

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



WIPO | PCT



(10) International Publication Number

WO 2010/065674 A9

(43) International Publication Date
10 June 2010 (10.06.2010)

- (51) International Patent Classification:
A01N 57/00 (2006.01) A61K 31/675 (2006.01)
- (21) International Application Number: PCT/US2009/066459
- (22) International Filing Date: 2 December 2009 (02.12.2009)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
- | | | |
|------------|------------------------------|----|
| 61/119,723 | 3 December 2008 (03.12.2008) | US |
| 61/173,590 | 28 April 2009 (28.04.2009) | US |
| 61/214,881 | 28 April 2009 (28.04.2009) | US |
| 61/182,958 | 1 June 2009 (01.06.2009) | US |
| 61/182,952 | 1 June 2009 (01.06.2009) | US |
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
- | | |
|----------|--------------------------|
| US | 61/182,952 (CON) |
| Filed on | 1 June 2009 (01.06.2009) |
- (71) Applicant (for all designated States except US): **PRESIDIO PHARMACEUTICALS, INC.** [US/US]; 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ZHONG, Min** [US/US]; C/o Presidio Pharmaceuticals, Inc., 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US). **LI, Leping** [US/US]; C/o Presidio Pharmaceuticals, Inc., 1700 Owens Street, Suite 585, San Francisco, CA 94158 (US).
- (74) Agents: **FARMER-KOPPENOL, Pauline** et al.; Fenwick & West LLP, Silicon Valley Center, 801 California Street, Mountain View, CA 94041 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))
- (48) Date of publication of this corrected version: 31 May 2012
- (15) Information about Correction: see Notice of 31 May 2012

(54) Title: INHIBITORS OF HCV NS5A

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

WO 2010/065674 A9

INHIBITORS OF HCV NS5A

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).

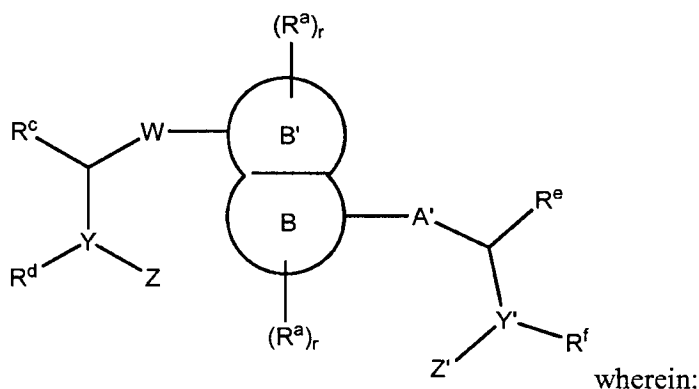
[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related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

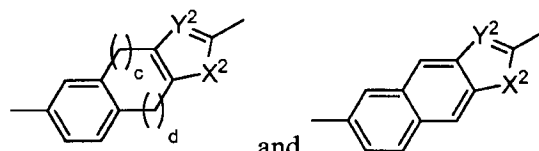
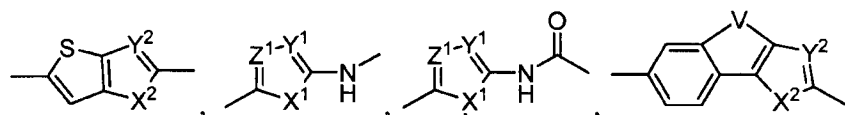
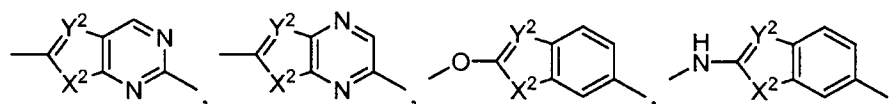
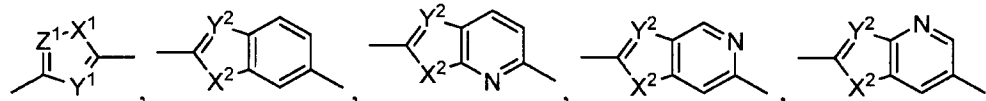
[0006] Essential features of the NS5A protein of HCV make it an ideal target for inhibitors. The present disclosure describes a class of compounds targeting the NS5A protein and methods of their use to treat HCV infection in humans.

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



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 , ,



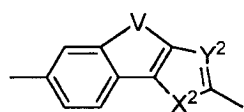
and wherein:

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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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,

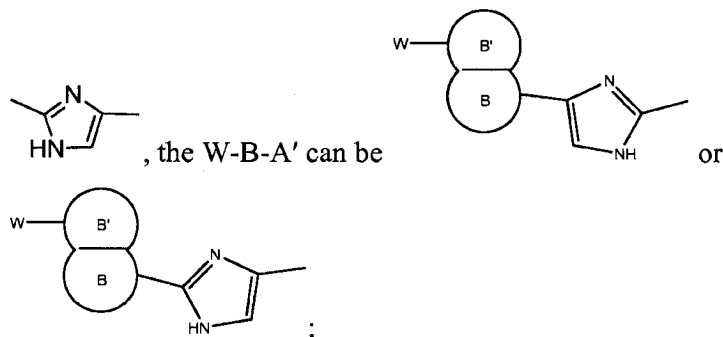
k is 0, 1, or 2,

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

-OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide, and

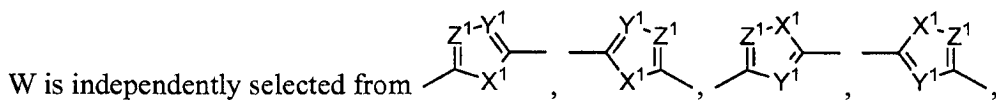
wherein B may be attached to either side of A' so that in the example of A' being

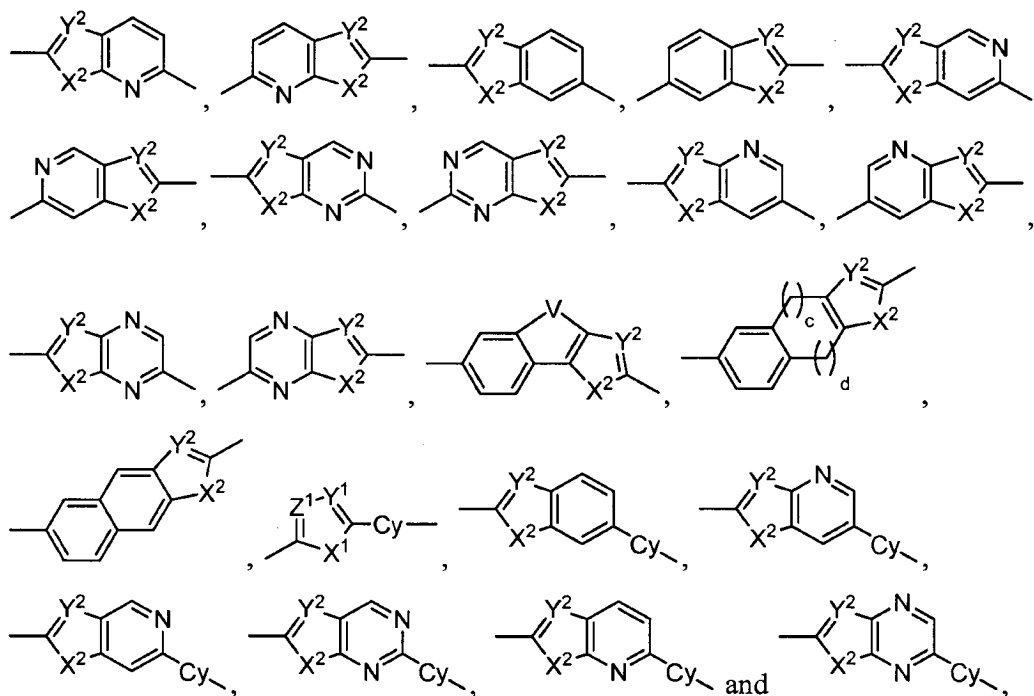


B and B' are each independently a 4- to 8-membered ring that is an aryl, heteroaryl, cycloalkyl, or heterocycle, wherein each hetero atom, if present, is independently N, O or S and wherein at least one of B or B' is aromatic;

each R^a is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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;





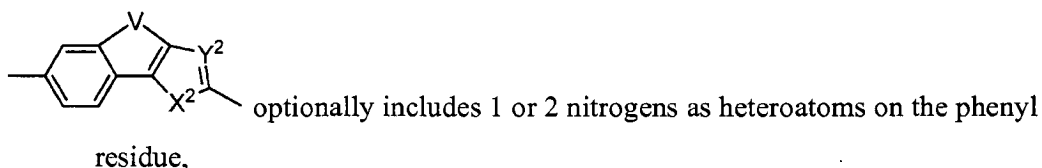
wherein:

X¹ is CH₂, NH, O or S,

Y¹, Y² and Z¹ are each independently CH or N,

X² is NH, O or S,

V is -CH₂-CH₂-, -CH=CH-, -N=CH-, -(CH₂)_a-N(R^N)-(CH₂)_b- or -(CH₂)_a-O-(CH₂)_b-,
 wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,



W is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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, C₁ to C₈ alkyl, C₁ to C₈ 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 $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$ and $-\text{S}(\text{O})_2-$,

each R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ 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,

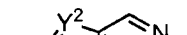
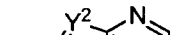
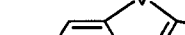
optionally, R⁷ and R⁸ together form a 4-7 membered ring,

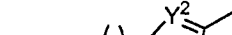
each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

[0008] In a first embodiment of the first aspect, A' is selected from the group consisting of a single bond, $-(\text{CR}_2)_n\text{O}-(\text{CR}_2)_p-$, $-(\text{CR}_2)_n\text{N}(\text{R}^N)-(\text{CR}_2)_p-$, $-(\text{CR}_2)_n\text{C}(\text{O})\text{N}(\text{R}^N)-(\text{CR}_2)_p-$, $-(\text{CR}_2)_n\text{N}(\text{R}^N)\text{C}(\text{O})\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ and $-(\text{CR}_2)_n\text{N}(\text{R}^N)\text{C}(\text{O})\text{O}-(\text{CR}_2)_p-$ and a heteroaryl

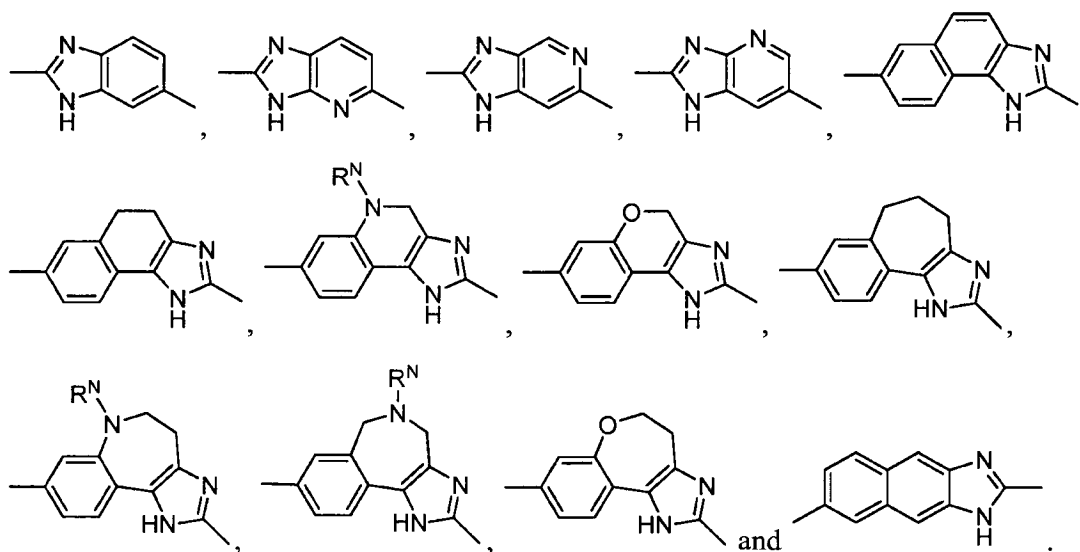
group selected from the group consisting of , , ,

, , , , 

 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,

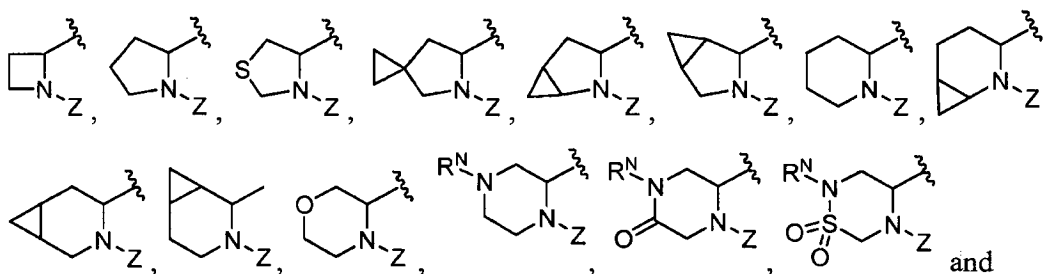
each hetero atom, if present, is independently N, O or S,

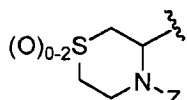
R^c and R^d are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle, and

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.

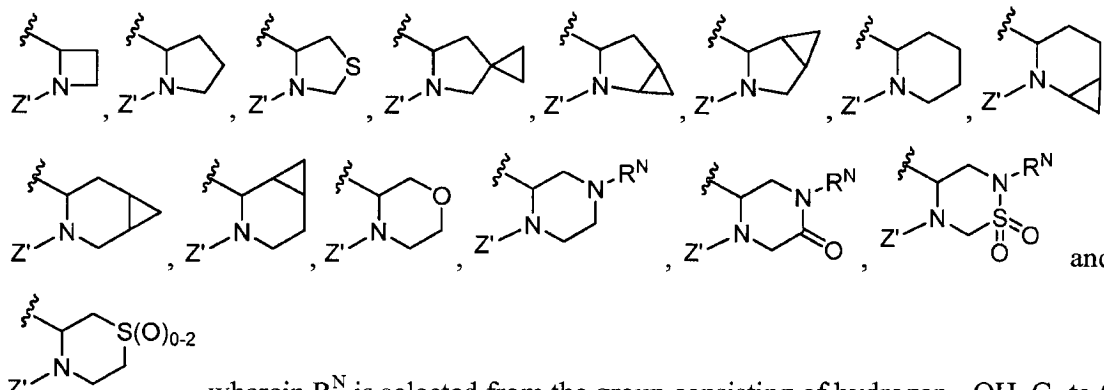
[0012] In a fifth embodiment of the first aspect, R^c and R^d are joined and form a heterocyclic fused ring system selected from the group consisting of:





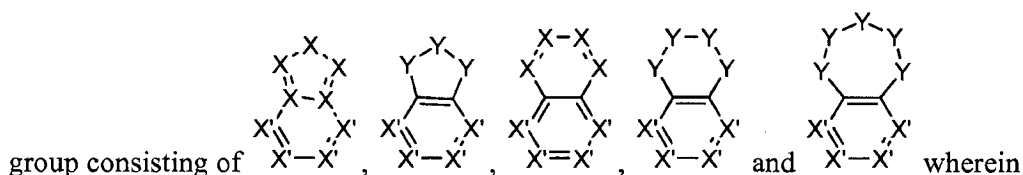
wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[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:



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



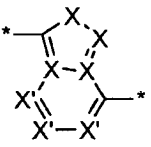
group consisting of $X-X'$, $X'-X'$, $X=X'$, $X'-X'$ and $X'-X'$ wherein

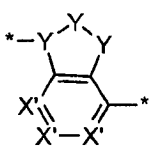
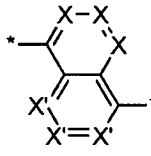
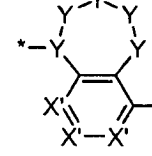
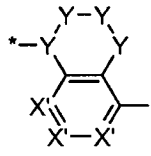
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

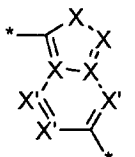
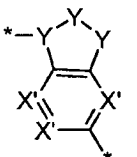
each X' is independently -N- or -CH-, with the proviso that no more than two X' are -N-;

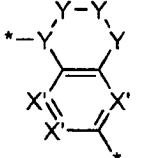
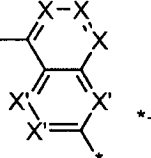
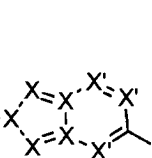
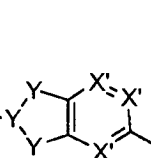
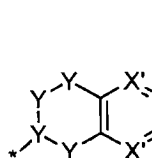
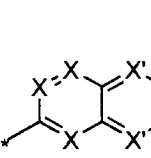
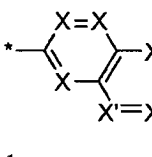
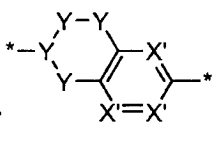
each Y is independently selected from -CH₂-, -NH-, -O-, -S-, -C(O)₂-, or -S(O)₁₋₂-; and

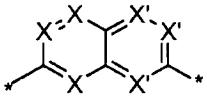
B and B' attach to the remainder of the compound at any available attachment point on the molecule.

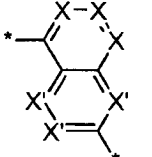
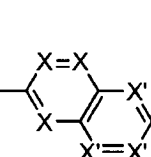
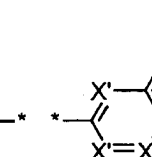
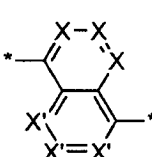
[0015] In an eighth embodiment of the first aspect, B and B' together is ,

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

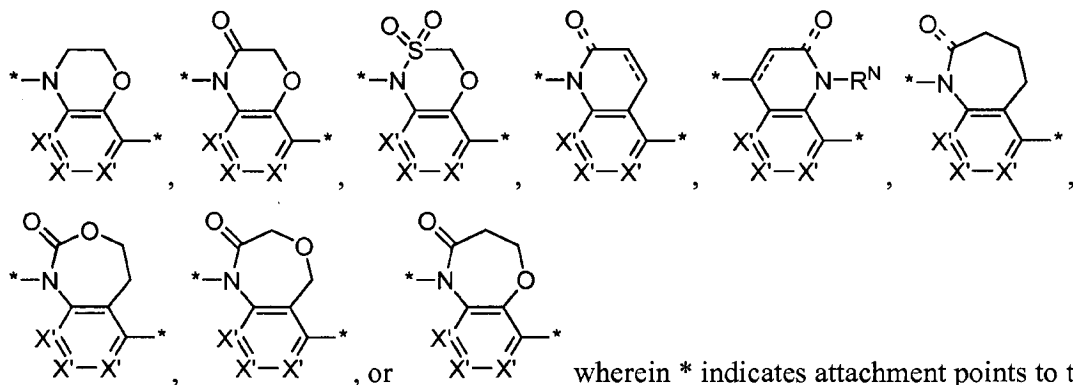
[0016] In a ninth embodiment of the first aspect, B and B' together is , ,

, , , , , , , 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 ,

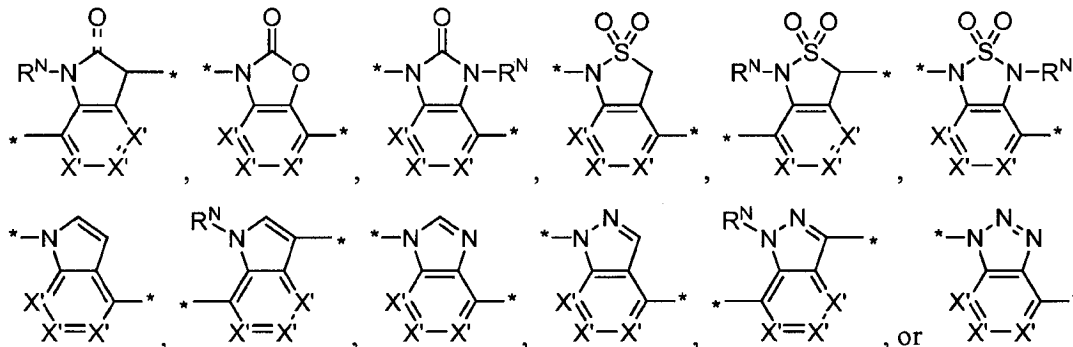
, , , or  wherein * indicates attachment points to the remainder of the compound wherein no more than 2 of X are nitrogen.

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

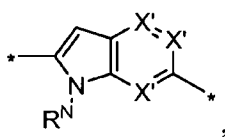


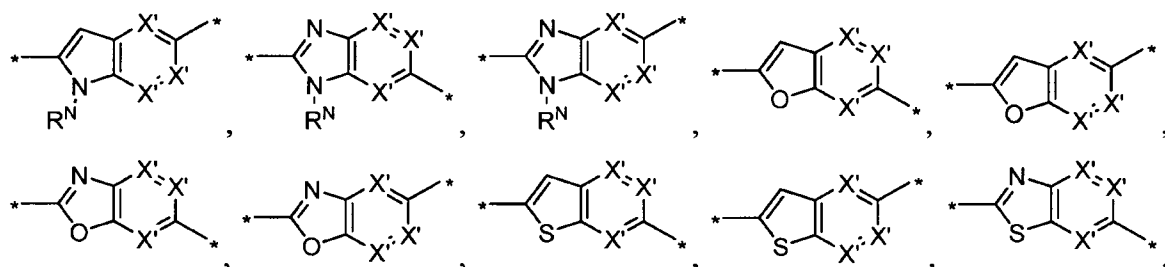
$\overset{\text{X}^N}{\text{X}}-\overset{\text{X}^N}{\text{X}}$, $\overset{\text{X}^N}{\text{X}}-\overset{\text{X}^N}{\text{X}}$, or $\overset{\text{X}^N}{\text{X}}-\overset{\text{X}^N}{\text{X}}$ wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group 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.

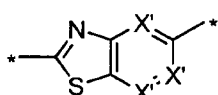
[0019] In a twelfth embodiment of the first aspect, B and B' together is



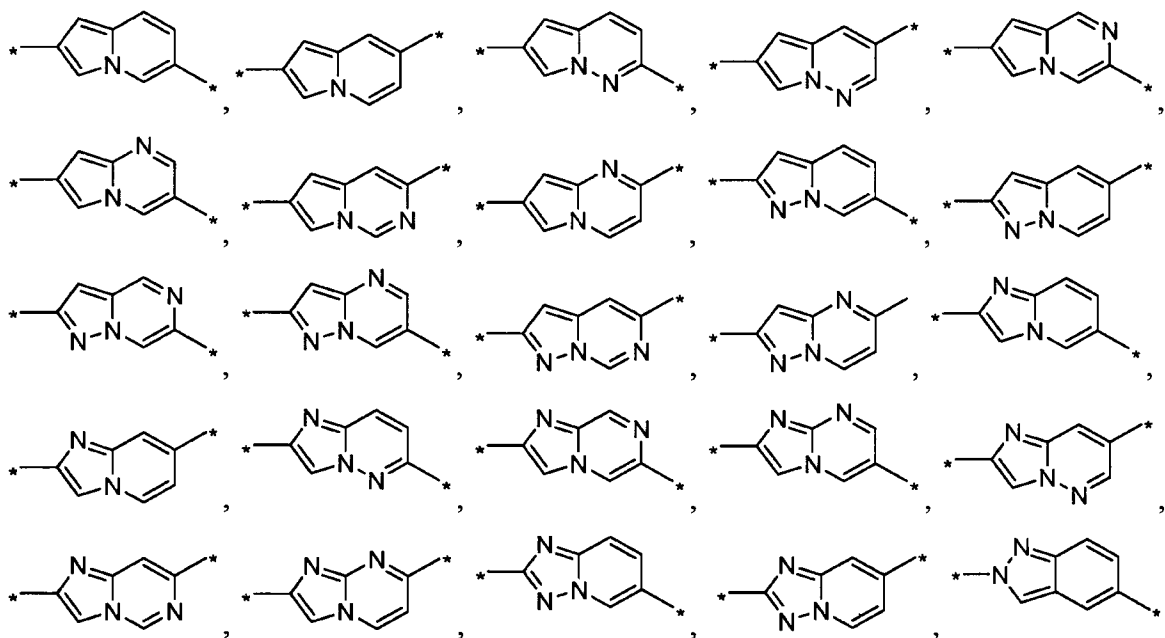
wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

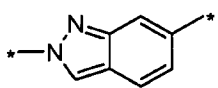
[0020] In a thirteenth embodiment of the first aspect, B and B' together is ,



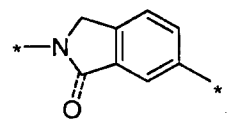
or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

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

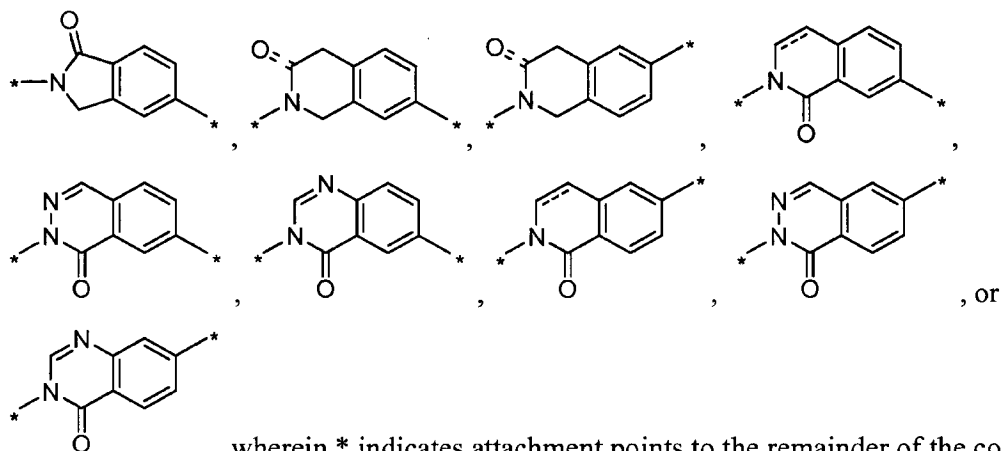


or  wherein * indicates attachment points to the remainder of the compound and the six-membered ring optionally contains one or two additional nitrogens as heteroatoms

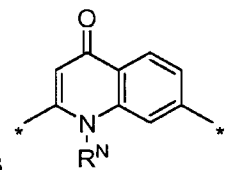
with the proviso that the total number of nitrogens in the six-membered ring does not exceed two.



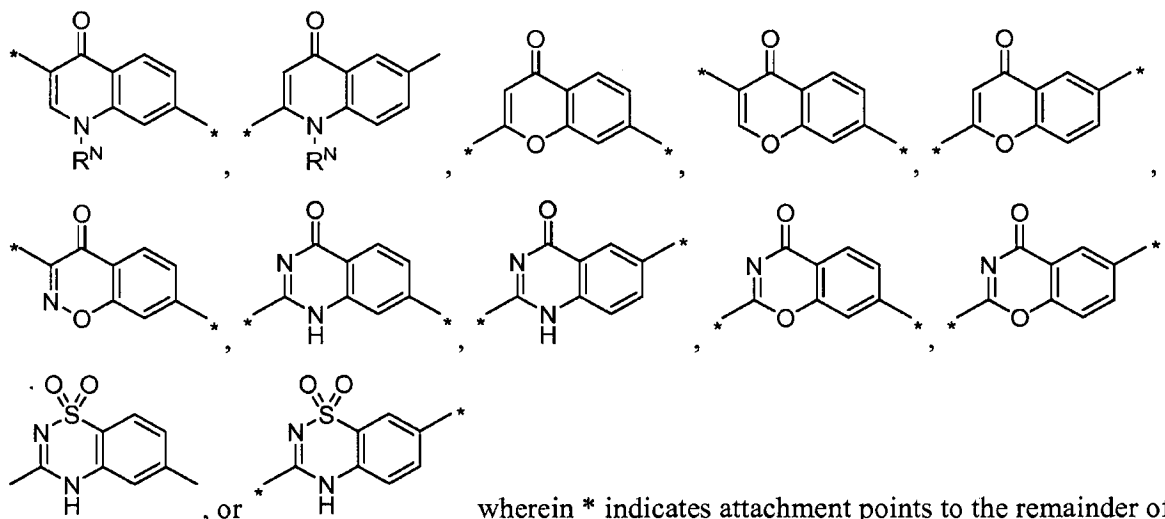
[0022] In a fifteenth embodiment of the first aspect, B and B' together is



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



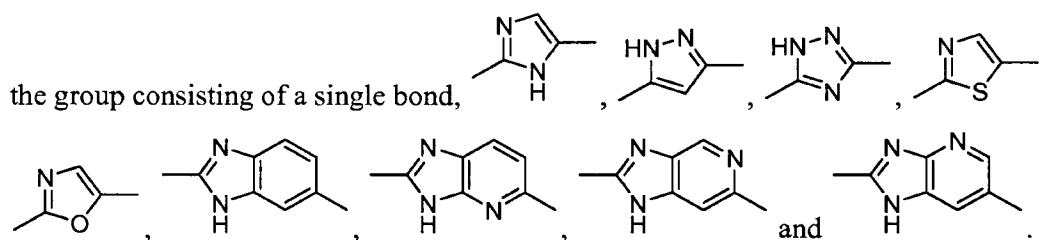
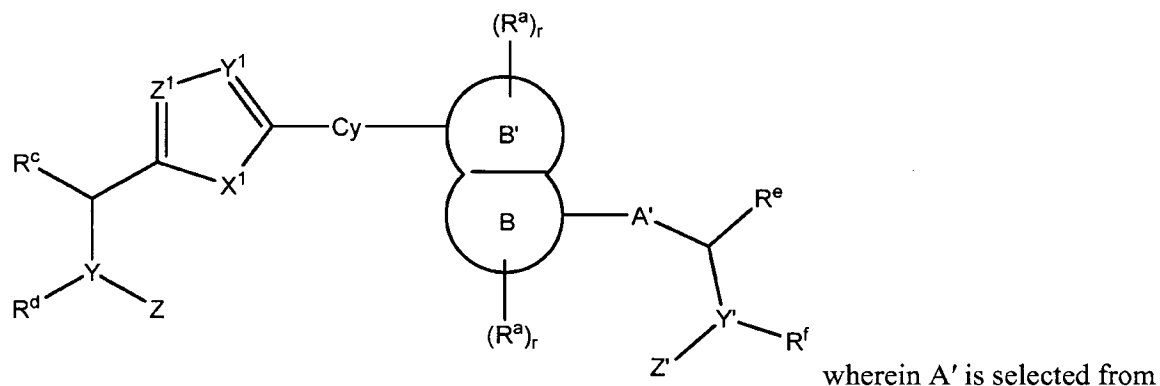
[0023] In a sixteenth embodiment of the first aspect, B and B' together is



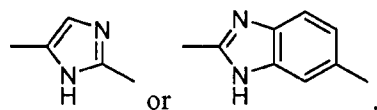
the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and

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.

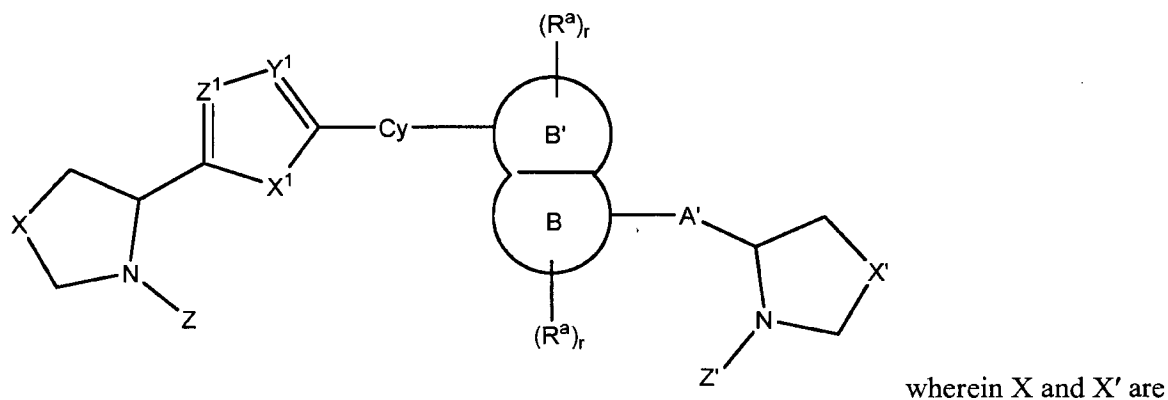
[0024] In a second aspect of the invention, compounds have formula II:



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

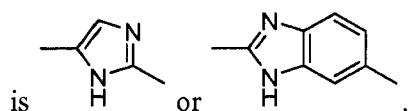


[0026] In a second embodiment of the second aspect, compounds have formula IIa:

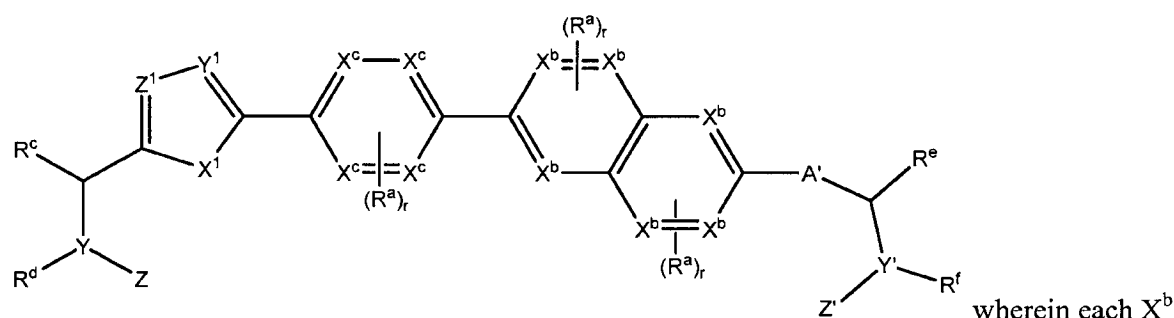


each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

[0027] In a third embodiment of the second aspect, compounds have formula IIa wherein A'

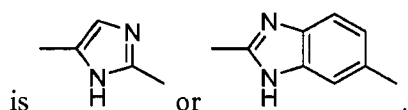


[0028] In a fourth embodiment of the second aspect, compounds have formula IIb:

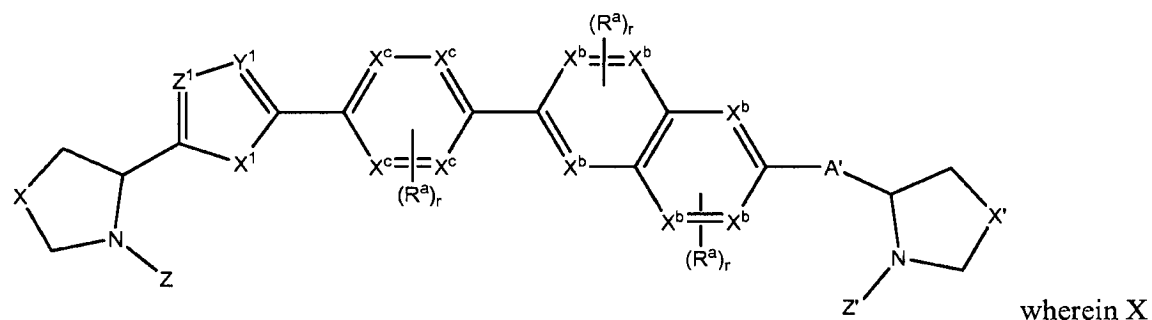


and X^c is independently C or N.

[0029] In a fifth embodiment of the second aspect, compounds have formula IIb wherein A'



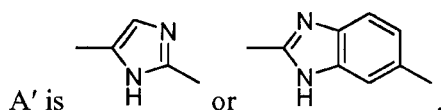
[0030] In a sixth embodiment of the second aspect, compounds have formula IIc:



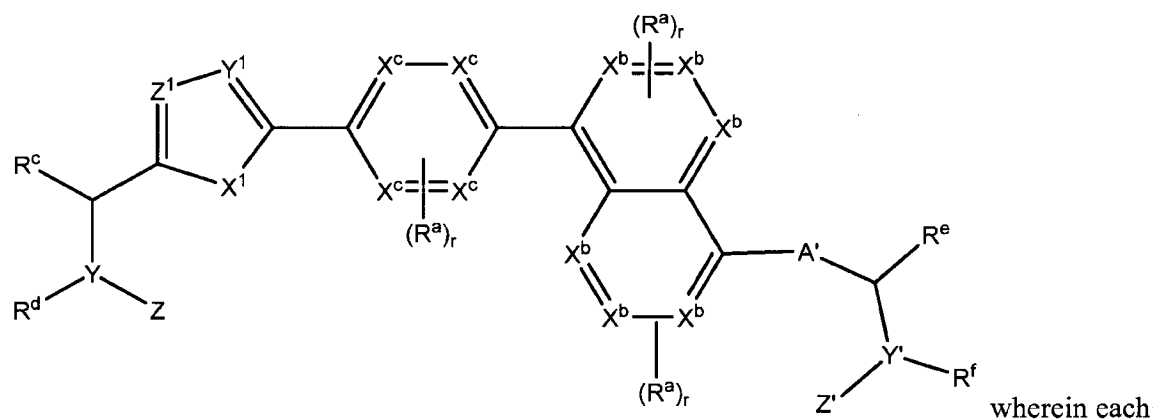
and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$,

$-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

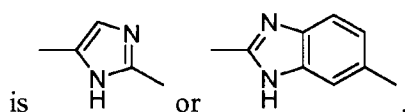


[0032] In an eighth embodiment of the second aspect, compounds have formula IIId:

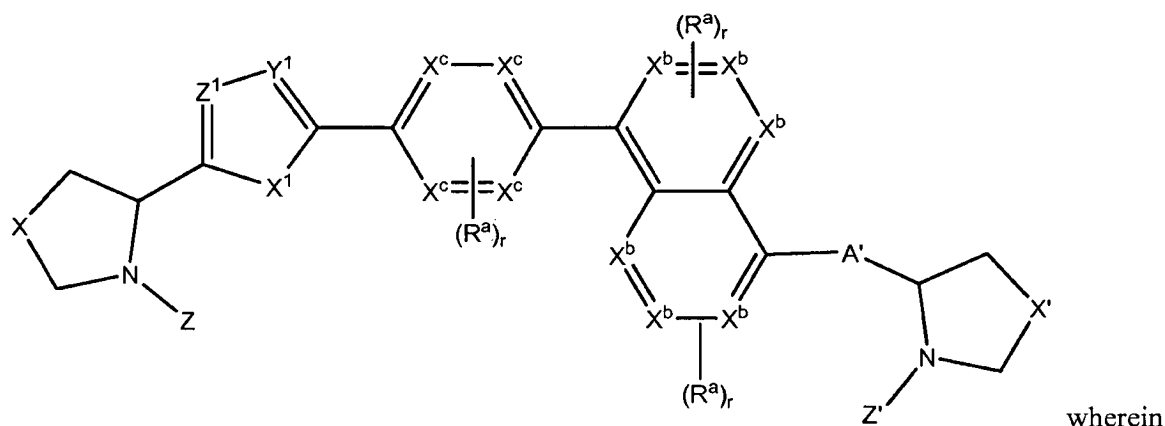


X^b and X^c is independently C or N.

[0033] In a ninth embodiment of the second aspect, compounds have formula IIId wherein A'

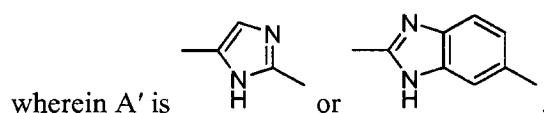


[0034] In a tenth embodiment of the second aspect, compounds have formula IIe:

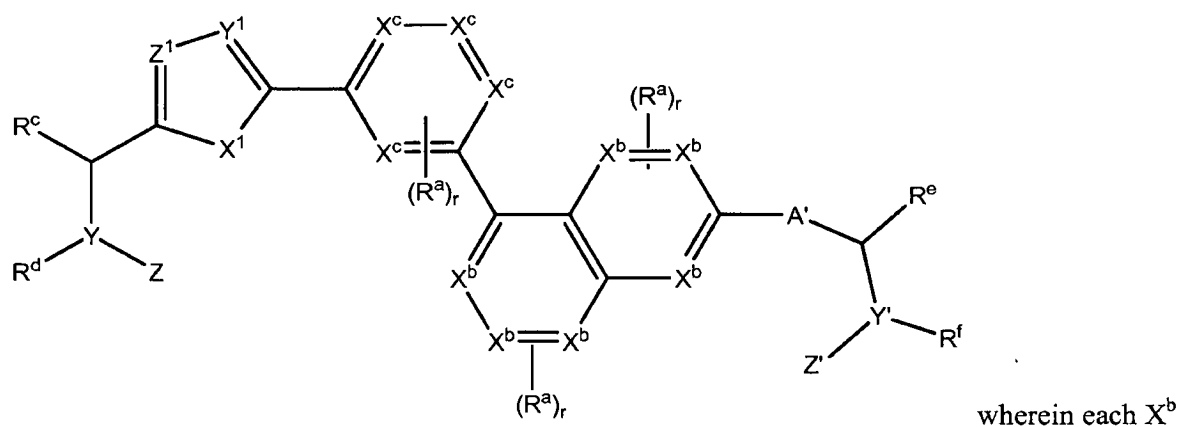


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

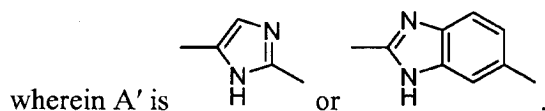


[0036] In a twelfth embodiment of the second aspect, compounds have formula IIIf:

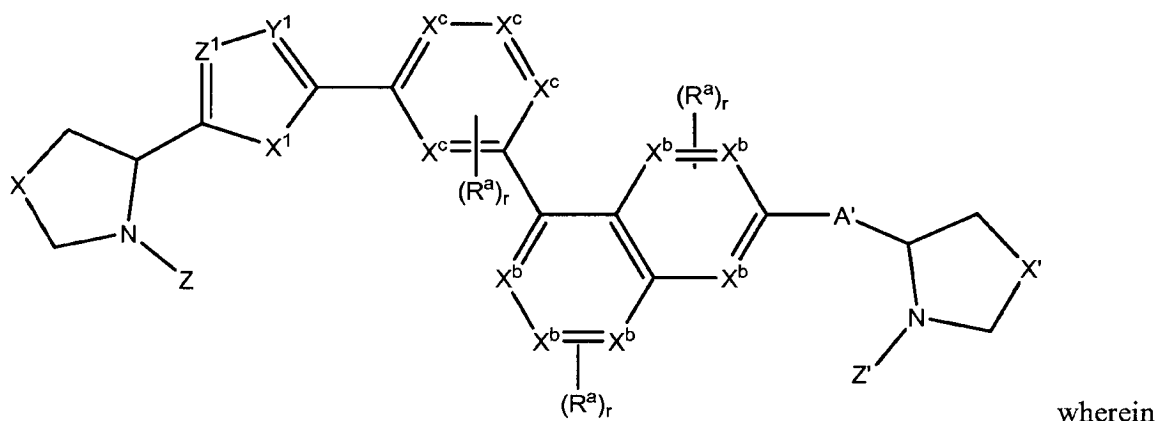


and X^c is independently C or N.

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

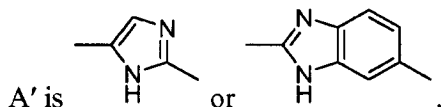


[0038] In a fourteenth embodiment of the second aspect, compounds have formula II g:

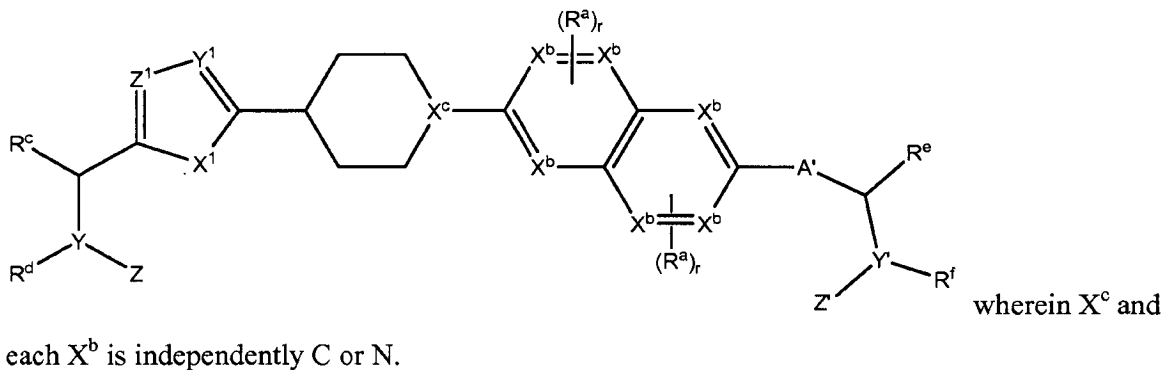


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

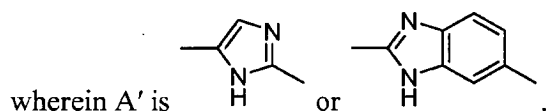
[0039] In a fifteenth embodiment of the second aspect, compounds have formula II g wherein



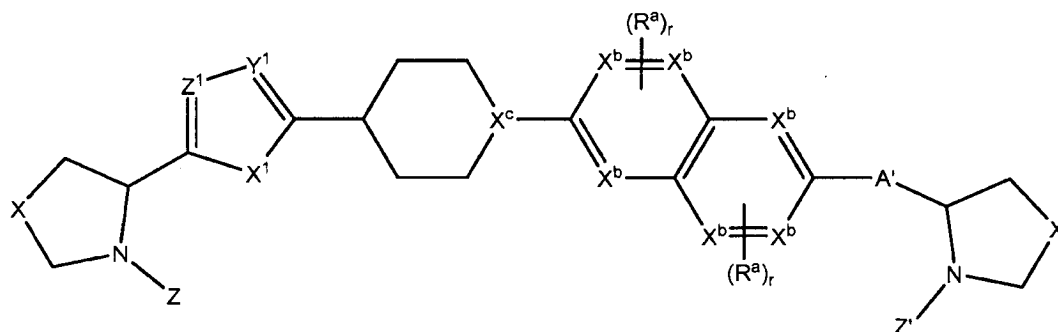
[0040] In a sixteenth embodiment of the second aspect, compounds have formula II h:



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

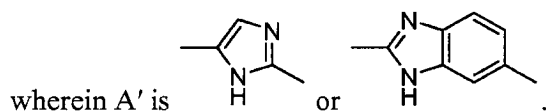


[0042] In an eighteenth embodiment of the second aspect, compounds have formula III:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

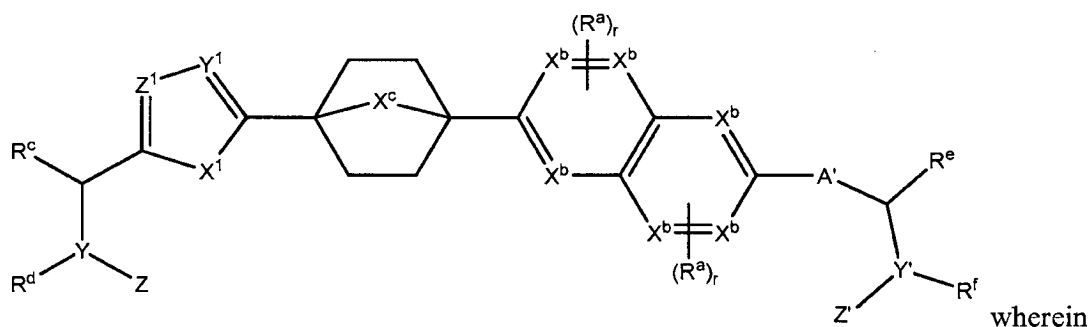
[0043] In a nineteenth embodiment of the second aspect, compounds have formula III



[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.

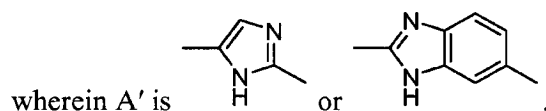
[0046] In a twenty-second embodiment of the second aspect, compounds have formula IIj:



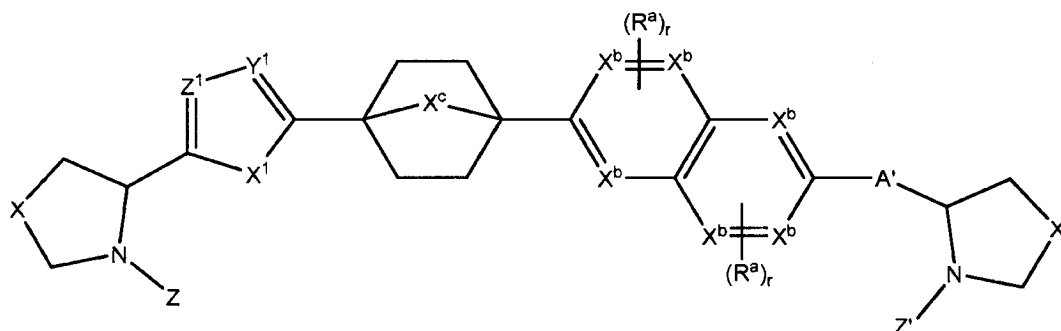
X^c is $-\text{CH}_2-$, $-\text{NH}-$ or $-\text{CH}_2\text{CH}_2-$, and

each X^b is independently C or N.

[0047] In a twenty-third embodiment of the second aspect, compounds have formula IIj

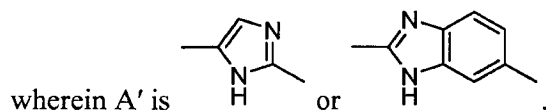


[0048] In a twenty-fourth embodiment of the second aspect, compounds have formula IIk:

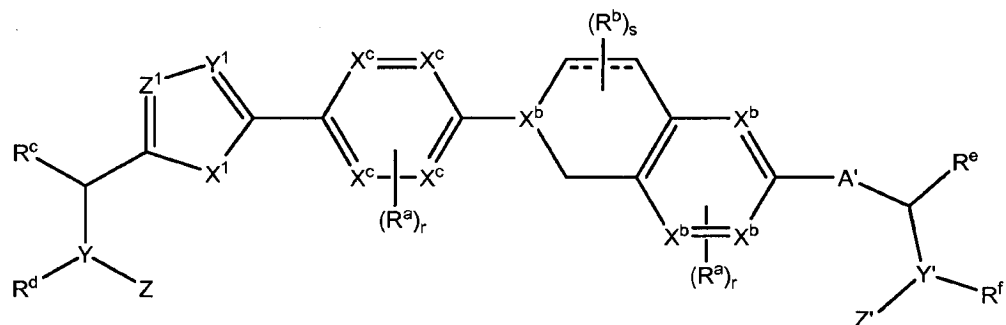


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

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



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



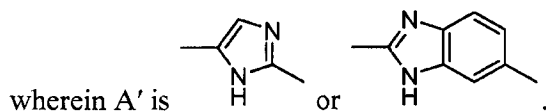
wherein:

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

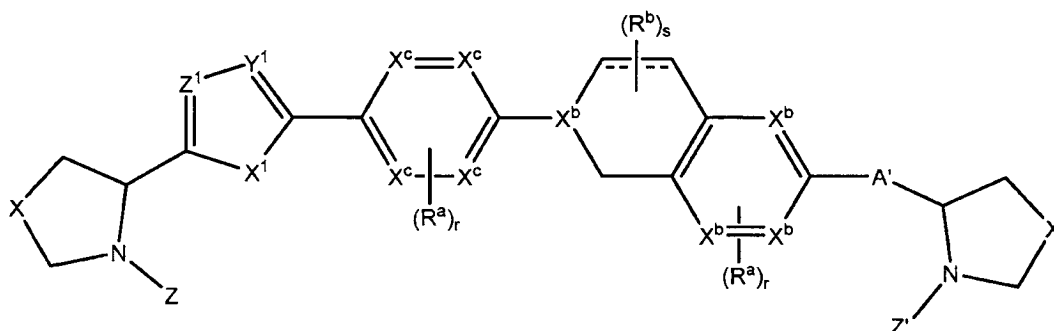
each R^b is selected from the group consisting of oxo, -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; and

s is 0, 1, 2, or 3.

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

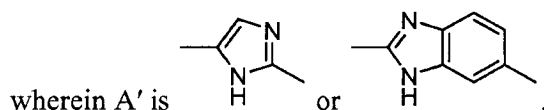


[0052] In a twenty-eighth embodiment of the second aspect, compounds have formula IIIm:

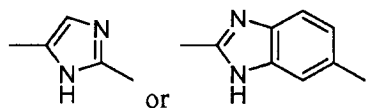


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

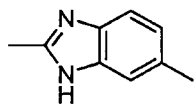
[0053] In a twenty-ninth embodiment of the second aspect, compounds have formula IIIm



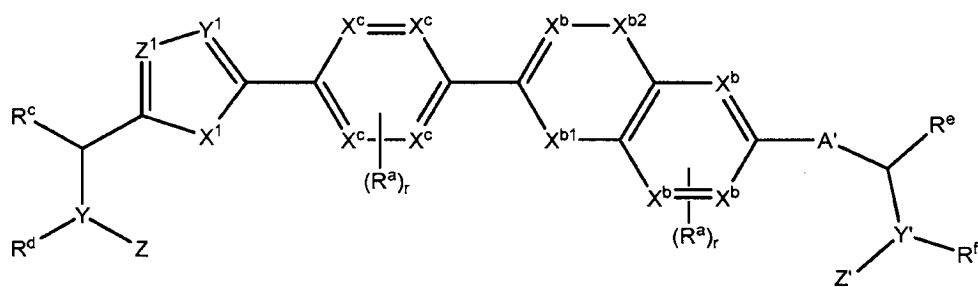
wherein A' is



or



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



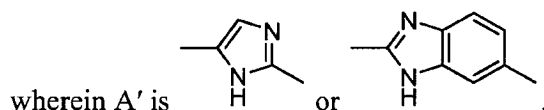
wherein:

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

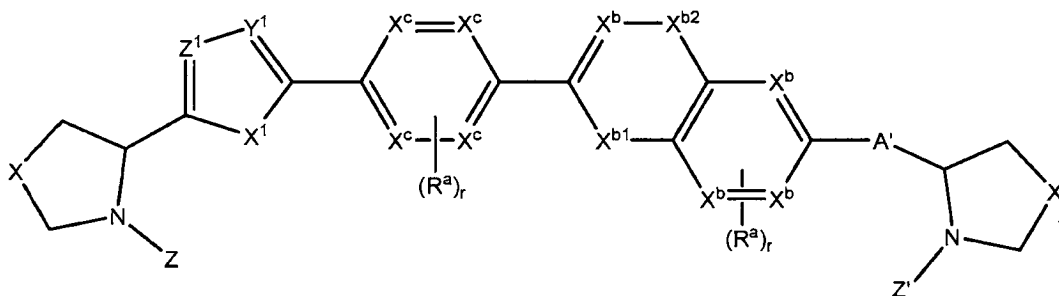
X^{b1} is N or O; and

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

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

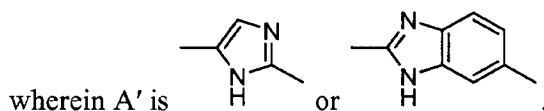


[0056] In a thirty-second embodiment of the second aspect, compounds have formula II_o:

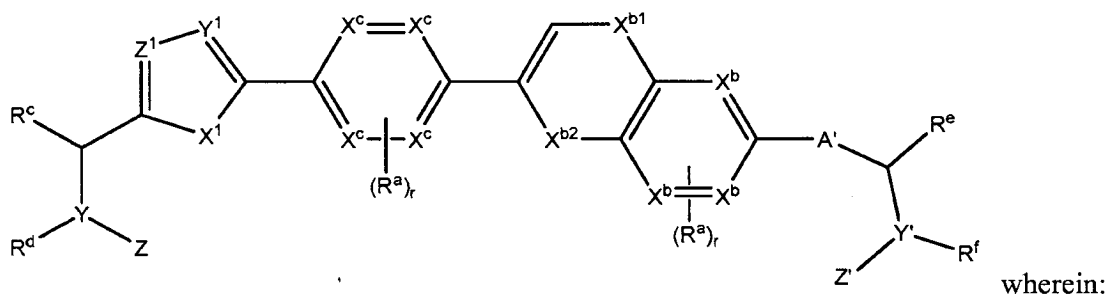


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 II_o



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

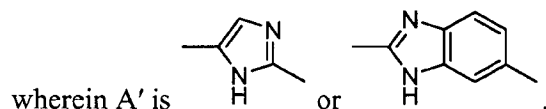


each X^b and X^c is independently C or N;

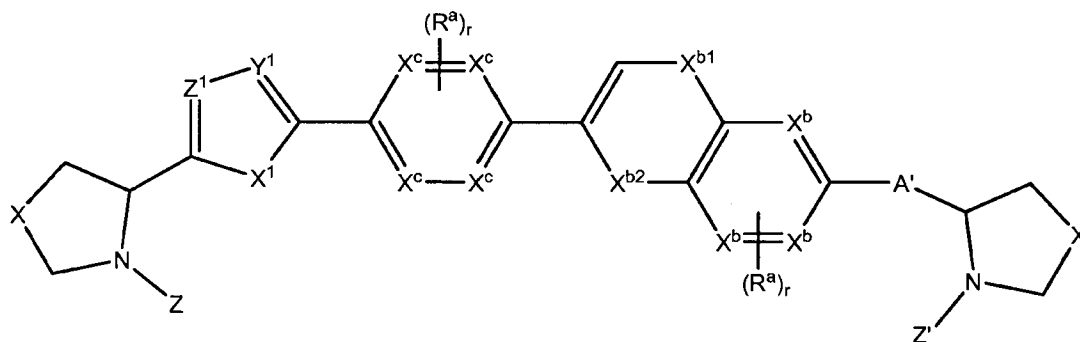
X^{b1} is N or O; and

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

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

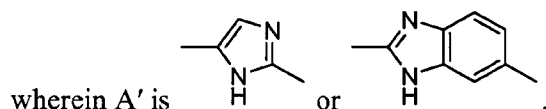


[0060] In a thirty-sixth embodiment of the second aspect, compounds have formula IIq:

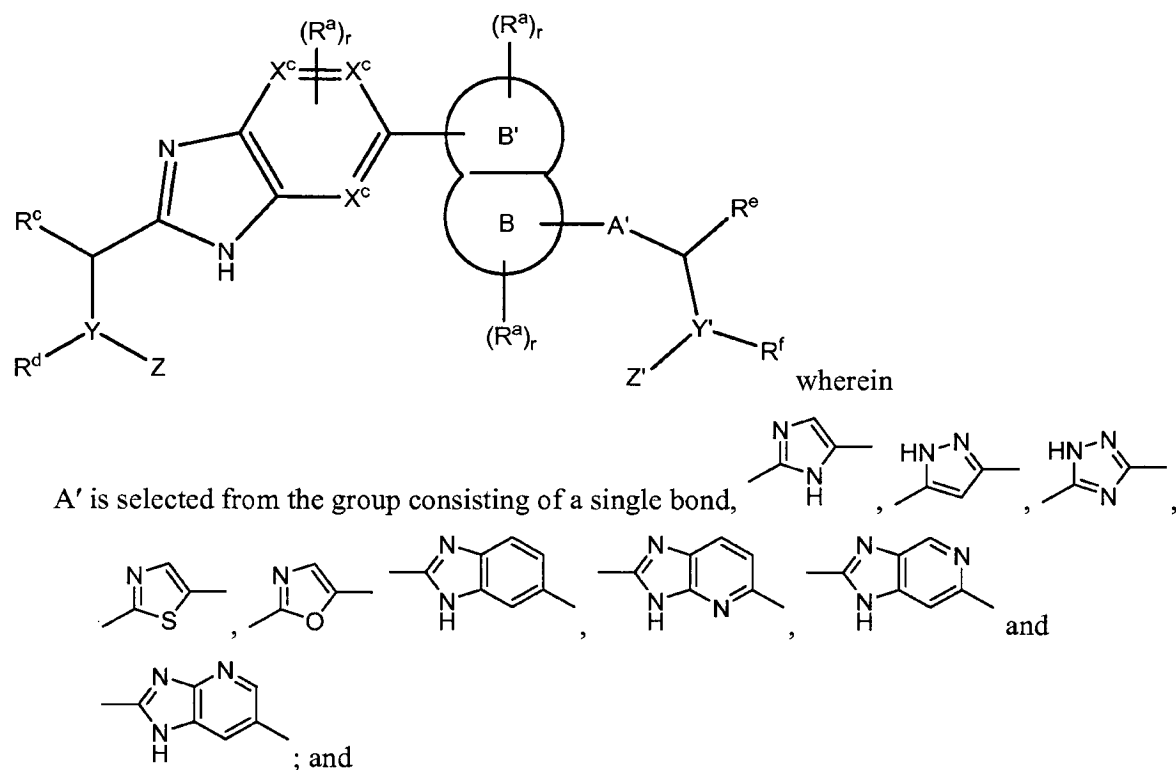


wherein X and X' are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8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

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

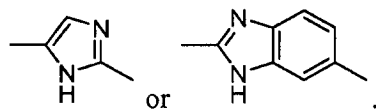


[0062] In a third aspect of the invention, compounds have formula III:

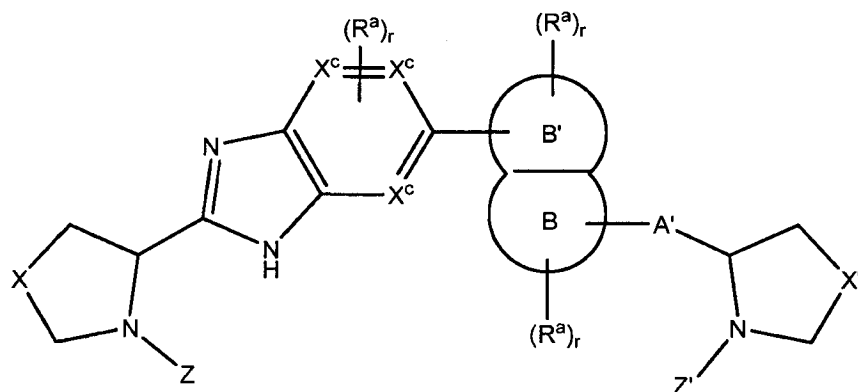


each X^c is independently C or N.

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

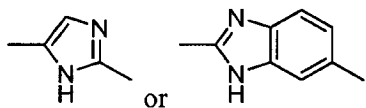


[0064] In a second embodiment of the third aspect, compounds have formula IIIa:

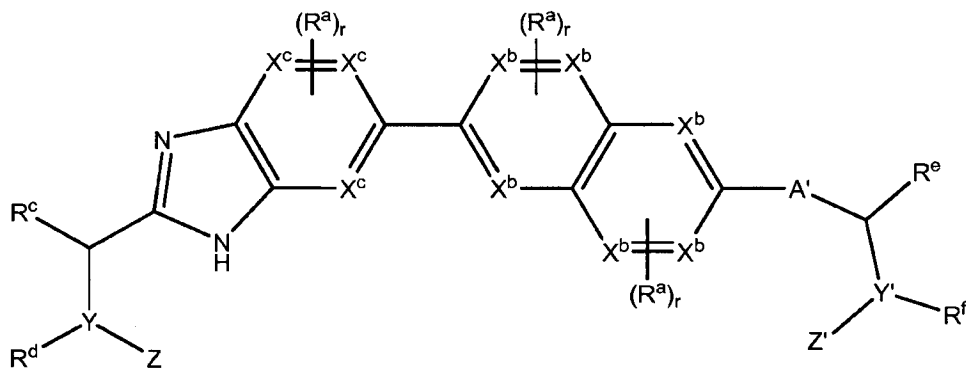


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

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



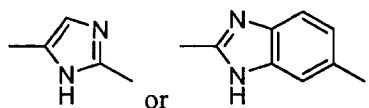
[0066] In a fourth embodiment of the third aspect, compounds have formula IIIb:



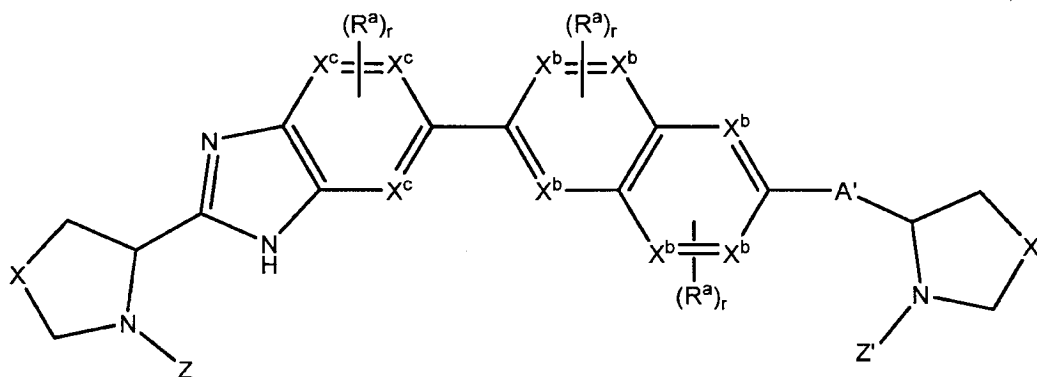
X^b is independently C or N.

wherein each

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



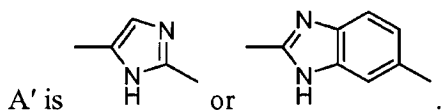
[0068] In a sixth embodiment of the third aspect, compounds have formula IIIc:



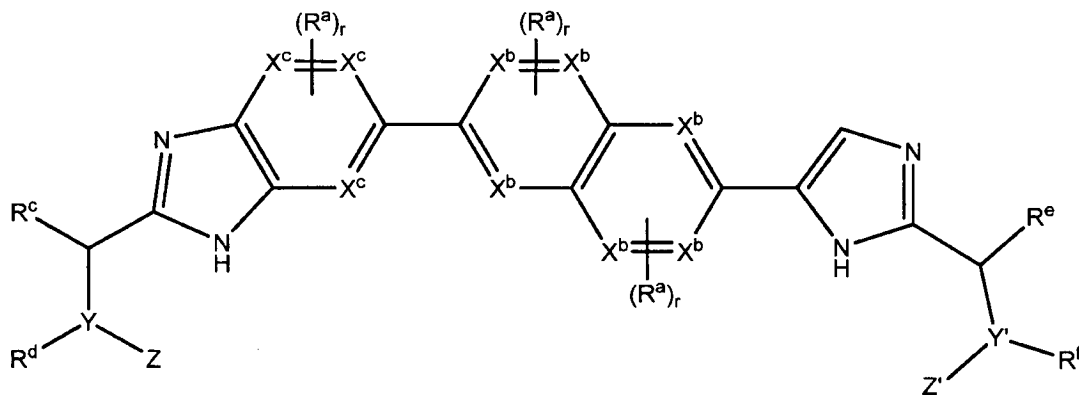
wherein

X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

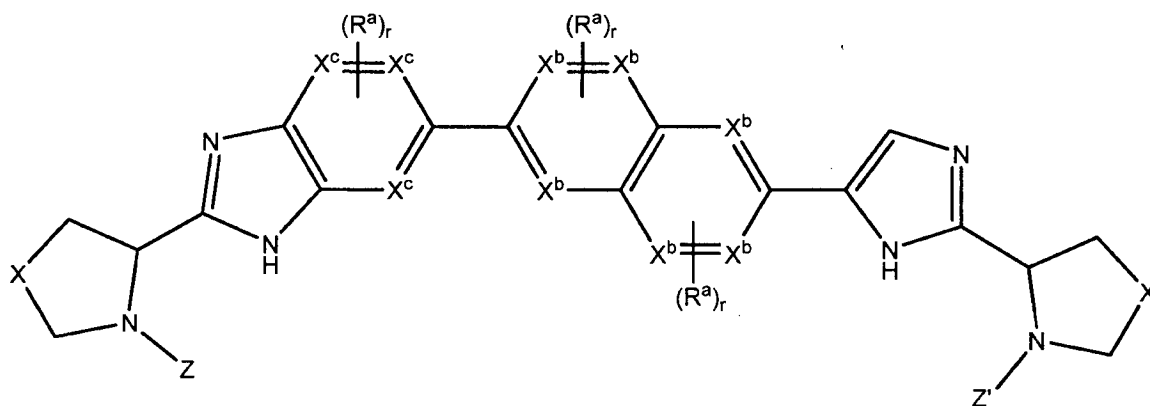
[0069] In a seventh embodiment of the third aspect, compounds have formula IIIc wherein



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

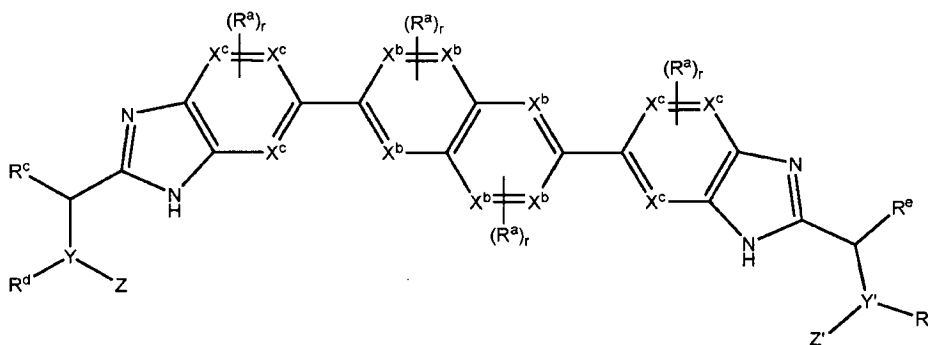


[0071] In a ninth embodiment of the third aspect, compounds have formula IIIe:

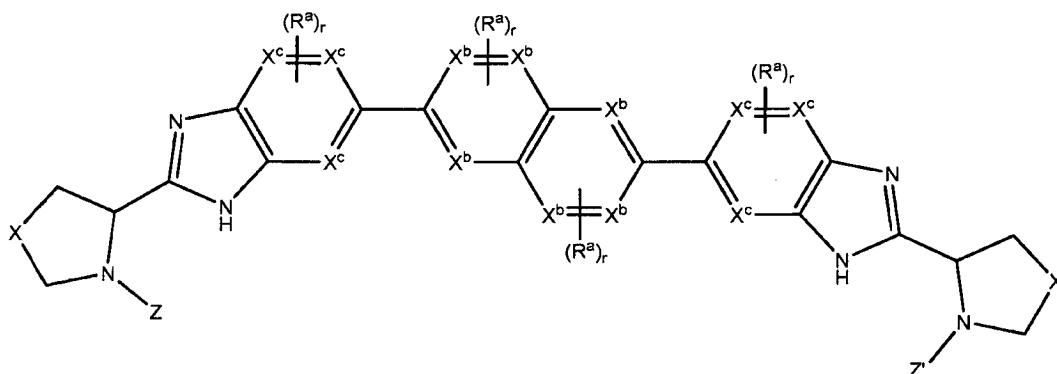


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

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

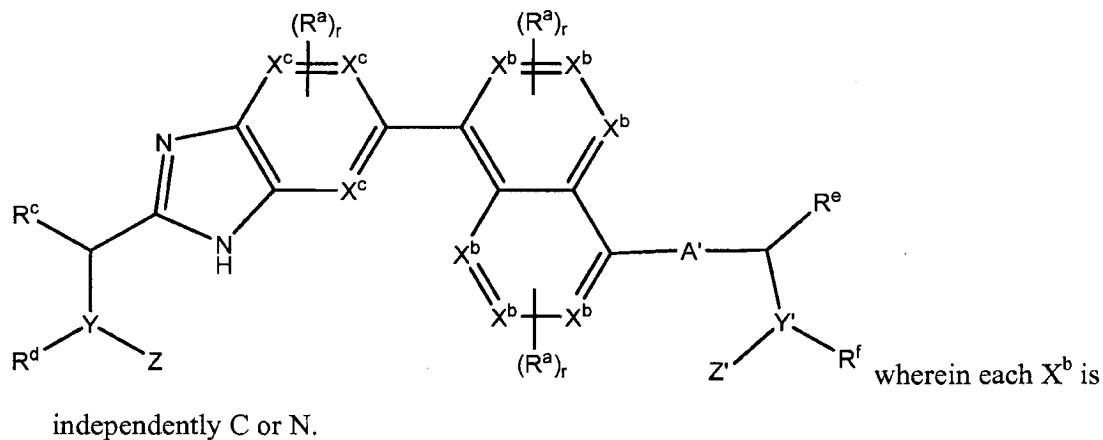


[0073] In an eleventh embodiment of the third aspect, compounds have formula IIIg:

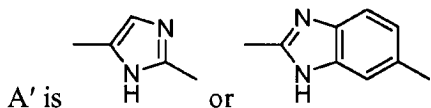


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

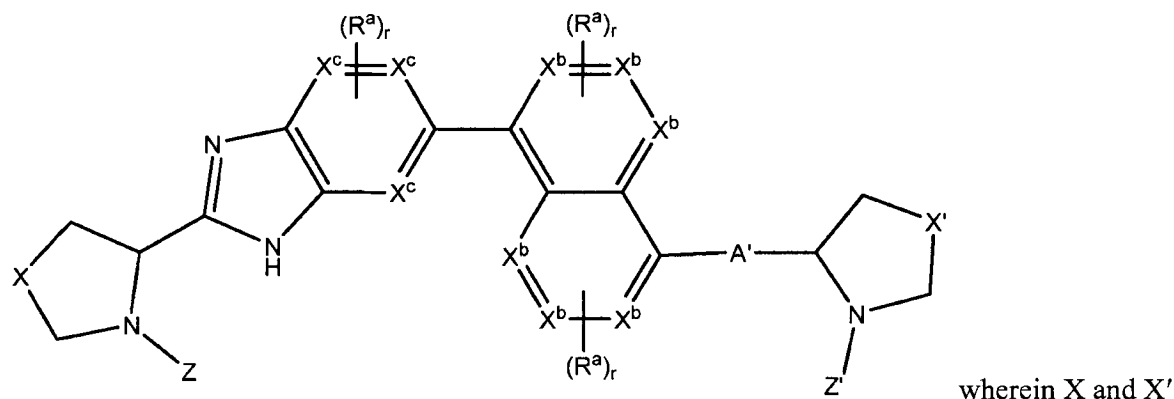
[0074] In a twelfth embodiment of the third aspect, compounds have formula IIIh:



[0075] In a thirteenth embodiment of the third aspect, compounds have formula IIIh wherein

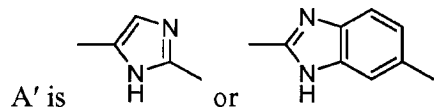


[0076] In a fourteenth embodiment of the third aspect, compounds have formula IIIi:

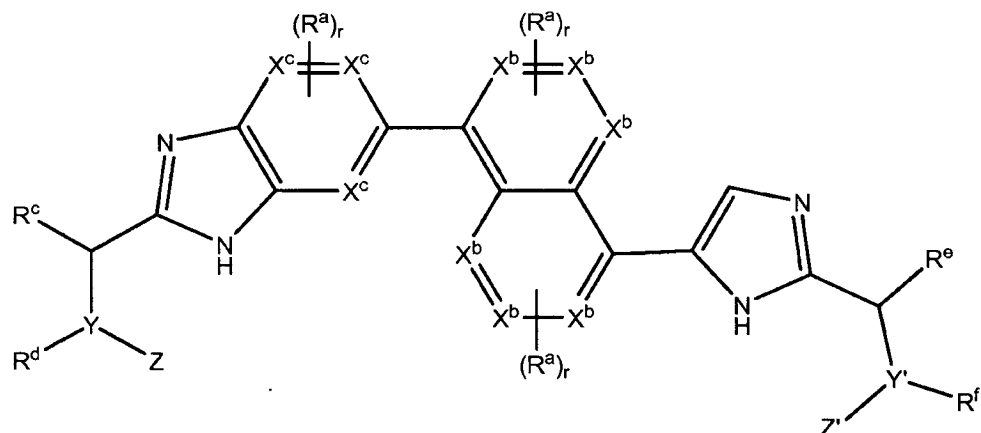


are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

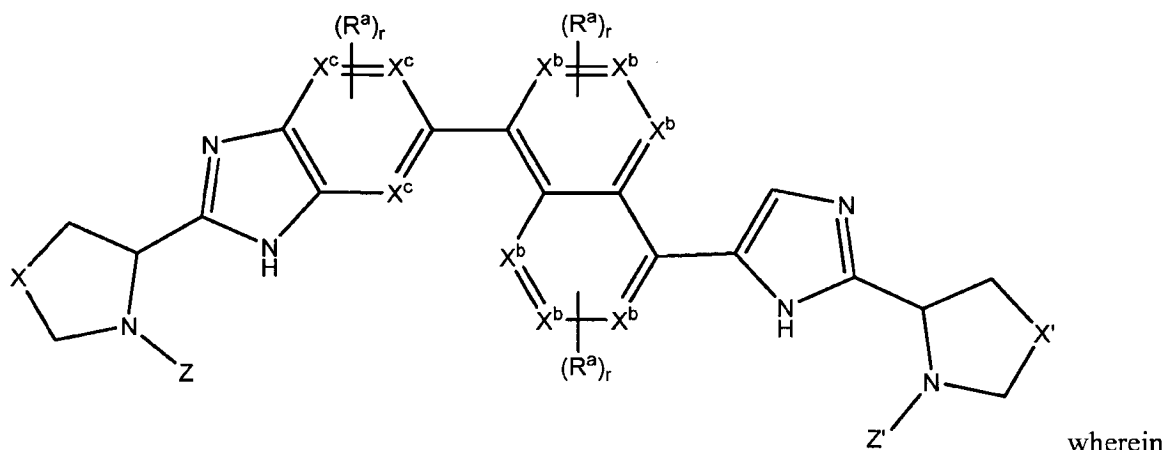
[0077] In a fifteenth embodiment of the third aspect, compounds have formula IIIi wherein



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

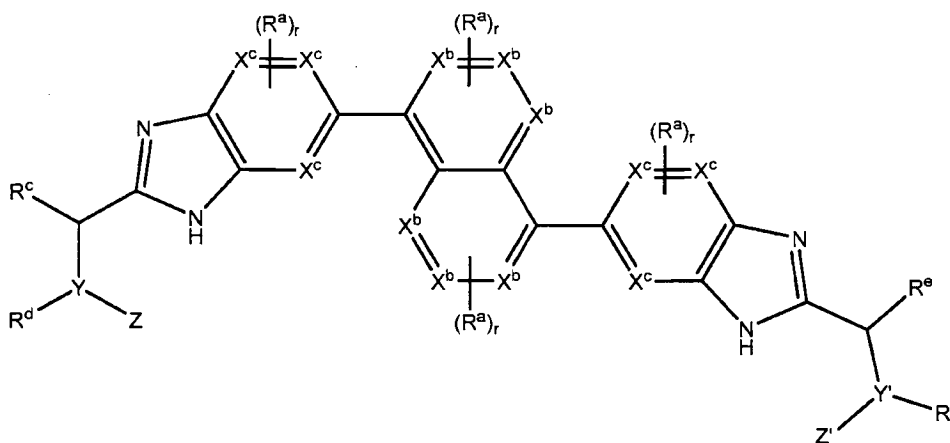


[0079] In a seventeenth embodiment of the third aspect, compounds have formula IIIk:

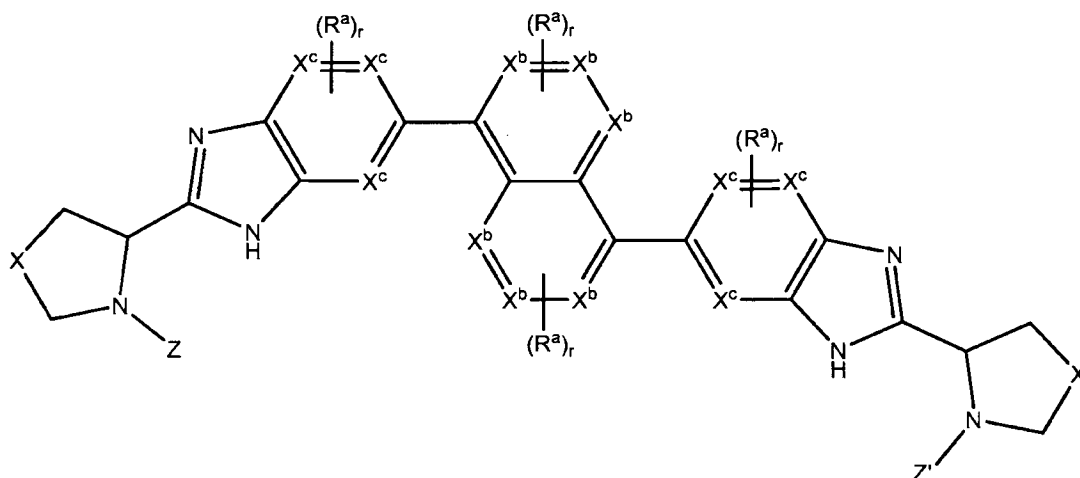


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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:

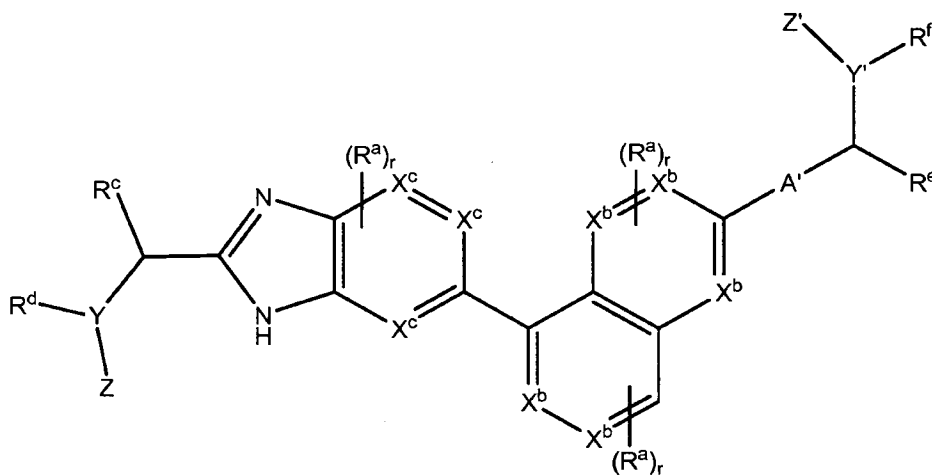


[0081] In a nineteenth embodiment of the third aspect, compounds have formula IIIm:



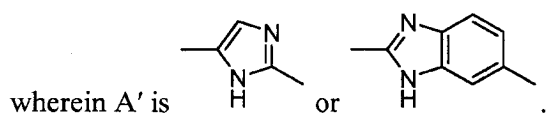
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

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

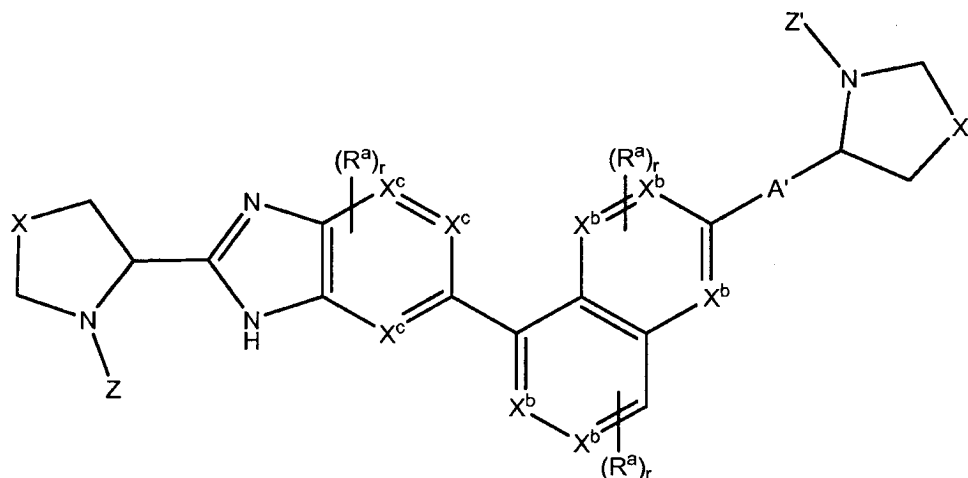


wherein each X^b is independently C or N.

