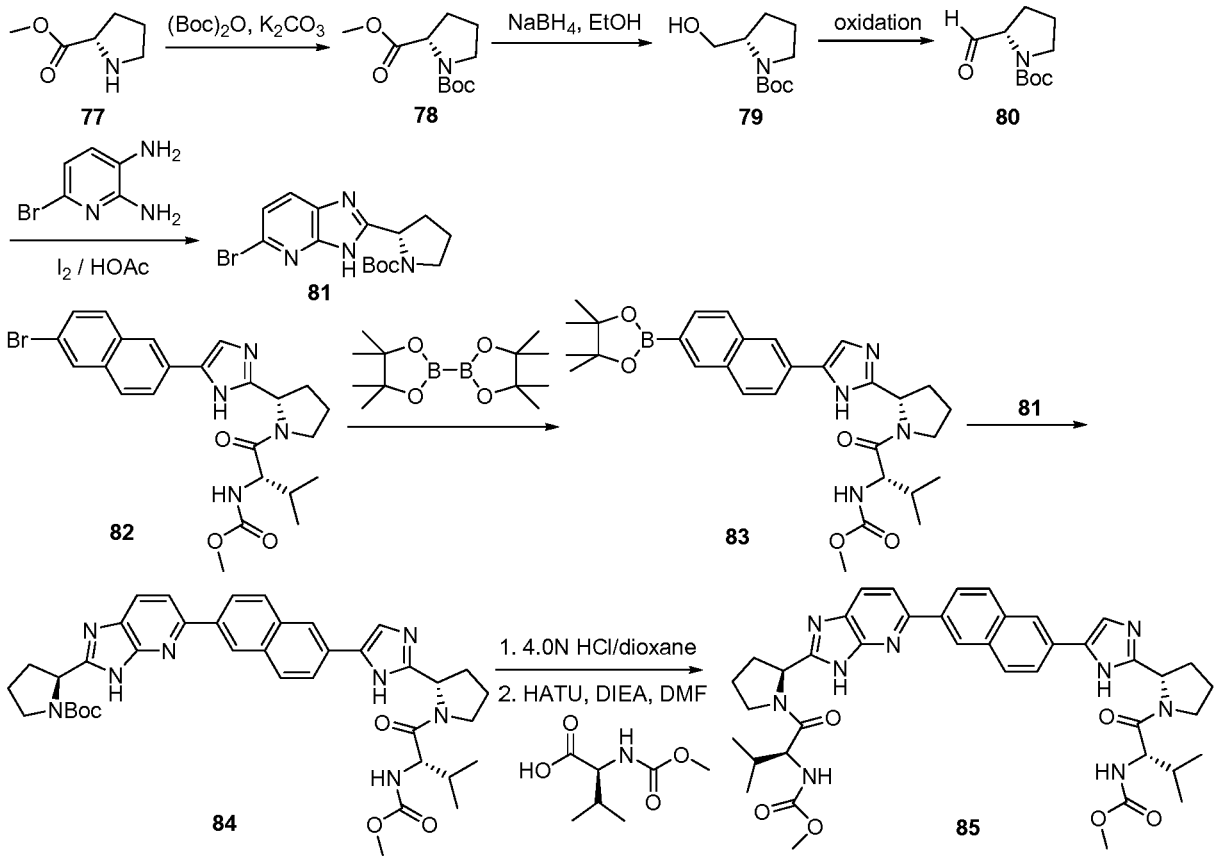
[0446] **Step b**. To a mixture of compound **71** (5.90 g, 21.8 mmol), (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (9.50 g, 26.2 mmol), $NaHCO_3$ (7.30 g, 87.2 mmol) in 1,2-dimethoxyethane (500 mL) and water (150 mL) was added $Pd(dppf)Cl_2$ (3.6 g, 4.4 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight, the reaction mixture was concentrated and the residue was diluted with EtOAc (250 mL) and water (50 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 5/1 (*v/v*)) to give compound **72** (5.30 g, 64% yield) as a yellow solid. LC-MS (ESI) *m/z* 381.2 $(M + H)^+$.

[0447] **Step c**. To a solution of compound **72** (2.0 g, 5.26 mmol) in 40 mL pyridine was drop-wisely added Tf_2O (3.71 g, 13.1 mmol) at 0 °C. After stirring at 0 °C for 1 h and at rt for 3 h, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/acetone = 4/1 (*v/v*)) to give compound **73** (2.04 g, 60% yield) as a yellow solid. LC-MS (ESI) *m/z* 645.1 $(M + H)^+$.

[0448] **Step d**. To a mixture of compound **73** (500 mg, 0.78 mmol), methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(6-(4,4,5,5-tertamethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)butan-2-ylcarbamate (**74**) (419 mg, 0.89 mmol), and $NaHCO_3$ (299 g, 3.56 mmol) in 1,2-dimethoxyethane (60 mL) and water (20 mL) was added $Pd(dppf)Cl_2$ (147 mg, 0.18 mmol) at rt under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was concentrated. The residue was diluted with EtOAc (100 mL) and water (25 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 1:1 (*v/v*)) to give compound **75** (0.40 g, 64% yield) as a yellow solid. LC-MS (ESI) *m/z* 707.4 $(M + H)^+$.

[0449] **Step e**. To a solution of compound **75** (114 mg, 0.161 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL) at rt. After stirring at rt for 3 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* 607.3 $(M + H)^+$.

[0450] **Step f**. Subsequently, the HCl salt was dissolved in DMF (2 mL), followed by adding Et_3N (0.11 mL, 0.81 mmol), N-Moc-L-Val-OH (32 mg, 0.18 mmol), and HATU (69 mg, 0.18 mmol) at rt. After stirring at rt for 1 h, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **76**. LC-MS (ESI): *m/z* 764.4 $(M + H)^+$.



Scheme 6-2

[0451] **Step a**. Referring to Scheme 6-2, a solution of compound **78** (50.0 g, 0.30 mol) in THF (500 mL) and H_2O (500 mL) was added K_2CO_3 (83 g, 0.60 mol) and $(Boc)_2O$ (73.0g, 0.330 mol). After stirring at rt overnight, the reaction mixture was concentrated and the residue was extracted with EtOAc (250 mL × 3). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **78** (62 g), which was used for the next step without further purification. LC-MS (ESI) *m/z* 230.1 $(M + H)^+$.

[0452] **Step b**. To a solution of compound **78** (60.0 g, 260 mmol) in EtOH (1 L) was slowly added $NaBH_4$ (50.0 g, 1.30 mol) at rt. After stirring at rt overnight, the reaction was quenched by

adding acetone (10 mL). The resulting mixture was concentrated and the residue was diluted with EtOAc (500 mL). The mixture was washed with brined and dried *in vacuo*. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/1 (*v/v*)) to give compound **79** (42.0 g, 80% yield) as a white solid. LC-MS (ESI) *m/z* 202.1 $(M + H)^+$.

[0453] **Step c**. To a solution of compound **79** (30.0 g, 150 mmol) and DMSO (35.0 g, 450 mmol) in DCM (1 L) was added oxalyl chloride (28.0 g, 220 mmol) at -78 °C. After stirring at -78 °C for 4 h, the reaction mixture was added Et_3N (60.0 g, 600 mol) and the resulting mixture was stirred for another 1 h at -78 °C. Subsequently, the reaction was quenched by adding H_2O. The organic layer was separated and the aqueous layer was extracted with DCM (200mL × 2). The extracts were combined, washed with brine, and dried with Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **80** (22.0 g) as a colorless oil, which was used immediately without further purification. LC-MS (ESI) *m/z* 200.1 $(M + H)^+$.

[0454] **Step d**. A mixture of compound **80** (7.7 g, 38.5 mmol), 6-bromopyridine-2,3-diamine (8.0 g, 42.8 mmol) (PCT Intl. Appl. **WO 2008021851**) , and iodine (1.08 g, 4.28 mmol) in AcOH (30 mL) was stirred at rt overnight. The reaction mixture was neutralized by adding saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc (200 mL × 3). The extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 80/1 (*v/v*)) to give compound **81** (7.8 g, 55% yield). LC-MS (ESI) *m/z* 367.1 $(M + H)^+$.

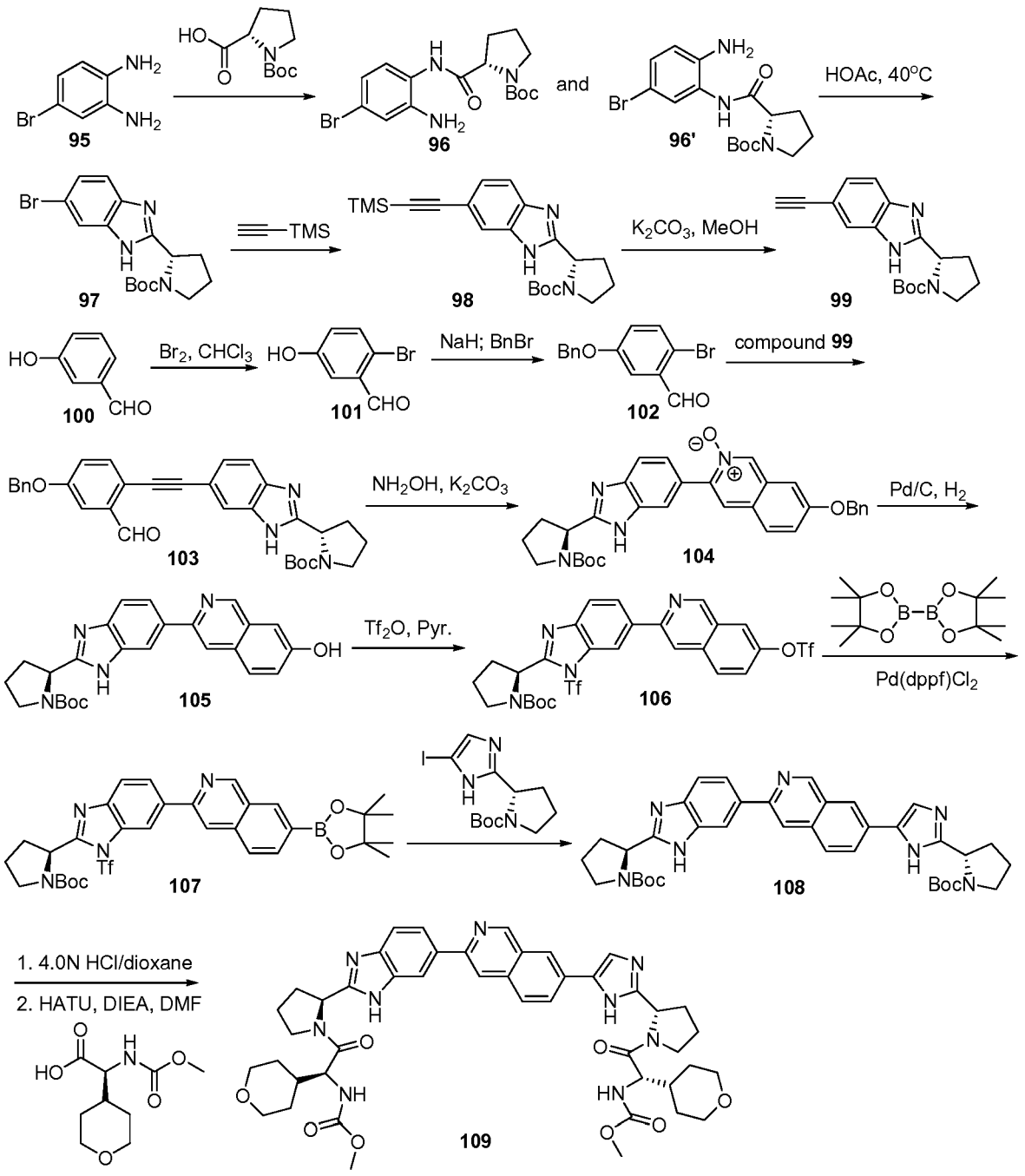
[0455] **Step e**. A mixture of compound **82** (10.0 g, 20.1 mmol), bis(pinacolato)diboron (7.65 g, 30.1 mmol), potassium acetate (6.89 g, 70.3 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (886 mg, 1.0 mmol) in 1,4-dioxane (200 mL) was stirred at 80 °C for 3 h under an atmosphere of N_2. The reaction mixture was filtered through CELITE™ 545 and the filtered cake was washed with EtOAc (200 mL × 3). The filtrate was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 50/1 (*v/v*)) to give compound **83** (9.8 g, 89% yield) as a white solid: LC-MS (ESI) *m/z* 547.3 $(M + H)^+$.

[0456] **Step f**. A mixture of compound **81** (2.0 g, 5.4 mmol), compound **83** (2.9 g, 5.4 mmol), $NaHCO_3$ (1.60 g, 18.9 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (239 mg, 0.27 mmol) in 1, 2-

dimethoxyethane (90 mL) and water (30 mL) was stirred at 80 °C overnight under an atmosphere of N_2. The reaction mixture was concentrated and the residue was added DCM (200 mL) and water (50 mL). The organic pahse was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 80/1 (*v/v*)) to give compound **84** (1.5 g, 40% yield) as a yellow solid. LC-MS (ESI) *m/z* 707.4 $(M + H)^+$.

[0457] **Step g**. To a solution of compound **84** (200 mg, 0.28 mmol) in 3 mL dioxane was added 4N HCl in dioxane (3 mL). After stirring at rt for 3 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* 607.3 $(M + H)^+$.

[0458] **Step h**. Subsequently, the HCl salt was dissolved in DMF (3 mL), and the resulting mixture was added Et_3N (0.20 mL, 1.4 mmol), N-Moc-L-Val-OH (55 mg, 0.31 mmol), and HATU (118 mg, 0.31 mmol). After stirring at rt for 1 h, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **85**. LC-MS (ESI): *m/z* 764.4 $(M + H)^+$.



Scheme 6-3

[0459] **Step a**. Referring to Scheme 6-3, to a solution of N-Boc-L-Pro-OH (29 g, 135 mmol) and DIPEA (29 g, 225 mmol) in THF (500 mL) was added HATU (51 g, 135 mmol) at rt. After stirring at rt for 10 min, 4-bromobenzene-1,2-diamine (**95**) (25 g, 135 mmol) was added and the resulting solution was stirred at rt for another several hours. Subsequently, the reaction mixture

was concentrated and the residue was diluted with EtOAc (500 mL). The resulting mixture was washed with water for several times (100 mL × 3) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give a mixture of crude compounds **96** and **96′**, which were used for the next step without further purification. LC-MS (ESI): *m/z* 384.1 $(M+H)^+$.

[0460] **Step b**. A mixture of crude compounds **96** and **96′** obtained from the reaction above in AcOH (1000 mL) was stirred at 40 °C for 12 h. Subsequently, the reaction mixture was carefully neutralized by adding saturated aqueous sodium bicarbonate solution to adjust the pH value to 8. The resulting mixture was extracted with EtOAc for several times (250 mL × 3). The extracts were combined, washed with water, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (Petroleum ether/EtOAc = 4/1 (*v/v*)) to give **97** (35 g, 71% yield, two steps from **95**) as a yellow solid. LC-MS (ESI): *m/z* 366.1 $(M+H)^+$.

[0461] **Step c**. A mixture of compound **97** (10.0 g, 27.3 mmol), trimethylsilylacetylene (4.0 g, 41.0 mmol), DIPEA (3.5 g, 27.3 mmol), CuI (220 mg, 1.15 mmol), PPh_3 (1.2 g, 4.6 mmol), and $Pd(PPh_3)_2Cl_2$ (1.6 g, 2.3 mmol) in anhydrous THF (200 mL) was refluxed overnight under an atmosphere of N_2. The reaction mixture was concentrated and the residue was diluted with EtOAc (250 mL). The mixture was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 3/1 (*v/v*)) to compound **98** (7.8 g, 85% yield). LC-MS (ESI): *m/z* 384.2 $(M+H)^+$.

[0462] **Step d**. A mixture of compound **98** (7.7 g, 20 mmol) and K_2CO_3 (27.6 g, 0.2 mol) in THF (150 mL) and MeOH (150 mL) was stirred at rt for 3 h. The reaction mixture was filtered through CELITE™ 545 and the filtered cake was washed with EtOAc (100 mL × 3). The filtrate was concentrated and the residue was diluted with DCM (250 mL). The mixture was washed with brined and ried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 2/1 (*v/v*)) to give compound **99** (4.7 g, 75% yield). LC-MS (ESI): *m/z* 312.2 $(M+H)^+$.

[0463] **Step e**. To a solution of *m*-hydroxybenzaldehyde (**100**) (30.0 g, 0.24 mol) in dry $CHCl_3$ (245 mL) was slowly added bromine (12.36 mL, 0.24 mol) over 40-45 min at rt. After

completion of the addition, the reaction mixture was stirred at rt for 3h. Subsequently, saturated aqueous $NaHCO_3$ was carefully added to neutralize the mixture. The organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **101** (37 g) as a brown solid. LC-MS (ESI): *m/z* 200.9 $(M + H)^+$.

[0464] **Step f**. To a solution of compound **101** (10 g, 49.8 mol) in anhydrous THF/DMF (5/1 (*v/v*), 120 mL) was added NaH (2.0 g, 51 mmol, 60% dispersion in mineral oil) at 0 °C under an atmosphere of N_2. After stirring at rt for 30 min, the mixture was added benzyl bromide (8.7 mL, 73 mmol) over 20-25 min. The resulting mixture was stirred at rt overnight and the reaction was quenched by adding saturated aqueous NH_4Cl (50 mL). The reaction mixture was concentrated and the residue was diluted with EtOAc (150 mL) and water (50 mL). The organic phase was washed with brine 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 compound **102** (11 g, 77% yield). LC-MS (ESI): *m/z* 291.0 $(M + H)^+$.

[0465] **Step g**. A mixture of compound **99** (2.80 g, 9.0 mmol), compound **102** (2.6 g, 9.0 mmol), $Pd(PPh)_2Cl_2$ (6.3 g, 0.9 mmol), CuI (2.55 g, 1.34 mmol), Et_3N (2.5 mL, 18 mmol), and PPh_3 (4.7 g, 1.8 mmol) in DMF (100 mL) was stirred at 60 °C for 12 h. Subsequently, the reaction mixture was concentrated. The residue was diluted with EtOAc (150 mL) and water (50 mL). The organic phase was washed with brined 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 compound **103** (4.0 g, 86% yield). LC-MS (ESI): *m/z* 522.2 $(M + H)^+$.

[0466] **Step h**. A solution of compound **103** (4.1 g, 7.9 mmol) in EtOH (100 mL) was added hydroxylamine hydrochloride (650 mg, 9.4 mmol) and NaOAc (770 mg, 9.4 mmol), respectively, at rt. After stirring at 60 °C for 2 h, the reaction mixture was added K_2CO_3 (1.64 g, 11.85 mmol) and water (20 mL). The resulting mixture was refluxed for 12 h. Subsequently, the reaction mixture was concentrated and the residue was diluted with EtOAc (200 mL) and water (20 mL). The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/Acetone = 5/1 (*v/v*) to DCM/MeOH = 5/1 (*v/v*)) to give compound **104** (1.5 g, 36% yield). LC-MS (ESI): *m/z* 537.2 $(M + H)^+$.

[0467] **Step i**. A mixture of compound **104** and 10% Pd/C (1.5 g) in MeOH (50 mL) was stirred at rt overnight under an atmosphere of H_2. Subsequently, the reaction mixture was filtered through CELITE^{TM}545 and the filtered cake was washed with MeOH (50 mL × 3). The filtrate was concentrated and the residue was purified by silica gel column chromatography to give compound **105** (670 mg, 56% yield). LC-MS (ESI): *m/z* 431.2 $(M + H)^+$.

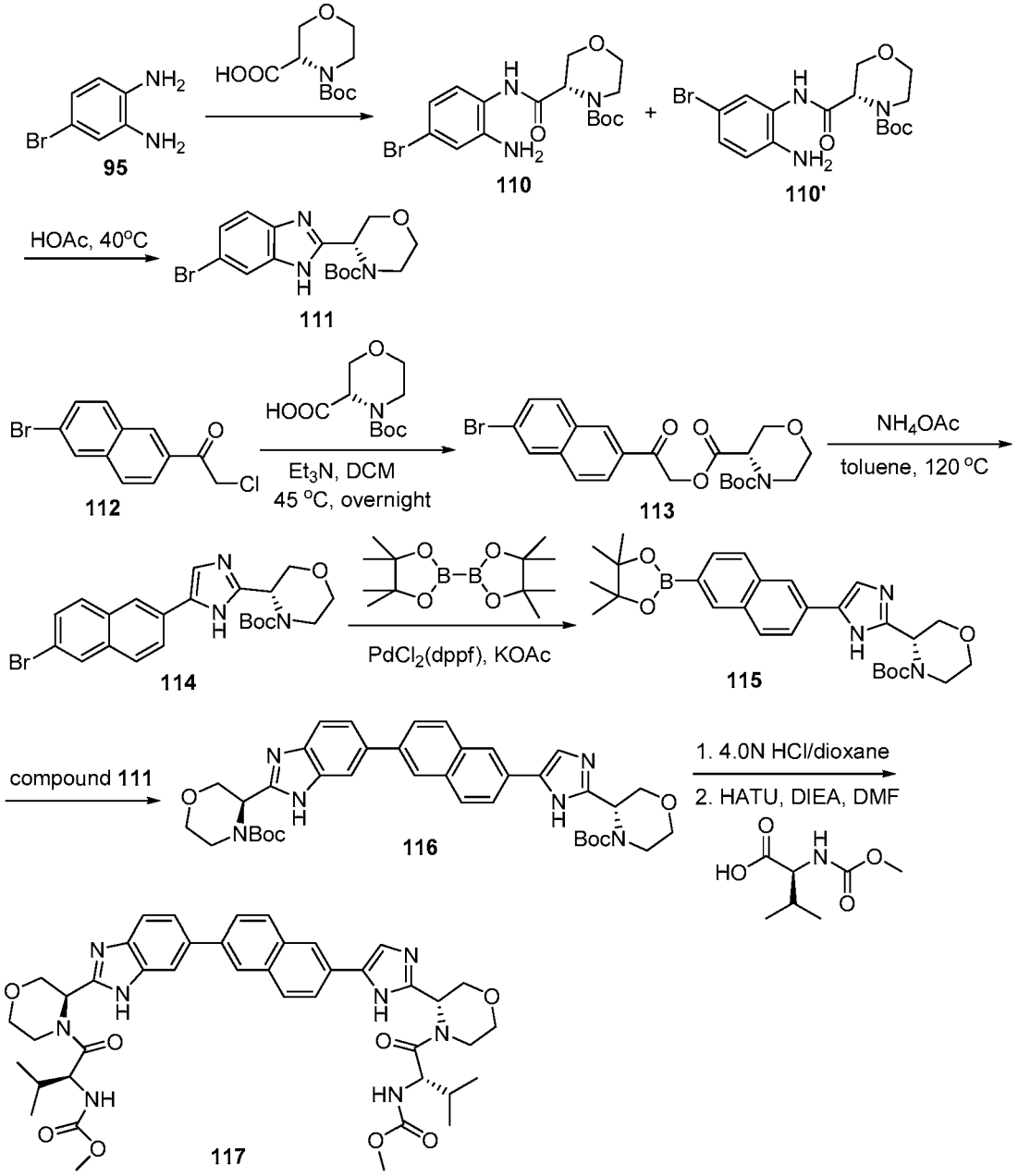
[0468] **Step j**. To a solution of compound **105** (650 mg, 1.5 mmol) in anhydrous pyridine (711 mg, 9.0 mmol) was added Tf_2O (1.07 g, 3.8 mmol) at 0 °C. After stirring at rt overnight, the reaction mixture was concentrated and the residue was dulited with EtOAc (100 mL). The mixthre was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 5/1 (*v/v*)) to give compound **106** (720 mg, 69% yield). LC-MS (ESI): *m/z* 695.1 $(M + H)^+$.

[0469] **Step k**. A mixture of compound **106** (410 mg, 0.6 mmol), bis(pinacolato)diboron (227 mg, 0.9 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (100 mg, 0.12 mmol), and KOAc (235 mg, 2.4 mmol) in dioxane (15 mL) was stirred at 80 °C for 1 h under an atmosphere of N_2. The reaction mixture was used for the next step without any work-up. LC-MS (ESI): *m/z* 673.2 $(M + H)^+$.

[0470] **Step l**. To the above reaction mixture was added (*S*)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (370 mg, 1.02 mmol), followed by $NaHCO_3$ (201 mg, 2.4 mmol), 1, 2-dimethoxyethane (4 mL), water (2 mL), and $Pd(dppf)Cl_2\cdot CH_2Cl_2$ (100 mg, 0.12 mmol) under an atmosphere of N_2. After stirring at 80 °C for 2 h under an atmosphere of N_2, the reaction mixture was added K_2CO_3 (691 mg, 5 mmol) and MeOH (20 mL). After stirring at rt for 30 min, the mixture was concentrated. The residue was diluted with EtOAc (150 mL) and water (50 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 5/1 (*v/v*)) to give compound **108** (140 mg, 36% yield; two steps from compound **107**). LC-MS (ESI) *m/z* 650.3 $(M + H)^+$.

[0471] **Step m**. To a solution of compound **108** (135 mg, 0.2 mmol) in dioxane (2 mL) was added 4 N HCl in dioxane (2 mL) at rt. After stirring at rt overnight, 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. LCMS (ESI): *m/z* 450.2 $(M + H)^+$.

[0472] **Step n**. Subsequently, the HCl salt was dissolved in DMF (2 mL) and the resulting mixture was added DIPEA (0.33 mL, 2.0 mmol), N-THPoc-L-Val-OH (108 mg, 0.50 mmol), and HATU (190 mg, 0.50 mmol). After stirring at rt for 15 min, the reaction mixture was added into ice water. The solid was collected by filtration and purified by preparative HPLC to give compound **109**. LC-MS (ESI): *m/z* 848.4 $(M + H)^+$.



Scheme 6-4

[0473] **Step a**.Referring to Scheme 6-4, to a solution of (*S*)-4-(*tert*-butoxycarbonyl)morphine-3-carboxylic acid (4.1 g, 22.0 mmol) and DIPEA (4.3g, 33.0 mmol) in THF (100 mL) was added compound **95** (4.6 g, 20.0 mmol) at rt. After stirring for 5 min, the reaction mixture was added HATU (7.6 g, 20.0 mmol) was added and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated and the residue was diluted with EtOAc (200 mL) and water (50 mL). The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give a crude mixture of compounds **110** and **110′**(10 g), which was used for the next step without further purification. LC-MS (ESI) *m/z* 400.1 $(M + H)^+$.

[0474] **Step b**. A mixture of compounds **110** and **110′** (10 g) in AcOH (50 mL) was stirred at 40 °C for 16 h. Subsequently, the reaction mixture was added into ice water (200 mL) and neutralized by adding saturated aqueous Na_2CO_3 to adjust pH value to pH 8. The resulting mixture was extracted with EtOAc (100 mL ×3) and the extracts were combined, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/3 (*v/v*)) to give compound **111** (4.5 g, 60% yield; two steps from **95**) as a yellow solid. LC-MS (ESI) *m/z* 382.1 $(M + H)^+$.

[0475] **Step c**. A solution of 1-(6-bromonaphthalen-2-yl)-2-chloroethanone (**112**) (27.0 g, 95.2 mmol) in DCM (200 mL) was added (*S*)-4-(*tert*-butoxycarbonyl)morphine-3-carboxylic acid (20.0 g, 86.6 mmol) and Et_3N (60.0 mL, 433 mmol), respectively. After stirring at 45°C overnight, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NH_4Cl (50 mL), and brine, respectively, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **113** (41.4 g), which was used for next step without further purification. LC-MS (ESI) *m/z* 478.1 $(M + H)^+$.

[0476] **Step d**. A mixture of crude compound **113** (41.4 g) and NH_4OAc (100g, 1.30 mol) in toluene (300 mL) was stirred at 120 °C overnight. The reaction mixture was concentrated and the residue was diluted with EyOAc (500 mL). The mixture was washed with water and dried with anhydrous Na2SO4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 6/1 to1/1 (*v/v*)) to give compound **114** (24g, 61% yield; two steps from **112**) as a yellow solid. LC-MS (ESI): *m/z* 458.1 $(M + H)^+$.

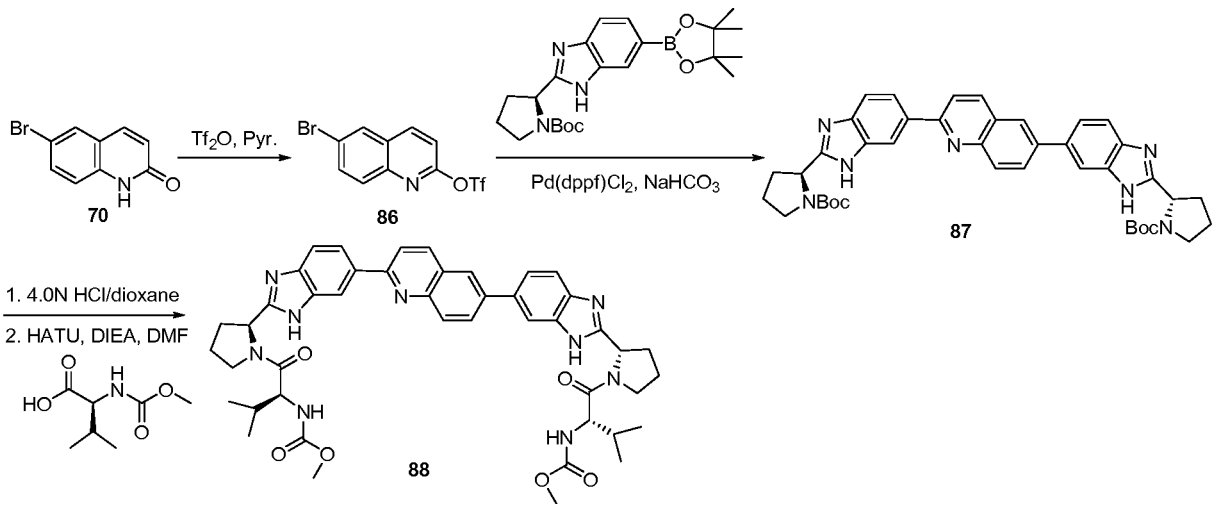
[0477] **Step e**. A mixture of compound **114** (3 g, 6.55 mmol), bis(pinacolato)diboron (1.83 g, 7.2 mmol), and K_2CO_3 (1.67 g, 17.03 mmol) in 1, 4-dioxane (100 mL) was added $Pd(dppf)Cl_2$·DCM (0.8 g, 0.98 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was filtered through CELITE^{TM}545 and the filtered cake was washed with EtOAc (100 mL × 3). The filtrate was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH = 50/1(*v/v*)) to give compound **115** (2.0 g, 61% yield). LC-MS (ESI): *m/z* 506.3 $(M + H)^+$.