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



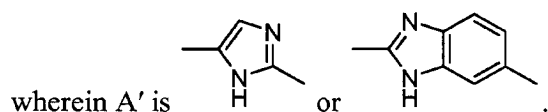
[0084] In a twenty-second embodiment of the third aspect, compounds have formula IIIIo:



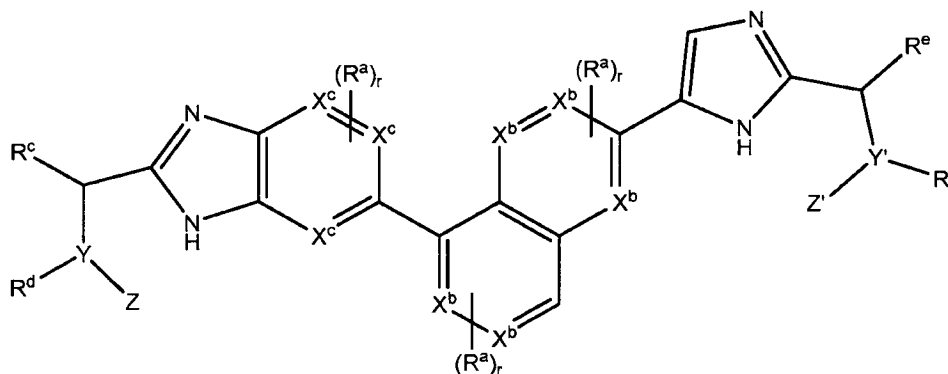
wherein X and

X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

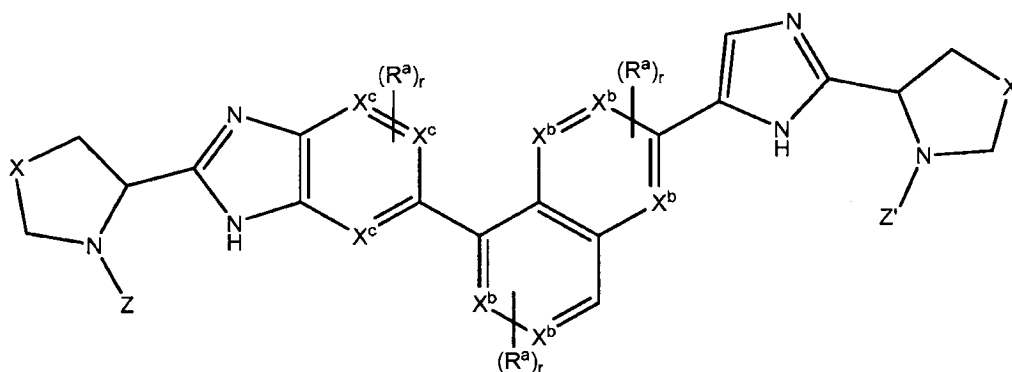
[0085] In a twenty-third embodiment of the third aspect, compounds have formula IIIIo



[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:

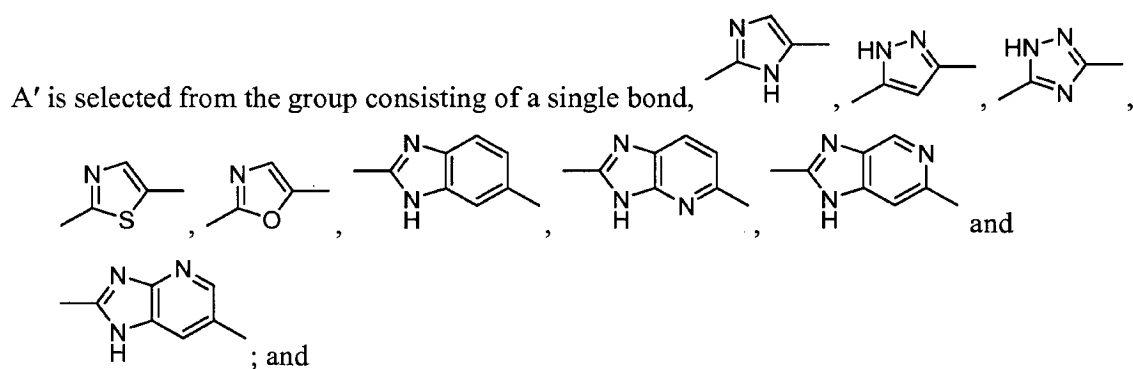
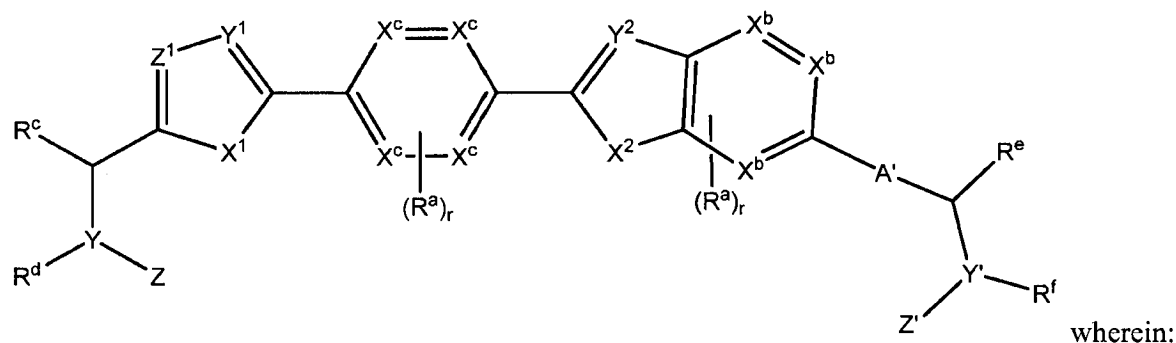


wherein X

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

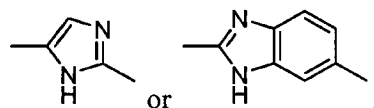
$-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, wherein R^1 is chosen from the group consisting 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:

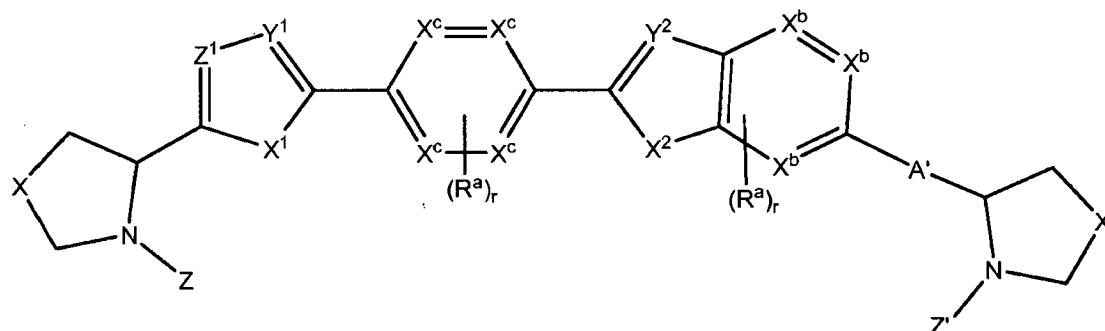


each X^b and X^c is independently C or N.

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



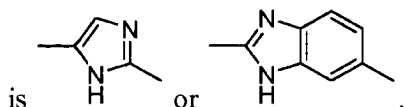
[0090] In a second embodiment of the fourth aspect, compounds have formula IVa:



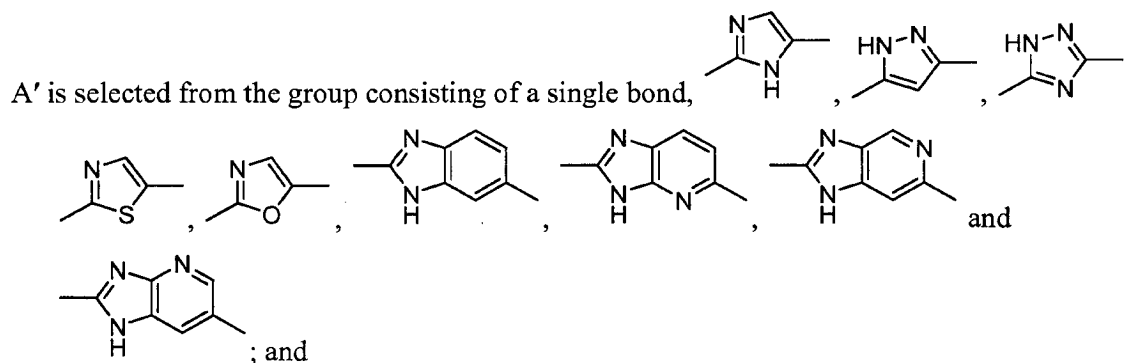
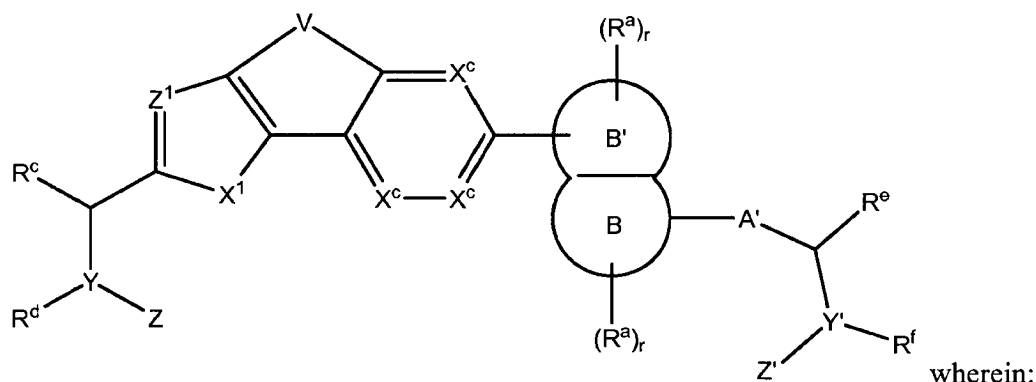
wherein X and X' are each independently selected from the group consisting of a bond,

$-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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'

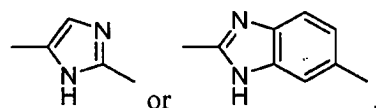


[0092] In a fifth aspect of the invention, compounds have formula V:

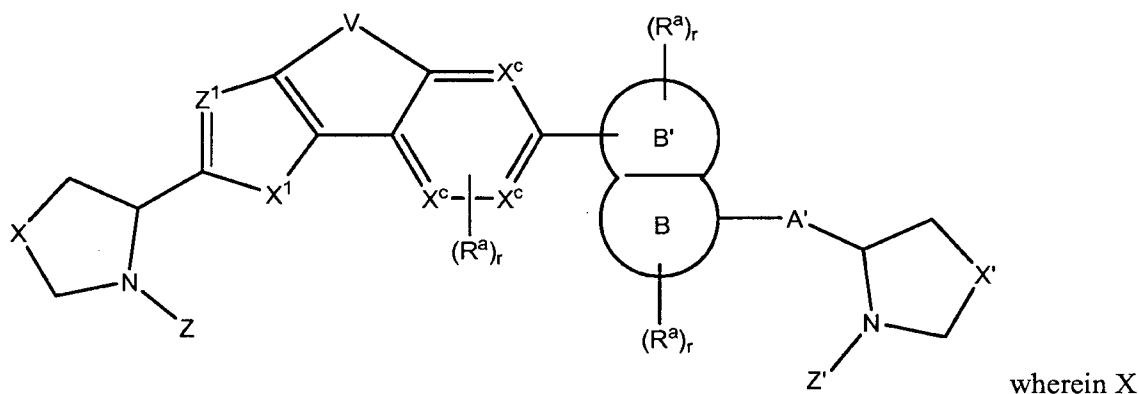


each X^c is independently C or N with the proviso that no more than two X^c are N.

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

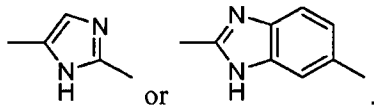


[0094] In a second embodiment of the fifth aspect, compounds have formula Va:

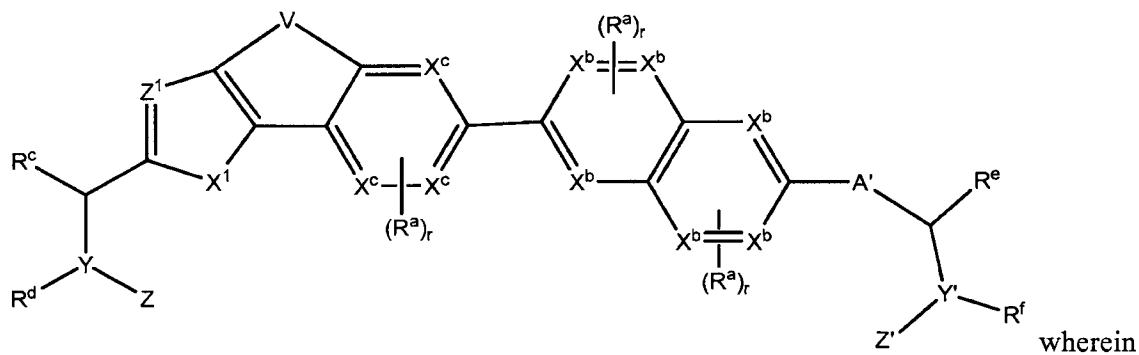


and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

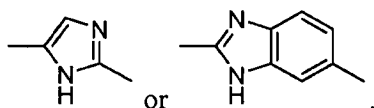


[0096] In a fourth embodiment of the fifth aspect, compounds have formula Vb:

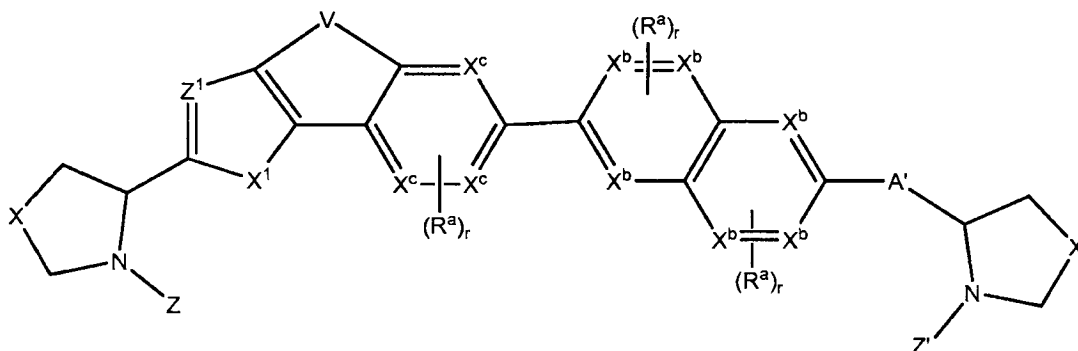


each X^b is independently C or N.

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

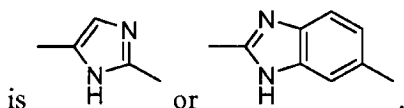


[0098] In a sixth embodiment of the fifth aspect, compounds have formula Vc:

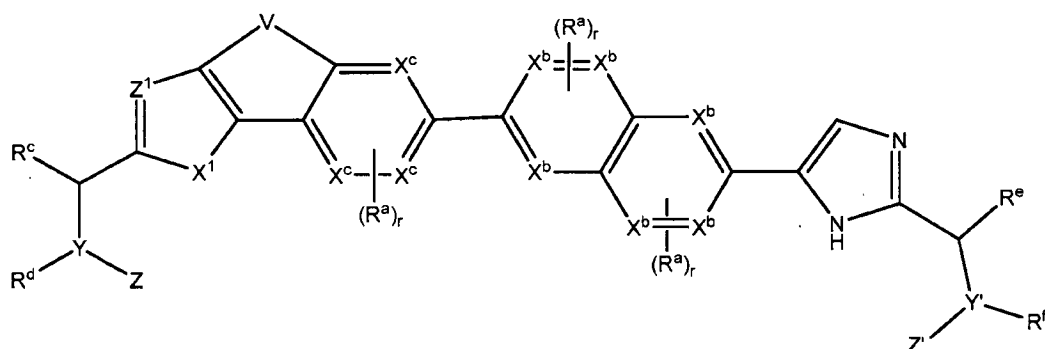


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

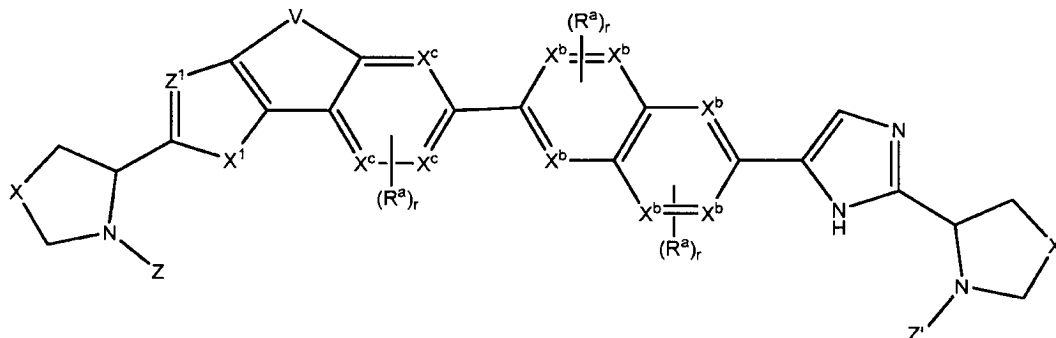
[0099] In a seventh embodiment of the fifth aspect, compounds have formula Vc wherein A' is



[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, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 $-\text{CN}$, $-\text{OCHF}_2$, $-\text{OCF}_3$, $-\text{CF}_3$, or $-\text{F}$.

[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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[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, -NO₂, CO₂R, 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, SO₂R, -SO₃R, -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, trifluoromethoxy and the like. It also includes divalent substituents linked to two separated oxygen atoms such as, without limitation, -O-(CH₂)₁₋₄-O-, -O-CF₂-O-, -O-(CH₂)₁₋₄-O-(CH₂CH₂-O)₁₋₄- and -(O-CH₂CH₂-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, -NO₂, -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, -SO₂R, -SO₃R, -S(O)₂N(R^N)₂, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

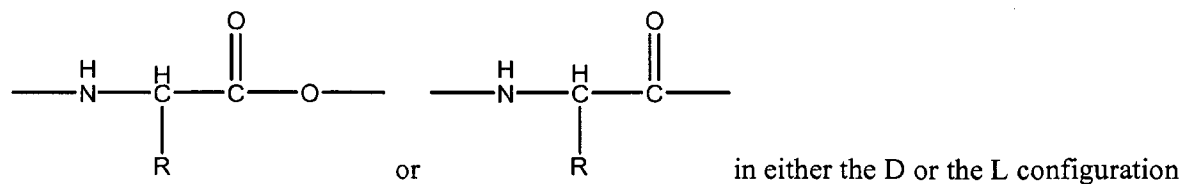
[0139] The term “alkylene,” “alkenylene” and “alkynylene” as used herein refers to the groups “alkyl,” “alkenyl” and “alkynyl” respectively, when they are divalent, ie, attached to two atoms.

[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-butyne, 3-methyl-1-butyne and the like. The alkynyl group may be optionally substituted with one or more substituents selected from halo, -CN, NO₂, CO₂R, 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, -SO₂R, -SO₃R, -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^N₂.

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



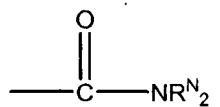
and includes but is not limited to the twenty “standard” amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine and histidine. The present invention 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, -NO₂, -CO₂R, -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, -SO₂R, -SO₃R, -S(O)₂N(R^N)₂, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

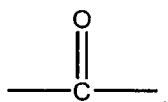
[0145] The terms “aryl,” “aromatic group” or “aromatic ring” as used herein contemplates substituted or unsubstituted single-ring and multiple aromatic groups (for example, phenyl, pyridyl and pyrazole, etc.) and polycyclic ring systems (naphthyl and quinoliny, etc.). The polycyclic rings may have two or more rings in which two atoms are common to two adjoining rings (the rings are “fused”) wherein at least one of the rings is aromatic, e.g., the other rings can be cycloalkyls, cycloalkenyls, aryl, heterocycles and/or heteroaryls. The aryl group may be optionally substituted with one or more substituents selected from halogen, alkyl, -CN, -NO₂, -CO₂R, -C(O)R, -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, -SO₂R, -SO₃R, -S(O)₂N(R^N)₂, -SiR₃, -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).

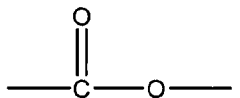
[0147] The term “carbamoyl” as used herein contemplates a group of the structure



[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, -NO₂, -CO₂R, -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, -SO₂R, -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, -NO₂, -CO₂R, -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, -SO₂R, -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, pyrazolopyridine and the like. The heterocyclic group may be optionally substituted with one or more substituents selected from the group consisting of halo, alkyl, -CN, -NO₂, -CO₂R, -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, -SO₂R, -SO₃R, -S(O)₂N(R^N)₂, -SiR₃, -P(O)R, phosphate, phosphonate, cycloalkyl, cycloalkenyl, aryl and heteroaryl.

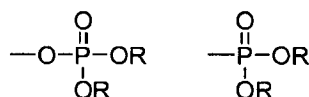
[0156] The term “oxo” as used herein contemplates an oxygen atom attached with a double bond.

[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

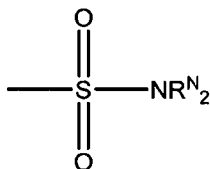
hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric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

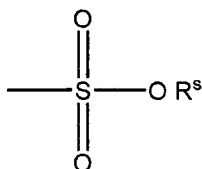


[0160] The terms “salts” and “hydrates” refers to the hydrated forms of the compound that would favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which 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

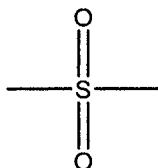


[0162] The term “sulfonate” as used herein contemplates a group having the structure

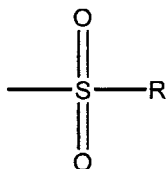


wherein R^s is selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkanoyl, or C₁-C₁₀ alkoxy carbonyl.

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



[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.

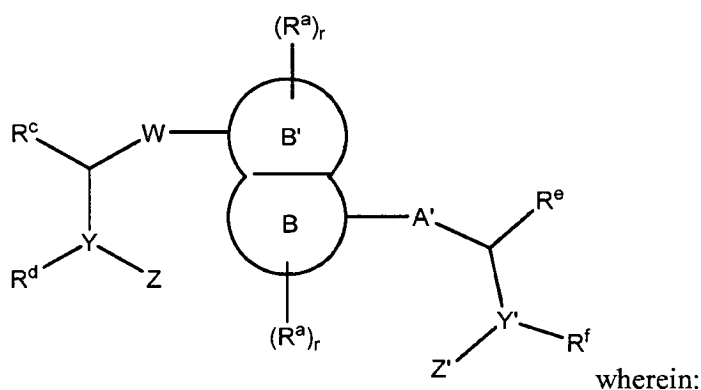
[0166] Each R is independently selected from hydrogen, -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide, amino, and oxo.

[0167] Each R^N is independently selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and

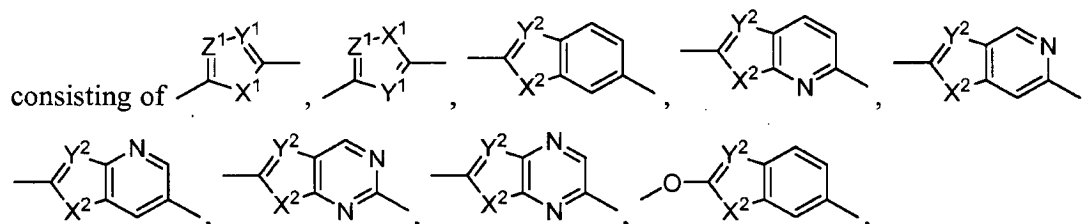
sulfonamide. Two R^N may be taken together with C, O, N or S to which they are attached to form a five to seven membered ring which may optionally contain a further heteroatom.

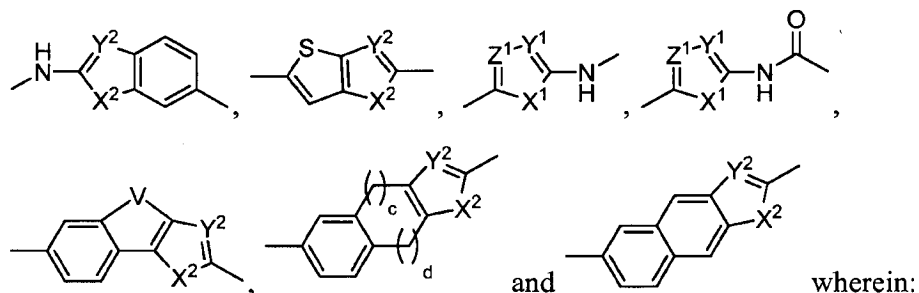
[0168] The compounds of the present invention may be used to inhibit or reduce the activity of HCV, particularly HCV's NS5A protein. In these contexts, inhibition and reduction of activity of the NS5A protein refers to a lower level of the measured activity relative to a control experiment in which the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



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



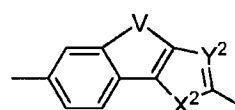


X^1 is CH_2 , NH , O or S ,

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

X^2 is NH , O or S ,

V is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $(\text{CH}_2)_a-\text{N}(\text{R}^N)-(\text{CH}_2)_b-$ or $-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-$,
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, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, 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 $-\text{OH}$, 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,

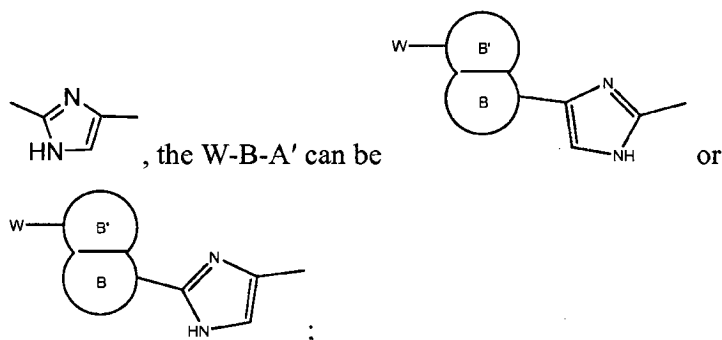
n and p are independently 0, 1, 2 or 3,

k is 0, 1, or 2,

each R is independently selected from the group consisting of hydrogen, halogen, -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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



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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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;

[illegible]

wherein:

X¹ is CH₂, 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 $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $(\text{CH}_2)_a-\text{N}(\text{R}^{\text{N}})-(\text{CH}_2)_b-$ or $-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-$,
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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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, C₁ to C₈ alkyl, C₁

to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, 1-3 amino acids, $-\text{[U-(CR}^4_2)_t\text{-NR}^5\text{-C(R}^4_2)_t\text{]}_u\text{-U-(CR}^4_2)_t\text{-NR}^7\text{-(CR}^4_2)_t\text{-R}^8$, $-\text{U-(CR}^4_2)_t\text{-R}^8$, and $-\text{[U-(CR}^4_2)_t\text{-NR}^5\text{-(CR}^4_2)_t\text{]}_u\text{-U-(CR}^4_2)_t\text{-O-(CR}^4_2)_t\text{-R}^8$, wherein,

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

each R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

R⁸ is selected from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-\text{C(O)-R}^{81}$, $-\text{C(S)-R}^{81}$, $-\text{C(O)-O-R}^{81}$, $-\text{C(O)-N-R}^{81}_2$, $-\text{S(O)}_2\text{-R}^{81}$ and $-\text{S(O)}_2\text{-N-R}^{81}_2$, wherein each R⁸¹ is independently chosen from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

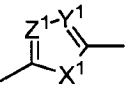
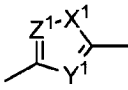
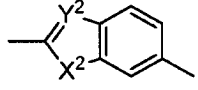
optionally, R⁷ and R⁸ together form a 4-7 membered ring,

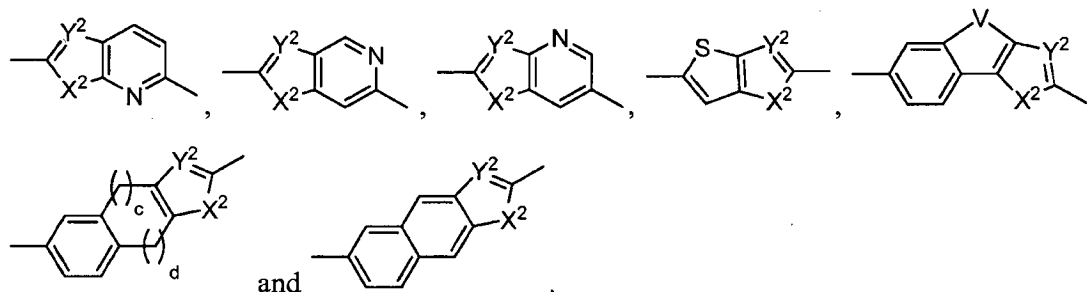
each t is independently 0, 1, 2, 3, or 4, and

u is 0, 1, or 2.

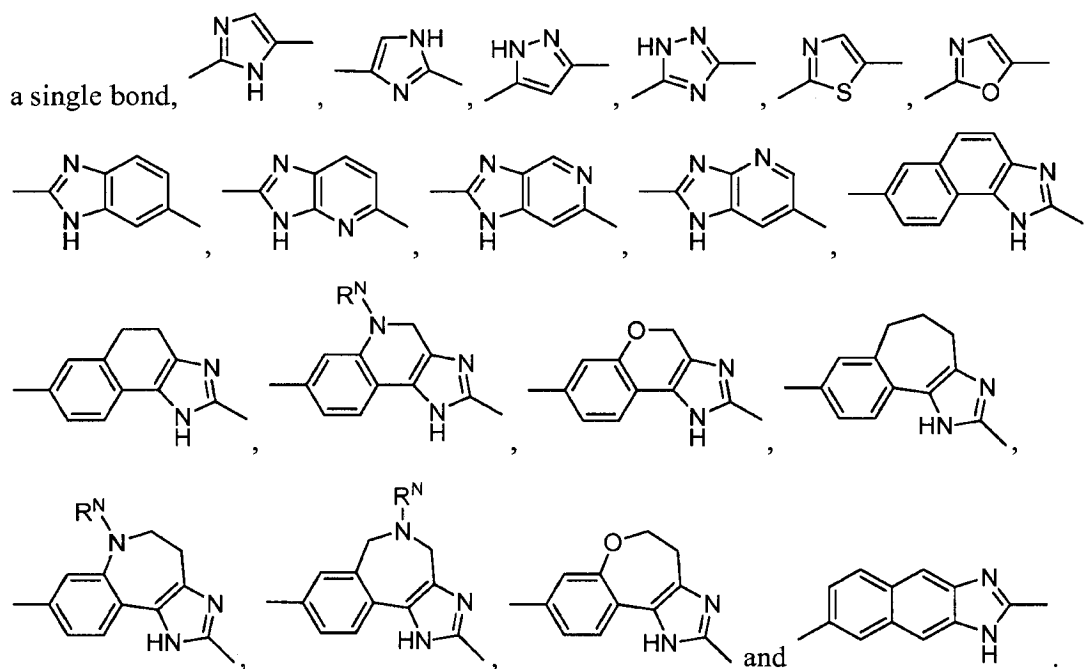
[0170] The compounds of the present invention include pharmaceutically acceptable salts of I as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0171] In a first embodiment of the first aspect, A' is selected from the group consisting of a single bond, $-(\text{CR}_2)_n\text{-O-(CR}_2)_p-$, $-(\text{CR}_2)_n\text{-N(R}^N\text{)-(CR}_2)_p-$, $-(\text{CR}_2)_n\text{-C(O)-N(R}^N\text{)-(CR}_2)_p-$, $-(\text{CR}_2)_n\text{-N(R}^N\text{)-C(O)-N(R}^N\text{)-(CR}_2)_p-$ and $-(\text{CR}_2)_n\text{-N(R}^N\text{)-C(O)-O-(CR}_2)_p-$ and a heteroaryl

group selected from the group consisting of , , ,



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



[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,

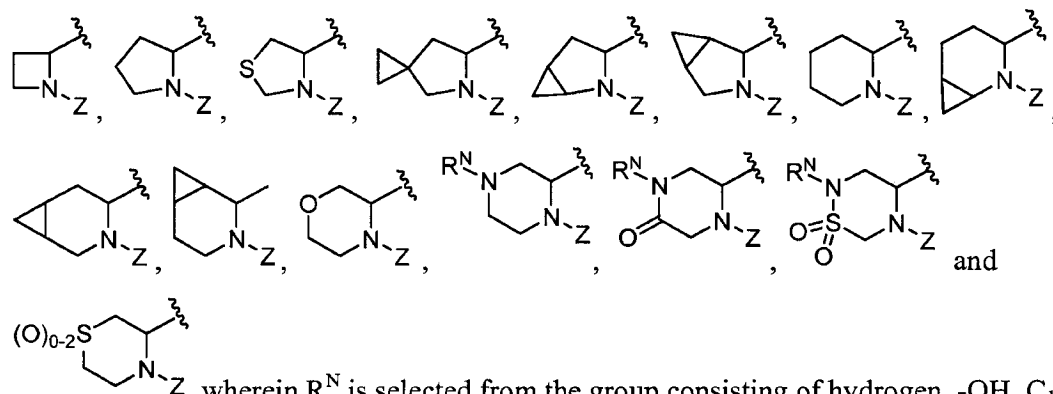
each hetero atom, if present, is independently N, O or S,

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.

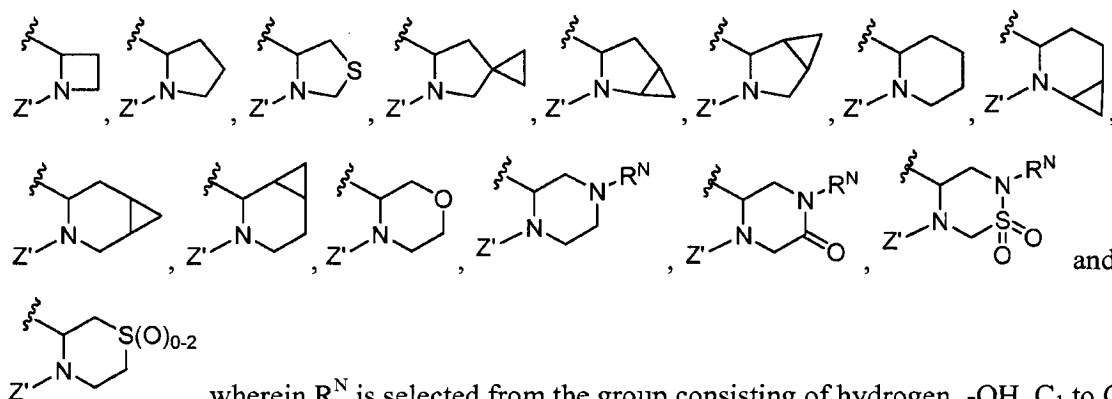
[0174] In a fourth embodiment of the first aspect, R^c and R^d or R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6-membered heterocycle.

[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:



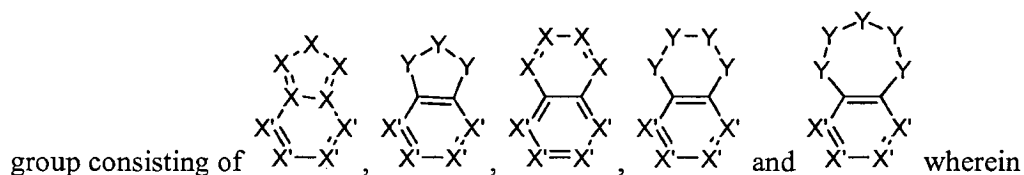
alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

[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:



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



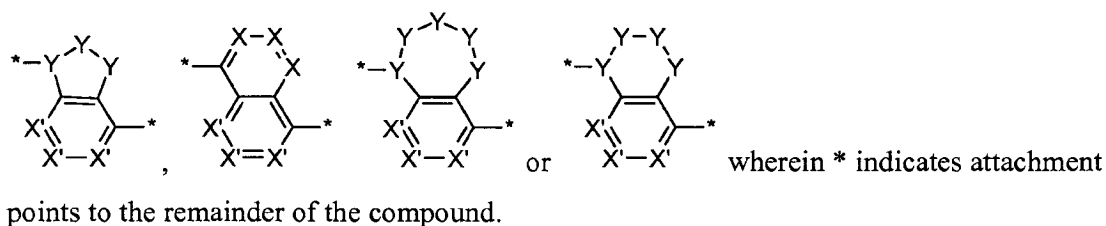
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

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

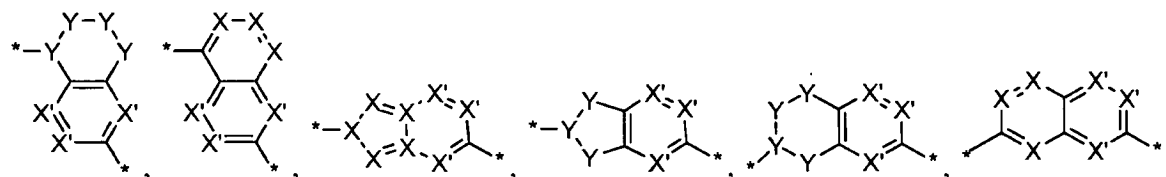
each Y is independently selected from -CH₂-, -NH-, -O-, -S-, -C(O)₂-, or -S(O)₁₋₂-; and

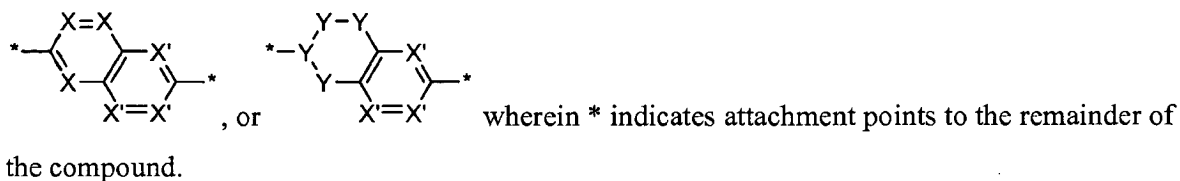
B and B' attach to the remainder of the compound at any available attachment point on the molecule.

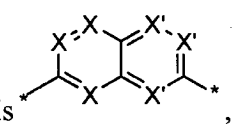
[0178] In an eighth embodiment of the first aspect, B and B' together is

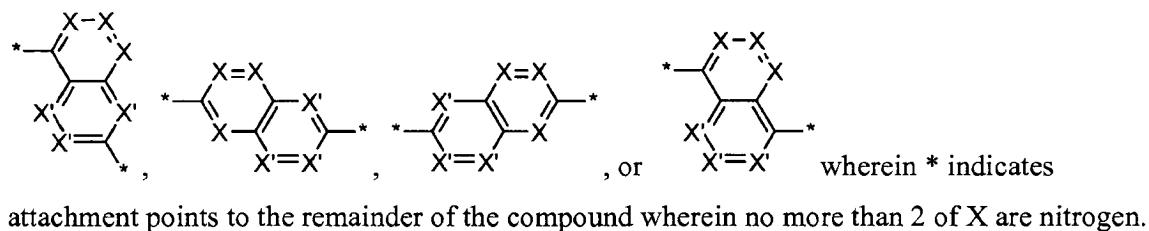


[0179] In a ninth embodiment of the first aspect, B and B' together is

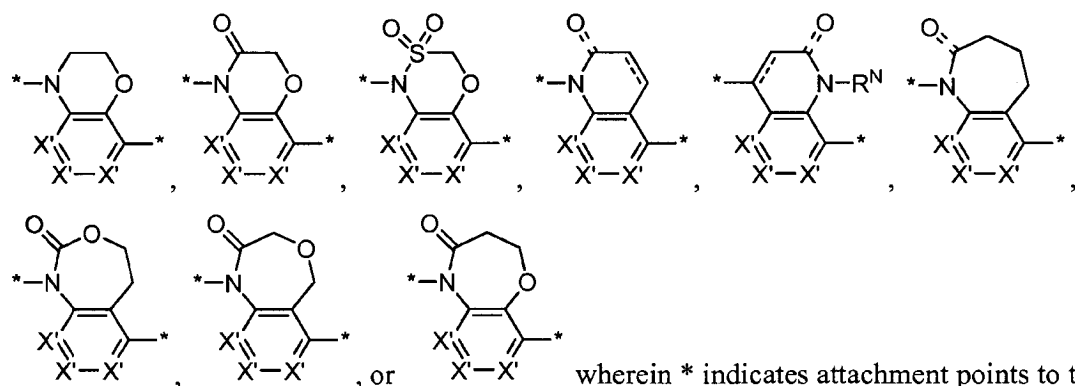




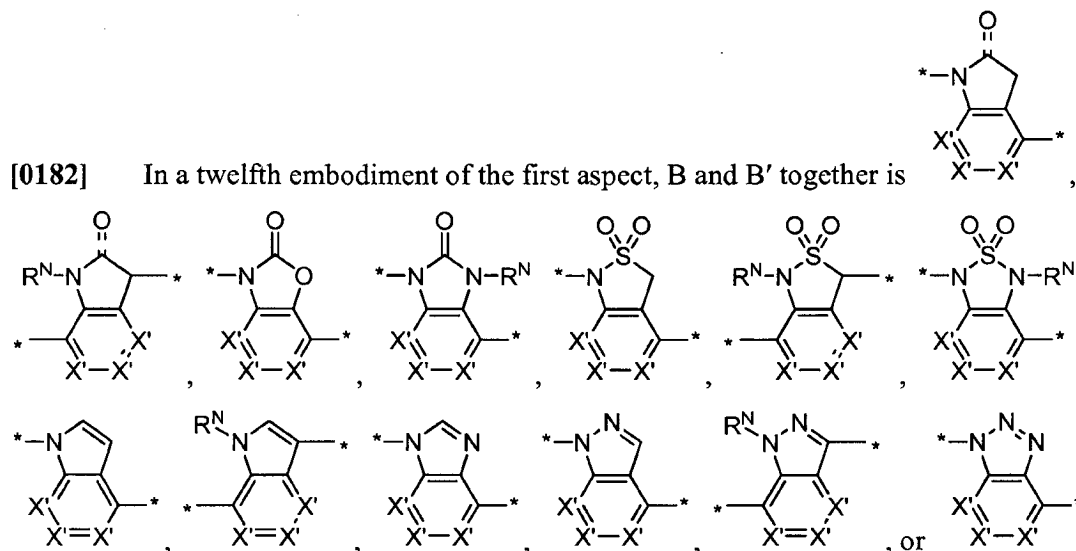
[0180] In a tenth embodiment of the first aspect, B and B' together is ,



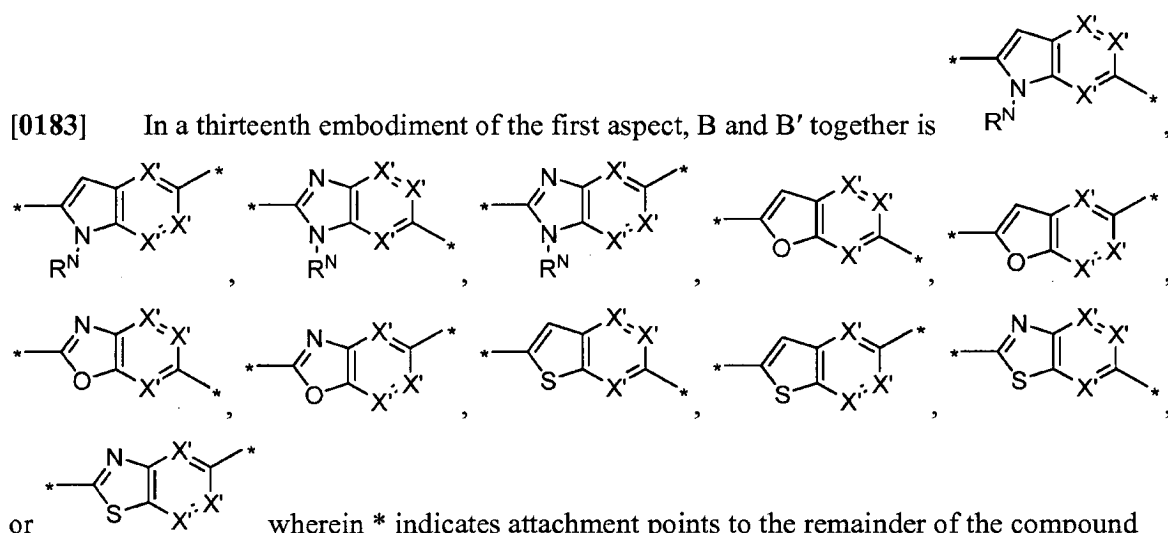
[0181] In an eleventh embodiment of the first aspect, B and B' together is



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.

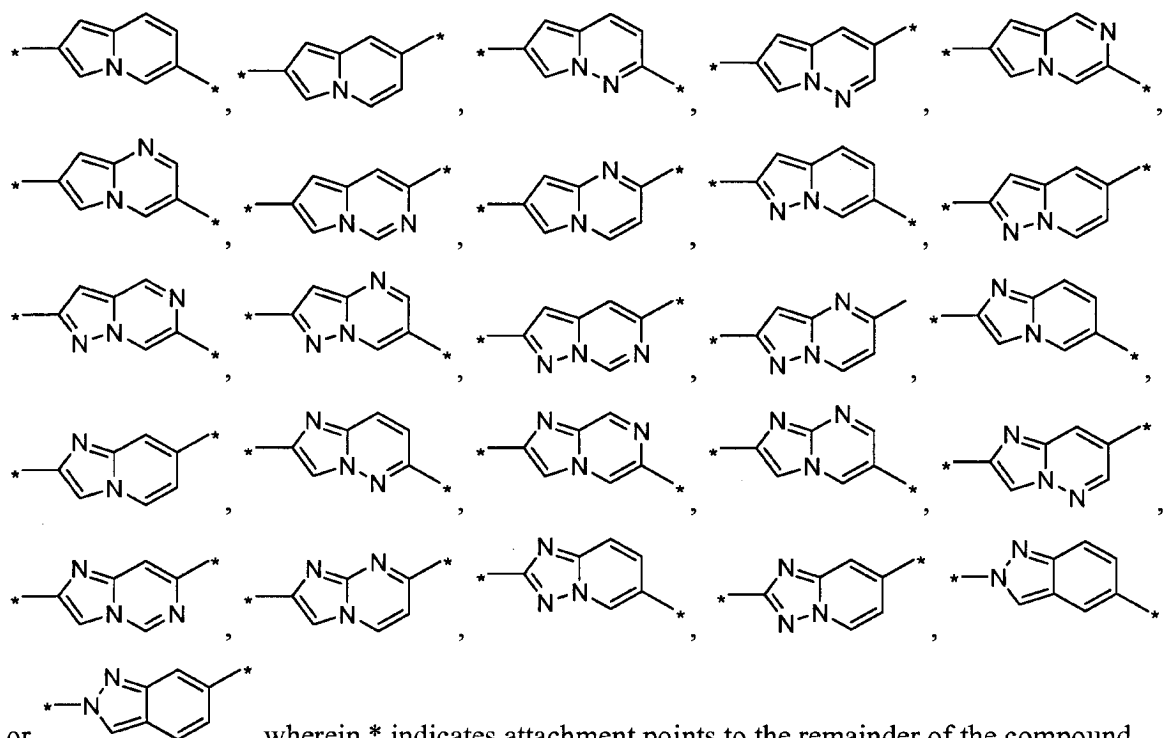


wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.



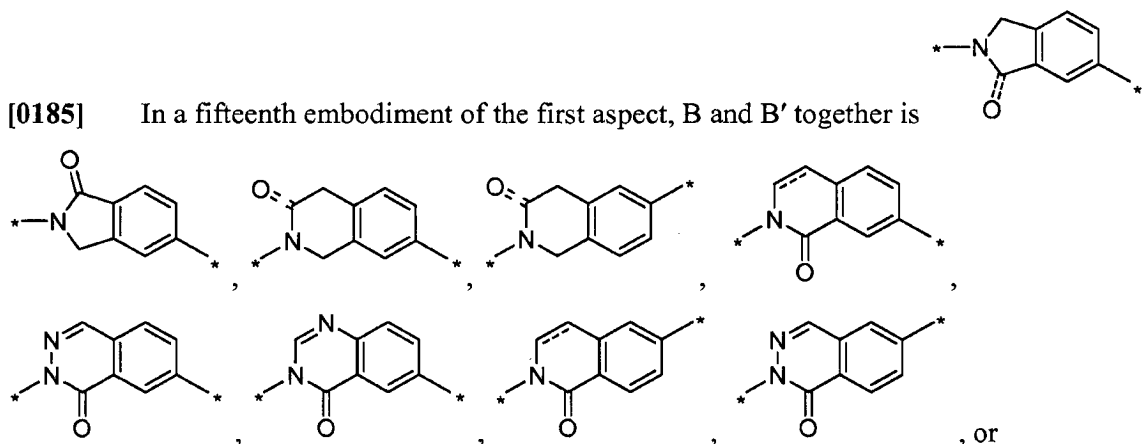
or  wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl,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

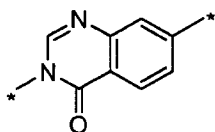
[0184] In a fourteenth embodiment of the first aspect, B and B' together is



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.

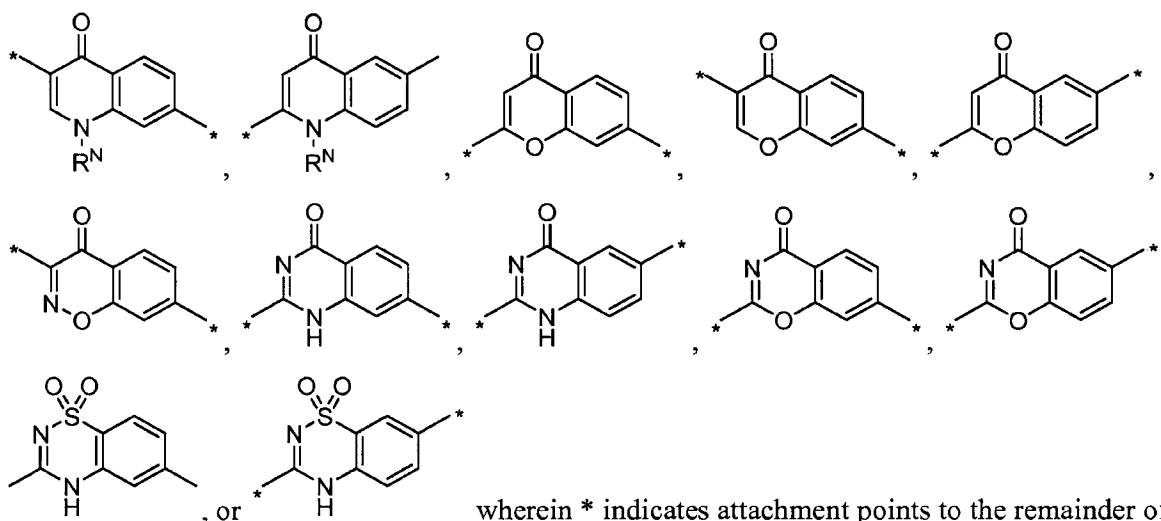
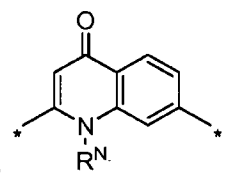
[0185] In a fifteenth embodiment of the first aspect, B and B' together is





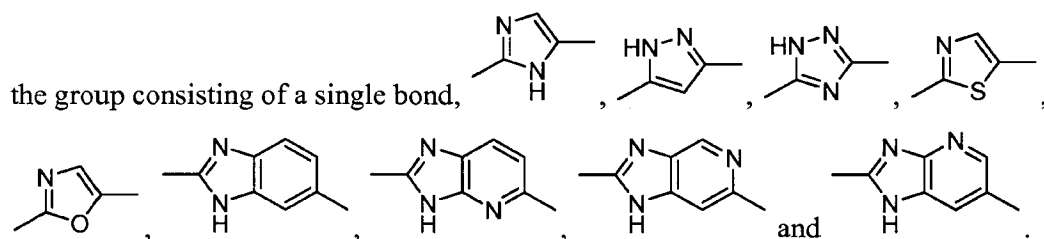
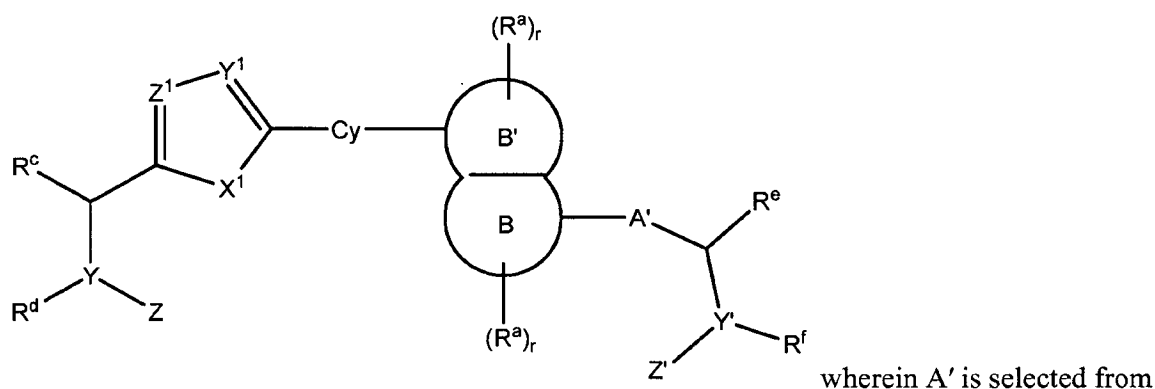
wherein * indicates attachment points to the remainder of the compound and the phenyl moiety optionally contains one or two nitrogens as heteroatoms.

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

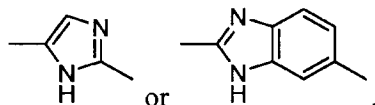


wherein * indicates attachment points to the remainder of the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

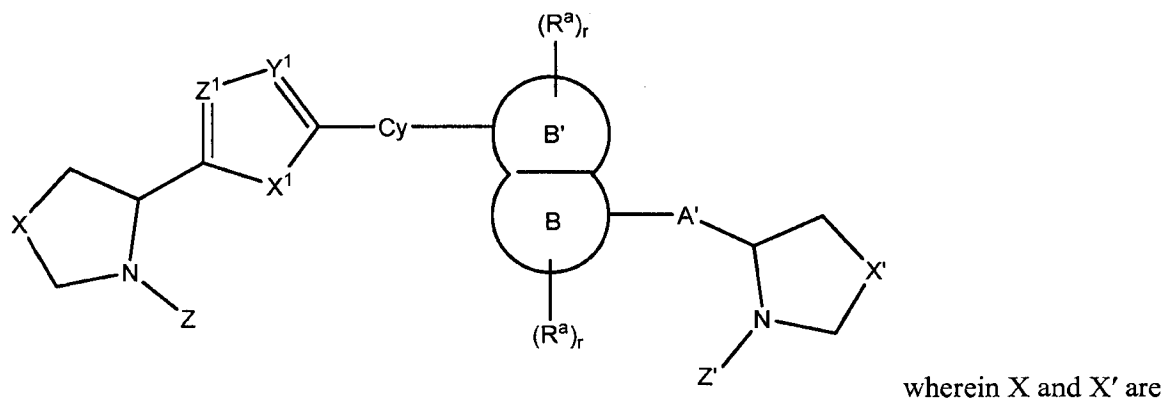
[0187] In a second aspect of the invention, compounds have formula II:



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



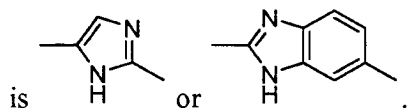
[0189] In a second embodiment of the second aspect, compounds have formula IIa:



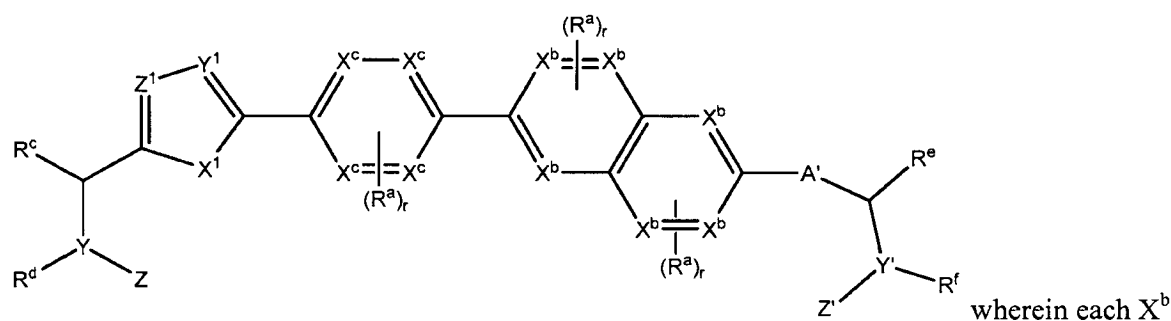
each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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'



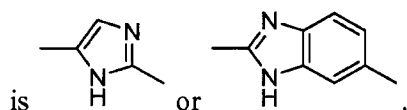
[0192] In a fourth embodiment of the second aspect, compounds have formula IIb:



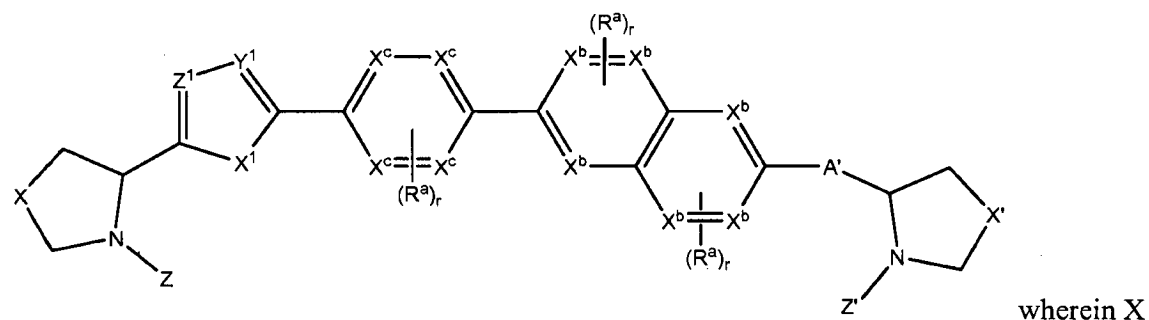
and X^c is independently C or N.

[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'



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

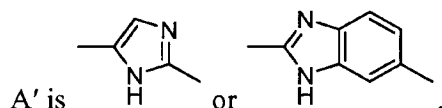


and X' are each independently selected from the group consisting of a bond, -CH₂-, -CH₂-CH₂-, -CH=CH-, -O-, -S-, -S(O)₁₋₂-, -CH₂O-, -CH₂S-, -CH₂S(O)₁₋₂- and

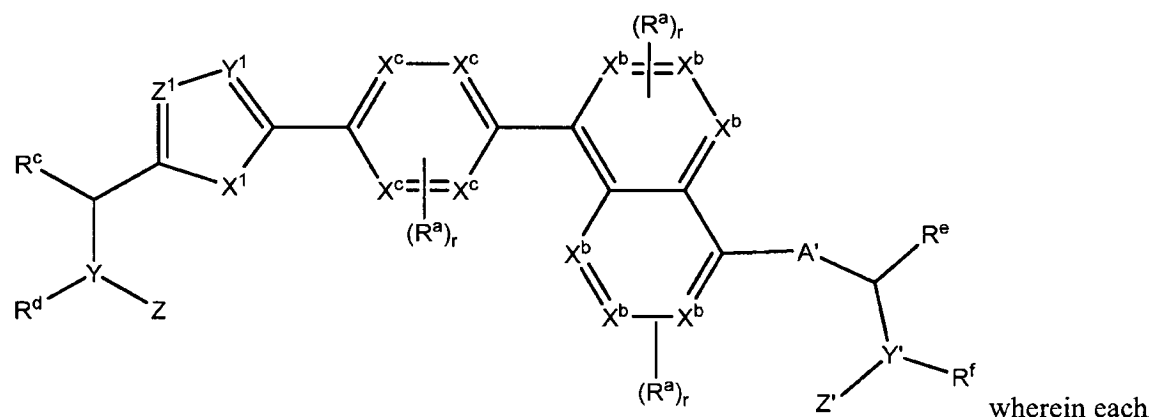
$-\text{CH}_2\text{N}(\text{R}^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[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



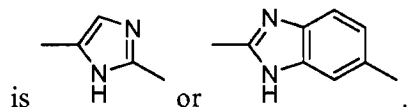
[0198] In an eighth embodiment of the second aspect, compounds have formula IIc:



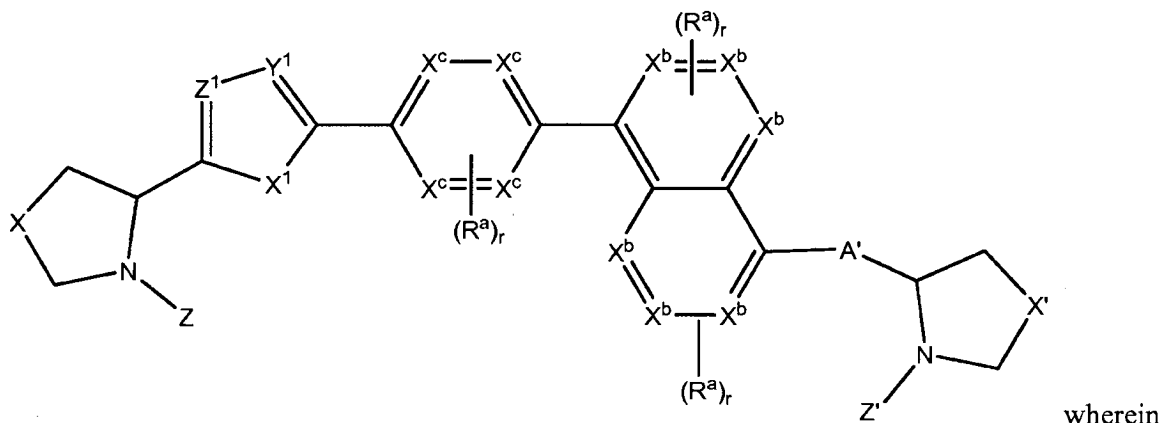
X^b and X^c is independently C or N.

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

[0200] In a ninth embodiment of the second aspect, compounds have formula IIc wherein A'



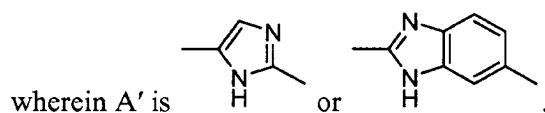
[0201] In a tenth embodiment of the second aspect, compounds have formula IIc:



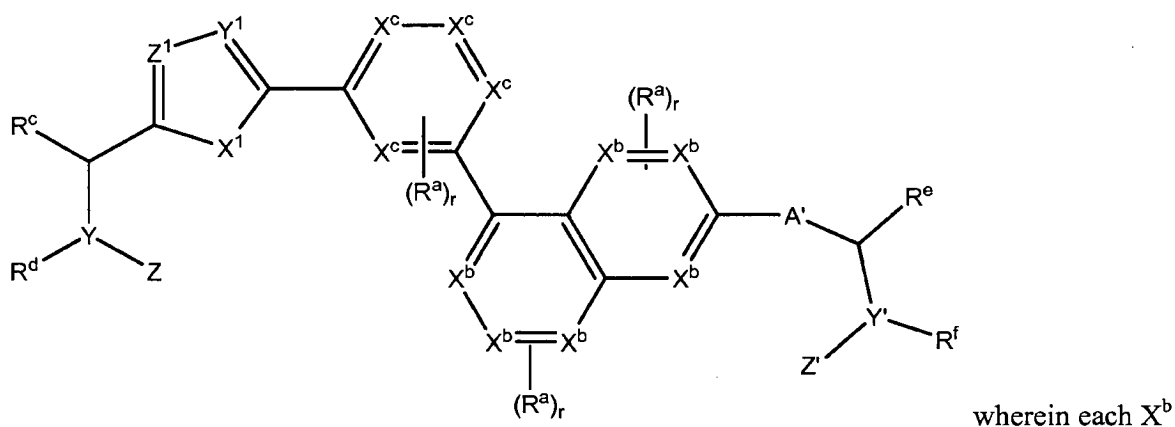
X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 IIc as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

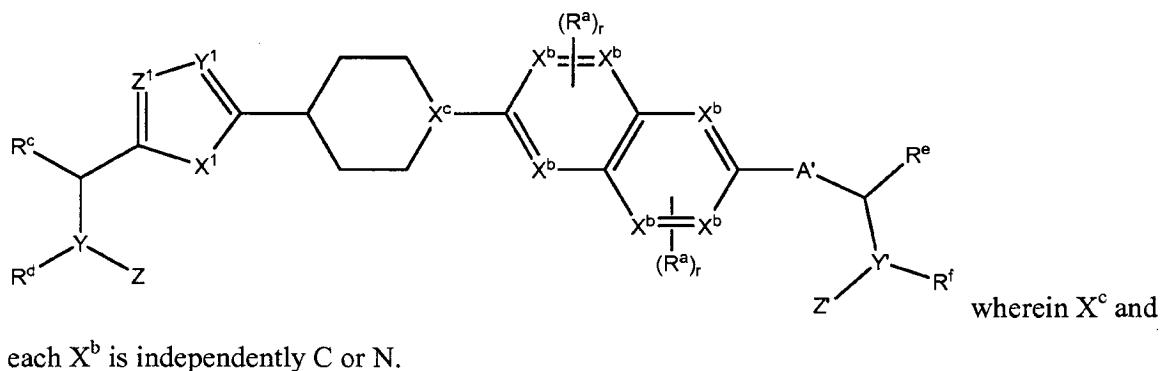
[0203] In an eleventh embodiment of the second aspect, compounds have formula IIc



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

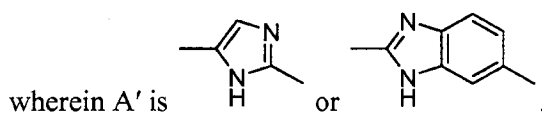


and X^c is independently C or N.

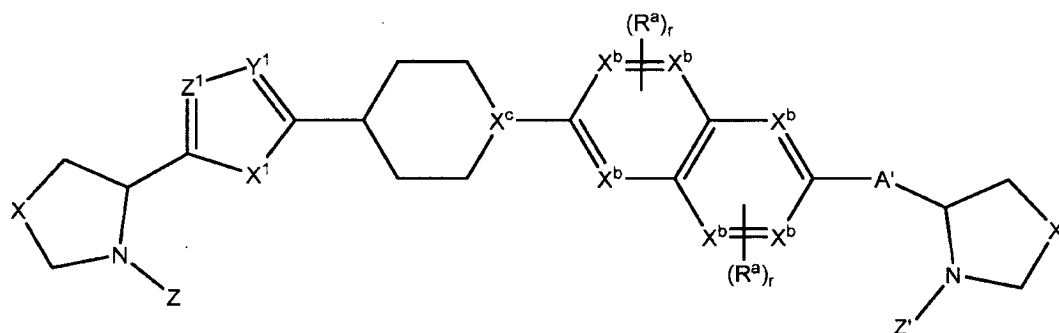


[0211] The compounds of the present invention include pharmaceutically acceptable salts of IIh as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0212] In a seventeenth embodiment of the second aspect, compounds have formula IIh



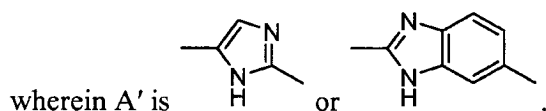
[0213] In an eighteenth embodiment of the second aspect, compounds have formula Iii:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, 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.

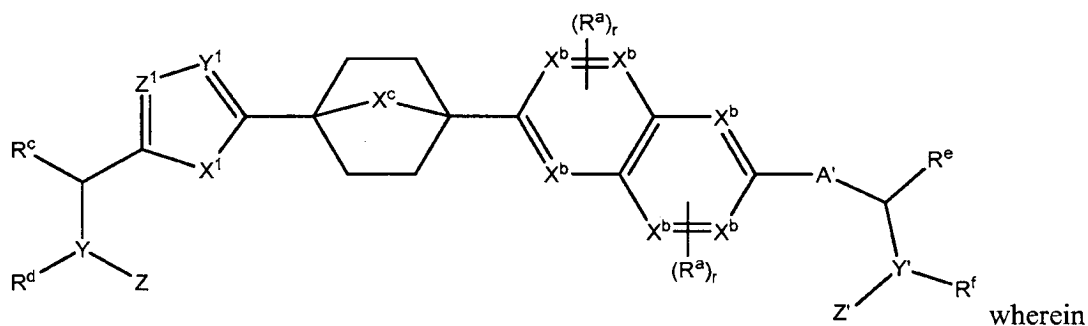
[0215] In a nineteenth embodiment of the second aspect, compounds have formula Iii



[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:

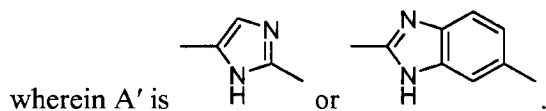


X^c is -CH₂-, -NH- or -CH₂-CH₂-, and

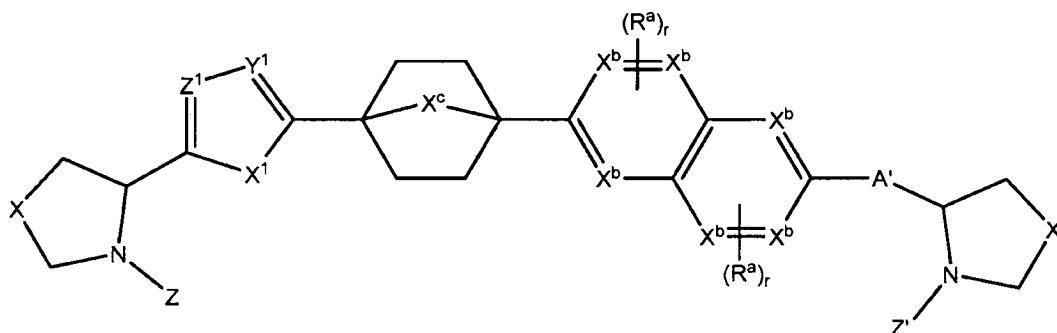
each X^b is independently C or N.

[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



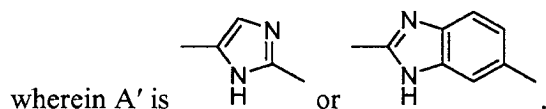
[0221] In a twenty-fourth embodiment of the second aspect, compounds have formula IIk:



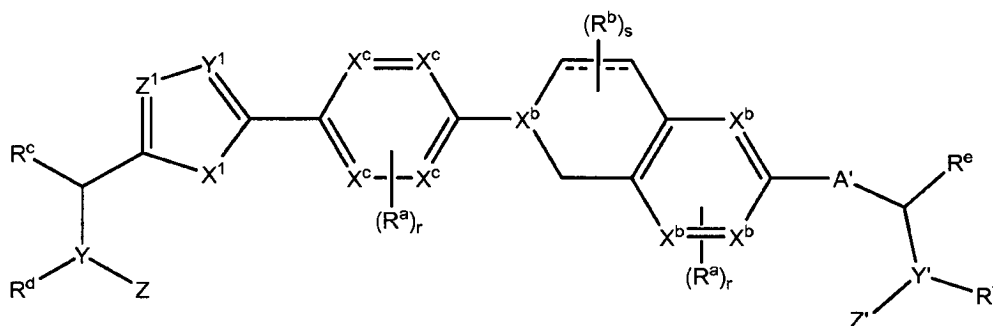
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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



[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;

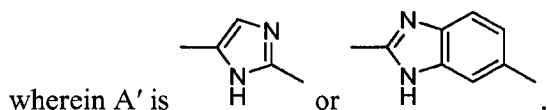
each R^b is selected from the group consisting of oxo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy,

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

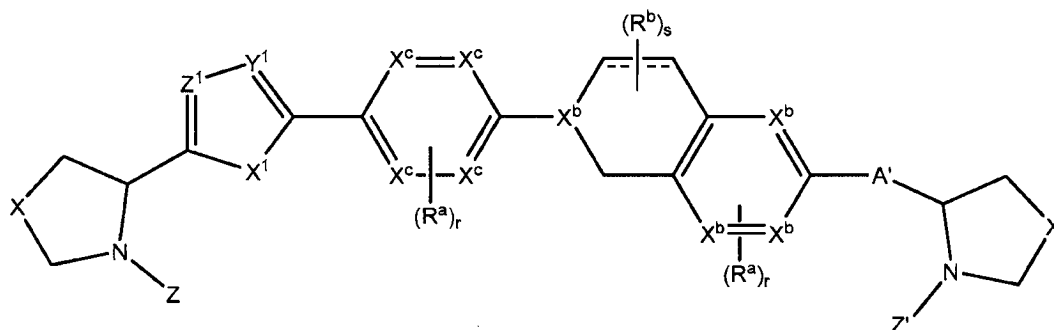
s is 0, 1, 2, or 3.

[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



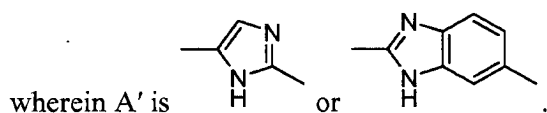
[0227] In a twenty-eighth embodiment of the second aspect, compounds have formula IIm:



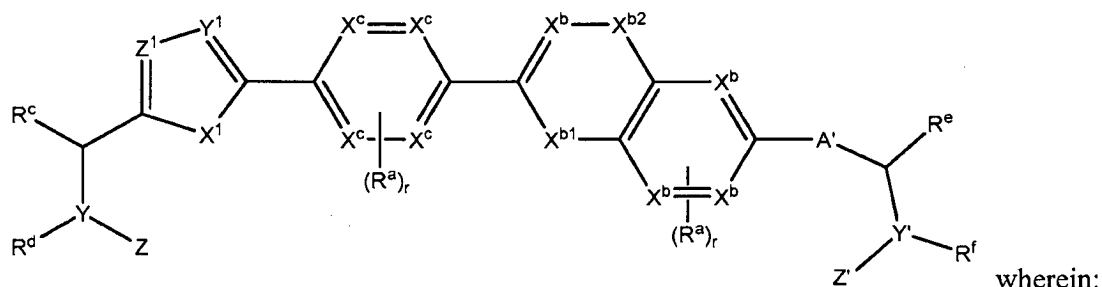
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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



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



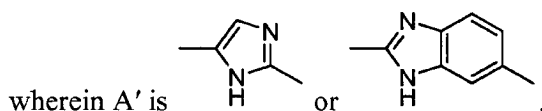
each X^b and X^c is independently C or N;

X^{b1} is N or O; and

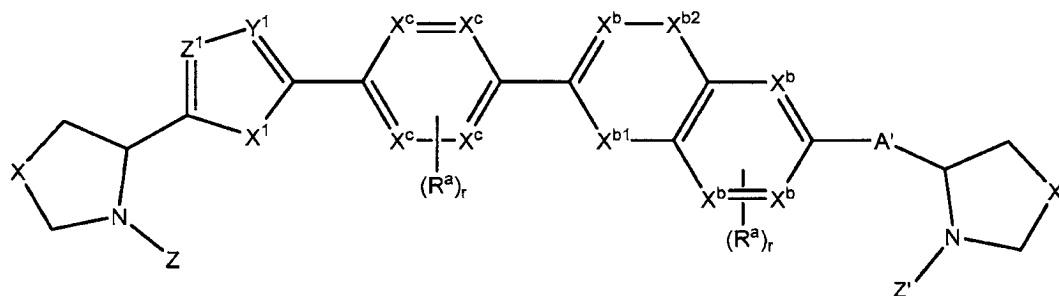
X^{b2} is $S(O)_2$ or $C(O)$.

[0231] The compounds of the present invention include pharmaceutically acceptable salts of **IIa** 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 IIIn



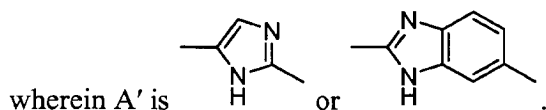
[0233] In a thirty-second embodiment of the second aspect, compounds have formula IIo:



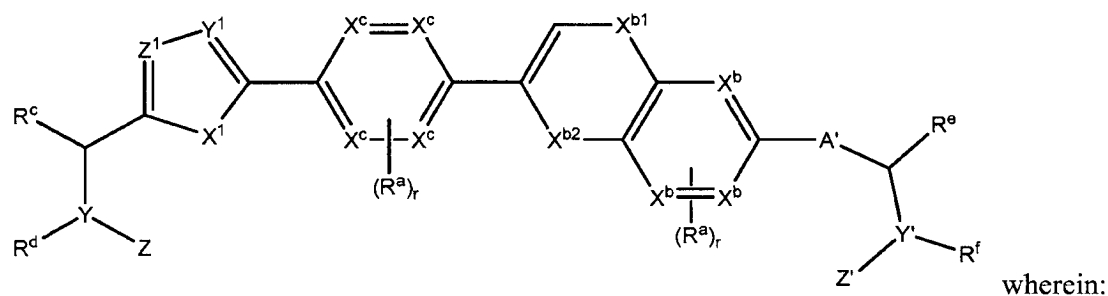
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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



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



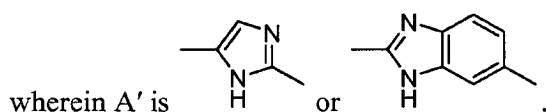
each X^b and X^c is independently C or N;

X^{b1} is N or O; and

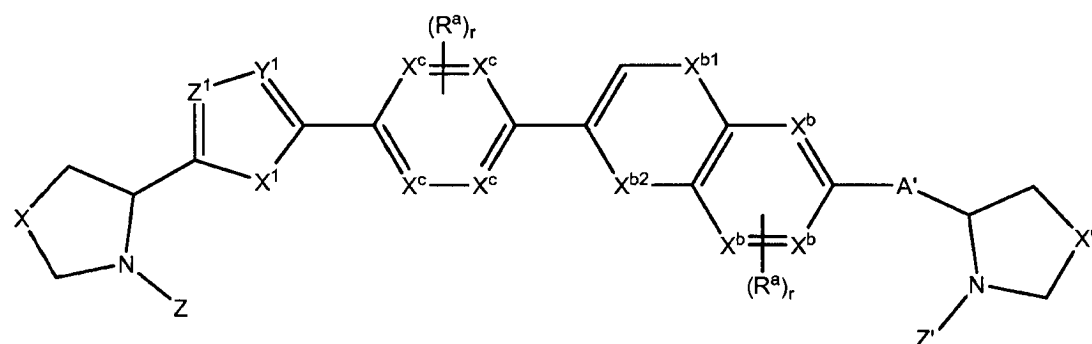
X^{b2} is $S(O)_2$ or $C(O)$.

[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



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

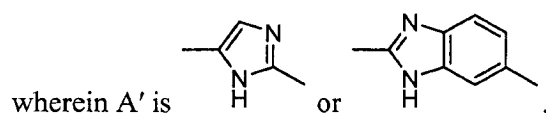


wherein X and X' are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1.2-}$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1.2-}$ and

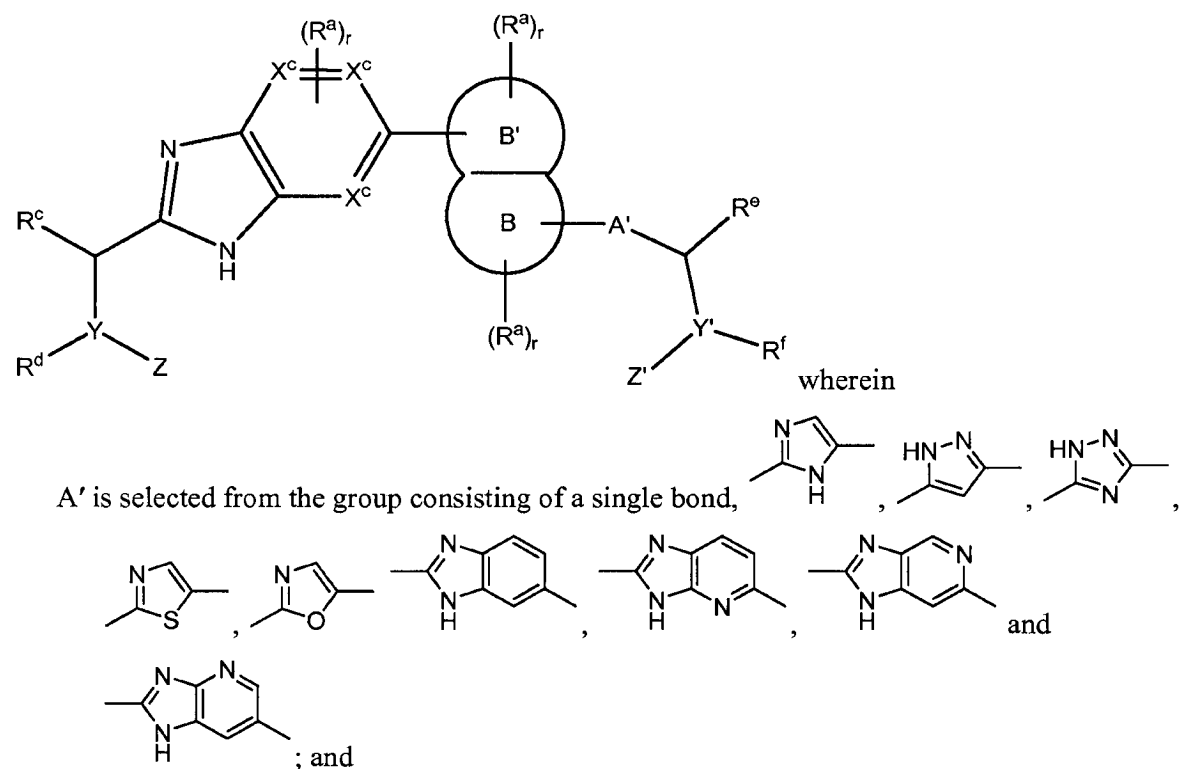
$-\text{CH}_2\text{N}(\text{R}^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

[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



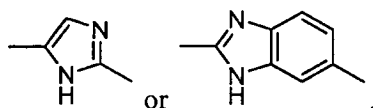
[0242] In a third aspect of the invention, compounds have formula III:



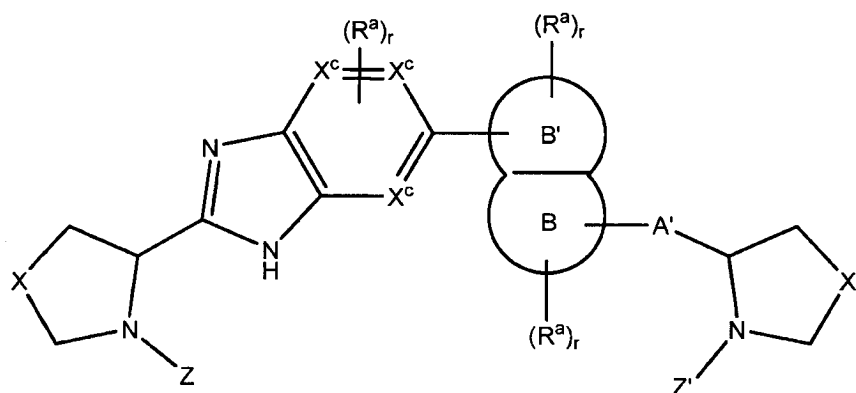
each X^c is independently C or N.

[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



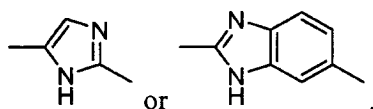
[0245] In a second embodiment of the third aspect, compounds have formula IIIa:



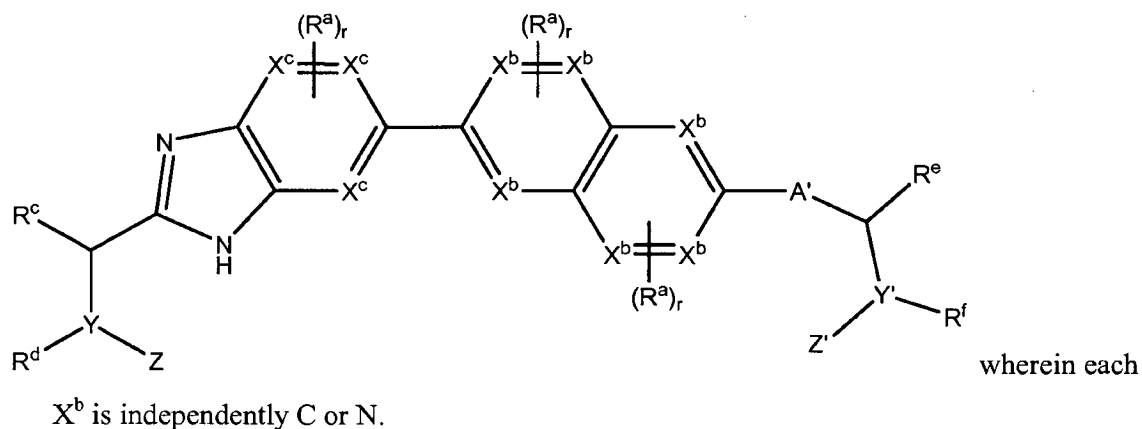
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

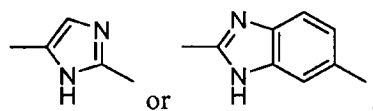


[0248] In a fourth embodiment of the third aspect, compounds have formula IIIb:

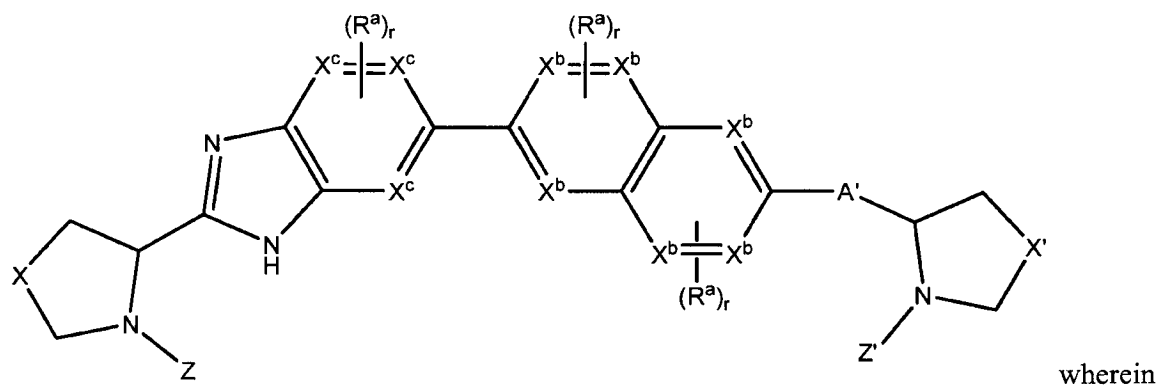


[0249] The compounds of the present invention include pharmaceutically acceptable salts of IIIb as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

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



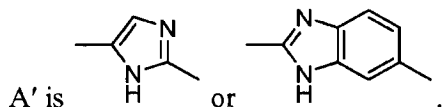
[0251] In a sixth embodiment of the third aspect, compounds have formula IIIc:



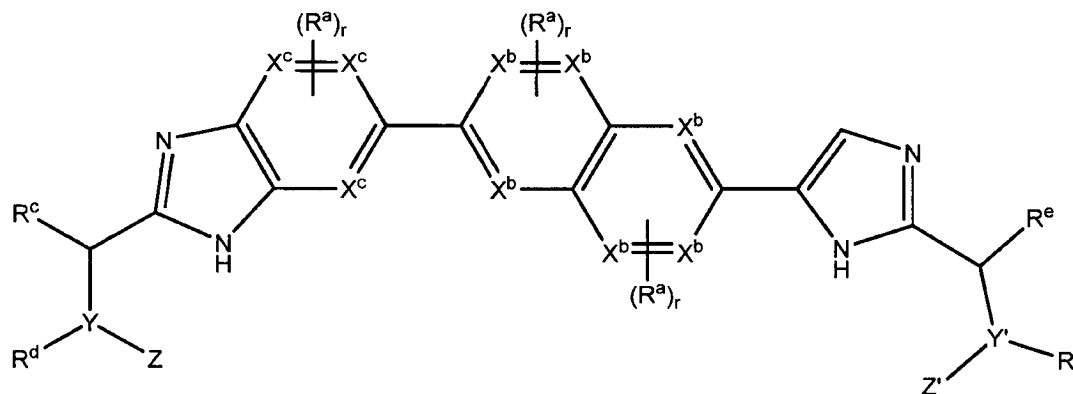
X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

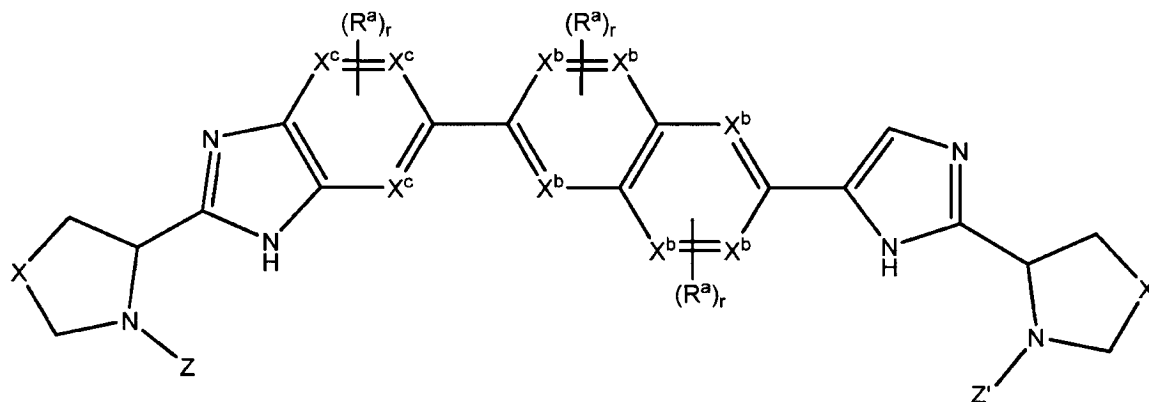


[0254] In an eighth embodiment of the third aspect, compounds have formula IIIId:



[0255] The compounds of the present invention include pharmaceutically acceptable salts of IIIId 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:

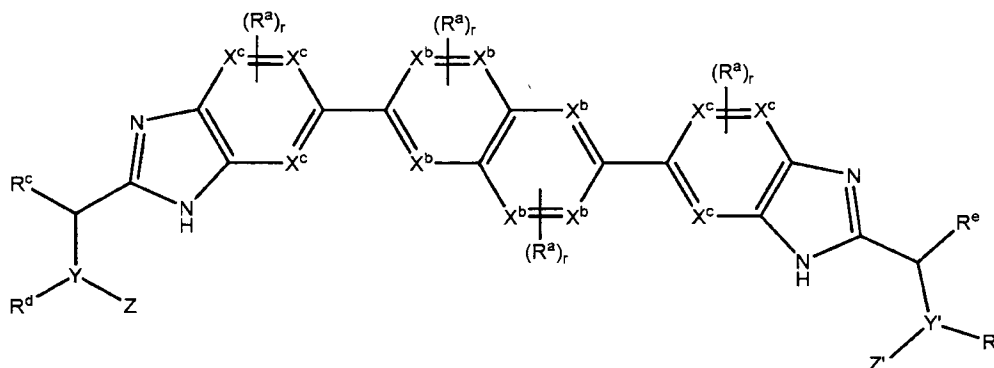


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

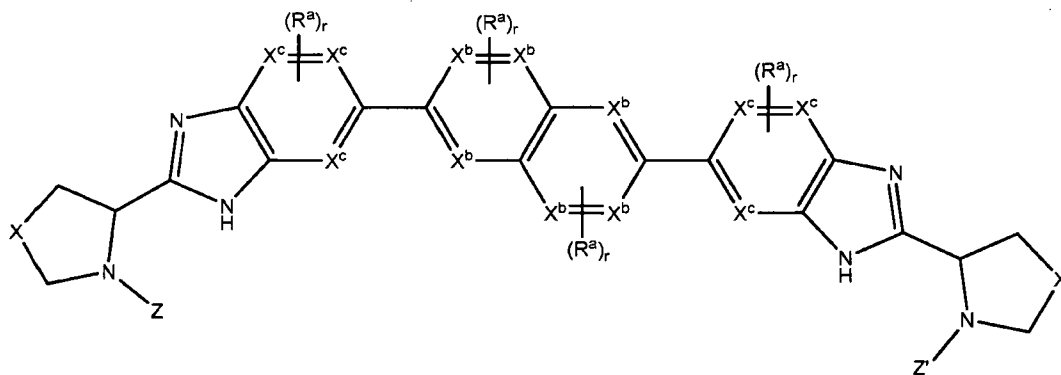
[0257] The compounds of the present invention include pharmaceutically acceptable salts of IIIe as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[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.

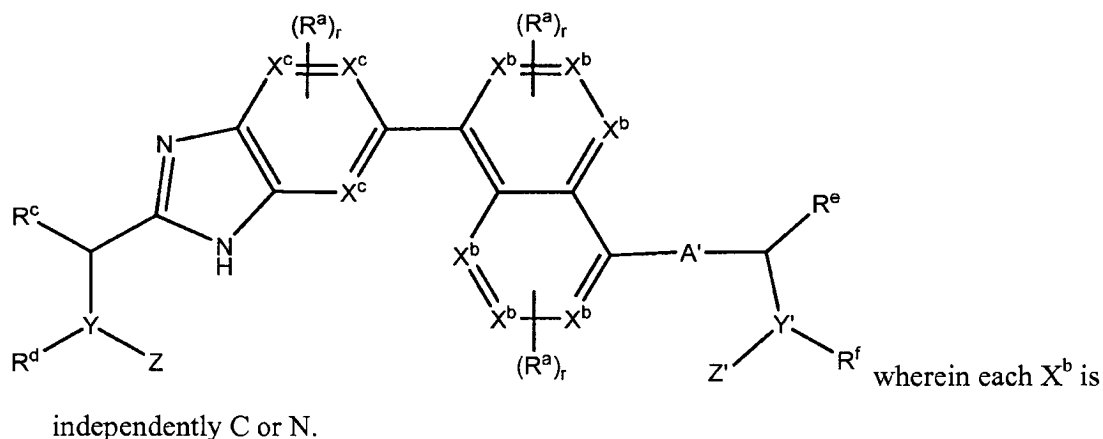
[0260] In an eleventh embodiment of the third aspect, compounds have formula IIIg:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

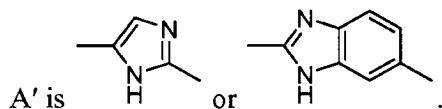
[0261] The compounds of the present invention include pharmaceutically acceptable salts of IIIg as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

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

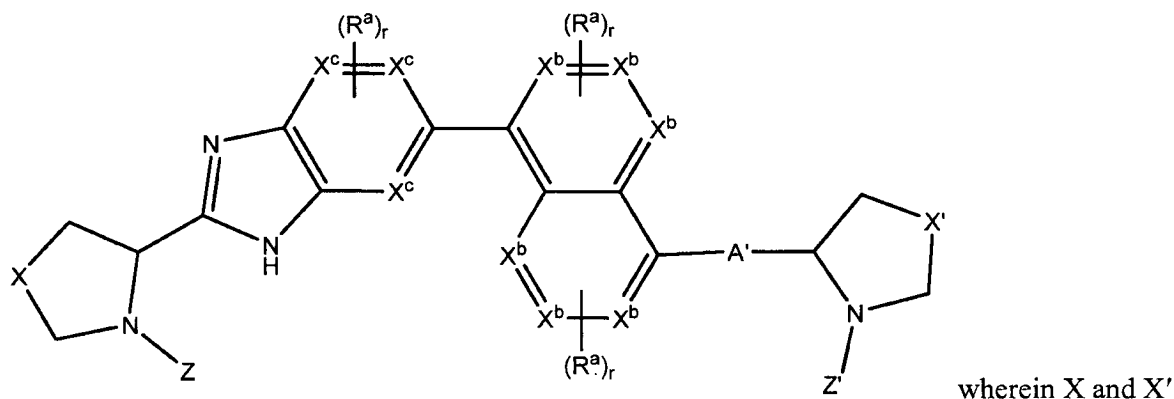


[0263] The compounds of the present invention include pharmaceutically acceptable salts of IIIh as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[0264] In a thirteenth embodiment of the third aspect, compounds have formula IIIh wherein



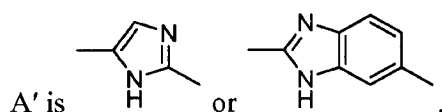
[0265] In a fourteenth embodiment of the third aspect, compounds have formula IIIi:



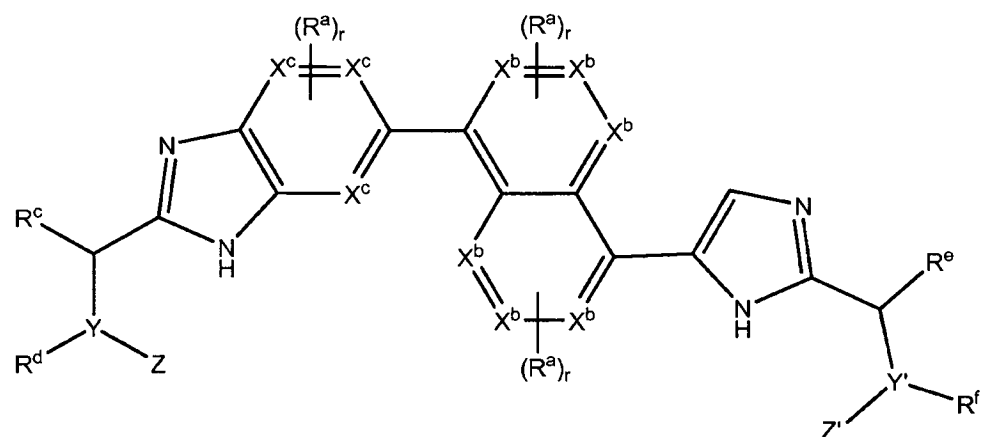
C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

[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

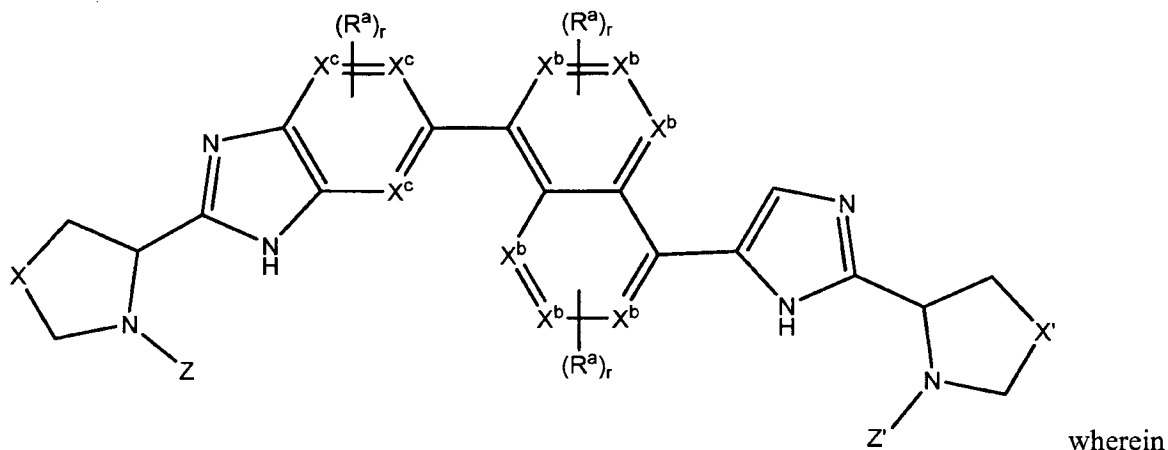


[0268] In a sixteenth embodiment of the third aspect, compounds have formula IIIj:



[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.

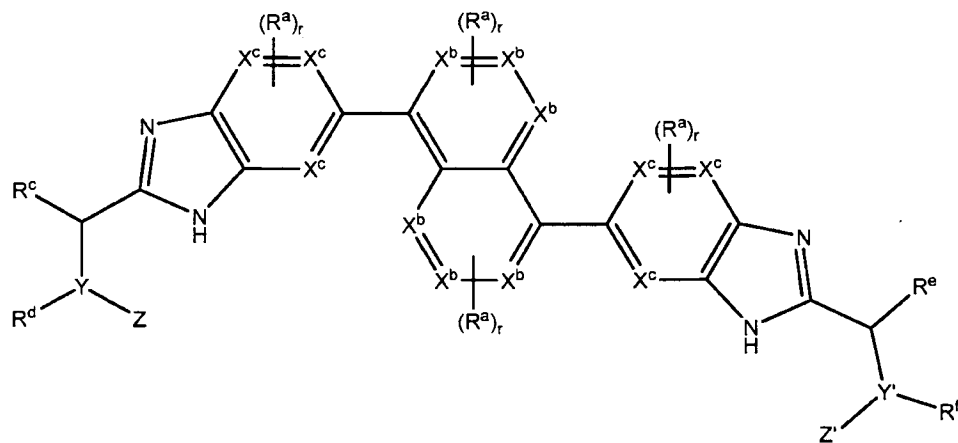
[0270] In a seventeenth embodiment of the third aspect, compounds have formula IIIk:



X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

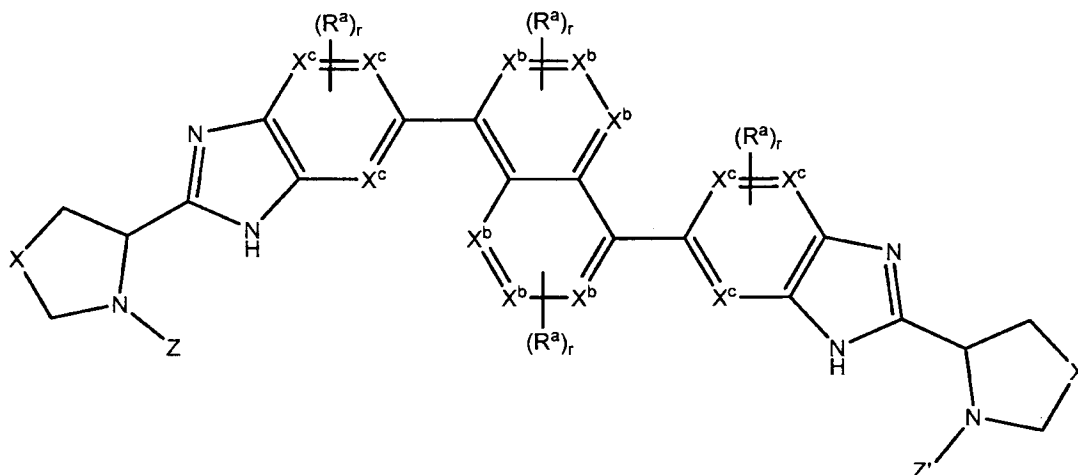
[0271] The compounds of the present invention include pharmaceutically acceptable salts of IIIk as well as an optically pure enantiomer, racemate or diastereomeric mixtures thereof.

[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.

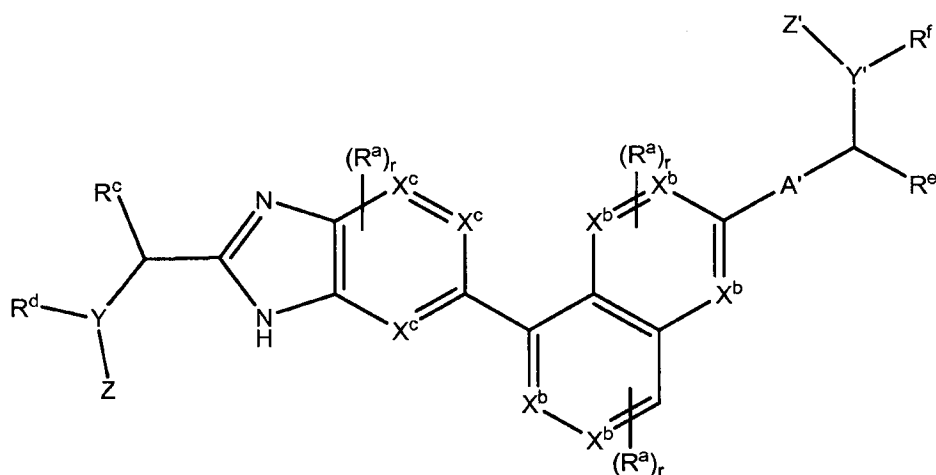
[0274] In a nineteenth embodiment of the third aspect, compounds have formula IIIm:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

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

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

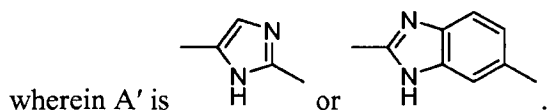


independently C or N.

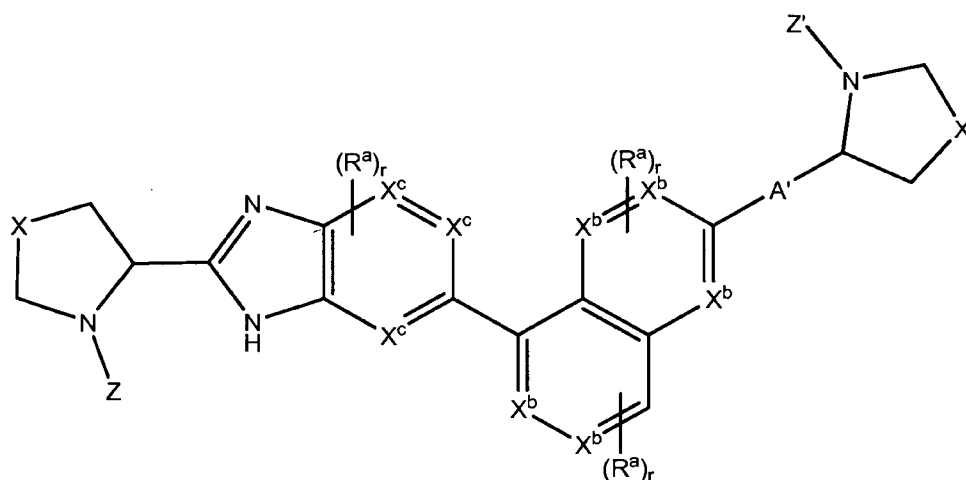
wherein each X^b is

[0277] The compounds of the present invention include pharmaceutically acceptable salts of IIIIn 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 IIIIn



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

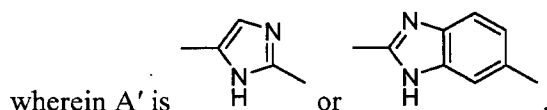


wherein X and

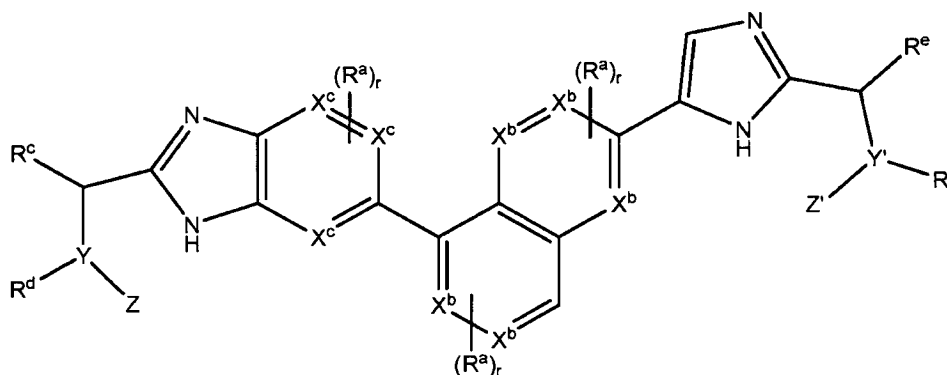
X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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

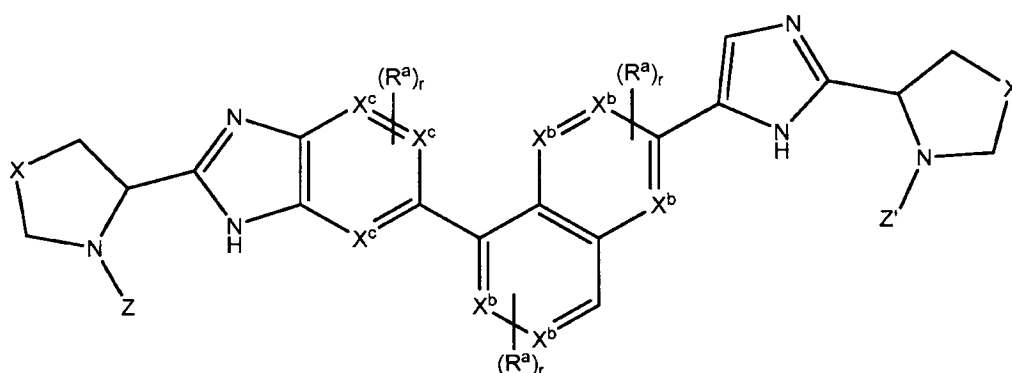


[0282] In a twenty-fourth embodiment of the third aspect, compounds have formula IIIp:



[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:

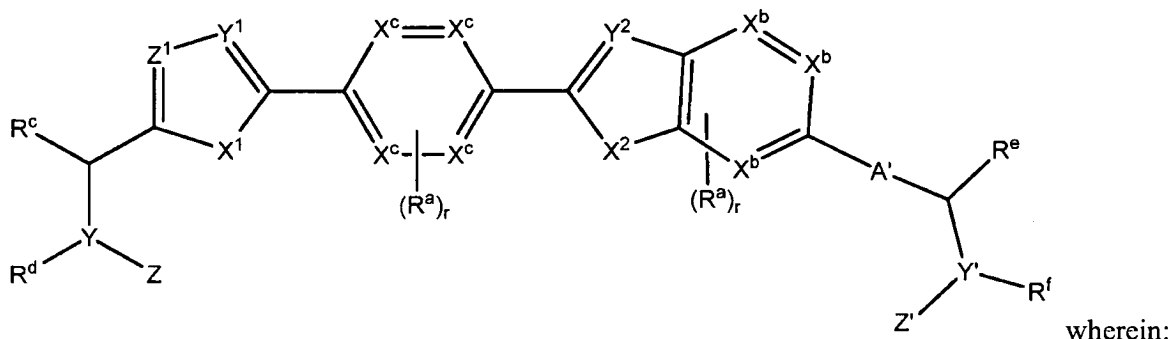


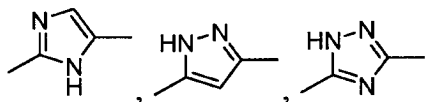
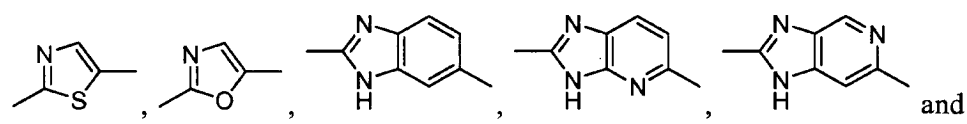
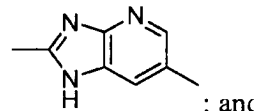
wherein X

and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, 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:

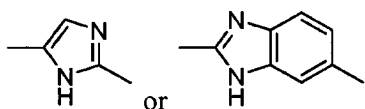


A' is selected from the group consisting of a single bond, , , and ; and

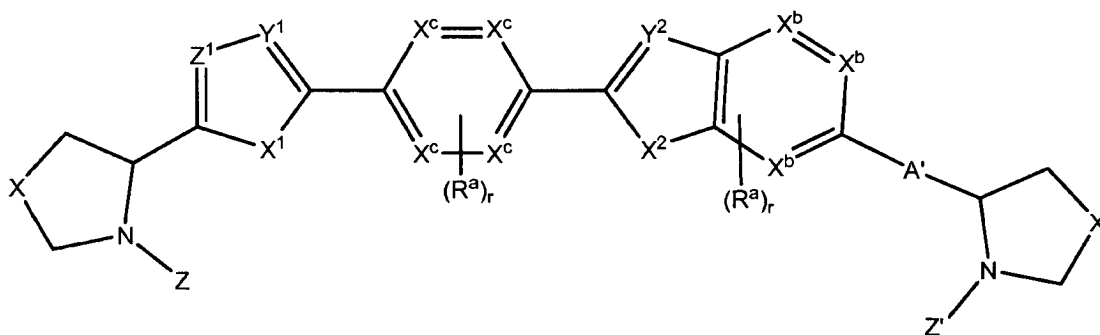
each X^b and X^c is independently C or N.

[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



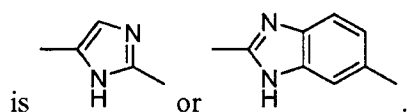
[0289] In a second embodiment of the fourth aspect, compounds have formula IVa:



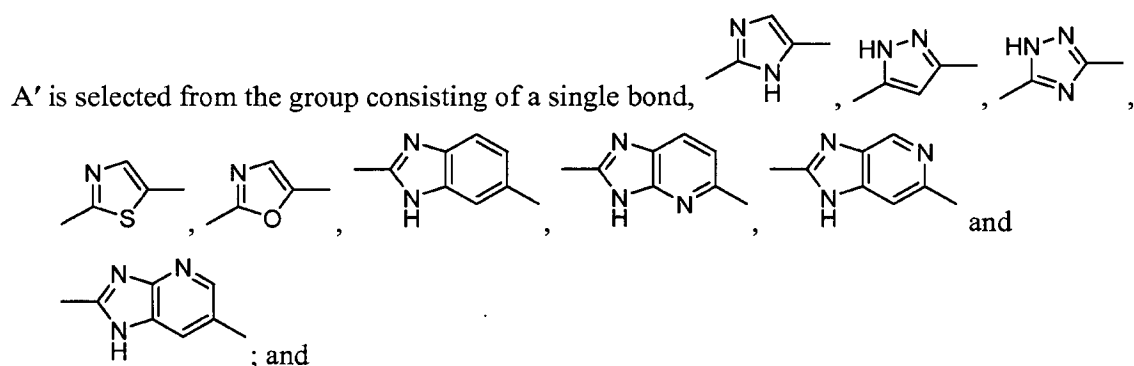
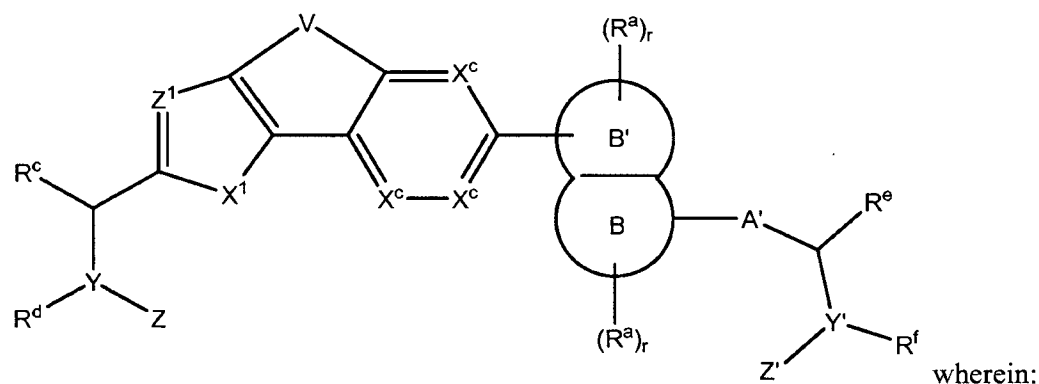
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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'



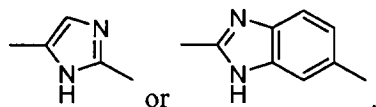
[0292] In a fifth aspect of the invention, compounds have formula V:



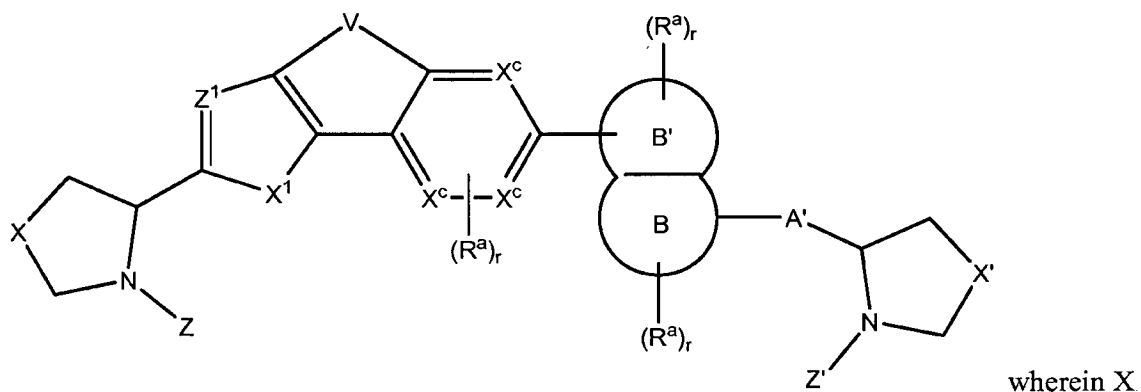
each X^c is independently C or N with the proviso that no more than two X^c are N.

[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



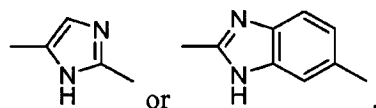
[0295] In a second embodiment of the fifth aspect, compounds have formula Va:



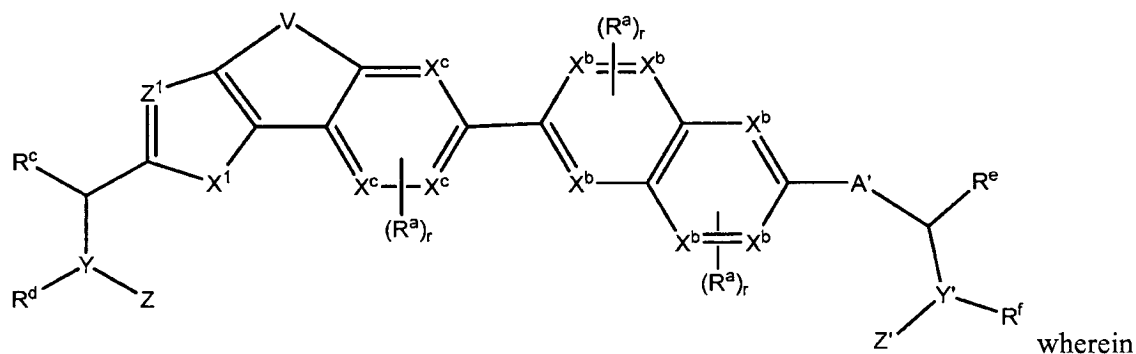
and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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



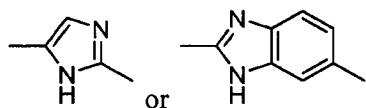
[0298] In a fourth embodiment of the fifth aspect, compounds have formula Vb:



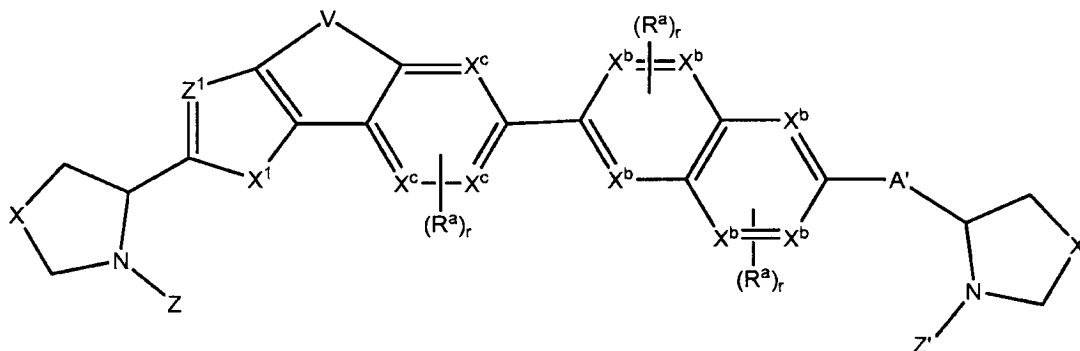
each X^b is independently C or N.

[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



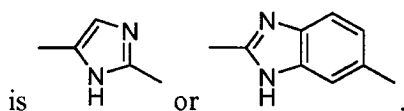
[0301] In a sixth embodiment of the fifth aspect, compounds have formula Vc:



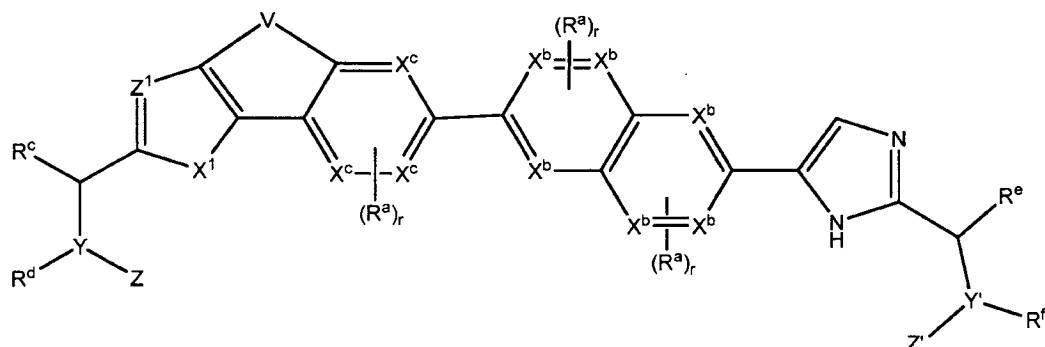
wherein X and X' are each independently selected from the group consisting of a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, $-S(O)_{1-2}-$, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_{1-2}-$ and $-CH_2N(R^1)-$, wherein R^1 is chosen from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8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

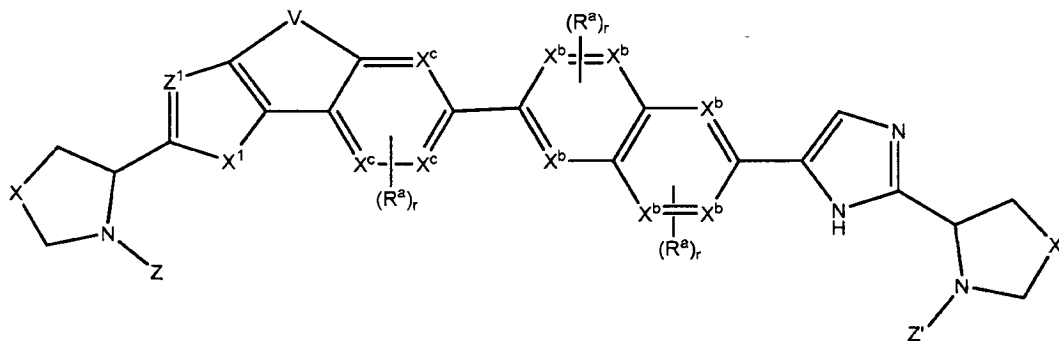


[0304] In an eighth embodiment of the fifth aspect, compounds have formula Vd:



[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, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 $-\text{CN}$, $-\text{OCHF}_2$, $-\text{OCF}_3$, $-\text{CF}_3$, or $-\text{F}$.

[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

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

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

[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 $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^{81}$.

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

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

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

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

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

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

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

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. Those skilled in the art will understand that alternative routes may also be used to reach the same and similarly functionalized intermediates and target molecules. Alternative reagents for a given transformation are also possible.

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

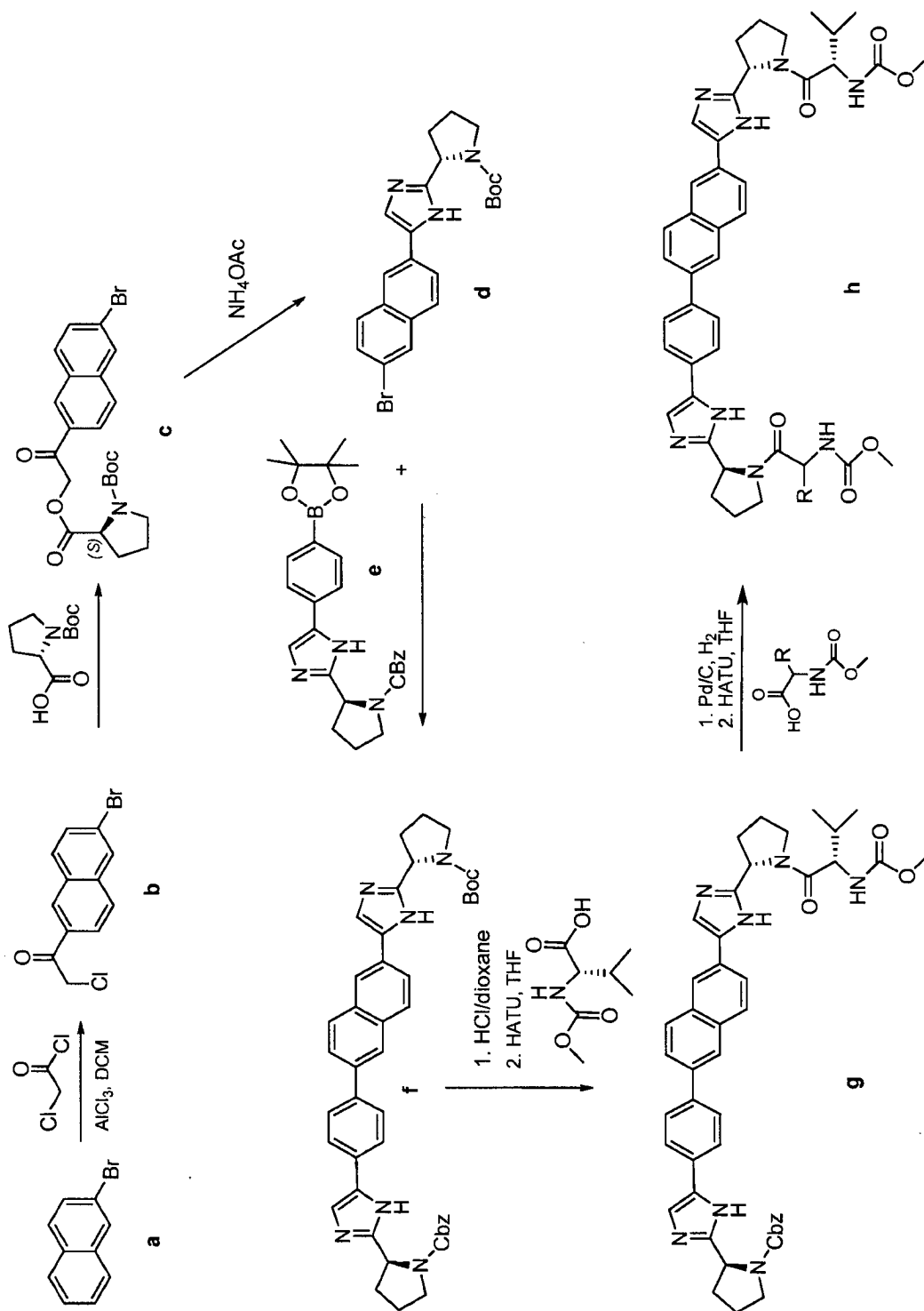
ACN	Acetonitrile
aq	Aqueous
Bn	Benzyl
BnOH	Benzyl alcohol
Boc	<i>t</i> -butoxycarbonyl
DCE	Dichloroethane
DCM	Dichloromethane
DIEA(DIPEA)	Diisopropylethylamine
DMA	<i>N,N</i> -Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium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

DTT	Dithiothreitol
EDC	Ethylcarbodiimide hydrochloride
EDCI	1-Ethyl-3-[3-(dimethylamino) propyl]carbodiimide hydrochloride
EDTA	Ethylene diamine tetraacetic acid
ESI	Electrospray Ionization
Et ₃ N, 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 Chromatography 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 0.1 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/ H₂O gradient (10%-90%) acetonitrile in H₂O with 0.1% formic acid as delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2 mM NH₄OAc in acetonitrile/ H₂O 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.



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.

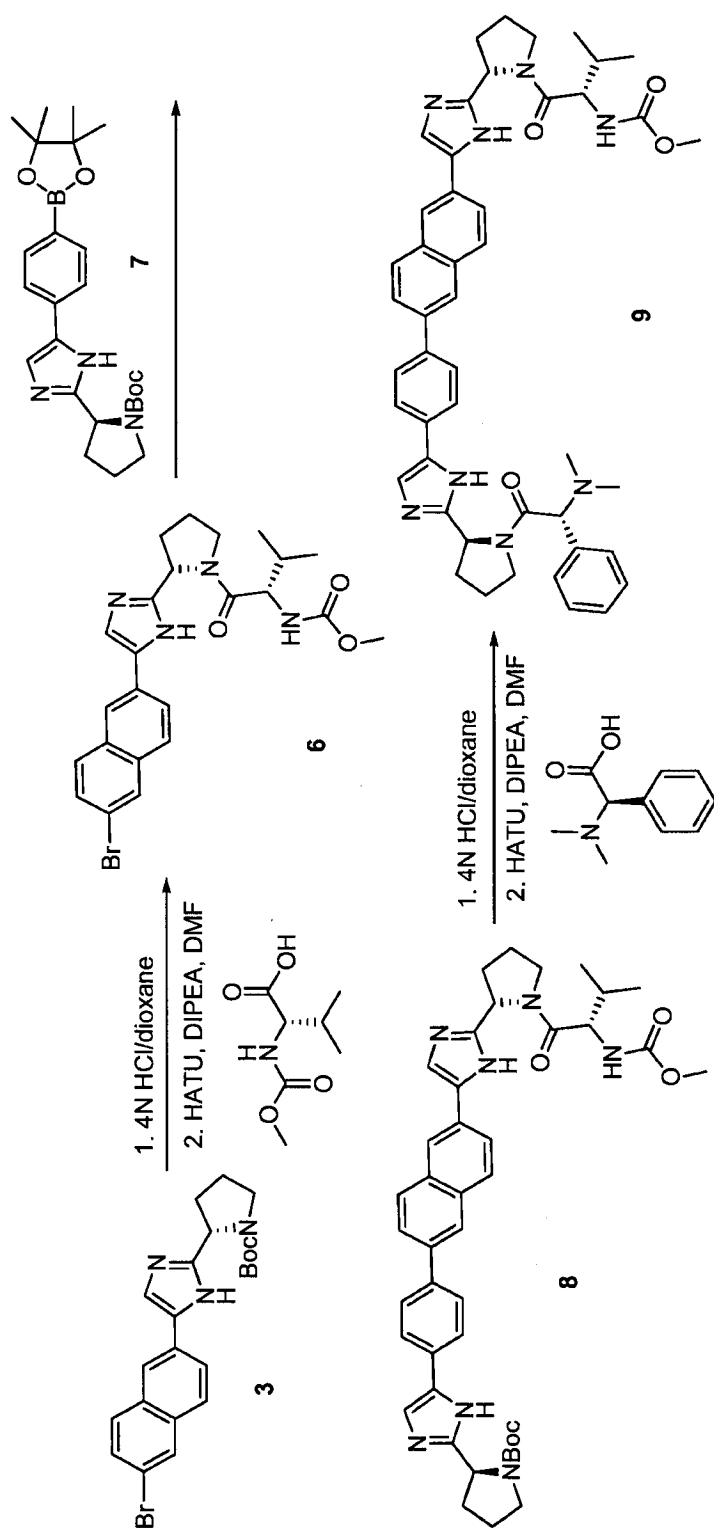
[0340] **Step a.** To a solution of 2-bromonaphthane **a** (62.0 g, 300 mmol) in DCM (1 L) was added AlCl₃ (44.0 g, 330 mmol) and 2-chloroacetyl chloride (34.0 g, 330 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then H₂O added (500 mL) and extracted. The organic layer was washed with H₂O, dried over anhydrous Na₂SO₄, 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: ¹H NMR (500 MHz, CDCl₃) 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 Et₃N (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 NH₄OAc (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 PPh₃ (1.2 g, 4.6 mmol), Pd(PPh₃)₄ (1.6 g, 2.3 mmol), and 2.0 M Na₂CO₃ solution. The mixture was refluxed under argon overnight. The organic solvent was removed under reduced pressure and the residue was treated with H₂O, 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).



Scheme 1-2

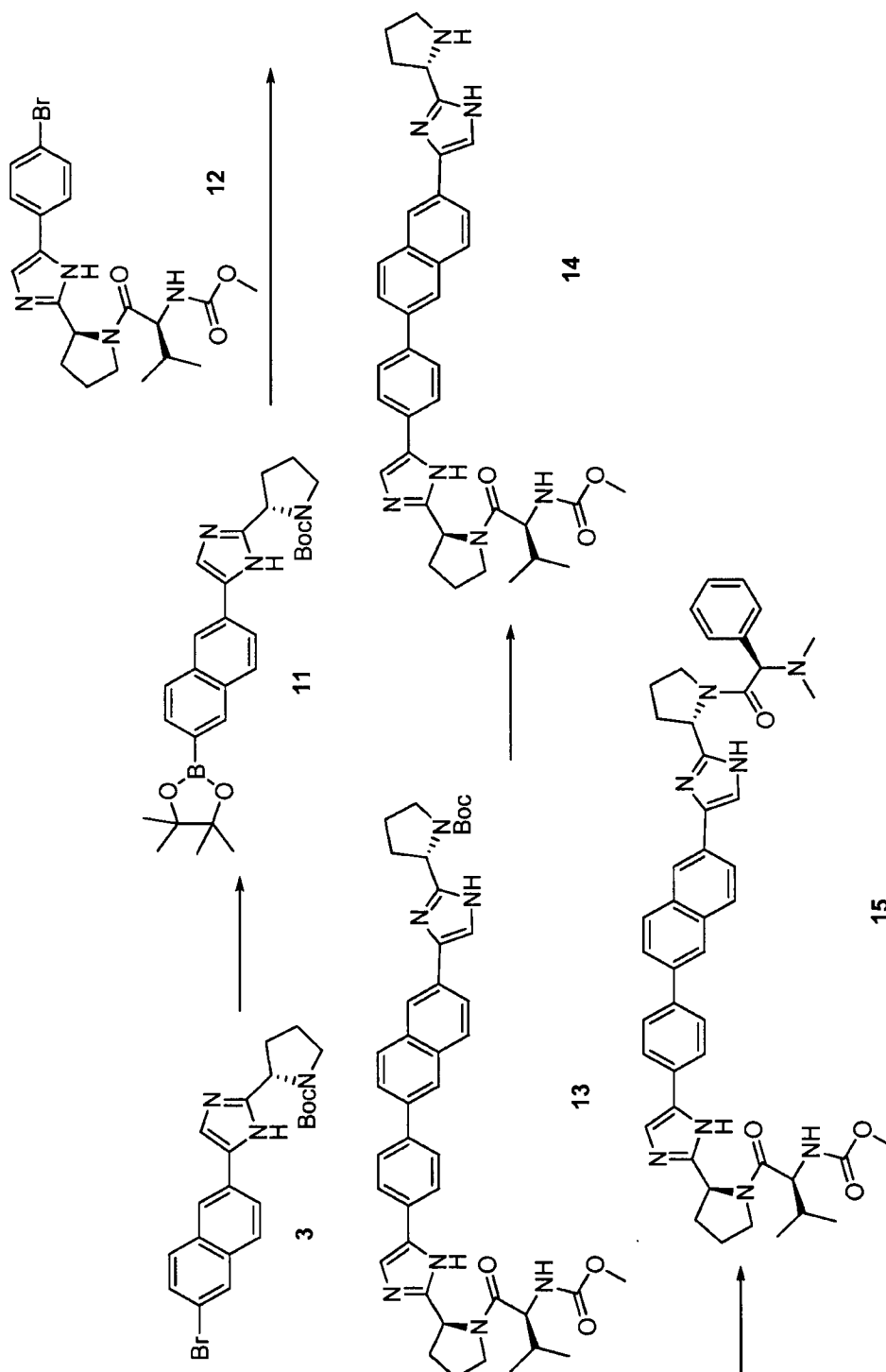
[0345] **Step a.** Referring to Scheme 1-2, to a solution of compound **3** (2.0 g, 4.5 mmol) in dioxane (25 mL) was added 4.0 N HCl in dioxane (25 mL). After stirring at rt for 4 h, the reaction mixture was concentrated and the residue was dried *in vacuo* to give a yellowish solid (2.1 g), which was 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 H₂O (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 NaHCO₃ (480 mg, 5.7 mmol) in 1,2-dimethoxyethane (15mL) and H₂O (5mL) was added Pd(dppf)Cl₂ (59 mg, 0.08 mmol). After stirring at 80°C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/CHCl₃ (100 mL) and H₂O (100 mL). The organic phase was separated and the aqueous phase was extracted with 20% methanol/CHCl₃ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na₂SO₄, 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 H₂O and DCM. The organic phase was washed successively with H₂O and brine, dried with anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **9**. LC-MS (ESI): *m/z* 793.4 (M+H)⁺.



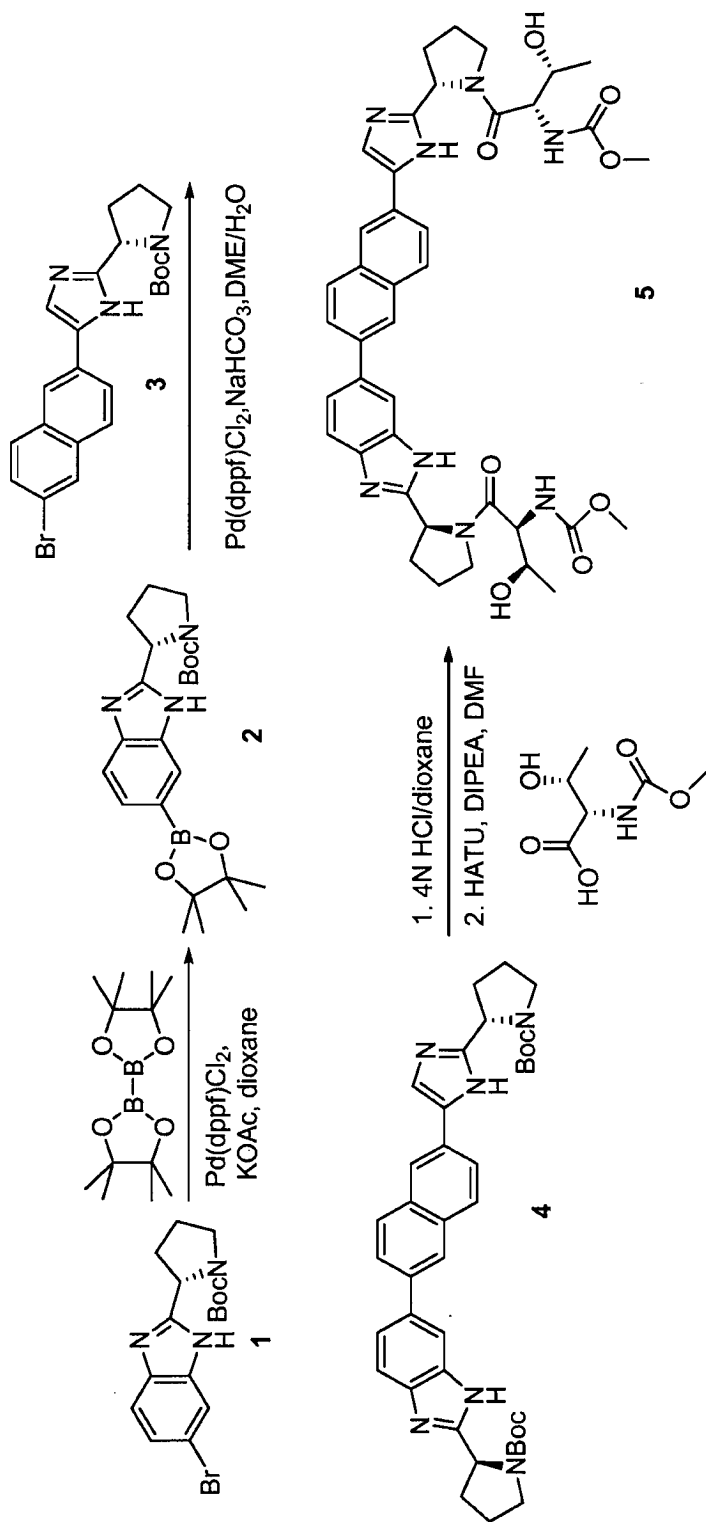
Scheme 1-3

[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)Cl₂ (440 mg, 0.6 mmol). After stirring at 80 °C for 3 h under an atmosphere of N₂, 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 NaHCO₃ (420 mg, 4.99 mmol) in 1, 2-dimethoxyethane (30 mL) and H₂O (10 mL) was added Pd(dppf)Cl₂ (139 mg, 0.19 mmol). After stirring at 80°C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/CHCl₃ (100 mL) and H₂O (100 mL). The aqueous phase was extracted with 20% methanol/CHCl₃ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na₂SO₄, 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 H₂O and DCM. The organic phase was consequently washed with H₂O and brine, dried with anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by prep-HPLC to give compound **15**. LC-MS (ESI): *m/z* 793.4 (M+H)⁺.