[0478] **Step f**. To a mixture of compound **111** (500 mg, 1.3 mmol), compound **115** (900 mg, 1.78 mmol), and $NaHCO_3$ (328 mg, 3.9 mmol) in DME (15 mL) and water (5 mL) was added $Pd(dppf)Cl_2$·DCM (106 mg, 0.13 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N_2, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL) and water (25 mL). The organic pahse was washed with brined and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was silica gel column chromatography (Petroleum ether/acetone = 4/1 (*v/v*)) to give compound **116** (310 mg, 35% yield) as a yellow solid. LC-MS (ESI): *m/z* 703.3 $(M + Na)^+$.

[0479] **Step g**. To a stirred solution of compound **116** (150 mg, 0.31 mmol) in dioxane (3.0 mL) was added4 N HCl in dioxane (3.0 mL) at rt. After stirring at rt for 3 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.

[0480] **Step h**. Subsequently, the HCl salt was dissolved in DMF (3.0 mL) and the resulting mixture was added DIPEA (0.43 mL, 2.5 mmol), N-Moc-L-Val-OH (136 mg, 0.78 mmol), and HATU (353 mg, 0.93 mmol), respectively. After stirring at rt for 2h, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **117**. LC-MS (ESI): *m/z* 795.4 $(M + H)^+$.

EXAMPLE 7 – Synthesis of compounds of Formula IIIg



Scheme 7-1

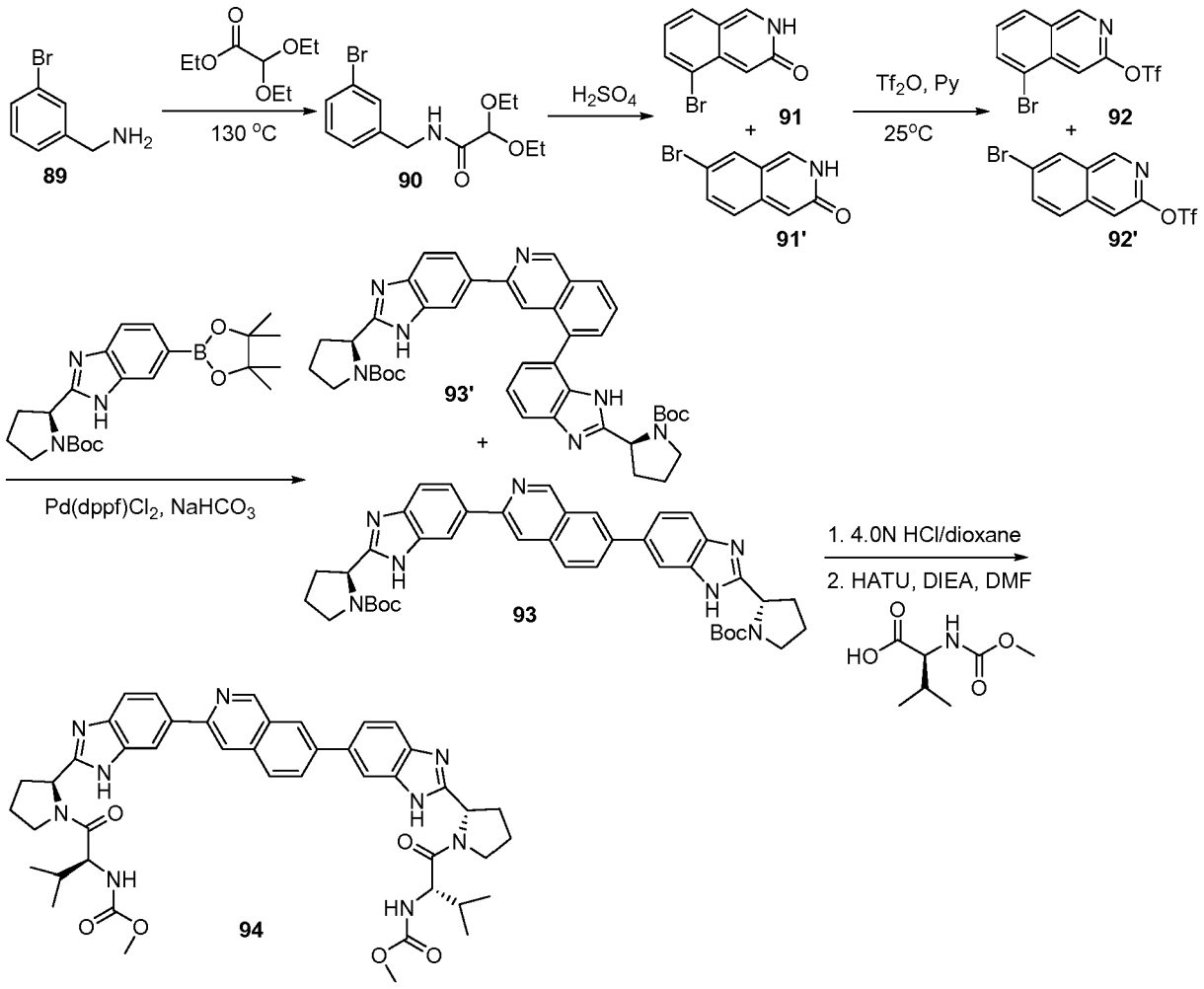
[0481] **Step a**.Referring to Scheme 7-1, to a solution of 6-bromoquinolin-2(1*H*)-one (**70**) (0.40 g, 1.8 mmol) in anhydrous pyridine (12 mL) was added drop-wisely with Tf_2O (0.81 g, 2.9 mmol) at 0 °C. After stirring at 0 °C for 1 h and at rt for 3 h, the reaction mixture was concentrated. The residue was dissolved in DCM (100 mL); the resulting mixture was washed with water (25 mL ×3) and dried with anhydrous Na2SO4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 2/1 (*v/v*)) to give compound **86** (0.54 g, 84% yield) as a yellow solid. LC-MS (ESI) *m/z* 355.9 $(M + H)^+$.

[0482] **Step b**. To a mixture of compound 86 (0.54 g, 1.5 mmol), (*S*)-tert-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (1.24 g, 3.0 mmol), and $NaHCO_3$ (1.01 g, 12.0 mmol) in 1,2-dimethoxyethane (30 mL) and water (10 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.27 g, 0.3 mmol) at rt under an atmosphere of N_2. After stirring at 80 °C overnight, the reaction mixture was concentrated. The residue was diluted with EtOAc (100 mL) and water (25 mL). The organic phase was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/1 (*v/v*)) to give compound **87** (1.0 g, 95% yield) as a yellow solid. LC-MS (ESI) *m/z* 700.4 $(M + H)^+$.

[0483] **Step c**. To a solution of compound **87** (100 mg, 0.14 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL) at rt. 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 directly for the next step without further purification. LC-MS (ESI) *m/z* 500.2 $(M + H)^+$.

[0484] **Step d**. Subsequently, the HCl salt was dissolved in DMF (2 mL) and the resulting mixture was added Et_3N (0.20 mL, 1.4 mmol), N-Moc-L-Val-OH (55 mg, 0.32 mmol), and HATU (122 mg, 0.32 mmol), respectively. After stirring at rt for 30 min, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **88**. LC-MS (ESI): *m/z* 814.3 $(M + H)^+$.



Scheme 7-2

[0485] **Step a**. Referring to Scheme 7-2, a mixture of compound **89** (7.44 g, 40.0 mmol) and Ethyl 2,2-diethoxyacetate (9.15 g, 52.0 mmol) was stirred at 130 °C for 7 h. The reaction mixture was dissolved in petroleum ether (250 mL). The resulting mixture was washed with sat. aq.

NH_4Cl and brine, respectively, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **90** (11.4 g) as a yellow oil, which was used for the next step without further purification. LC-MS (ESI) *m/z* 316.0 $(M + H)^+$.

[0486] **Step b**. A mixture of compound **90** (12.4 g, 40 mmol) in conc. H_2SO_4 (50mL) was stirred at rt for 5h. Subsequently, the reaction mixture was poured into ice-water. The suspension was filtered and the filtrate was neutralized with 10% NH_4OH. The solid was collected by filtration, washed with water, and dried *in vacuo* to give a mixture of compounds **91** and **91′**. LCMS (ESI) *m/z* 224.0 $(M + H)^+$.

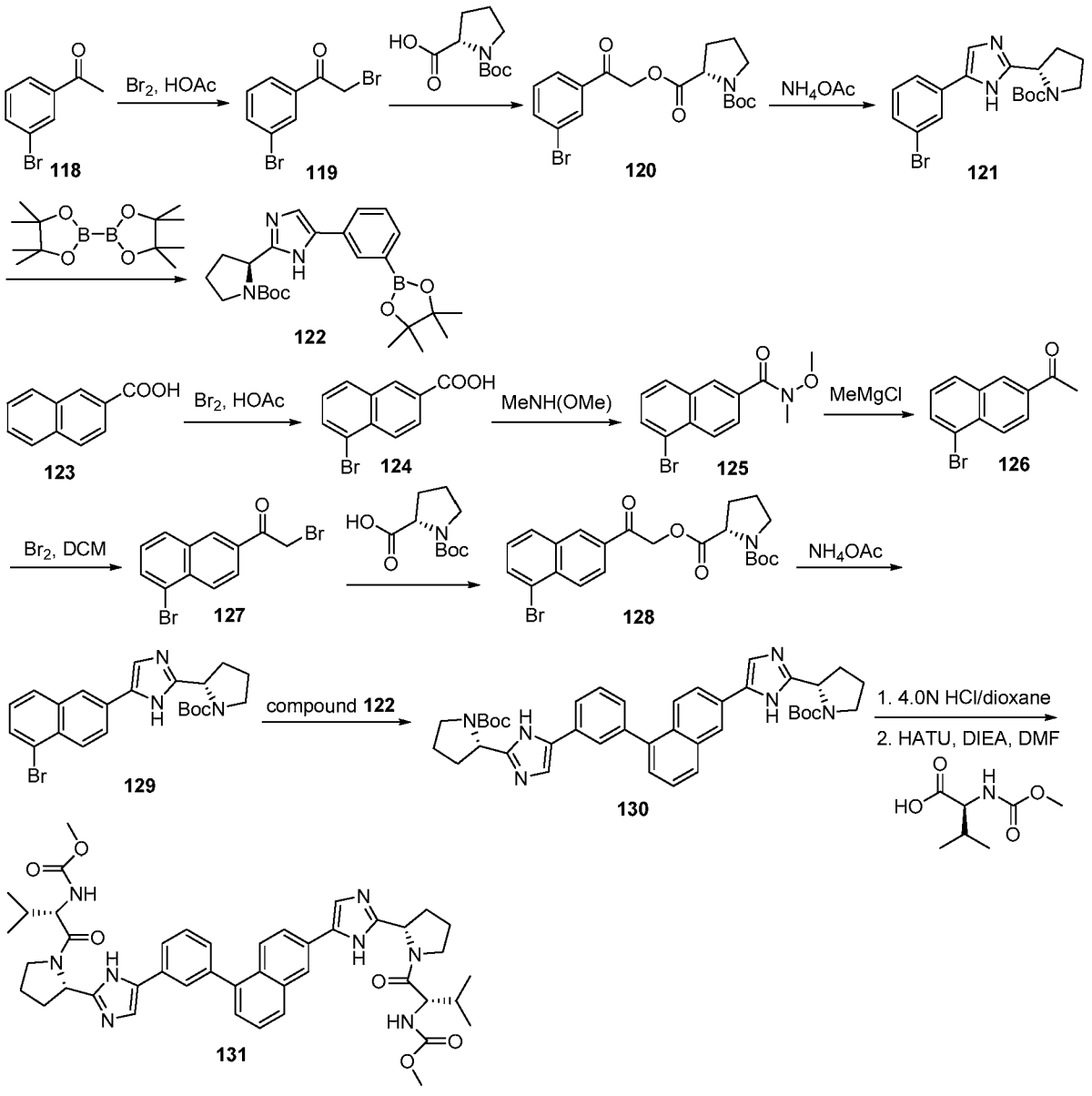
[0487] **Step c**. A mixture of compounds **92** and **92′** (222 mg, 1.0 mmol) in anhydrous pyridine (5 mL) was added Tf_2O (0.5 mL) at 0 °C. After stirring at rt for 8 h, the reaction mixture was concentrated and the residue was dissolved in DCM (50 mL). The mixture was washed with water (25 mL × 3) and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified with silica gel column chromatography (EtOAc/Petroleum ether = 5/1 (*v/v*)) to give a mixture of compounds **92** and **92′** (160 mg, 45% yield) as a yellow oil. LC-MS (ESI) *m/z* 355.9 $(M + H)^+$.

[0488] **Step d**. To a mixture of compounds **92** and **92′** (160 mg, 0.45 mmol), (*S*)-tert-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (463 mg, 1.12 mmol), and $NaHCO_3$ (227 mg, 2.7 mmol) in 1,2-dimethoxyethane (30 mL) and water (10 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (80 mg, 0.09 mmol) at rt under an atmosphere of N_2. After stirring at 80 °C overnight, the reaction mixture was concentrated and the residue was added EtOAc (100 mL) and water (20 mL). The organic phase was isolated, washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 1/1 (*v/v*)) to give compound **93** (180 mg, 57% yield) and compound **93′** (60 mg, 19% yield). LC-MS (ESI) *m/z* 700.4 $(M + H)^+$.

[0489] **Step e**. To a solution of compound **93** (100 mg, 0.14 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL). After stirring at rt for 3 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* 500.2 $(M + H)^+$.

[0490] **Step f**. Subsequently, the HCl salt was dissolved in DMF (2 mL) and the mixture was added Et_3N (0.2 mL, 1.4 mmol), N-Moc-L-Val-OH (55 mg, 0.32 mmol), and HATU (122 mg, 0.32 mmol), respectively. After stirring at rt for 1hr, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **94**. LC-MS (ESI): *m/z* 814.4 $(M + H)^+$.

EXAMPLE 8 – Synthesis of compounds of Formula IIg



Scheme 8-1

[0491] **Step a**. Referring to Scheme 8-1, to a solution of compound **118** (57.5 g, 290 mmol) in HOAc (100 mL) was slowly added Br_2 (49.0 g, 290 mmol) at rt. After stirring at rt for 2 h, the reaction mixture was slowly added saturated aqueous $NaHCO_3$. The organic phase was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound 119 (60 g), which was used for next step without further purification. LC-MS (ESI): *m/z* 276.9 $(M+H)^+$.

[0492] **Step b**. To a solution of compound **119** (25.0 g, 89.9 mmol) in CH_3CN (100 mL) was added (*S*)-N-Boc-Pro-OH (19.4 g, 89.9 mmol), followed by Et_3N (37.35 mL, 269.7 mmol) at rt. After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was diluted with DCM (250 mL). The mixture was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give compound **120** (37 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 313.2 $(M-100+H)^+$.

[0493] **Step c**. A mixture of crude compound **120** (37 g) and NH_4OAc (69.2 g, 899 mol) in xylene (100 mL) was stirred at 140 °C overnight. The reaction mixture was concentrated and the residue was diluted with DCM (500 mL). The mixture was washed with brine and dried with anhydrous Na2SO4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 10/1 (*v/v*)) to give compound **121** (12 g, 40% yield; three steps from compound **119**) as a white solid. LC-MS (ESI): *m/z* 392.1 $(M+H)^+$.

[0494] **Step d**. To a mixture of compound **121** (3 g, 7.65 mmol), bis(pinacolato)diboron (4.24 g, 16.8 mmol), KOAc (1.87 g, 19.1 mmol) in 1,4-dioxane (200 mL) was added $Pd(dppf)Cl_2$ (624 mg, 0.765 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight under an atmosphere of N2, the reaction mixture was filtered through CELITE™545 and the filtered cake was washed with EtOAc (100 mL × 3). The filtrate was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified with silica gel column chromatography (Petroleum ether/acetone = 8/1 (*v/v*)) to give compound **122** (2.9 g, 86% yield) as a gray solid. LC-MS (ESI) *m/z* 440.3 $(M+H)^+$.

[0495] **Step e**. To a boiling solution of 2-naphthoic acid (**123**) (50.0 g, 290 mmol) in HOAc (100 mL) was slowly added a mixture of Br_2 (46.3 g, 290 mmol) and I_2 (1.25g, 43.5mmol). After completing the addition, the reaction mixture was refluxed for 30 min. The reaction mixture was

coled to rt and filtered. The solid was washed with HOAc and dried *in vacuo* to give crude compound **124** (50 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 251.0 $(M + H)^+$.

[0496] **Step f**. A mixture of compound 124 (10.0 g, 39.8 mmol) in CH_3CN (200 mL) was added EDCI (18.3 g, 95.5 mmol), Et_3N (16.08 mL, 159.2 mmol), and *N,O*-Dimethylhydroxylamine hydrochloride (4.8 g, 50 mmol) at rt. After stirring at rt overnight, the reaction mixture was concentrated and the residue was diluted with DCM (250 mL). The mixture was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, respectively and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 8/1 (*v/v*)) to give compound 125 (3.6 g, 31% yield) as a white solid. LC-MS (ESI): *m/z* 294.0 $(M + H)^+$.

[0497] **Step g**. To a solution of compound **125** (3.60 g, 12.2 mmol) in THF (150 mL) was slowly added 3M MeMgCl in THF (8.31 mL) at 0°C. After stirring at 0°C for 1 h and at rt for 1 h, the reaction was quenched by adding saturated aqueous NH_4Cl (5 mL). The solven was removed and the residue was diluted with DCM. The mixture was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/AcOEt = 10/1 (*v/v*)) to give compound **126** (3.05 g, 100% yield) as a white solid. LC-MS (ESI): *m/z* 249.0 $(M + H)^+$.

[0498] **Step h**. To a solution of compound **126** (3.05 g, 12.2 mmol) in DCM (100 mL) was slowly added Br_2 (1.93 g, 12.2 mmol) in DCM (10 mL) at rt. After stirring at rt for 2h, the reaction was quenched by adding saturated aqueous NaHCO3 (10 mL). The organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give crude compound **127** (4.0 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 326.9 $(M + H)^+$.

[0499] **Step i**. To a solution of crude compound **127** (4.0 g) in CH_3CN (15 mL) was added (*S*)-N-Boc-Pro- OH (3.14 g, 14.6 mmol) and Et_3N (3.70 g, 36.6 mmol). After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was diluted with DCM (200 mL). Subsequently, the mixture was washed with saturated aqueous NH_4Cl and water respective, and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to

give crude compound **128** (5.6 g), which was used for the next step without further purification. LC-MS (ESI): *m/z* 462.1 $(M + H)^+$.

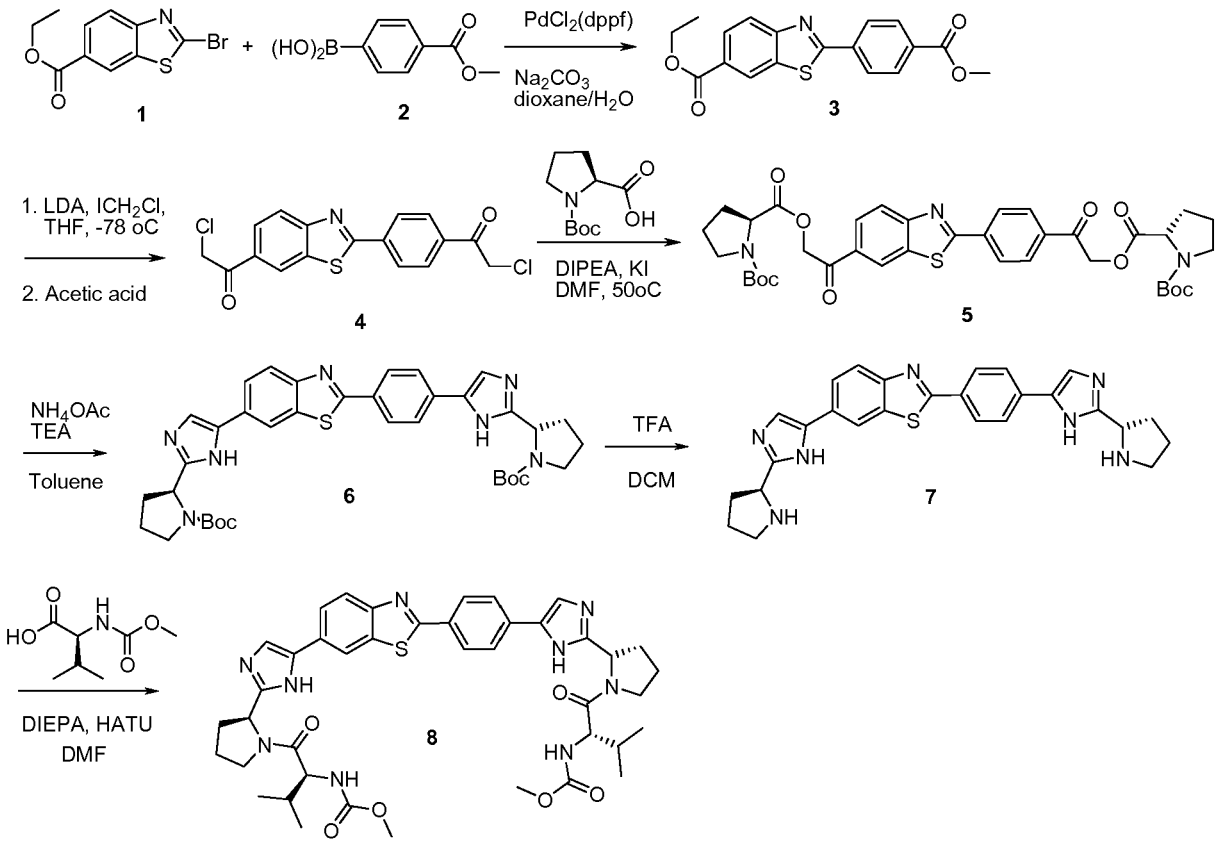
[0500] **Step j**. A mixture of crude compound **128** (5. 6 g) and NH_4OAc (9.36 g, 122 mmol) in toluene (80 mL) was stirred at 110 °C overnight. The reaction mixture was concentrated and the residue was diluted with DCM (250 mL). The mixture was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 5/1 (*v/v*)) to give compound **129** (3.0 g, 56 yield) as a white solid. LC-MS (ESI): *m/z* 442.1 $(M + H)^+$.

[0501] **Step k**. To a mixture of compound **122** (633 mg, 1.44 mmol), compound **129** (500 mg, 1.31 mmol), and $NaHCO_3$ (330 mg, 3.01 mmol) in 1, 2-dimethoxyethane (15 mL) and water (5 mL) was added $Pd(dppf)Cl_2$ (107 mg, 0.131 mmol) under an atmosphere of N_2. After stirring at 80 °C overnight, the reaction mixture was concentrated and the residue was diluted with EtOAc (50 mL) and water (20 mL). The organic phase was washed with brine 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 compound **130** (400 mg, 45% yield) as a yellow solid. LC-MS (ESI): *m/z* 675.4 $(M + H)^+$.

[0502] **Step l**. To a solution of compound **130** (150 mg, 0.22 mmol) in dioxane (2.0 mL) was added 4N HCl in dioxane (2.0 mL) at rt. After stirring at rt for 3 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* 475.3 $(M + H)^+$.

[0503] **Step m**. Subsequently, the HCl salt was dissolved in DMF (2.0 mL) and the mixture was added DIPEA (0.36 mL, 2.2 mmol), N-Moc-L-Val-OH (86 mg, 0.49 mmol), and HATU (202 mg, 0.49 mmol) at rt. After stirring at rt for 1 h, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give compound **131**. LC-MS (ESI): *m/z* 789.4 $(M + H)^+$.

EXAMPLE 9 – Synthesis of compounds of Formula IVa



Scheme 9-1

[0504] **Step a**.Referring to Scheme 9-1, a mixture of 2-bromobenzothiazole **1** (2.72 g, 9.5 mmol), 4-methoxycarbonylphenylboronic acid (**2**) (1.80 g, 10 mmol), $Pd(dppf)Cl_2$ (388 mg, 0.475 mmol) in 2 M Na_2CO_3 (10 mL) and dioxane (20 mL) was treated by a repeated process of degas-and-refilled-with-nitrogen three times. The reaction mixture was then stirred at 95 °C in nitrogen atmosphere for 4 h. After being cooled, the mixture was diluted with THF, and then filtered through a pad of CELITE™545. The filtrate was concentrated and the crude product was directly purified by flash chromatography (using methylene chloride as eluent) to give compound **3** (1.96 g, 60% yield) as a white solid.

[0505] **Step b**. A solution of *n*-butyllithium (2.5 M in hexane, 25.3 mL, 63.1 mmol) was slowly added into a solution of diisopropylamine (6.97 g, 68.8 mmol) in THF (20 mL) at -78 °C over 15 min. After addition, the solution was allowed to stir for 30 min at -78 °C and then warm up to 0 °C. The LDA solution was cooled to -78 °C for next step.

[0506] **Step c**. A solution of **3** (1.96 g, 5.74 mmol) and chloroiodomethane (7.30 g, 41.2 mmol) in THF (15 mL) was cooled to -78 °C. The LDA solution prepared above was slowly cannulated into this solution over 20 min. The resulting mixture was stirred for additional 1 h. The reaction was quenched by slowly adding a solution of acetic acid in THF (1/1 (*v/v*), 40 mL) at -78 °C. The reaction mixture was warmed up to rt and then diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. A combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product **4** (1.80 g) was dried *in vacuo*and the residue was used directly for next condensation reaction.

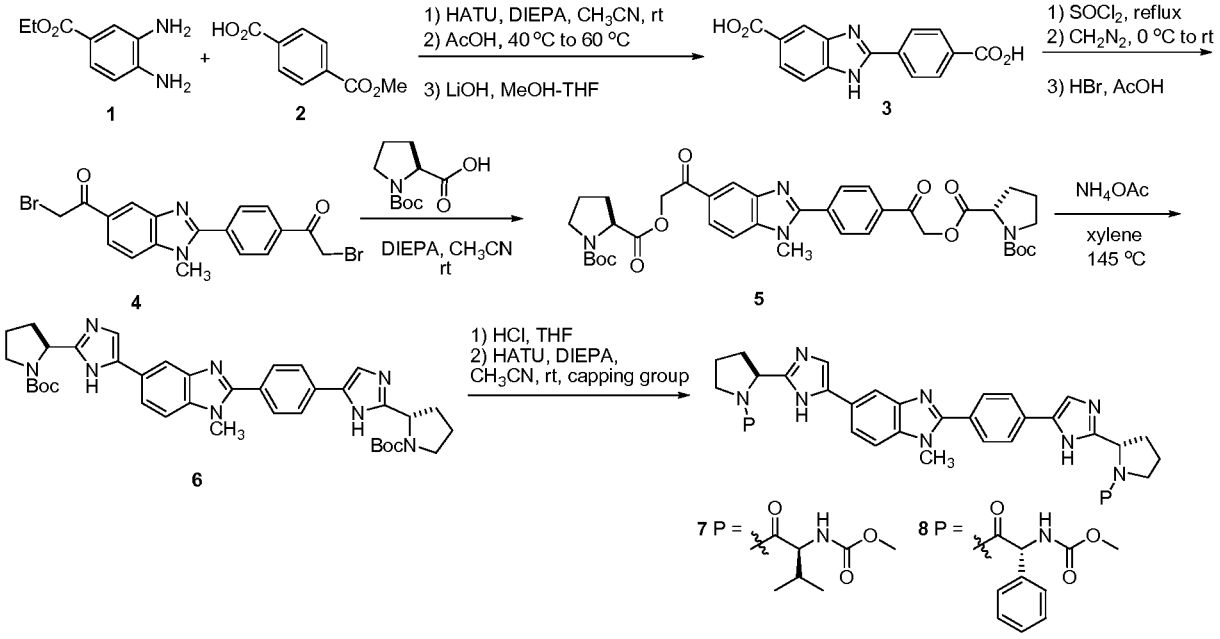
[0507] **Step d**. A mixture of **4** (0.59 g, 1.61 mmol), N-Boc-L-Proline (0.83 g, 3.85 mmol), KI (0.64 g, 3.85 mmol) and diisopropylethylamine (0.64 g, 3.85 mmol) in DMF (40 mL) was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was treated with water. The solid was collected by filtration and washed with water twice. After being dried in vacuum, the crude product was purified by flash chromatography (ethyl acetate/hexanes = 1/9to1/5 (*v/v*)) to afford **5** (0.92 g, 67% yield) as a white solid.

[0508] **Step e**. A mixture of diester **5** (0.81 g, 1.12 mmol), ammonium acetate (2.59 g, 33.5 mmol) and triethylamine (3.39 g, 33.5 mmol) in toluene (100 mL) in a sealed tube was stirred at 140 °C for 90 min. After being cooled, the reaction mixture was transferred into a flask and concentrated to dryness. The residue was partitioned between chloroform and water, and the organic layer was washed with water and brine, and concentrated. The crude product was purified by flash chromatography (NH_4OH/acetone/ethyl acetate = 1/2/100 (*v/v/v*)) to give compound **6** (0.51 g, 67% yield) as a white solid.

[0509] **Step f**. Trifluoroacetic acid (3 mL) was slowly added into a solution of **6** in methylene chloride (10 mL) at rt. The resulting mixture was stirred at the temperature for 1 h, and concentrated to dryness. The residue was dissolved in water, and the aqueous solution was basified to pH 11. The product was extracted with chloroform 5 times. After removal of the solvent, **7** (274 mg, 76%) was obtained as its TFA salt.

[0510] **Step g**. A mixture of N-methoxycarbonyl-L-valine (40 mg, 0.23 mmol), DIPEA (98 mg, 0.76 mmol) and HATU (87 mg, 0.23 mmol) in DMF was stirred at rt for 30 min. **7** (80 mg, 0.076 mmol) was added as solid. The reaction mixture was stirred at rt for 2 h, and then dropped into water. The precipitate was formed and collected by filtration. The crude product was

purified by prep HPLC to afford compound **8** (16 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8-7.6 (4H, m), 7.5-7.3 (3H, m), 7.08 (2H, s), 5.5-5.4 (2H, d), 5.3-5.2 (2H, m), 5.05 (1H, s), 4.5-4.3 (2H, m), 4.2-4.1 (1H, m), 3.8-4.0 (4H, m), 3.74 (6H, s), 2.6-2.0 (10H, m), 1.10 (6H, d), 1.95 (6H, d) ppm. LC-MS (ESI): *m/z* 796.4 $(M+H)^+$.



Scheme 9-2

[0511] **Step a**.Referring to Scheme 9-2, to a mixture of compound **2** (6.31 g, 35 mmol) and HATU (14.63 g, 38.5 mmol,) in CH_3CN (150 mL) was added slowly DIEPA (9.05 g, 11.35 mL, 70 mmol). The resulting mixture was stirred at rt for 15 min. To the mixture was added 3,4-diamino-benzoic acid ethyl ester **1** (6.31 g, 35 mmol) at rt, and stir continued at rt for 17 h. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. (3x150 mL). Combined organic phases were washed with H_2O (2x200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography eluting hexane/EtOAc = 3/1 to 2/1 (*v/v*) to give an amide (11.2 g, 94%)as yellow-brown solid. LC-MS (ESI): *m/z* $(M+H)^+$: 343**,** $(M-H)^-$: 341.

[0512] **Step b**. A mixture of the product (11.2 g, 33 mmol) from above reaction in AcOH (100 mL) was heated at 40 °C for 18 h. The temperature was allowed to warm to 60 °C, and further heated the mixture for 24 h. All starting material was consumed based on LC-MS analysis. The excess solvent was removed on a rotary evaporator to give a crude mixture, which

was subject to purification by column chromatography eluting with hexane/EtOAc = 3/1 (*v/v*) to give a functionalized benzimidazole (10.2 g, 96% yield). LC-MS (ESI): *m/z* 325.1 $(M+H)^+$..

[0513] **Step c**. A mixture of the product (10.2 g, 31 mmol) from the above reaction and LiOH (7.54 g, 0.31 mol) in MeOH (200 mL) was heated under reflux condition for 60 h. The milky mixture was acidified with 10% HCl solution to adjust the pH 1 to give white precipitates. The precipitate was collected by filtration and then dried *in vacuo* to afford compound **3** (8.9 g, quantitative yiled), which was used for the next step without further purification. LC-MS (ESI): *m/z* 283.1 $(M+H)^+$.

[0514] **Step d**. A mixture of **3** (8.9 g, 31 mmol) in thionyl chloride (60 mL) was refluxed for 3 h. The reaction mixture was concentrated and the residue was dried in vacuo to give acid chloride, which was mL suspended in a mixture of dried diethyl ether (200 mL)/THF (50 mL). To the suspension was added dropwise a flash generated diazomethane solution (approximately 166 mmol of diazomethane solution generated from 251 mmol of 4-N,N-trimethyl-benzenesulfonamide) at 0 ^oC, and then stirred it at 0 ^oC to rt overnight (20 h). All volatile was removed on a rotary evaporator to give a residue. The residue was purified by column chromatography eluting hexanes/EtOAc = 3/1 (*v/v*) to give a yellow solid (1.89 g, 17% yield).

[0515] **Step e**. To a mixture of 2-diazo-1-{2-[4-(2-diazo-acetyl)-phenyl]-1-methyl-1H-benzoimidazol-5-yl}-ethanone obtained from above (1.89 g, 5.49 mmol) in AcOH (50 mL) was added slowly HBr (48 % in AcoH, 1.62 mL, 14.31 mmol) at rt. The resulting mixture was stirred at rt for 13 h, and then all volatile was removed on a rotary evaporator to give crude mixture. The crude mixture was further dried with toluene on a rotary evaporator (2 x 25 mL) to give compound **4** as yellow solid, which was used for the next step without further purification. LC-MS (ESI): *m/z* 448.9 $(M+H)^+$.

[0516] **Step f**. To a crude mixture of compound **4** (~5.49 mmol) in CH_3CN (50 mL) was added N-Boc-L-Proline (2.59 g, 12.01 mmol), followed by adding DIEPA (3.71 mL, 22.9 mmol) at rt. The resulting mixture was stirred at rt for 5 h, and quenched with H_2O. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with H_2O (50 mL) and brined (50 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was used for the next step without further purification. LC-MS (ESI): *m/z* 719.3 $(M+H)^+$.

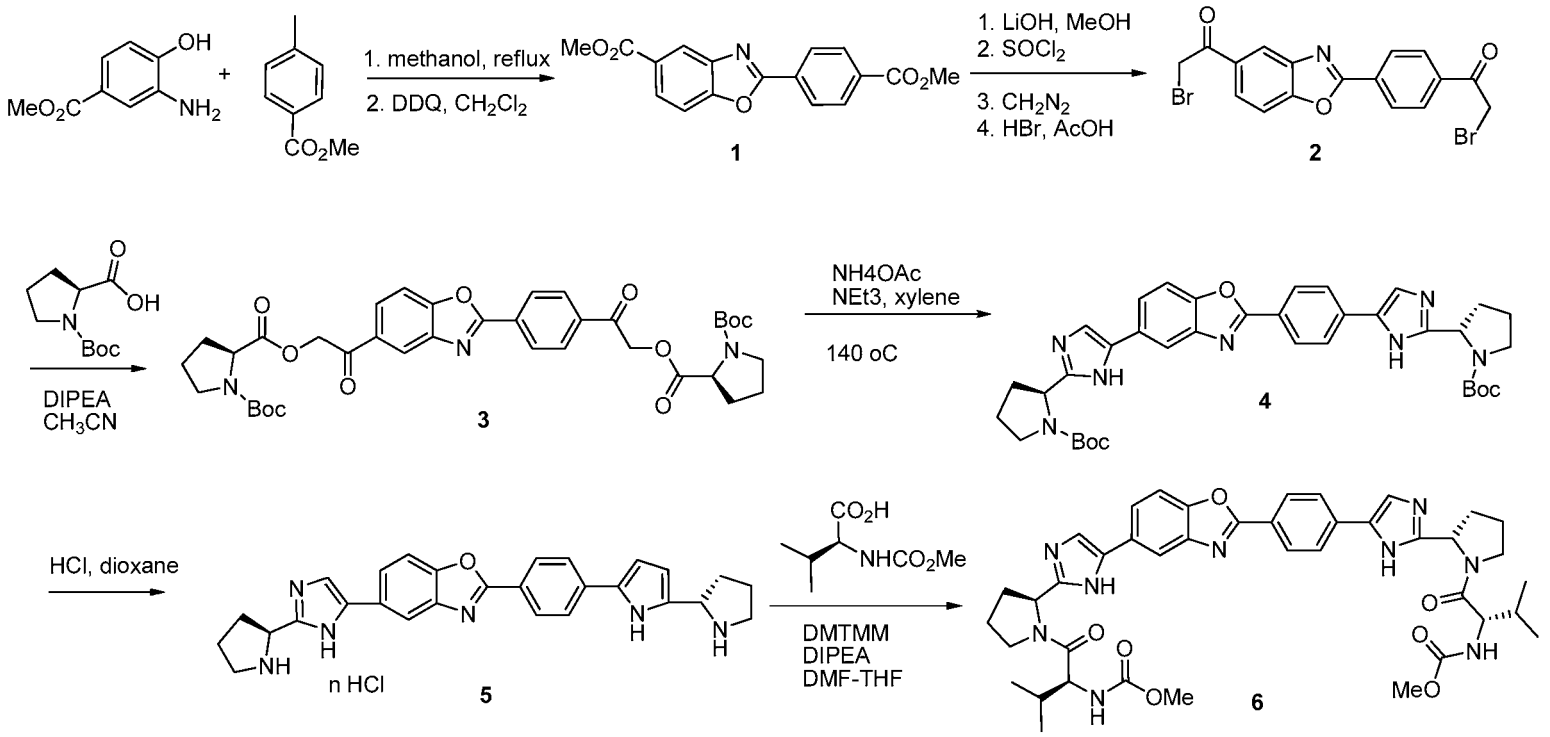
[0517] **Step g**. To a crude solution of **5** (~5.72 mmol) in xylene (50 mL) was added NH_4OAc (6.61 g, 85.8 mmol). The resulting mixture was heated at 145 °C for 1.5 h, and then all solvent was removed on a rotary evaporator to give a crude mixture, which was subject to column chromatography eluting with hexane:EtOAc = 1:3 to EtOAc only. Yellow-brown solid was obtained as compound **6** (717 mg). LC-MS (ESI): *m/z* 679.4 $(M+H)^+$.

[0518] **Step h**. To a crude solution of **6** (717 mg, 1.06 mmol) in THF (7.5 mL) was added HCl (4.0 M in dioxane, 10 mL) at rt. The resulting mixture was stirred at rt for 16 h, and then all volatile was removed on a rotary evaporator to give yellow solid. The yellow solid was washed with diethyl ether (2 x 10 mL) and then further dried on in vacuo to give an HCL salt, which was used for the next step without further purification. LC-MS (ESI): *m/z* 479.3. ^1H NMR spectrum showed the crude product was a mixture of two regioisomers with a ratio of 1:1. $(M+H)^+$.

[0519] **Step i**. To a crude solution of the HCl salt (48 mg, ~0.1mmol), N-Boc-L-Val-OH (35 mg, 0.2 mmol), and HATU (76 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added DIEPA (65 μL, 0.4 mmol). The resulting mixture was stirred at rt for 2.5 h, and then all solvent was removed on a rotary evaporator to give crude mixture. The crude mixture was purified by prep-HPLC eluting H_2O to CH_3CN. Two regioisomers were obtained as 10.0 mg (yellow solid, **7**) and 8.7 mg (yellow solid, **7′**), respectively. Characterization of **7**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 7.19-7.92 (m, 8H), 5.39-5.86 (m, 2H), 5.21-5.34 (m, 2H), 4.30-4.42 (m, 2H), 3.60-3.78 (m, 12H), 2.76 (Br s, 1H), 2.20-2.44 (m, 4H), 1.98-2.18 (m, 4H), 0.89-1.12 (m, 12H) ppm. LC-MS (ESI): m/z $(M+2)/2^+$: 397, $(M+1)^+$: 794.

[0520] Characterization of compound 7′. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (Br s, 1H), 7.10-7.84 (m, 8H), 5.44-5.64 (m, 2H), 5.22-5.32 (m, 2H), 4.39 (t, J = 6.6 Hz, 2H), 3.63-4.00 (m, 12H), 2.68 (br s, 1H), 2.21-2.38 (m, 4H), 2.00-2.16 (m, 4H), 0.87-1.07 (m, 12H). LC-MS (ESI): *m/z* 793.4 $(M+H)^+$.

[0521] The N-Moc-D-Phg-OHcapped analog **8** were obtained by following the same procedure as that used for synthesizing compounds 7 and 7' and using N-Moc-D-Phg-OH instead of N-Moc-L-Val-OH as an amide reagent. ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 7.23-8.00 (m, 18H), 5.42-5.60 (m, 2H), 5.24-5.40 (m, 2H), 3.86 (br s, 4H), 3.56-3.74 (m, 6H), 2.64-2.86 (m, 2H), 2.00-2.36 (m, 4H), 1.91 (br s, 2H) ppm. LC-MS (ESI): *m/z* $(M+2)/2^+$: 431, $(M+1)^+$: 860.


1. methanol, reflux
2. DDQ, CH2Cl2
1. LiOH, MeOH
2. SOCl2
3. CH2N2
4. HBr, AcOH
DIPEA
CH3CN
NH4OAc
NEt3, xylene
140 oC
HCl, dioxane
n HCl
DMTMM
DIPEA
DMF-THF
1
2
3
4
5
6

Scheme 9-3

[0522] **Step a**. A mixture of methyl 3-amino-4-hydroxybenzoate (2.5 g, 15 mmol) and methyl 4-formylbenzoate (2.46 g, 15 mmol) in methanol (75 mL) was stirred at rt overnight. The solvent was evaporated under reduced pressure and the remaining residue was dissolved in dichloromethane (150 mL). DDQ (3.5 g, 15.4 mmol) was added and the reaction mixture was stirred at rt for 1 h. Saturated $NaHCO_3$ (200 mL) was added. The suspension was filtered off, the resulting solid was washed with saturated $NaHCO_3$ (50 mL), water (50 mL), and ethyl acetate (100 mL) and dried in vacuo to give compound **1** (4 g, 86% yield) as yellow solid.

[0523] **Step b**. A mixture of diester **1** (4 g, 12.8 mmol) and lithium hydroxide monohydrate (2.7 g, 64 mmol) in a solvent mixture of methanol and water (60 mL, methanol/water=1/5) was refluxed for 6 h. Methanol was evaporated and the remaining aqueous solution was neutralized by HCl (con). The resulting suspension solution was filtered off, the solid was washed with water (50 mL) and dried *in vacuo* to give the corresponding dicarboxylic acid (3.3 g, 95% yield) as yellow solid.

[0524] **Step c**. A sample of the dicarboxylic acid (2.88 g, 10.2 mmol) was suspended in thionyl chloride (30 mL), the mixture refluxed for 6 h. The reaction mixture was evaporated under reduced pressure and dried *in vacuo* to provide the corresponding diacyl chloride (3.25 g) as yellow solid.

[0525] **Step d**. A suspension of the diacyl chloride obtained (1.5 g, 4.7 mmol) in ether was treated with diazomethane (71 mL, 0.33 N in ether, 23 mmol) at 0 °C for 2 h. The solvent was evaporated under reduced pressure and dried *in vacuo* to give the corresponding diazoketone (1.55 g) as yellow solid. LC-MS (ESI): *m/z* 332.1 $[M+H]^+$.

[0526] **Step e**. The diazoketone obtained (1.55 g, 4.7 mmol) was suspended in acetic acid (10 mL) and the mixture was drop-wisely added 48% HBr in AcOH (3.93 g, 23.3 mmol) at 0 °C. The reaction mixture was then warmed up to rt and stirred for 1 h. Saturated Na_2CO_3 was added slowly into the reaction mixture to neutralize the acid. The resulting suspension solution was filtered off and the solid was washed with water and dried *in vacuo* to give bromoketone **2** (1.38 g, 69% yield) as yellow solid.

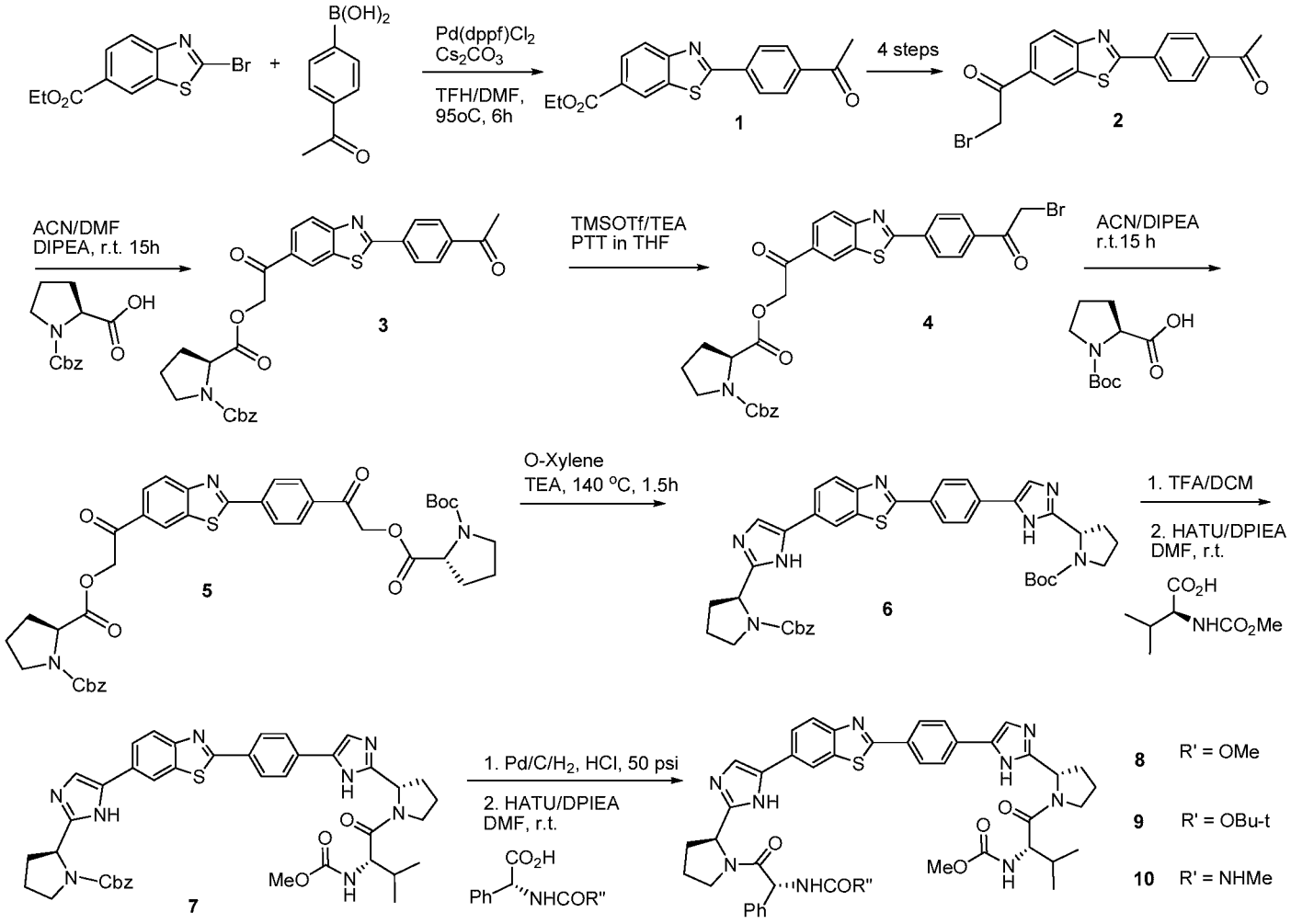
[0527] **Step f**. A solution of bromoketone **2** (1.38 g, 3.2 mmol), N-Boc-LProline (2.7 g, 12.6 mmol) and DIPEA (2.2 mL, 12.6 mmol) in acetonitrile (3 mL) was stirred at rt overnight.

Acetonitrile was evaporated and the remaining residue was partitioned between ethyl acetate (50 mL) and water (25 mL). The organic phase was then collected and dried over Na_2SO_4. After concentration under reduced pressure, the crude product was purified over silica gel (ethyl acetate/hexane=35/65) to give ester **3** (0.56 g, 25% yield) as yellow solid. LC-MS (ESI): *m/z* 706.3 $[M+H]^+$.

[0528] **Step g**. A mixture of ester **3** (560 mg, 0.8 mmol) and ammonium acetate (1.84 g, 24 mmol) in degassed xylene (3.3 mL) in a sealed parr bottle was stirred at 140 ^oC for 90 min. Upon removal of volatile solvents the residual material was purified by silica gel chromotagraphy (ethyl acetate 100%, then ethyl acetate/methanol=90/10 (*v/v*)) to give bisimidazole **4** (474 mg, 89% yield) as yellow solid. LC-MS (ESI): *m/z* 666.3 $[M+H]^+$.

[0529] **Step h**. To a solution of bisimidazole **4** (474 mg, 0.71 mmol) in THF (20 mL) was added 4N HCl in dioxane (3.6 mL, 14 mmol) at rt. The reaction mixture was stirred at rt for 2 h. The solvent was evaporated and the residue was dried *in vacuo* to give **5** (ca. 330 mg) as yellow HCL salt, which was used for the next step without further purification. LC-MS (ESI): m/z 465.2 $[M+H]^+$.

[0530] **Step i**. To a solution of **5** (135 mg, 0.29 mmol), N-Moc_L-Val-OH (152.6 mg, 0.87 mmol) and DMTMM (240.5 mg, 0.87 mmol) in a solvent mixture of DMF-THF (2 mL, DMF/THF=1/3 (*v/v*)) was added DIPEA (0.5 mL, 2.9 mmol) at rt. The reaction mixture was stirred at rt for 2 h. THF was evaporated and the remaining reaction mixture was purified via prep-HPLC to provide compound **6** as white solid. ^1H NMR (300 MHz, CD_3OD) δ 0.92 (m, 12 H), 2.05 (m, 4 H). 2.26 (m, 4 H), 3.65 (s, 6 H), 3.9 (m, 2 H), 3.99 (m, 2 H), 4.22 (m, 2H), 5.18 (m, 2H), 7.33 (s, 1H), 7.48 (s, 1H), 7.64 (d, J=8.7 Hz, 1 H), 7.73 (d, J=8.1 Hz, 1 H), 7.88 (d, J=8.1 Hz, 2 H), 7.99 (s, 1H), 8.21 (d, J=8.7 Hz, 2H) ppm. LC-MS (ESI): *m/z* 780.4 $(M+H)^+$.


B(OH)2
Pd(dppf)Cl2
Cs2CO3
TFH/DMF,
95oC, 6h
4 steps
1
2
ACN/DMF
DIPEA, r.t. 15h
3
TMSOTf/TEA
PTT in THF
4
ACN/DIPEA
r.t.15 h
5
O-Xylene
TEA, 140 °C, 1.5h
6
1. TFA/DCM
2. HATU/DPIEA
DMF, r.t.
1. Pd/C/H2, HCl, 50 psi
2. HATU/DPIEA
DMF, r.t.
7
8 R' = OMe
9 R' = OBu-t
10 R' = NHMe

Scheme 9-4

[0531] **Step a**. Referring to Scheme 9-4, ethyl 2-bromo-6-benothiazolecarboxylate (100 mg, 0.35 mmol), 4-acetylphenylboronic acid (69 mg, 0.42 mmol), $Pd(dppf)Cl_2$ (14 mg, 0.05 mmol) and Cs_2CO_3 (228 mg, 0.70 mmol) were dissolved in a mixed solvent (THF/DMF = 3:2, 5 mL) in a Schlenk flask. The reaction mixture was degassed and refilled with nitrogen three times. The flask was heated to 95 °C under nitrogen 6 h, cooled to rt. The solvent was removed under reduced pressure and the residue was re-dissolved in dichloromethane (DCM). The DCM solution was washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4, concentrated, purified by silica gel column (DCM/MeOH = 9.8/0.2 (*v/v*)) to give **1** as slight yellow solid (70 mg, 62% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.17-8.21 (m, 3H), 8.06-8.13 (m, 3H), 4.43 (q, 2H), 2.66 (s, 3H), 1.44 (t, 3H) ppm. LC-MS (ESI): *m/z* 326.1 $(M+H)^+$.

[0532] **Step b**. To a suspension of **1** (4.0 g, 12.3 mmol) in the solvent mixture of THF/MeOH/H_2O (100 mL) was added $LiOH.H_2O$ (2.58 g, 61.5 mmol). The reaction mixture was stirred at rt overnight. The volatile was removed, and water (50 mL) was added and the pH was adjusted to 1-2 with 2N HCl. The precipitate was filtered and dried to give a free acid (3.6 g, 100%) as white solid. LC-MS (ESI) *m/z*: 298.0 $(M+H)^+$.

[0533] **Step c**. A sample of the acid (3g, 10 mmol) was suspended in thionyl chloride (50 mL), heated to refluxing for 2 h. The volatile was removed under reduced pressure and the residue (3.2 g) was dried *in vacuo* to give the corresponding acyl chloride.

[0534] **Step d**. To the suspension of the acyl chloride above (3 g, 9.5 mmol) in the mixed solvent of DCM/THF (7/3 (*v/v*), 100 mL) at 0°C was added fresh-made diazomethane (5.0 equiv.) in diethyl ether. The reaction mixture was stirred from 0°C to rt 1h. LC-MS and ^1H NMR showed reaction was completed. The solvent was removed to give crude product diazoketone. ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.20-8.23 (d, *J* = 7.5, 2H), 8.08-8.15 (m, 3H), 7.86 (d, *J* = 7.8, 1H), 6.0 (s, 1H), 2.68 (s, 3H) ppm.

[0535] **Step e**. The dizoketone was dissolved in acetic acid (50 mL) and HBr (1.1 equiv, 48% aq. solution) was added, stirred at rt for 1h, concentrated to give compound **2** (4.5 g).

[0536] **Step f**. To a solution of the N-Cbz_L-Proline (3.59 g, 14.4 mmol) in acetonitrile (100 mL) and DMF (50 mL) was added diisopropylethylamine (6.0 mL, 36 mmol) and **2** (4.5 g, 12 mmol) in acetonitrile (50 mL). The reaction mixture was stirred at rt overnight. The solvent was

removed and product was extracted with dichloromethane (3x), washed with $NaHCO_3$ (200 mL) and brine, dried over Na_2SO_4. After removal of the solvent, the crude product was purified on silica column (Hexane/EtOAc = 1/1 (*v/v*)) to give **3** (1.2 g). LC-MS (ESI): *m/z* 543.2 $(M+H)^+$.

[0537] **Step g**. To a solution of **3** (1.2 g, 2.2 mmol) and TEA (2.18 mL, 13.2 mmol) in DCM was added TMS-OTf (0.8 mL, 4.4 mmol) at –78 °C. After the reaction was stirred to r.t overnight, PTT (910 mg, 2.42 mmol) was added. The reaction was stirred at rt for 2h and quenched with $NaHCO_3$ solution. The mixture was partitioned between water and CH_2Cl_2 (3x), and the organic phase was washed with brine, dried, filtered and concentrated *in vacuo* to give crude compound **4** (1.37 g).

[0538] **Step h**. To a solution of N-Boc-L-Proline (568 mg, 2.6 mmol) in acetonitrile (10 mL) was added DIPEA (0.54 mL, 3.3 mmol) and **4** (1.37 g, 2.2 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at rt overnight. The solvent was removed and product was extracted with dichloromethane (3x), washed with $NaHCO_3$ (200 mL) and brine, dried with Na_2SO_4. After removal of the solvent, the crude product was purified on silica column (Hexanes/EtOAc = 1/1 (v/v)) to give **5** (900 mg, 54% yield). LC-MS (ESI): *m/z* 756.3 $(M+H)^+$.

[0539] **Step i**. To a solution of **5** (900 mg, 1.19 mmol) in *o*-xylene (20 mL) in a pressure tube was added ammonium acetate (2.75 g, 35.7 mmol) and triethylamine (5 mL, 35.7 mmol). The tube was sealed and heated to 140 °C for 1.5h, cooled to rt The volatile component was removed in vacuum, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried, filtered and concentrated in vacuum. The resulting crude material was purified by a flash chromatography (Hex: EA: MeOH = 5:5:1) to provide **6** as yellow residue (630 mg, 74% yield). LC-MS (ESI): *m/z* 716.3 $(M+H)^+$.

[0540] **Step j**. To a solution of **6** (630 mg, 0.88 mmol) in DCM (20 mL) was added TFA (5 mL). The reaction mixture was stirred at rt for 2 h; TFA was removed to give a TFA salt, which was used for the next step without further purification.

[0541] **Step k**. To a solution of the TFA salt (550 mg, 0.88 mmol) in DMF (10 mL) was added N-Moc-L-Val-OH (308 mg, 1.76 mmol), HATU (502 mg, 1.32 mmol) and DIPEA (871 μL, 5.28 mmol). The reaction was stirred at rtrt overnight. The solvent was removed under reduced pressure. The crude product was purified on silica gel column (CH_2Cl_2/MeOH = 9.8 / 0.2 (*v/v*)) to give **7** (500 mg, 74% yield). LC-MS (ESI): *m/z* 773.3 $(M+H)^+$.

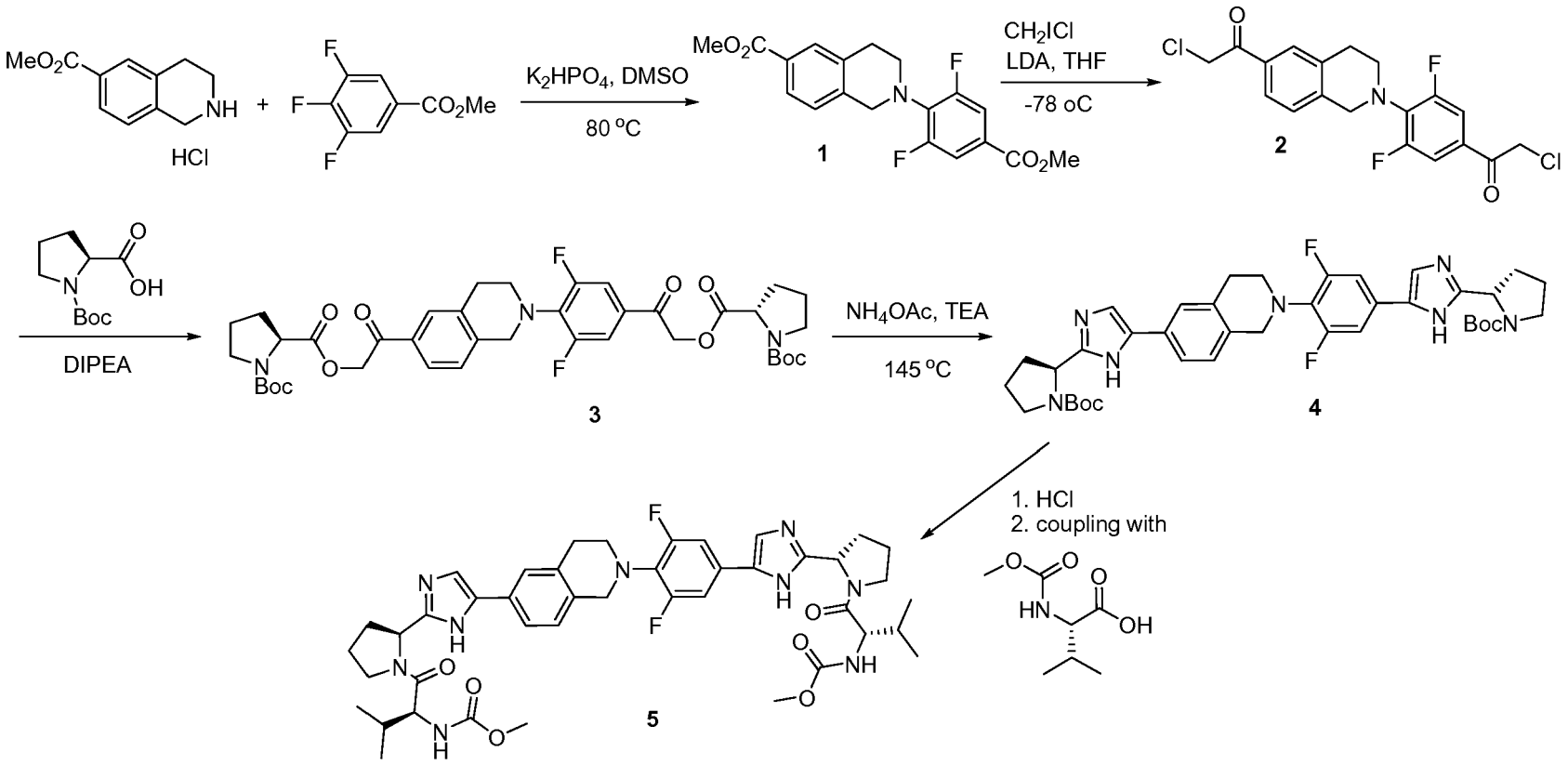
[0542] **Step l**. To a solution of **7** (500 mg, 0.647 mmol) in MeOH (20 mL) was added Pd/C (50 mg) and several drops of con. HCl, purged with H_2. The reaction mixture was shaken in the shaker under 60 psi for 48h. The mixture was filtered on CELITE™ and concentrated; the residue was purified on silica gel column (DCM/MeOH = 8/2 (*v/v*)) to give a free amine (300 mg).

[0543] **Step m**. To a solution of the free amine from Step 8a (100 mg, 0.16 mmol) in DMF (5 mL) was added N-Moc-D-Phg-OH (43 mg, 0.204 mmol), HATU (60 mg, 0.157 mmol) and DIPEA (155 μL, 0.942 mmol). The reaction was stirred at rtrt overnight. The solvent was removed under reduced pressure. The crude product was purified on preparative HPLC to give **8** (33 mg), in which R" is a methyl group. LC-MS (ESI): *m/z* 830.3 $(M+H)^+$.