Scheme 2-1

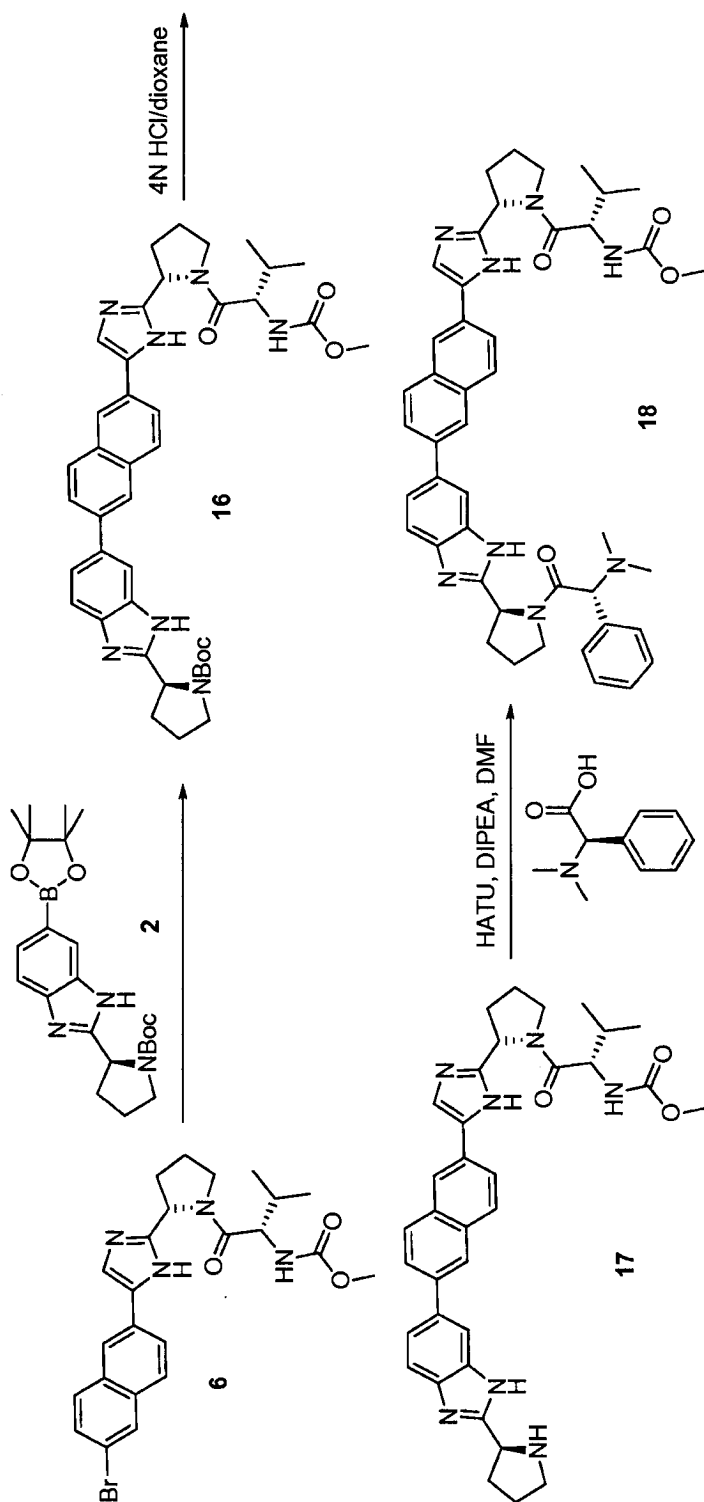
EXAMPLE 2 – Synthesis of compounds of Formula IIIe

[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)Cl₂ (400 mg, 0.5 mmol). After stirring at 80 °C for 3 h under an atmosphere of N₂, 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 NaHCO₃ (333 mg, 3.96 mmol) in 1, 2-dimethoxyethane (30 mL) and H₂O (10 mL) was added Pd(dppf)Cl₂ (74 mg, 0.1 mmol). After stirring at 80°C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/CHCl₃ (100 mL) and H₂O (100 mL). The organic phase was separated and the aqueous phase was extracted with 20% methanol/CHCl₃ (100 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na₂SO₄, 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 H₂O and DCM. The organic phase was consequently washed with H₂O and brine, dried with anhydrous Na₂SO₄, 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)⁺.

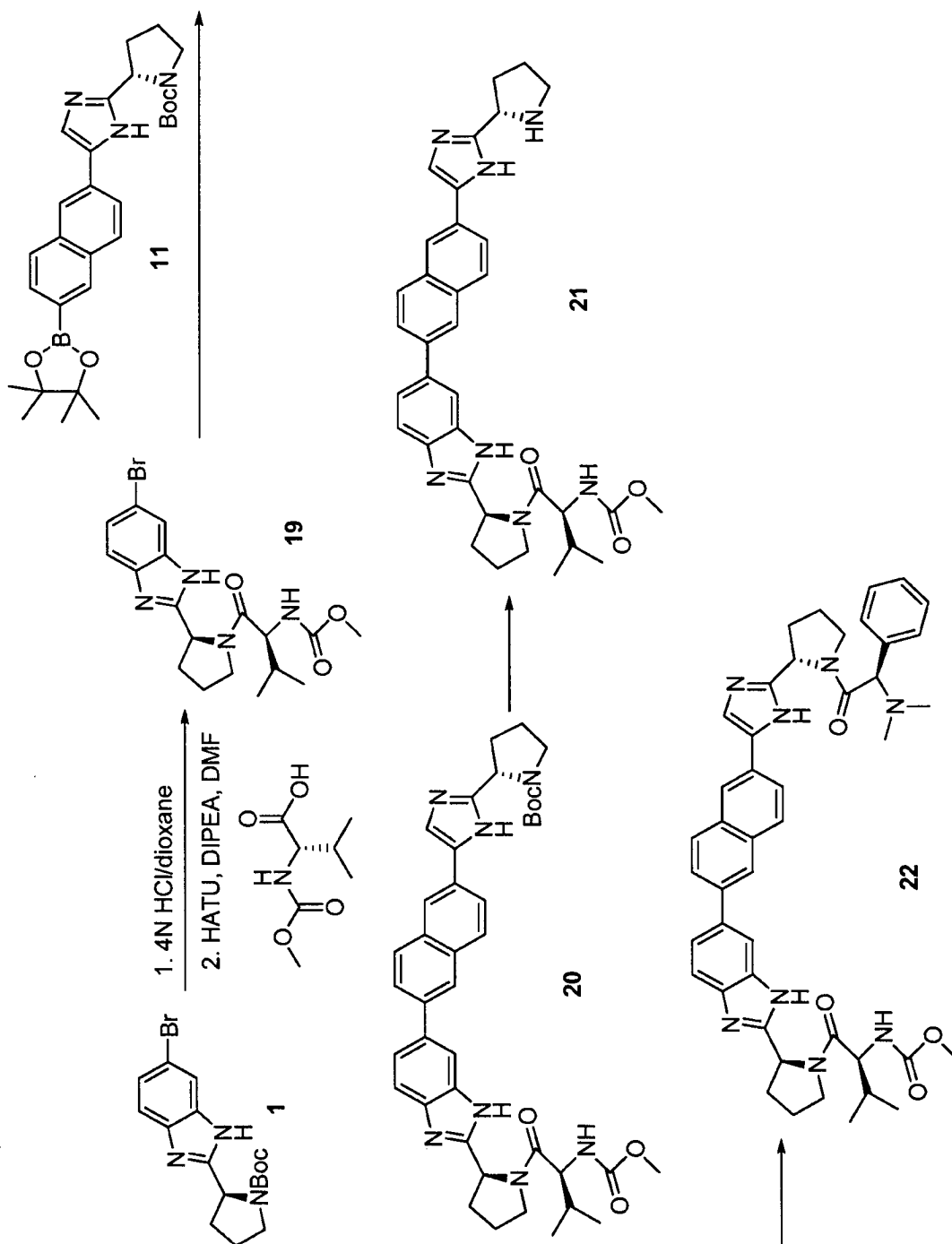


Scheme 2-2

[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 NaHCO₃ (823 mg, 9.8 mmol) in 1, 2-dimethoxyethane (30 mL) and H₂O (10 mL) was added Pd(dppf)Cl₂ (103 mg, 0.14 mmol). After stirring at 80 °C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was partitioned between 20% methanol/CHCl₃ (150 mL) and H₂O (150 mL). The aqueous phase was extracted with 20% methanol/CHCl₃ (150 mL) again. The combined organic phase was consequently washed with brine, dried with anhydrous Na₂SO₄, 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 H₂O and DCM. The organic phase was consequently washed with H₂O and brine, dried with anhydrous Na₂SO₄, 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.

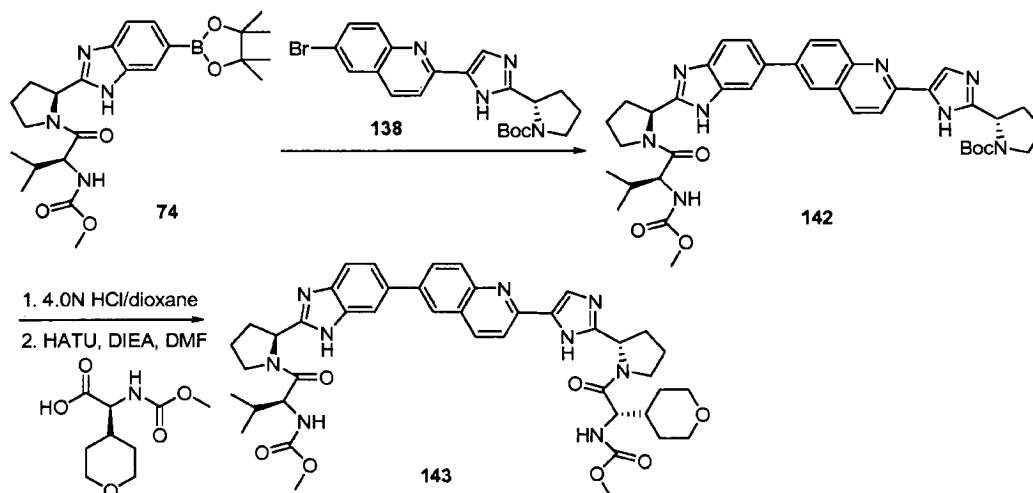
[0362] **Step b.** To a solution of the salt (10.9 mmol) in DMF (30 mL) was added DIPEA (5.8 mL, 33.0 mmol), followed by adding N-methoxycarbonyl-L-valine (2.1 g, 12.1 mmol) and HATU (4.6 g, 12.1 mmol). After stirring at rt for 1h, the reaction mixture was partitioned between H₂O and DCM. The organic phase was consequently washed with H₂O and brine, dried with anhydrous Na₂SO₄, 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 NaHCO₃ (561 mg, 6.6 mmol) in 1, 2-dimethoxyethane (60 mL) and H₂O (20 mL) was added Pd(dppf)Cl₂ (183 mg, 0.25 mmol). After stirring at 80 °C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was then partitioned between 20% methanol/CHCl₃ (100 mL) and H₂O (100 mL). The aqueous phase was extracted with 20% methanol/CHCl₃ (100 mL) again. The combined organic phase was consequently washed with brine, dried with Na₂SO₄, 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 H₂O and DCM. The organic phase was washed successively with H₂O and brine, dried

with anhydrous Na₂SO₄, 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

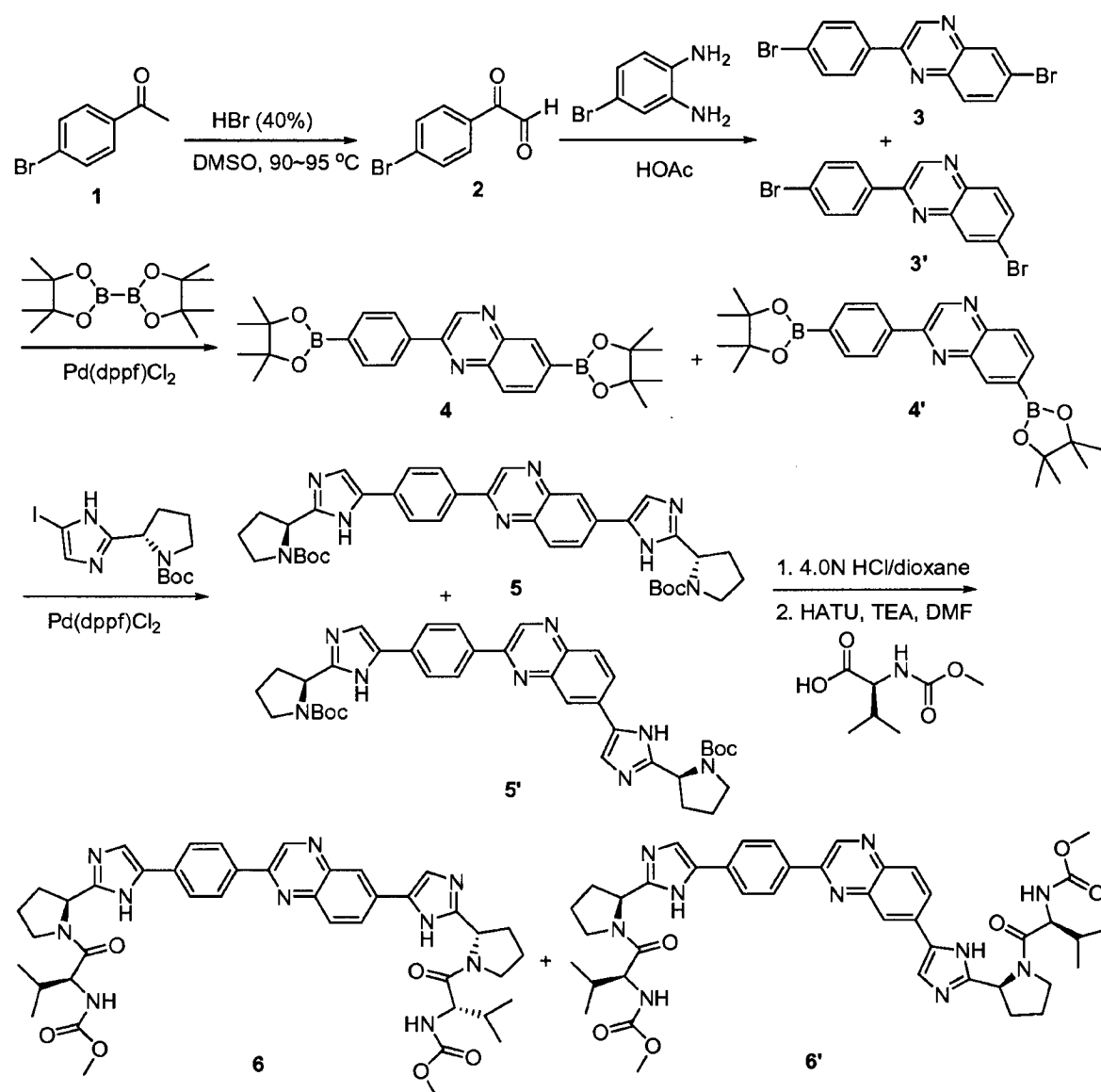
[0366] **Step a.** To a mixture of compound **74** (510 mg, 1.09 mmol), compound **138** (300 mg, 0.68 mmol), NaHCO₃ (228 mg, 2.72 mmol) in 1, 2-dimethoxyethane (20 mL) and H₂O (5 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (111 mg, 0.140 mmol) at rt under an atmosphere of N₂. After stirring at 80°C overnight under an atmosphere of N₂, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL) and H₂O (25 mL). The organic phase 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/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-yl)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 H₂O and the resulting mixture was kept at 50~60 °C. The yellow solid was collected by filtration and re-crystallized in acetone/H₂O (1/19 (v/v)) two times to give compound **2** (50 g, 87% yield). LC-MS (ESI): m/z 212.9 (M+H)⁺.

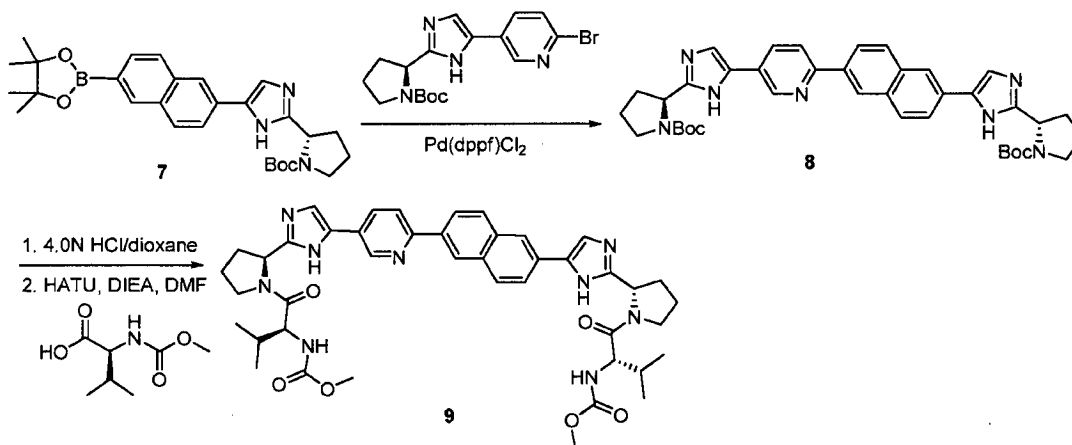
[0370] **Step b.** A mixture of **2** (19.0 g, 80.0 mmol) and 4-bromobenzene-1, 2-diamine (15.0 g, 80.0 mmol) in HOAc (180 mL) was refluxed overnight. Subsequently, the reaction mixture was poured into ice H₂O. The solid was collected by filtration and purified by silica gel column chromatography to 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)Cl₂·CH₂Cl₂ (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 H₂O and dried with anhydrous Na₂SO₄. 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)Cl₂·CH₂Cl₂ (427 mg, 0.44 mmol) in DME/H₂O (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 Na₂SO₄. 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 Et₃N (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 H₂O (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 MgSO₄. 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)⁺.



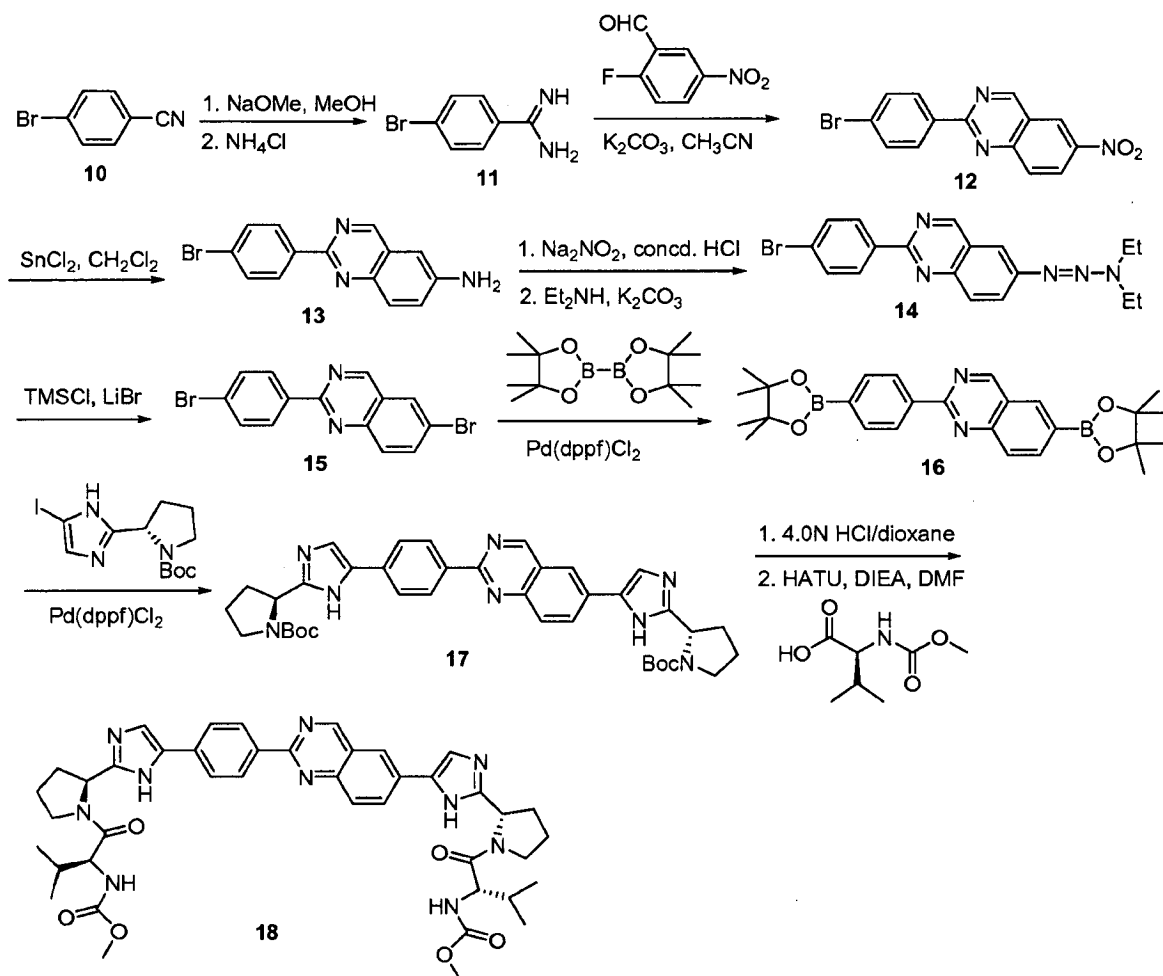
Scheme 3-2

[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 NaHCO₃ (625 mg, 7.44 mmol) in 1, 2-dimethoxyethane (100 mL) and H₂O (30 mL) was added Pd(dppf)Cl₂ (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 CH₂Cl₂ (200 mL). The organic layer was washed with H₂O and dried with anhydrous Na₂SO₄. 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 H₂O (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 MgSO₄. The solvent was removed and the residue was purified by preparative HPLC and to give compound 9. ¹H NMR (500 MHz, CDCl₃) 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 for 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) $m/z = 199.0$ ($\text{M}+\text{H}$)⁺.

[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) $m/z = 330.0$ ($\text{M}+\text{H}$)⁺.

[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 NaHCO₃ 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 Na₂SO₄. 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 NaNO₂ (76 mg, 1.1 mmol) in H₂O (1 mL) drop wise at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was added to a solution of K₂CO₃ (207 mg, 1.5 mmol) and Et₂NH (0.11 g, 1.5 mmol) in ice H₂O (1 mL). Subsequently, ether (100 mL) was added to the mixture. The organic layer was separated, washed with H₂O (15 mL) and dried with anhydrous Na₂SO₄. 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 NaHCO₃ solution (30 mL). The mixture was concentrated and the residue was extracted with CH₂Cl₂ (50 mL × 3). The extracts were combined, washed with brine, and dried with anhydrous Na₂SO₄. 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)⁺.

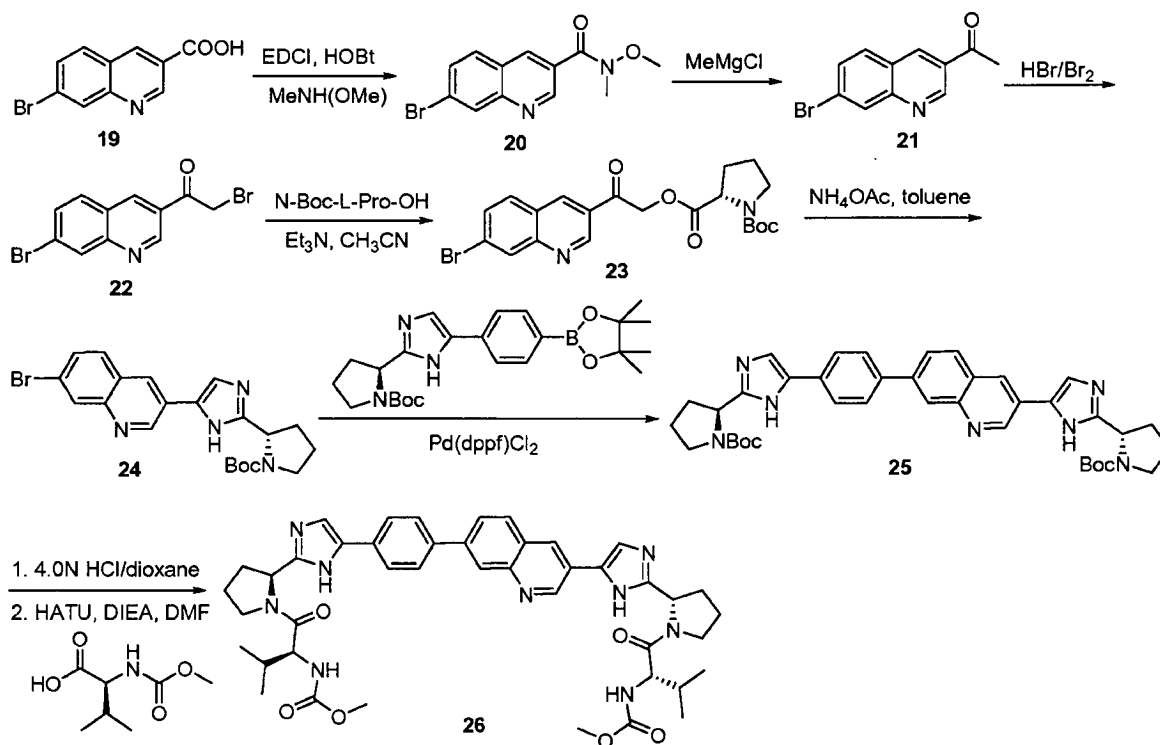
[0383] **Step f.** To a solution of **15** (300 mg, 0.82 mmol) in dioxane (20 mL) was sequentially added bis(pinacolato)diboron (915 mg, 3.63 mmol), potassium acetate (403 mg, 4.12 mmol), and Pd(dppf)Cl₂ (134 mg, 0.160 mmol) at rt under an atmosphere of Ar. After stirring at 80 °C for 17 h under an atmosphere of Ar, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with H₂O and dried with anhydrous Na₂SO₄. 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/H₂O (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), NaHCO₃ (443 mg, 5.28 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (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 Na₂SO₄. 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 H₂O (50 mL). The suspension was filtered and the solid was purified by preparative HPLC to give compound **18**. ¹H NMR (500 MHz, CD₃OD) 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), $\text{MeNH(OMe)}\cdot\text{HCl}$ (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 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M} + \text{H}$)⁺.

[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 Br₂ (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 H₂O (100 mL). The mixture was extracted with EtOAc (100 mL × 3). The extracts were combined and washed with saturated NaHCO₃ (30 mL × 3) and dried with anhydrous Na₂SO₄. 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 CH₃CN (15 mL) was respectively added N-Boc-L-Pro-OH (300 mg, 1.36 mol) and Et₃N (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)⁺.

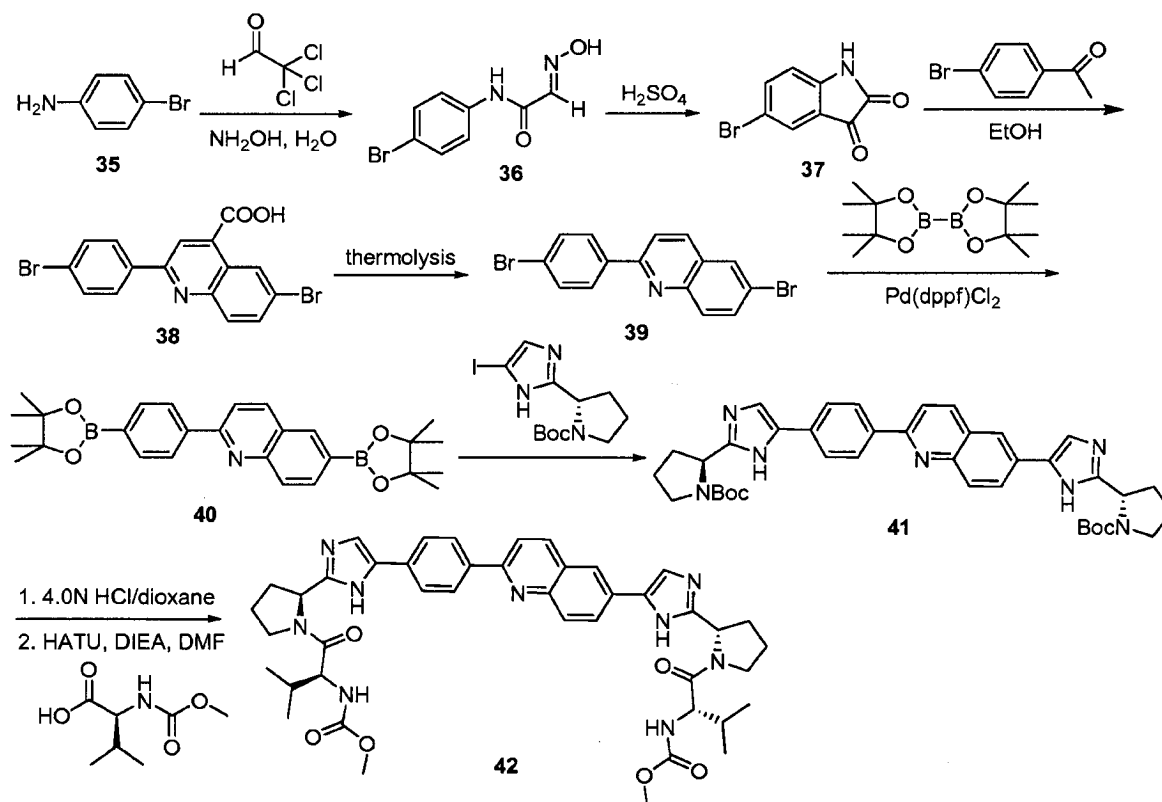
[0391] **Step e.** A mixture of compound **23** (580 mg, 1.25 mmol) and NH₄OAc (962 mg, 12.5 mmol) in toluene (25 mL) was stirred at 110 °C overnight. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (Petroleum ether/EtOAc = 9/1(v/v)) to give compound **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)pyrrolidine-1-carboxylate (378 mg, 0.860 mmol), and NaHCO₃ (253 mg, 3.01 mmol) in 1, 2-dimethoxyethane (15 mL) and H₂O (5 mL) was added Pd(dppf)Cl₂ (35 mg, 0.04 mmol) under an atmosphere of N₂. After stirring at 80 °C overnight under an atmosphere of N₂, the reaction mixture was concentrated. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The extracts were combined and washed with brine and dried with anhydrous Na₂SO₄. 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**. ¹H NMR (500 MHz, CD₃OD) 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 trichloroacetaldehyde (7.2 g, 48 mmol) in water (120 mL) was added Na_2SO_4 (104 g), followed by 4-bromobenzaniline (**35**) in concd. aq. HCl (10 mL) and $\text{NH}_2\text{OH} \cdot \text{HCl}$ (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 H₂SO₄ (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 Na₂SO₄. 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)⁺.

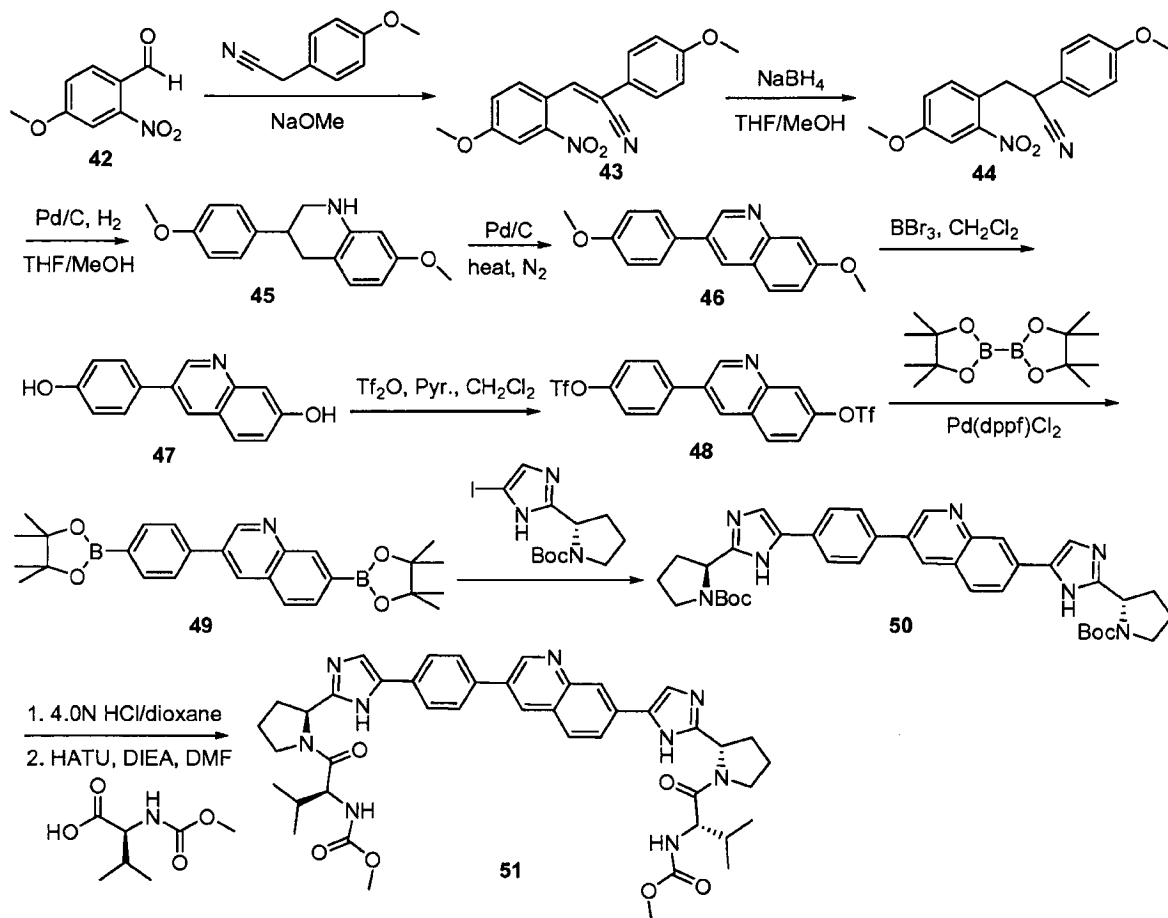
[0398] **Step d.** A flask that charged with compound **5** (1.2 g, 2.95 mmol) was heated to 300 °C for 30 min under an atmosphere of Ar. The solid was then purified by silica gel column chromatography (Petroleum ether/EtOAc = 19:1 (v/v)) to give compound **39** (160 mg, 15% yield) as a yellow solid. 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)Cl₂ (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 H₂O (50 mL) 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 **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/H₂O (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), NaHCO₃ (220 mg, 2.6 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (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 Na₂SO₄. 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 H₂O. The solid was collected by filtration and purified by preparative HPLC to give compound **42**. ¹H NMR (500 MHz, CD₃OD) 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. ¹H NMR (500 MHz, CDCl₃) 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 NaBH₄ (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 $\times$ 2). The extracts were combined, washed with brine, and dried with anhydrous Na₂SO₄. 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 H₂. The resulting mixture was filtered through CELITETM545; the filtered cake was washed with MeOH (50 mL $\times$ 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, CDCl₃) 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 CH₂Cl₂ (30 mL) was added 4 N BBr₃/CH₂Cl₂ (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 $\times$ 2). The extracts were combined, washed with brine, and dried with anhydrous Na₂SO₄. 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)⁺.

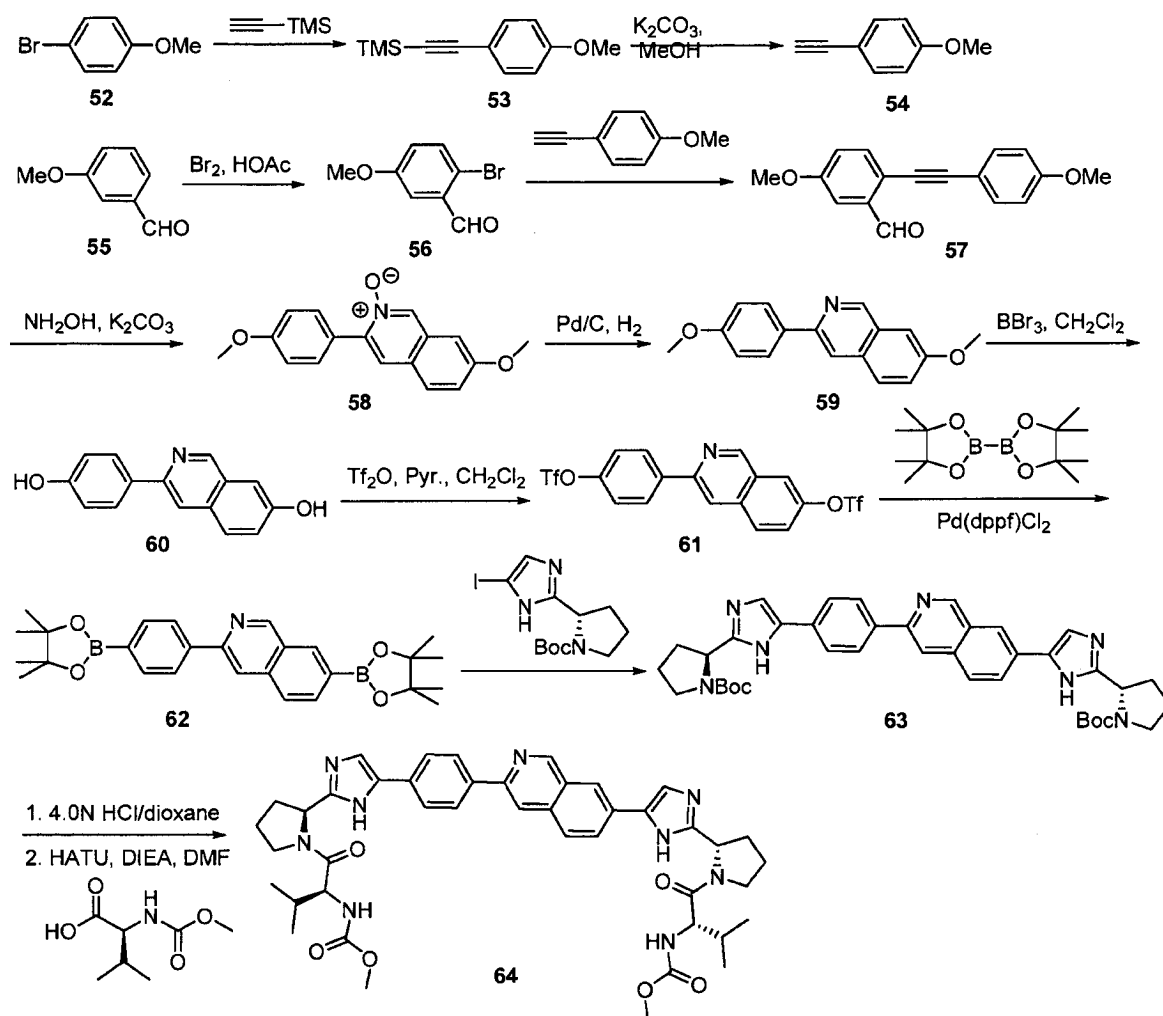
[0408] **Step f.** To a solution of compound **47** (0.82 g, 3.5 mmol) and pyridine (1.3 g, 16 mmol) in CH₂Cl₂ (45 mL) was added and Tf₂O (3.6 g, 13 mmol) at 0 °C. After stirring at rt for 30 min, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (Petroleum 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)Cl₂ (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 H₂O (50 mL) 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 **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/H₂O (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), NaHCO₃ (289 mg, 3.44 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (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 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 **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, CD₃OD) 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(PPh₃)₂Cl₂ (3.51 g, 5.0 mmol), and PPh₃ (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 Na₂SO₄. 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 (100 mL) 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 CELITETM 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 CH₂Cl₂ (75 mL) was added 4N BBr₃ in CH₂Cl₂ (12 mL, 45 mmol) at -40 °C under an atmosphere of N₂. After stirring at rt overnight, the reaction was quenched by adding water (10 mL). Subsequently, the mixture was treated with saturated aqueous NaHCO₃ to adjust the pH value to 8. The organic layer 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/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 CH₂Cl₂ (120 mL) was added Tf₂O (5.84 g, 20.7 mmol) in CH₂Cl₂ (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)⁺.

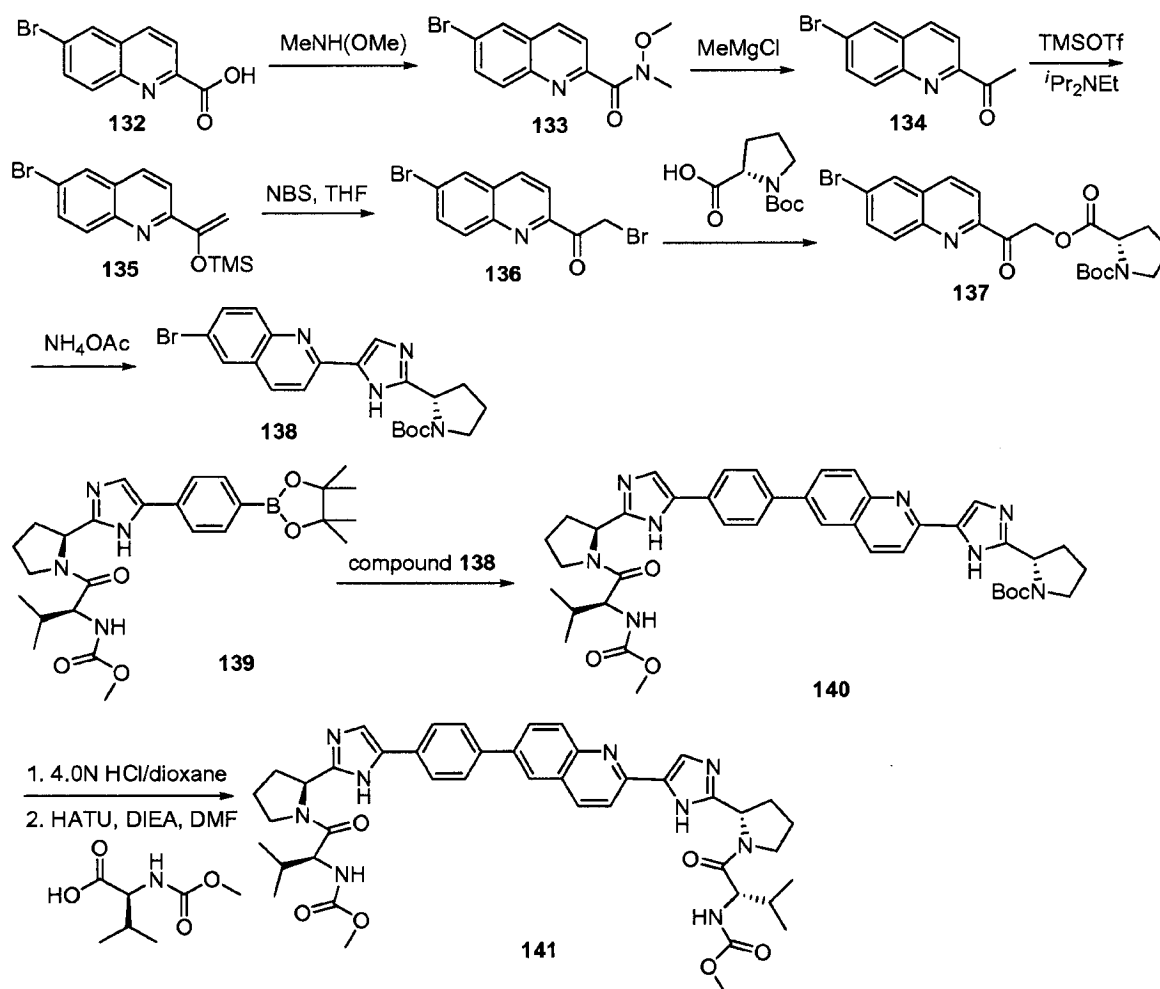
[0421] **Step i.** A mixture of compound **61** (2.0 g, 4.0 mmol), bis(pinacolato)diboron (5.1 g, 20 mmol), potassium acetate (2.7 g, 28 mmol), and Pd(dppf)Cl₂ (0.98 g, 1.2 mmol) and dioxane (80 mL) was stirred at 80 °C overnight under an atmosphere of Ar. Subsequently, the reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with H₂O (50 mL) 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 **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/H₂O (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), NaHCO₃ (2.7 g, 32 mmol), and Pd(dppf)Cl₂ (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 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 **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 1. 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 H₂O. The solid was collected by filtration and purified by preparative HPLC to give compound **64**. ¹H NMR (500 MHz, CD₃OD) 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 Et₃N (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 NH₄Cl and brine, respectively, and dried with anhydrous Na₂SO₄. 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 NH₄Cl. The reaction mixture was concentrated and the residue was added saturated aqueous NaHCO₃ (25 mL) and EtOAc (100 mL). The organic phase was washed with brine and dried with anhydrous Na₂SO₄. 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 ^tPr₂NEt (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 NaHCO₃ and brine, respectively, and dried with anhydrous Na₂SO₄. 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 Na₂SO₄. 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 Et₃N (3.31 g, 32.7 mmol) were added. After stirring

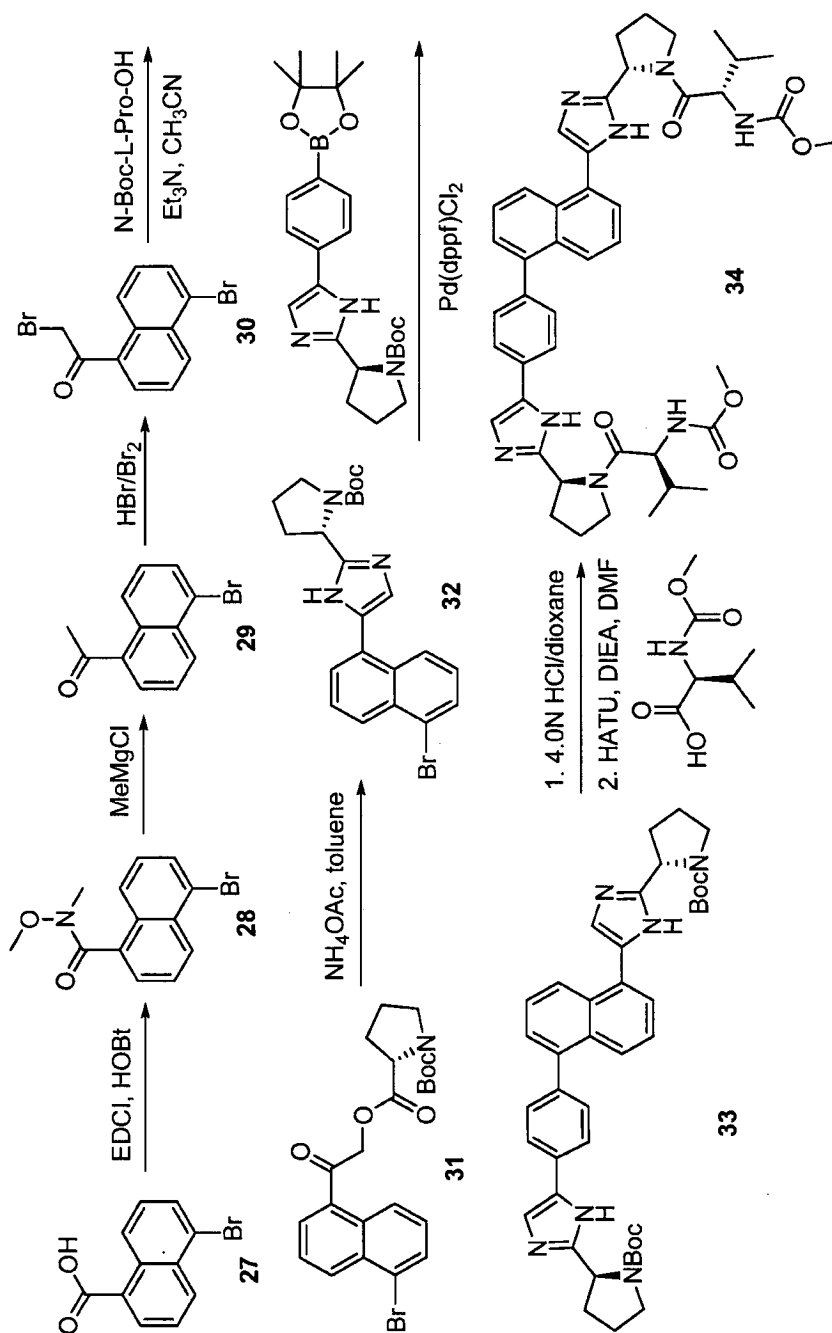
at rt for 5 h, the reaction mixture was washed with saturated aqueous NaHCO_3 and brine, respectively, and dried with anhydrous Na_2SO_4 . The solvent was removed and the residue was dried *in vacuo* to give crude compound **137** (5.0 g), which was used for the next step without further purification.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

[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 ($\text{M}+\text{H}$)⁺.

[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 $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ (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 ($\text{M}+\text{H}$)⁺.

[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 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 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M}+\text{H}$)⁺.



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 CH₃CN (200 mL) was added EDCI (5.8 g, 30 mmol), HOBT (675 mg, 30 mmol), MeNH(OMe)·HCl (2.93 g, 30 mmol), and Et₃N (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 N₂. 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. NH₄Cl. The reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL). The organic phase was washed with sat. aq. NaHCO₃ and dried with anhydrous Na₂SO₄. 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 (100 mL) was drop-wisely added Br₂ (18.8 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 NaHCO₃, and the organic phase was dried with anhydrous Na₂SO₄. 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 Et₃N (1.7 mL, 12.2 mmol) at rt. After stirring at rt for 2 h, the reaction mixture was washed with saturated NH₄Cl, and brine, respectively; the organic phase was dried with anhydrous Na₂SO₄. 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)⁺.

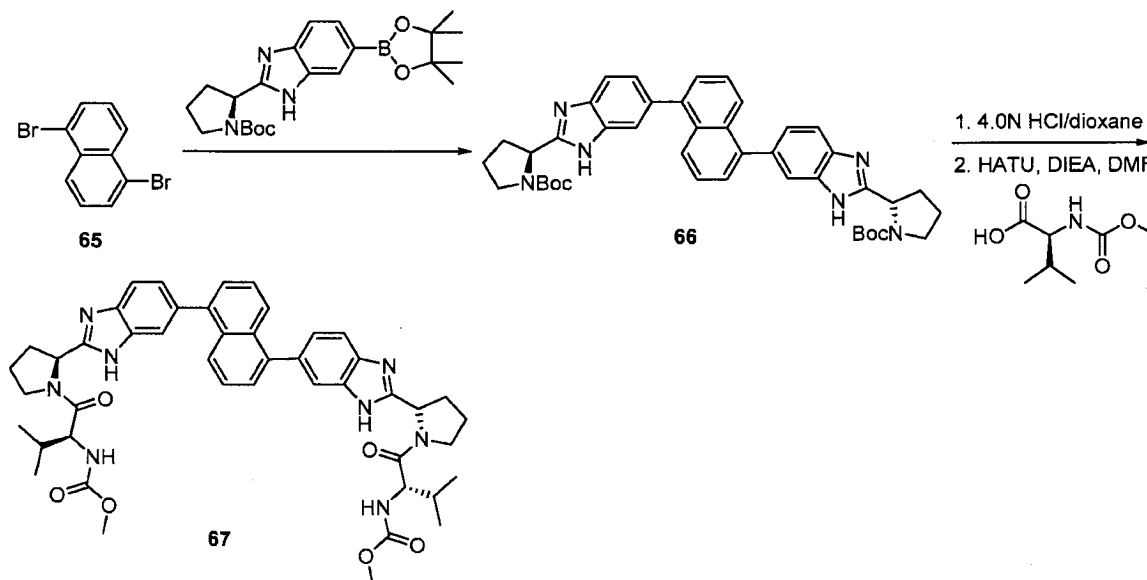
[0438] **Step e.** A mixture of compound **31** (2.4 g, 5.2 mmol) and NH_4OAc (4.0 g, 52 mmol) in toluene (52 mL) stirred at 110 °C overnight. Subsequently, the reaction mixture was cooled to rt and diluted with EtOAc (100 mL). The mixture was washed with saturated aqueous Na_2CO_3 (50 mL $\times$ 2), 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 ($\text{M}+\text{H}$)⁺.

[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)pyrrolidine-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 $\text{Pd}(\text{dppf})\text{Cl}_2$ (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 $\times$ 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 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M}+\text{H}$)⁺.

EXAMPLE 5 – Synthesis of compounds of Formula IIII



Scheme 5-1

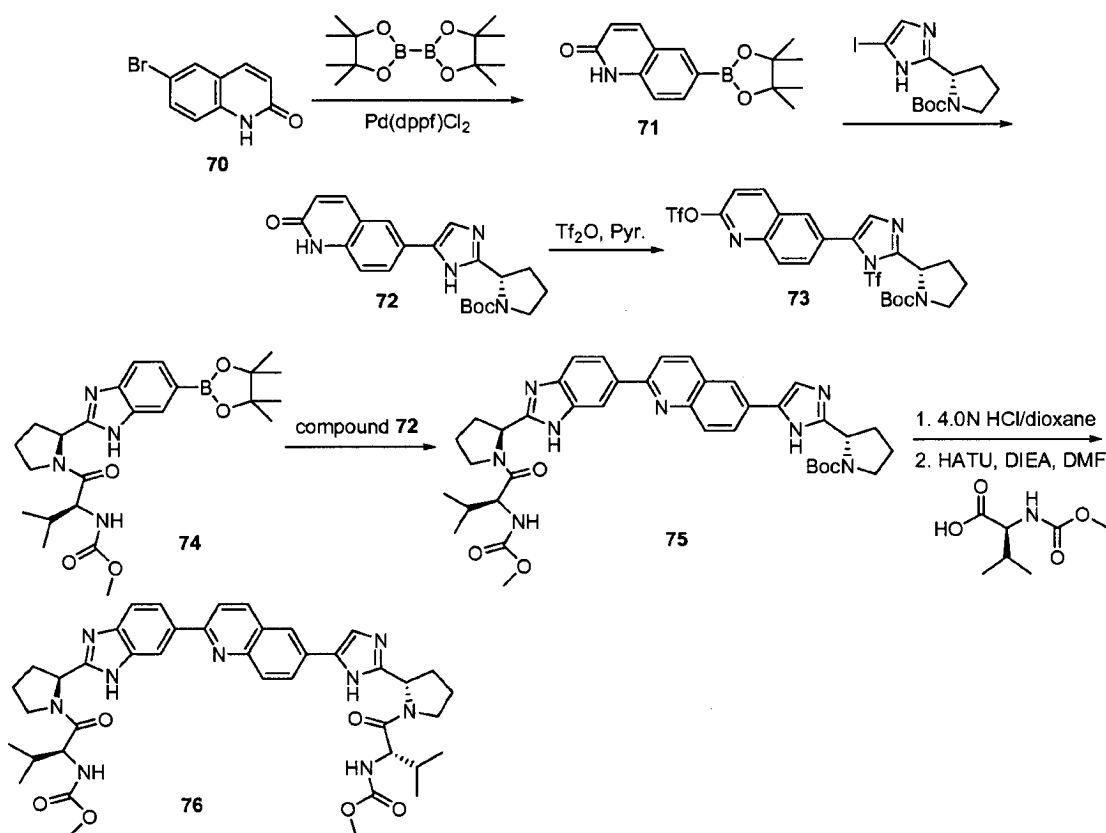
[0442] **Step a.** Referring to Scheme 5-1, a mixture of compound **65** (300 mg, 1.05 mmol), (*S*)-tert-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (1.14 g, 2.75 mmol), and NaHCO₃ (740 mg, 8.80 mmol) in 1, 2-dimethoxyethane (30 mL) and water (10 mL) were added Pd(dppf)Cl₂ (179 mg, 0.220 mmol) at rt under an atmosphere of N₂. After stirring at 80 °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 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 **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), K₂CO₃ (10.50 g, 107.1 mmol) in 1,4-dioxane (600 mL) was added Pd(dppf)Cl₂ (2.9 g, 3.6 mmol) at rt under an atmosphere of N₂. After stirring at 80 °C for 3 h under an atmosphere of N₂, the reaction mixture was cooled to rt and filtered through Celiirt® 545. The filtered cake was washed with EtOAc (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 Na₂SO₄. 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)⁺.

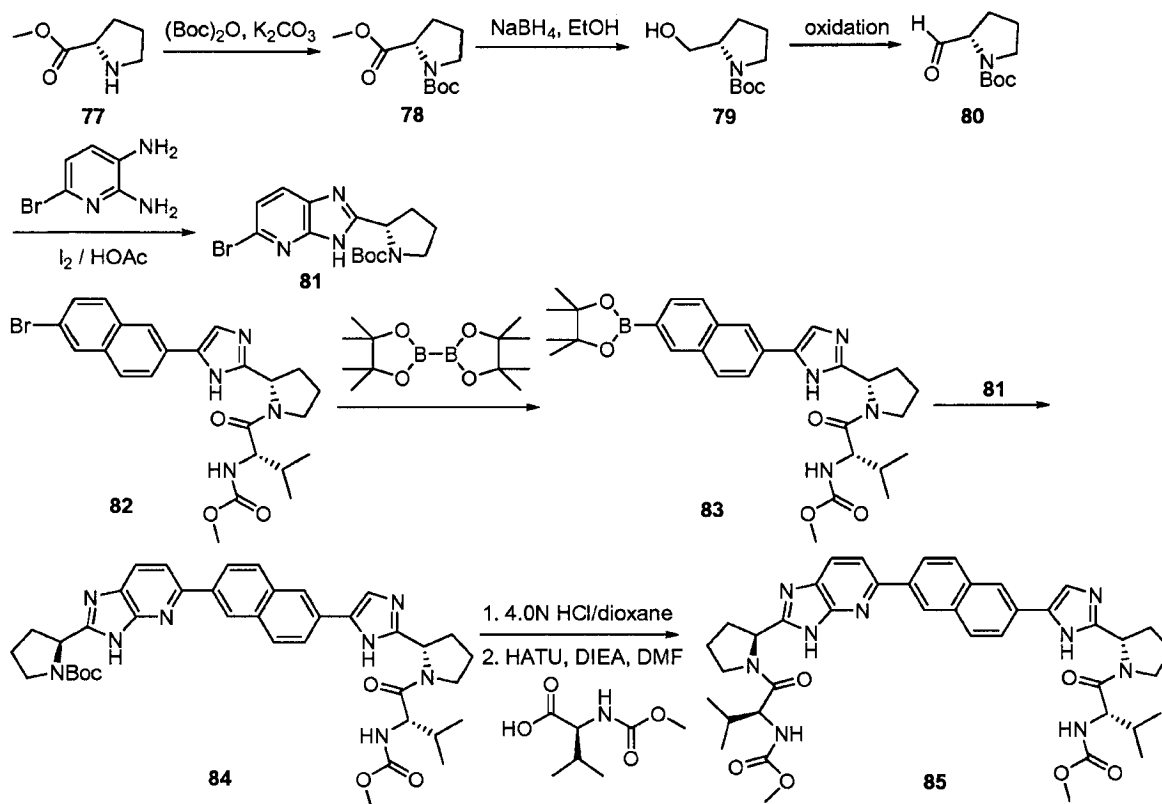
[0446] **Step b.** To a mixture of compound **71** (5.90 g, 21.8 mmol), (*S*)-*tert*-butyl 2-(5-iodo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (9.50 g, 26.2 mmol), NaHCO₃ (7.30 g, 87.2 mmol) in 1,2-dimethoxyethane (500 mL) and water (150 mL) was added Pd(dppf)Cl₂ (3.6 g, 4.4 mmol) under an atmosphere of N₂. 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 Na₂SO₄. 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 Tf₂O (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-*tert*-amethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)butan-2-yl)carbamate (**74**) (419 mg, 0.89 mmol), and NaHCO₃ (299 g, 3.56 mmol) in 1,2-dimethoxyethane (60 mL) and water (20 mL) was added Pd(dppf)Cl₂ (147 mg, 0.18 mmol) at rt under an atmosphere of N₂. After stirring at 80 °C overnight under an atmosphere of N₂, 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 Na₂SO₄. 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 Et₃N (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 H₂O (500 mL) was added K₂CO₃ (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 Na₂SO₄. 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 NaBH₄ (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 brine 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 Et₃N (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 H₂O. 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 Na₂SO₄. 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 NaHCO₃. The resulting mixture was extracted with EtOAc (200 mL × 3). The extracts were combined, washed with brine, and dried with anhydrous Na₂SO₄. 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)⁺.

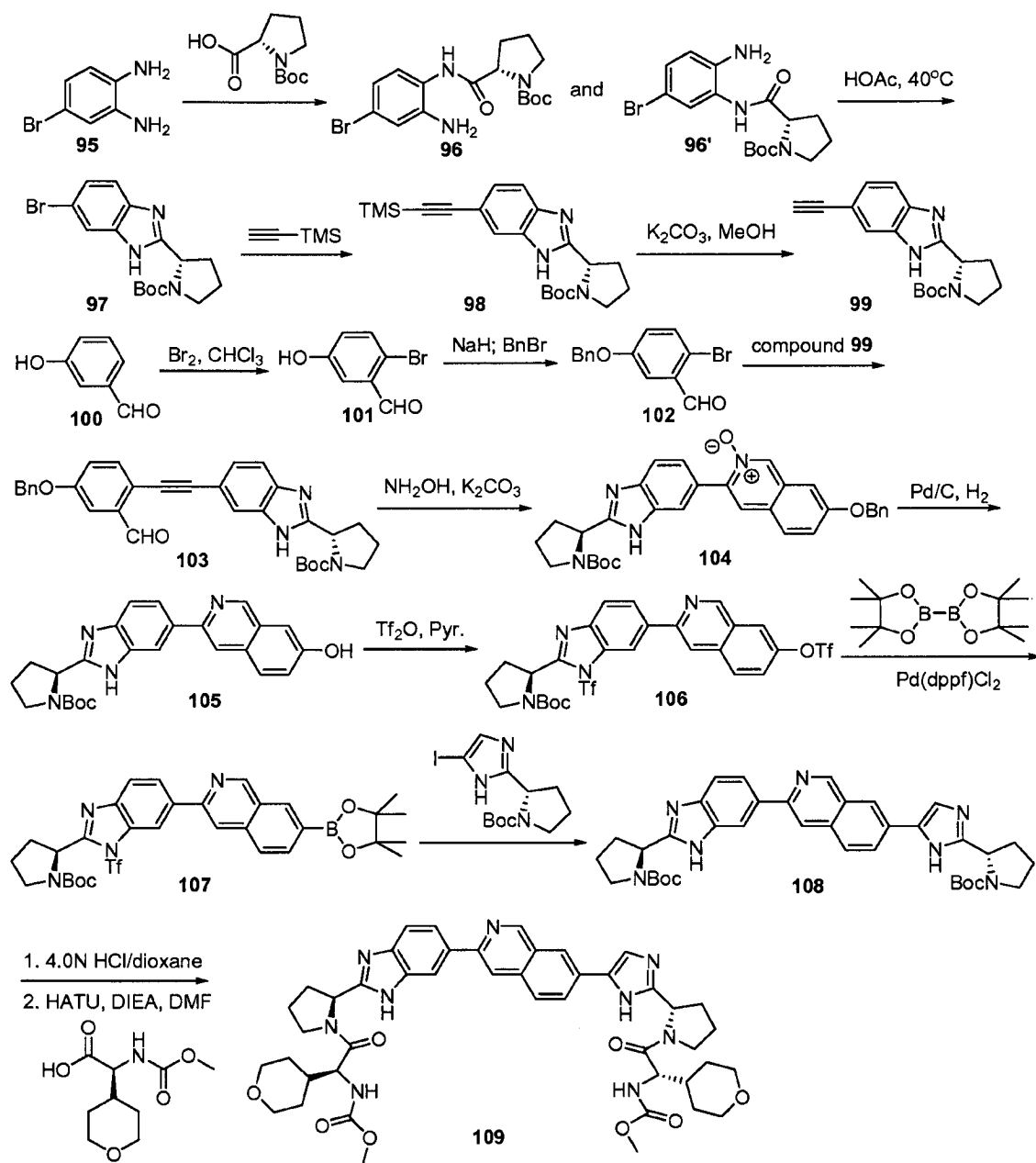
[0455] **Step e.** A mixture of compound **82** (10.0 g, 20.1 mmol), bis(pinacolato)diboron (7.65 g, 30.1 mmol), potassium acetate (6.89 g, 70.3 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (886 mg, 1.0 mmol) in 1,4-dioxane (200 mL) was stirred at 80 °C for 3 h under an atmosphere of N₂. The reaction mixture was filtered through CELITE™ 545 and the filtered cake was washed with EtOAc (200 mL × 3). The filtrate was washed with brine and dried with anhydrous Na₂SO₄. 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), NaHCO₃ (1.60 g, 18.9 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (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 N₂. The reaction mixture was concentrated and the residue was added DCM (200 mL) and water (50 mL). The organic phase was washed with brine and dried with anhydrous Na₂SO₄. 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 Et₃N (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 $\times$ 3) and dried with anhydrous Na₂SO₄. 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 $\times$ 3). The extracts were combined, washed with water, and dried with anhydrous Na₂SO₄. 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), PPh₃ (1.2 g, 4.6 mmol), and Pd(PPh₃)₂Cl₂ (1.6 g, 2.3 mmol) in anhydrous THF (200 mL) was refluxed overnight under an atmosphere of N₂. The reaction mixture was concentrated and the residue was diluted with EtOAc (250 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/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 K₂CO₃ (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 CELITETM 545 and the filtered cake was washed with EtOAc (100 mL $\times$ 3). The filtrate was concentrated and the residue was diluted with DCM (250 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 = 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 CHCl₃ (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 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M} + \text{H}$)⁺.

[0465] **Step g.** A mixture of compound **99** (2.80 g, 9.0 mmol), compound **102** (2.6 g, 9.0 mmol), $\text{Pd}(\text{PPh})_2\text{Cl}_2$ (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 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 **103** (4.0 g, 86% yield). LC-MS (ESI): m/z 522.2 ($\text{M} + \text{H}$)⁺.

[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 ($\text{M} + \text{H}$)⁺.

[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 H₂. Subsequently, the reaction mixture was filtered through CELITETM545 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)⁺.

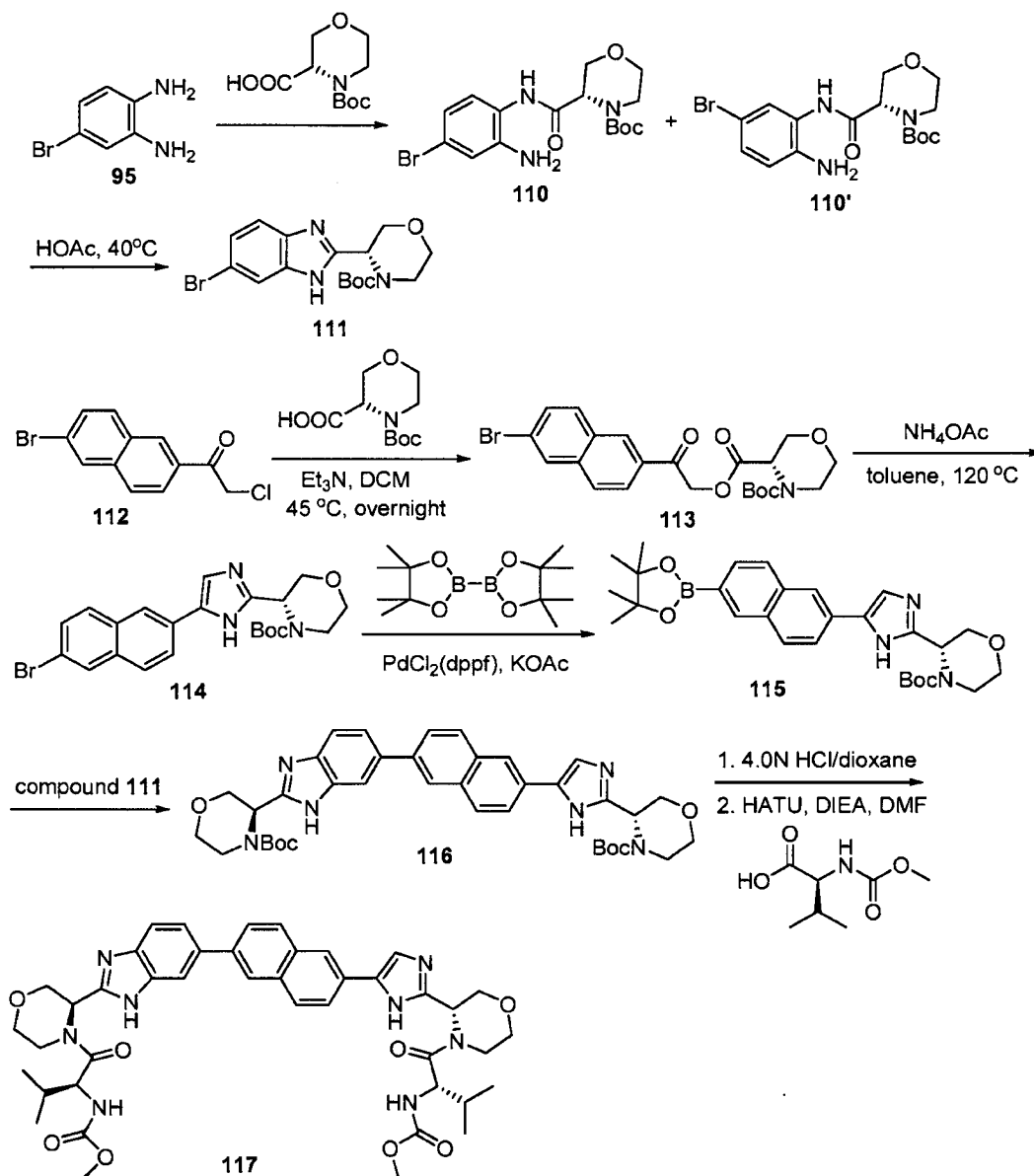
[0468] **Step j.** To a solution of compound **105** (650 mg, 1.5 mmol) in anhydrous pyridine (711 mg, 9.0 mmol) was added Tf₂O (1.07 g, 3.8 mmol) at 0 °C. After stirring at rt overnight, the reaction mixture was concentrated and the residue was diluted with EtOAc (100 mL). The mixture was washed with brine and dried with anhydrous Na₂SO₄. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/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), PdCl₂(dppf)·CH₂Cl₂ (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 N₂. 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 NaHCO₃ (201 mg, 2.4 mmol), 1, 2-dimethoxyethane (4 mL), water (2 mL), and Pd(dppf)Cl₂·CH₂Cl₂ (100 mg, 0.12 mmol) under an atmosphere of N₂. After stirring at 80 °C for 2 h under an atmosphere of N₂, the reaction mixture was added K₂CO₃ (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 Na₂SO₄. 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 (4.3 g, 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 Na₂SO₄. 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 Na₂CO₃ 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 Na₂SO₄. 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 Et₃N (60.0 mL, 433 mmol), respectively. After stirring at 45 °C overnight, the reaction mixture was washed with saturated aqueous NaHCO₃ (50 mL), saturated aqueous NH₄Cl (50 mL), and brine, respectively, and dried with anhydrous Na₂SO₄. 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)⁺.

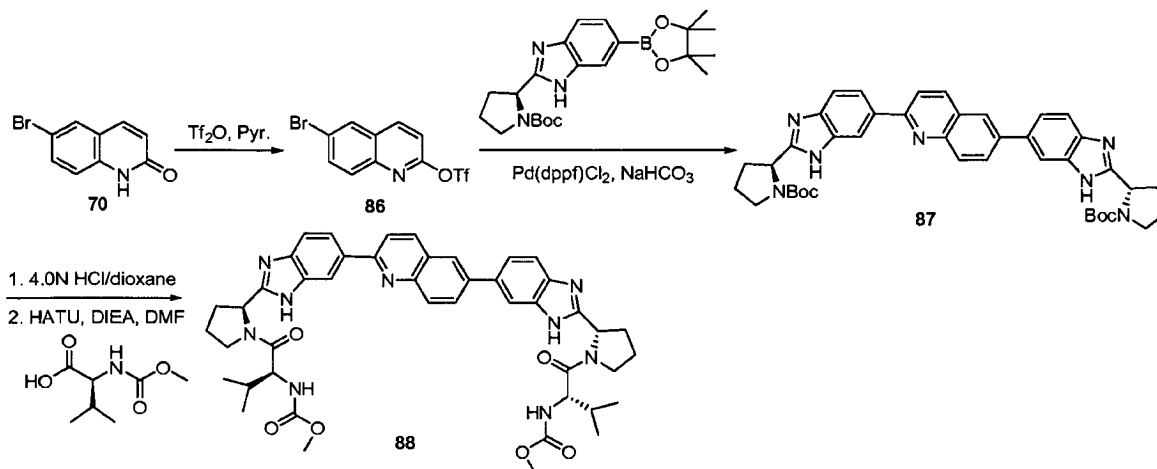
[0476] **Step d.** A mixture of crude compound **113** (41.4 g) and NH₄OAc (100g, 1.30 mol) in toluene (300 mL) was stirred at 120 °C overnight. The reaction mixture was concentrated and the residue was diluted with EtOAc (500 mL). The mixture was washed with water and dried with anhydrous Na₂SO₄. The solvent was removed and the residue was purified by silica gel column chromatography (Petroleum ether/acetone = 6/1 to 1/1 (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 $Pd(dppf)Cl_2 \cdot DCM$ (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 CELITETM545 and the filtered cake was washed with EtOAc (100 mL $\times$ 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 $Pd(dppf)Cl_2 \cdot DCM$ (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 phase was washed with brine 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 added 4 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**

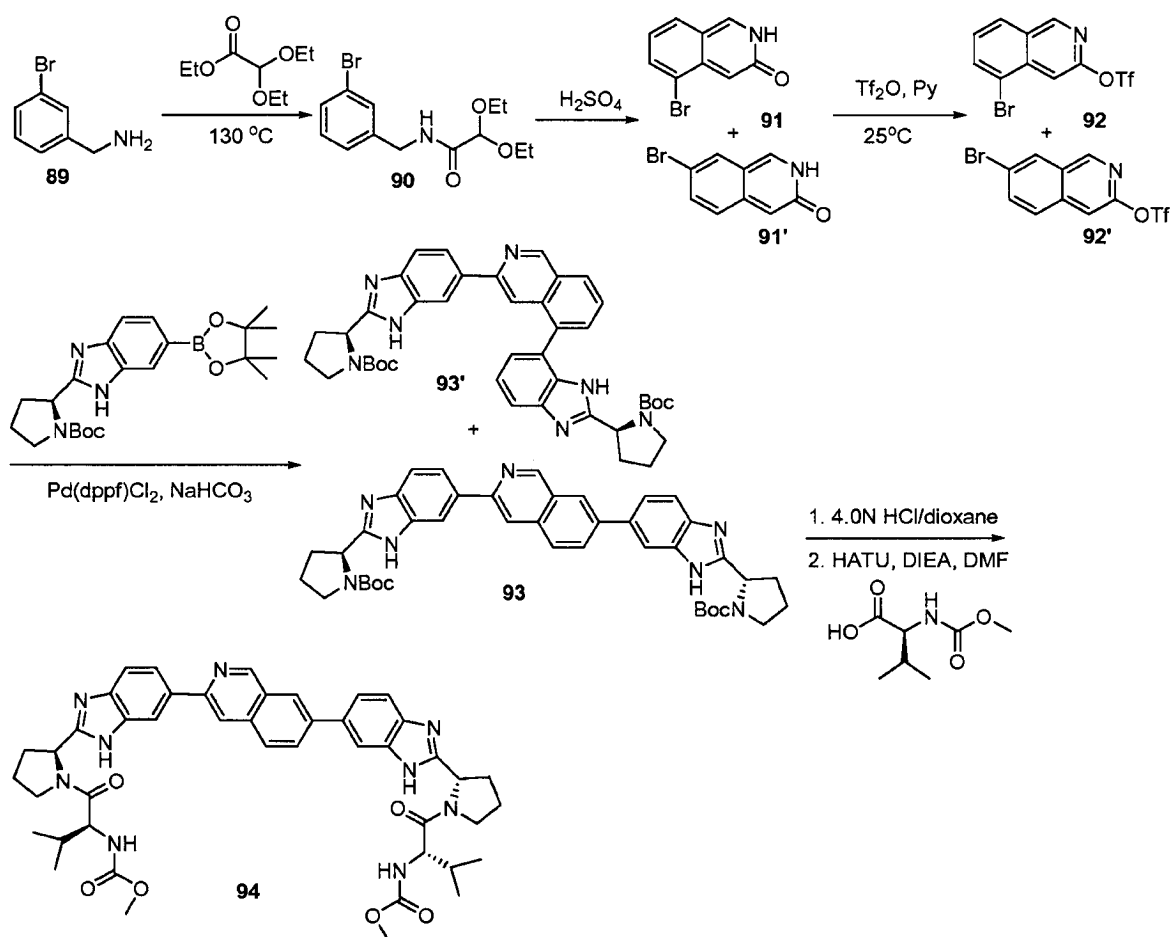
[0481] **Step a.** Referring to Scheme 7-1, to a solution of 6-bromoquinolin-2(1H)-one (70) (0.40 g, 1.8 mmol) in anhydrous pyridine (12 mL) was added drop-wisely with TiF_4 (0.81 g, 2.9 mmol) at 0 °C. After stirring at 0 °C for 1 h and at rt for 3 h, the reaction mixture was concentrated. The residue was dissolved in DCM (100 mL); the resulting mixture was washed with water (25 mL $\times$ 3) 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 86 (0.54 g, 84% yield) as a yellow solid. LC-MS (ESI) m/z 355.9 ($\text{M} + \text{H}$)⁺.