[0544] **Additional Examples.** Similarly taking a sample of the free amine from Step 8a and by substituting N-Boc-D-Phg-OH for N-Moc-D-Phg-OH in Step b above, the corresponding N-Boc analog **9** was obtained (75 mg). LC-MS (ESI) *m/z*: 872.4 $(M+H)]^+$.

[0545] Taking a sample of **9** (70 mg, 0.08 mmol) in DCM (15 mL) and treated with TFA (4 mL). The corresponding de-Boc product was obtained as a TFA salt.

[0546] To a solution of the TFA salt in THF (10 mL) was added DIPEA (132 μL, 0.8 mmol) and CDI (39 mg, 0.24 mmol). The reaction was stirred at rtrt until the reaction completed (monitored by LC-MS). To the solution was added methyl amine hydrochloride (54 mg, 0.8 mmol). The reaction was stirred at rtrt overnight. The solvent was removed and the residue was purified by prep-HPLC to give compound **10** (12 mg) LC-MS (ESI): *m/z* 829.4 $(M+H)^+$.


MeO2C
NH
HCl
F
F
F
CO2Me
K2HPO4, DMSO
80 °C
1
CH2ICl
LDA, THF
-78 oC
2
Cl
O
Boc
DIPEA
3
NH4OAc, TEA
145 °C
4
BocN
NBoc
1. HCl
2. coupling with
HN
OH
5

Scheme 10-1

EXAMPLE 10 – Synthesis of compounds of Formula IIm

[0547] **Step a**. Referring to Scheme 10-1, a mixture of methyl 1,2,3,4-tetrahydroisoquinoline-6-carboxylate hydrochloride (4.28 g, 18.8 mmol), 3,4,5-trifluorobenzoic acid methyl ester (3.8 g, 20 mmol) and K_2HPO_4 (17.0 g, 98 mmol) in 60 mL of DMSO was stirred at 80 °C for 8 hours. After cooling down, the resulting mixture was partitioned in 800 mL of EtOAc and 800 mL of H_2O. The organic layer was washed with H_2O followed by brine and dried (Na_2SO_4). After concentration, the residue was purified by silica gel column chromatography (hexanes/ethyl acetate (v/v), 3/1 to 1/1) to afford compound **1** (4.1 g, 60% yield) as slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.88 (m, 2H), 7.48 – 7.62 (m, 2H), 7.13 (d, 1H), 4.55 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.58 (t, 2H), 3.04 (t, 2H) ppm.

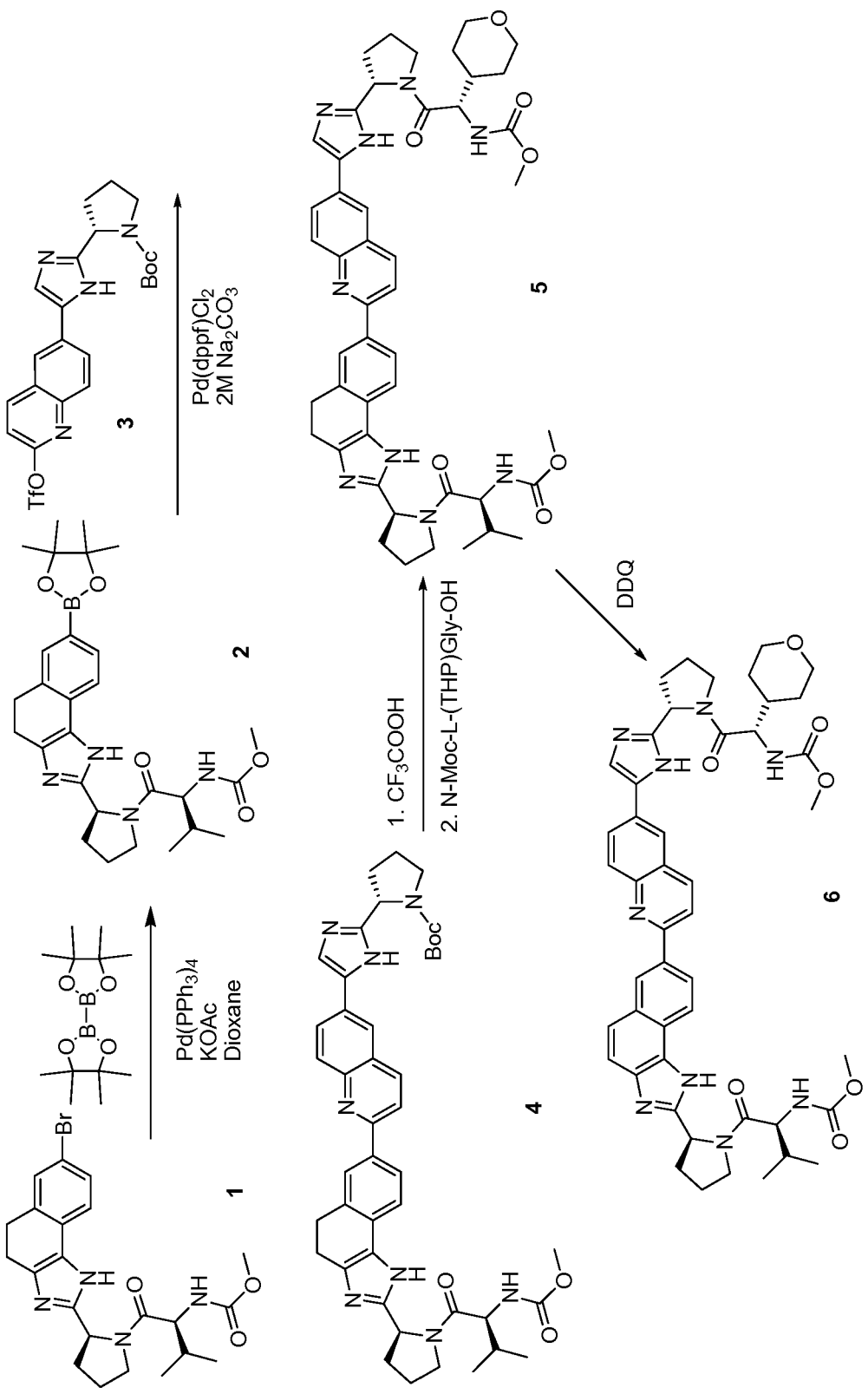
[0548] **Step b**. To a solution of **1** (2.0 g, 5.53 mmol) and chloroiodomethane (5.86 g, 33.2 mmol) in THF (40 mL) was added LDA (precooled to -78 °C, freshly made from 10 mL diisoproylamine and 26.5 mL of 2.5 M *n*-BuLi in hexanes in 40 mL of THF) at -78 °C via cannula over 20 min. The reaction mixture was stirred for two hours at -78 °C before it was quenched by dropwise addition of 12 mL of AcOH/THF (v/v, 1/1). The resulting mixture was warmed up and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with H_2O and dried over Na_2SO_4. After concentration, the residue was purified by the flash column chromatography (silica, hexanes/ethyl acetate, v/v, 4/1) to afford compound **2** (1.19 g, 54% yield) as brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.81 (m, 2H), 7.42 – 7.56 (m, 2H), 7.20 (d, 1H), 4.69 (s, 2H), 4.61 (s, 2H), 4.57 (s, 2H), 3.64 (t, 2H), 3.07 (t, 2H) ppm.

[0549] **Step c**. Compound **2** (1.19 g, 2.99 mmol), N-Boc-L-Proline (1.65 g, 7.64 mmol), KI (1.27 g, 7.65 mmol) and DIPEA (1.32 mL, 7.63 mmol) were dissolved in CH_3CN (15.3 mL). The reaction mixture was then heated to 50 oC in an oil bath for 4 h and cooled to rt. The solvent was removed under vacuum, and the crude was partitioned in EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined EtOAc layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash column chromatograph eluted with hexanes/ethyl acetate (2/1 to 1/1 (*v/v*)) to afford **3** as a yellow solid (1.1 g, 49% yield).

[0550] **Step d**. Compound **3** (1.0 g, 1.32 mmol), NH_4OAc (2.89 g, 39.6 mmol), TEA (5.52 mL, 96.6 mL) were dissolved in xylene (6.6 mL). The reaction mixture in a sealed tube was then

heated to 140 °C in an oil bath for 2 h and then cooled to rt. EtOAc and H_2O were added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined EtOAc layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash column chromatograph eluted with hexanes/ethyl acetate (1/2 to 0/1 (*v/v*)) to afford **4** as yellow solid (0.7 g, 74% yield).

[0551] **Step 5**. A sample of compound **4** (0.50 g, 0.70 mmol), dissolved in dioxane (2 mL) with stirring, was treated with 4M HCl in dioxane (14.3 mL, 57.3 mmol). 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 next without further purification.rt The HCl salt (50 mg, 0.097mmol) and N-Moc-L-Valine (34 mg, 0.194 mmol) were dissolved in DMF (2 mL). DIPEA (0.2 mL, 1.16 mmol) and DMTMM (53.6 mg, 0.19 mmol) were added to the mixture. After stirring at rt for overnight, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give rt compound **5** (9.3 mg) as a light yellow solid ^{1}H NMR (CD_3OD, 300 MHz) δ 8.18 (1H, s), 7.52-6.99 (7H, m), 5.35-5.27 (1H, m), 5.19-5.11 (2H, m), 4.33 (2H, s), 4.25-4.19 (2H,m), 4.03-3.95 (3H, m), 3.90-3.80 (2H, m), 3.70-3.65 (6H, s), 3.50-3.45 (2H, m), 3.00-2.95 (2H, m), 2.40-1.98 (12H, m), 0.99-0.88 (12H, m) ppm. LC-MS (ESI): *m/z* 830.4 $(M+H)^+$.


Br
1
Pd(PPh3)4
KOAc
Dioxane
2
TfO
3
Pd(dppf)Cl2
2M Na2CO3
Boc
4
1. CF3COOH
2. N-Moc-L-(THP)Gly-OH
5
DDQ
6

Scheme 11-1

EXAMPLE 11 – Synthesis of compounds of Formula Vc

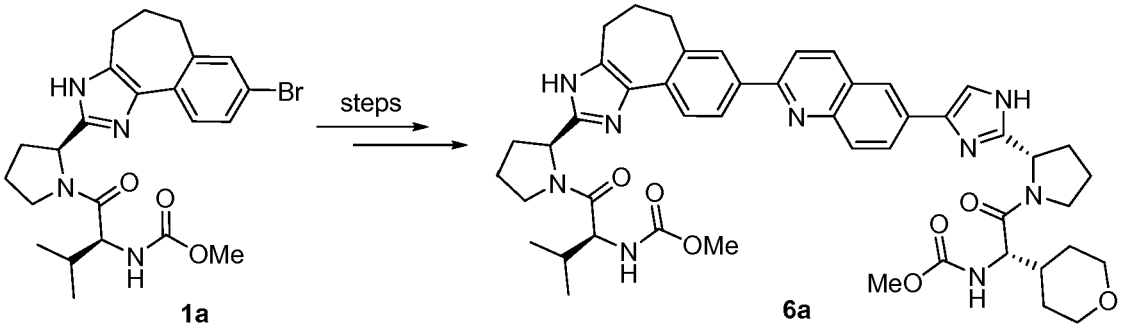
[0552] **Step a**.Referring to Scheme 11-1, to a solution of the bromide **1** (2.0 g, 4.2 mmol, prepared according to published conditions) in dioxane (60 mL) was added bis(pinacolato)diboron (4.32 g, 17 mmol), $Pd(PPh_3)_4$ (0.49 g, 0.42 mmol) and potassium acetate (2.06 g, 21 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80° C for 5 h, and then diluted with ethyl acetate (150 mL). The organic phase was washed with H_2O (20 mL), dried over sodium sulfate and concentrated in vacuo. The residue was further purified by silica gel column chromatography (haxanes/ethyl acetate =1/4 to 0/1 (*v/v*)) to give **2** (1.73 g, 79% yield). LC-MS (ESI): *m/z* 523.3 $(M+H)^+$.

[0553] **Step b**. A mixture of 2-quinolinol triflate 3 (0.72 g, 1.4 mmol), boronic ester **2** (0.73 g, 1.4 mmol), $Pd(dppf)Cl_2$-DCM (114 mg, 0.14 mmol) in 2 M Na_2CO_3 (2.8 mL) and dioxane (5.6 mL) was treated by a process of degas-and-refilled-with-nitrogen three times. The reaction mixture was then stirred at 90° C under nitrogen atmosphere for 4 h. After being cooled, the mixture was diluted with THF, and then filtered through a pad of CELITE™. The filtrate was concentrated and the crude product was purified by flash chromatography (NH_4OH/acetonitrile/ethyl acetate, 1:8:100) affording a pure product **4** (0.80 g, 75% yield) as *a* white solid. LC-MS (ESI): *m/z* 759.4 $(M+H)^+$.

[0554] **Step c**. Trifluoroacetic acid (2.5 mL) was slowly added into a solution of **4** (0.80 g, 1.5 mmol) in CH_2Cl_2 (5.0 mL) at rtrt. The resulting mixture was stirred at rtrt for 2 h, and then concentrated to dryness. The crude product was dried *in vacuo* to give a TFA salt, which was used for the next step without further purification. LCMS (ESI): *m/z* 659.3 $(M+H)^+$.

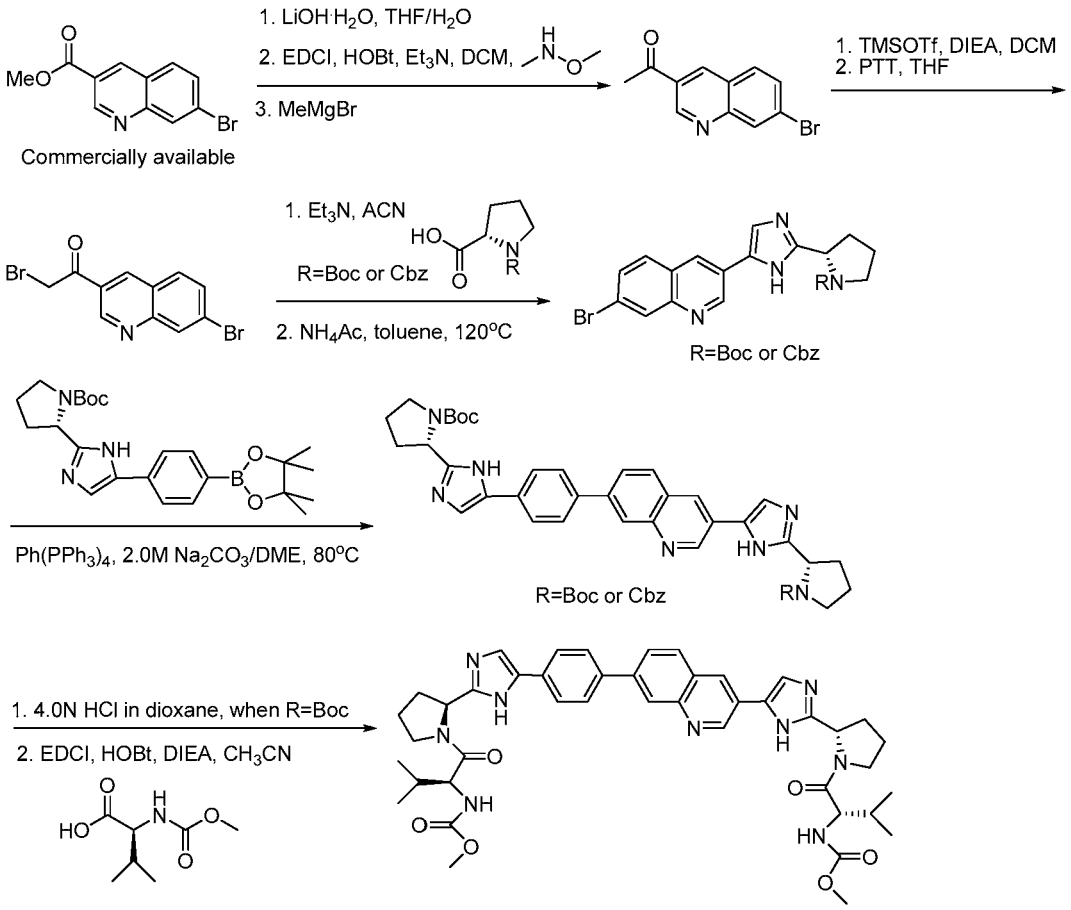
[0555] **Step d**. To a mixture of the TFA salt (69.1 mg, 0.11 mmol) obtained from above reaction in DMF (3 mL) was added DIPEA (0.23 mL, 1.4 mmol), followed by L- N-methoxycarbonyl-(4-tetrahydro-2*H*-pyran-4-yl)glycine (30 mg, 0.14 mmol) and HATU (52 g, 0.14 mmol). After stirring at rt for 2 h, the reaction mixture was slowly dropped into H_2O while stirring. The resulting precipitate was collected by filtration. The crude product was purified by prep-HPLC to afford product **5** (34.5 mg). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90 (m, 1H), 7.80-7.60 (m, 4H), 7.5 (m, 2H), 7.36 (d, 1H), 7.10 (broad s, 2H), 7.56 (d, 1H), 7.44 (d, 1H), 5.28 (m, 2H), 4.54 (t, 1H), 4.42 (t, 1H), 4.10-3.93 (m, 7H), 3.68 (m, 7H), 3.42 (m, 2H), 3.00-2.22 (m, 8H), 2.08 (m, 5H), 1.80-1.40 (4H), 1.10-0.90 (m, 6H) ppm LC-MS (ESI): *m/z* 858.4 $(M+H)^+$.

[0556] **Step e**. A solution of compound **5** (37.7 mg, 0.044 mmol), DDQ (10.0 mg, 0.044 mmol) in 6 mL of benzene was refluxed for 2.5 h. After removal of the solvent, the crude product was purified by prep-HPLC to afford **6** (23 mg) as yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40-7.40 (m, 10H), 7.22 (s, 1H), 5.60-5.40 (m, 3H), 5.30 (m, 2H), 4.60-4.40 (m, 2H), 4.20-3.80 (m, 6H), 3.70 (m, 7H), 3.44 (m, 3H), 2.50-2.00 (m, 13H), 1.10-0.92 (m, 6H) ppm. LC-MS (ESI): *m/z* 856.4 $(M+H)^+$.

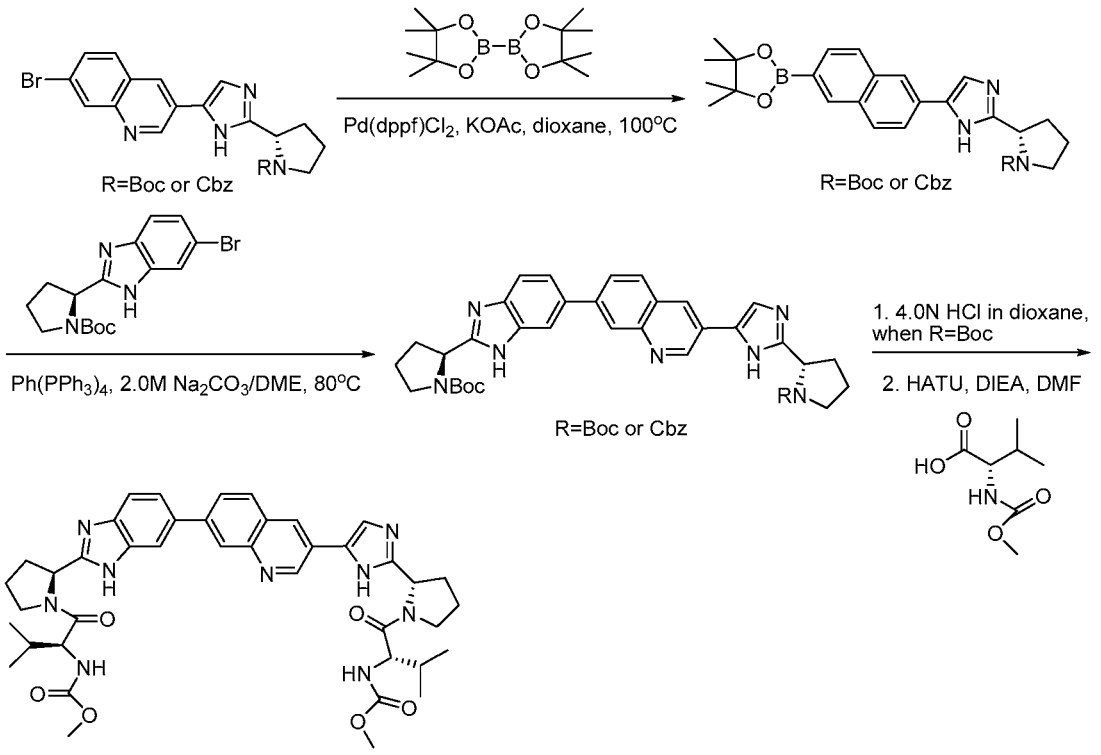


[0557] Following procedures and conditions described in Scheme 11-1 and substituting compound **1a** for compound **1**, compound **6a** was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 9.21-9.18 (m, 1H), 8.79 (s, 1H), 8.56-8.50 (m, 3H), 8.26-8.19 (m, 3H), 8.10-8.07 (m, 1H), 5.32-5.25 (m, 2H), 4.34-4.24 (m, 2H), 4.13-4.06 (m, 2H), 3.95-3.89 (m, 4H), 3.67 (s, 6H), 3.24-3.09 (m, 6H), 2.65-2.10 (m, 12H), 1.60-1.30 (m, 4H), 1.01 – 0.91 (m, 6H) ppm; LC-MS (ESI): *m/z* 872.4 $(M+H)^+$.

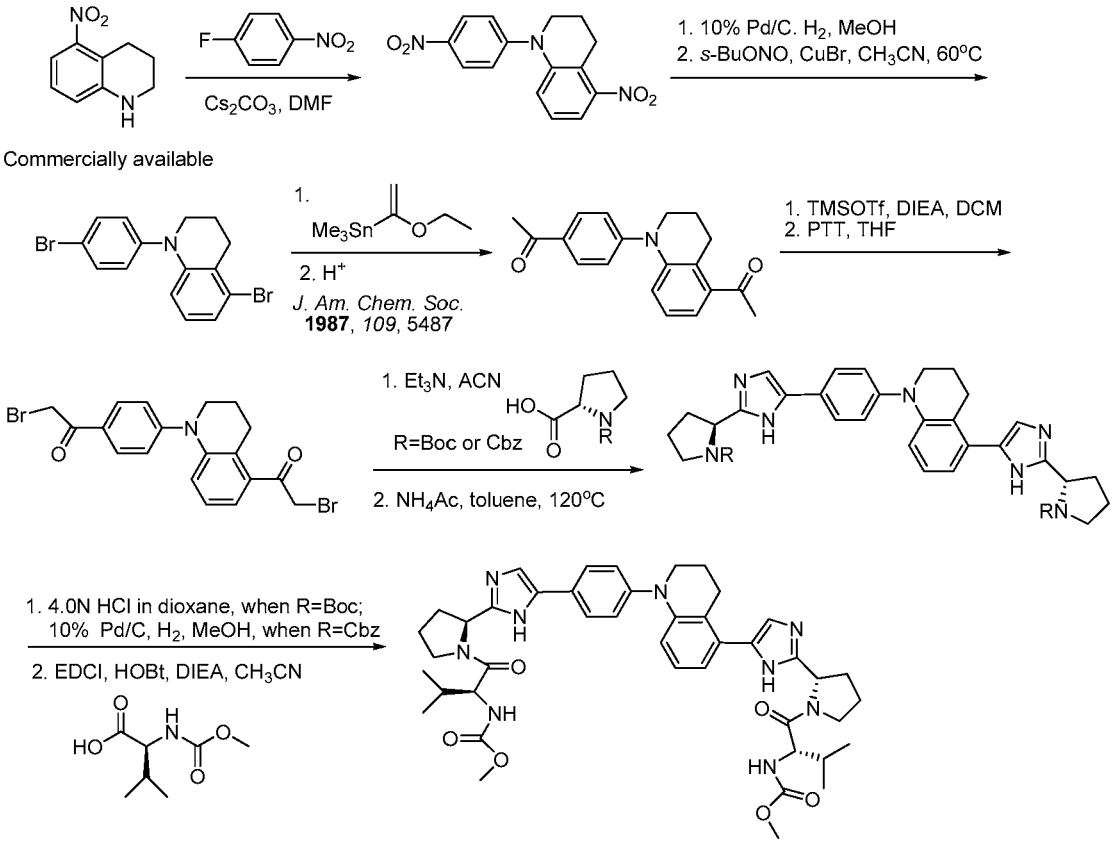
EXAMPLE 12 – Additional Synthetic Schemes for Compounds of the Invention



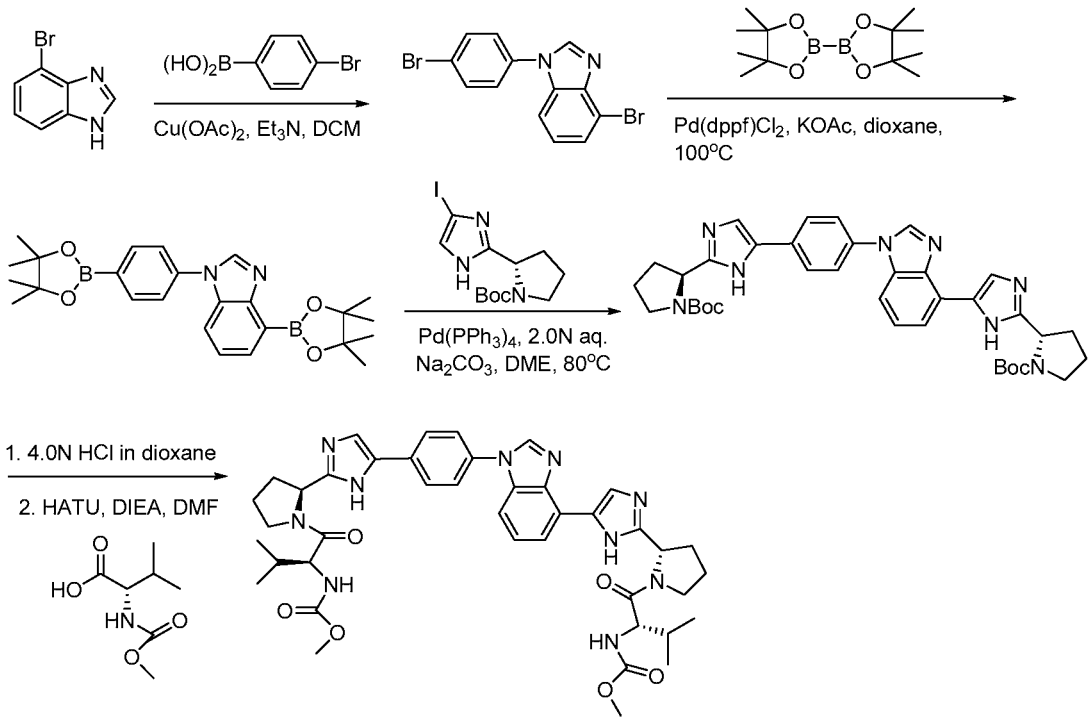
Scheme 12-1


Br
N
N
H
RN
R=Boc or Cbz
Pd(dppf)Cl2, KOAc, dioxane, 100°C
B
O
O
R=Boc or Cbz
Br
NBoc
Ph(PPh3)4, 2.0M Na2CO3/DME, 80°C
R=Boc or Cbz
1. 4.0N HCl in dioxane, when R=Boc
2. HATU, DIEA, DMF
HO
HN
O
NH

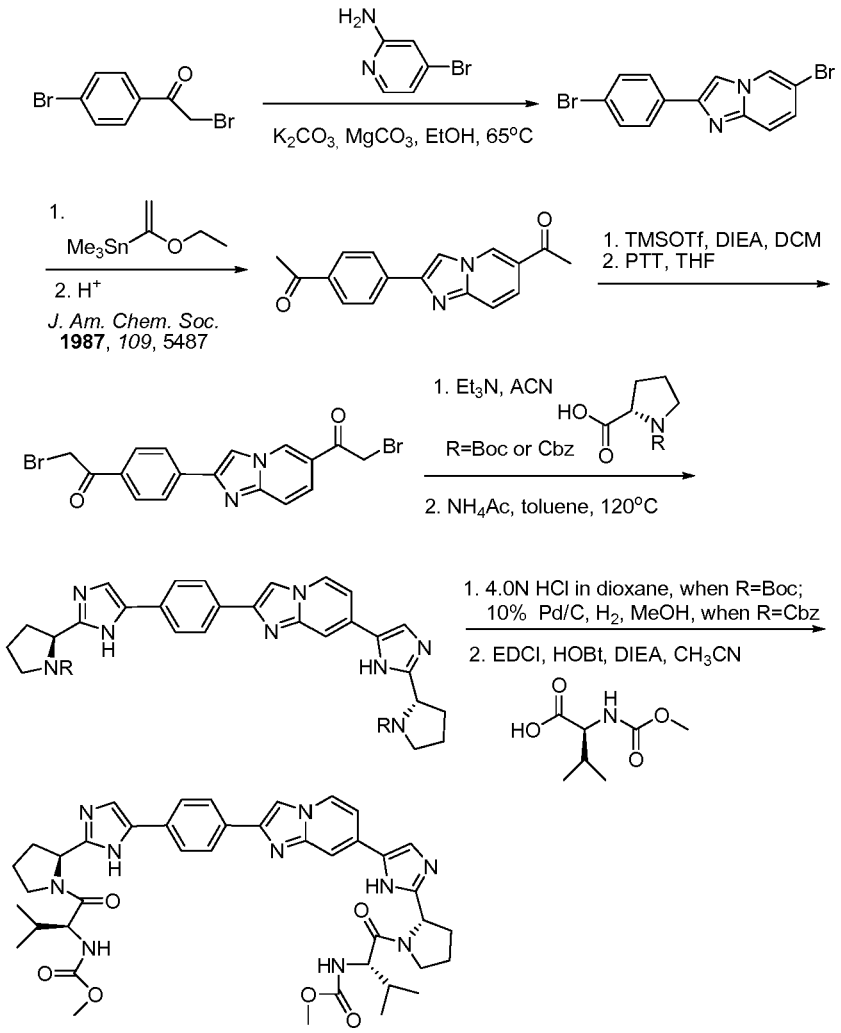
Scheme 12-2


NO2
F
NO2
Cs2CO3, DMF
O2N
N
NO2
1. 10% Pd/C. H2, MeOH
2. s-BuONO, CuBr, CH3CN, 60°C
Commercially available
Br
N
Br
1.
Me3Sn
O
2. H+
J. Am. Chem. Soc.
1987, 109, 5487
1. TMSOTf, DIEA, DCM
2. PTT, THF
1. Et3N, ACN
HO
N
R
R=Boc or Cbz
2. NH4Ac, toluene, 120°C
NR
RN
1. 4.0N HCl in dioxane, when R=Boc;
10% Pd/C, H2, MeOH, when R=Cbz
2. EDCI, HOBt, DIEA, CH3CN
HO
H
N
O

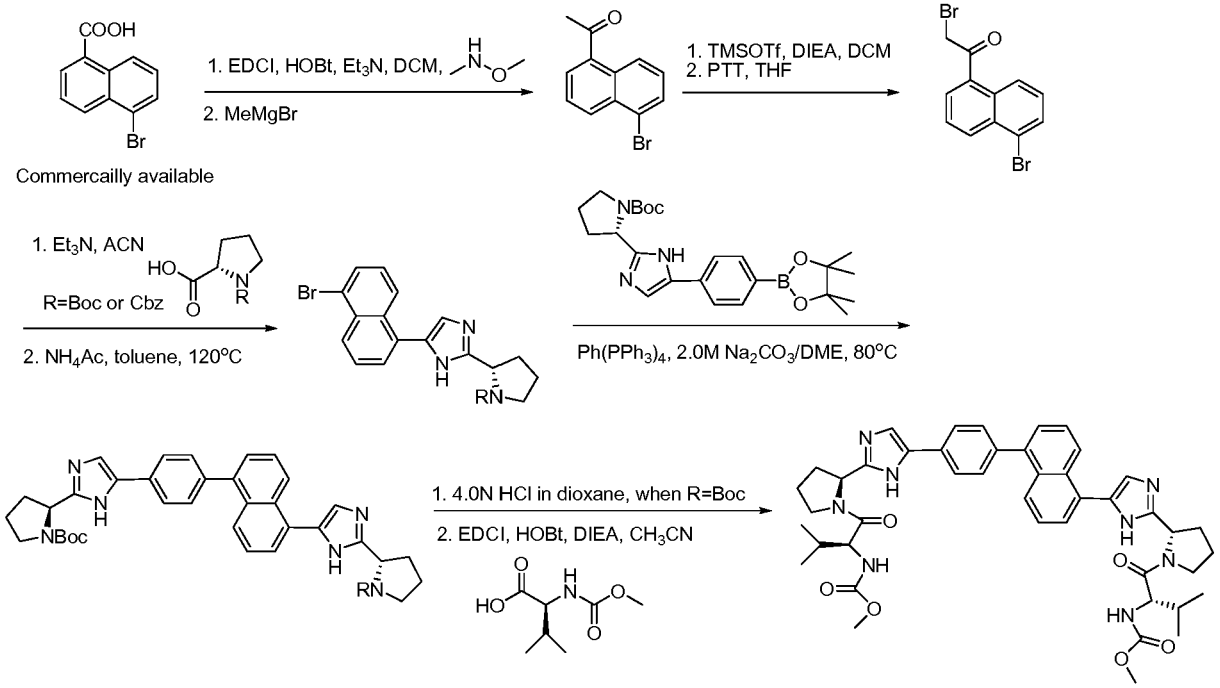
Scheme 12-3


Br
(HO)2B
Br
Cu(OAc)2, Et3N, DCM
Br
Br
Pd(dppf)Cl2, KOAc, dioxane,
100°C
I
BocN
Pd(PPh3)4, 2.0N aq.
Na2CO3, DME, 80°C
NBoc
BocN
1. 4.0N HCl in dioxane
2. HATU, DIEA, DMF
HO
HN
NH
HN

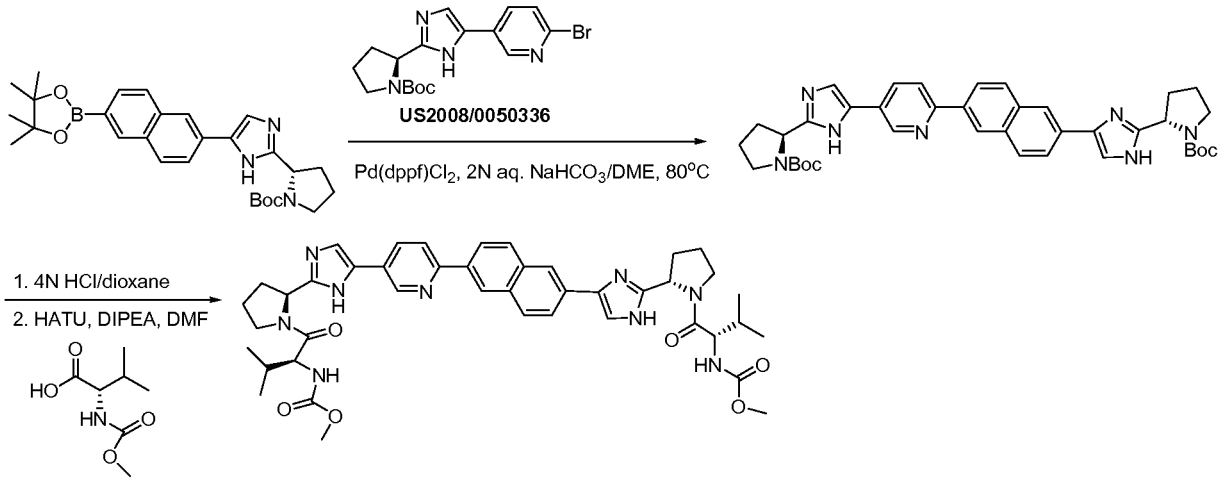
Scheme 12-4


H_2N
Br
Br
Br
Br
N
N
K_2CO_3, $MgCO_3$, EtOH, 65°C
1.
Me_3Sn
O
2. H^+
J. Am. Chem. Soc.
1987, 109, 5487
1. TMSOTf, DIEA, DCM
2. PTT, THF
1. Et_3N, ACN
HO
N
R
R=Boc or Cbz
O
2. NH_4Ac, toluene, 120°C
NR
HN
RN
1. 4.0N HCl in dioxane, when R=Boc;
10% Pd/C, H_2, MeOH, when R=Cbz
2. EDCI, HOBt, DIEA, CH_3CN
HO
H
N
O
NH
HN

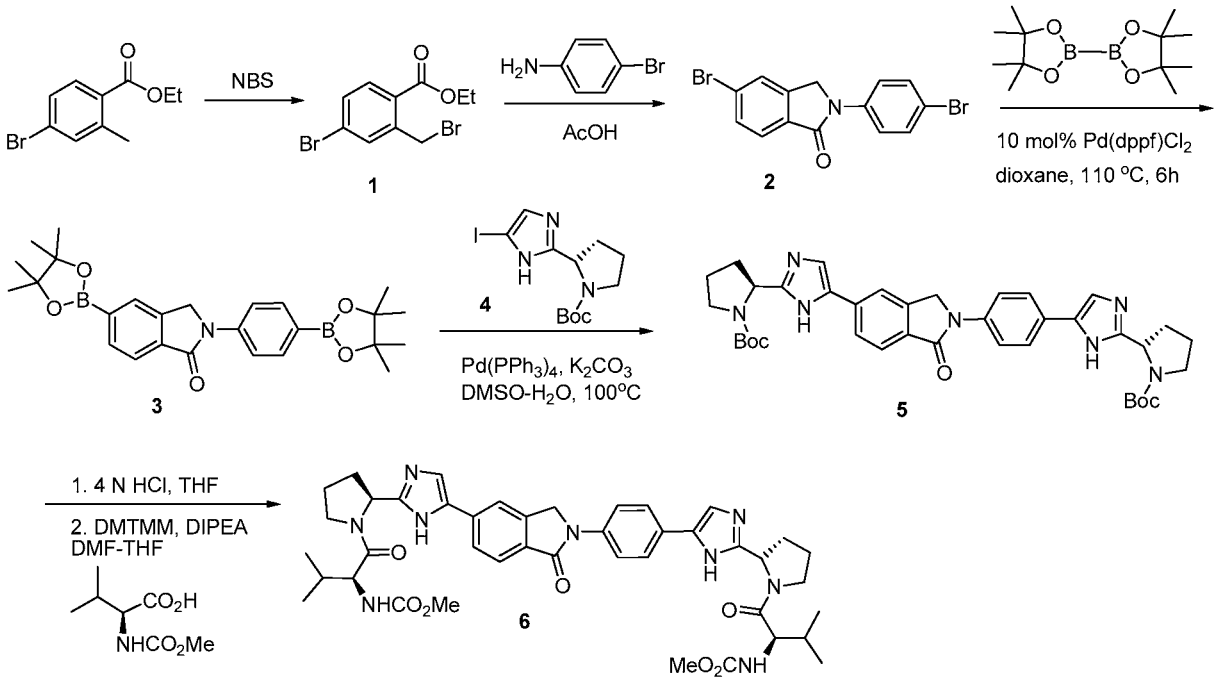
Scheme 12-5



Scheme 12-6



Scheme 12-7



Scheme 12-8

[0558] **Step a**. Referring to Scheme 12-8, a mixture of ethyl 4-bromo-2-methylbenzoate (1.0 g, 4.11 mmol) and NBS (1.15 g, 6.46 mmol) in CCl_4 (13.7 mL) was heated to reflux for 6 h. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure to obtain yellow oil **1** (1.47 g) which contained approx. 25% of unreacted starting material by LC/MS. The crude material was used without further purification.

[0559] **Step b**. Crude ester **1** (4.11 mmol) was dissolved in glacial acetic acid (13.7 mL), and 4-bromoanaline (0.85 g, 4.93 mmol) was added to the solution. The reaction mixture was then heated to reflux for 12 h and cooled to rt. H_2O (150 mL) was added and neutralized with solid Na_2CO_3 to pH 7. The aqueous solution was extracted with ethyl acetate (3x100 mL), and the organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash column chromatograph eluted with hexanes/ethyl acetate (12/1 to 10/1) to removed byproduct and then with pure ethyl acetate to afford brown solid **2** (0.54 g, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.69 (m, 3H), 7.68-7.67 (m, 2H), 7.65-7.52 (m, 2H), 4.82 (m, 2H) ppm.

[0560] **Step c**. A mixture of compound **2** (0.54 g, 1.46 mmol), pinacol diborane (0.82 g, 3.22 mmol), KOAc (0.86 g 8.76 mmol), and Pd catalyst (0.12 g, 0.15 mmol) in dioxane (28 mL) was

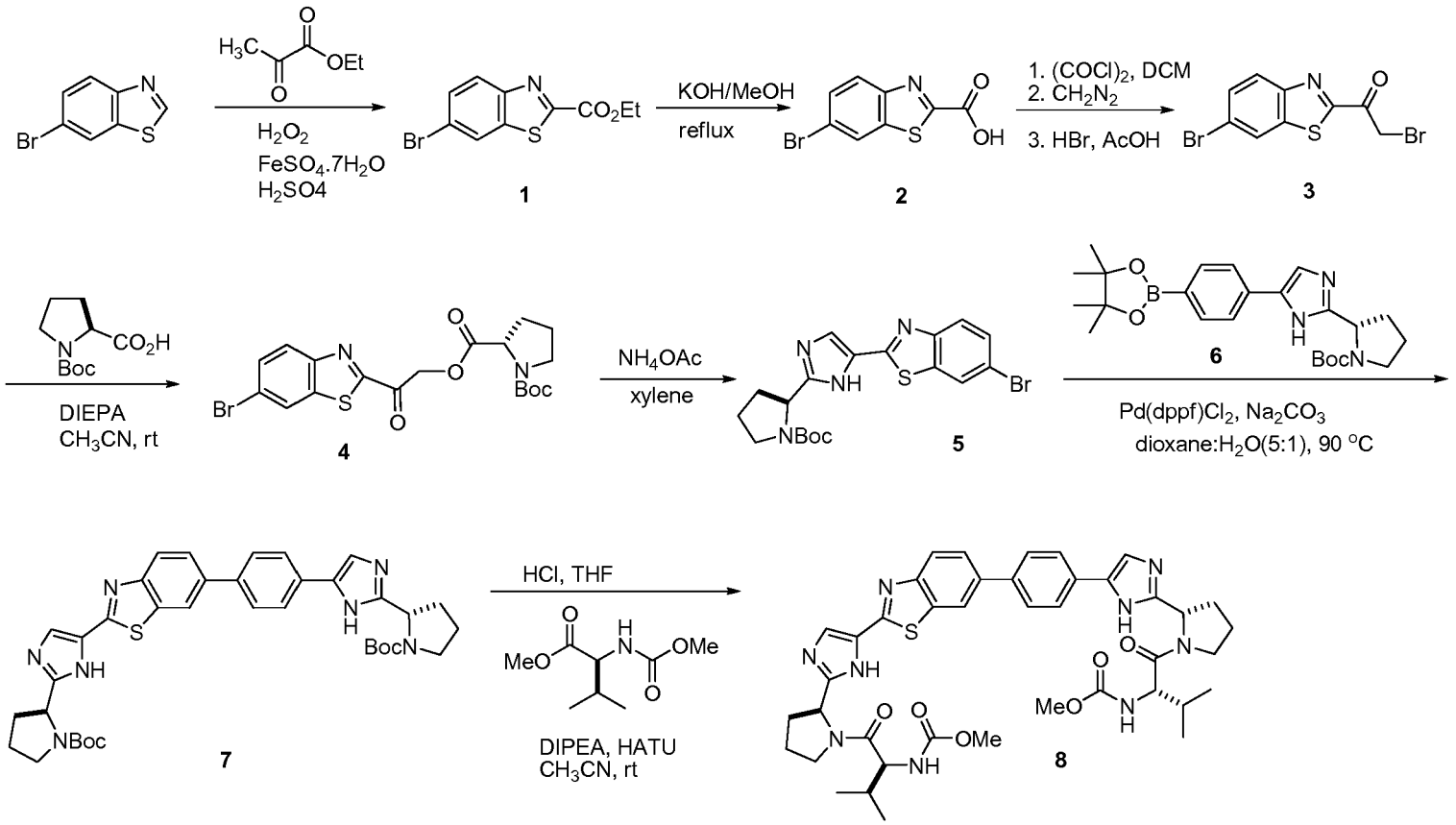
heated at 110 °C for 30 h. The reaction mixture was cooled to rt and diluted with H_2O. The aqueous layer was extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash column chromatograph eluted with ethyl acetate to afford dark yellow solid **3** (0.49 g, 73% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.70 (m, 7H), 4.81 (s, 2H), 1.40-1.20 (m, 24H) ppm.

[0561] **Step d**. A mixture of **3** (400 mg, 0.87 mmol), iodoimidazole compound **4** (630 mg, 1.73 mmol) and $Pd(PPh_3)_4$ (200mg, 0.17 mmol) and potassium carbonate (311 mg, 2.25 mmol) in DMSO (10 mL) and H_2O (3.5 mL) was heated at 100 °C for 14h. The reaction mixture was cooled to rt and diluted with H_2O and extracted with dichloromethane. The combine organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash column chromatography (ethyl acetate/ methanol = 97/ 3 (*v/v*)) to afford **5** (357 mg, 61% yield) as a light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95-6.90 (m, 9H), 4.95(m, 2H), 3.41 (m, 4H), 2.95 (m, 2H), 2.28-1.85 (m, 6H), 1.50 (s, 9H), 1.48 (s, 9H) ppm.

[0562] **Step e**. To a stirred suspension of **5** (40 mg, 0.059 mmol) in THF (0.6 mL) at rt was added 4 N HCl solution in 1,4-dioxane (0.6 mL), and the mixture was stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo* to give an HCl salt (37 mg, 100% yield), which was used without purification in the next step. LC-MS (ESI) *m/z*: $[(M+2H)/2]^+$ 478.5.

[0563] **Step f**. To a stirred solution of HCl salt from above (37 mg, 0.059 mmol) and N-methoxycarbonyl-L-valine (22.6 mg, 0.13 mmol) in DMF (2 mL) was added HATU (49 mg, 0.13 mmol) followed by diisopropylethyl amine (0.1 mL, 0.59 mmol). After being stirred at rt for 4 h, the reaction mixture was diluted with H_2O and extracted with dichloromethane. The combine organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product, which was purified by prep HPLC to give **6** (6.4 mg, 14% yield) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95-7.20 (m, 9H), 5.20 (m, 2H), 4.40-3.61 (m, 6H), 3.34 (s, 6H), 3.20-1.90 (m, 12H), 0.95 (dd, 6H), 0.90 (dd, 6H). LC-MS (ESI) *m/z*: $[M-H]^-$ 793.

[0564] **Step g**. Similarly, the six-membered analogs (**2a**, **2b**, **2c**) of compound **2** were prepared following published procedures. Compounds **2a**, **2b** and **2c** were further transformed following the same synthetic sequences and conditions described above afford their perspective analogs of compound **6**.


H2O2
FeSO4.7H2O
H2SO4
KOH/MeOH
reflux
1. (COCl)2, DCM
2. CH2N2
3. HBr, AcOH
DIEPA
CH3CN, rt
NH4OAc
xylene
Pd(dppf)Cl2, Na2CO3
dioxane:H2O(5:1), 90 °C
HCl, THF
DIPEA, HATU
CH3CN, rt

Scheme 12-9

[0565] **Step a**. Referring to Scheme 12-9, to ethyl pyruvate (24.4 g, 23.4 mL, 210 mmol) was added dropwise H_2O_2 (35%, 13.6 g, 13.6 mL, 140 mmol) at 0 °C followed by stirring for 5 min. To a mixture of 6-bromo-benzothiazole (10.0 g, 46.7 mmol) in H_2O (45 mL) and H_2SO_4 (13.7 g, 7.5 mL, 140 mmol) was added simultaneously the fresh prepared ethyl pyruvate mixture and $FeSO_4 \cdot 7H_2O$ (38.9 g, 140 mmol) in H_2O (90 mL) at 0 °C. The resulting mixture was kept at 0 °C and stirred at rt overnight. To the mixture was added additional H_2SO_4 (27.4 g, 15.0 mL, 280 mmol) followed by fresh prepared ethyl pyruvate mixture (28.8 g of ethyl pyruvate, 46.8 mL, 420 mmol and H_2O_2 35%, 27.2 g, 27.2 mL, 280 mmol) and $FeSO_4$ $7H_2O$ (77.8 g, 280 mmol) in H_2O (180 mL) at 0 °C. After stirring at 0 °C for 7.5 h, excess ice was added to the reaction mixture and the pH was adjusted to 10-11 with a 2.0 M KOH solution. The basic mixture was extracted with EtOAc (5 x 300 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to give yellow oil. The crude product **1** was used for the next step without further purification. LC-MS (ESI) m/z: $(M+1)^+$ 288.

[0566] **Step b**. To a crude mixture of **1** (~46.7 mmol) in MeOH (250 mL) was added KOH (25.2 g, 450 mmol). After the mixture was heated under reflux condition for 3 h, all volatile was removed on a rotary evaporator to give a brown solid. The brown solid was dissolved in H_2O (200 mL) and then extracted with EtOAc (3x200 mL). The pH of the aqueous phase was adjusted to 3-4 with 10 % HCl solution and extracted with EtOAc (5x200 mL). Combined organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to give **2** as a yellow solid (9.66 g, 80% yield). LC-MS (ESI) m/z $(M+1)^+$ 260.

[0567] **Step c**. To a mixture of **2** (1.43 g, 5.5 mmol) in DCM (50 mL) was added slowly oxayl chloride (14.0 g, 9.5 mL, 110 mmol) followed by one drop of DMF at rt. After the resulting mixture was stirred at rt overnight (15 h), all volatiles were removed on a rotary evaporator. The crude mixture was used for the next step without purification.

[0568] **Step d**. To a solution of 6-bromo-benzothiazole-2-carbonyl chloride **2** (~5.5 mmol) in THF (50 mL) was added dropwise flash generated diazomethane solution (approximately 16.6 mmol of diazomethane solution generated from 25.1 mmol of 4-N,N-trimethyl-benzenesulfonamide) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then the temperature was allowed to warm to rt. After the stirring was continued at rt for 2.5 h, all

volatile was removed on a rotary evaporator. The crude mixture was used for the next step without further purification.

[0569] **Step e**. To a mixture of 1-(6-bromo-benzothiazol-2-yl)-2-diazo-ethanone obtained from above (~5.5 mol) in AcOH (30 mL) was slowly added aqueous HBr (48 %, 0.69 mL, 6.1 mmol) at rt. The resulting mixture was stirred at rt for an additional 2 h. All volatile was removed on a rotary evaporator to give dark solid. The crude mixture was further dried by azeotropic evaporation with toluene on a rotary evaporator (15 mL X 2). Compound 3 was obtained as a dark brown solide, which was used for the next step without further purification.

[0570] **Step f**. To a crude mixture of 2-bromo-1-(6-bromo-benzothiazol-2-yl)-ethanone A7 (~5.5 mmol) in CH_3CN (50 mL) was added pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (1.31 g, 6.1 mmol) followed by addition of DIPEA (2.14g, 2.69 mL, 16.6 mmol) at rt. The resulting mixture was stirred at rt for 5 h, and then quenched with H_2O. The mixture was extracted with EtOAc (3x50 mL), and then the combined organic phases were washed with H_2O (50 mL) and brined (50 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography eluting with hexanes/EtOAc = 6:1 to 4:1 (*v/v*) to give the title compounds as brown solid (297 mg, 12% for total 4 steps from **2**). LC-MS (ESI) *m/z*: $(M+H)^+$ 493.

[0571] **Step g**. To a solution of (S)-2-(2-(6-bromobenzo[d]thiazol-2-yl)-2-oxoethyl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate 4 (297 mg, 0.63 mmol) in xylene (5.0 mL) was added NH_4OAc (488 mg, 6.32 mmol). The resulting mixture was heated at 145 °C for 2 h, and then all solvent was removed on a rotary evaporator to give a crude mixture, which was subject to column chromatography eluting with hexanes:EtOAc (1:1 to 0:1 ratio). Compound **5** was obtained as brown solid (65 mg, 23 %). LC-MS (ESI) *m/z*: $(M+H)^+$ 451.

[0572] **Step h**. A mixture of **5** (43 mg, 0.1 mmol), **6** (44 mg, 0. 1 mmol, prepared as described previously), $Pd(dppf)Cl_2$ (4 mg, 5 μmol), and Na_2CO_3 (35 mg, 0.33 mmol) in dioxane/H_2O (2.0 mL/0.4 mL) was purged with N_2. The resulting mixture was stirred at 90 °C for 8 h, and then diluted with H_2O. The reaction mixture was extracted with EtOAc, and combined organic was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography eluting with hexanes:EtOAc = 1:3 (*v/v*) to give **7** a yellow solid (60 mg, 60 % yield). LC-MS (ESI) *m/z*: $(M+H)^+$ 683; $(M-H)^-$ 681.

[0573] **Step i**. To a crude solution of compound **7** (717 mg, 1.056 mmol) in THF (7.5 mL) was added HCl (4.0 M in dioxane, 10 mL) at rt. The resulting mixture was stirred at rt for 16 h, and then all volatile was removed on a rotary evaporator to give yellow solid. The yellow solid was washed with diethyl ether (2x10 mL) and then further dried on a rotary evaporator to give yellow solid. The crude solid was used for the next step without further purification. The deprotected free amine from above (48 mg, ~0.1mmol) was dissolved in CH_3CN (1.0 mL), was treated with N-methoxycarbonyl-L-valine (35 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol) and DIEPA (52 mg, 65 μL, 0.4 mmol). The resulting mixture was stirred at rt for 2.5 h, and then all solvents were removed on a rotary evaporator to give crude mixture. The crude mixture was purified by prep-HPLC eluting H_2O to CH_3CN, and the isolated compound was ~80% purity. The product was further purified by prep-TLC eluting with EtOAc with 5% NH_4OH to give product **8** (4.5 mg) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (Br s, 1H), 7.58-7.84 (m, 5H), 7.28-7.46 (m, 4H), 5.38-5.58 (m, 4H), 4.36-4.42 (m, 2H), 3.87-3.98 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.10-2.40 (m, 2H), 1.20-1.40 (m, 8H), 0.81- 0.91(m, 12H). LC-MS (ESI) *m/z*: $(M+H)^+$ 795.

[0574]

Biological Activity

[0575] Biological activity of the compounds of the invention was determined using an HCV replicon assay. The 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.

[0576] On Day 1 (the day after plating), each compound is added in triplicate to the cells. Plates incubated for 72 h prior to running the luciferase assay. 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 = (Average Compound Value/Average Control)*100

[0577] The EC_{50} value was determined using GraphPad Prism and the following equation:

Y = Bottom + (Top-Bottom)/ (1+10^ ((LogIC50-X)*HillSlope))

[0578] EC_{50} values of compounds are repeated several times in the replicon assay.

[0579] Example compounds of the disclosed invention are illustrated in Tables 1 and 2. Table 1 includes inhibitory activity for many of the compounds with respect to HCV 1b. Additionally mass spectrometry results are provided. Table 2 provides additional example compounds of the invention. 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.

Pharmaceutical Compositions

[0580] An eleventh aspect of the invention provides a pharmaceutical composition comprising 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. A thorough discussion of pharmaceutically acceptable excipients and salts is available in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990).

[0581] 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.

[0582] 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.

[0583] 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.

[0584] 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.

[0585] A twelfth aspect of the invention provides use of the compounds of the invention in the manufacture of a medicament.

[0586] In a first embodiment of the twelfth aspect, the medicament is for the treatment of hepatitis C.

[0587] A thirteenth 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.

CombinationTherapy

[0588] 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.

[0589] 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 ™.

[0590] 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).

[0591] 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.

[0592] 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.

[0593] 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

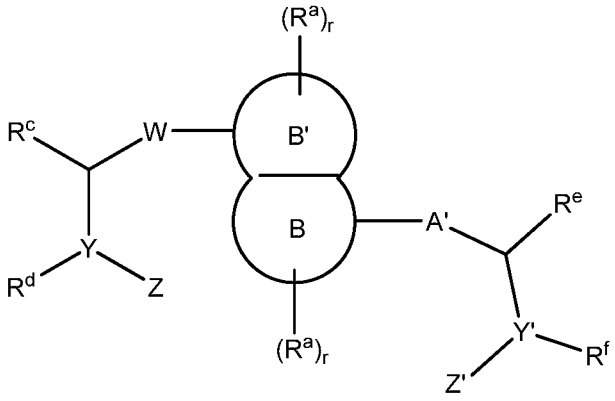
invention or where one treatment comprises a compound of the invention and the other comprises one or more biologically active agents) or it can be treatment with both agents at the same time (concurrently). Sequential therapy can include a reasonable time after the completion of the first therapy before 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.

[0594] 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.

[0595] 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.

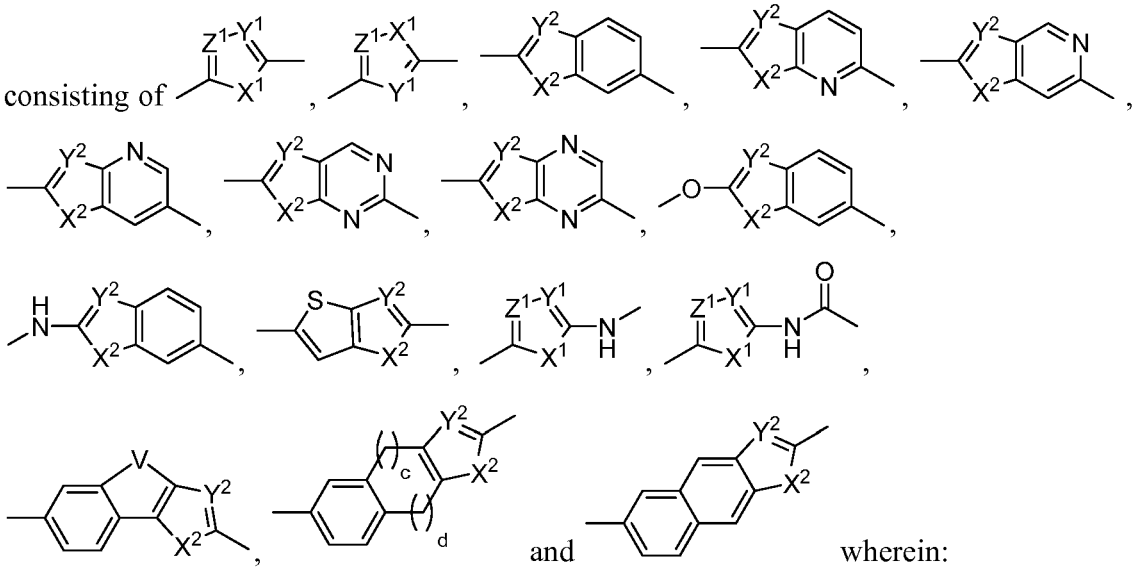
CLAIMS

1. A compound having formula I:



wherein:

A′ is selected from the group consisting of single bond, $–(CR_2)_n–C(O)–(CR_2)_p–$, $–(CR_2)_n–O–(CR_2)_p–$, $–(CR_2)_n–N(R^N)–(CR_2)_p–$, $–(CR_2)_n–S(O)_k–N(R^N)–(CR_2)_p–$, $–(CR_2)_n–C(O)–N(R^N)–(CR_2)_p–$, $–(CR_2)_n–N(R^N)–C(O)–N(R^N)–(CR_2)_p–$, $–(CR_2)_n–C(O)–O–(CR_2)_p–$, $–(CR_2)_n–N(R^N)\text{-}S(O)_k\text{-}N(R^N)–(CR_2)_p\text{-}$ and $–(CR_2)_n–N(R^N)\text{-}C(O)–O–(CR_2)_p–$ and a heteroaryl group selected from the group consisting of



and

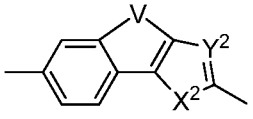
wherein:

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,

V is $-CH_2-CH_2-$, -CH=CH-, -N=CH-, $(CH_2)_a-N(R^N)-(CH_2)_b-$ or $-(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,



optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

the carbons of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of halogen, -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,

the nitrogens, if present, of the heteroaryl group are each independently optionally substituted with a substituent selected from the group consisting of -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,

a and b are independently 1, 2, or 3.

c and d are independently 1 or 2,

n and p are independently 0, 1, 2 or 3,

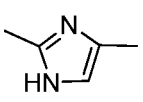
k is 0, 1, or 2,

each R is independently selected from the group consisting of hydrogen, halogen, -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,

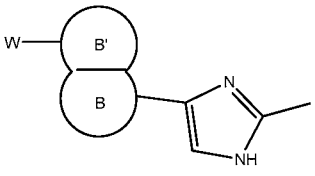
each R^N is independently selected from the group consisting of hydrogen, -OH, C_1

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

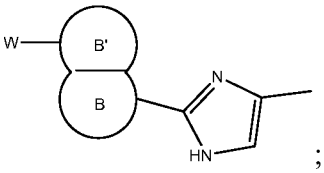
wherein B may be attached to either side of A′ so that in the example of A′ being



, the W-B-A′ can be



or



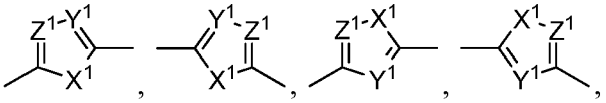
;