[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)-1H-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 $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (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 ($\text{M} + \text{H}$)⁺.

[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 Et₃N (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.

NH₄Cl and brine, respectively, and dried with anhydrous Na₂SO₄. 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. H₂SO₄ (50 mL) was stirred at rt for 5 h. Subsequently, the reaction mixture was poured into ice-water. The suspension was filtered and the filtrate was neutralized with 10% NH₄OH. 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)⁺.

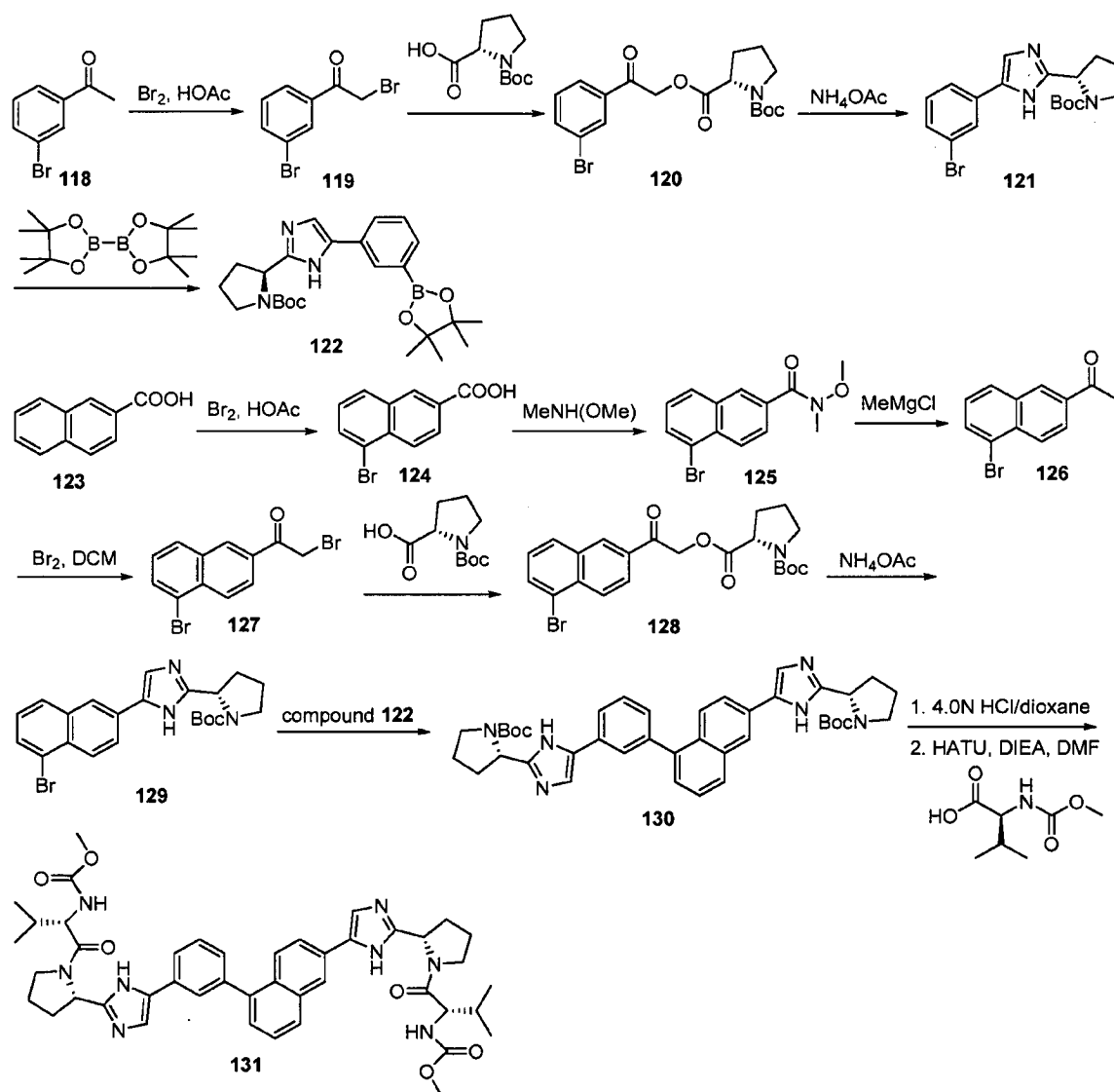
[0487] **Step c.** A mixture of compounds **92** and **92'** (222 mg, 1.0 mmol) in anhydrous pyridine (5 mL) was added Tf₂O (0.5 mL) at 0 °C. After stirring at rt for 8 h, the reaction mixture was concentrated and the residue was dissolved in DCM (50 mL). The mixture was washed with water (25 mL × 3) and dried with anhydrous Na₂SO₄. 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 NaHCO₃ (227 mg, 2.7 mmol) in 1,2-dimethoxyethane (30 mL) and water (10 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (80 mg, 0.09 mmol) at rt under an atmosphere of N₂. 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 Na₂SO₄. 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 Et₃N (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 1 hr, 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 Br₂ (49.0 g, 290 mmol) at rt. After stirring at rt for 2 h, the reaction mixture was slowly added saturated aqueous NaHCO₃. The organic phase was washed with brine and dried with anhydrous Na₂SO₄. 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 CH₃CN (100 mL) was added (*S*)-N-Boc-Pro-OH (19.4 g, 89.9 mmol), followed by Et₃N (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 Na₂SO₄. 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 NH₄OAc (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)Cl₂ (624 mg, 0.765 mmol) under an atmosphere of N₂. 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 Na₂SO₄. 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 Br₂ (46.3 g, 290 mmol) and I₂ (1.25g, 43.5mmol). After completing the addition, the reaction mixture was refluxed for 30 min. The reaction mixture was

cooled 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 CH₃CN (200 mL) was added EDCI (18.3 g, 95.5 mmol), Et₃N (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 NH₄Cl, saturated aqueous NaHCO₃, and brine, respectively and dried with anhydrous Na₂SO₄. 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 NH₄Cl (5 mL). The solvent was removed and the residue was diluted with DCM. 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/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 Br₂ (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 Na₂SO₄. 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 CH₃CN (15 mL) was added (*S*)-N-Boc-Pro- OH (3.14 g, 14.6 mmol) and Et₃N (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 NH₄Cl and water respectively, and dried with anhydrous Na₂SO₄. The solvent was removed and the residue was dried *in vacuo* to

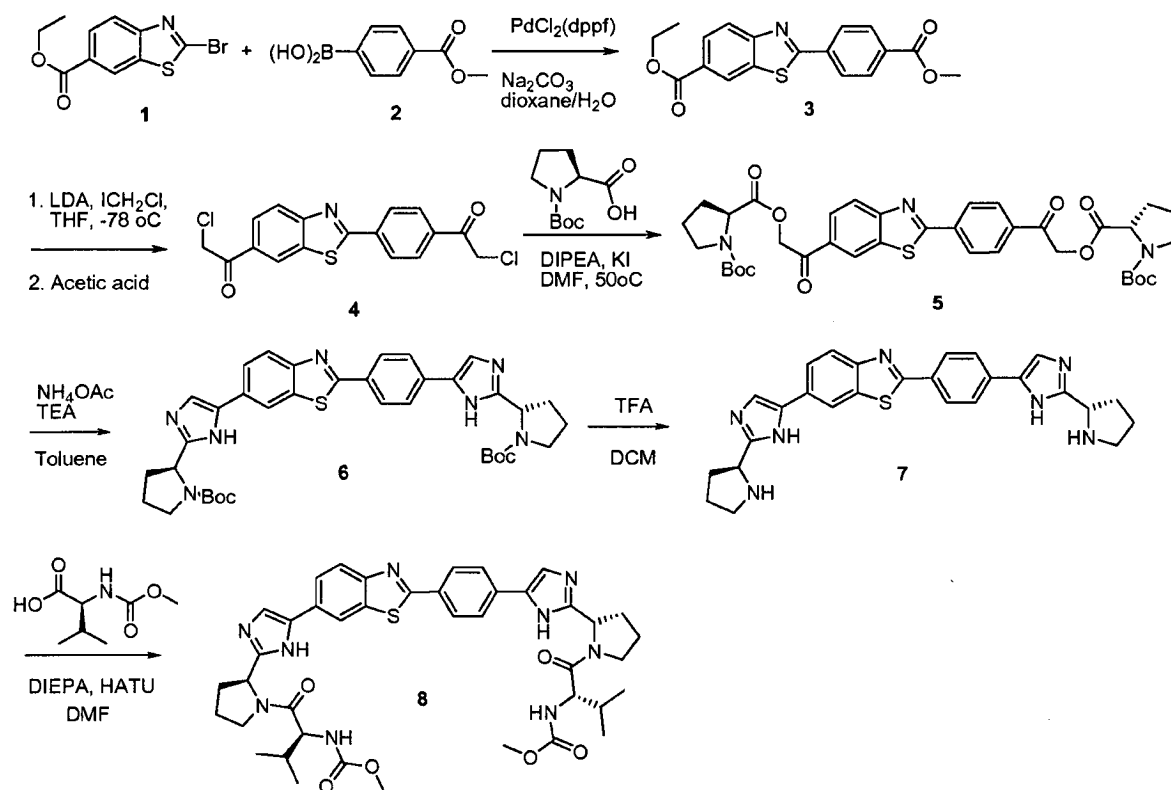
give crude compound **128** (5.6 g), which was used for the next step without further purification. LC-MS (ESI): m/z 462.1 ($M + H$)⁺.

[0500] **Step j.** A mixture of crude compound **128** (5.6 g) and NH₄OAc (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 Na₂SO₄. 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 NaHCO₃ (330 mg, 3.01 mmol) in 1, 2-dimethoxyethane (15 mL) and water (5 mL) was added Pd(dppf)Cl₂ (107 mg, 0.131 mmol) under an atmosphere of N₂. 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 Na₂SO₄. 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), $\text{Pd}(\text{dppf})\text{Cl}_2$ (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 CELITETM 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 chloriodomethane (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.

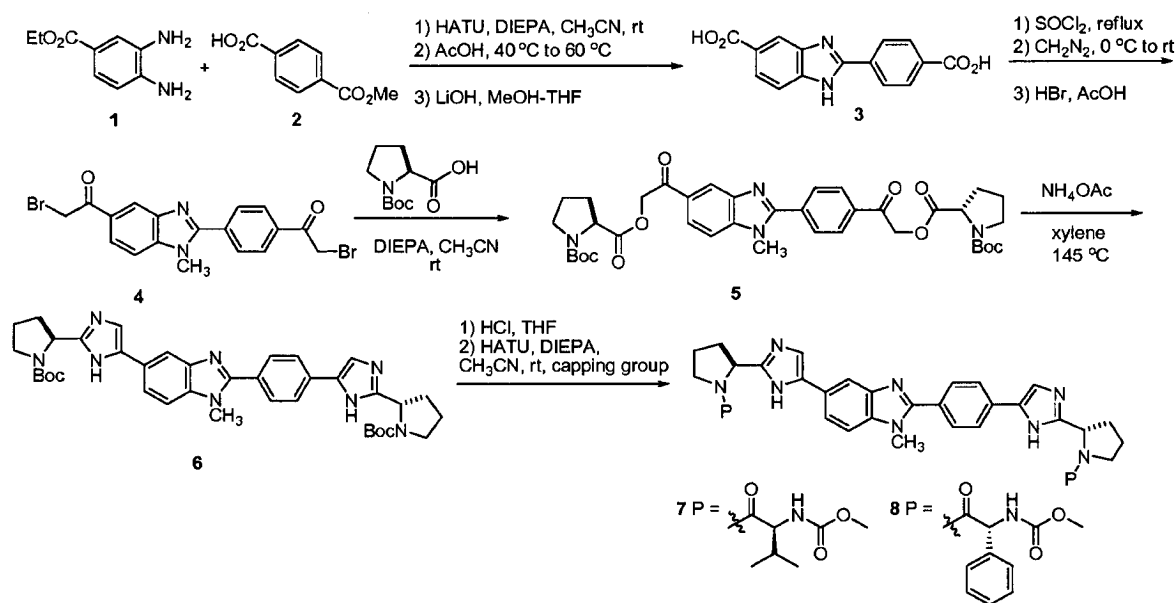
[0507] **Step d.** A mixture of **4** (0.59 g, 1.61 mmol), N-Boc-L-Proline (0.83 g, 3.85 mmol), KI (0.64 g, 3.85 mmol) and diisopropylethylamine (0.64 g, 3.85 mmol) in DMF (40 mL) was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was treated with water. The solid was collected by filtration and washed with water twice. After being dried in vacuum, the crude product was purified by flash chromatography (ethyl acetate/hexanes = 1/9 to 1/5 (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 (NH₄OH/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). ^1H 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 ($\text{M}+\text{H}$) $^+$.



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 ($\text{M}+\text{H}$) $^+$: 343, ($\text{M}-\text{H}$) $^-$: 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 yield), 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 °C, and then stirred it at 0 °C 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-benzimidazol-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 CH₃CN (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 H₂O. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with H₂O (50 mL) and brined (50 mL), dried over Na₂SO₄, 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)⁺.

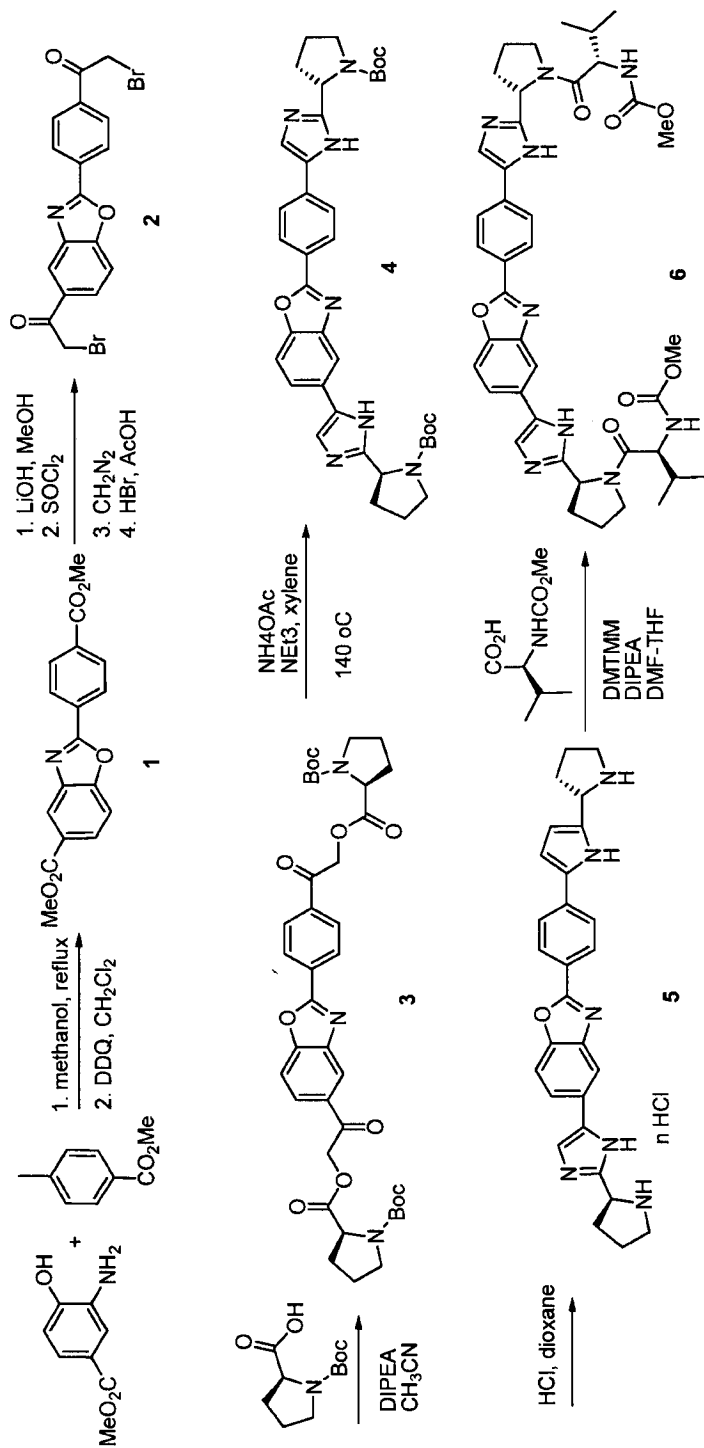
[0517] **Step g.** To a crude solution of **5** (~5.72 mmol) in xylene (50 mL) was added NH_4OAc (6.61 g, 85.8 mmol). The resulting mixture was heated at 145 °C for 1.5 h, and then all solvent was removed on a rotary evaporator to give a crude mixture, which was subject to column chromatography eluting 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 ($\text{M}+\text{H}$)⁺.

[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. ($\text{M}+\text{H}$)⁺.

[0519] **Step i.** To a crude solution of the HCl salt (48 mg, ~0.1 mmol), 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 ($\text{M}+2$)/2⁺: 397, ($\text{M}+1$)⁺: 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 ($\text{M}+\text{H}$)⁺.

[0521] The N-Moc-D-Phg-OH capped 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 ($\text{M}+2$)/2⁺: 431, ($\text{M}+1$)⁺: 860.



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 NaHCO₃ (200 mL) was added. The suspension was filtered off, the resulting solid was washed with saturated NaHCO₃ (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 Na₂CO₃ 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.

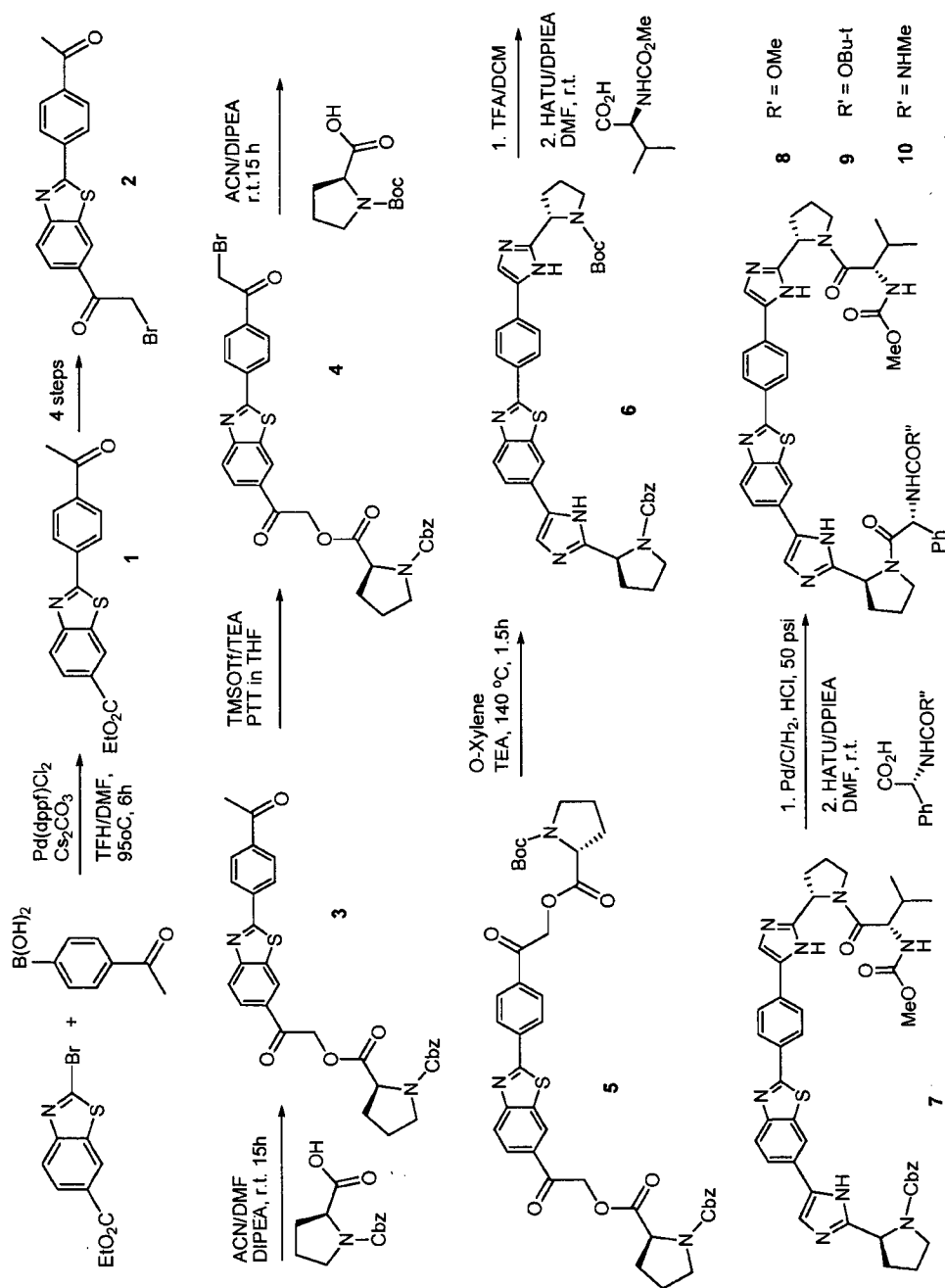
[0527] **Step f.** A solution of bromoketone **2** (1.38 g, 3.2 mmol), N-Boc-LProline (2.7 g, 12.6 mmol) and DIPEA (2.2 mL, 12.6 mmol) in acetonitrile (3 mL) was stirred at rt overnight.

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 Na₂SO₄. 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 °C for 90 min. Upon removal of volatile solvents the residual material was purified by silica gel chromatography (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, CD₃OD) 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)⁺.



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)Cl₂ (14 mg, 0.05 mmol) and Cs₂CO₃ (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 NaHCO₃, brine and dried with Na₂SO₄, 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, CDCl₃) 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/H₂O (100 mL) was added LiOH·H₂O (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, CDCl₃) 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 NaHCO₃ (200 mL) and brine, dried over Na₂SO₄. 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 NaHCO₃ solution. The mixture was partitioned between water and CH₂Cl₂ (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 NaHCO₃ (200 mL) and brine, dried with Na₂SO₄. 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 CH₂Cl₂, 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 (CH₂Cl₂/MeOH = 9.8 / 0.2 (v/v)) to give **7** (500 mg, 74% yield). LC-MS (ESI): *m/z* 773.3 (M+H)⁺.

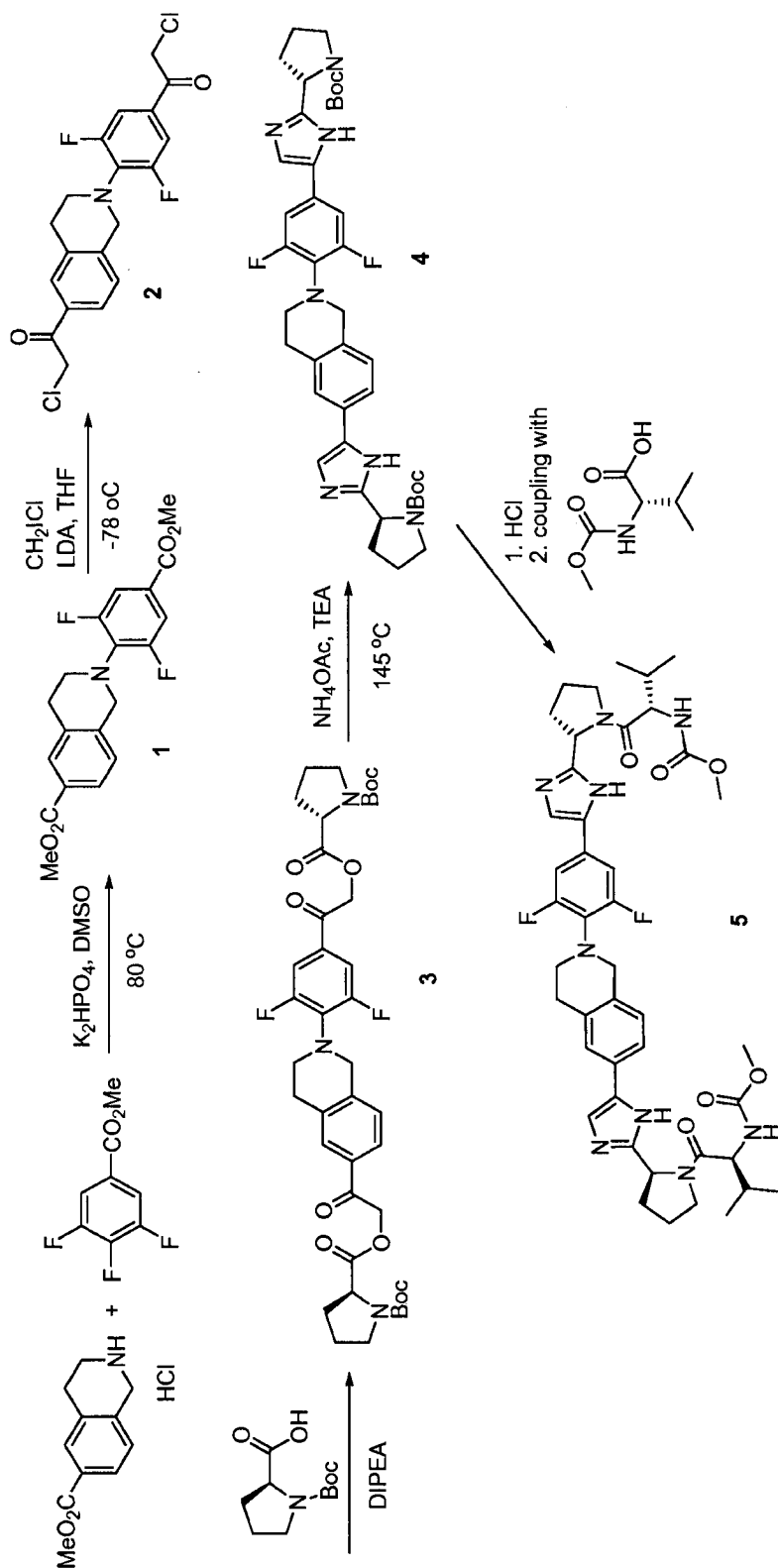
[0542] **Step l.** To a solution of **7** (500 mg, 0.647 mmol) in MeOH (20 mL) was added Pd/C (50 mg) and several drops of con. HCl, purged with H₂. The reaction mixture was shaken in the shaker under 60 psi for 48h. The mixture was filtered on CELITETM and concentrated; the residue was purified on silica 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 μ L, 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 μ L, 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)⁺.



Scheme 10-1

EXAMPLE 10 – Synthesis of compounds of Formula II_m

[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 K₂HPO₄ (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 H₂O. The organic layer was washed with H₂O followed by brine and dried (Na₂SO₄). 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. ¹H NMR (300 MHz, CDCl₃) 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.

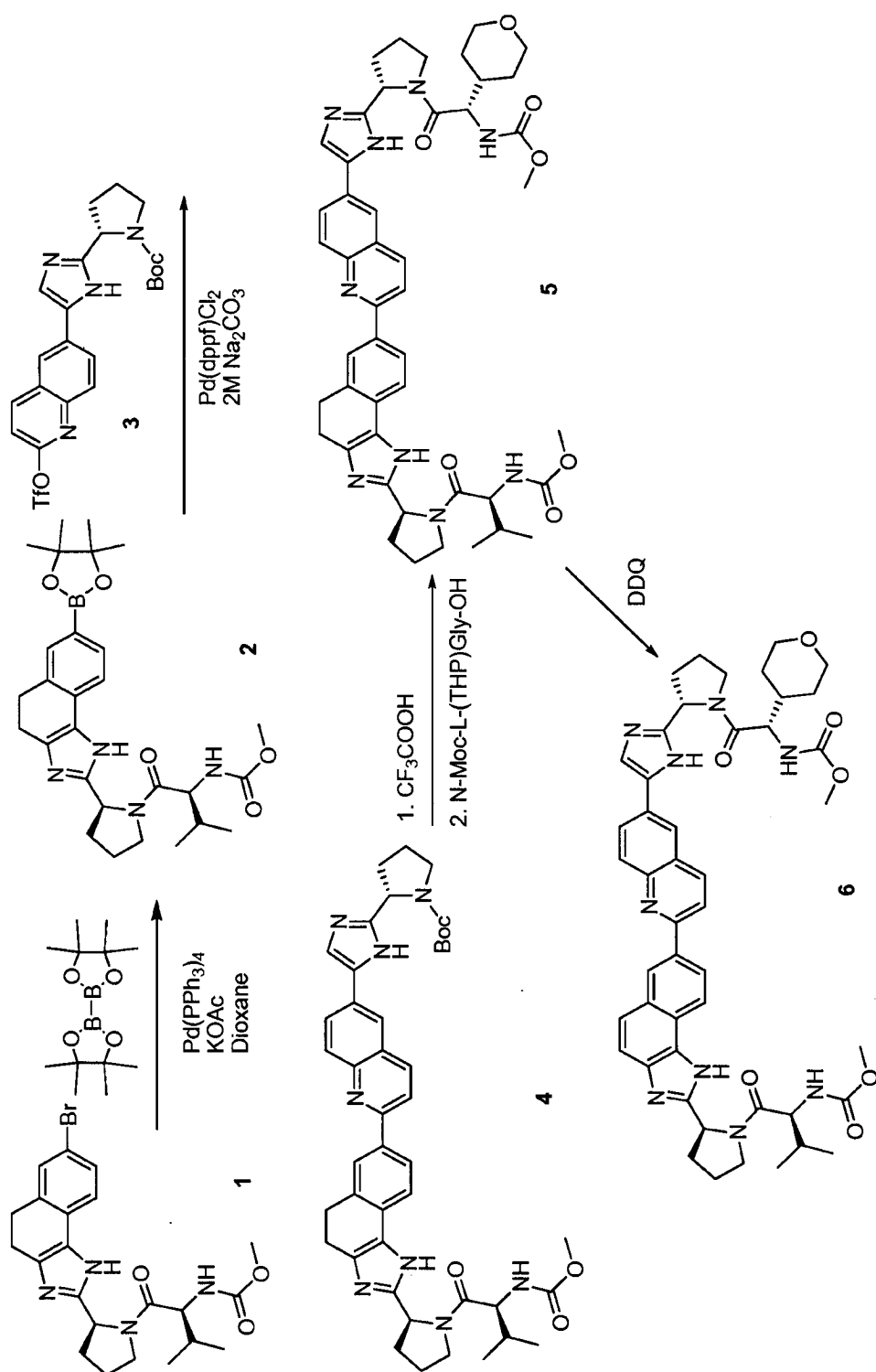
[0548] **Step b.** To a solution of **1** (2.0 g, 5.53 mmol) and chloriodomethane (5.86 g, 33.2 mmol) in THF (40 mL) was added LDA (precooled to -78 °C, freshly made from 10 mL diisopropylamine and 26.5 mL of 2.5 M *n*-BuLi in hexanes in 40 mL of THF) at -78 °C via cannula over 20 min. The reaction mixture 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 NaHCO₃. The organic layer was washed with H₂O and dried over Na₂SO₄. 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. ¹H NMR (300 MHz, CDCl₃) 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 CH₃CN (15.3 mL). The reaction mixture was then heated to 50 °C 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 H₂O (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 Na₂SO₄, 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), NH₄OAc (2.89 g, 39.6 mmol), TEA (5.52 mL, 96.6 mmol) 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 H₂O 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 Na₂SO₄, 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. 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 ¹H NMR (CD₃OD, 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)⁺.



Scheme 11-1

EXAMPLE 11 – Synthesis of compounds of Formula Vc

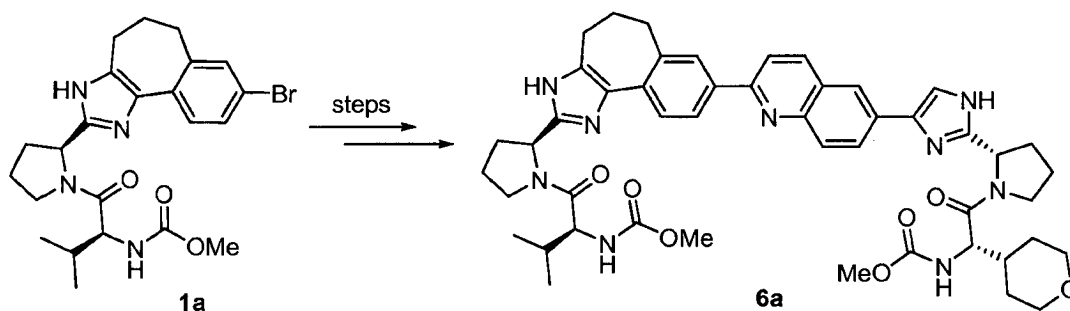
[0552] **Step a.** Referring to Scheme 11-1, to a solution of the bromide **1** (2.0 g, 4.2 mmol, prepared according to published conditions) in dioxane (60 mL) was added bis(pinacolato)diboron (4.32 g, 17 mmol), Pd(PPh₃)₄ (0.49 g, 0.42 mmol) and potassium acetate (2.06 g, 21 mmol) under nitrogen atmosphere. 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 H₂O (20 mL), dried over sodium sulfate and concentrated in vacuo. The residue was further purified by silica gel column chromatography (hexanes/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)Cl₂-DCM (114 mg, 0.14 mmol) in 2 M Na₂CO₃ (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 (NH₄OH/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)⁺.

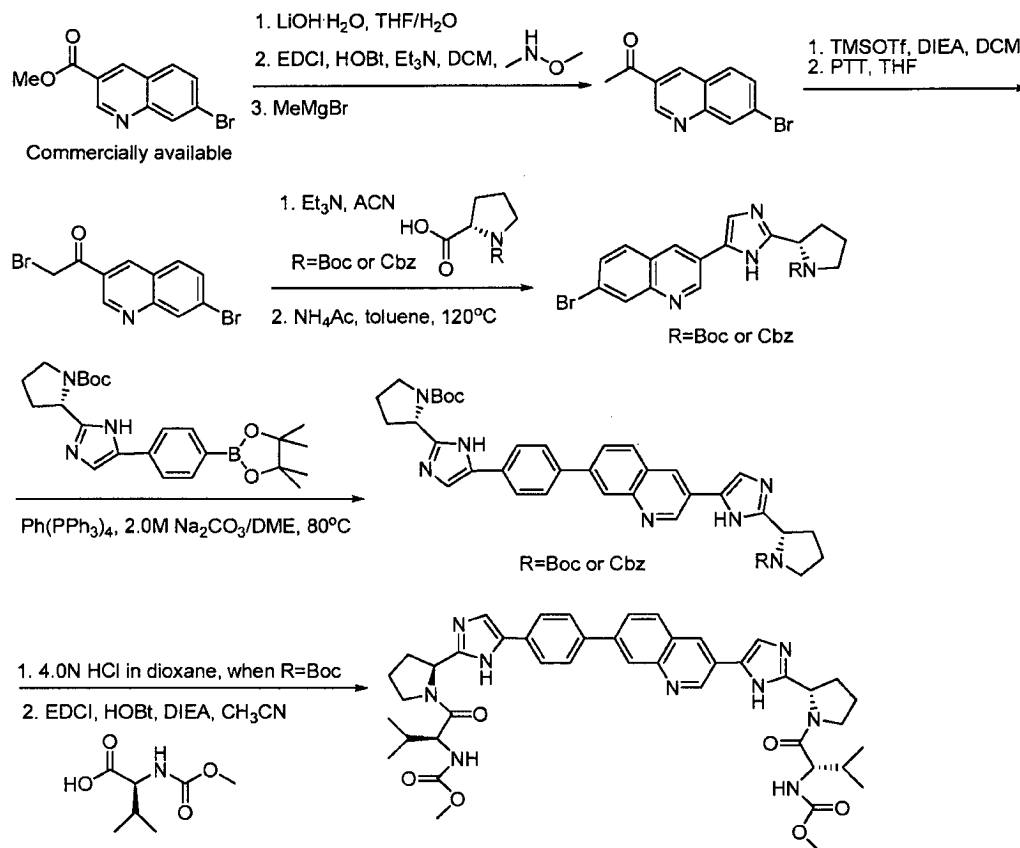
[0554] **Step c.** Trifluoroacetic acid (2.5 mL) was slowly added into a solution of **4** (0.80 g, 1.5 mmol) in CH₂Cl₂ (5.0 mL) at rtrt. The resulting mixture was stirred at rtrt for 2 h, and then concentrated to dryness. The crude product was dried *in vacuo* to give a TFA salt, which was used for the next step without further purification. LCMS (ESI): *m/z* 659.3 (M+H)⁺.

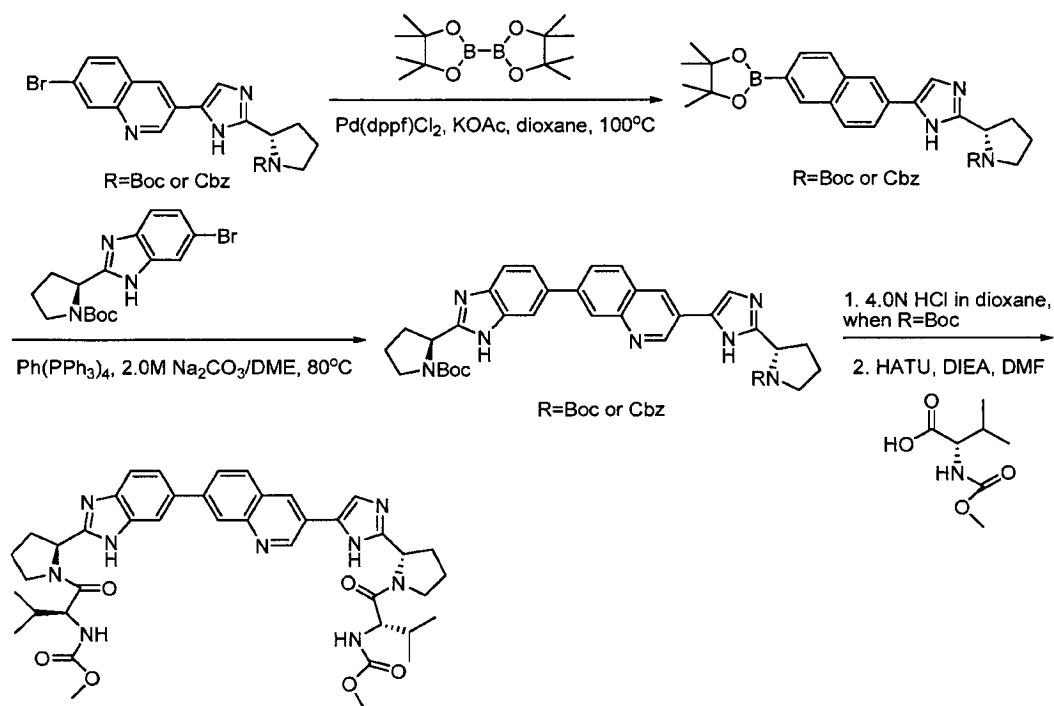
[0555] **Step d.** To a mixture of the TFA salt (69.1 mg, 0.11 mmol) obtained from above reaction in DMF (3 mL) was added DIPEA (0.23 mL, 1.4 mmol), followed by L- N-methoxycarbonyl-(4-tetrahydro-2H-pyran-4-yl)glycine (30 mg, 0.14 mmol) and HATU (52 g, 0.14 mmol). After stirring at rt for 2 h, the reaction mixture was slowly dropped into H₂O 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 (CDCl₃, 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. ^1H 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 ($\text{M}+\text{H}$) $^+$.

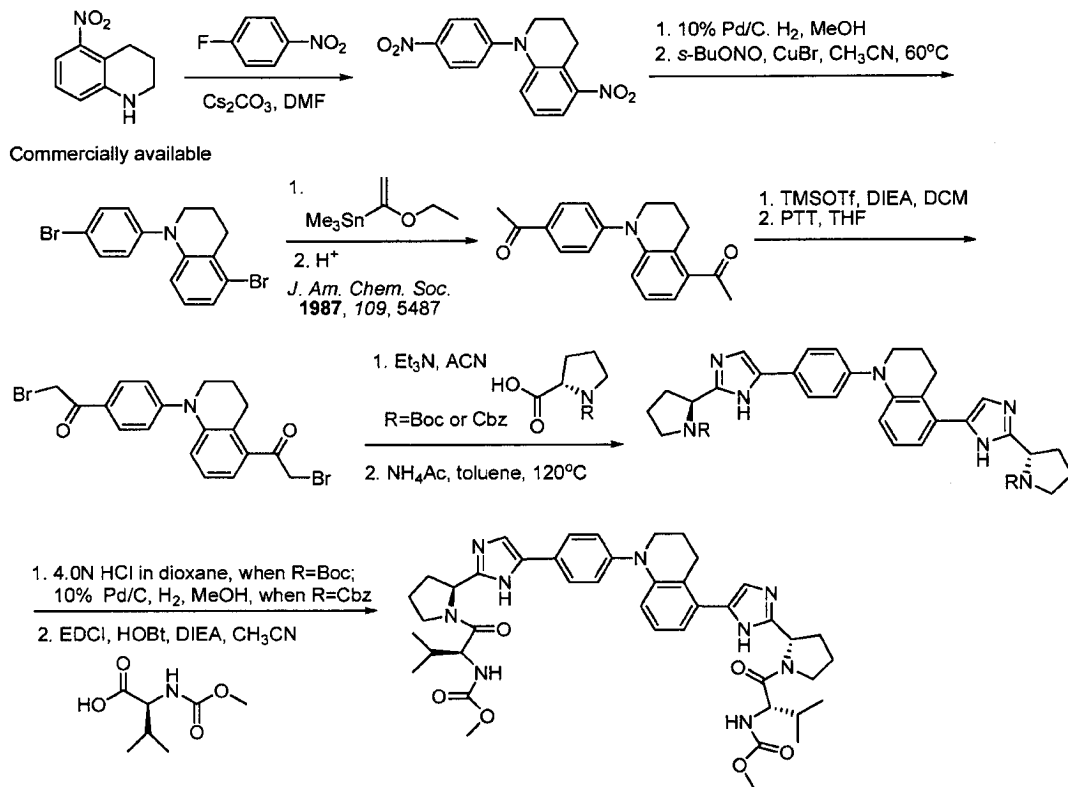


[0557] Following procedures and conditions described in Scheme 11-1 and substituting compound **1a** for compound **1**, compound **6a** was prepared. ^1H NMR (300 MHz, CD_3OD) δ 9.21-9.18 (m, 1H), 8.79 (s, 1H), 8.56-8.50 (m, 3H), 8.26-8.19 (m, 3H), 8.10-8.07 (m, 1H), 5.32-5.25 (m, 2H), 4.34-4.24 (m, 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 ($\text{M}+\text{H}$) $^+$.

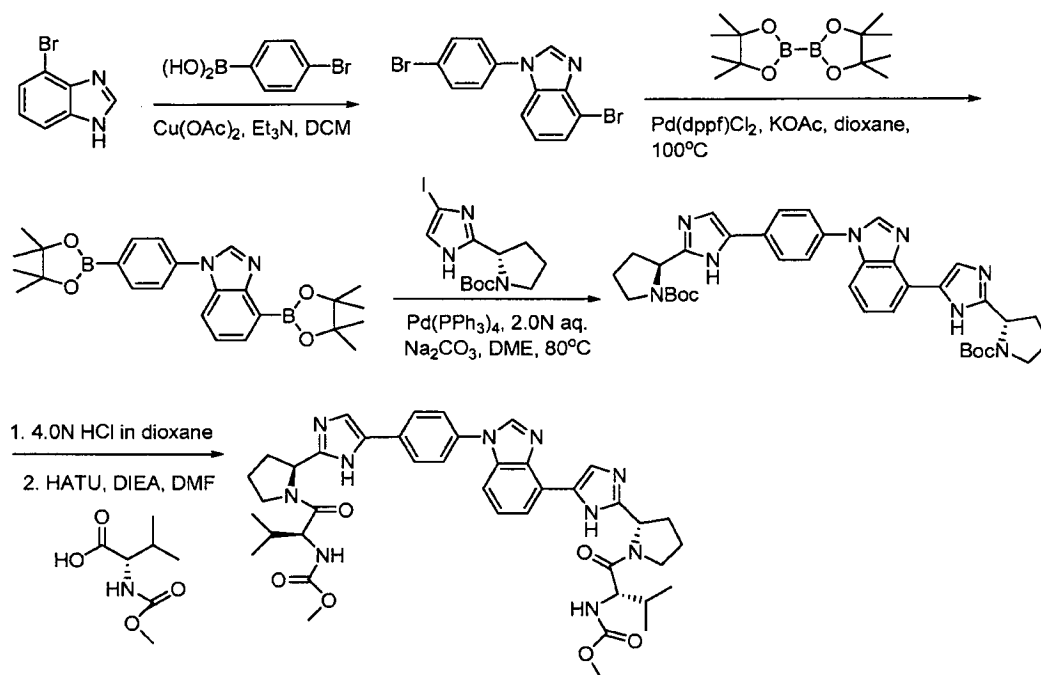
EXAMPLE 12 – Additional Synthetic Schemes for Compounds of the Invention**Scheme 12-1**



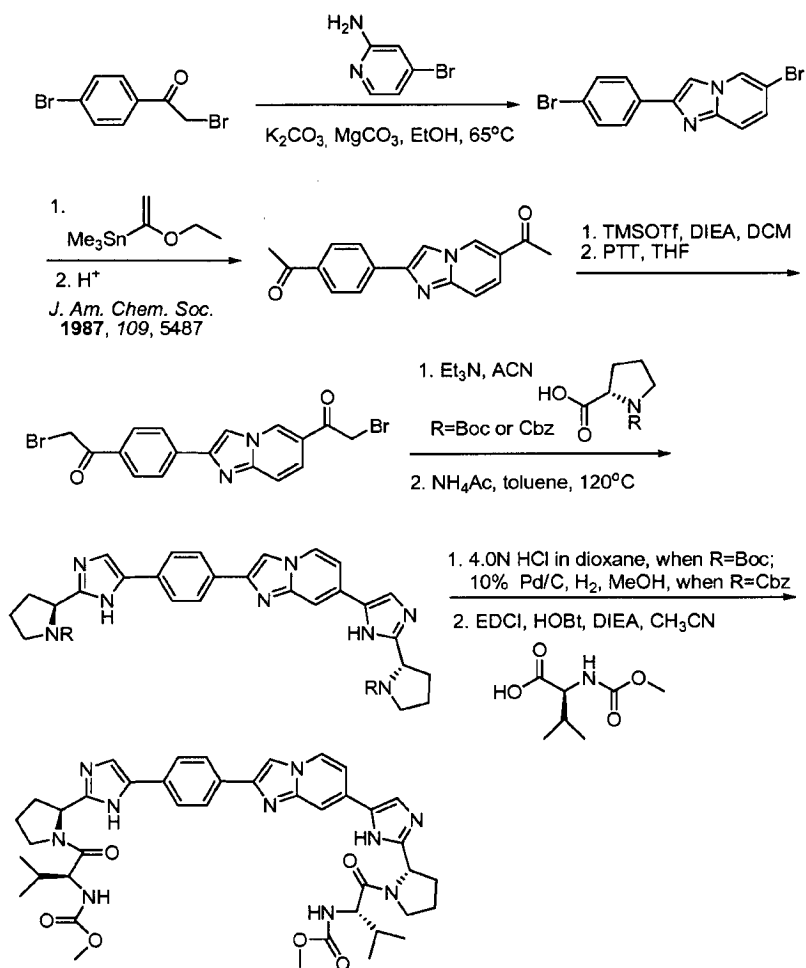
Scheme 12-2



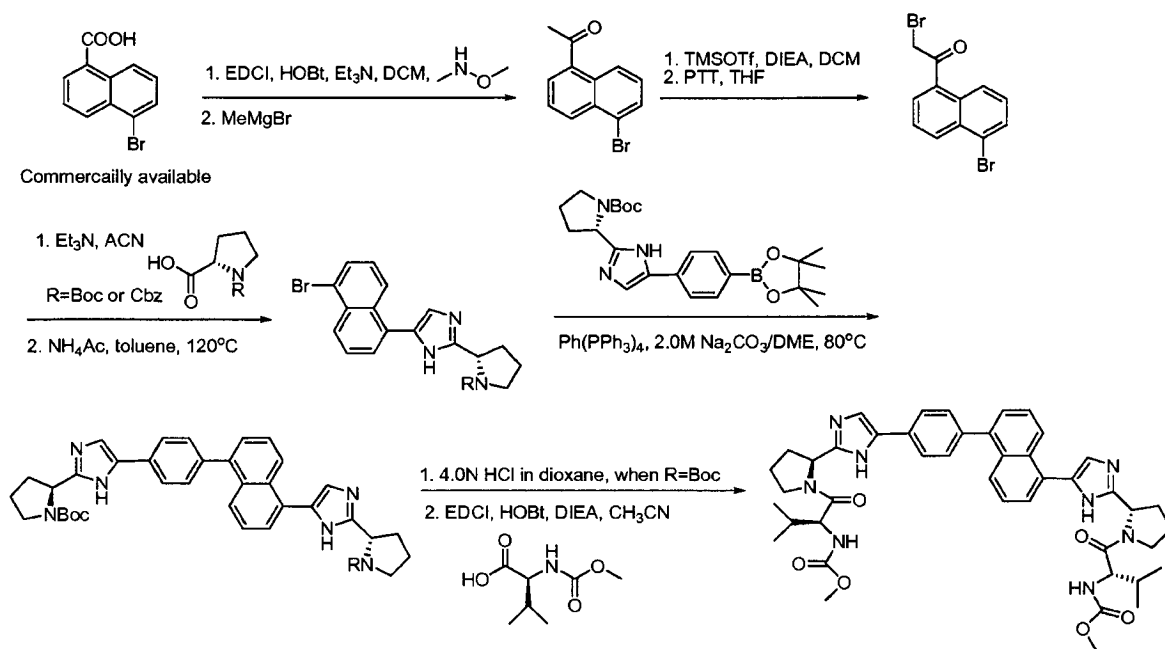
Scheme 12-3



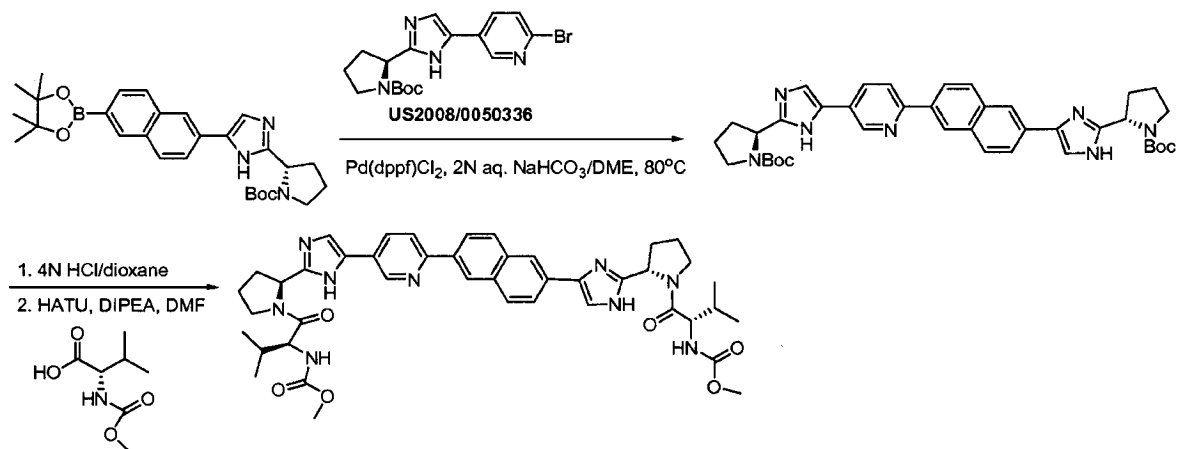
Scheme 12-4



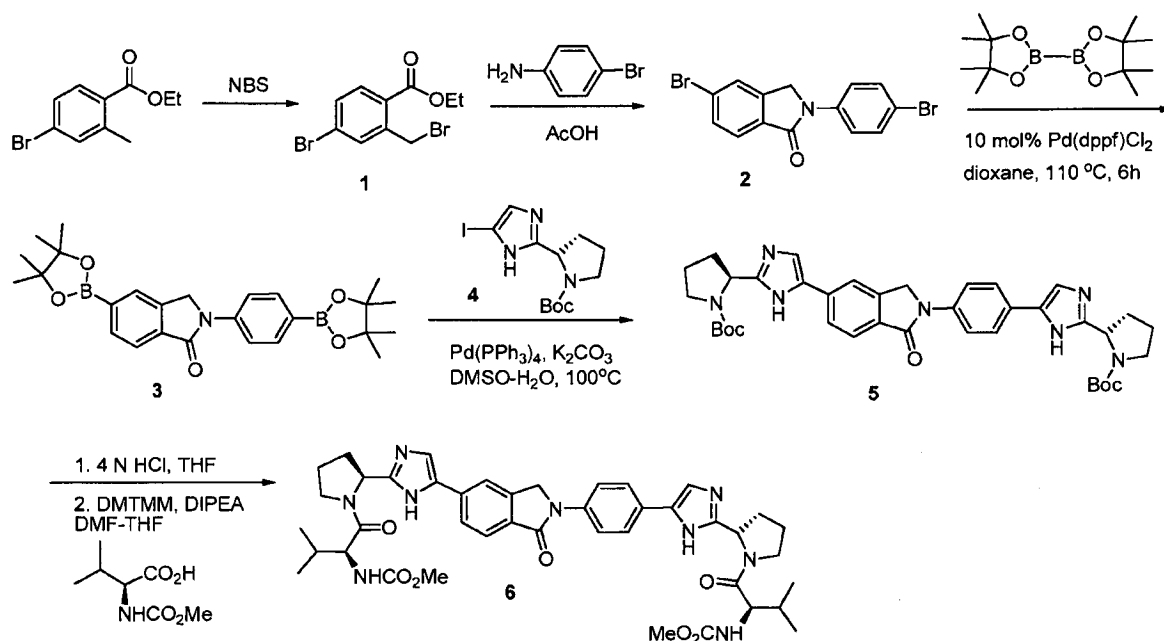
Scheme 12-5



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-bromoaniline (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). ^1H 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

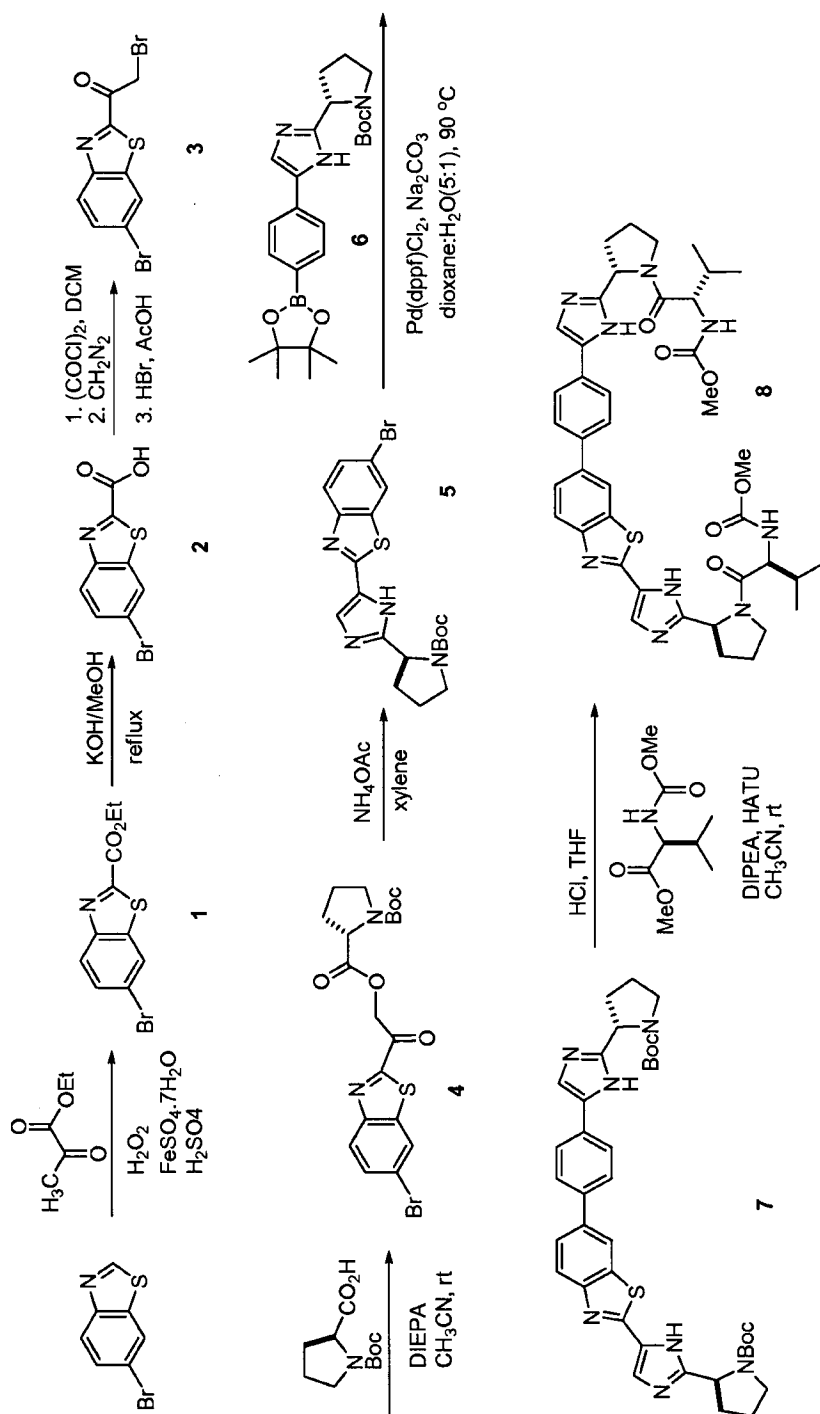
heated at 110 °C for 30 h. The reaction mixture was cooled to rt and diluted with H₂O. The aqueous layer was extracted with ethyl acetate, and the organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The crude material was purified by flash column chromatograph eluted with ethyl acetate to afford dark yellow solid **3** (0.49 g, 73% yield). ¹H NMR (300 MHz, CDCl₃) 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(PPh₃)₄ (200mg, 0.17 mmol) and potassium carbonate (311 mg, 2.25 mmol) in DMSO (10 mL) and H₂O (3.5 mL) was heated at 100 °C for 14h. The reaction mixture was cooled to rt and diluted with H₂O and extracted with dichloromethane. The combine organic layers were dried over Na₂SO₄, 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 (CDCl₃, 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 H₂O and extracted with dichloromethane. The combine organic layers were dried over Na₂SO₄, 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 (CDCl₃, 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**.



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 H₂O₂ (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 H₂O (45 mL) and H₂SO₄ (13.7 g, 7.5 mL, 140 mmol) was added simultaneously the fresh prepared ethyl pyruvate mixture and FeSO₄ · 7H₂O (38.9 g, 140 mmol) in H₂O (90 mL) at 0 °C. The resulting mixture was kept at 0 °C and stirred at rt overnight. To the mixture was added additional H₂SO₄ (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 H₂O₂ 35%, 27.2 g, 27.2 mL, 280 mmol) and FeSO₄ · 7H₂O (77.8 g, 280 mmol) in H₂O (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 Na₂SO₄, 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 H₂O (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 Na₂SO₄, 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 oxalyl 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 solid, 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 CH₃CN (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 H₂O. The mixture was extracted with EtOAc (3x50 mL), and then the combined organic phases were washed with H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, 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 NH₄OAc (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)Cl₂ (4 mg, 5 μmol), and Na₂CO₃ (35 mg, 0.33 mmol) in dioxane/H₂O (2.0 mL/0.4 mL) was purged with N₂. The resulting mixture was stirred at 90 °C for 8 h, and then diluted with H₂O. The reaction mixture was extracted with EtOAc, and combined organic was dried over Na₂SO₄, 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 CH₃CN (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 μ L, 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 H₂O to CH₃CN, and the isolated compound was ~80% purity. The product was further purified by prep-TLC eluting with EtOAc with 5% NH₄OH to give product 8 (4.5 mg) as a white solid. ¹H NMR (300 MHz, CDCl₃) 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.

$$\% \text{ Control} = (\text{Average Compound Value} / \text{Average Control}) * 100$$

[0577] The EC₅₀ value was determined using GraphPad Prism and the following equation:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope}))}$$

[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.

Combination Therapy

[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-nucleosidic HCV polymerase (replicase) inhibitors useful in the invention, include, but are not limited to, HCV-796, HCV-371, VCH-759, VCH-916, VCH-222, ANA-598, MK-3281, ABT-333, ABT-072, PF-00868554, BI-207127, GS-9190, A-837093, JKT-109, GL-59728 and GL-60667.

[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 ATM, Roferon-ATM, Canferon-A300TM, AdvaferonTM, InfergenTM, HumoferonTM, Sumiferon MPTM, AlfaferoneTM, IFN- β TM, FeronTM and the like; polyethylene glycol derivatized (pegylated) interferon compounds, such as PEG interferon- α -2a (PegasysTM), PEG interferon- α -2b

(PEGIntronTM), pegylated IFN- α -con1 and the like; long acting formulations and derivatizations of interferon compounds such as the albumin-fused interferon, AlbuferonTM, LocteronTM and the like; interferons with various types of controlled delivery systems (e.g. ITCA-638, omega-interferon delivered by the DUROSTM 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 ENBRELTM, REMICADETM and HUMIRATM.

[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

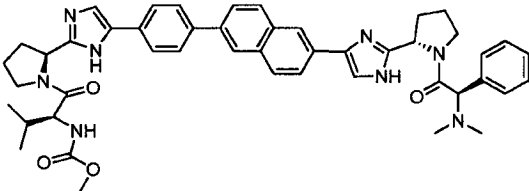
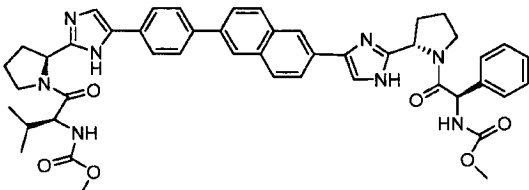
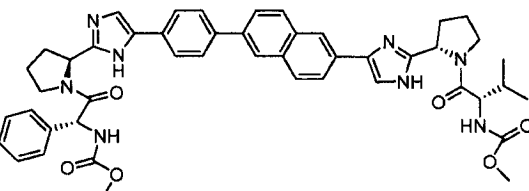
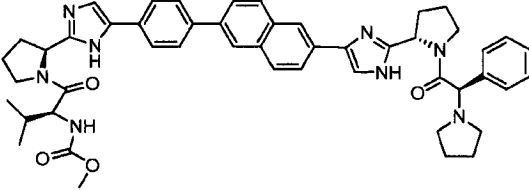
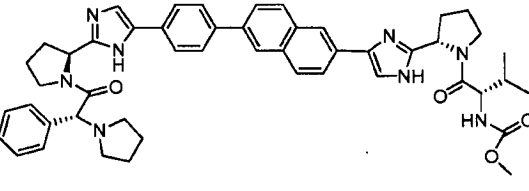
invention or where one treatment comprises a compound of the invention and the other comprises one or more biologically active agents) or it can be treatment with both agents at the same time (concurrently). Sequential therapy can include a reasonable time after the completion of the first therapy before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

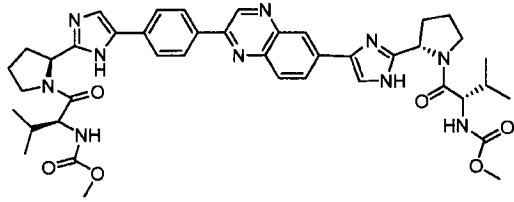
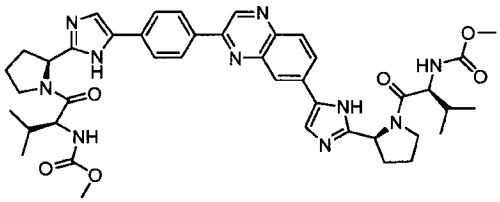
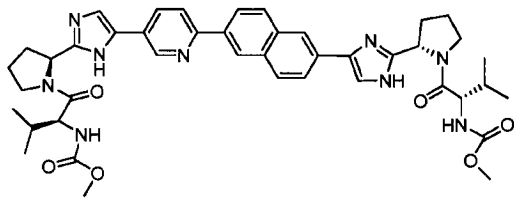
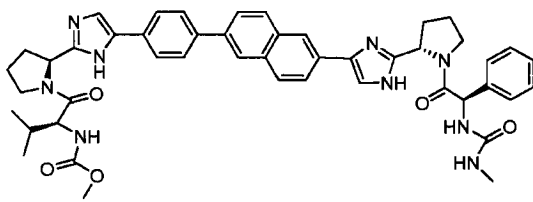
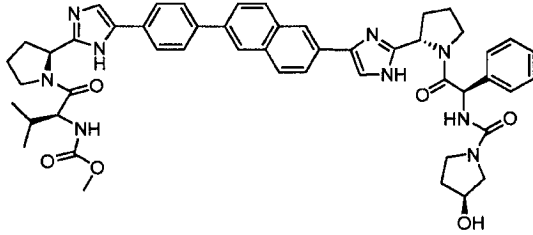
[0594] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

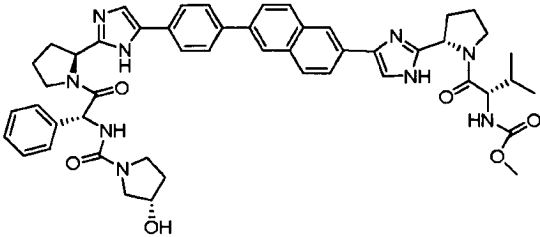
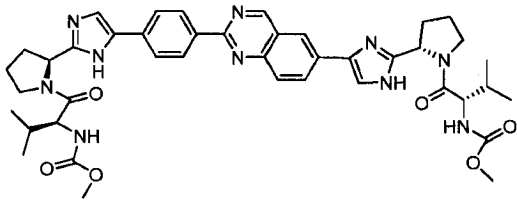
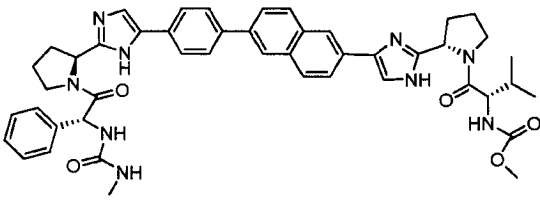
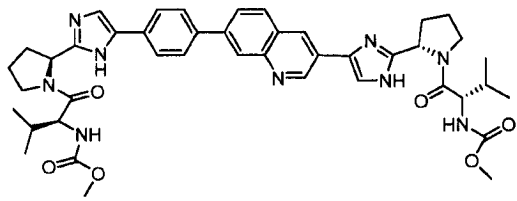
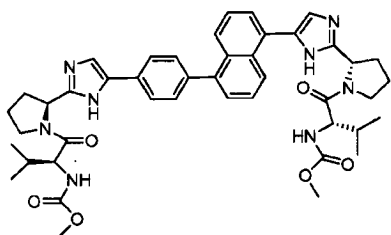
[0595] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the invention as defined in the appended claims.