B and B′ are each independently a 4- to 8-membered ring that is an aryl, heteroaryl, cycloalkyl, or heterocycle, wherein each hetero atom, if present, is independently N, O or S and wherein at least one of B or B′ is aromatic;

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; and if B or B′ is not aromatic, it may also be substituted with one or more oxo;

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

W is independently selected from



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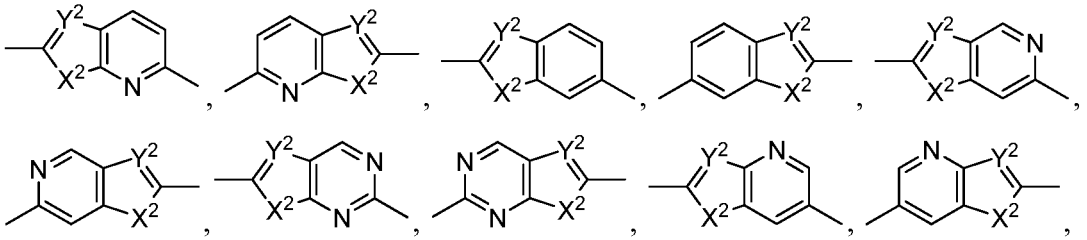

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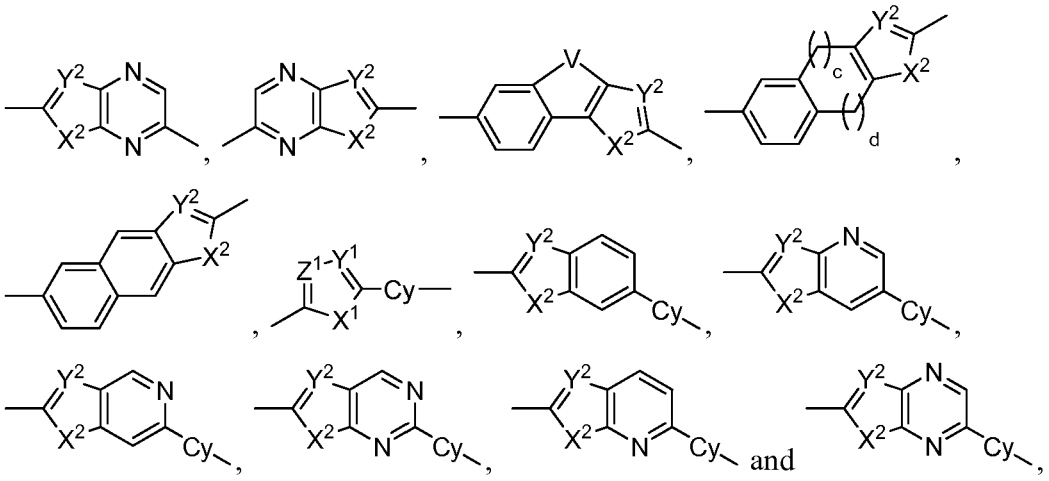


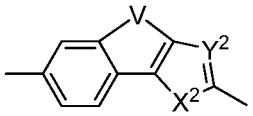
wherein:

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,

V is $–CH_2-CH_2-$, -CH=CH-, -N=CH-, $(CH_2)_a-N(R^N)-(CH_2)_b-$ or $–(CH_2)_a-O-(CH_2)_b-$, wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,

 optionally includes 1 or 2 nitrogens as heteroatoms on the phenyl residue,

W 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,

W and ring B′ can be connected through either a carbon or a nitrogen atom on B′, 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 $-S(O)_2-$,

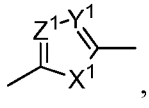
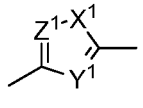
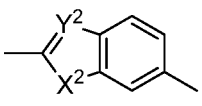
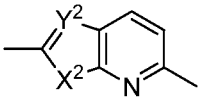
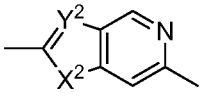
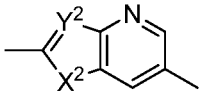
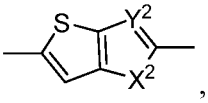
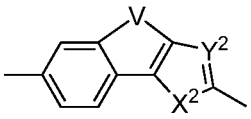
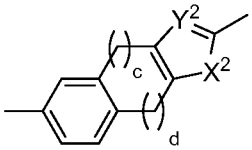
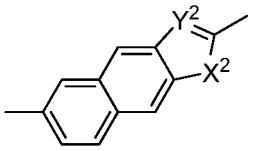
each R^4, R^5 and R^7 is independently selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

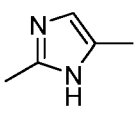
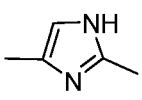
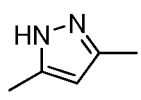
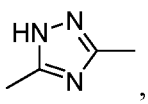
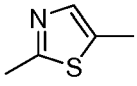
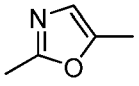
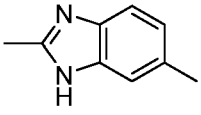
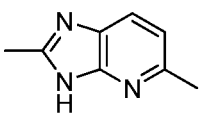
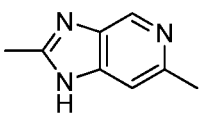
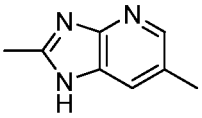
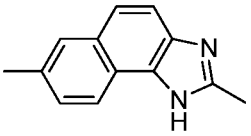
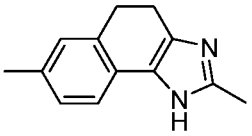
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, -C(O)-R^{81}, -C(S)-R^{81}, -C(O)-O-R^{81}, -C(O)-N-R^{81}_2, -$S(O)_2$-R^{81} and -$S(O)_2$-N-R^{81}_2, wherein each R^{81} is independently chosen from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

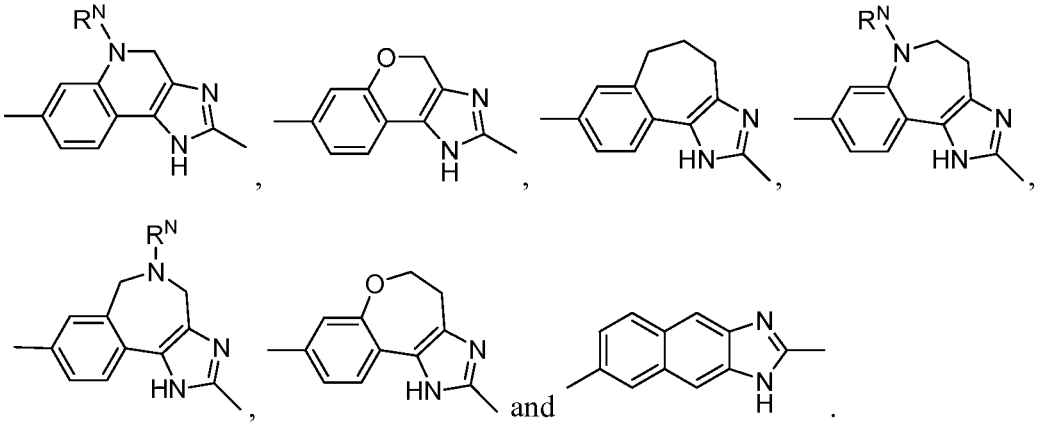
optionally, R^7 and R^8 together form a 4-7 membered ring,

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

u is 0, 1, or 2.

2. The compound of claim 1 wherein A′ is selected from the group consisting of a single bond, $-(CR_2)_n-O-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$, $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$ and $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ and a heteroaryl group selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  and  .

3. The compound of claim 2 wherein A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



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,

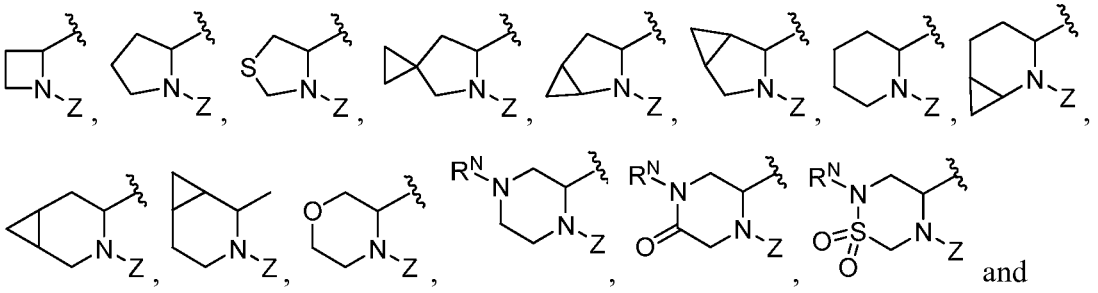
each hetero atom, if present, is independently N, O or S,

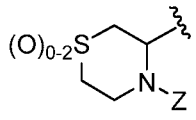
R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle, and

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.

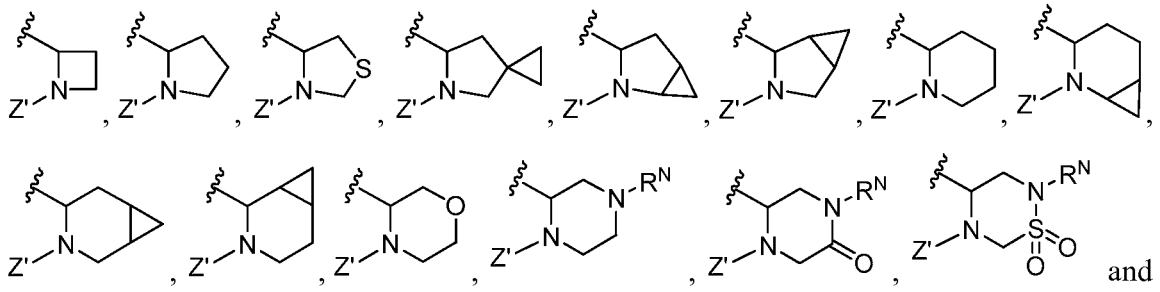
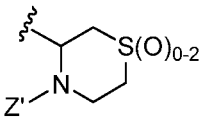
5. The compound of claim 4 wherein one or both of R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

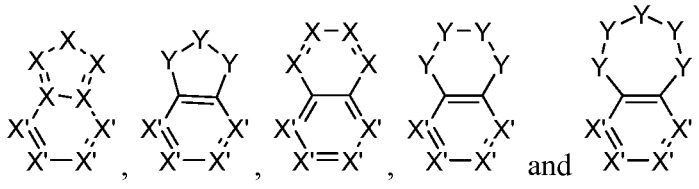
6. The compound of claim 4 wherein R^c and R^d are joined and form a heterocyclic fused ring system selected from the group consisting of:



 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 any one of claims 1 to 7 wherein B and B′ together is selected from the group consisting of  wherein

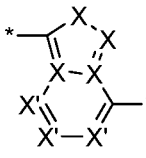
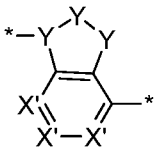
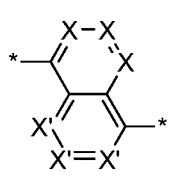
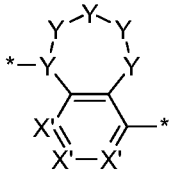
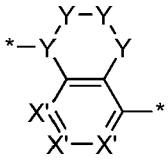
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

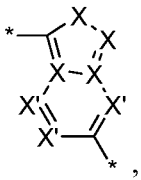
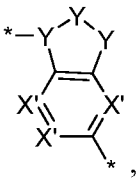
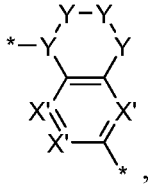
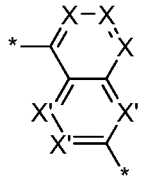
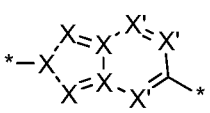
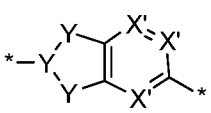
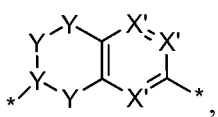
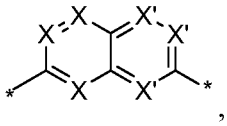
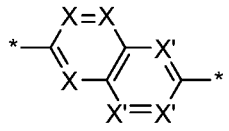
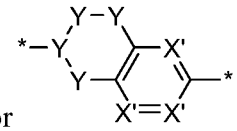
each X′ is independently –N– or –CH–, with the proviso that no more than two X′ are –N–;

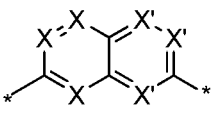
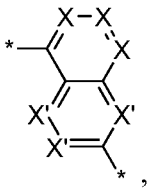
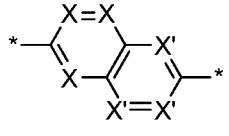
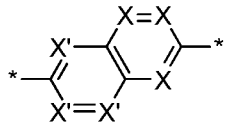
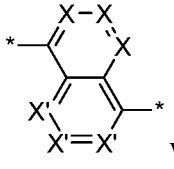
each Y is independently selected from -CH_2-, -NH- , -O-, -S-, -$C(O)_2$–, or –$S(O)_{1-2}$–; and

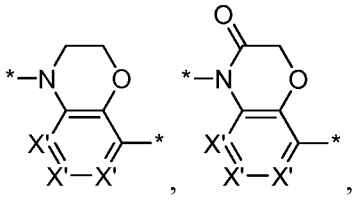
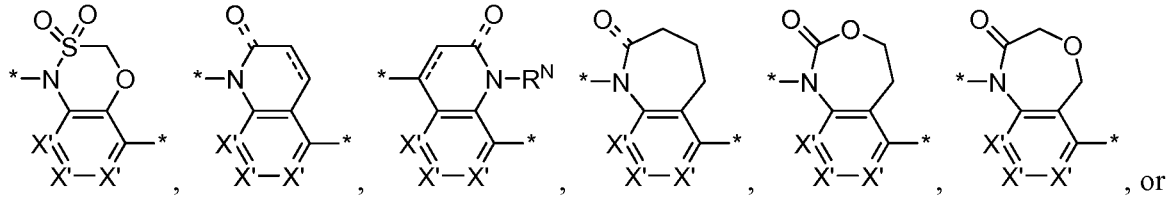
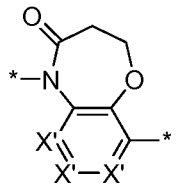
B and B′ attach to the remainder of the compound at any available attachment point on the

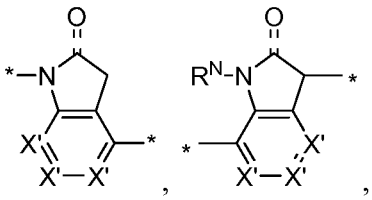
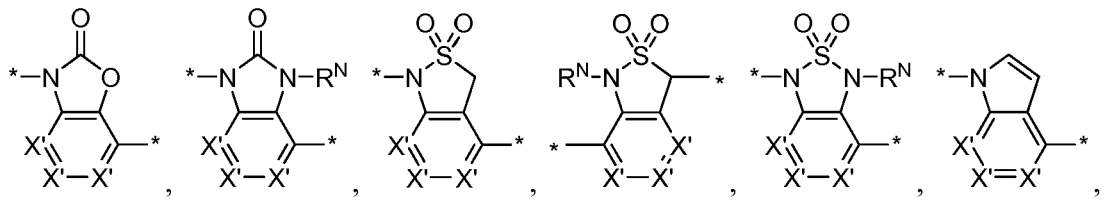
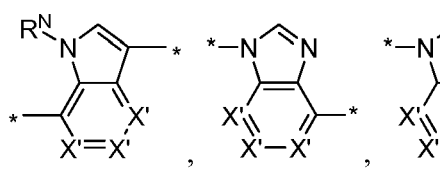
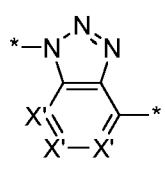
molecule.

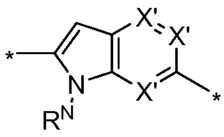
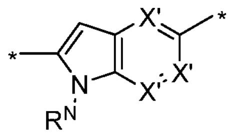
9. The compound of claim 8 wherein B and B′ together is  ,  ,   or  wherein * indicates attachment points to the remainder of the compound.

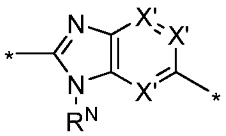
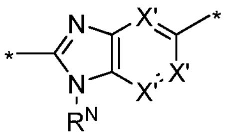
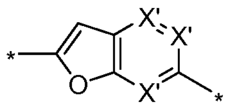
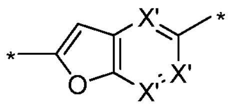
10. The compound of claim 8 wherein B and B′ together is  ,  ,  ,  ,  ,  ,  ,  ,  , or  wherein * indicates attachment points to the remainder of the compound.

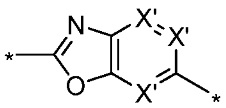
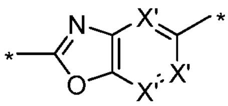
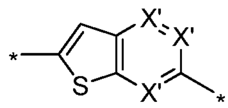
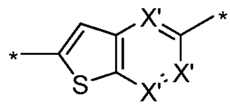
11. The compound of claim 8 wherein B and B′ together is  ,  ,  ,  , or  wherein * indicates attachment points to the remainder of the compound wherein no more than 2 of X are nitrogen.

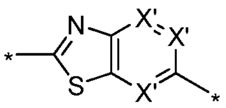
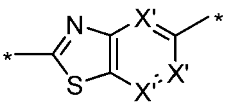
12. The compound of claim 8 wherein B and B′ together is  ,  , or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

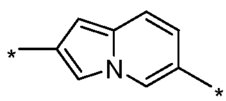
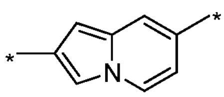
13. The compound of claim 8 wherein B and B′ together is  ,  ,  , or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

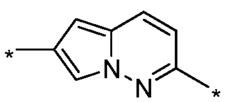
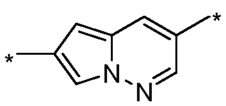
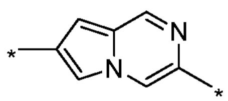
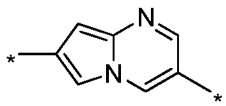
14. The compound of claim 8 wherein B and B′ together is  ,  ,

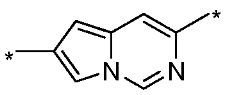
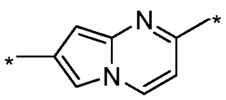
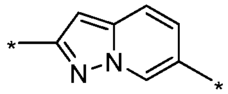
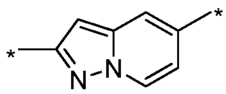
 ,  ,  ,  ,

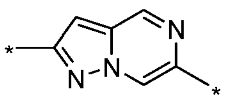
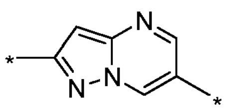
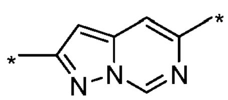
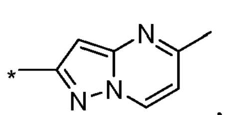
 ,  ,  ,  ,

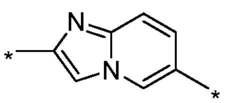
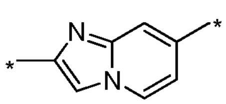
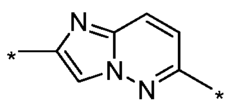
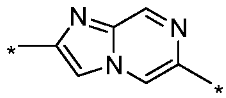
 , or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

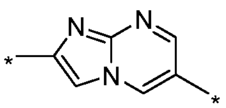
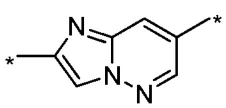
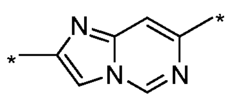
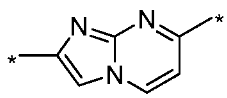
15. The compound of claim 8 wherein B and B′ together is  ,  ,

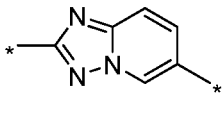
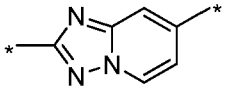
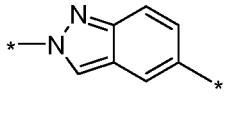
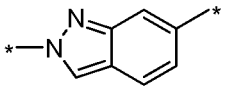
 ,  ,  ,  ,

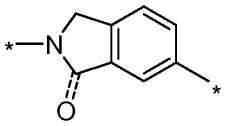
 ,  ,  ,  ,

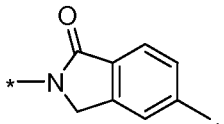
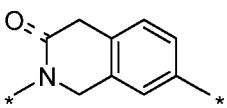
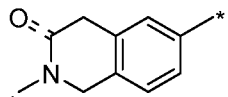
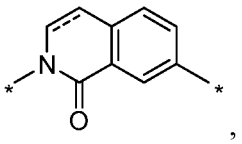
 ,  ,  ,  ,

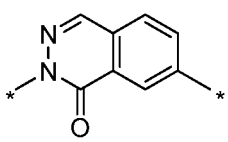
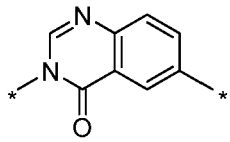
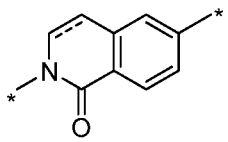
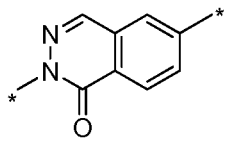
 ,  ,  ,  ,

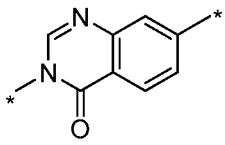
 ,  ,  ,  ,

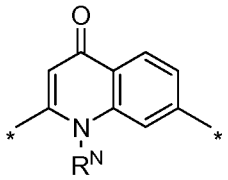
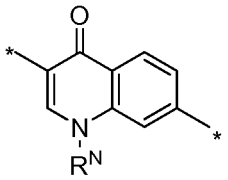
 ,  ,  , or  wherein * indicates attachment points to the remainder of the compound and the six-membered ring optionally contains one or two additional nitrogens as heteroatoms with the proviso that the total number of nitrogens in the six-membered ring does not exceed two.

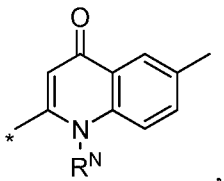
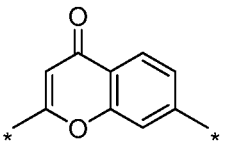
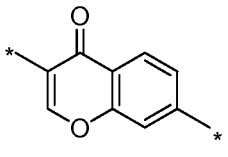
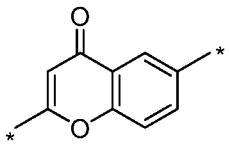
16. The compound of claim 8 wherein B and B′ together is  ,

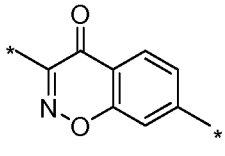
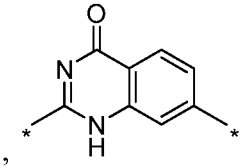
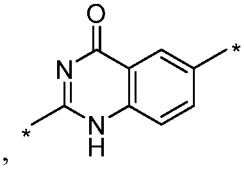
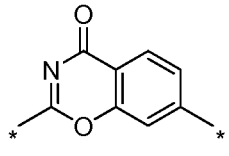
 ,  ,  ,  ,

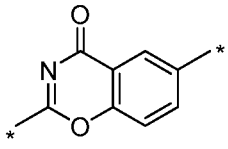
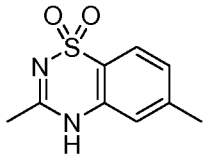
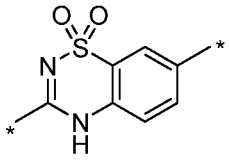
 ,  ,  ,  , or

 wherein * indicates attachment points to the remainder of the compound and the phenyl moiety optionally contains one or two nitrogens as heteroatoms.

17. The compound of claim 8 wherein B and B′ together is  ,  ,

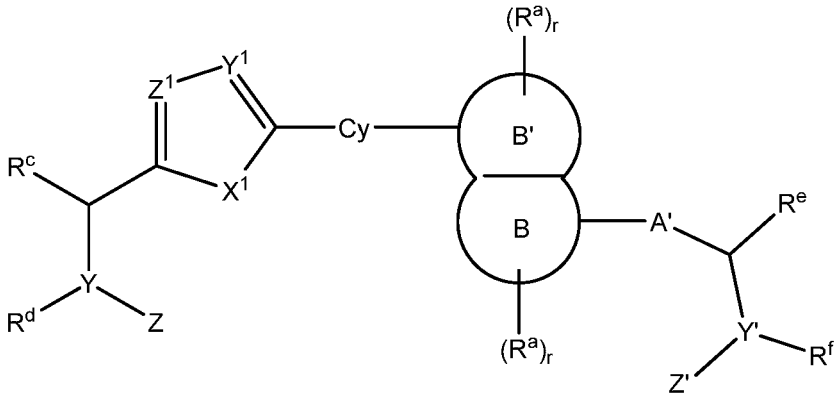
 ,  ,  ,  ,

 ,  ,  ,  ,

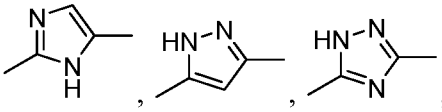




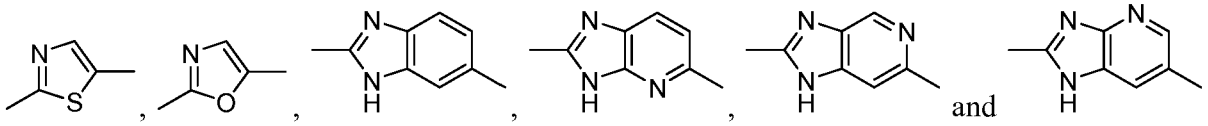
wherein * indicates attachment points to the remainder of the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

18. The compound of claim 1 having formula II:



wherein A′ is selected from the group consisting of a single bond,

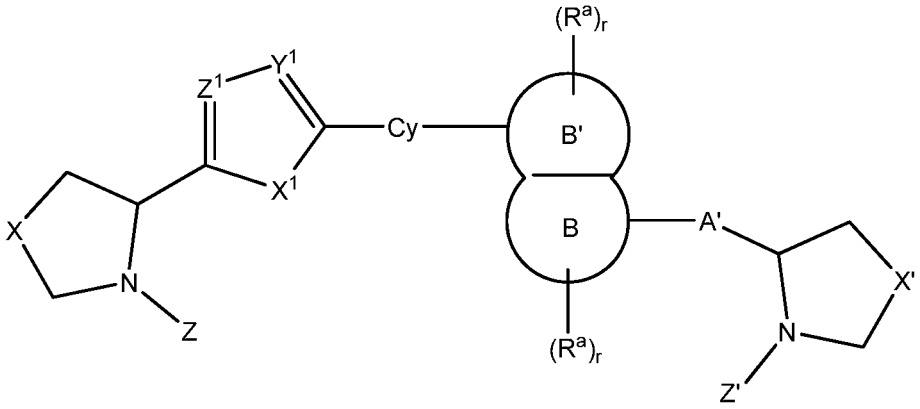




and

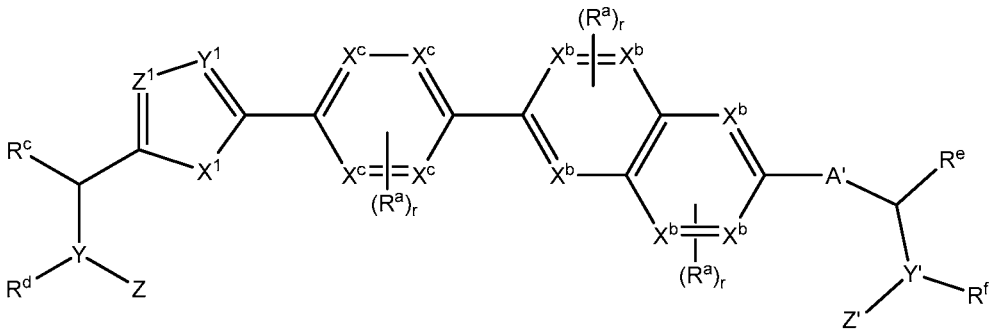
.

19. The compound of claim 18 having formula IIa:



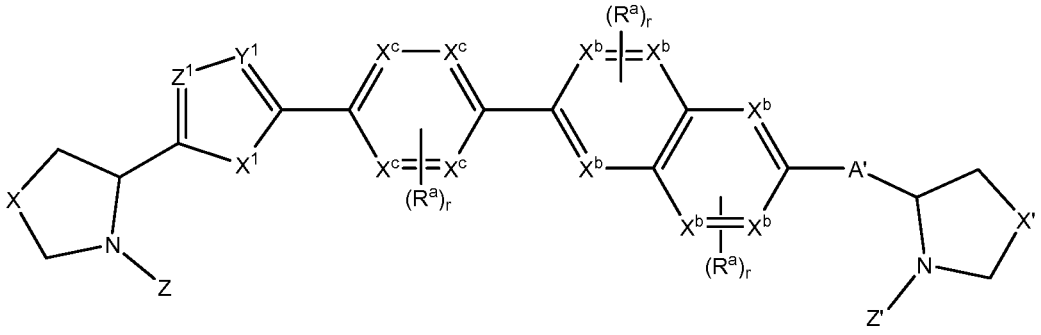
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, $–CH=CH–$, $–O–$, $–S–$, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

20. The compound of claim 18 having formula IIb:



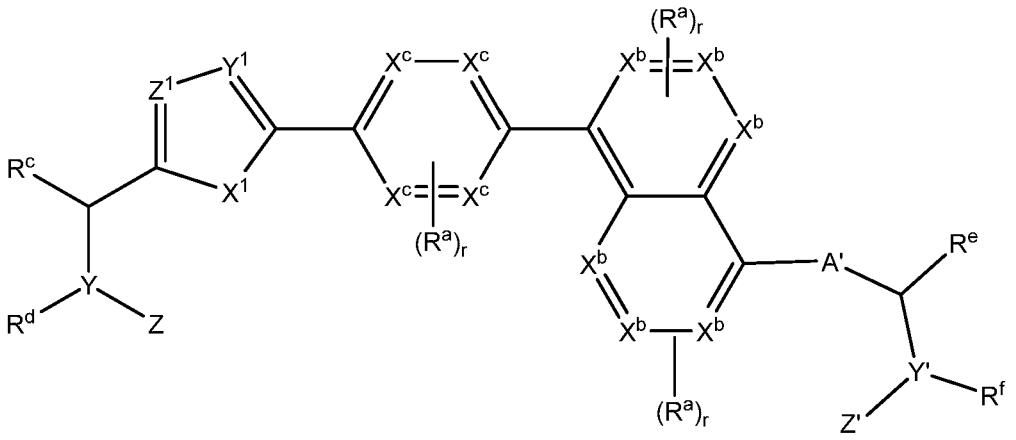
wherein each X^b and X^c is independently C or N.

21. The compound of claim 20 having formula IIc:



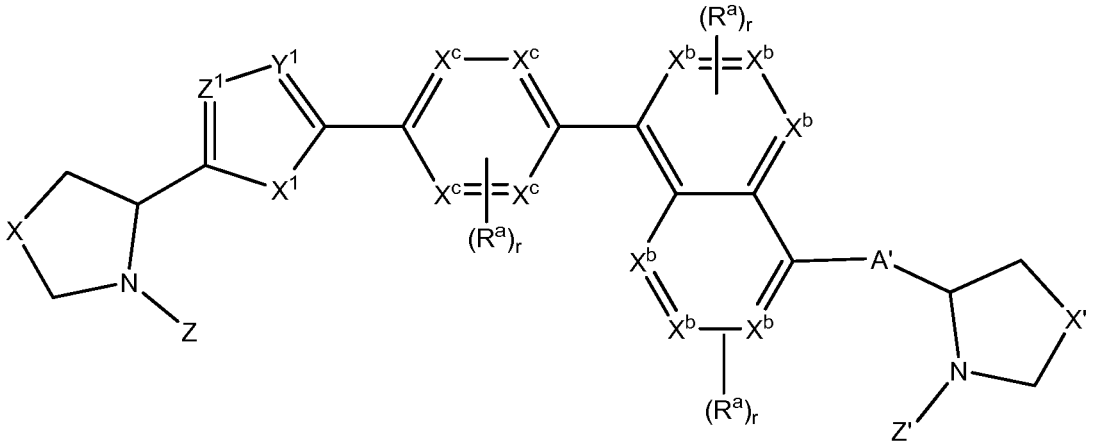
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

22. The compound of claim 18 having formula IId:



wherein each X^b and X^c is independently C or N.

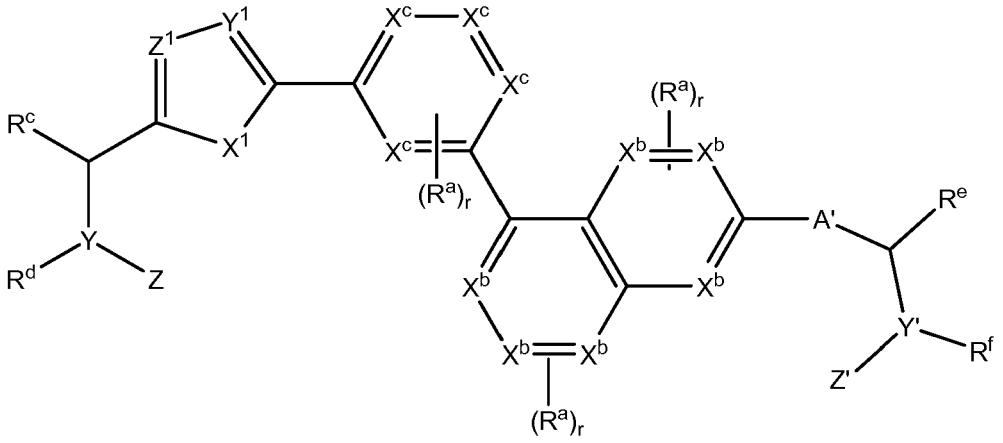
23. The compound of claim 22 having formula IIe:



wherein

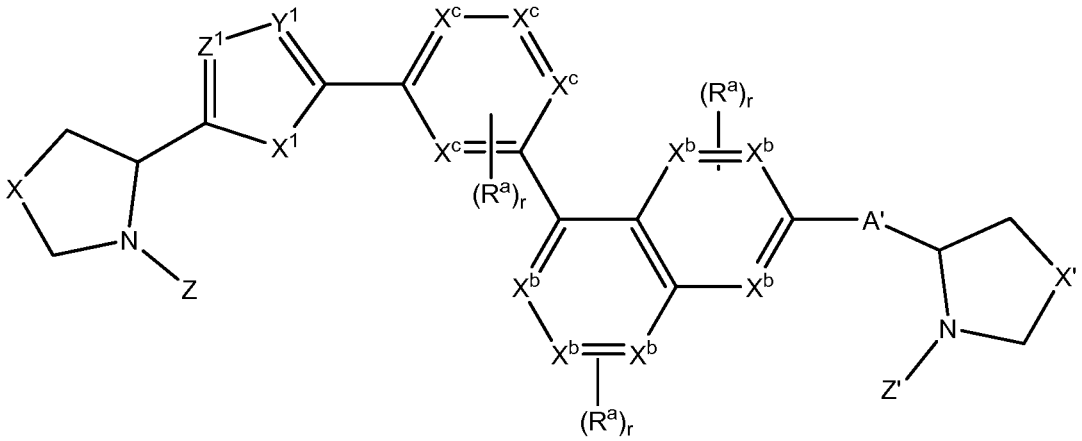
X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

24. The compound of claim 18 having formula IIf:



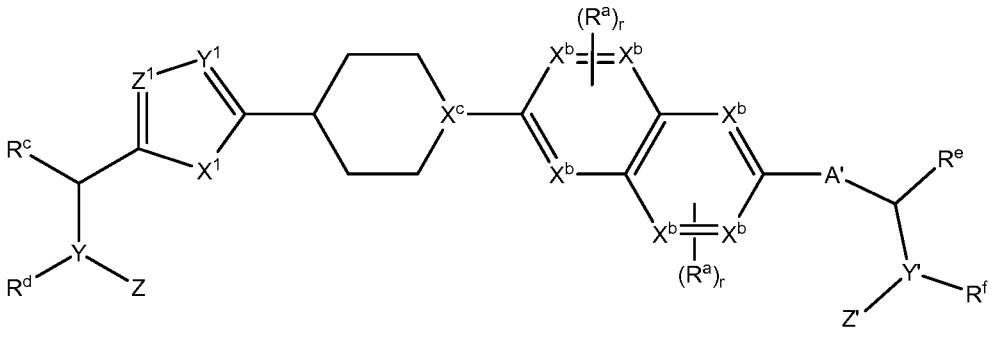
wherein each X^b and X^c is independently C or N.

25. The compound of claim 24 having formula IIg:



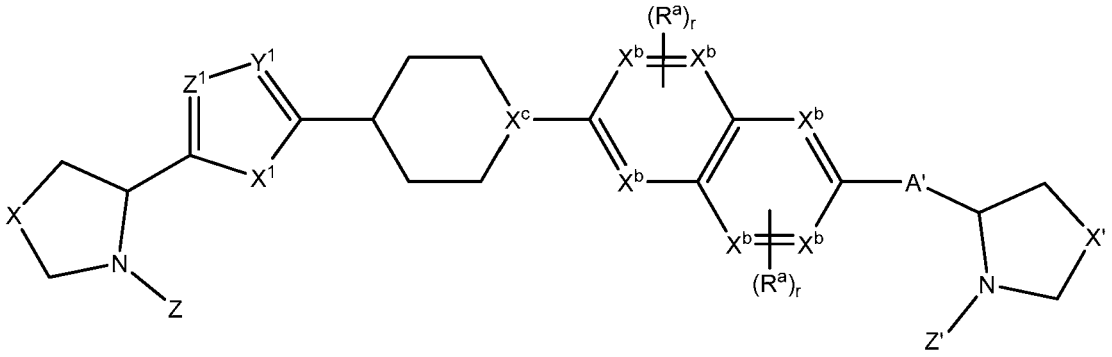
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

26. The compound of claim 18 having formula IIh:



wherein X^c and each X^b is independently C or N.

27. The compound of claim 26 having formula IIi:

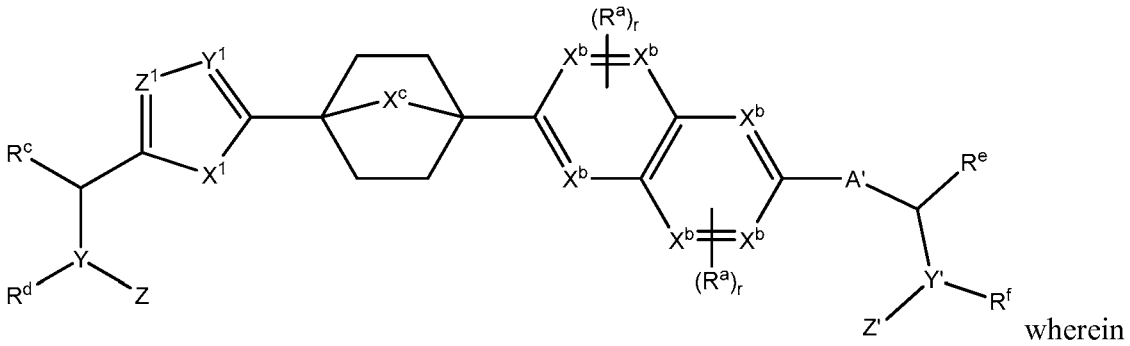


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

28. The compound of claim 26 or claim 27 wherein X^c is C.

29. The compound of claim 26 or claim 27 wherein X^c is N.

30. The compound of claim 18 having formula IIj:

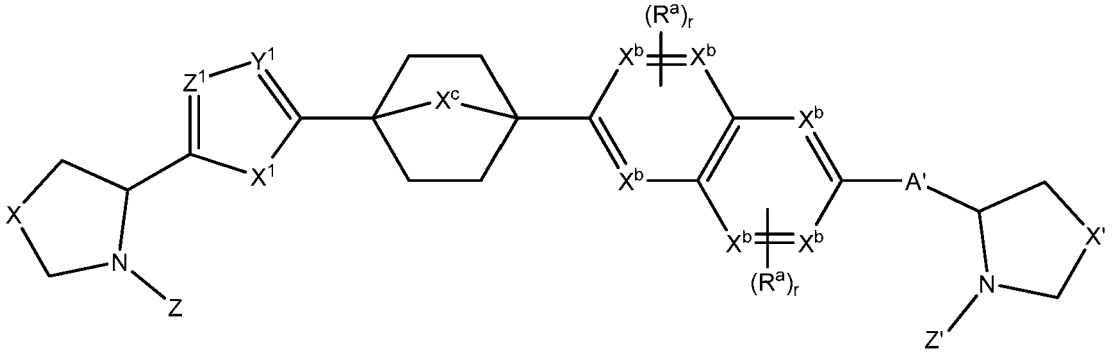


wherein

X^c is $–CH_2–$, –NH– or $–CH_2–CH_2–$; and

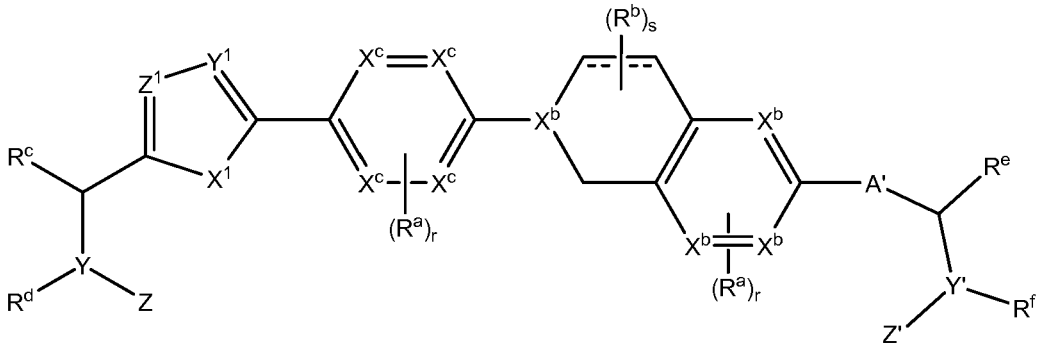
each X^b is independently C or N.

31. The compound of claim 30 having formula IIk:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

32. The compound of claim 18 having formula IIl:



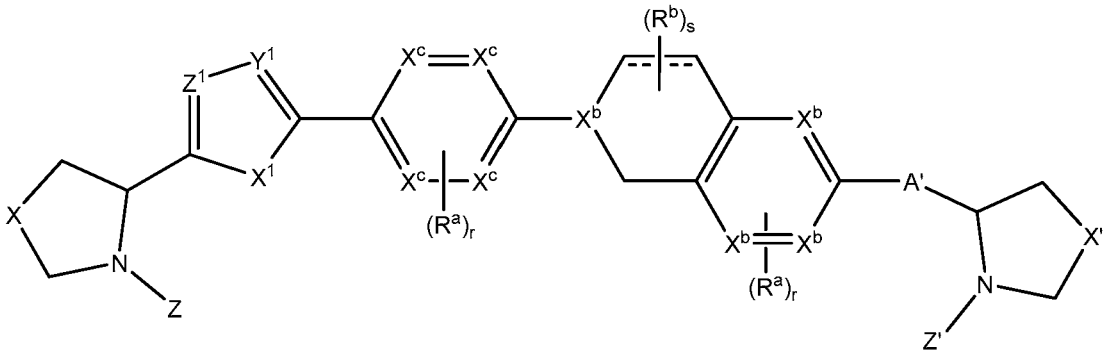
wherein:

each X^b and X^c is independently C or N;

each R^b is selected from the group consisting of oxo, -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

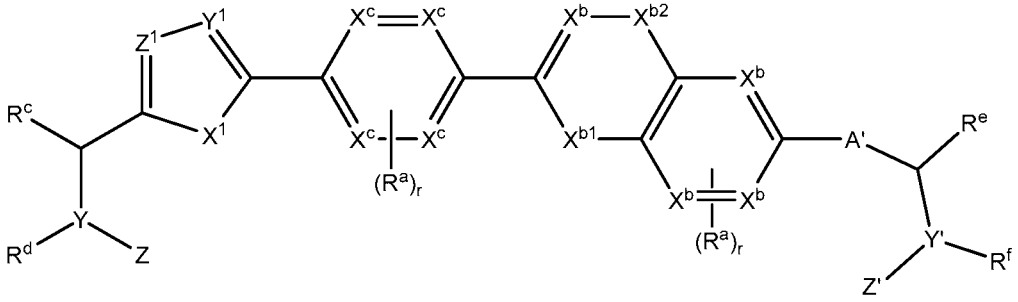
s is 0, 1, 2, or 3.

33. The compound of claim 32 having formula IIm:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

34. The compound of claim 18 having formula IIn:



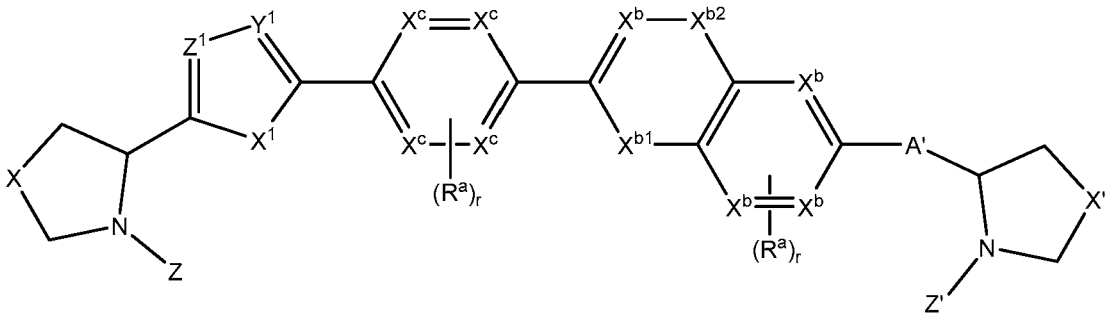
wherein:

each X^b and X^c is independently C or N;

X^{b1} is N or O; and

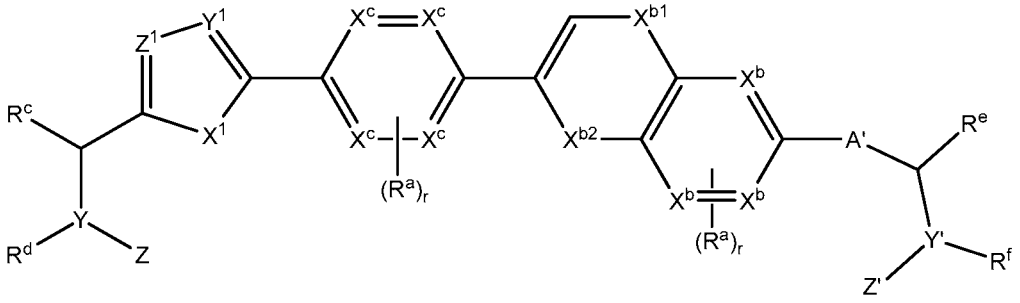
X^{b2} is $S(O)_2$ or C(O).

35. The compound of claim 34 having formula IIo:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

36. The compound of claim 18 having formula IIp:



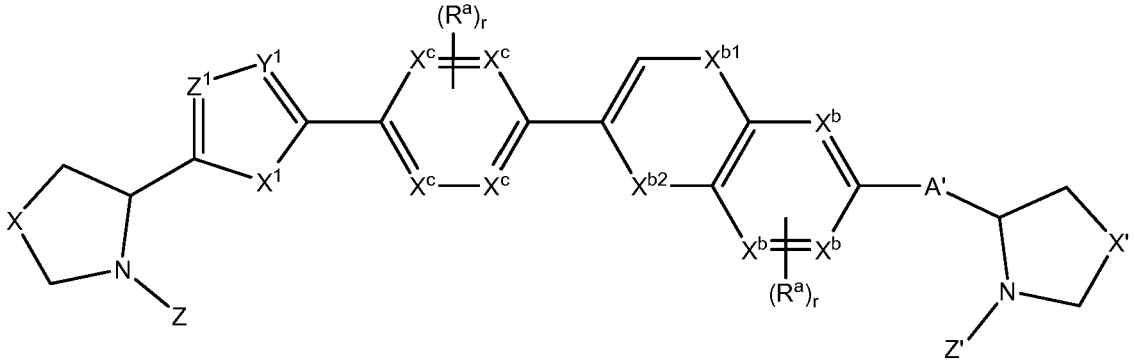
wherein:

each X^b and X^c is independently C or N;

X^{b1} is N or O; and

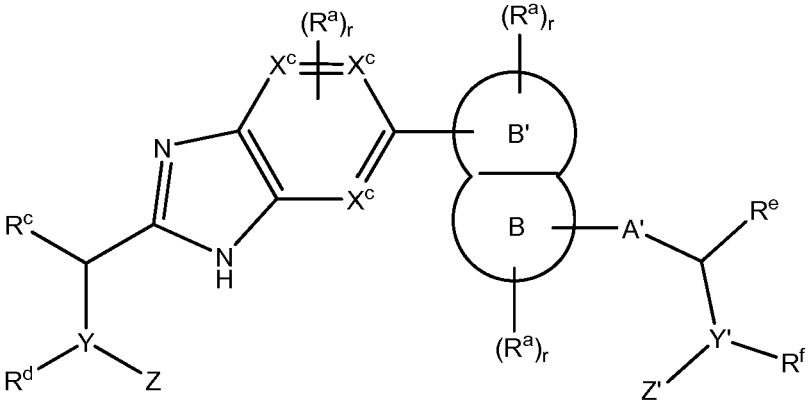
X^{b2} is $S(O)_2$ or C(O).

37. The compound of claim 36 having formula IIq:

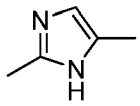
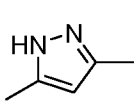
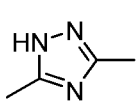
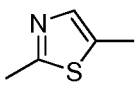
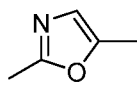
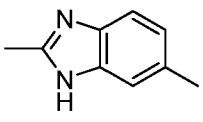
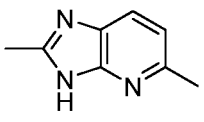
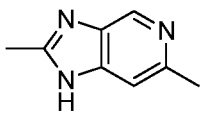
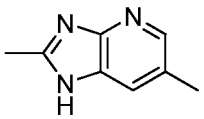


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

38. The compound of claim 1 having formula III:

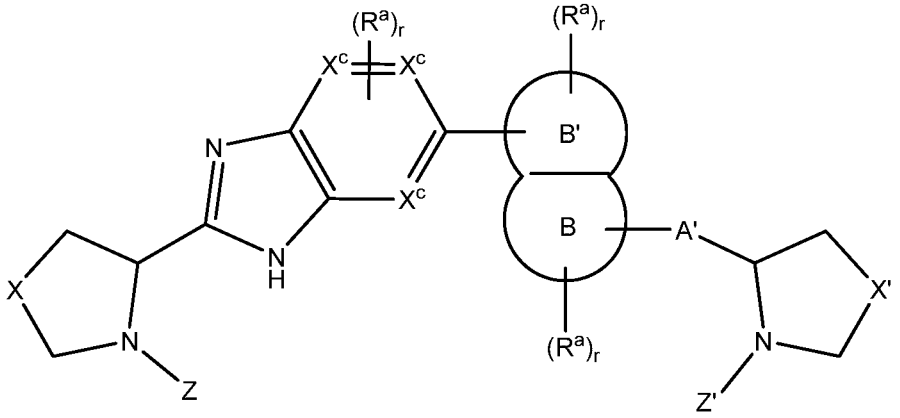


wherein

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and  ; and

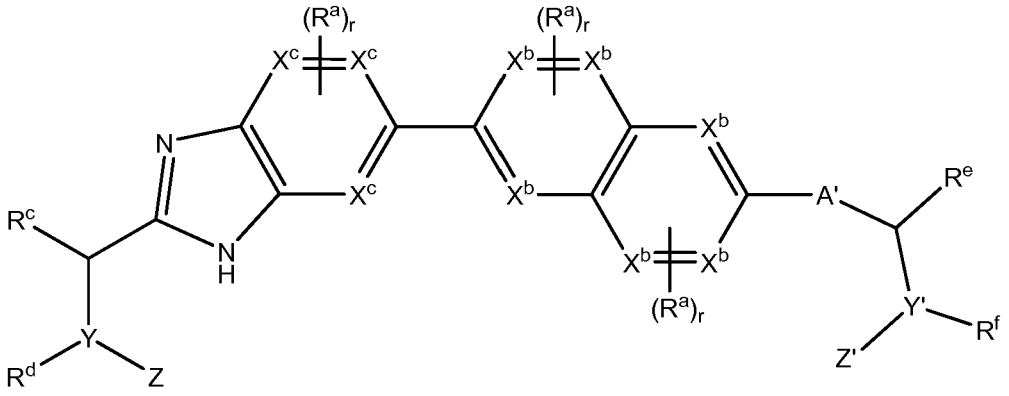
each X^c is independently C or N.

39. The compound of claim 38 having formula IIIa:



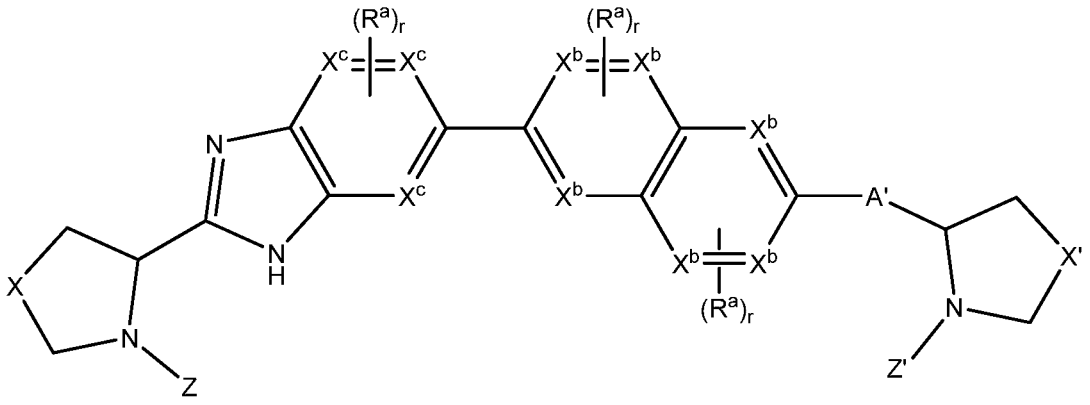
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, $–CH=CH–$, $–O–$, $–S–$, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

40. The compound of claim 38 having formula IIIb:



wherein each X^b is independently C or N.

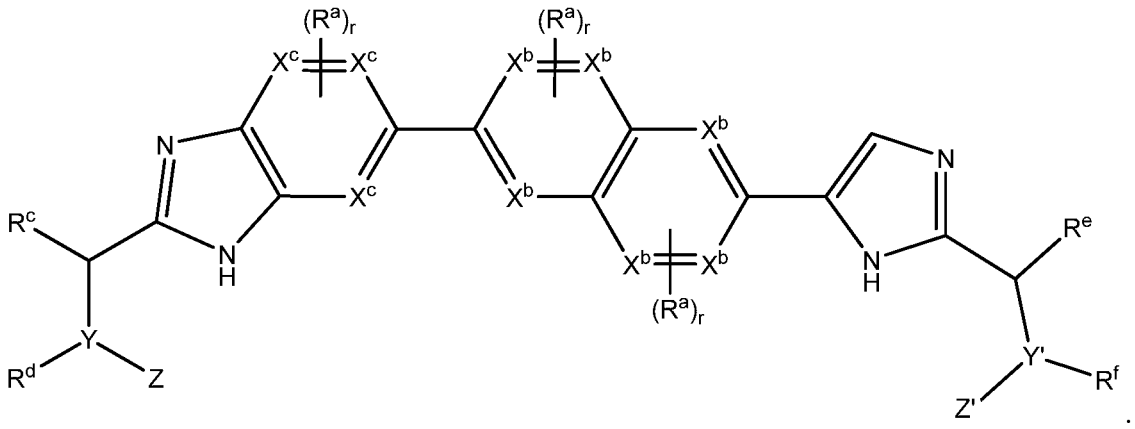
41. The compound of claim 40 having formula IIIc:



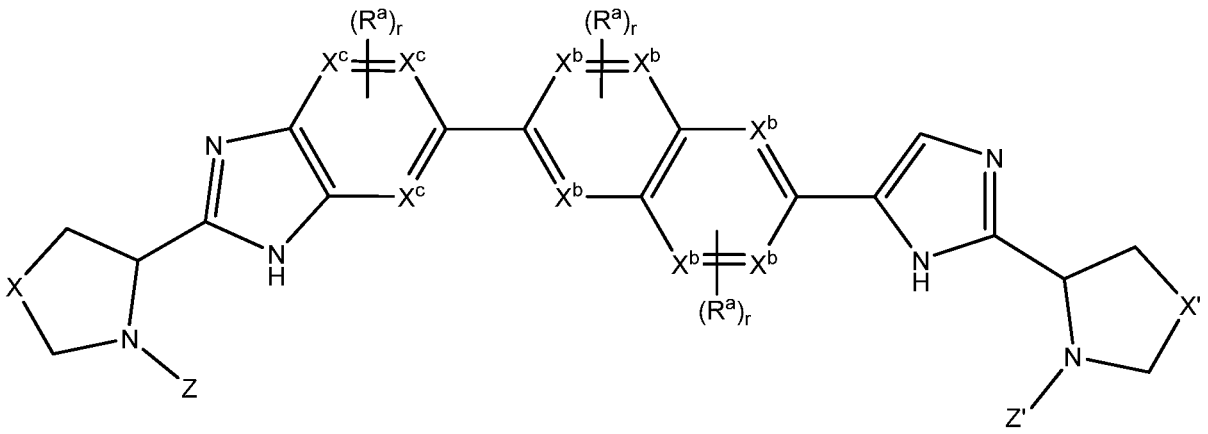
wherein

X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1\text{-}2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1\text{-}2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

42. The compound of claim 40 having formula IIId:

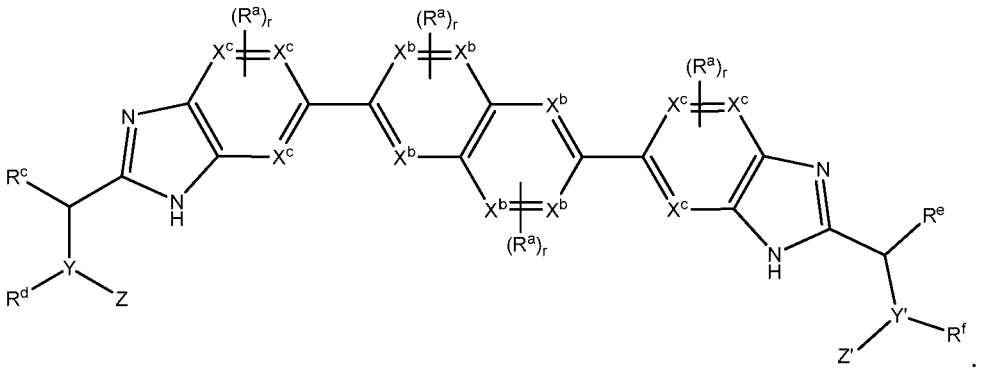


43. The compound of claim 42 having formula IIIe:

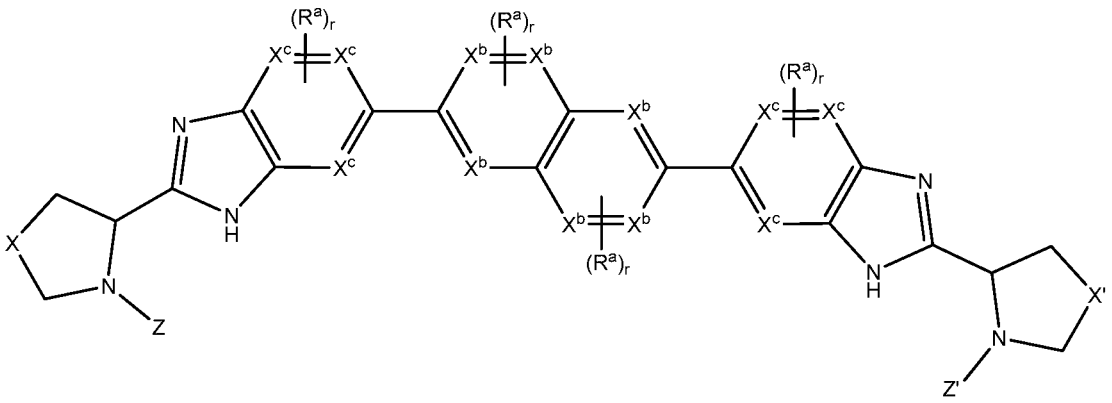


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

44. The compound of claim 40 having formula IIIf:

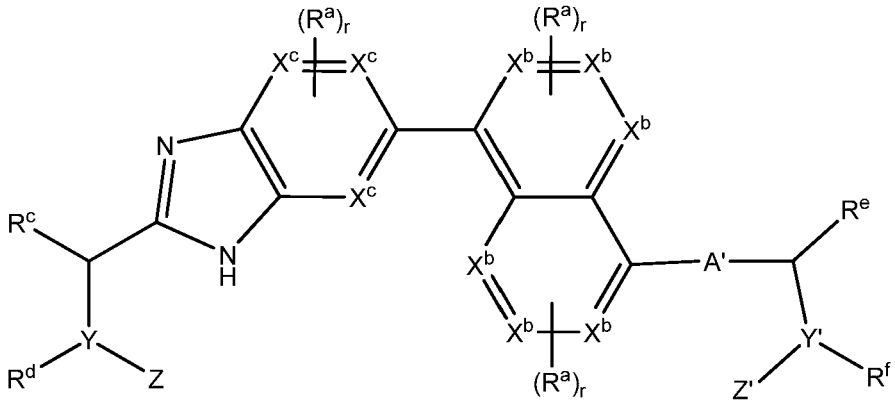


45. The compound of claim 44 having formula IIIg:



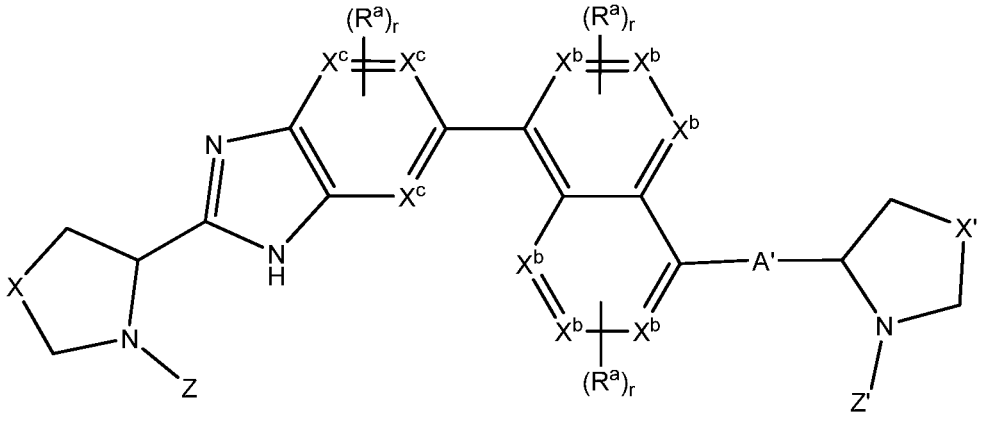
wherein X and X′ are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

46. The compound of claim 38 having formula IIIh:



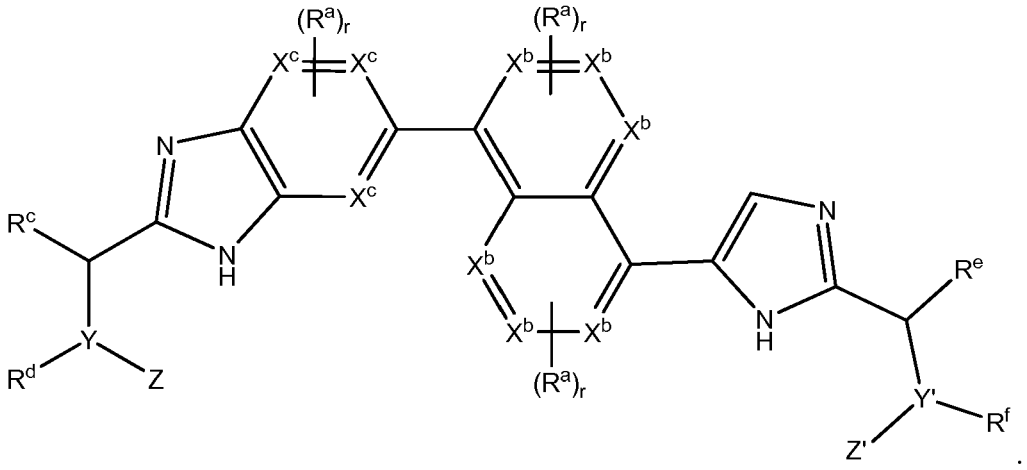
wherein each X^b is independently C or N.