Table 1

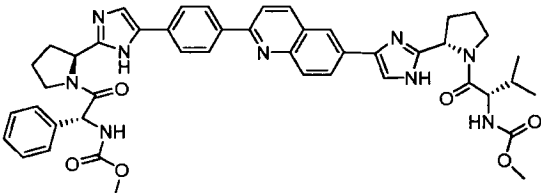
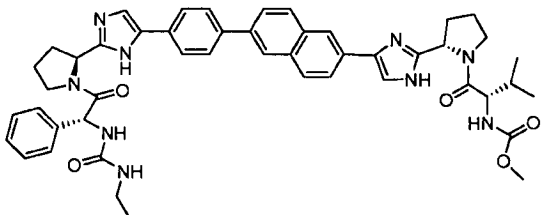
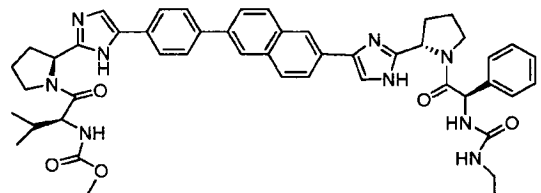
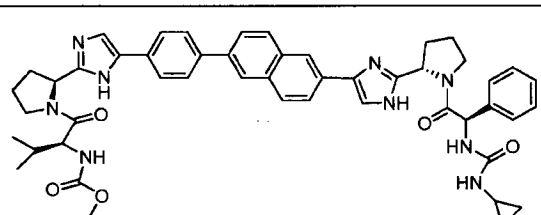
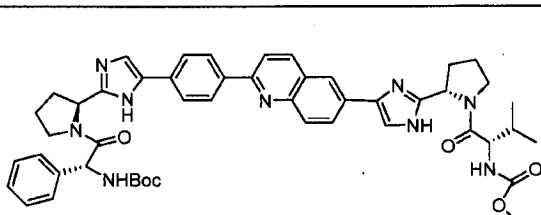
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
1		****	789.4
2		***	789.4
3		****	821.4
4		****	793.4
5		****	793.4

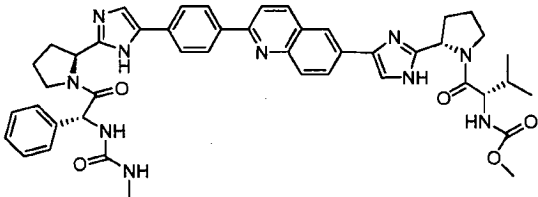
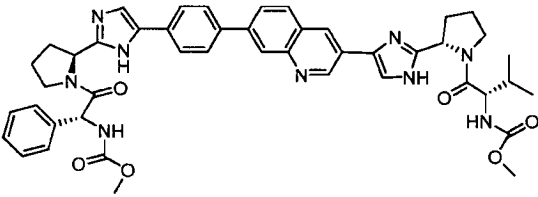
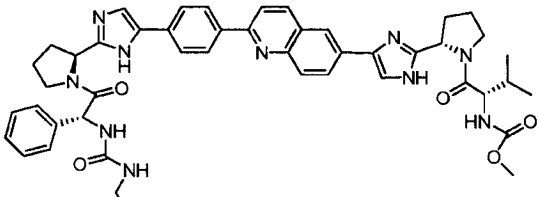
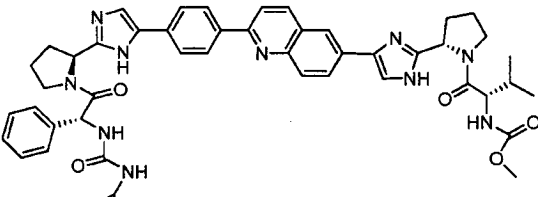
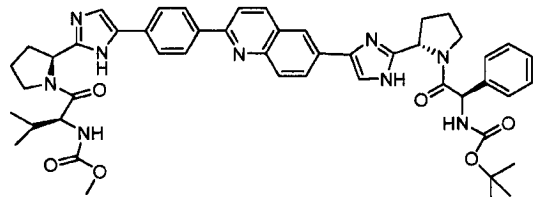
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
6		****	793.4
7		****	823.4
8		****	823.4
9		****	819.4
10		****	819.4

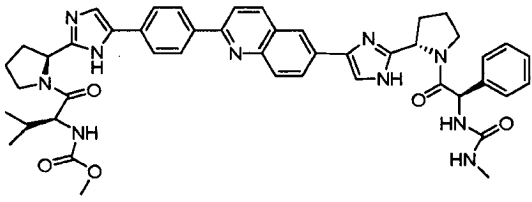
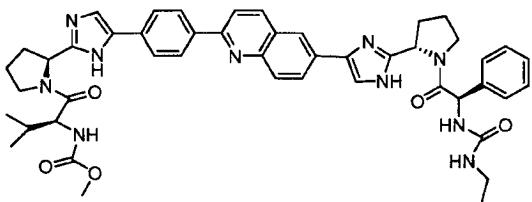
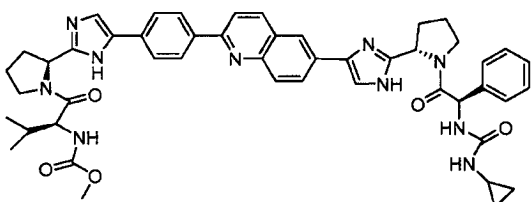
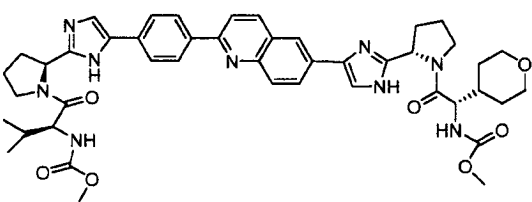
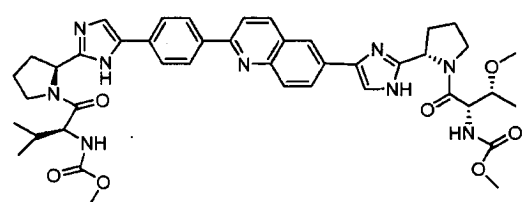
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
11		****	791.4
12		***	791.4
13		****	790.4
14s		****	822.4
15		****	878.4

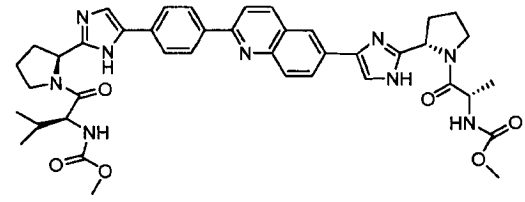
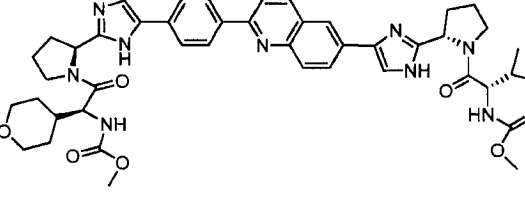
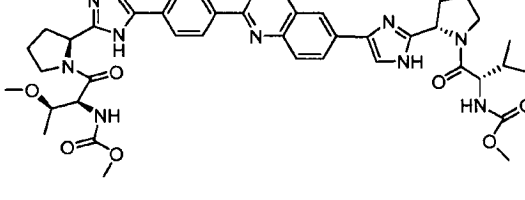
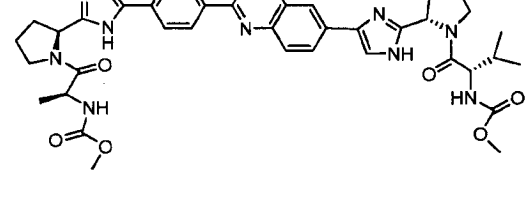
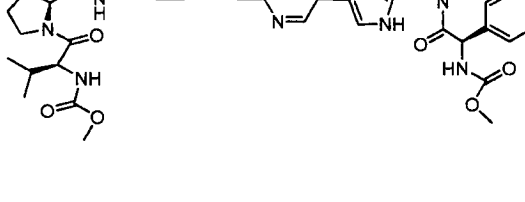
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
16		****	878.4
17		****	791.4
18		****	822.4
19		****	790.4
20		****	789.4

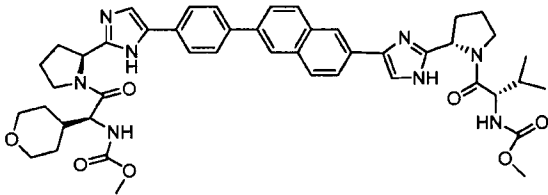
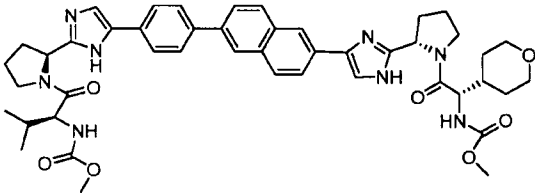
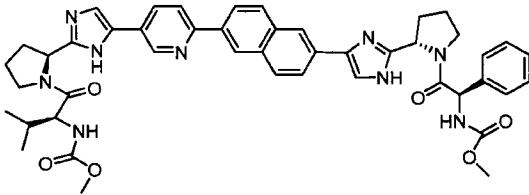
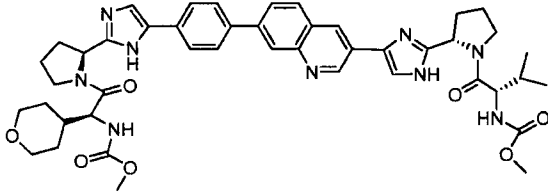
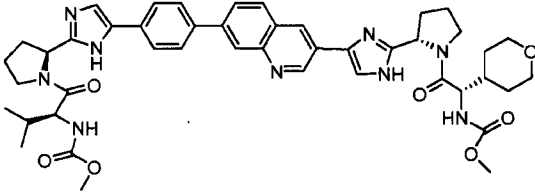
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
21		****	790.4
22		****	790.4
23		****	864.4
24		****	848.4
25		****	864.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
26		****	824.4
27		****	836.4
28		****	836.4
29		****	848.4
30		****	866.4

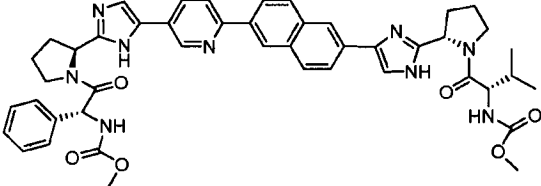
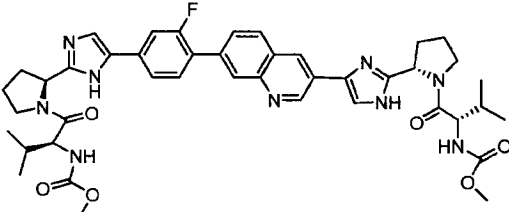
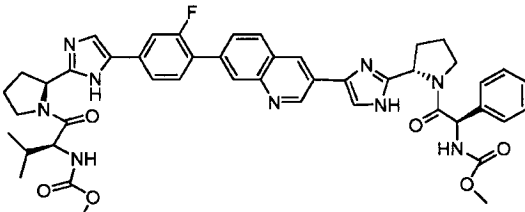
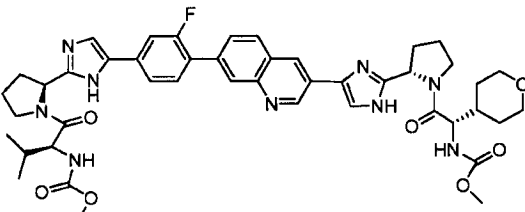
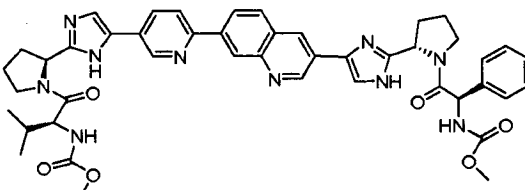
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
31		****	823.4
32		****	824.4
33		****	837.4
34		****	849.4
35		****	866.4

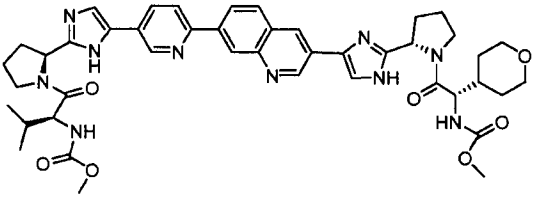
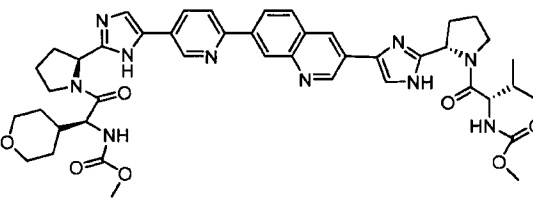
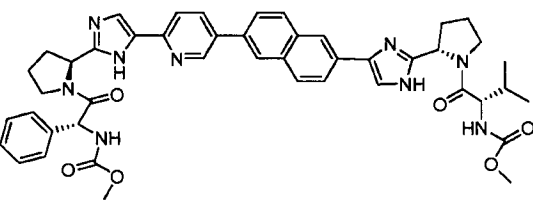
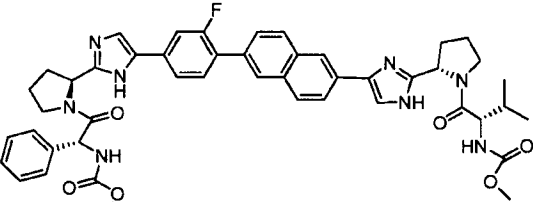
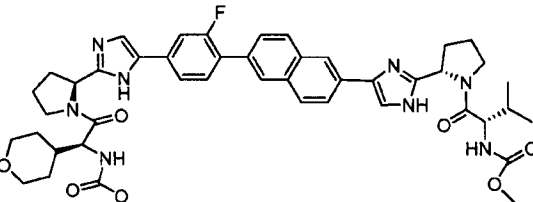
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
36		****	823.4
37		****	837.4
38		****	849.4
39		****	832.4
40		****	806.4

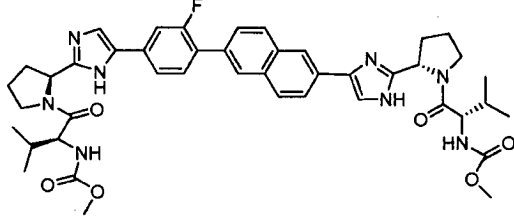
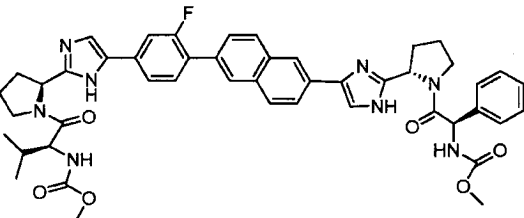
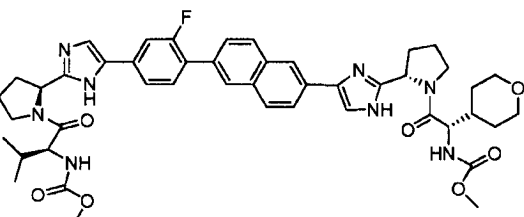
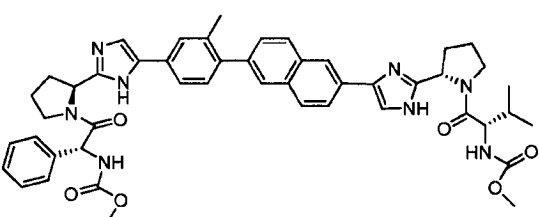
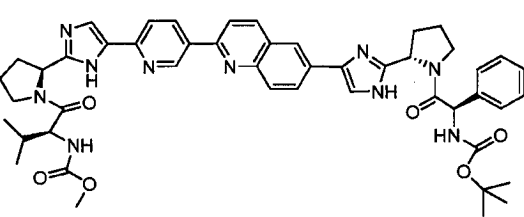
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
41		****	762.4
42		****	832.4
43		****	806.4
44		****	762.4
45		****	824.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
46		****	831.4
47		****	831.4
48		****	824.4
49		****	832.4
50		****	832.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
51		****	832.4
52		****	832.4
53		****	791.4
54		****	859.4
55		****	877.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
56		****	824.4
57		****	808.4
58		****	842.4
59		****	850.4
60		****	825.4

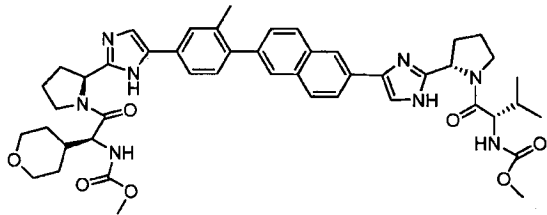
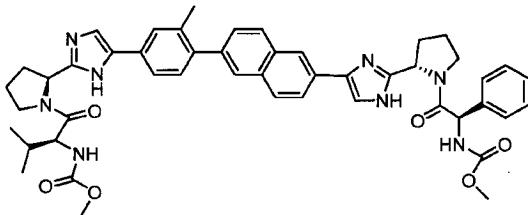
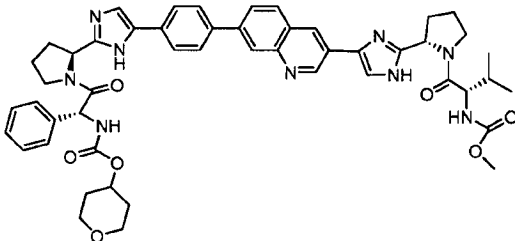
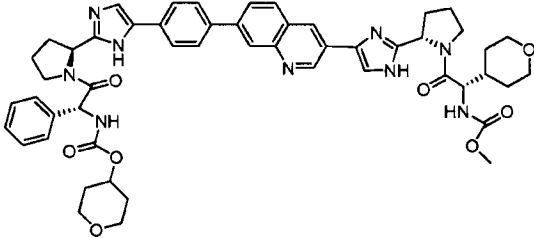
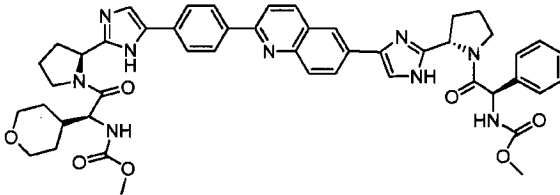
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
61		****	833.4
62		****	833.4
63		****	824.4
64		****	841.4
65		****	849.4

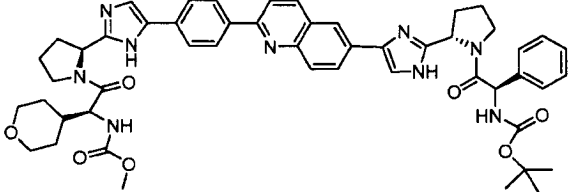
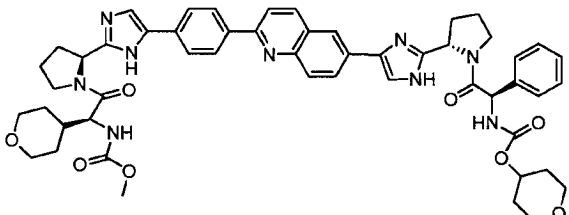
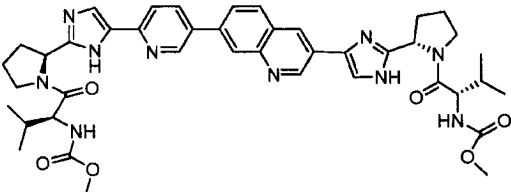
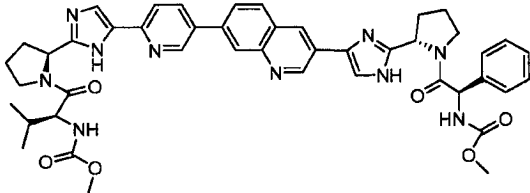
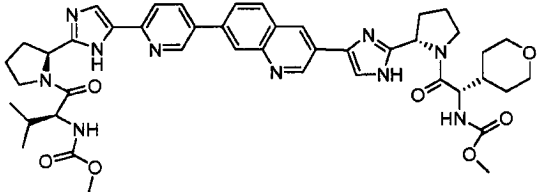
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
66		****	807.4
67		****	841.4
68		****	849.4
69		****	837.4
70		****	867.4

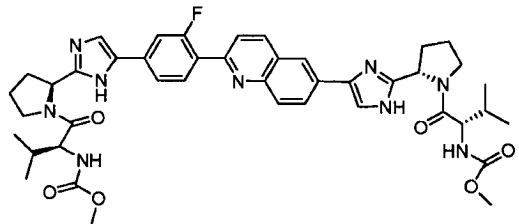
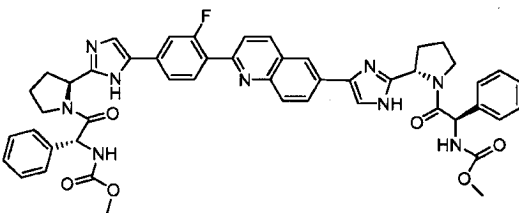
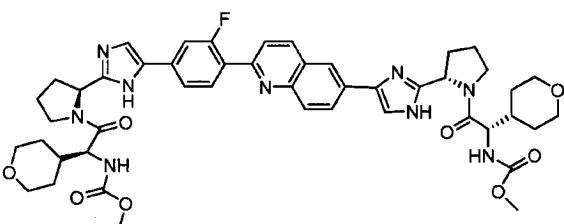
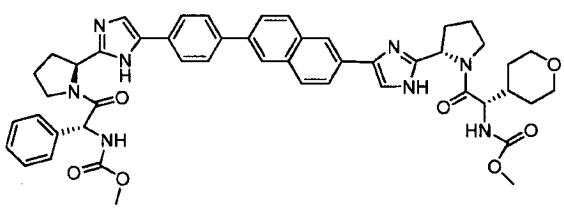
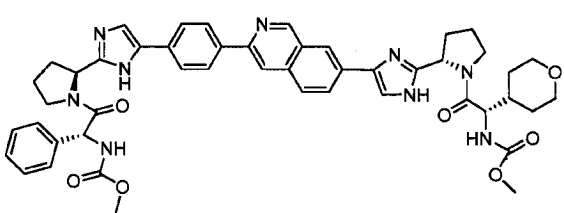
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
71		****	866.4
72		****	908.4
73		****	874.4
74		****	791.4
75		****	875.5

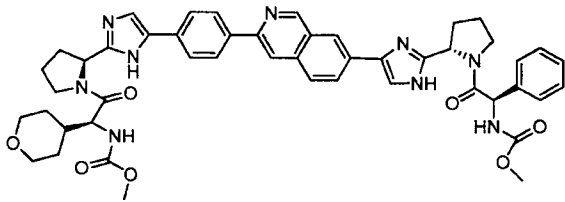
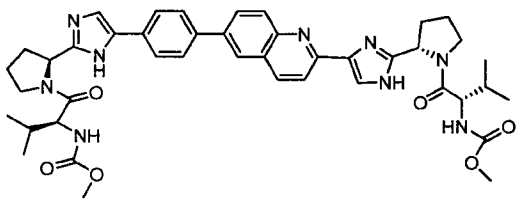
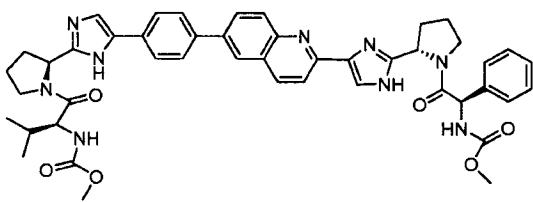
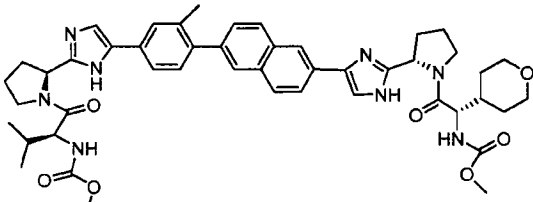
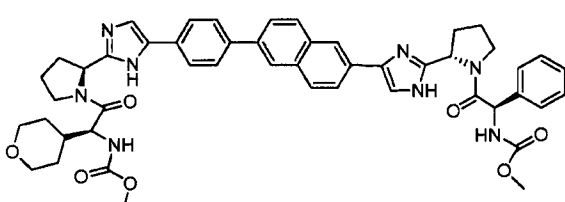
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
76		****	806.4
77		**	874.4
78		****	888.4
79		****	820.4
80		****	859.4

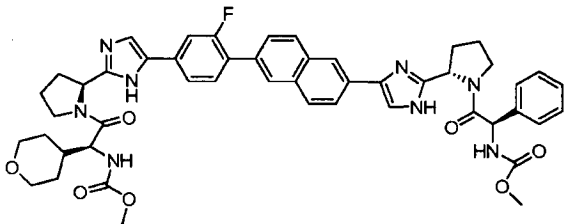
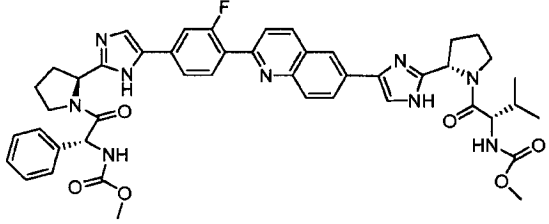
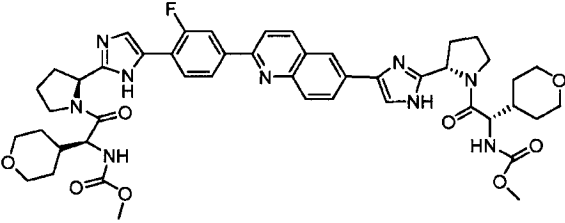
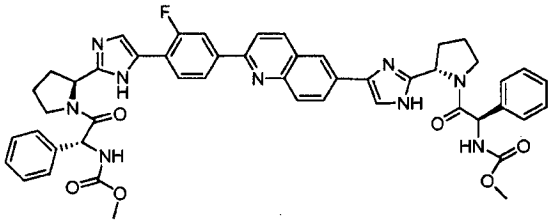
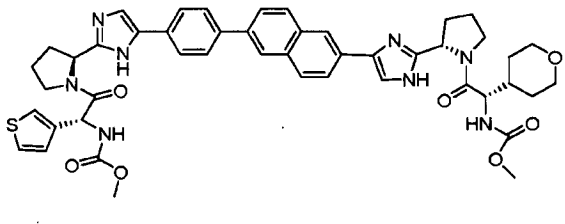
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
81		****	895.4
82		****	867.4
83		****	790.4
84		****	832.4
85		****	803.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
86		****	845.4
87		****	837.4
88		****	894.4
89		****	936.4
90		****	866.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
91		****	908.4
92		****	936.4
93		****	791.4
94		****	825.4
95		****	833.4

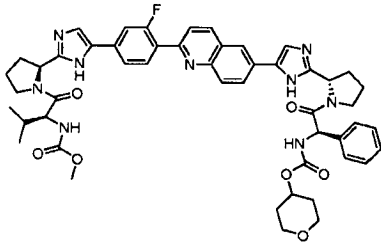
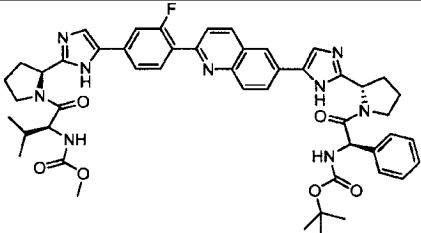
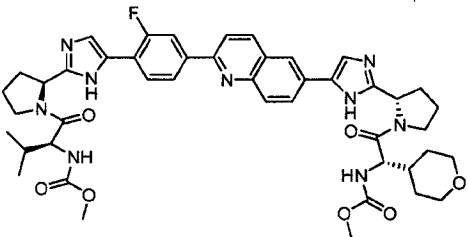
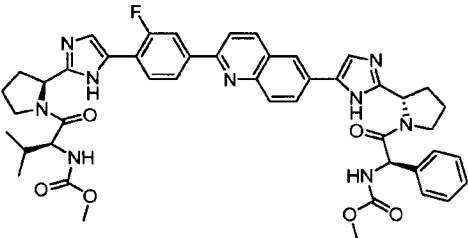
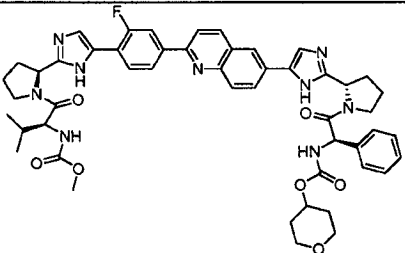
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
96		****	808.4
97		****	876.4
98		****	892.4
99		****	865.4
100		****	866.4

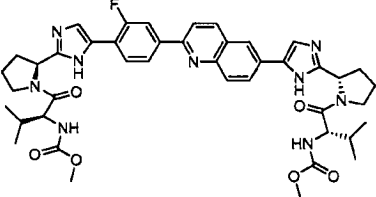
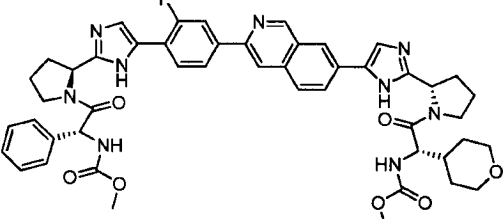
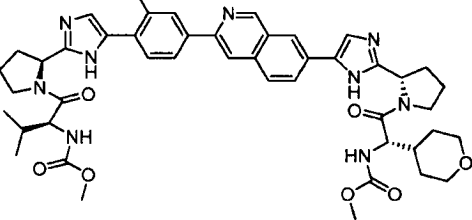
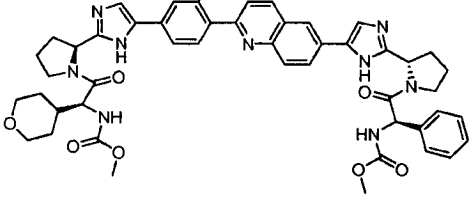
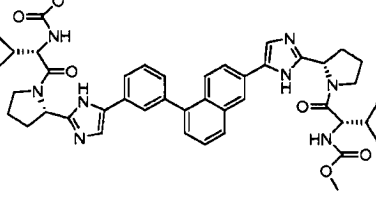
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
101		****	866.4
102		****	790.4
103		****	824.4
104		****	845.4
105		****	865.4

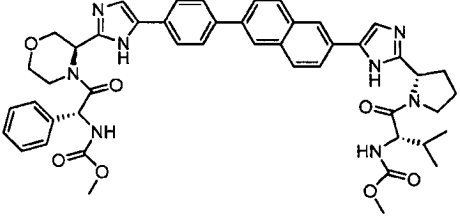
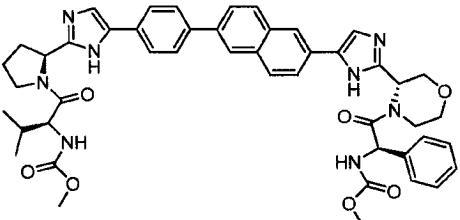
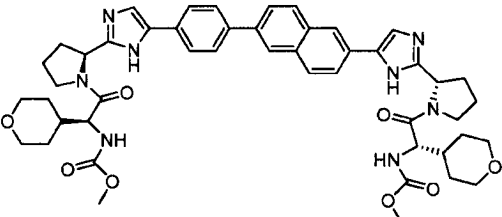
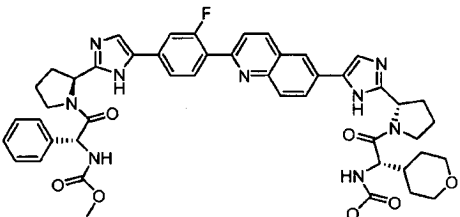
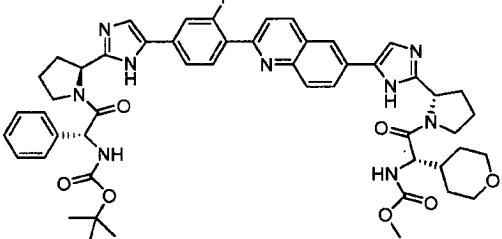
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
106		****	883.4
107		****	842.4
108		****	892.4
109		****	876.4
110		****	871.4

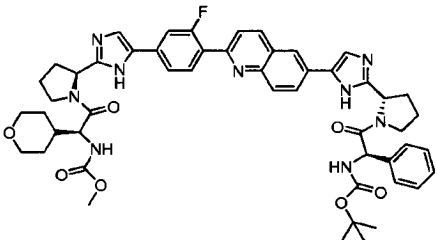
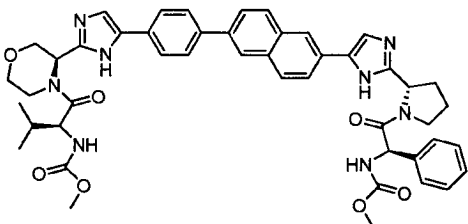
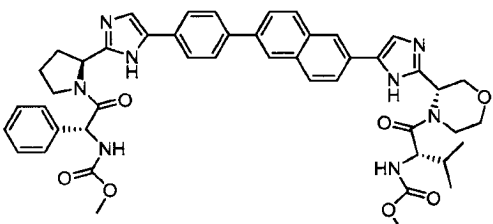
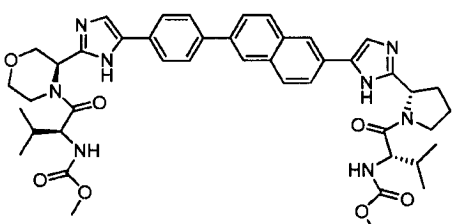
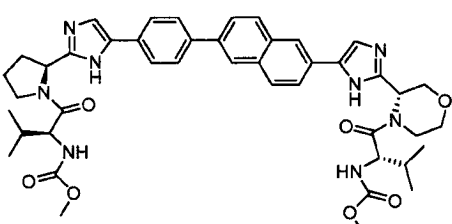
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
111		****	883.4
112		****	935.4
113		****	935.4
114		****	883.4
115		****	839.4

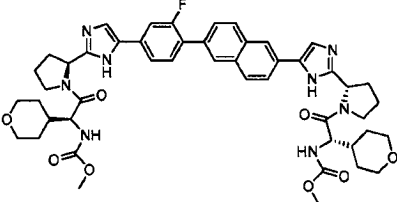
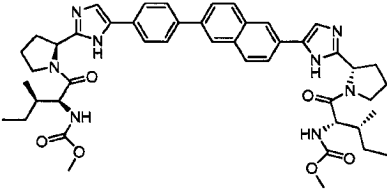
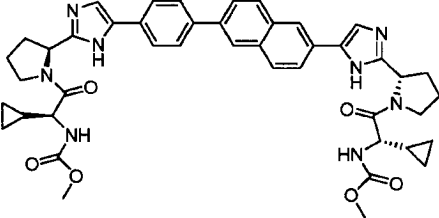
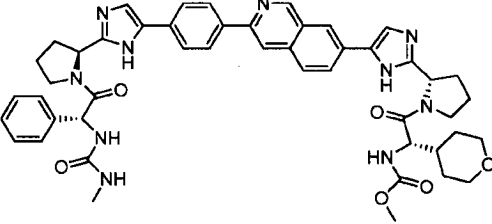
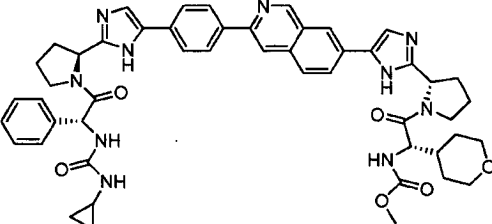
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
116		****	835.4
117		****	936.4
118		****	908.4
119		****	842.4
120		****	850.4

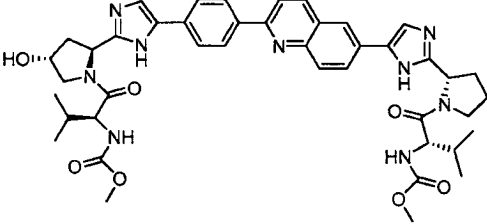
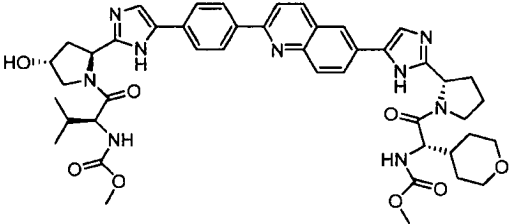
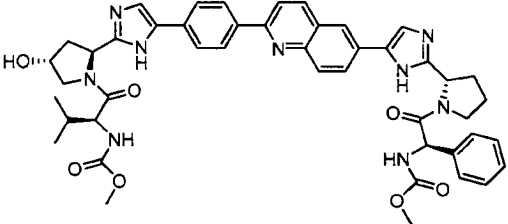
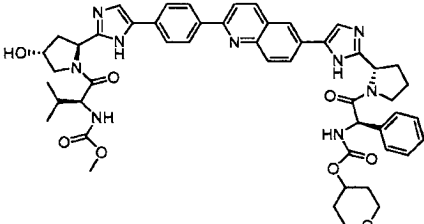
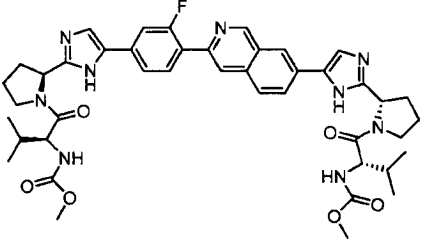
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
121		****	912.4
122		****	884.4
123		****	850.4
124		****	842.4
125		****	912.4

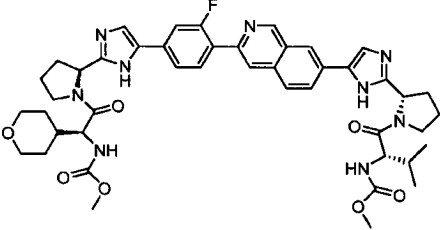
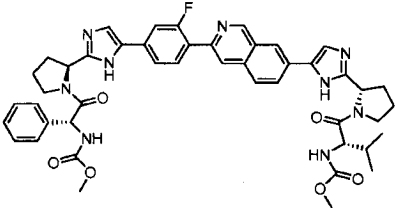
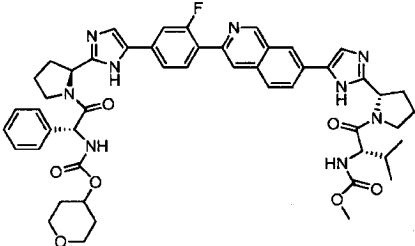
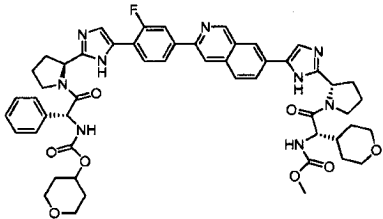
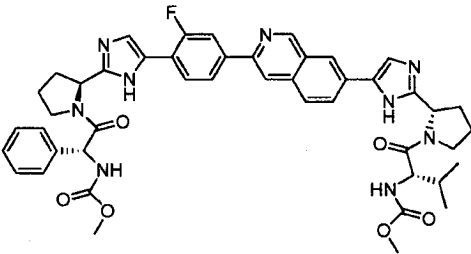
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
126		****	808.4
127		****	884.4
128		****	850.4
129		****	884.4
130		****	789.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
131		****	839.4
132		****	839.4
133		****	873.4
134		****	884.4
135		****	926.4

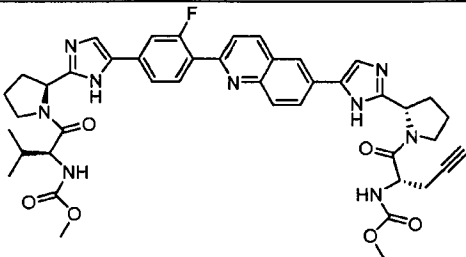
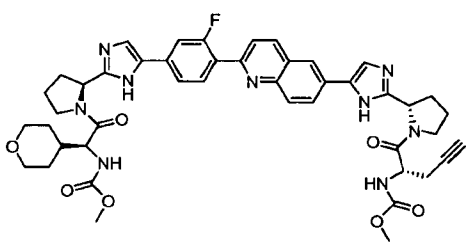
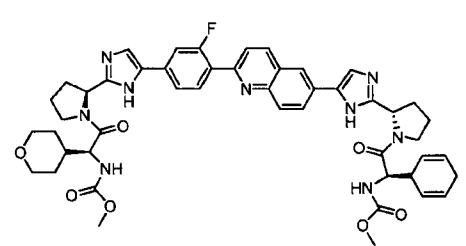
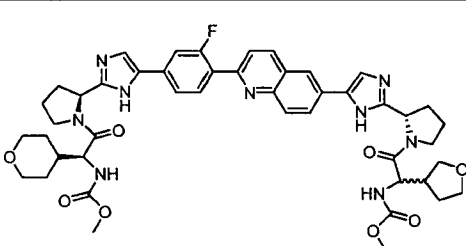
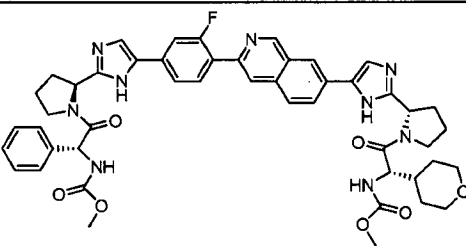
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
136		****	926.4
137		****	839.4
138		****	839.4
139		****	805.4
140		****	805.4

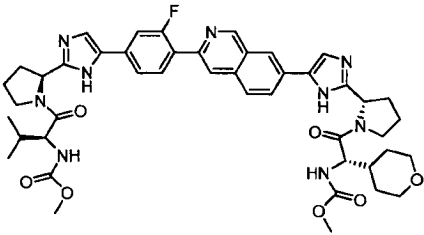
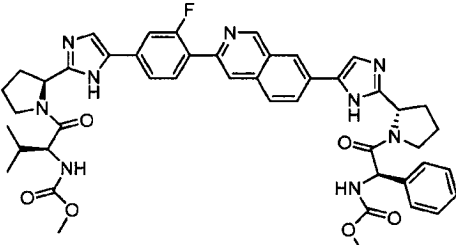
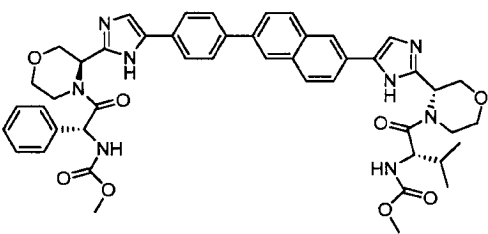
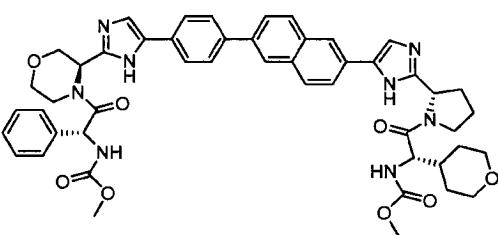
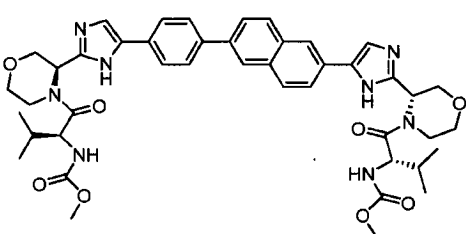
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
141		****	891.4
142		****	817.4
143		****	785.4
144		****	865.4
145		****	891.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
146		****	806.4
147		****	848.4
148		****	840.4
149		****	910.4
150		****	808.4

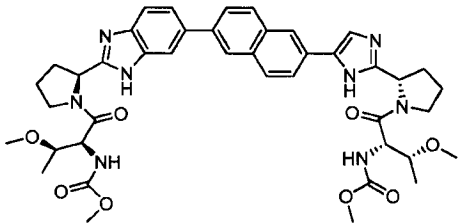
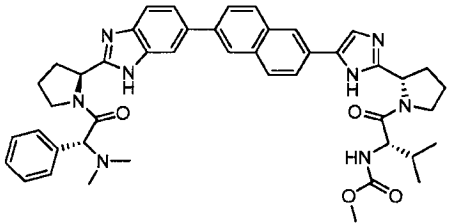
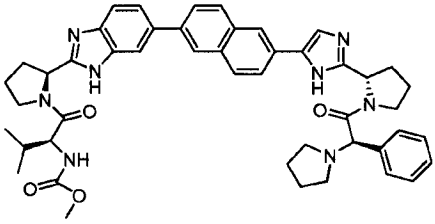
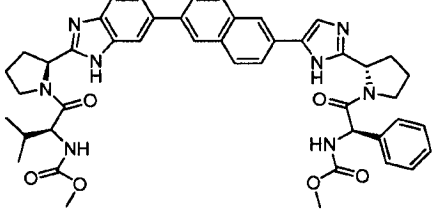
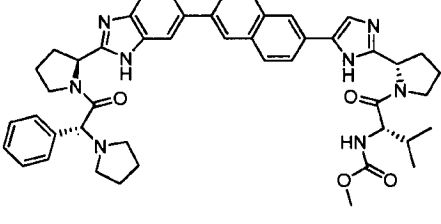
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
151		****	850.4
152		****	842.4
153		****	912.4
154		****	954.4
155		****	842.4

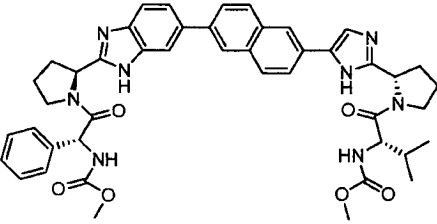
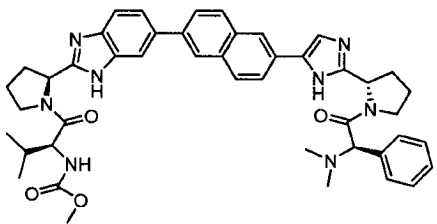
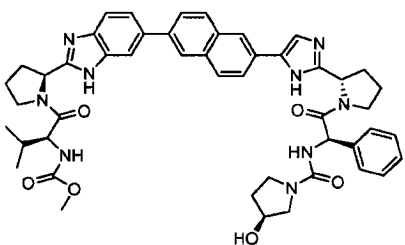
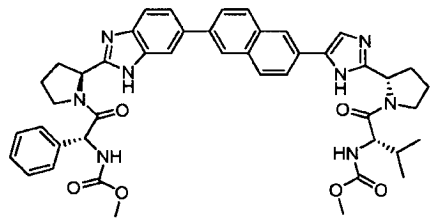
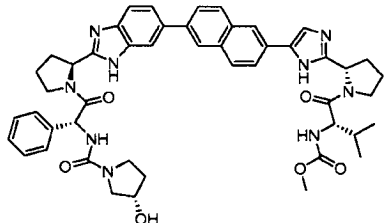
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
156		****	912.4
157			816.4
158			858.4
159			806.4
160			848.4

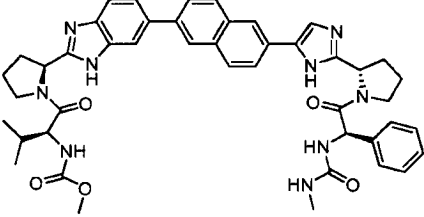
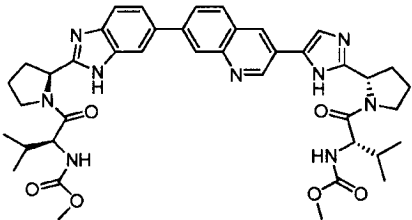
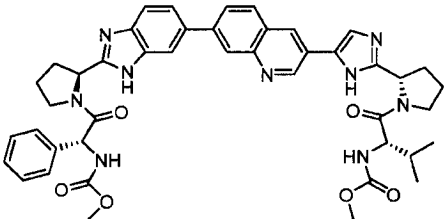
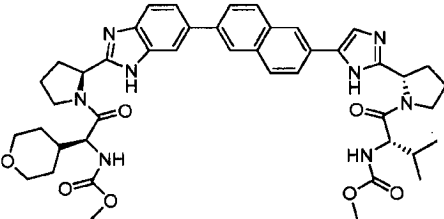
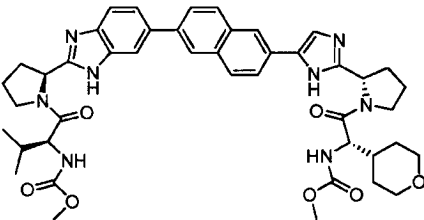
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
161			804.4
162			846.4
163			886.4
164			878.4
165			884.4

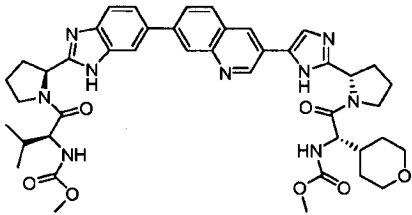
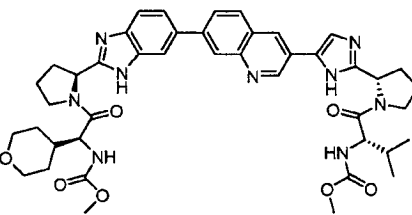
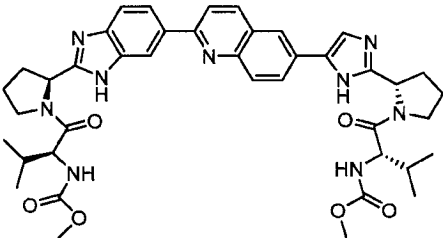
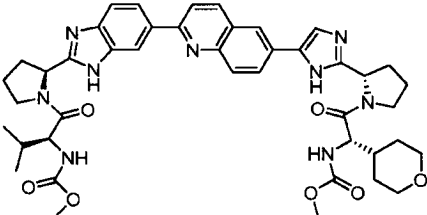
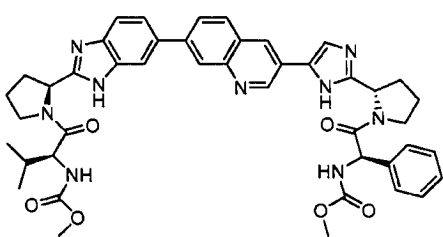
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
166			850.4
167			842.4
168			855.4
169			881.4
170			821.4

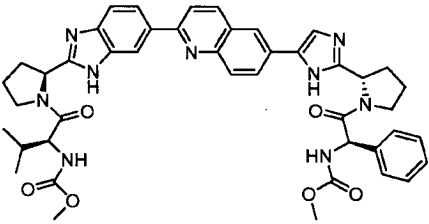
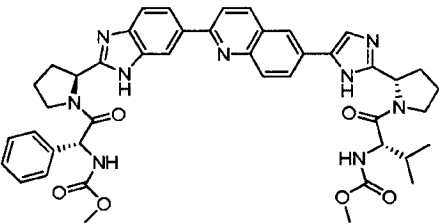
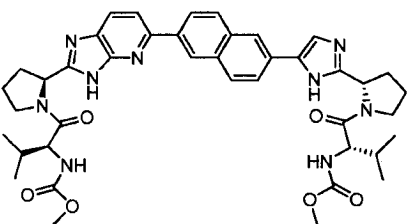
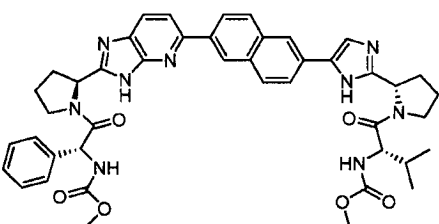
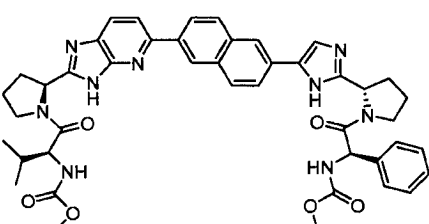
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
171			845.4
172			841.4
173			761.4
174		****	763.4
175		****	767.3

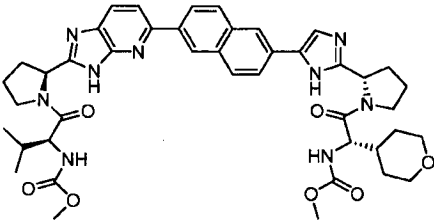
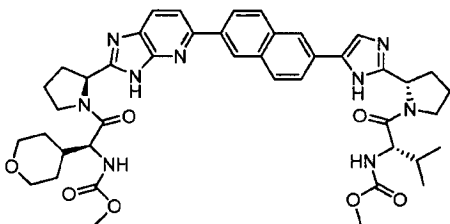
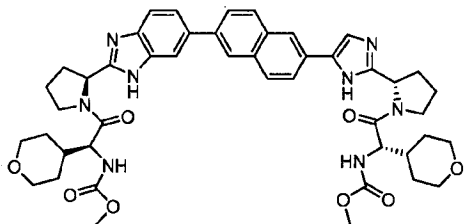
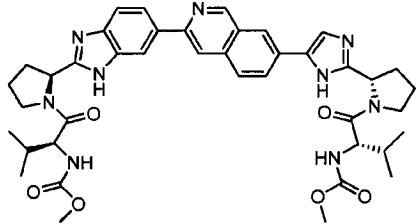
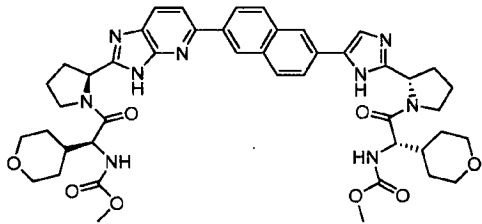
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
176		****	795.4
177		****	767.4
178		****	793.4
179		****	797.4
180		****	793.4

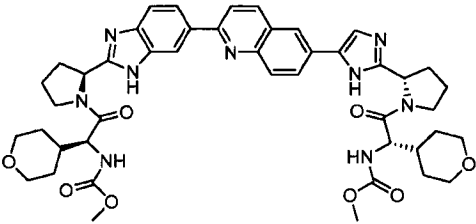
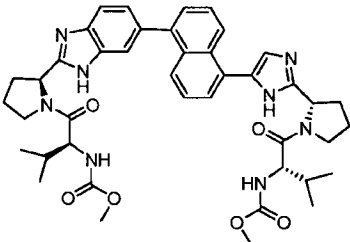
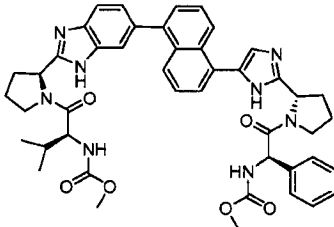
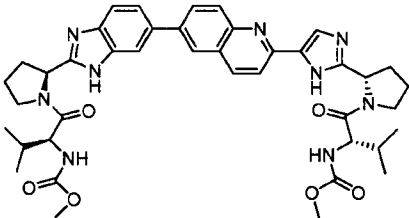
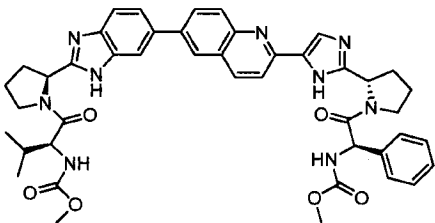
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
181		****	797.4
182		****	767.4
183		****	852.4
184		****	797.4
185		****	852.4

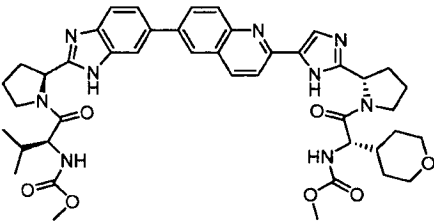
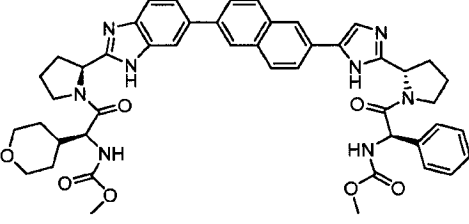
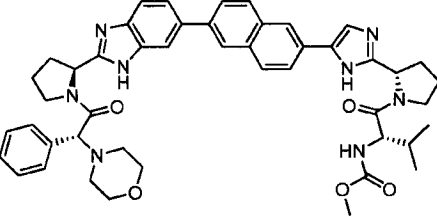
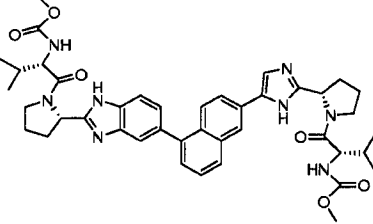
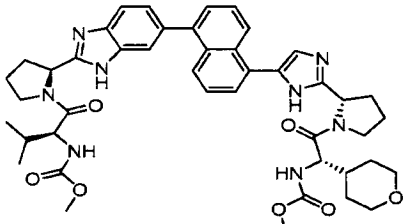
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
186		****	796.4
187		****	764.4
188		***	798.4
189		****	805.4
190		****	805.4

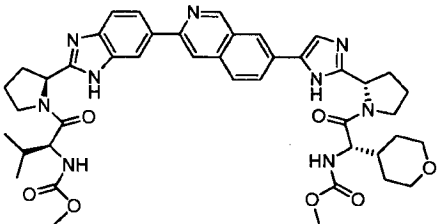
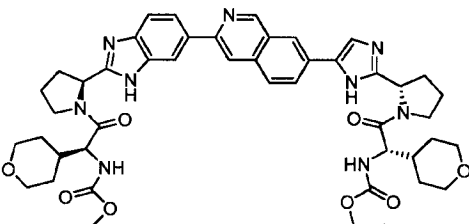
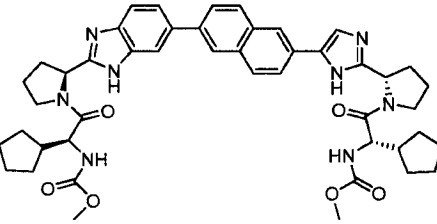
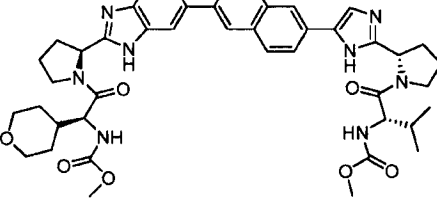
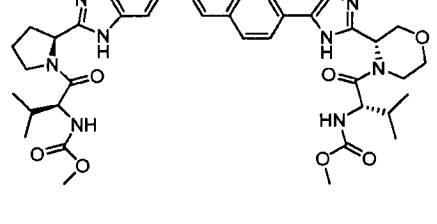
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
191		****	806.4
192		****	806.4
193		****	764.4
194		****	806.4
195		****	798.4

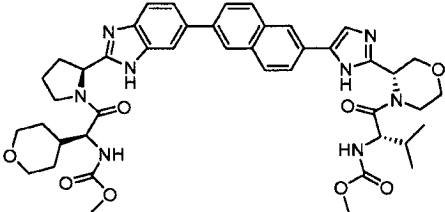
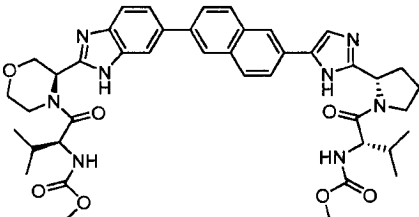
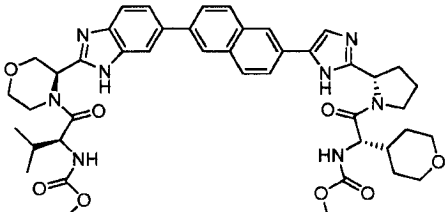
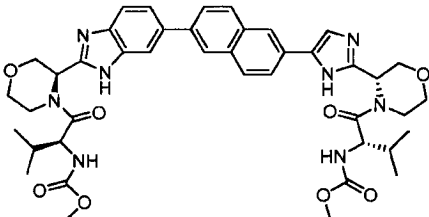
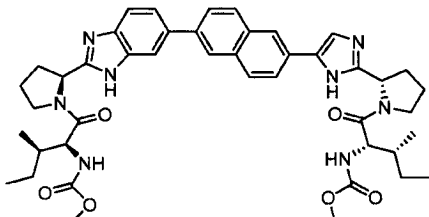
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
196		****	798.4
197		****	798.4
198		****	764.4
199		****	798.4
200		****	798.4

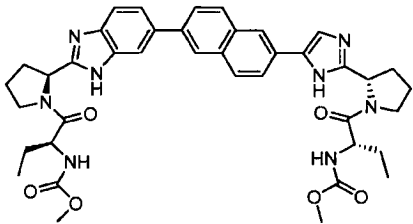
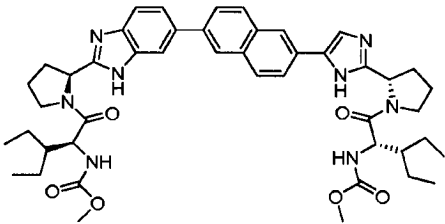
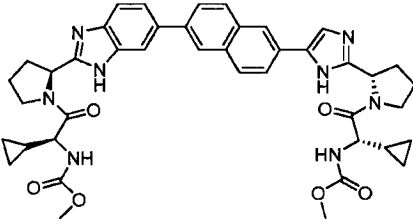
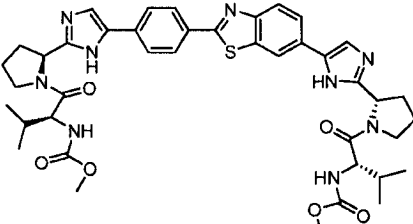
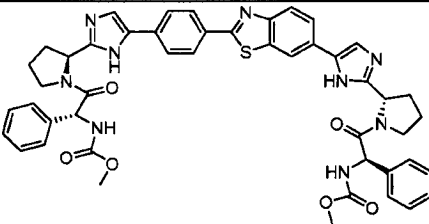
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
201		****	806.4
202		****	806.4
203		****	847.4
204		****	764.4
205		****	848.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
206		***	848.4
207		****	763.4
208		****	797.4
209		****	764.4
210		****	798.4

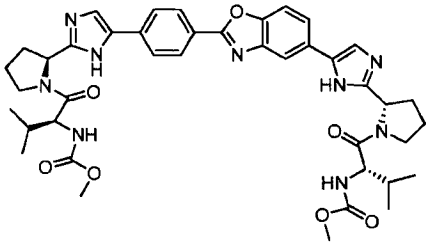
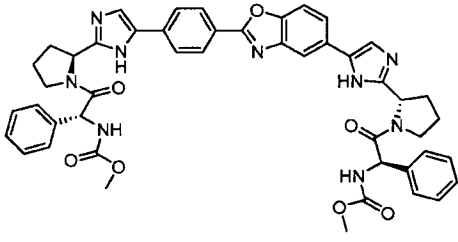
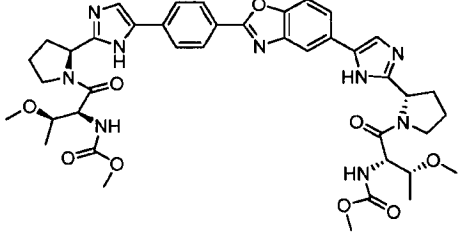
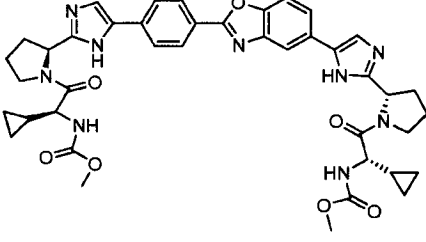
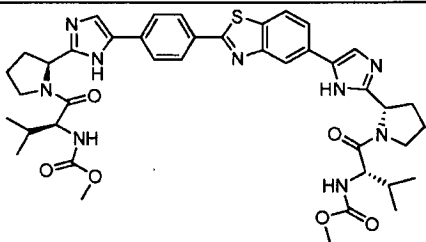
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
211		****	806.4
212		****	839.4
213		****	809.4
214		**	763.4
215		****	805.4

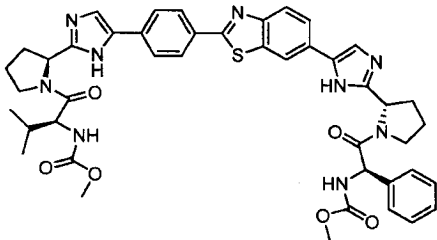
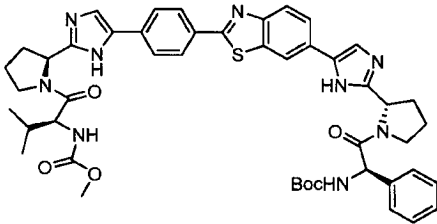
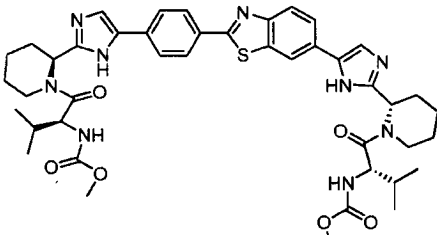
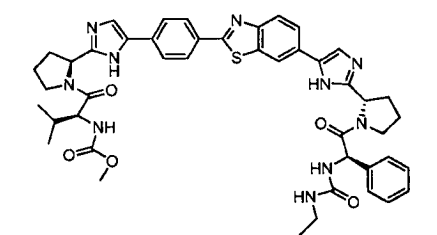
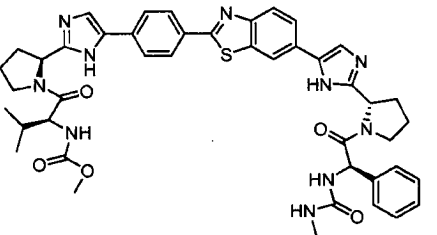
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
216		****	806.4
217		***	848.4
218		****	815.4
219			806.4
220			779.4

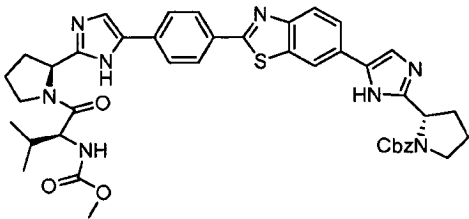
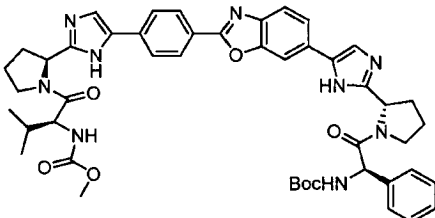
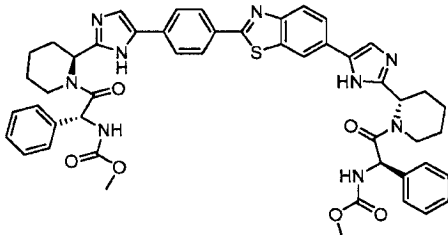
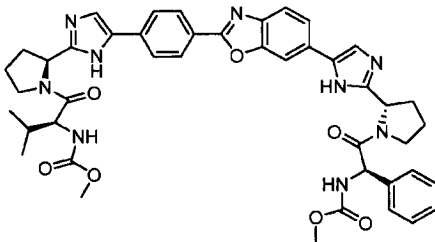
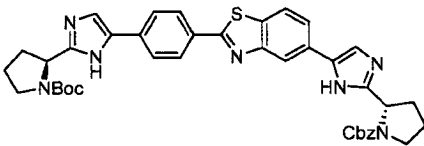
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
221			821.4
222			779.4
223			821.4
224			795.4
225			791.4

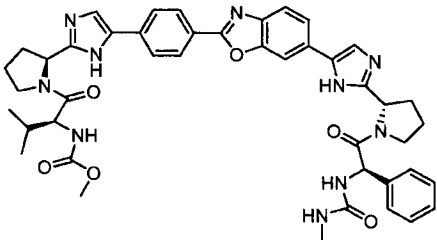
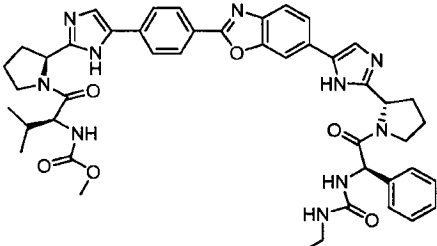
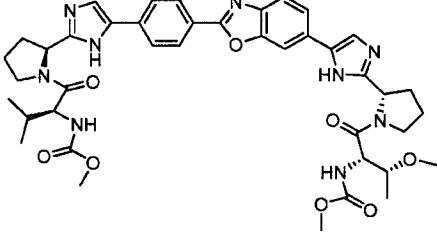
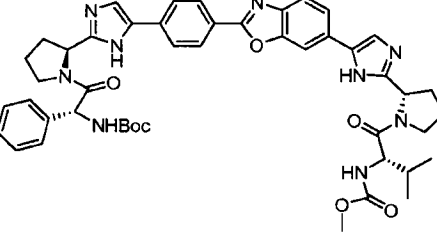
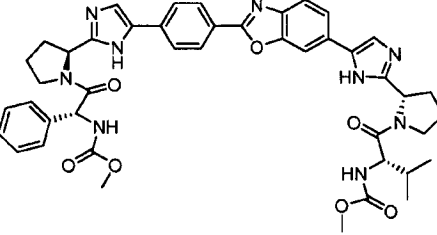
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
226			735.4
227			819.4
228			759.4
229		****	796.4
230		****	864.3

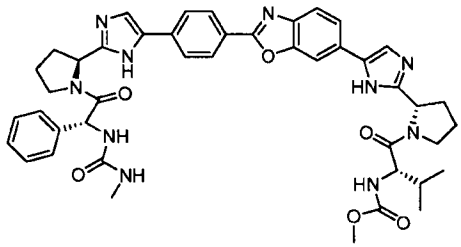
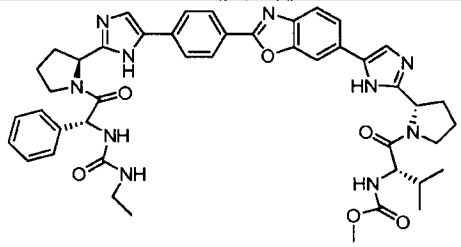
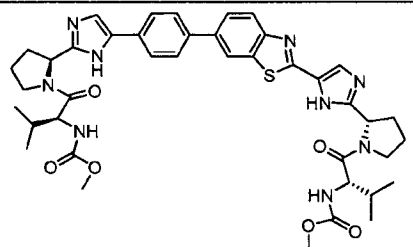
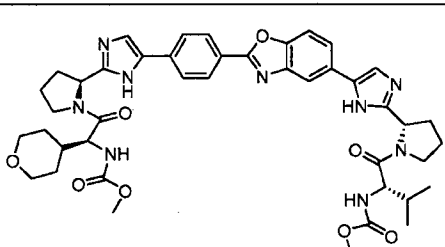
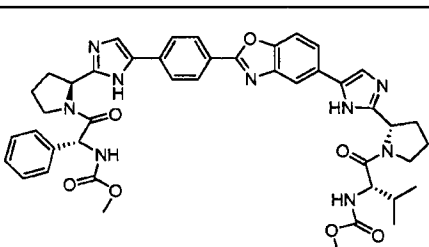
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
231		****	793.4
232		****	793.4
233		****	861.4
234		****	780.4
235		****	848.3

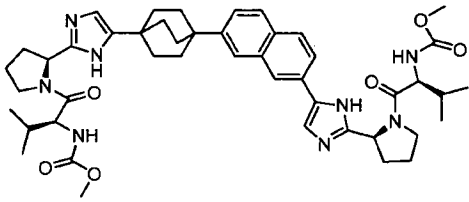
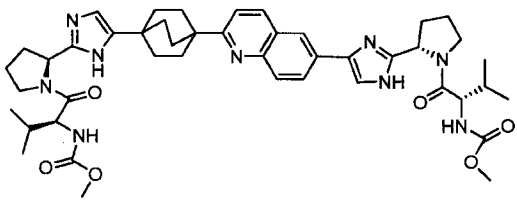
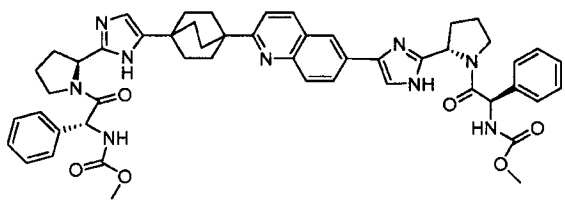
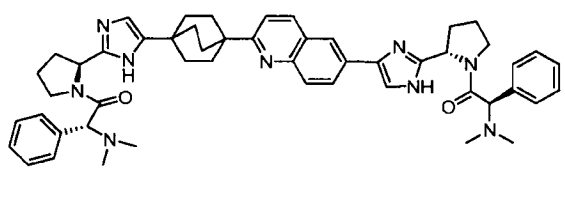
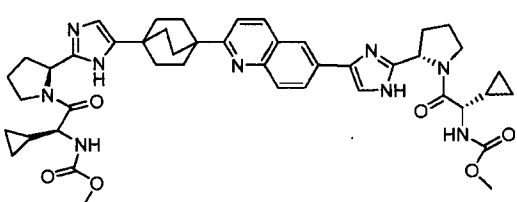
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
236		****	780.4
237		****	848.3
238		****	812.4
239		****	776.3
240		****	796.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
241		****	830.3
242		****	872.4
243		****	824.4
244		****	843.4
245		****	829.4

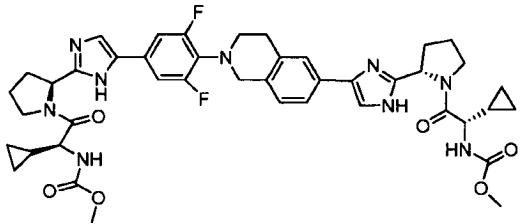
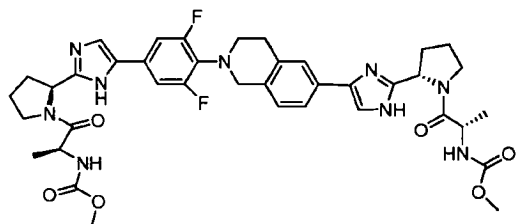
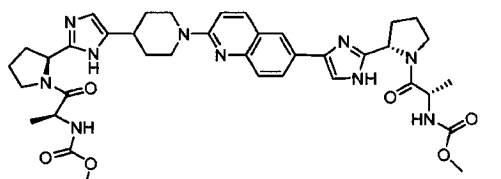
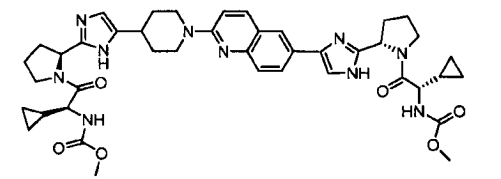
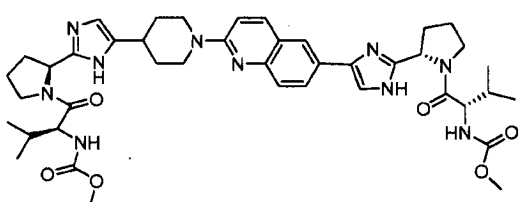
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
246		****	773.3
247		****	856.4
248		****	892.4
249		****	814.4
250		**	716.3

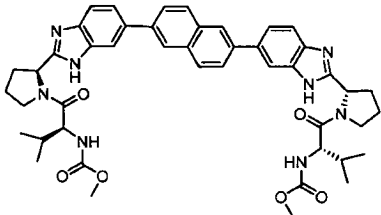
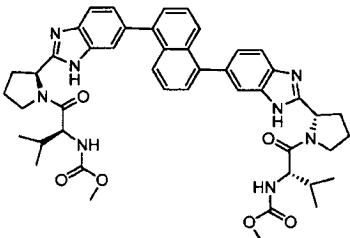
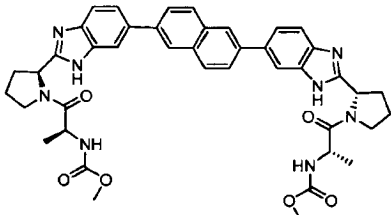
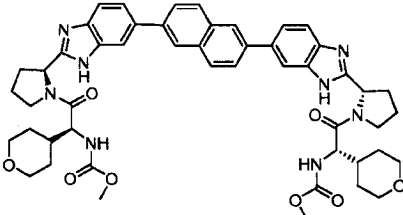
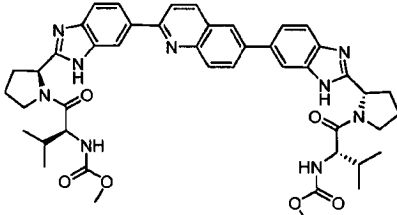
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
251		****	813.4
252		****	827.4
253		****	796.4
254		****	856.4
255		****	814.4

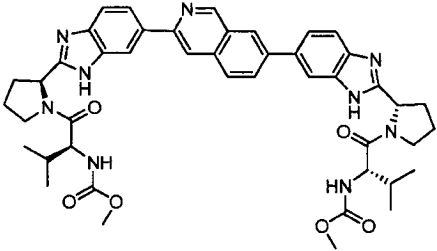
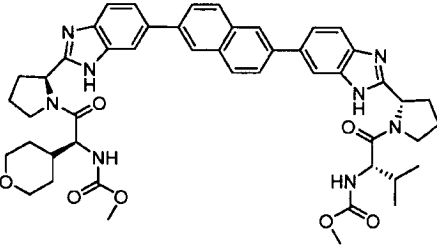
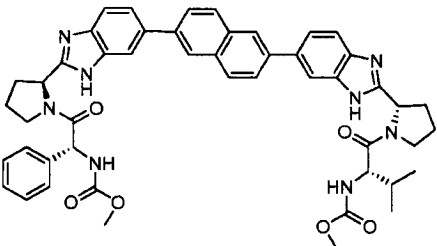
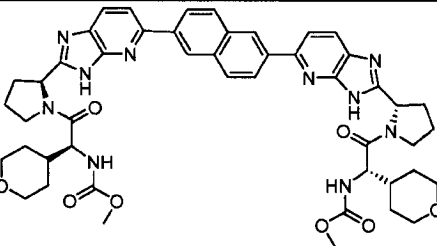
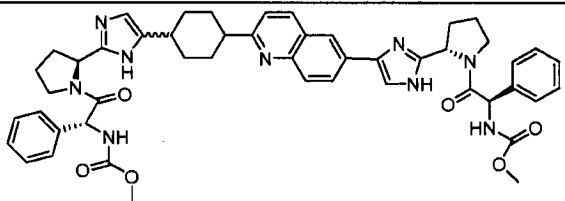
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
256		****	813.4
257		****	827.4
258		****	796.4
259		****	822.4
260		****	814.4

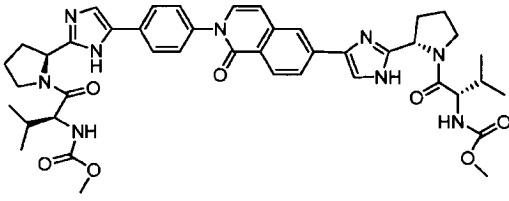
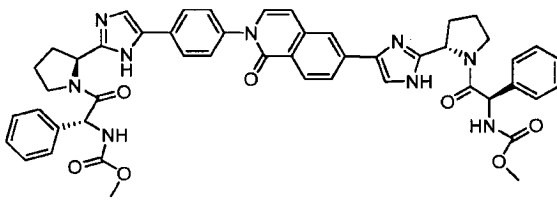
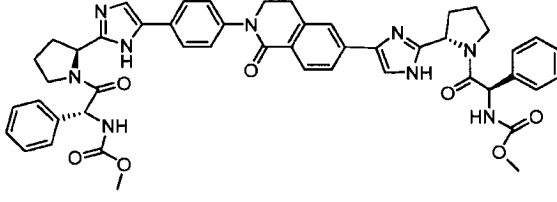
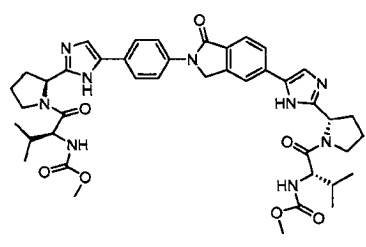
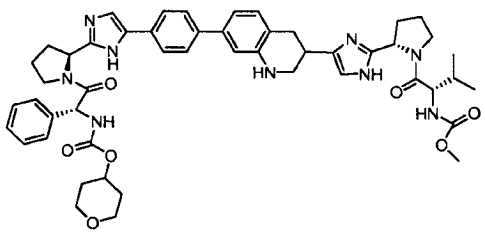
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
261		***	821.5
262		****	822.5
263		****	890.4
264		***	830.5
265		****	818.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
266		****	766.4
267		*	508.3
268		**	708.4
269		****	830.4
270		****	898.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
271		****	826.4
272		****	774.3
273		***	741.4
274		***	793.4
275		****	797.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
276		****	813.4
277		****	813.4
278		****	757.3
279		****	897.4
280		****	814.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
281		****	814.4
282		****	855.4
283		****	847.4
284			899.4
286		****	864.4

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
287		****	806.4
288		****	874.4
289		****	876.4
290		****	794.4
291		****	898.5

Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H)+
292		****	816.4
293		****	858.4
294		****	850.4
295		****	920.4
296		****	814.4