47. The compound of claim 46 having formula IIIi:

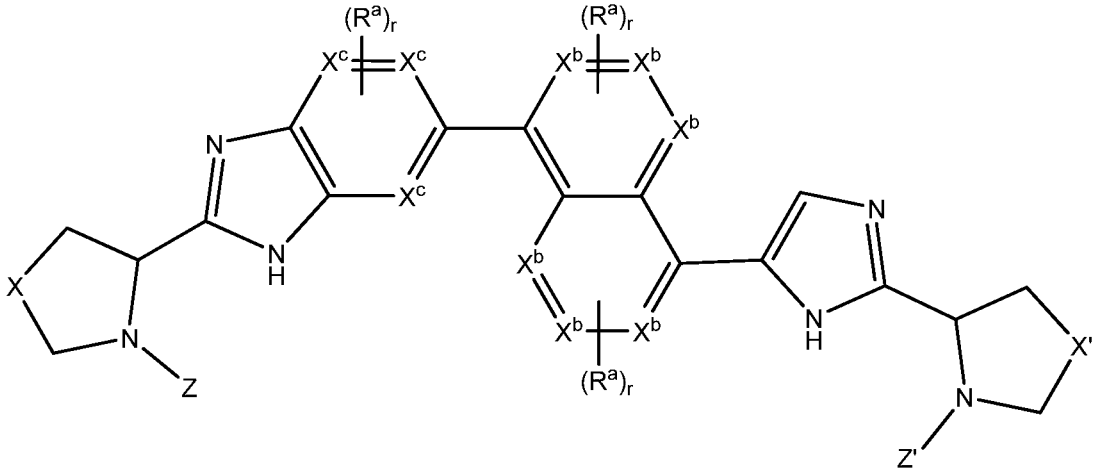


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

48. The compound of claim 46 having formula IIIj:



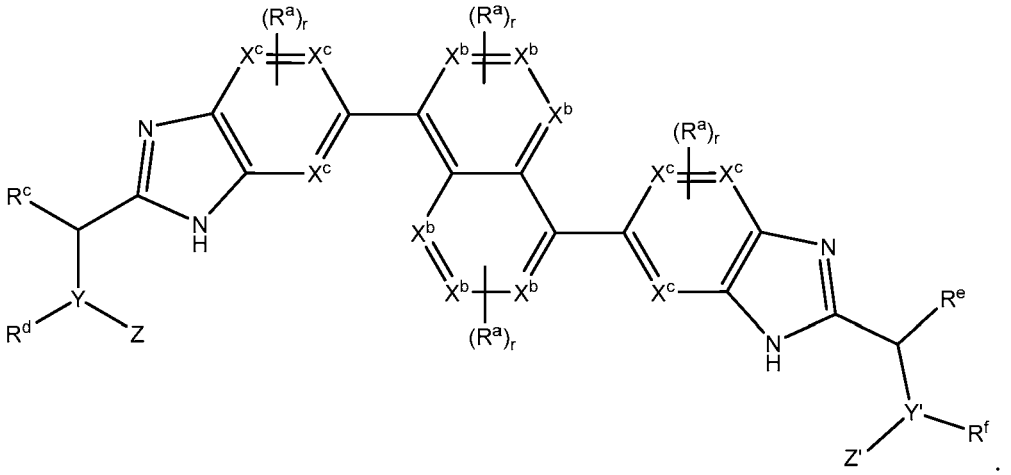
49. The compound of claim 48 having formula IIIk:



wherein

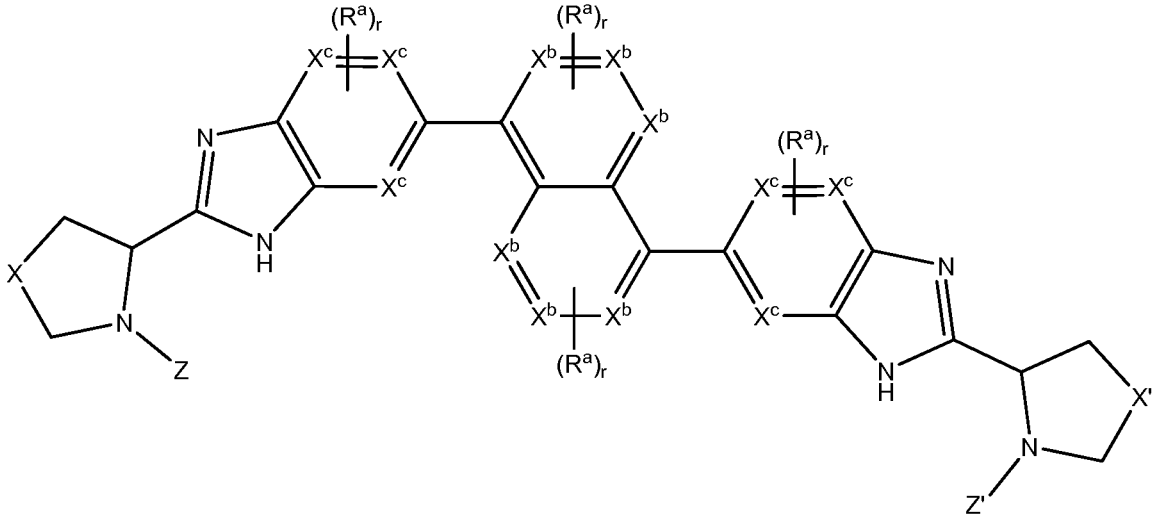
X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

50. The compound of claim 46 having formula IIIl:



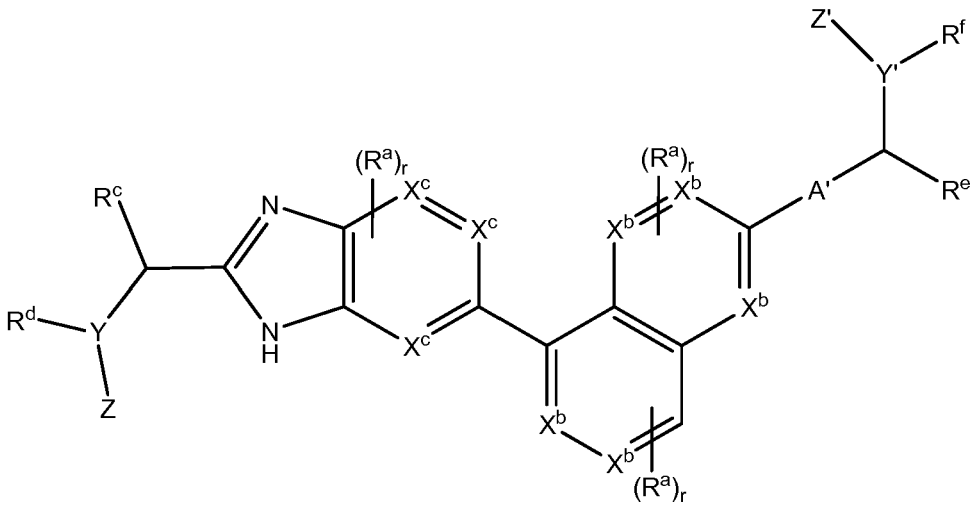
.

51. The compound of claim 50 having formula IIIm:



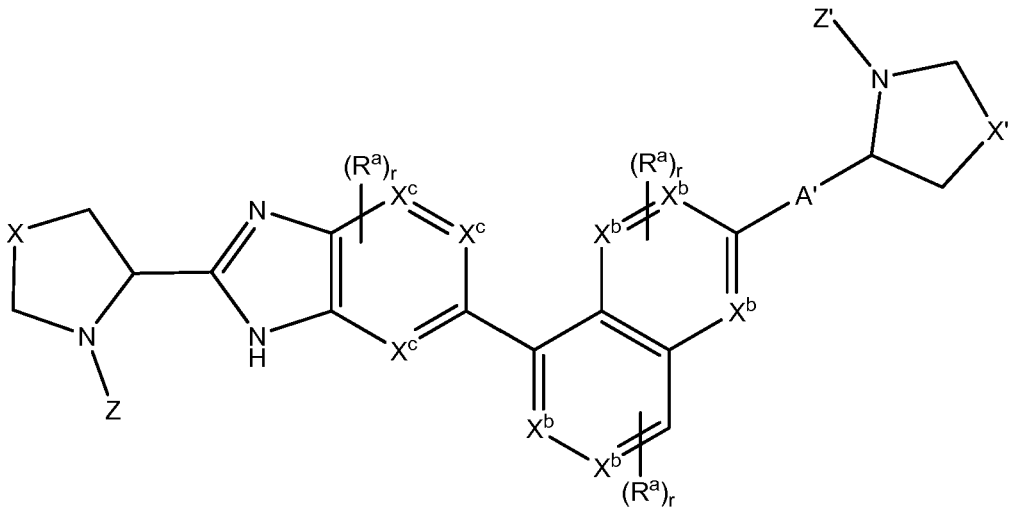
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

52. The compound of claim 38 having formula IIIn:



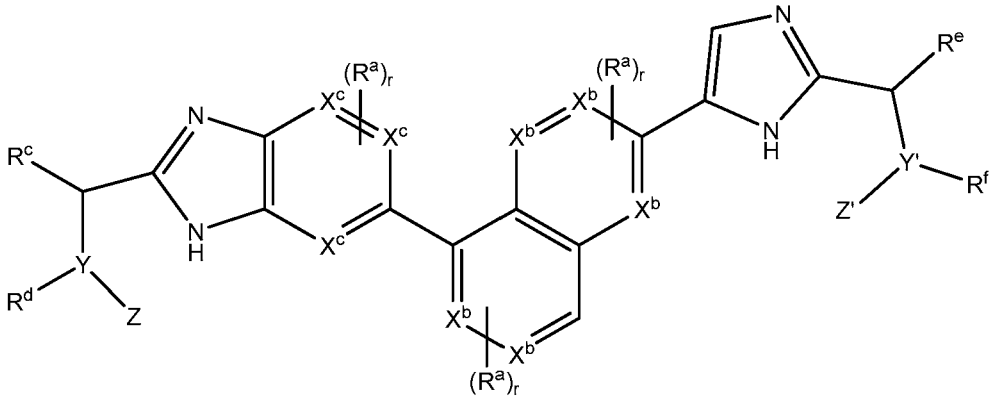
wherein each X^b is independently C or N.

53. The compound of claim 52 having formula IIIo:



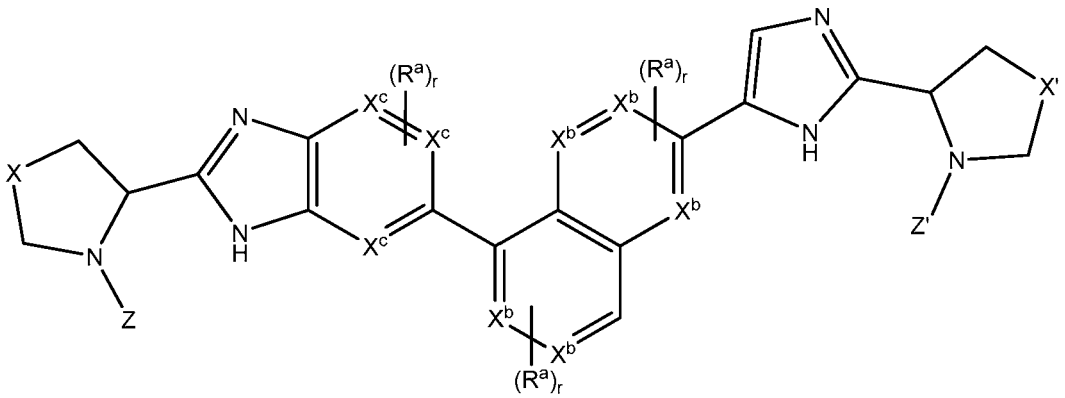
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

54. The compound of claim 52 having formula IIIp:



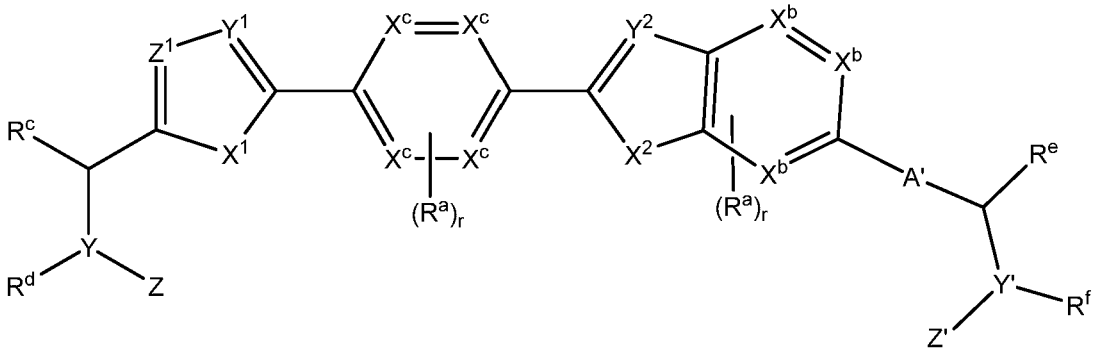
.

55. The compound of claim 54 having formula IIIq:

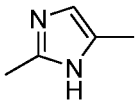
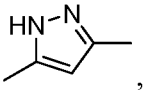
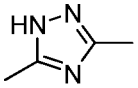
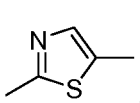
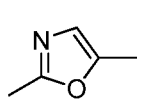
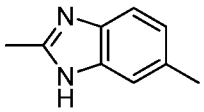
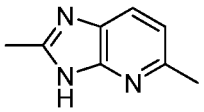
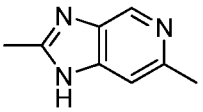


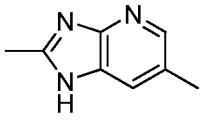
wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

56. The compound of claim 1 having formula IV:



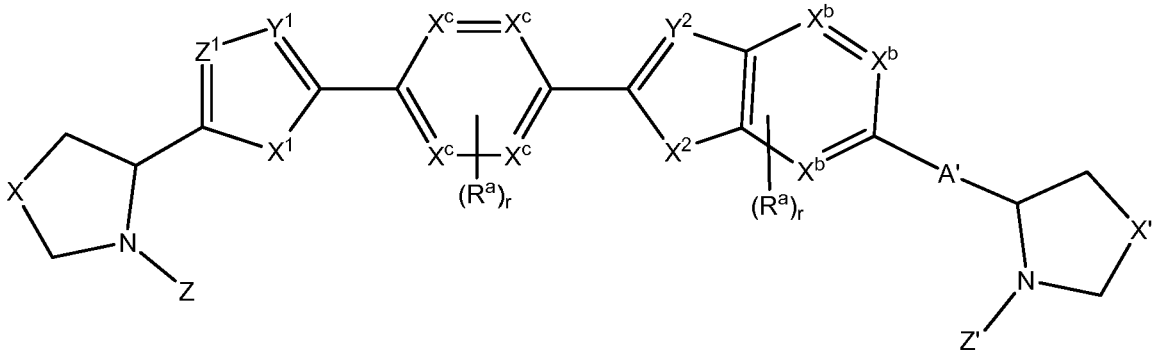
wherein:

A′ is selected from the group consisting of a single bond,  ,  ,  ,  ,  ,  ,  ,  and


; and

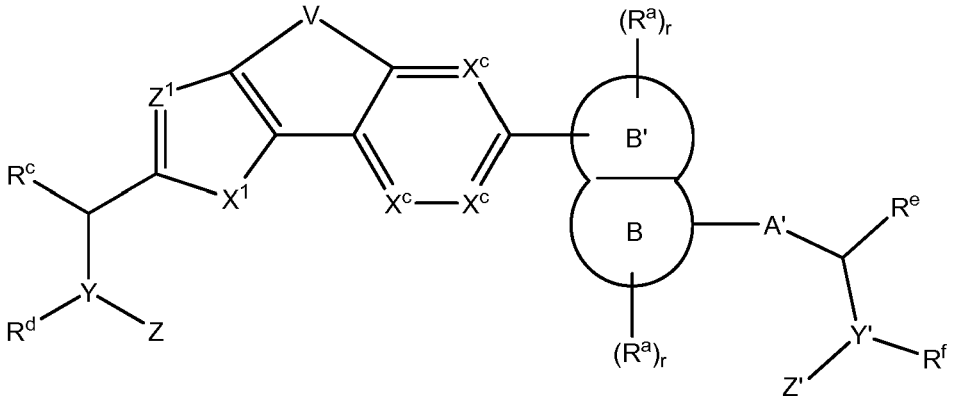
each X^b and X^c is independently C or N.

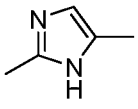
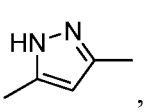
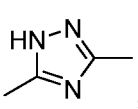
57. The compound of claim 55 having formula IVa:

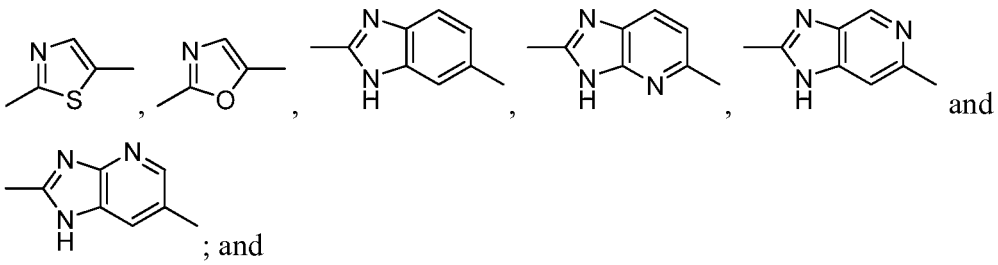


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1\text{-}2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1\text{-}2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

58. The compound of claim 1 having formula V:

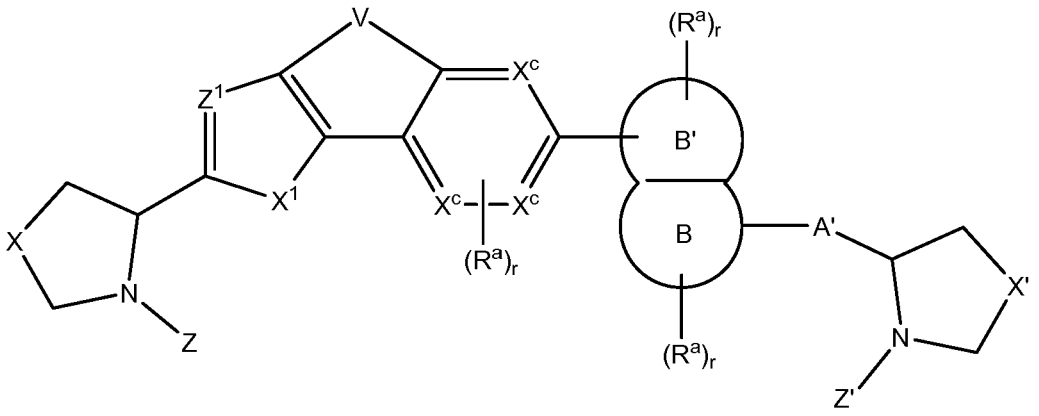

wherein:

A′ is selected from the group consisting of a single bond,  ,  ,  ,

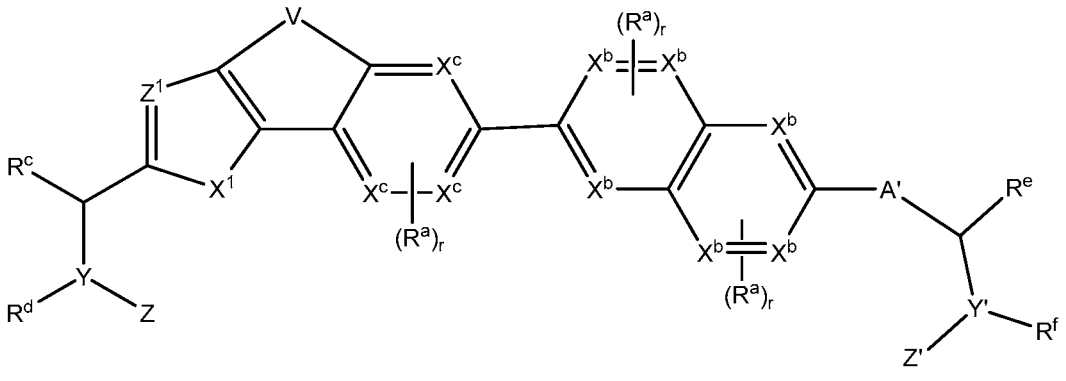

and ; and

each X^c is independently C or N with the proviso that no more than two X^c are N.

59. The compound of claim 57 having formula Va:

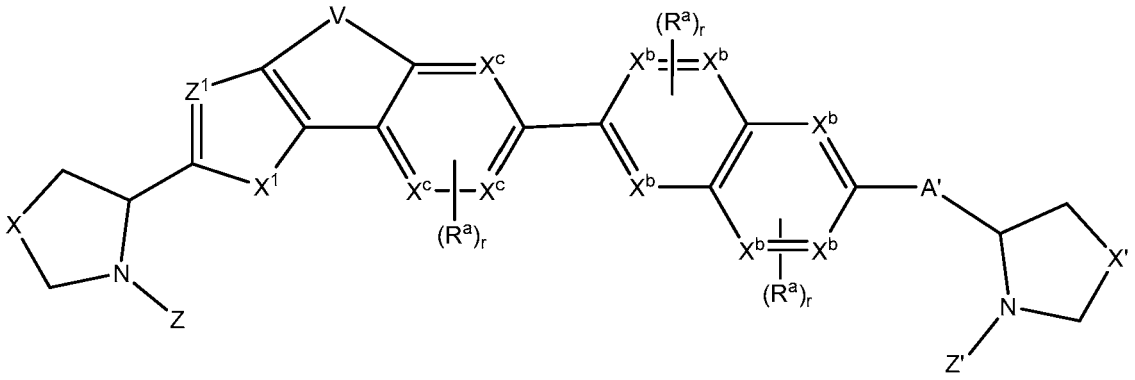

wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

60. The compound of claim 57 having formula Vb:


wherein

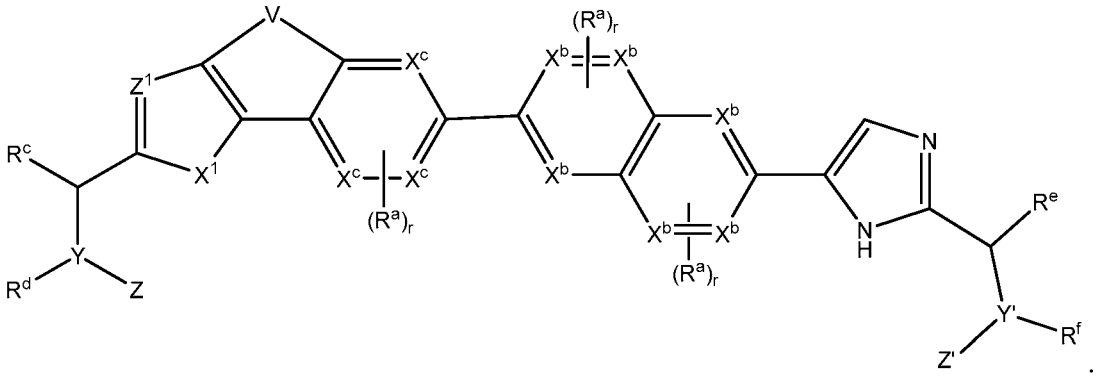
each X^b is independently C or N.

61. The compound of claim 59 having formula Vc:

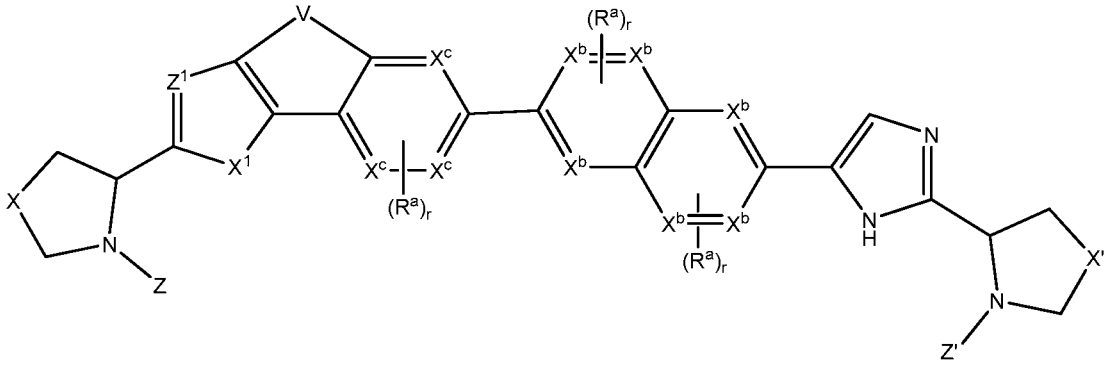


wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

62. The compound of claim 59 having formula Vd:



63. The compound of claim 61 having formula Ve:



wherein X and X′ are each independently selected from the group consisting of a bond, $–CH_2–$, $–CH_2–CH_2–$, –CH=CH–, –O–, –S–, $–S(O)_{1-2}–$, $–CH_2O–$, $–CH_2S–$, $–CH_2S(O)_{1-2}–$ and $–CH_2N(R^1)–$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

64. The compound of any one of claims 18, 20, 22, 24, 26, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60 and 62 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.

65. The compound according to claim 64 wherein one of R^c and R^d or R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

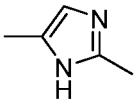
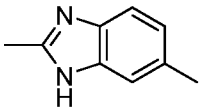
66. The compound according to claim 64 wherein both of R^c and R^d and R^e and R^f are joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

67. The compound according to any one of claims 18-63 wherein each R^a is independently

–CN,–$OCHF_2$, –OCF_3, –CF_3, or –F.

68. The compound according to any one of claims , 20, 22, 24, 26, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60 and 62 wherein one of Y and Y′ is N.

69. The compound of claim 68 wherein both Y and Y′ are N.

70. The compound of any one of claims 18-41, 46, 47, 52, 53, 56-61 wherein A′ is  or  .

71. The compound according to any one of claims 1-70 wherein Z and Z′ are each 1-3 amino acids.

72. The compound according to claim 71 wherein the amino acids are in the D configuration.

73. The compound of any one of claims 1-70 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.

74. The compound of claim 73 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.

75. The compound of claim 74 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.

76. The compound of claim 74 wherein one or both of Z and Z′ are
–U–$(CR^4_2)_t$–NR^7–$(CR^4_2)_t$–R^8.

77. The compound of claim 74 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.

78. The compound of claim 77 wherein one or both of Z and Z′ are

$-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

79. The compound of claim 77 wherein one or both of Z and Z′ are $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

80. The compound of claim 79 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

81. The compound of claim 77 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$.

82. The compound of claim 81 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^{81}$.

83. The compound of claim 82 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-R^{81}$.

84. The compound of claim 81 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-O-R^{81}$.

85. The compound of claim 84 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_n-NR^7-C(O)-O-R^{81}$.

86. The compound of claim 73 wherein one or both of Z and Z′ are $-U-(CR^4_2)_t-R^8$.

87. The compound of claim 86 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-R^8$.

88. The compound of claim 73 wherein one or both of Z and Z′ are $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

89. The compound of claim 88 wherein one or both of Z and Z′ are $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

90. The compound of claim 89 wherein one or both of Z and Z′ are $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

91. The compound of claim 88 wherein one or both of Z and Z′ are

$-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$.

92. A pharmaceutical composition comprising any one of the compounds of claims 1-55.

93. The use of the compound of any one of claims 1-92 in the manufacture of a medicament.

94. The use of a compound of claim 93 wherein the medicament is for the treatment of hepatitis C.

95. 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 1-92.