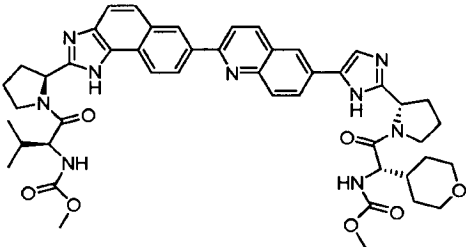
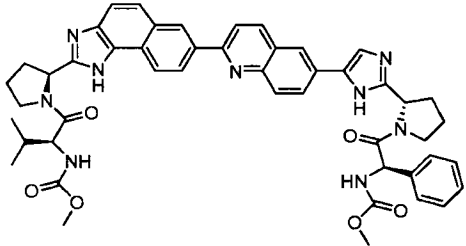
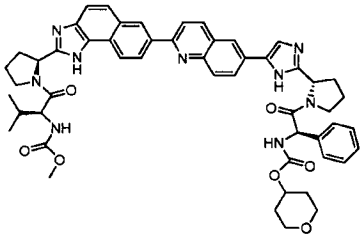
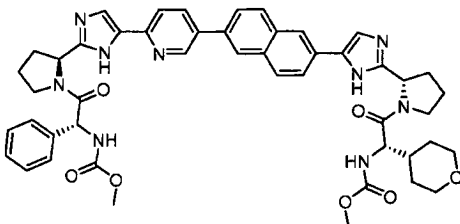
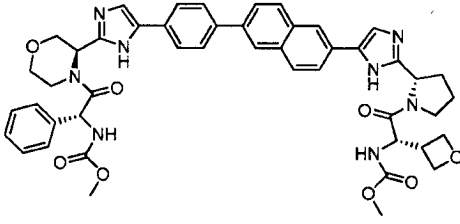
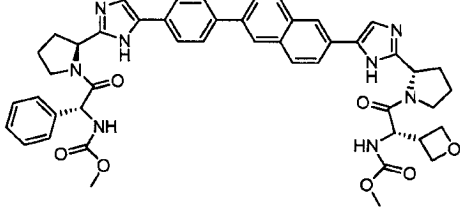
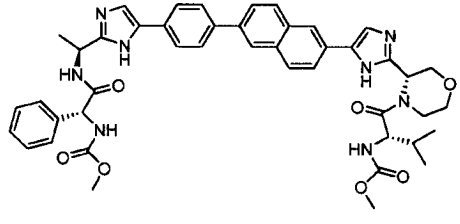
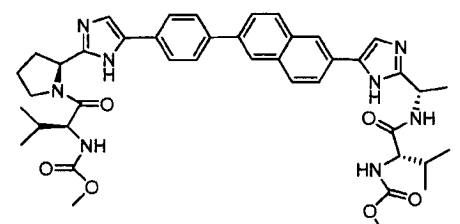
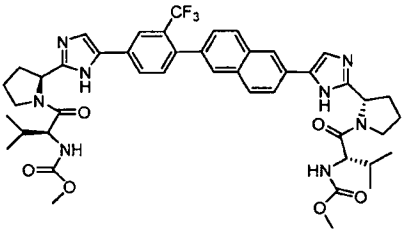
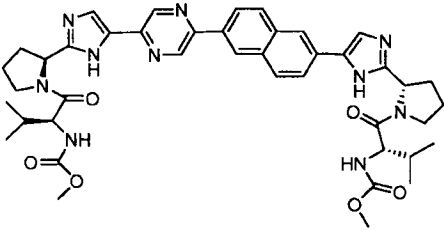
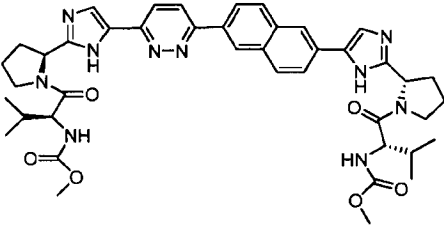
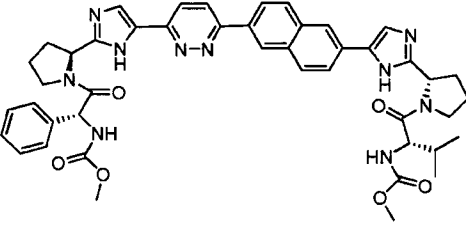
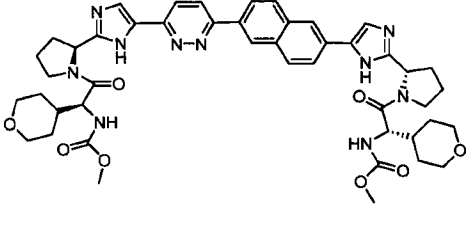
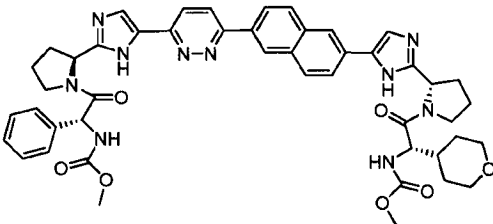
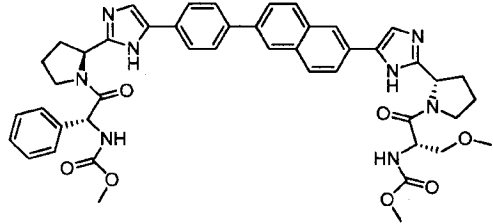
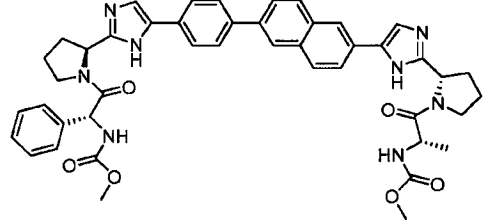
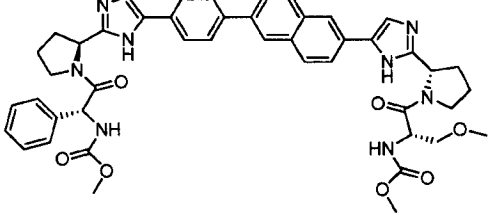
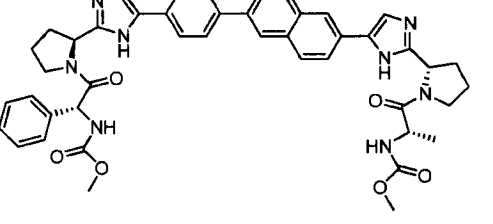
Compound	Structure	Inhibition of HCV genotype 1b	MS (M+H) ⁺
297		****	856.4
298		****	848.4
299		****	918.4

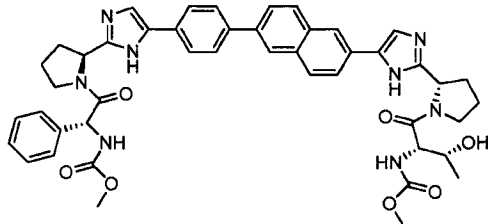
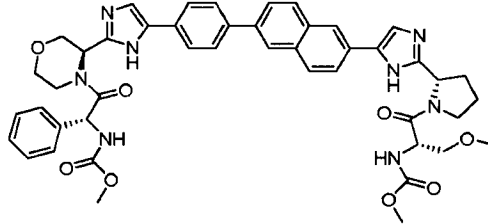
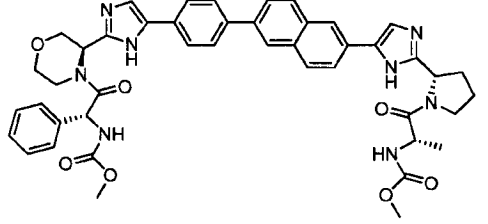
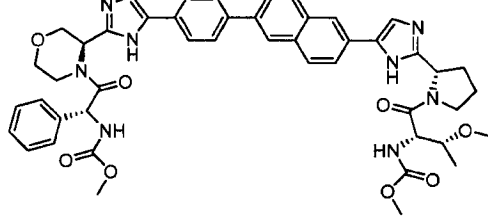
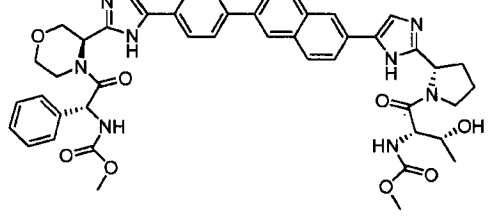
Table 2

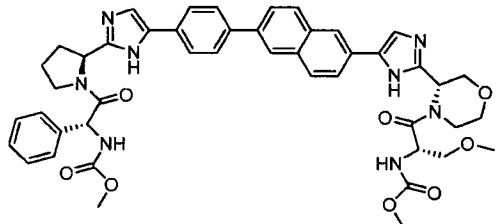
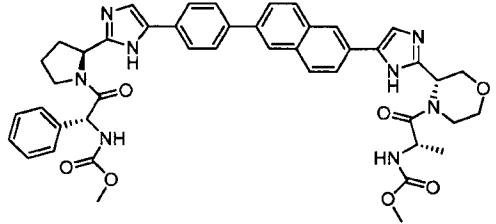
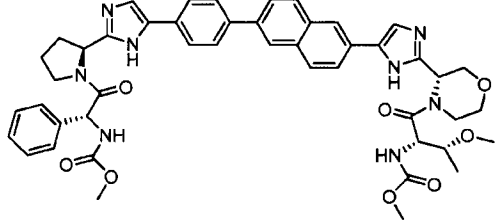
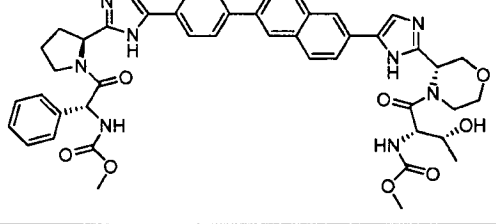
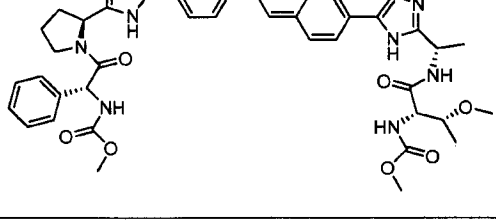
Compound	Structure
300	
301	
302	
303	
304	

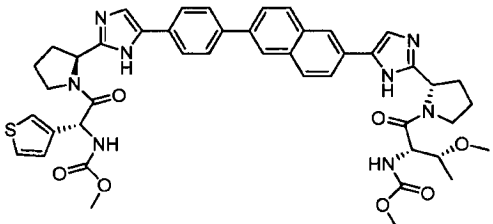
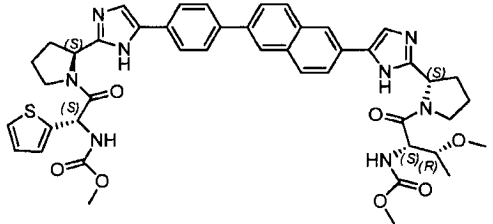
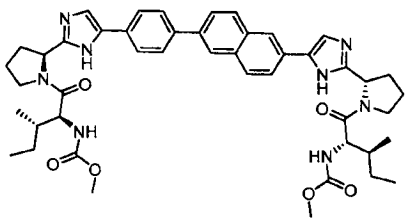
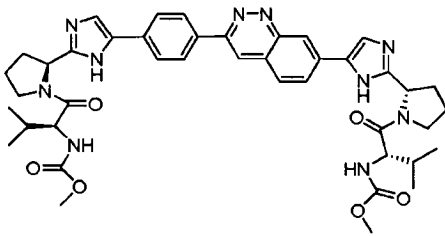
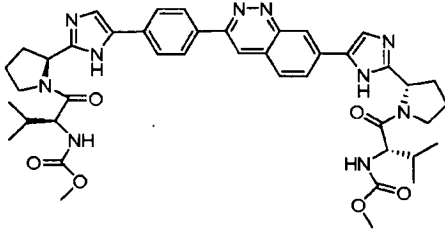
Compound	Structure
305	
306	
307	
308	
309	

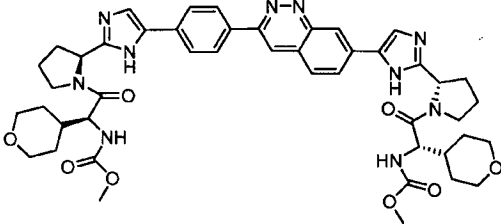
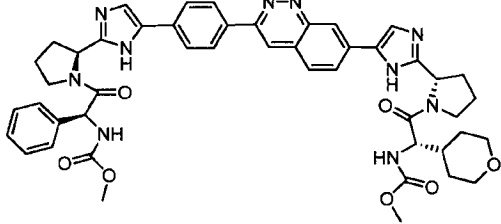
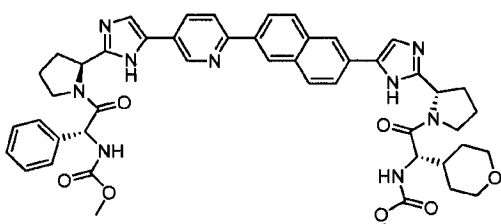
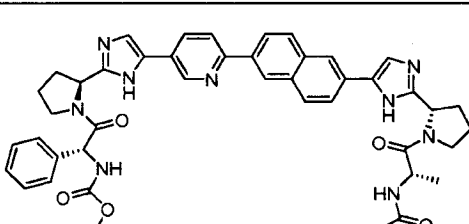
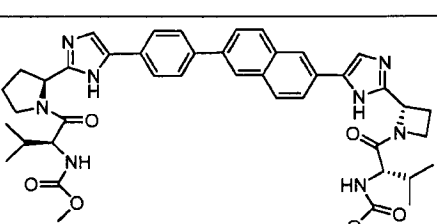
Compound	Structure
310	
311	
312	
313	
314	

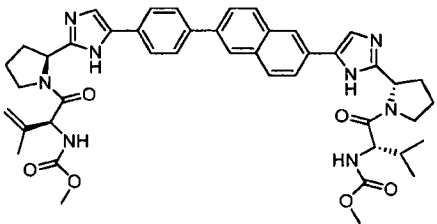
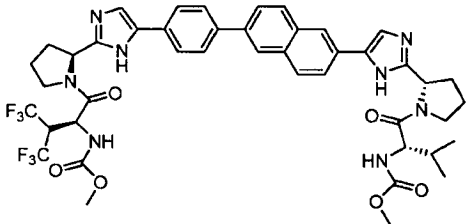
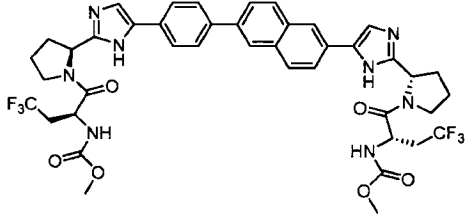
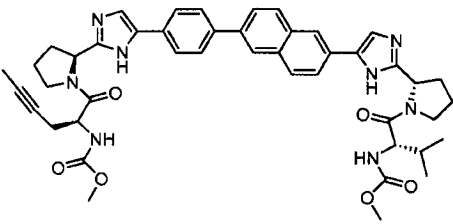
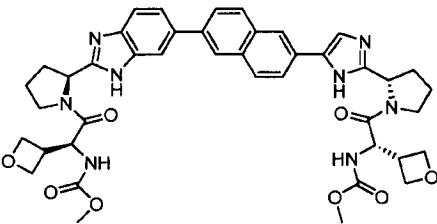
Compound	Structure
315	
316	
317	
318	
319	

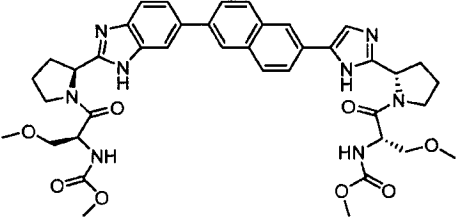
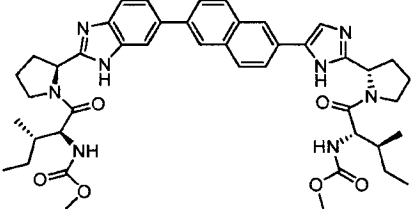
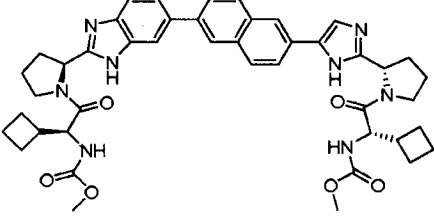
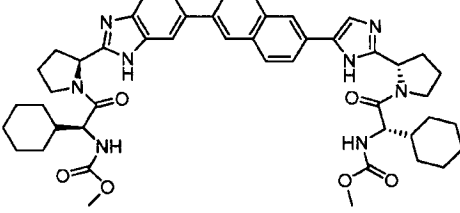
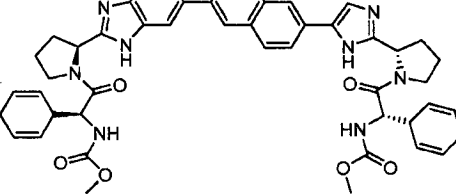
Compound	Structure
320	
321	
322	
323	
324	

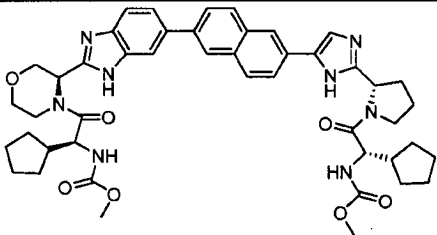
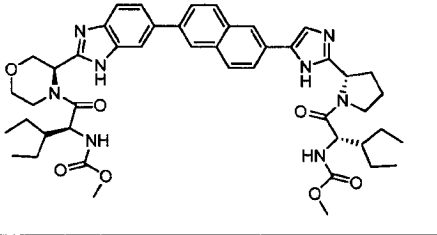
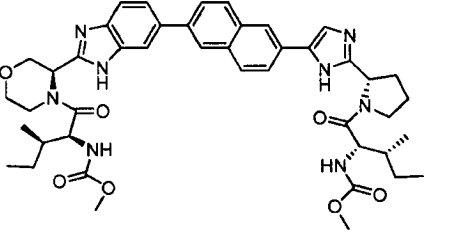
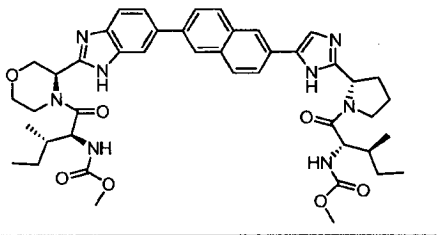
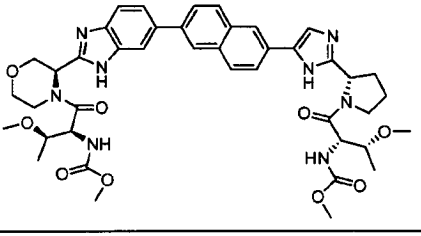
Compound	Structure
325	
326	
327	
328	
329	

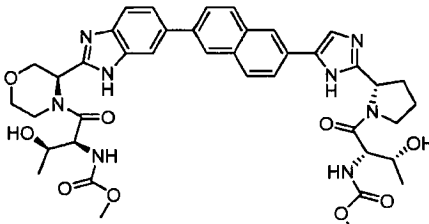
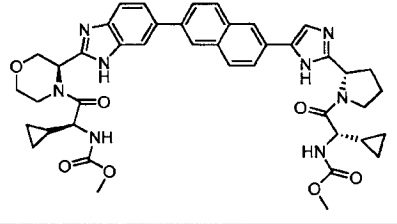
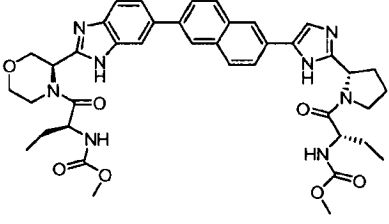
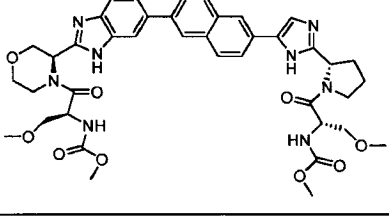
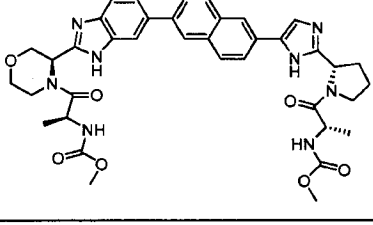
Compound	Structure
330	
331	
332	
333	
334	

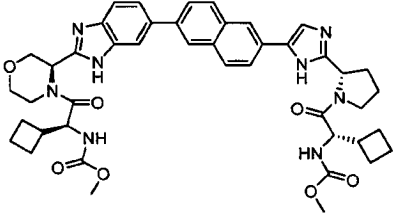
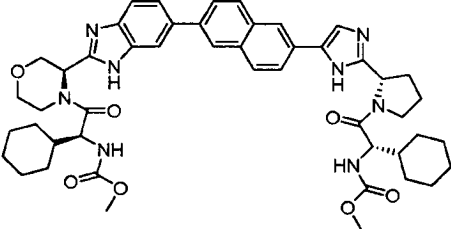
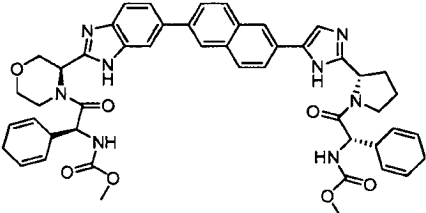
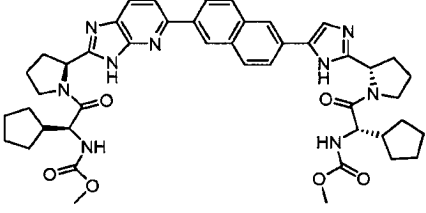
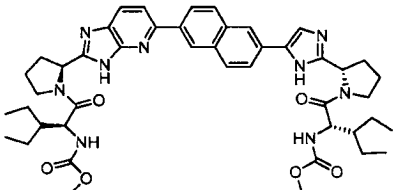
Compound	Structure
335	
336	
337	
338	
339	

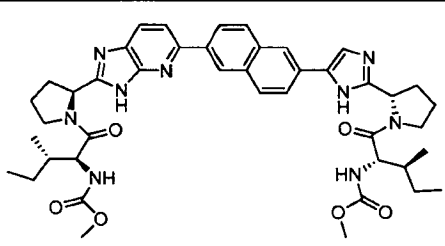
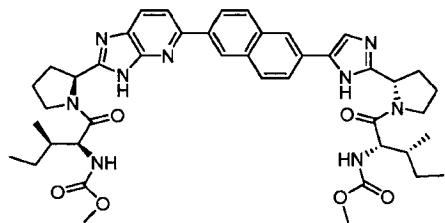
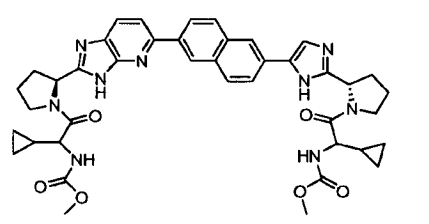
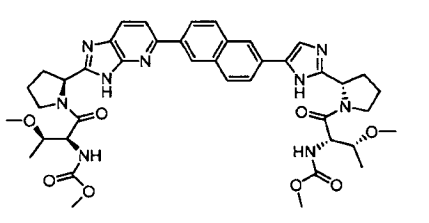
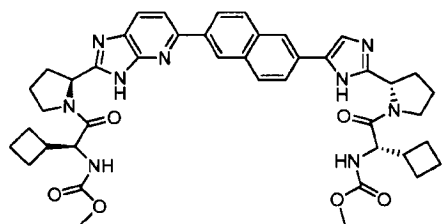
Compound	Structure
340	
341	
342	
343	
344	

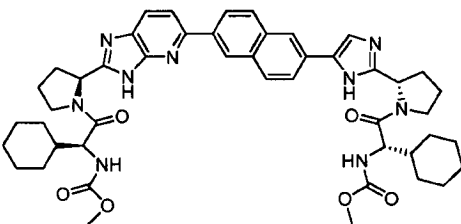
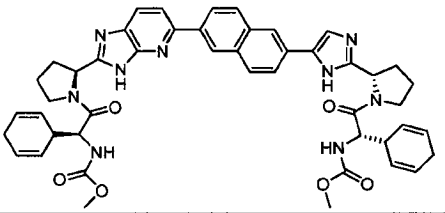
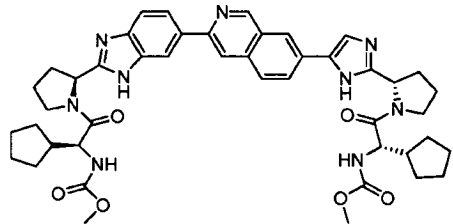
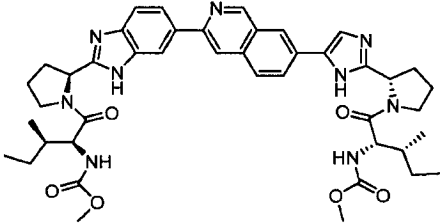
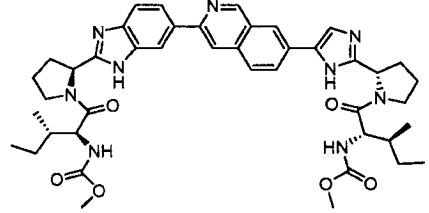
Compound	Structure
345	
346	
347	
348	
349	

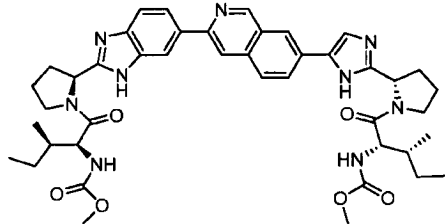
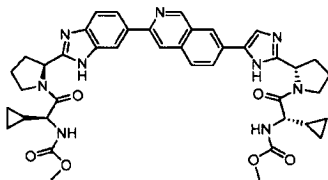
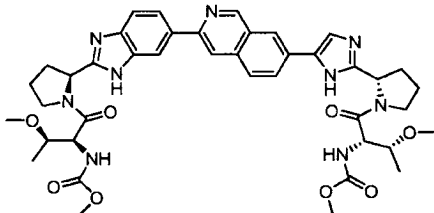
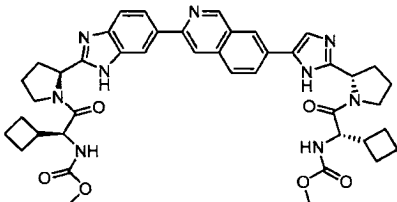
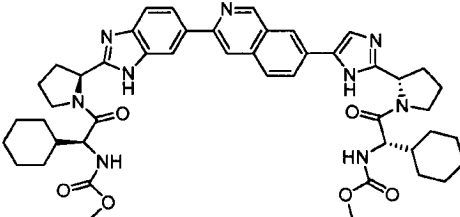
Compound	Structure
350	
351	
352	
353	
354	

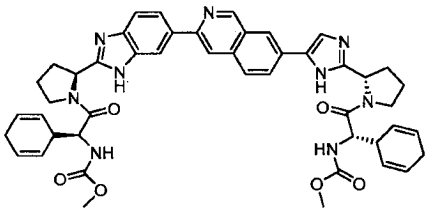
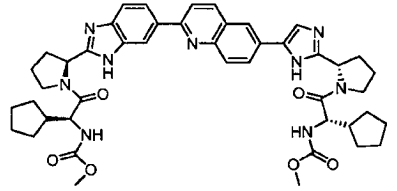
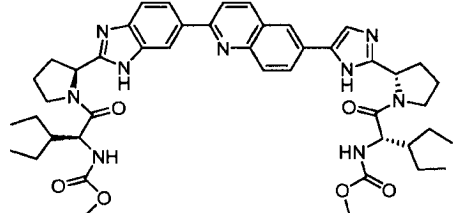
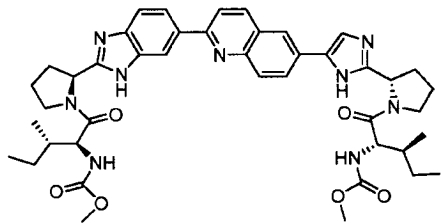
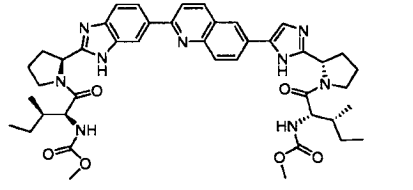
Compound	Structure
355	
356	
357	
358	
359	

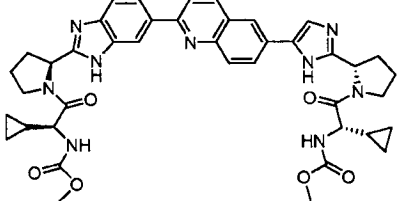
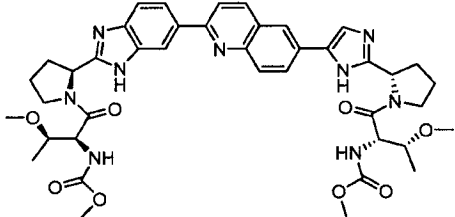
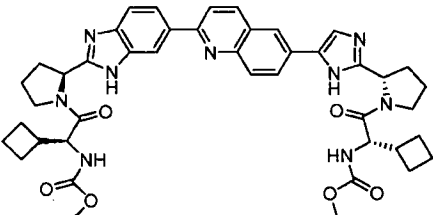
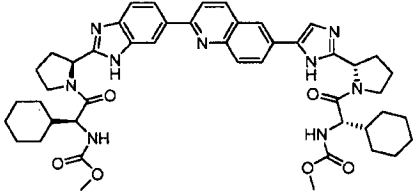
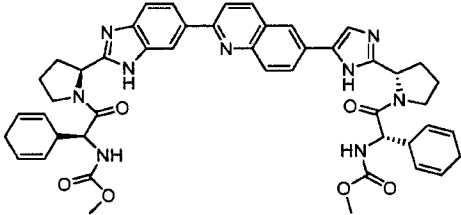
Compound	Structure
360	
361	
362	
363	
364	

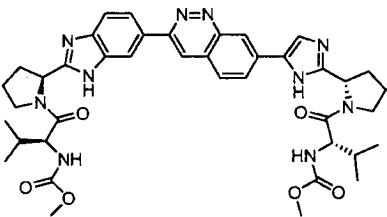
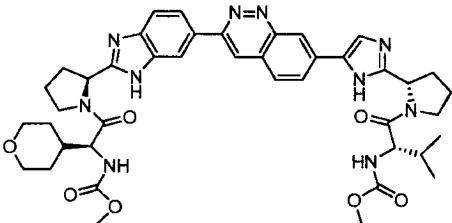
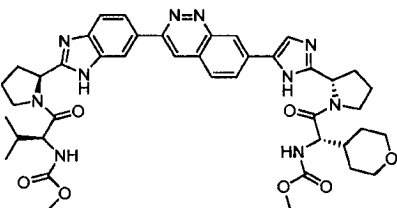
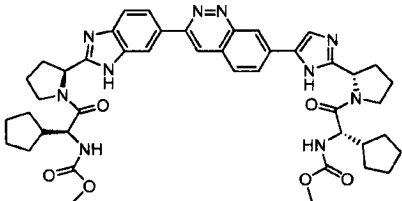
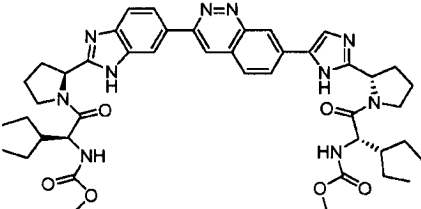
Compound	Structure
365	
366	
367	
368	
369	

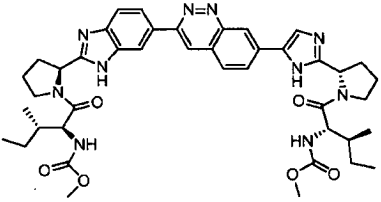
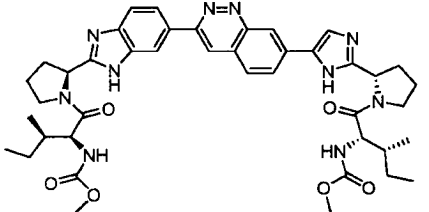
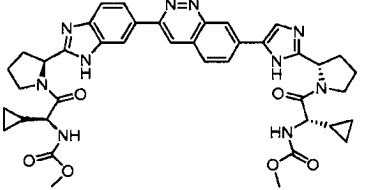
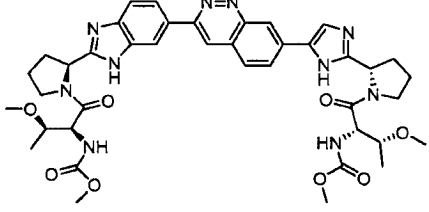
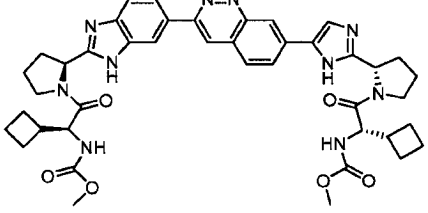
Compound	Structure
370	
371	
372	
373	
374	

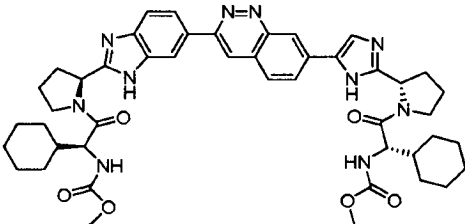
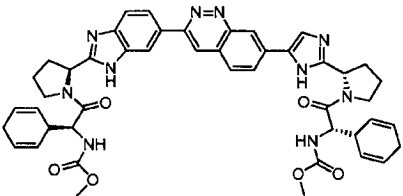
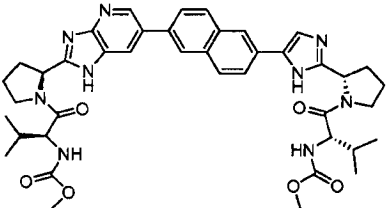
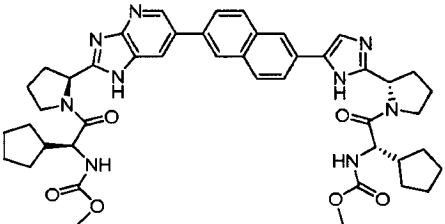
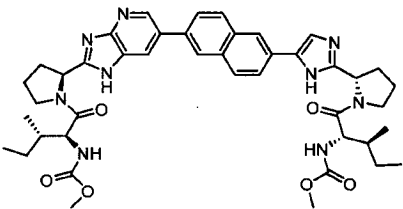
Compound	Structure
375	
376	
377	
378	
379	

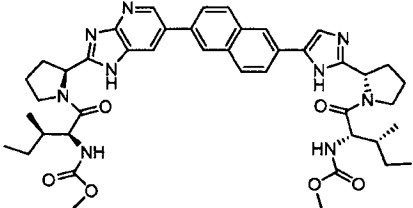
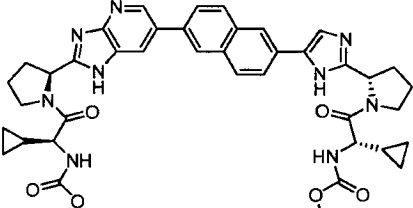
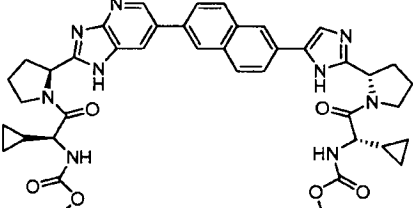
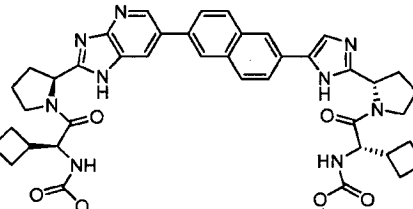
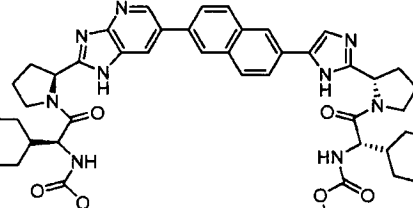
Compound	Structure
380	
381	
382	
383	
384	

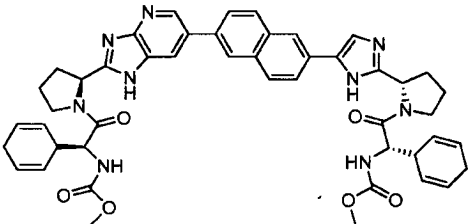
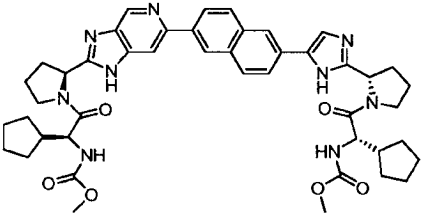
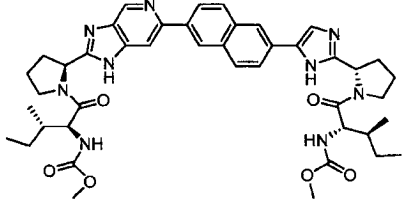
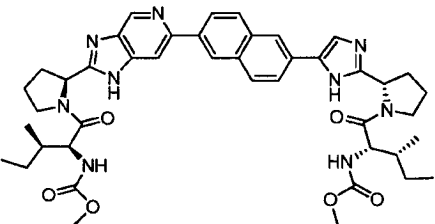
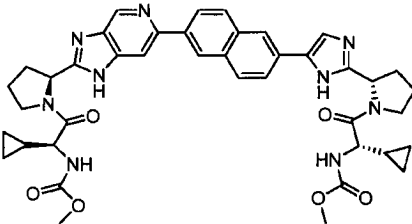
Compound	Structure
385	
386	
387	
388	
389	

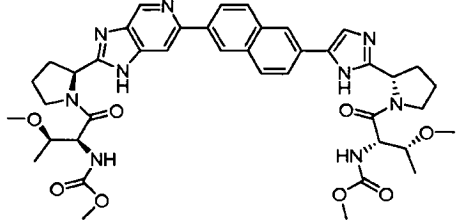
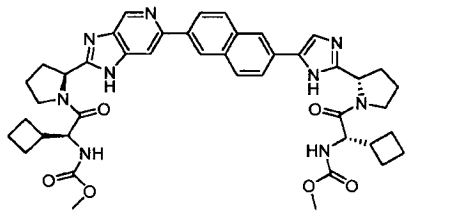
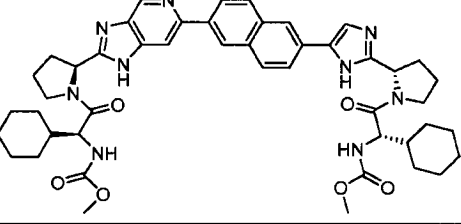
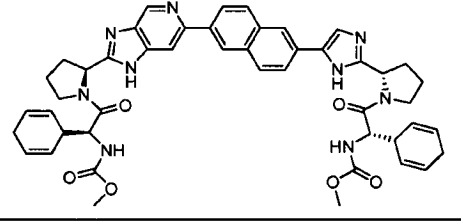
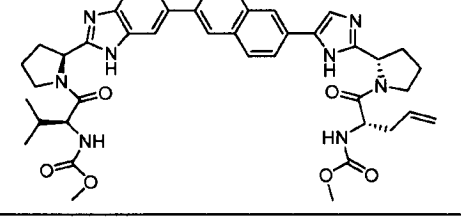
Compound	Structure
390	
391	
392	
393	
394	

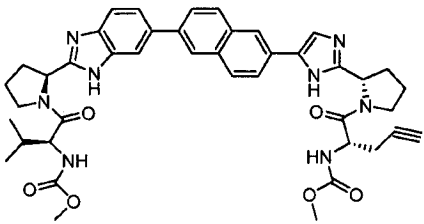
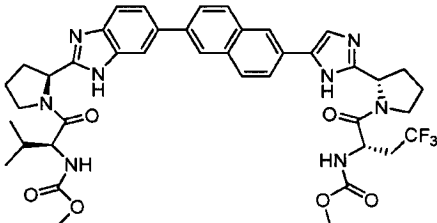
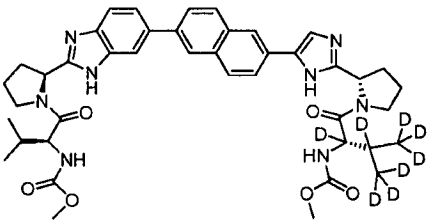
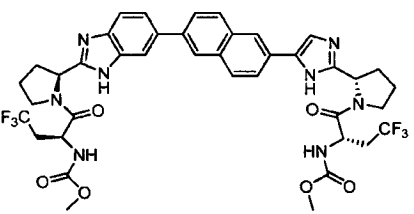
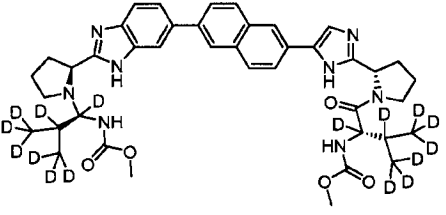
Compound	Structure
395	
396	
397	
398	
399	

Compound	Structure
400	
401	
402	
403	
404	

Compound	Structure
405	
406	
407	
408	
409	

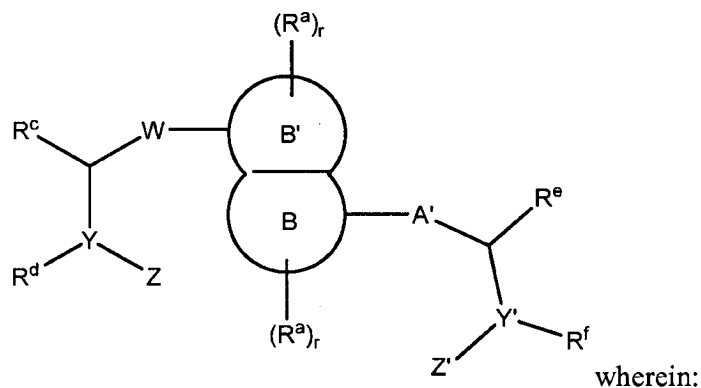
Compound	Structure
410	
411	
412	
413	
414	

Compound	Structure
415	
416	
417	
418	
419	

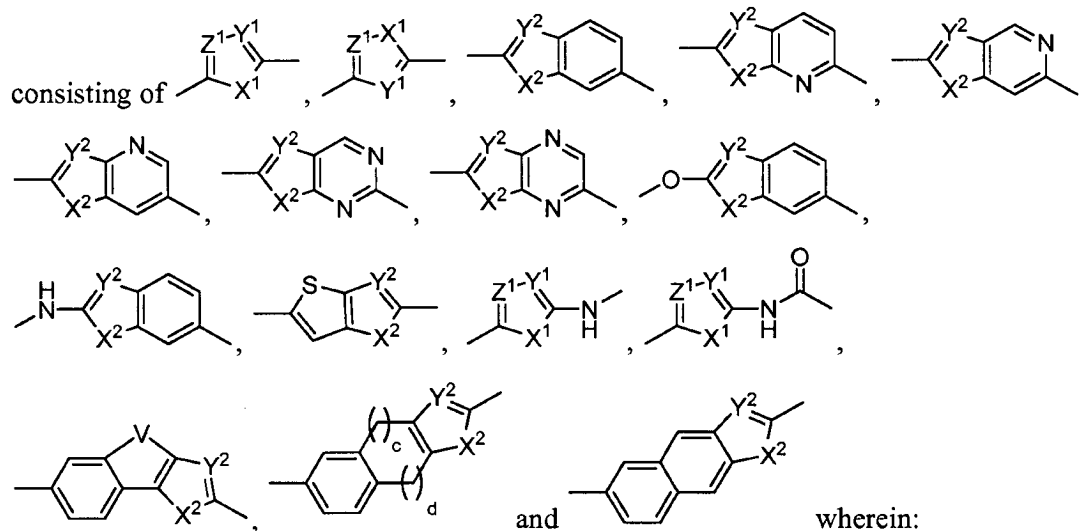
Compound	Structure
420	
421	
422	
423	
424	

CLAIMS

1. A compound having formula I:



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

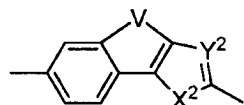


X^1 is CH_2 , NH, O or S,

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

X^2 is NH, O or S,

V is $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $(\text{CH}_2)_a-\text{N}(\text{R}^{\text{N}})-(\text{CH}_2)_b-$ or $-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-$, 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, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, 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 $-\text{OH}$, 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,

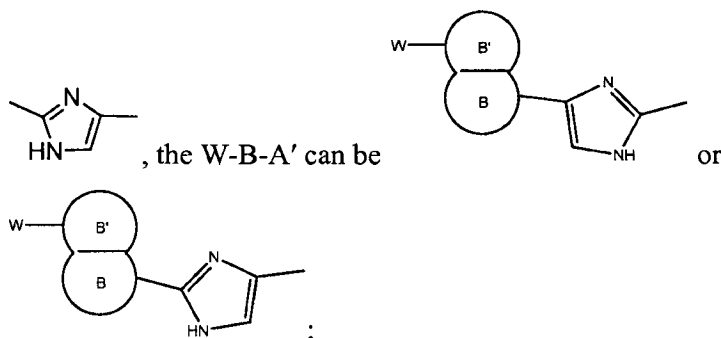
k is 0, 1, or 2,

each R is independently selected from the group consisting of hydrogen, halogen, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, 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, $-\text{OH}$, C_1

to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide and

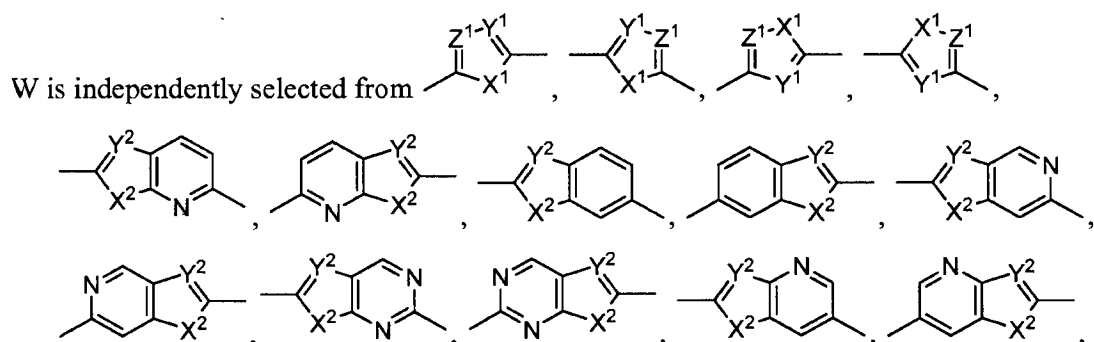
wherein B may be attached to either side of A' so that in the example of A' being

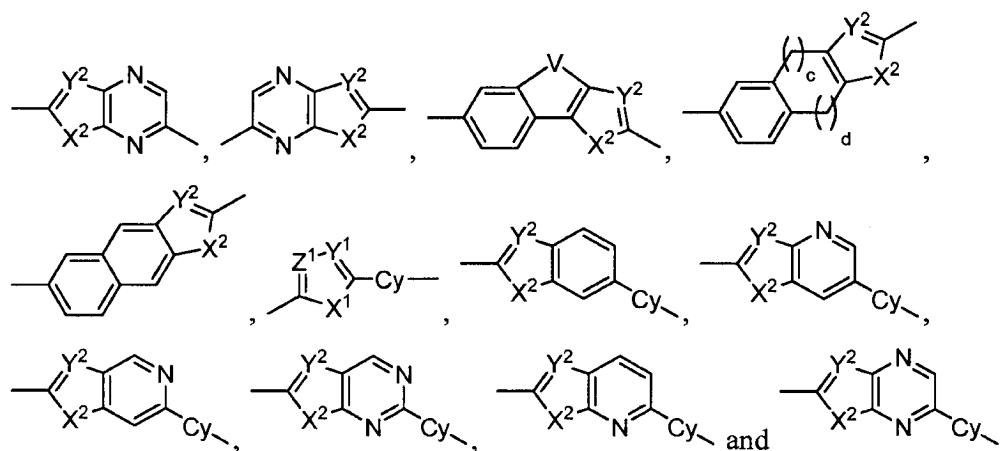


B and B' are each independently a 4- to 8-membered ring that is an aryl, heteroaryl, cycloalkyl, or heterocycle, wherein each hetero atom, if present, is independently N, O or S and wherein at least one of B or B' is aromatic;

each R^a is independently selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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;





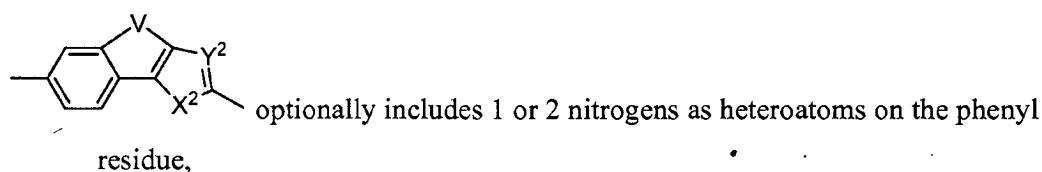
wherein:

X¹ is CH₂, 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 $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $(\text{CH}_2)_a-\text{N}(\text{R}^{\text{N}})-(\text{CH}_2)_b-$ or $-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-$,
wherein a and b are independently 0, 1, 2, or 3 with the proviso that a and b are not both 0,



W is optionally substituted with one or more substituents selected from the group consisting of -OH, -CN, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, -NO₂, halogen, C₁ to C₁₂ alkyl, C₁ to C₁₂ 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, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl and a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl, wherein,

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

each of R^c, R^d, R^e and R^f may optionally be substituted by C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, aralkyl, or a 4- to 8- membered ring which may be cycloalkyl, heterocycle, heteroaryl or aryl and wherein each heteroatom, if present, is independently N, O or S,

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, C₁ to C₈ alkyl, C₁ to C₈ 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 R⁴, R⁵ and R⁷ is independently selected from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl and aralkyl,

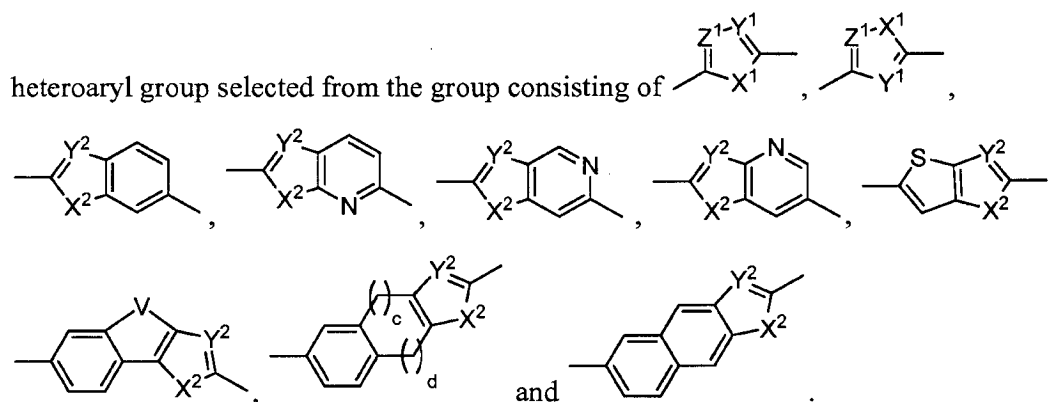
R^8 is selected from the group consisting of hydrogen, C_1 to C_8 alkyl, C_1 to C_8 heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, $-C(O)-R^{81}$, $-C(S)-R^{81}$, $-C(O)-O-R^{81}$, $-C(O)-N-R^{81}_2$, $-S(O)_2-R^{81}$ and $-S(O)_2-N-R^{81}_2$, wherein each R^{81} is independently chosen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

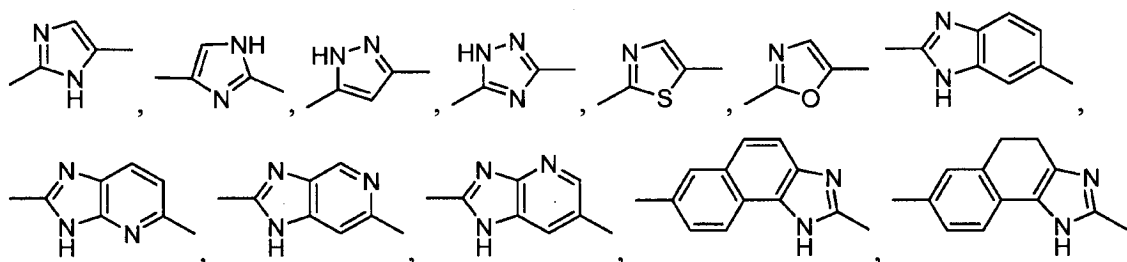
each t is independently 0, 1, 2, 3, or 4, and

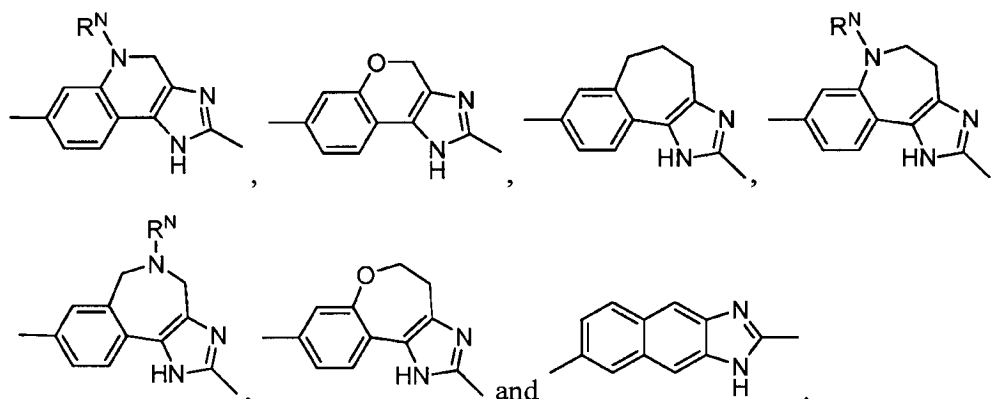
u is 0, 1, or 2.

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



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

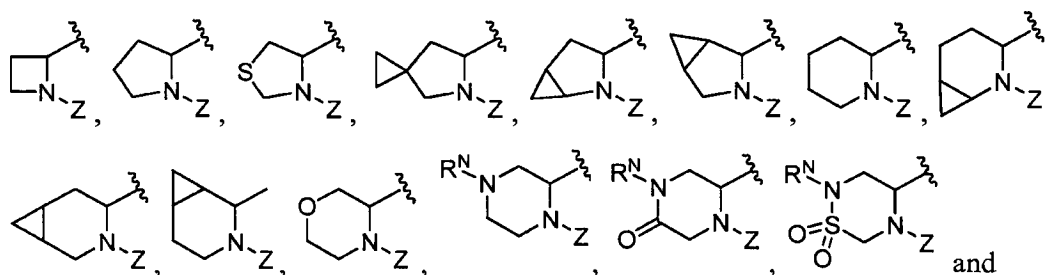
R^c , R^d , R^e and R^f are each independently selected from the group consisting of: hydrogen, C_1 to C_8 alkyl and C_1 to C_8 heteroalkyl, wherein,

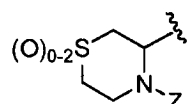
each hetero atom, if present, is independently N, O or S,

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

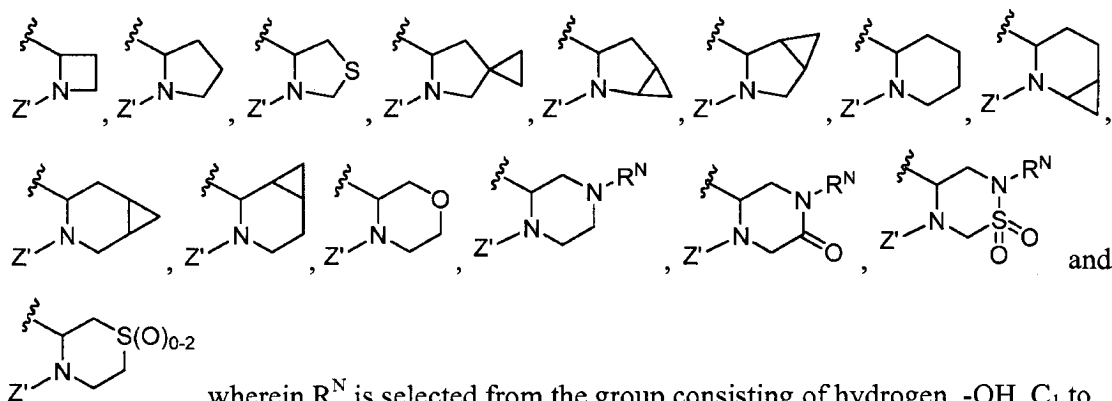
R^e and R^f are optionally joined to form a 4- to 8-membered heterocycle which is optionally fused to another 3- to 6- membered heterocycle.

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:

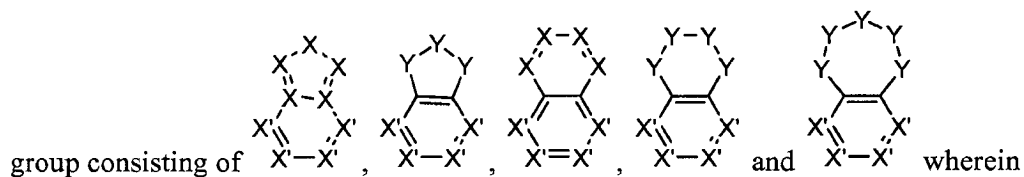



 wherein R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

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:



8. The compound of any one of claims 1 to 7 wherein B and B' together is selected from the



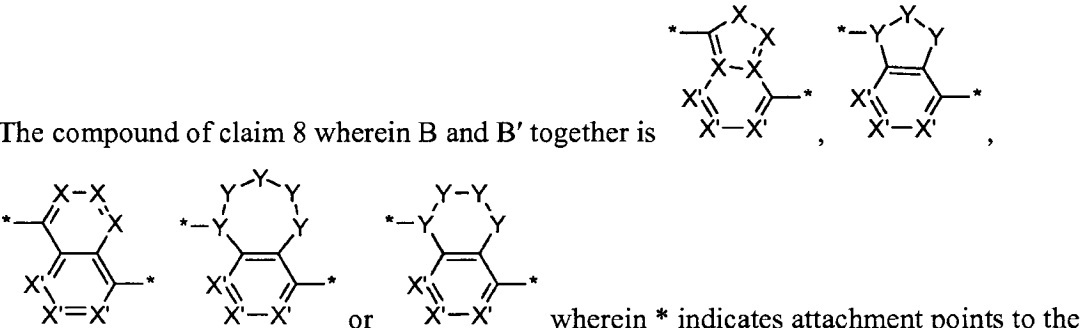
each X is independently N or C and if C, may include a hydrogen as necessary to complete the valence shell;

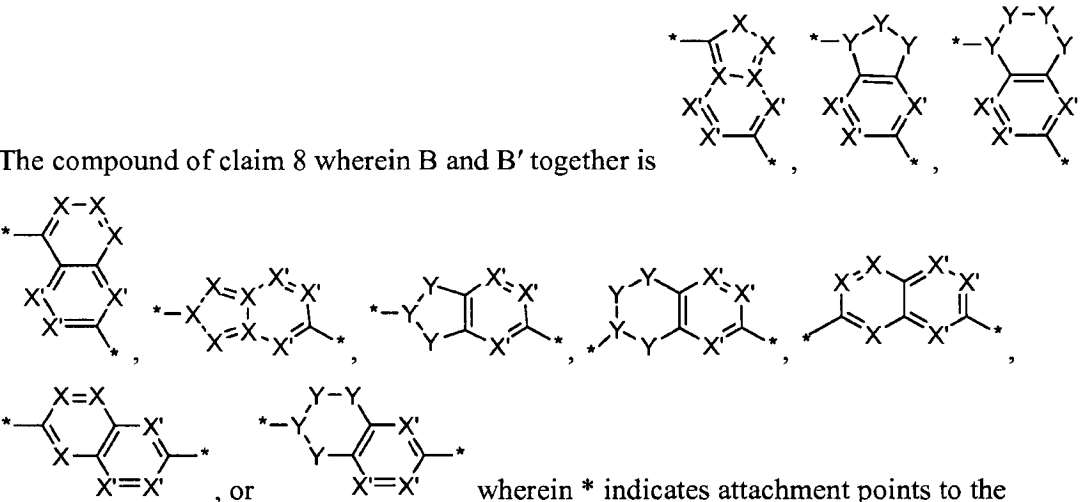
each X' is independently -N- or -CH-, with the proviso that no more than two X' are -N-;

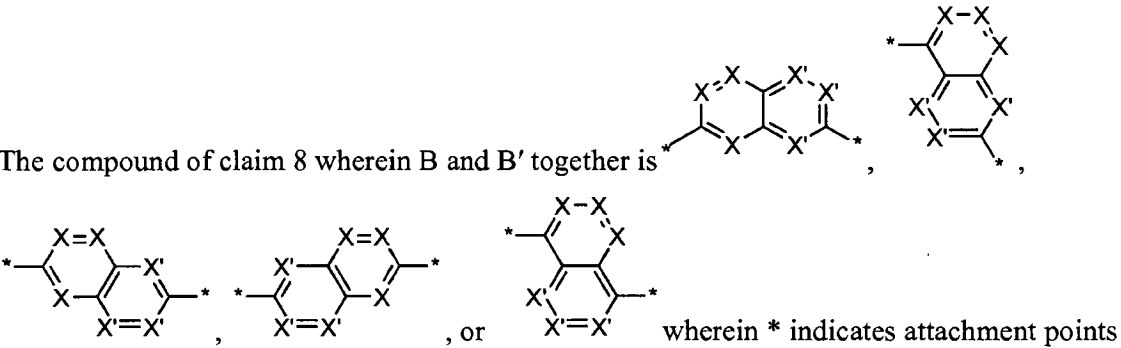
each Y is independently selected from -CH₂-, -NH-, -O-, -S-, -C(O)₂-, or -S(O)_{1.2}-; and

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

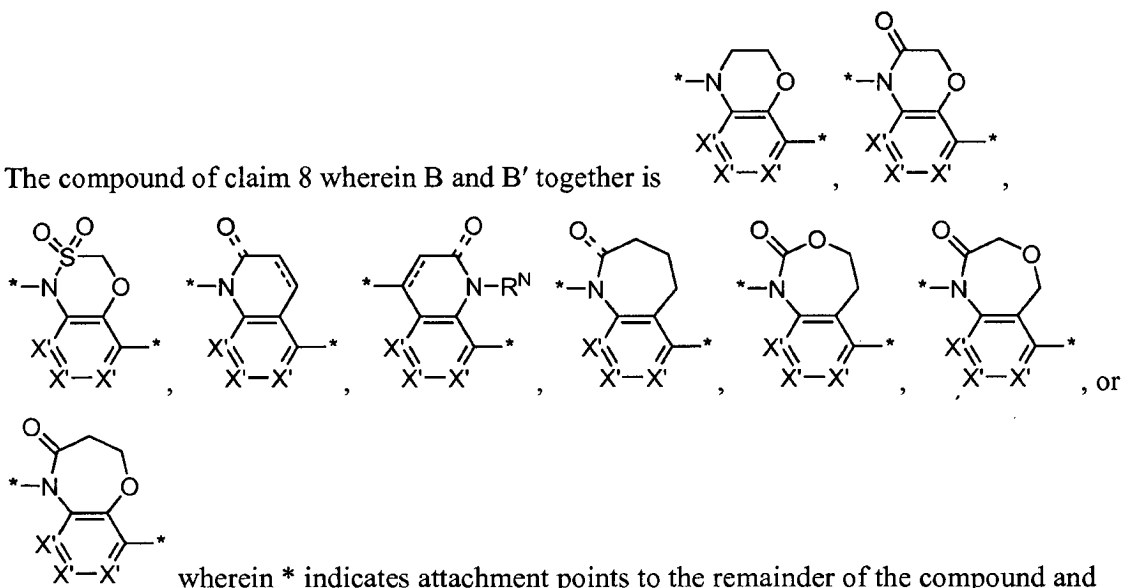
molecule.

9. The compound of claim 8 wherein B and B' together is
- 
- wherein * indicates attachment points to the remainder of the compound.

10. The compound of claim 8 wherein B and B' together is
- 
- wherein * indicates attachment points to the remainder of the compound.

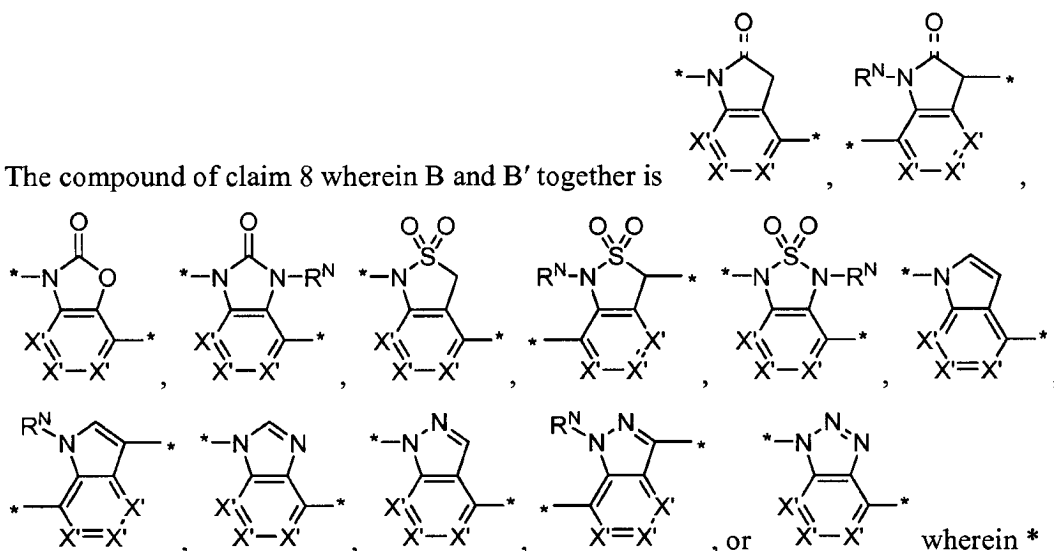
11. The compound of claim 8 wherein B and B' together is
- 
- wherein * indicates attachment points to the remainder of the compound wherein no more than 2 of X are nitrogen.

12. The compound of claim 8 wherein B and B' together is



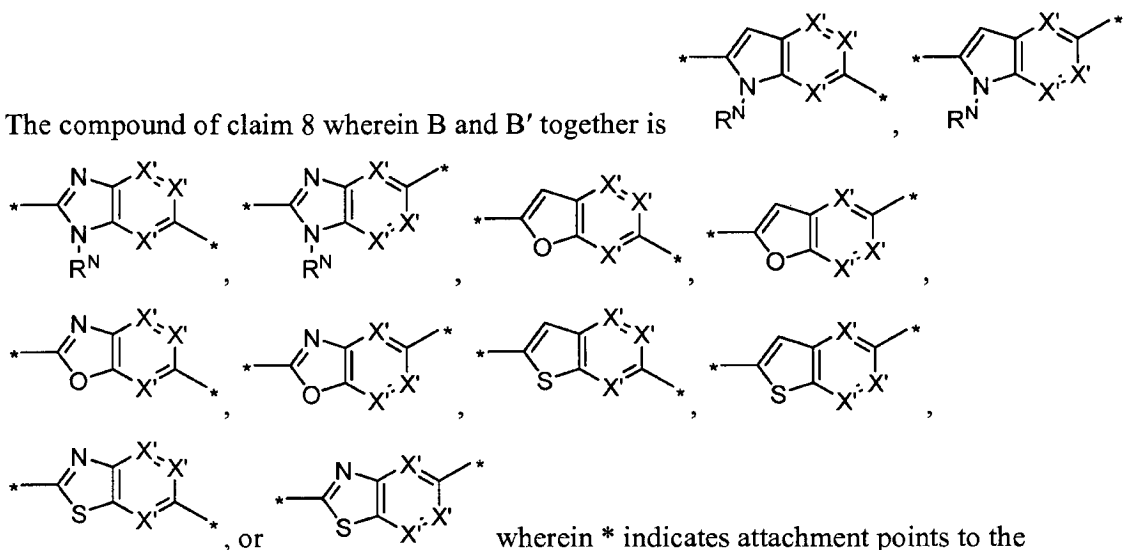
R^N is selected from the group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

13. The compound of claim 8 wherein B and B' together is



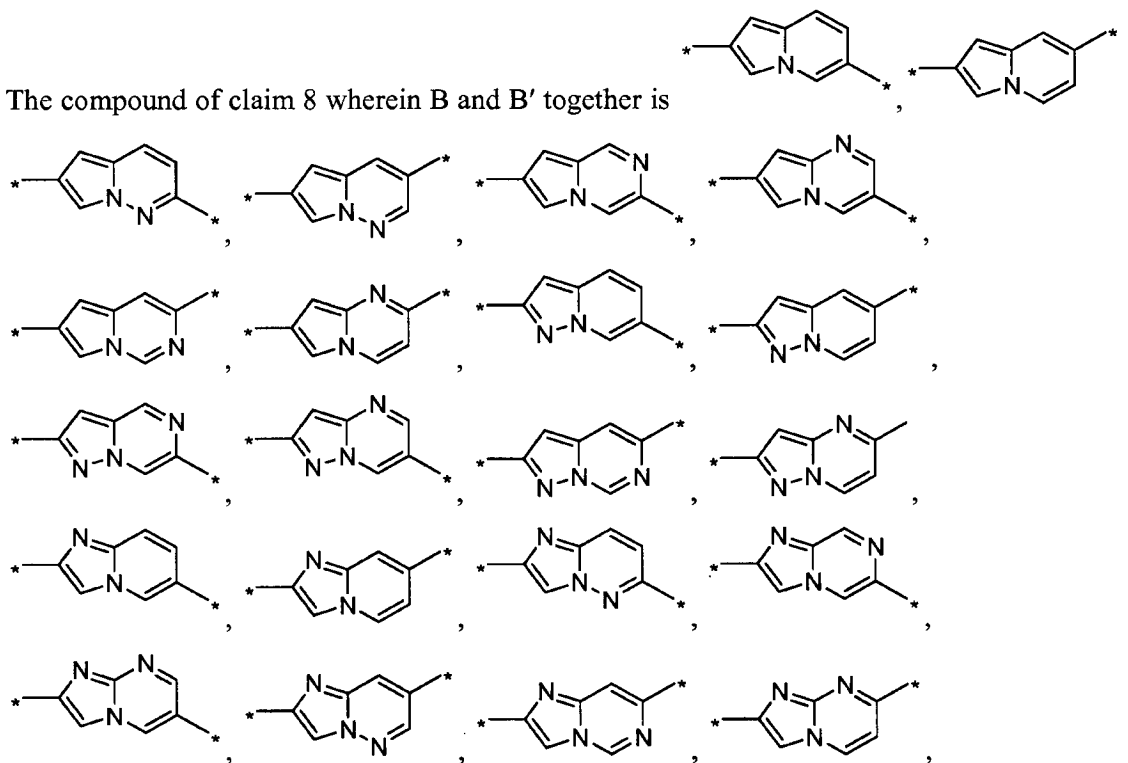
group consisting of hydrogen, -OH, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

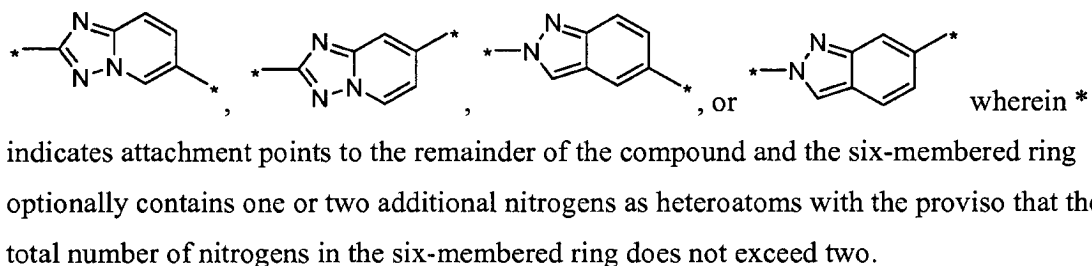
14. The compound of claim 8 wherein B and B' together is



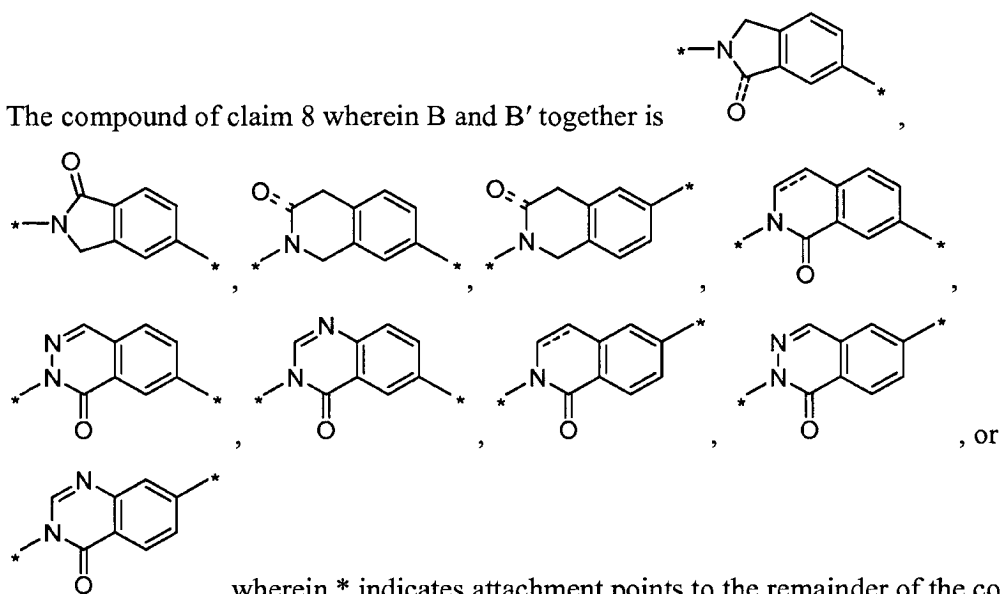
wherein * indicates attachment points to the remainder of the compound and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

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

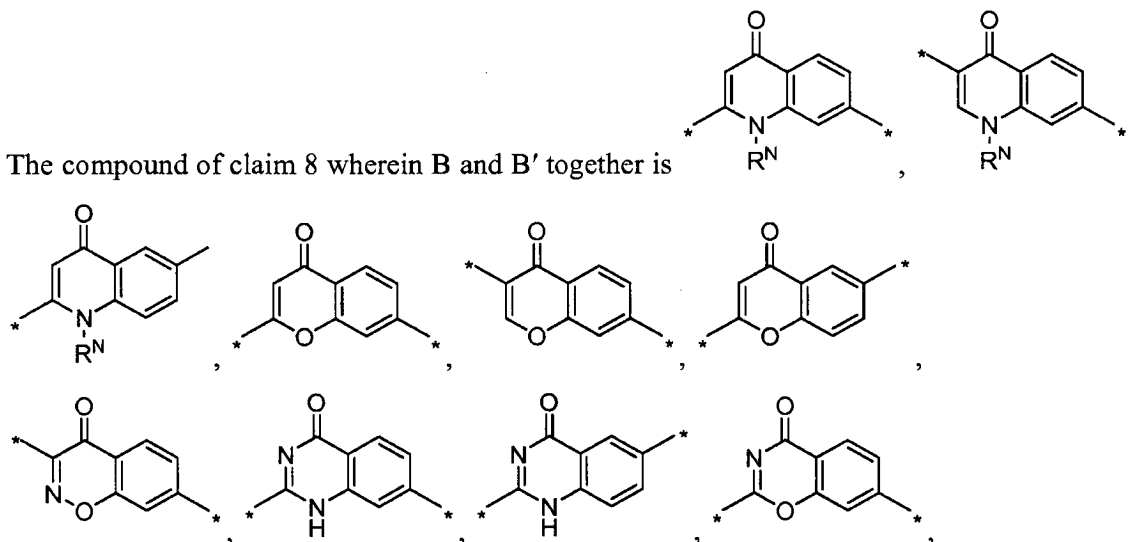


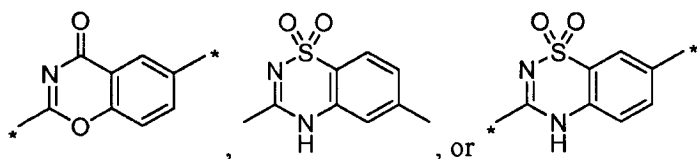


16. The compound of claim 8 wherein B and B' together is



17. The compound of claim 8 wherein B and B' together is

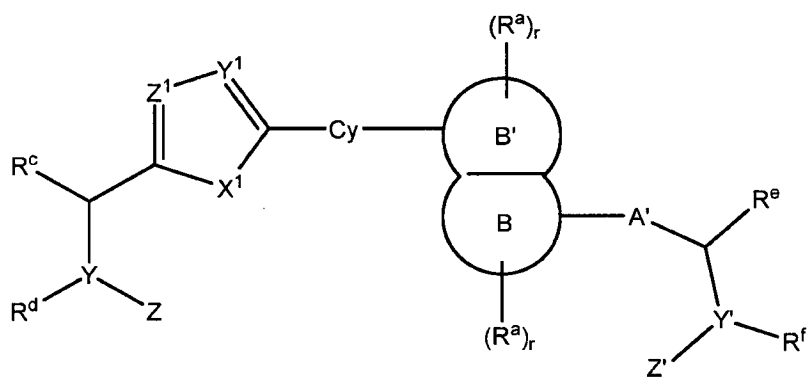




wherein * indicates attachment

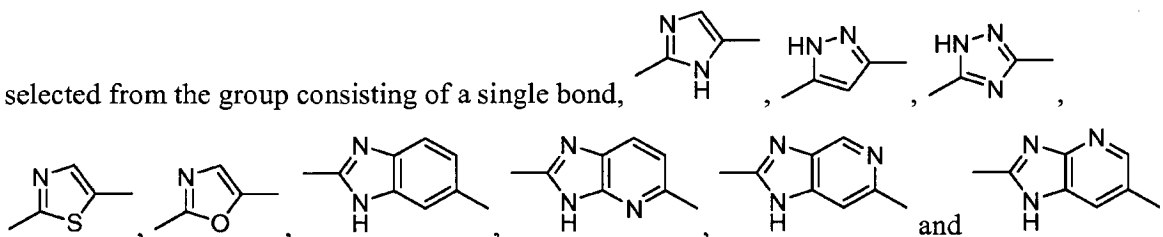
points to the remainder of the compound; the phenyl moiety optionally contains one or two nitrogens as heteroatoms; and R^N is selected from the group consisting of hydrogen, -OH, C₁ to C₁₂ alkyl, C₁ to C₁₂ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxycarbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate and sulfonamide.

18. The compound of claim 1 having formula II:

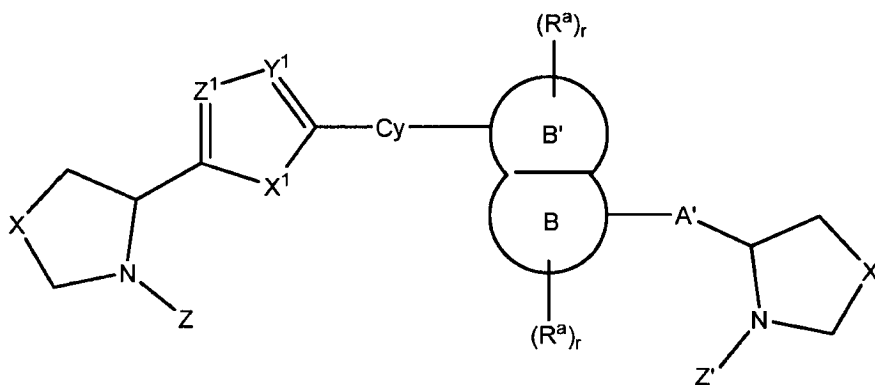


wherein A' is

selected from the group consisting of a single bond,

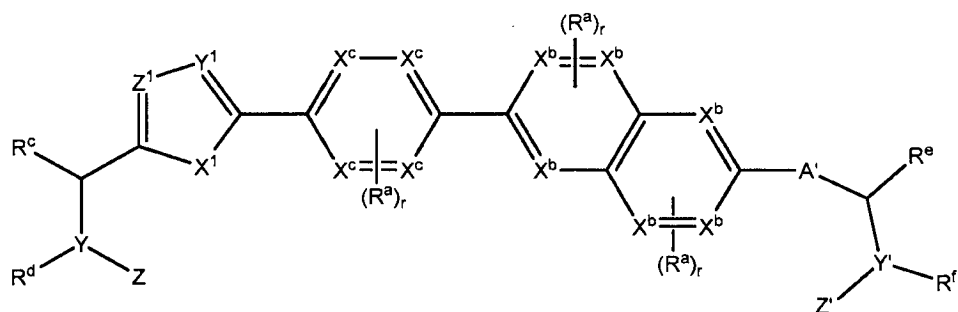


19. The compound of claim 18 having formula IIa:



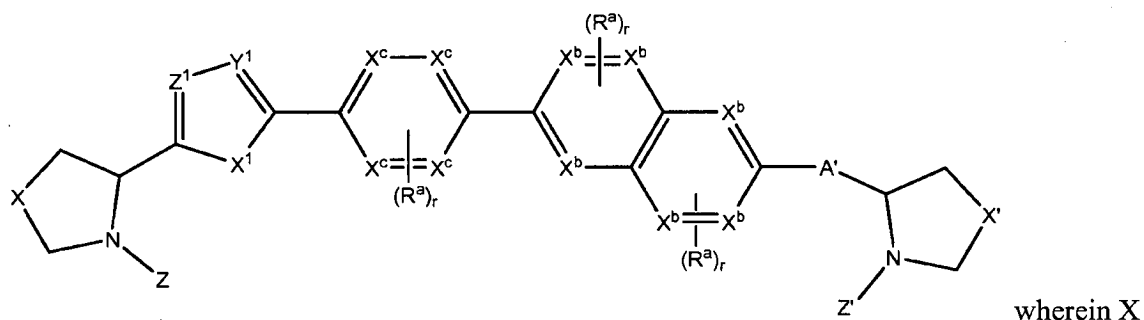
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

20. The compound of claim 18 having formula IIb:



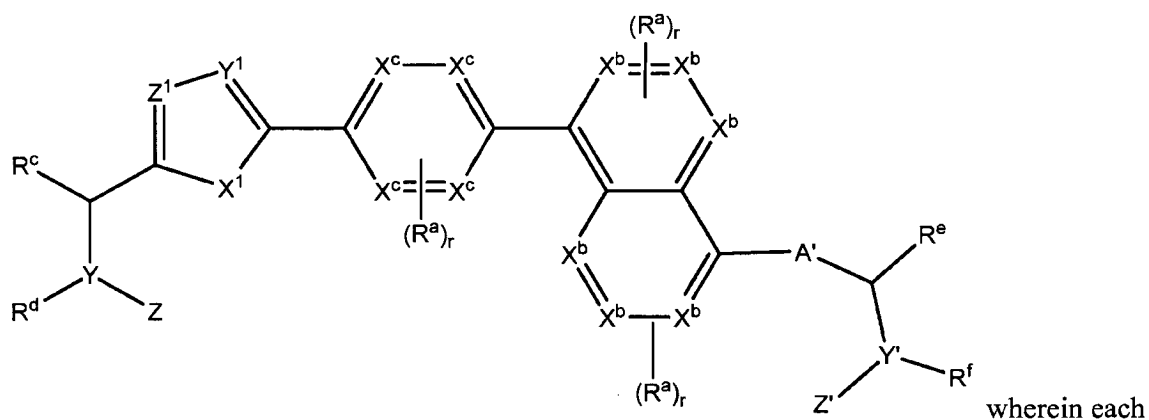
wherein each X^b and X^c is independently C or N.

21. The compound of claim 20 having formula IIc:



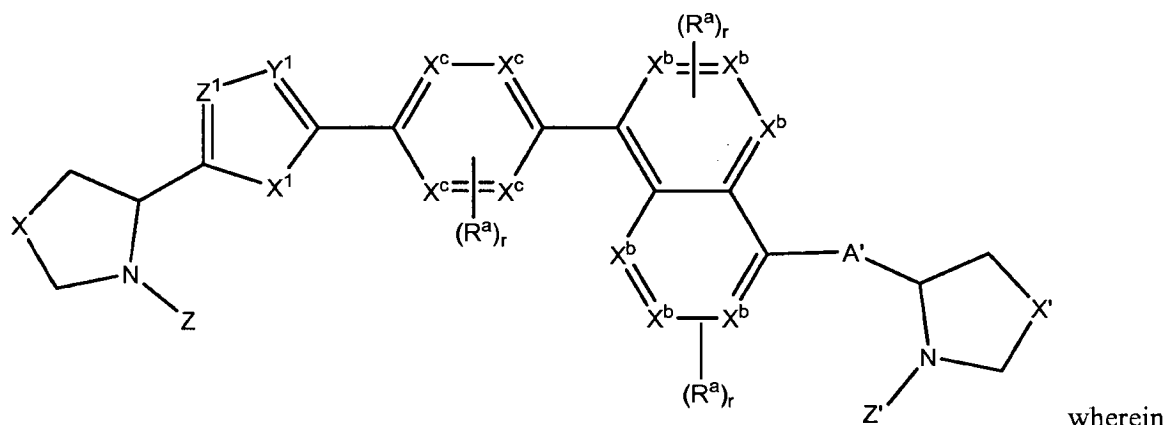
and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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:



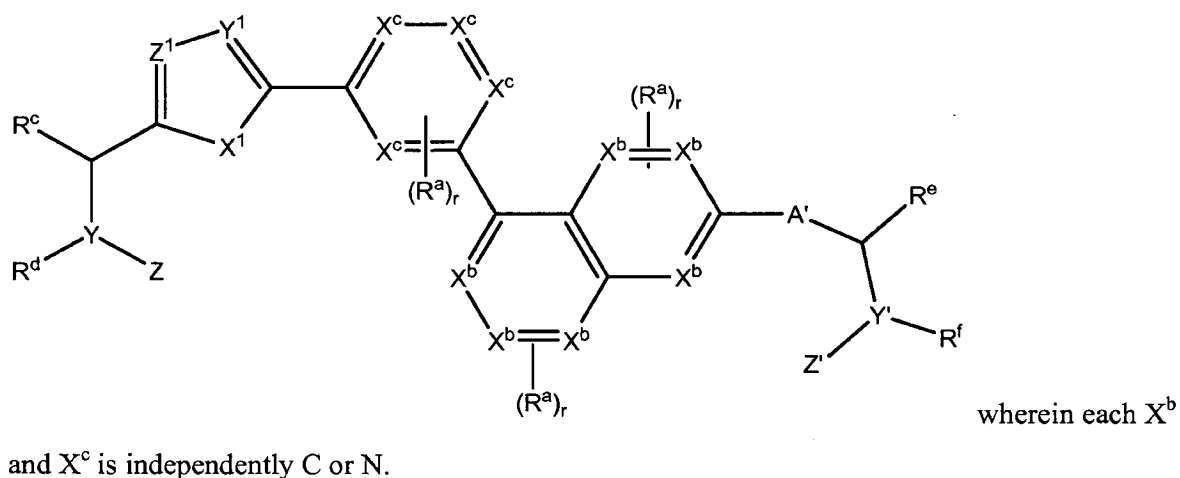
X^b and X^c is independently C or N.

23. The compound of claim 22 having formula IIe:

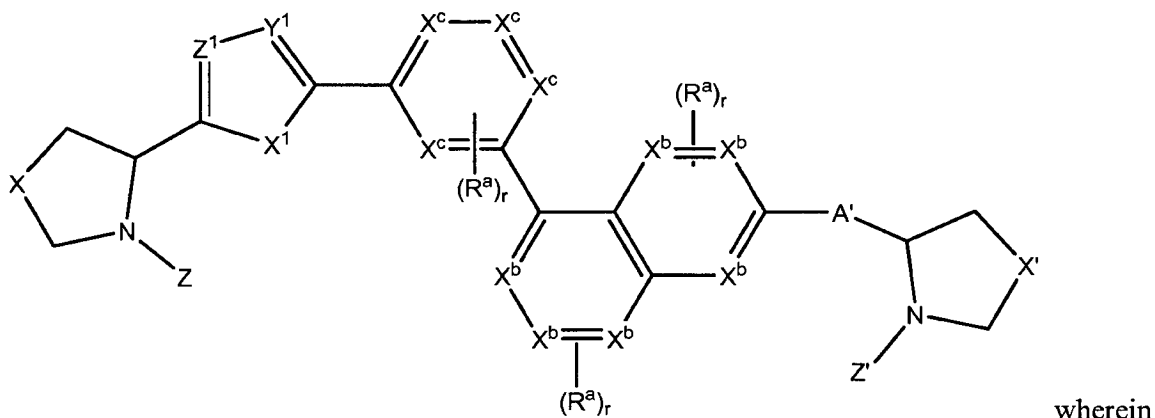


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 IIc:

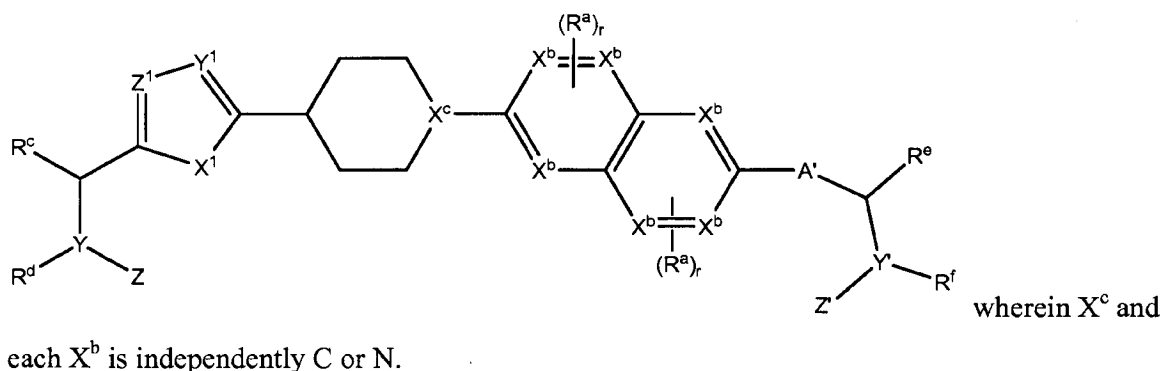


25. The compound of claim 24 having formula IIg:

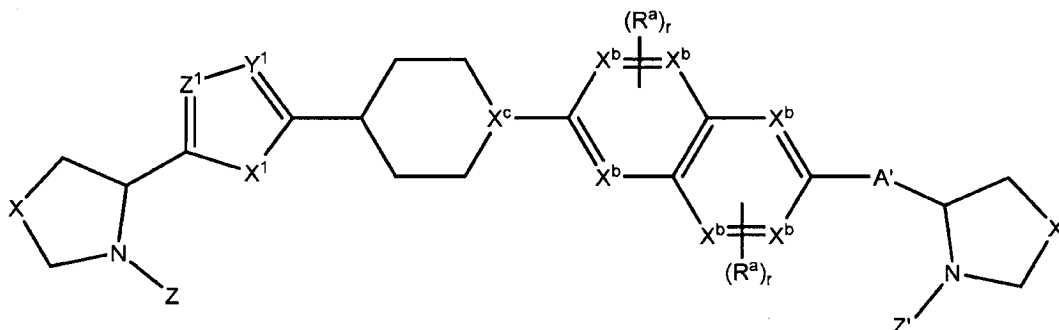


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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:



27. The compound of claim 26 having formula IIi:

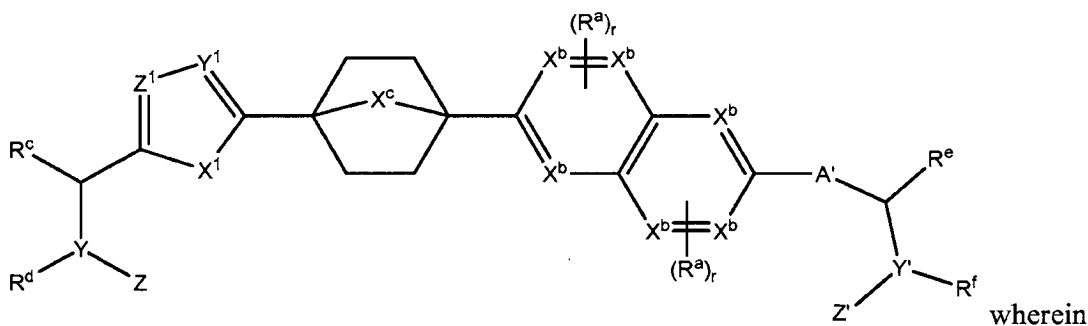


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

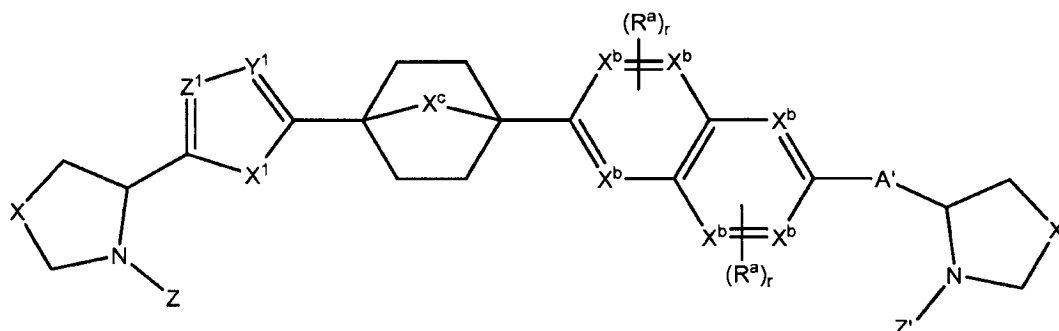
30. The compound of claim 18 having formula IIj:



X^c is $-\text{CH}_2-$, $-\text{NH}-$ or $-\text{CH}_2\text{CH}_2-$; and

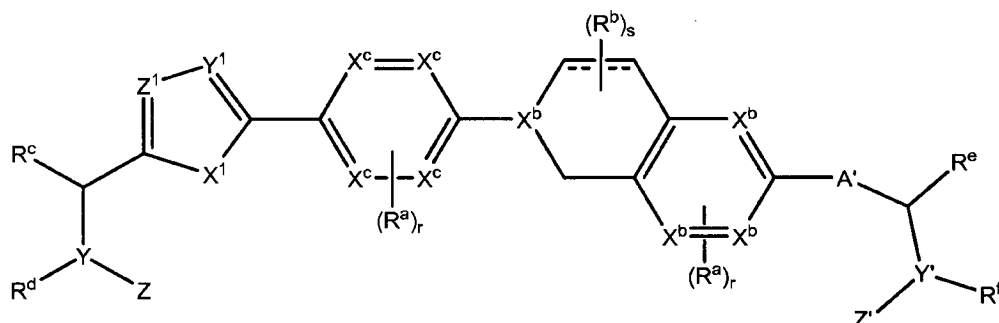
each X^b is independently C or N.

31. The compound of claim 30 having formula IIIk:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

32. The compound of claim 18 having formula III:



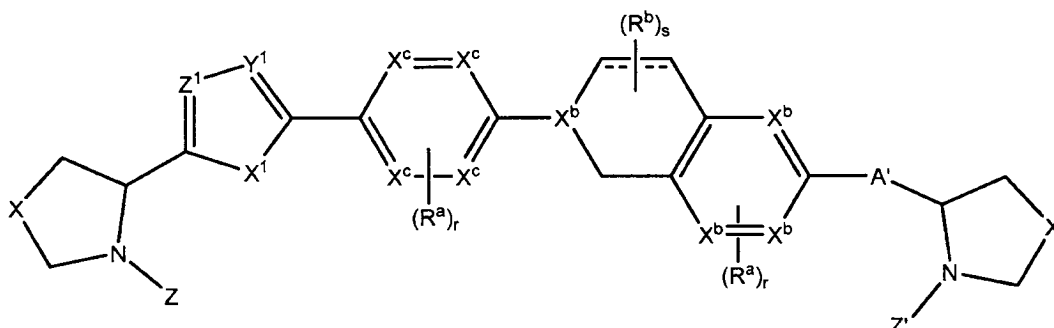
wherein:

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

each R^b is selected from the group consisting of oxo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, halogen, C_1 to C_{12} alkyl, C_1 to C_{12} heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkoxy, alkoxy carbonyl, alkanoyl, carbamoyl, substituted sulfonyl, sulfonate, sulfonamide and amino; and

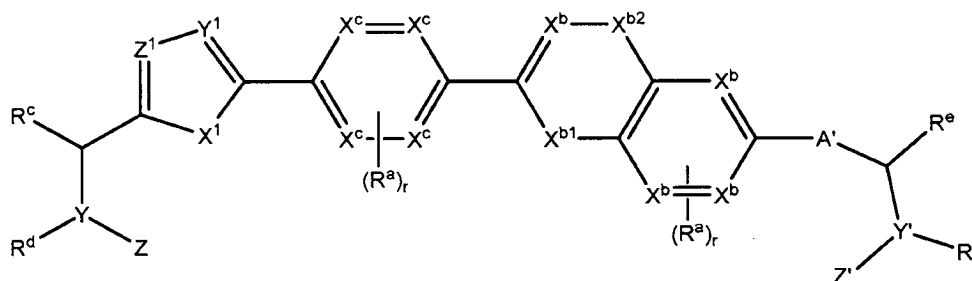
s is 0, 1, 2, or 3.

33. The compound of claim 32 having formula IIIm:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 IIa:



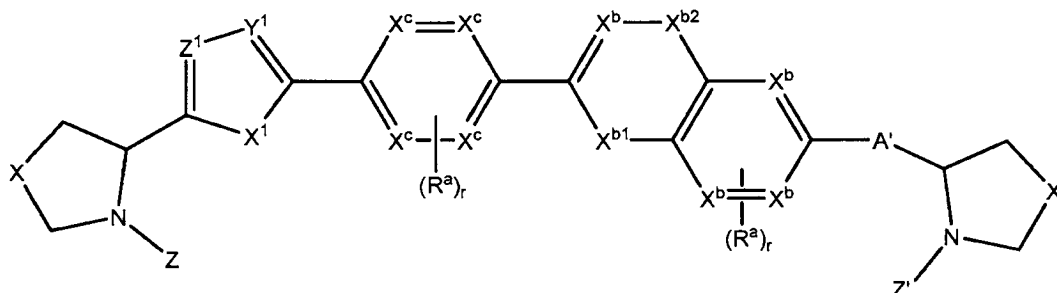
wherein:

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

X^{b1} is N or O; and

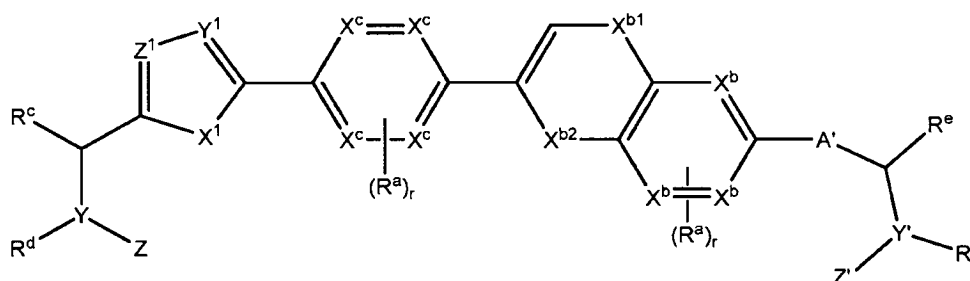
X^{b_2} is $S(O)_2$ or $C(O)$.

35. The compound of claim 34 having formula IIo:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

36. The compound of claim 18 having formula IIp:



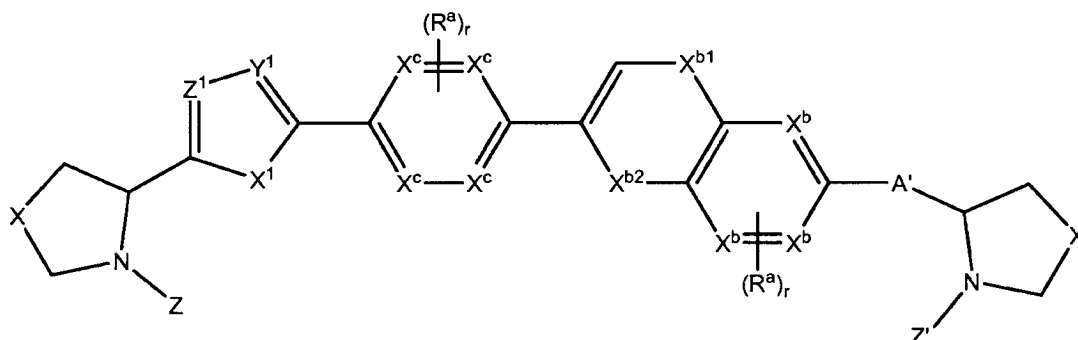
wherein:

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

X^{b1} is N or O; and

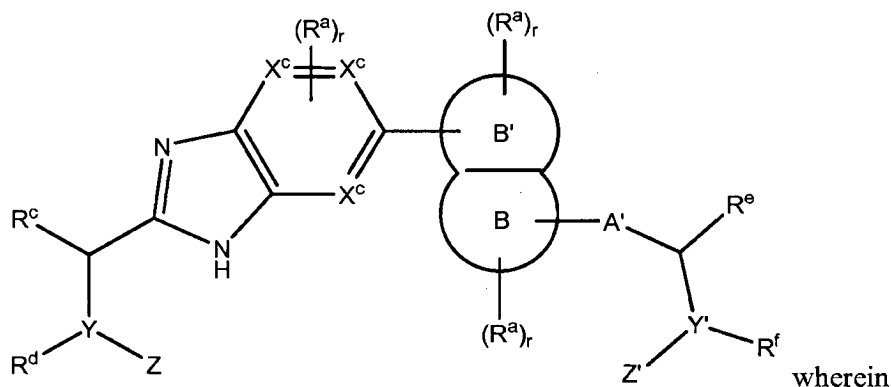
X^{b2} is $\text{S}(\text{O})_2$ or $\text{C}(\text{O})$.

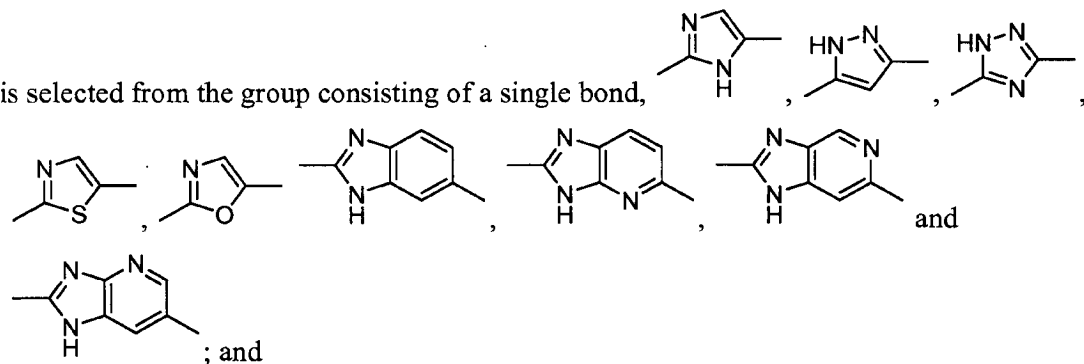
37. The compound of claim 36 having formula IIq:



wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

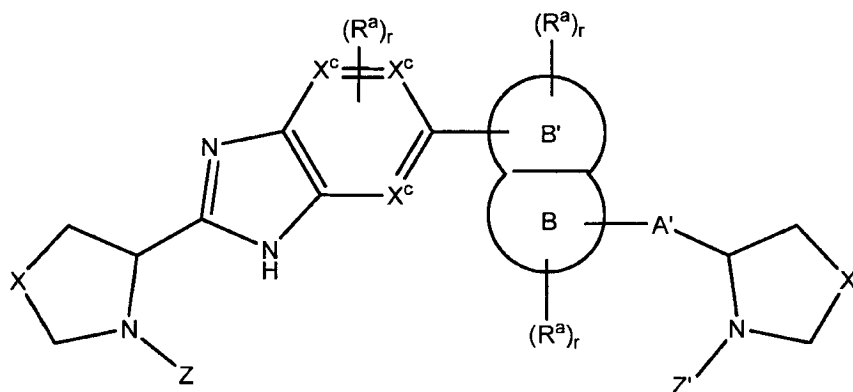
38. The compound of claim 1 having formula III:



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

each X^c is independently C or N.

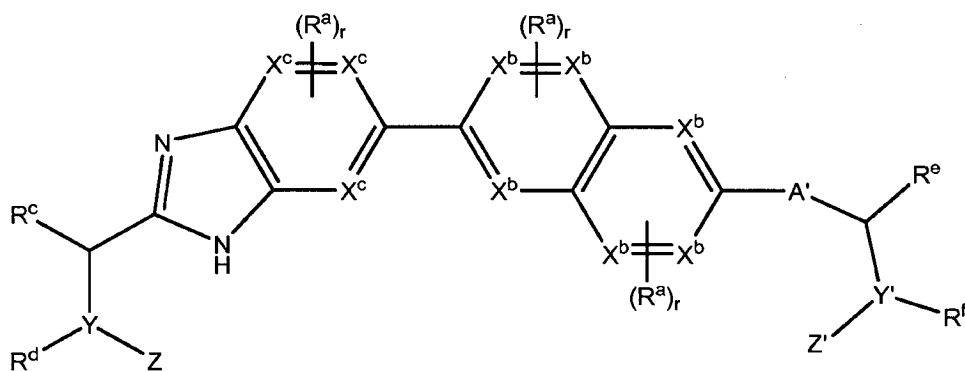
39. The compound of claim 38 having formula IIIa:



wherein X and X' are

each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

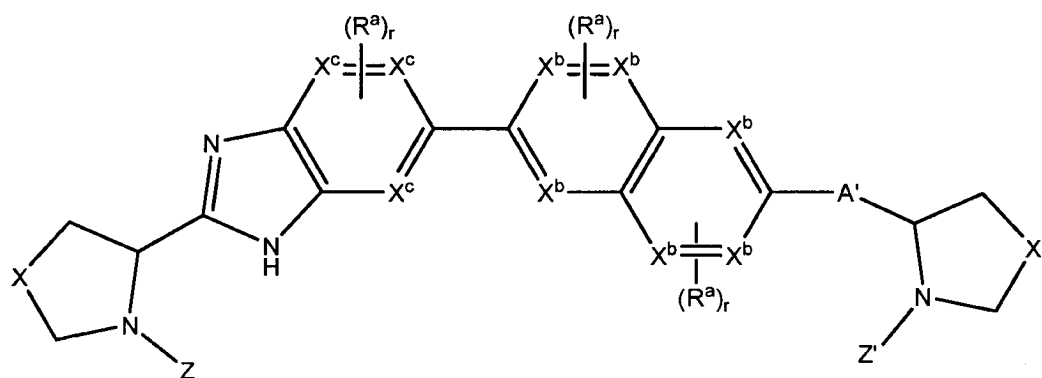
40. The compound of claim 38 having formula IIIb:



wherein each

X^b is independently C or N.

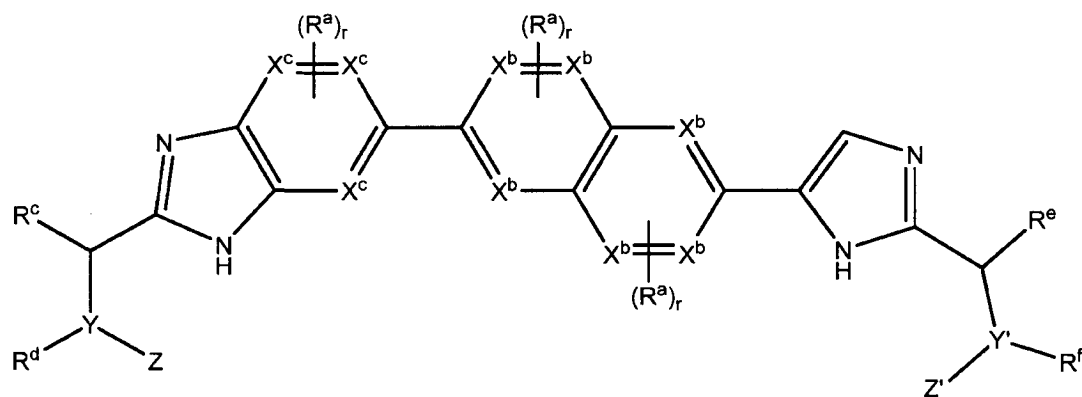
41. The compound of claim 40 having formula IIIc:



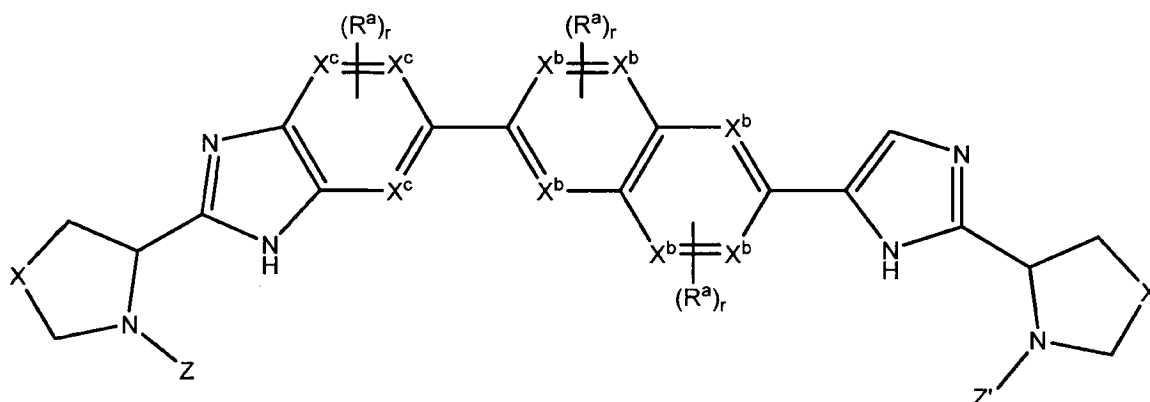
wherein

X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 IIIId:

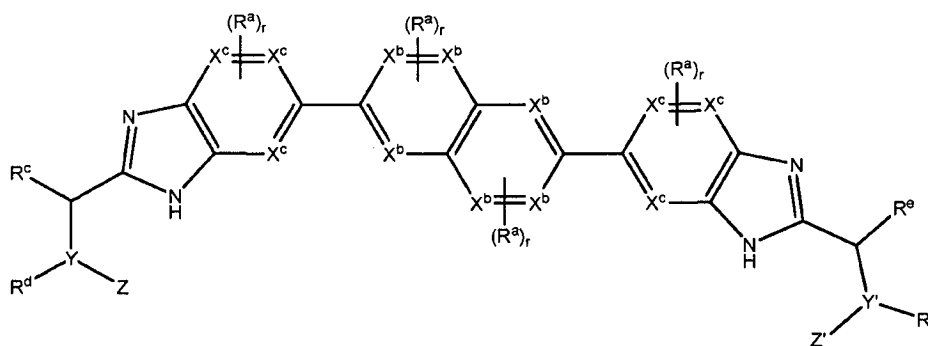


43. The compound of claim 42 having formula IIIe:

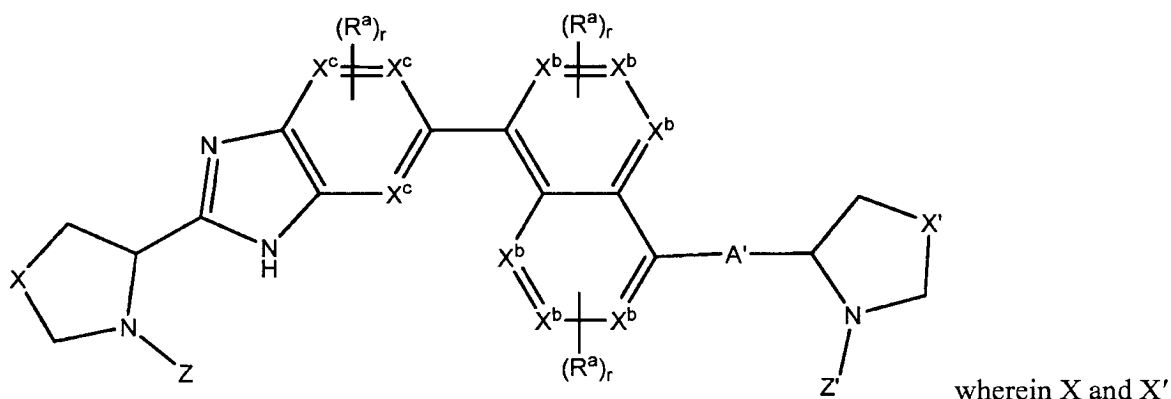


wherein X and X' are each independently selected from the group consisting of a bond, -CH₂-, -CH₂-CH₂-, -CH=CH-, -O-, -S-, -S(O)₁₋₂-, -CH₂O-, -CH₂S-, -CH₂S(O)₁₋₂- and -CH₂N(R¹)-, wherein R¹ is chosen from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxycarbonyl, carbamoyl and substituted sulfonyl.

44. The compound of claim 40 having formula IIIf:

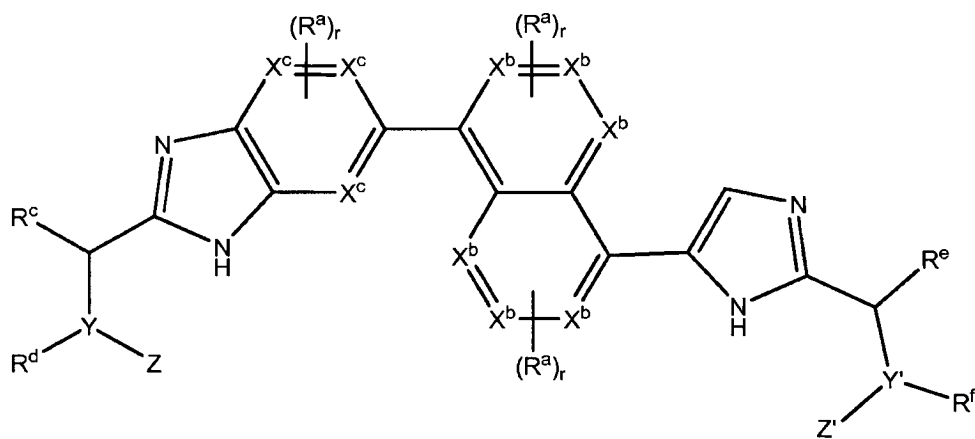


47. The compound of claim 46 having formula IIIi:

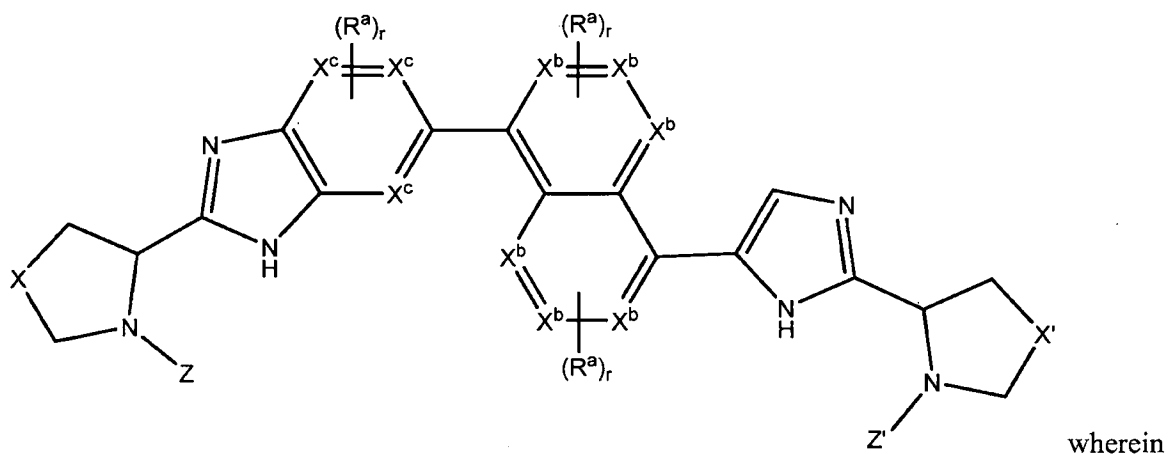


are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

48. The compound of claim 46 having formula IIIj:

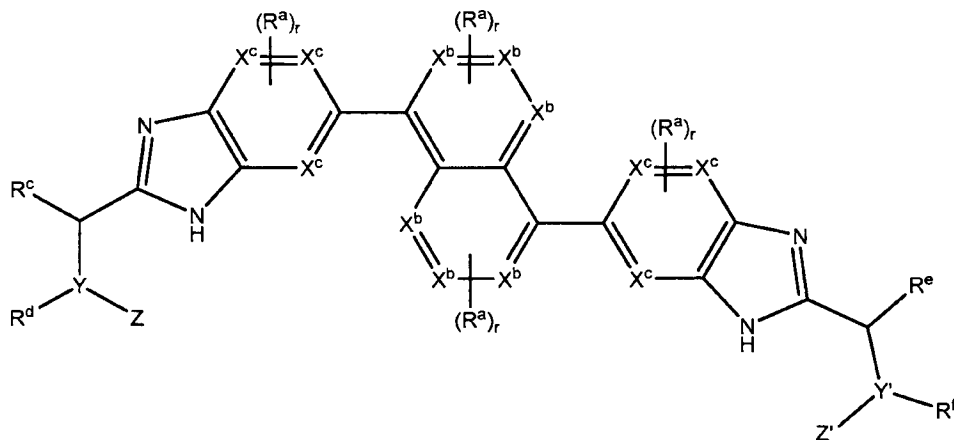


49. The compound of claim 48 having formula IIIk:

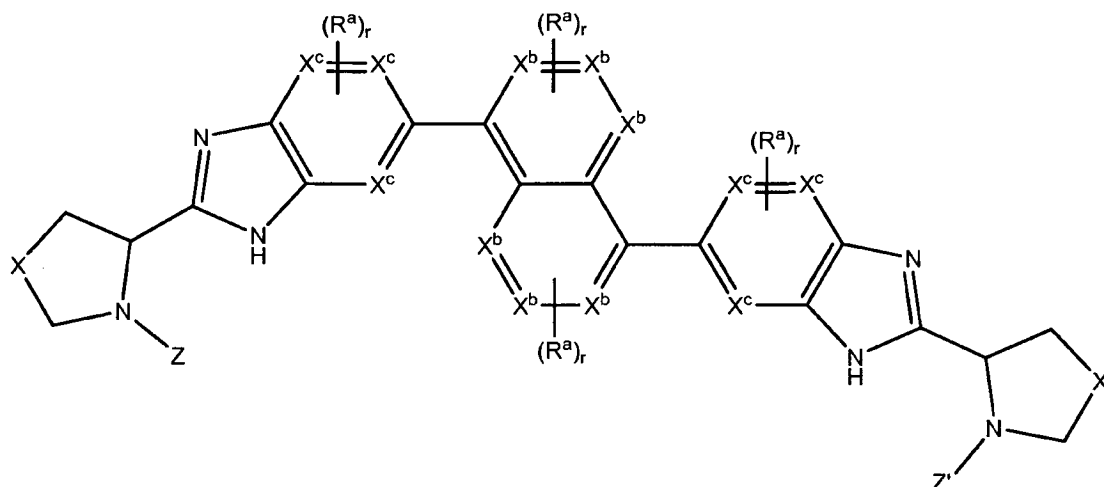


X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

50. The compound of claim 46 having formula IIIl:

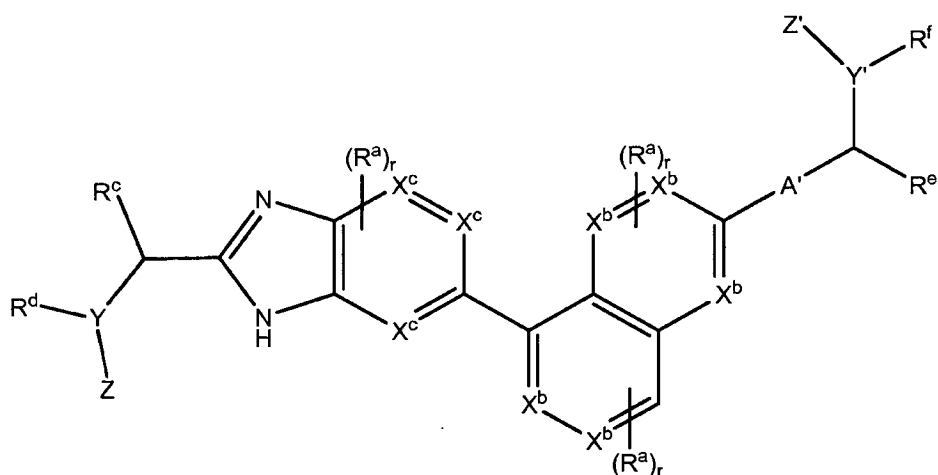


51. The compound of claim 50 having formula III_m:



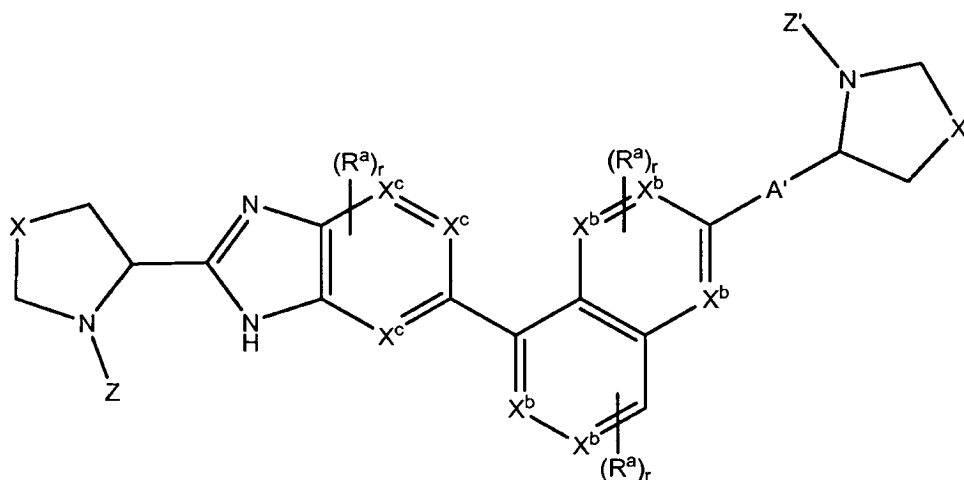
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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 III_n:



wherein each X^b is independently C or N.

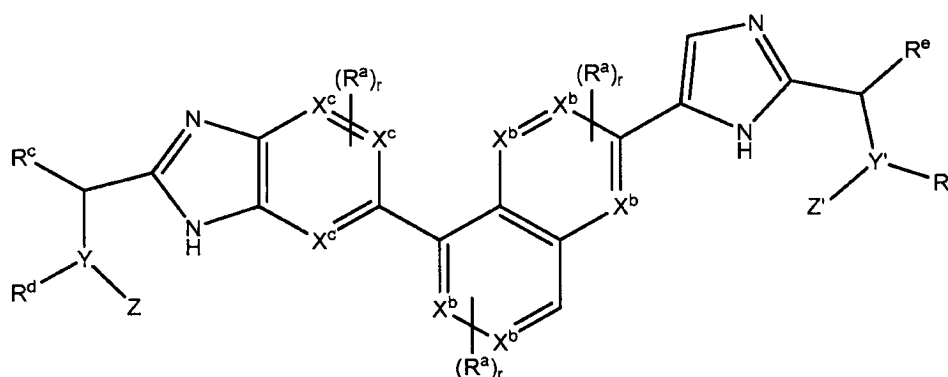
53. The compound of claim 52 having formula IIIo:

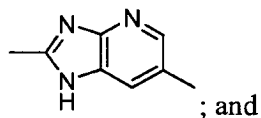


wherein X and

X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

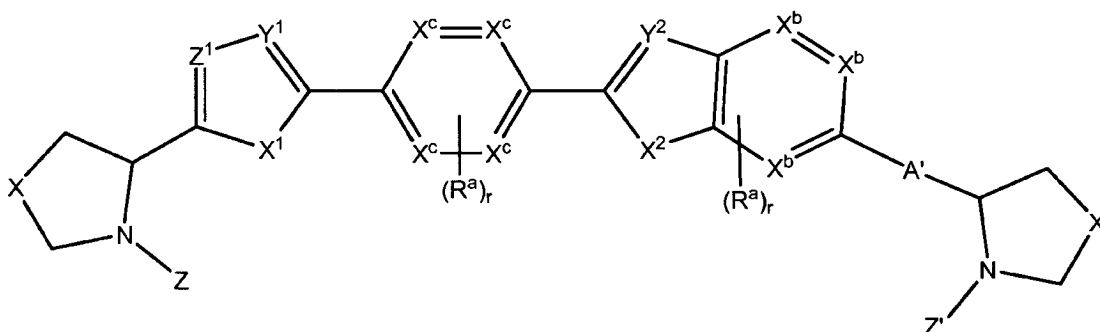
54. The compound of claim 52 having formula IIIp:





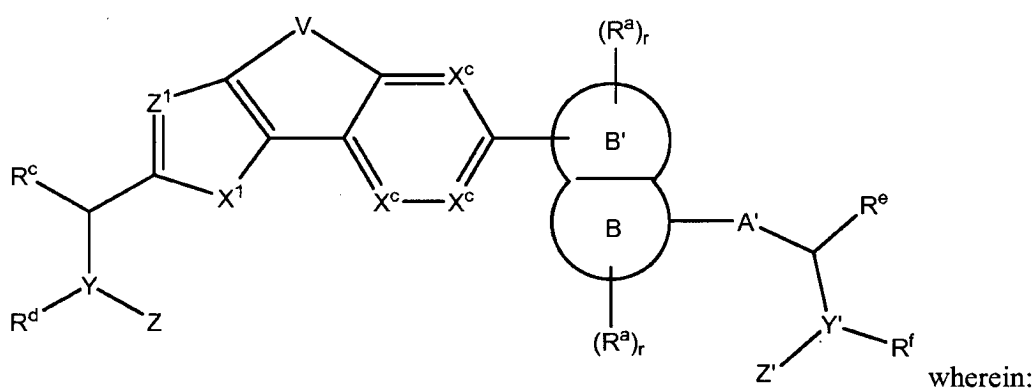
each X^b and X^c is independently C or N.

57. The compound of claim 55 having formula IVa:

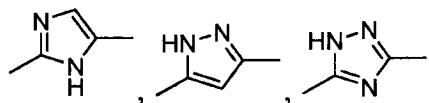


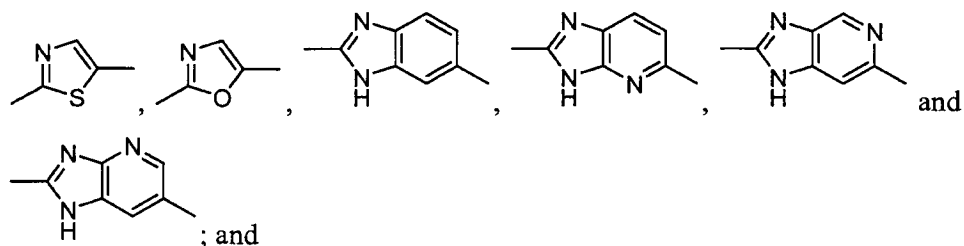
wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

58. The compound of claim 1 having formula V:



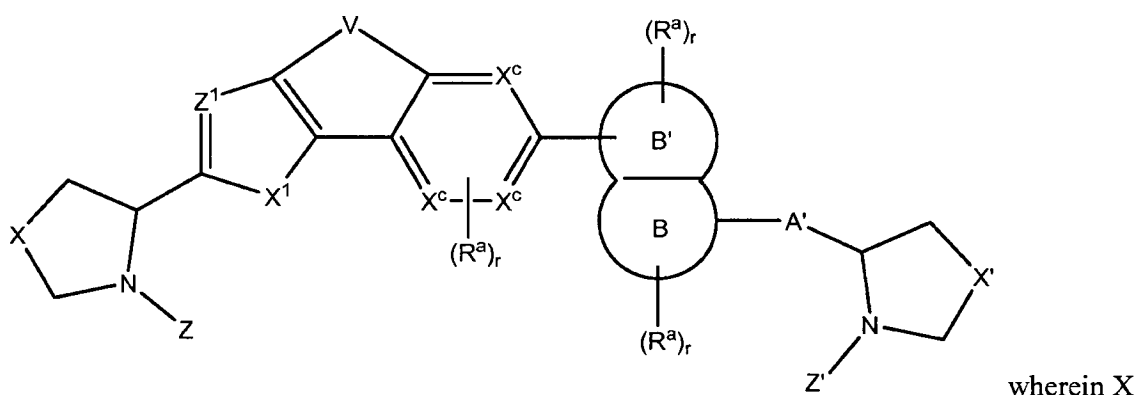
A' is selected from the group consisting of a single bond,





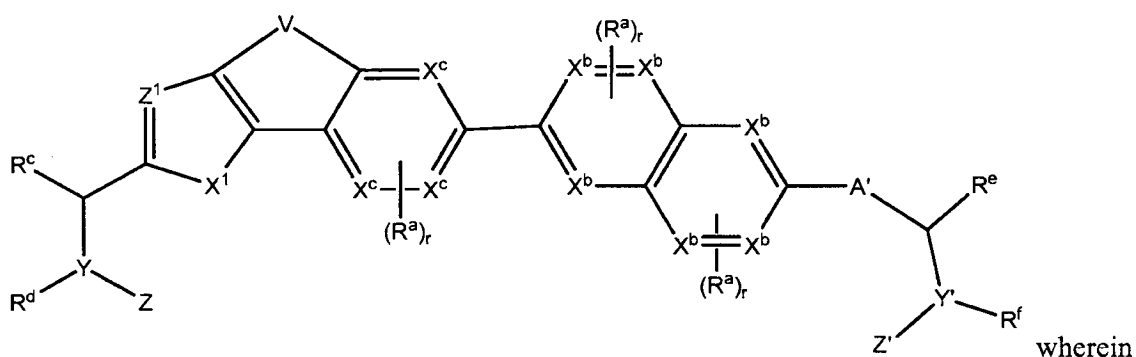
each X^c is independently C or N with the proviso that no more than two X^c are N.

59. The compound of claim 57 having formula Va:



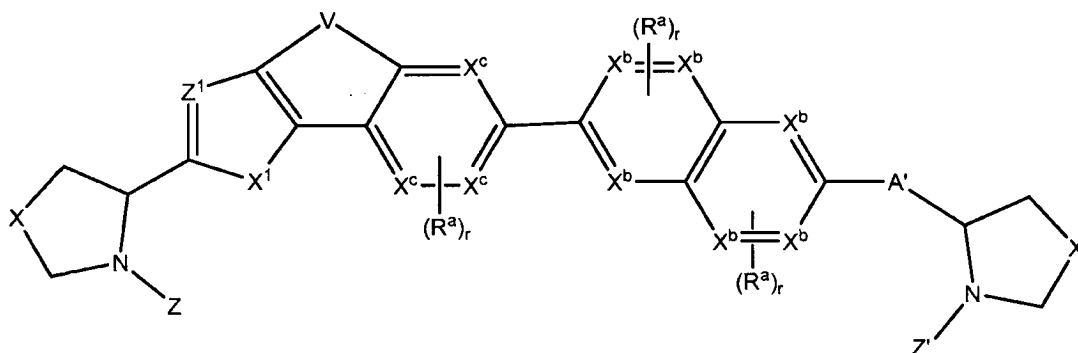
and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, wherein R¹ is chosen from the group consisting of hydrogen, C₁ to C₈ alkyl, C₁ to C₈ heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aralkyl, alkanoyl, alkoxy carbonyl, carbamoyl and substituted sulfonyl.

60. The compound of claim 57 having formula Vb:



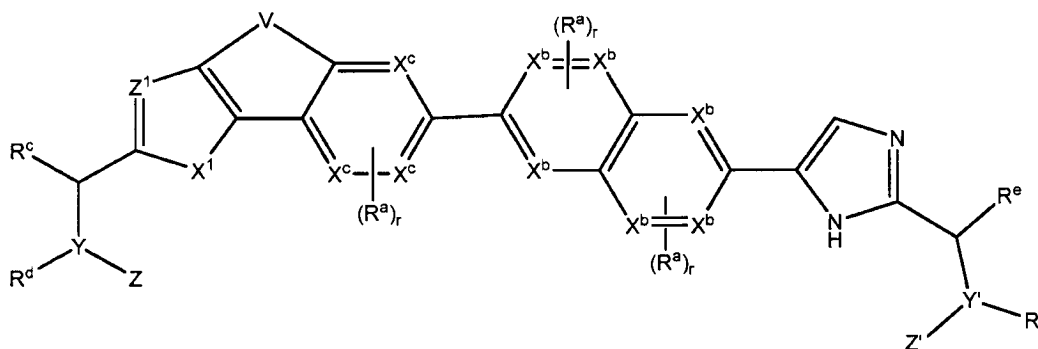
each X^b is independently C or N.

61. The compound of claim 59 having formula Vc:

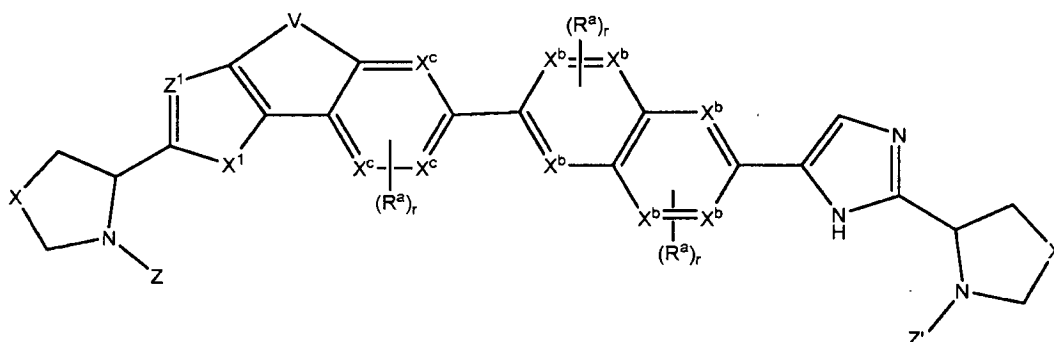


wherein X and X' are each independently selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_{1-2}-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ and $-\text{CH}_2\text{N}(\text{R}^1)-$, 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.

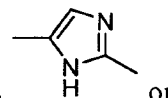
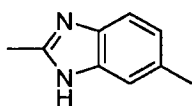
67. The compound according to any one of claims 18-63 wherein each R^a is independently

—CN, —OCHF₂, —OCF₃, —CF₃, 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—(CR⁴₂)_t—NR⁵—(CR⁴₂)_t—U—(CR⁴₂)_t—NR⁷—(CR⁴₂)_t—R⁸,
—U—(CR⁴₂)_t—R⁸ and —[U—(CR⁴₂)_t—NR⁵—(CR⁴₂)_t—U—(CR⁴₂)_t—O—(CR⁴₂)_t—R⁸.

74. The compound of claim 73 wherein one or both of Z and Z' are

—[U—(CR⁴₂)_t—NR⁵—(CR⁴₂)_t—U—(CR⁴₂)_t—NR⁷—(CR⁴₂)_t—R⁸.

75. The compound of claim 74 wherein one or both of Z and Z' are

—U—(CR⁴₂)_t—NR⁵—(CR⁴₂)_t—U—(CR⁴₂)_t—NR⁷—(CR⁴₂)_t—R⁸.

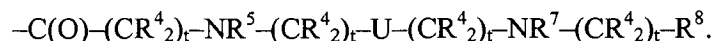
76. The compound of claim 74 wherein one or both of Z and Z' are

—U—(CR⁴₂)_t—NR⁷—(CR⁴₂)_t—R⁸.

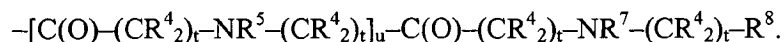
77. The compound of claim 74 wherein either one or both of Z and Z' are

—[C(O)—(CR⁴₂)_t—NR⁵—(CR⁴₂)_t—U—(CR⁴₂)_t—NR⁷—(CR⁴₂)_t—R⁸.

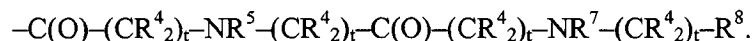
78. The compound of claim 77 wherein one or both of Z and Z' are



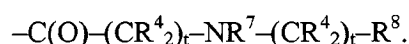
79. The compound of claim 77 wherein one or both of Z and Z' are



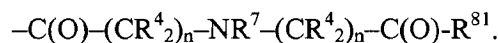
80. The compound of claim 79 wherein one or both of Z and Z' are



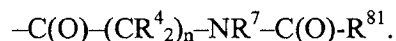
81. The compound of claim 77 wherein one or both of Z and Z' are



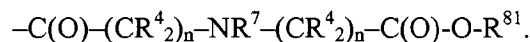
82. The compound of claim 81 wherein one or both of Z and Z' are



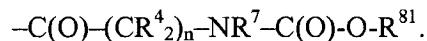
83. The compound of claim 82 wherein one or both of Z and Z' are



84. The compound of claim 81 wherein one or both of Z and Z' are



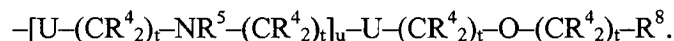
85. The compound of claim 84 wherein one or both of Z and Z' are



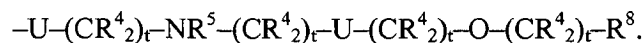
86. The compound of claim 73 wherein one or both of Z and Z' are $-U-(CR^4_2)_t-R^8$.

87. The compound of claim 86 wherein one or both of Z and Z' are $-C(O)-(CR^4_2)_t-R^8$.

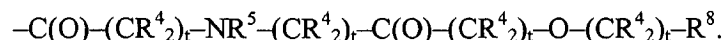
88. The compound of claim 73 wherein one or both of Z and Z' are



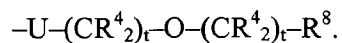
89. The compound of claim 88 wherein one or both of Z and Z' are



90. The compound of claim 89 wherein one or both of Z and Z' are



91. The compound of claim 88 wherein one or both of Z and Z' are



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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/66459

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 57/00; A61K 31/675 (2010.01)

USPC - 514/79-81

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/79-81

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/277, 279, 332, 359, 408, 410 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (USPT, PGPB, EPAB, JPAB); Google Scholar

Search terms: hepatitis C, thiazol, benzothiazol, pyrrolidine, dicarboxylate, NS5A, non structural, naphthalene, quinoline, quinoxaline, benzo, phenyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0050336 A1 (BACHAND et al.) 28 February 2008 (28.02.2008) entire document, especially para [0009]	1-6, 18-66, 68-69
Y	US 2007/0185175 A1 (LIU et al.) 09 August 2007 (09.08.2007) entire document, especially para [0008]	1-6, 18-66, 68-69
Y	US 2005/0026923 A1 (AN et al.) 03 February 2005 (03.02.2005) entire document, especially para [0018]	20-55, 60-66, 68-69

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 February 2010 (16.02.2010)

Date of mailing of the international search report

04 MAR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/66459

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7-17, 67 and 70-95
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.



(12) 发明专利申请

(10) 申请公布号 CN 104163816 A

(43) 申请公布日 2014. 11. 26

(21) 申请号 201410221684. 8

C07D 413/14 (2006. 01)

(22) 申请日 2009. 12. 02

C07D 417/14 (2006. 01)

(30) 优先权数据

A61K 31/4178 (2006. 01)

61/119, 723 2008. 12. 03 US

A61K 31/4184 (2006. 01)

61/173, 590 2009. 04. 28 US

A61K 31/4709 (2006. 01)

61/214, 881 2009. 04. 28 US

A61K 31/498 (2006. 01)

61/182, 952 2009. 06. 01 US

A61K 31/4439 (2006. 01)

61/182, 958 2009. 06. 01 US

A61K 31/517 (2006. 01)

A61K 31/4725 (2006. 01)

(62) 分案原申请数据

A61K 31/437 (2006. 01)

200980154543. 6 2009. 12. 02

A61K 31/5377 (2006. 01)

(71) 申请人 普雷西迪奥制药公司

A61K 31/428 (2006. 01)

地址 美国加利福尼亚州

A61K 31/423 (2006. 01)

(72) 发明人 M·钟 L·李

A61P 1/16 (2006. 01)

A61P 31/14 (2006. 01)

(74) 专利代理机构 北京万慧达知识产权代理有限公司 11111

代理人 杨颖 张金芝

(51) Int. Cl.

C07D 403/14 (2006. 01)

C07D 405/14 (2006. 01)

C07D 401/14 (2006. 01)

C07D 471/04 (2006. 01)

权利要求书25页 说明书221页

(54) 发明名称

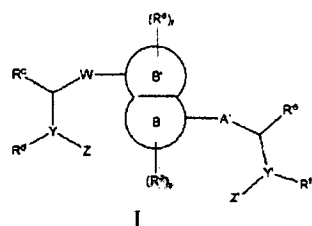
HCV NS5A 的抑制剂

(57) 摘要

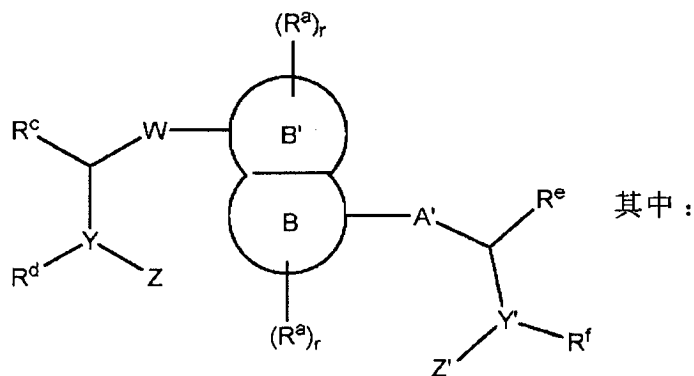
本发明涉及一种具有通式 I 结构的可用于抑制丙型肝炎病毒 (“HCV”) 复制、特别是抑制 HCV 的非结构 5A (“NS5A”) 蛋白功能的化合物及其组合物, 以及该化合物在制备治疗丙型肝炎的药物

CN 104163816 A

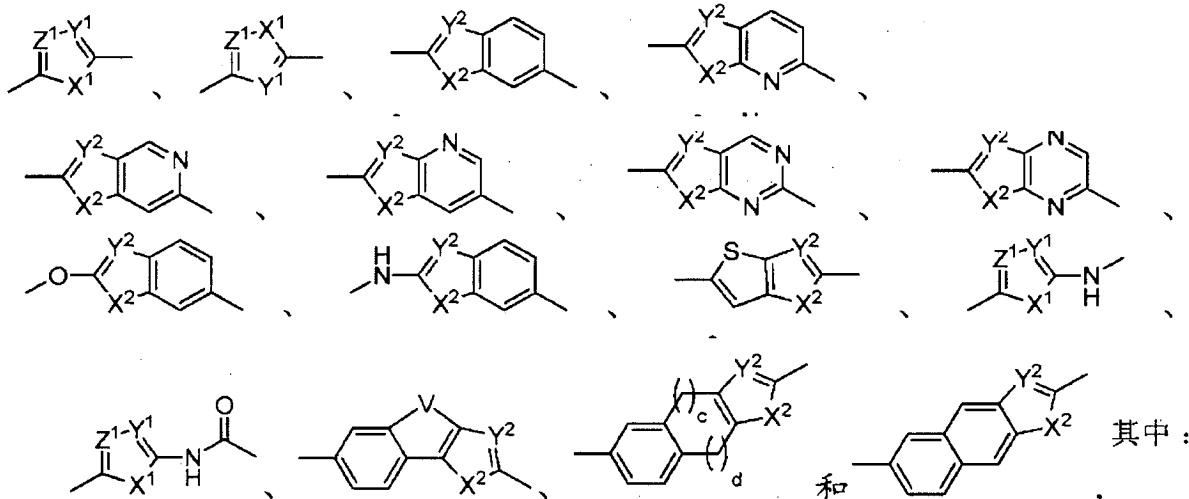
中的用途。



1. 一种化合物, 如式 I 所示:



A' 选自单键、 $-(\text{CR}_2)_n-\text{C}(\text{O})-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{O}-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{S}(\text{O})_k-\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{C}(\text{O})-\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{N}(\text{R}^N)-\text{C}(\text{O})-\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{C}(\text{O})-\text{O}-(\text{CR}_2)_p-$ 、 $-(\text{CR}_2)_n-\text{N}(\text{R}^N)-\text{S}(\text{O})_k-\text{N}(\text{R}^N)-(\text{CR}_2)_p-$ 和 $-(\text{CR}_2)_n-\text{N}(\text{R}^N)-\text{C}(\text{O})-\text{O}-(\text{CR}_2)_p-$ 以及杂芳基, 所述杂芳基选自

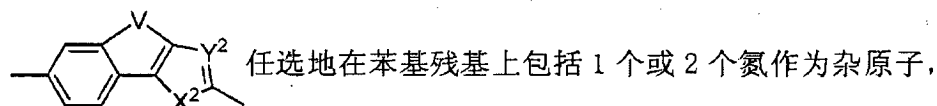


X^1 为 CH_2 、 NH 、 O 或 S ,

Y^1 、 Y^2 和 Z^1 各自独立地为 CH 或 N ,

X^2 为 NH 、 O 或 S ,

V 为 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{N}=\text{CH}-$ 、 $(\text{CH}_2)_a-\text{N}(\text{R}^N)-(\text{CH}_2)_b-$ 或 $-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-$, 其中 a 和 b 独立地为 0、1、2 或 3, 前提是 a 和 b 不均为 0,



杂芳基的碳任选各自独立地由选自以下的取代基取代: 卤素、 $-\text{OH}$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

杂芳基的氮在存在时任选各自独立地由选自以下的取代基取代: $-\text{OH}$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、

取代的磺酰基、磺酸酯基和磺酰胺基,

a 和 b 独立地为 1、2 或 3,

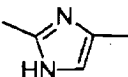
c 和 d 独立地为 1 或 2,

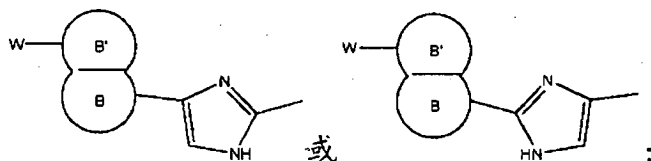
n 和 p 独立地为 0、1、2 或 3,

k 为 0、1 或 2,

各 R 独立地选自氢、卤素、-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

各 R^N 独立地选自氢、-OH、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基, 且

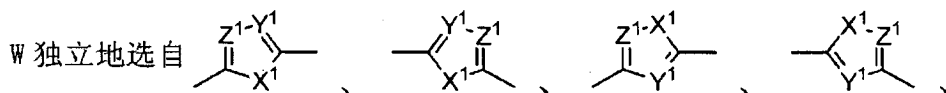
其中 B 可附接到 A' 的任一侧上, 使得在 A' 为  的实例中, W-B-A' 可为

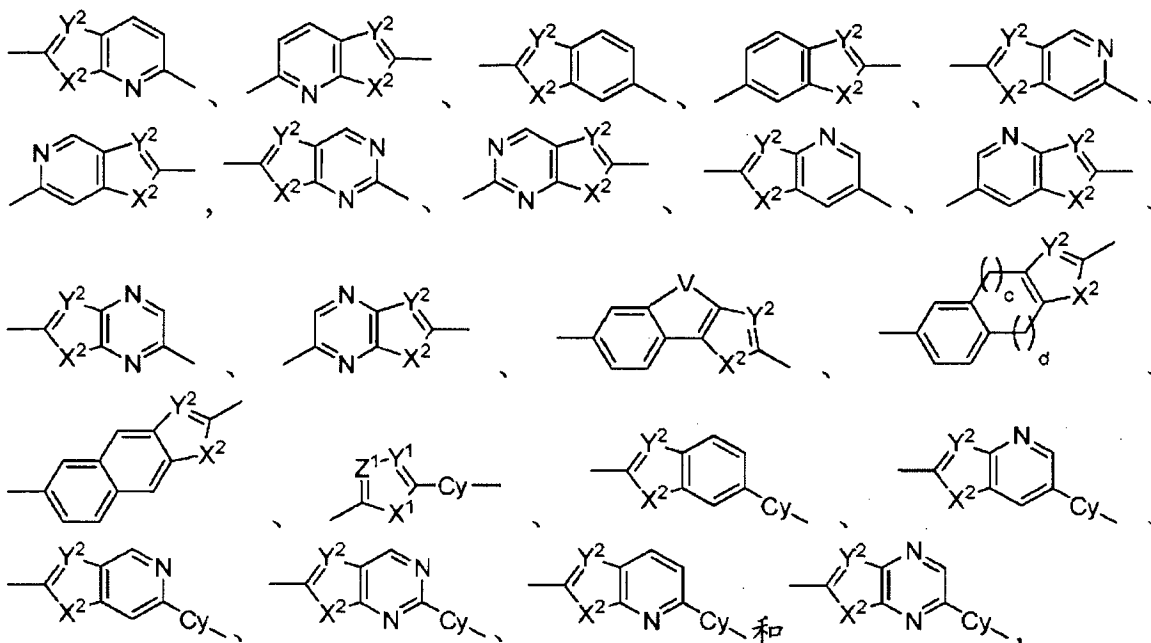


B 和 B' 各自独立地为 4 至 8 元环, 所述环是芳基、杂芳基、环烷基或杂环基, 其中各杂原子在存在时独立地为 N、O 或 S, 且其中 B 或 B' 中的至少一者为芳族的;

各 R^a 独立地选自 -OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基; 且如果 B 或 B' 不为芳族的, 则其也可由一个或多个氧代基取代;

各_r 独立地为 0、1、2 或 3;





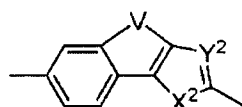
其中：

X¹ 为 CH₂、NH、O 或 S，

Y¹、Y² 和 Z¹ 各自独立地为 CH 或 N，

X² 为 NH、O 或 S，

V 为 -CH₂-CH₂-, -CH=CH-, -N=CH-, (CH₂)_a-N(R^N)-(CH₂)_b- 或 -(CH₂)_a-O-(CH₂)_b-, 其中 a 和 b 独立地为 0、1、2 或 3, 前提是 a 和 b 不均为 0,



任选地在苯基残基上包括 1 个或 2 个氮作为杂原子，

W 任选地由选自以下的一个或多个取代基所取代：-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基，

W 和环 B' 可通过 B' 上的碳或氮原子连接，且

Cy 为单环、双环或三环 5 至 12 元环烷基、杂环基、芳基或杂芳基，其中最多三个杂原子独立地为 N、S 或 O，且其任选地由选自以下的一个或多个取代基所取代：-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；

各 R^c、R^d、R^e 和 R^f 独立地选自：氢、C₁ 至 C₃ 烷基、C₁ 至 C₈ 杂烷基、芳烷基和可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环，其中，

各杂原子在存在时独立地为 N、O 或 S，

R^c、R^d、R^e 和 R^f 中的每个可任选地由 C₁ 至 C₉ 烷基、C₁ 至 C₉ 杂烷基、芳烷基或可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环取代，其中各杂原子在存在时独立地为 N、O 或 S，

R^c 与 R^d 任选地连接形成 4 至 8 元杂环，所述杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合；且

R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 所述杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合;

Y 和 Y' 各自独立地为碳或氮; 且

Z 和 Z' 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、1-3 个氨基酸、 $-[U-(CR^4)_t-NR^5-C(R^4)_t]_u-U-(CR^4)_t-NR^7-(CR^4)_t-R^8$ 、 $-U-(CR^4)_t-R^8$ 和 $-[U-(CR^4)_t-NR^5-(CR^4)_t]_u-U-(CR^4)_t-O-(CR^4)_t-R^8$, 其中

U 选自 $-C(O)-$ 、 $-C(S)-$ 和 $-S(O)_2-$,

各 R^4 、 R^5 和 R^7 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基和芳烷基,

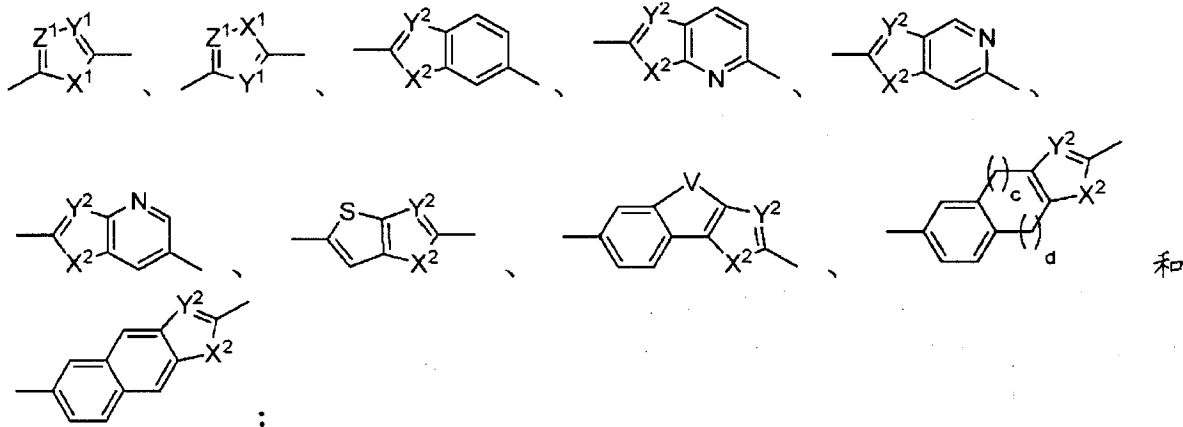
R^8 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、 $-C(O)-R^{81}$ 、 $-C(S)-R^{81}$ 、 $-C(O)-O-R^{81}$ 、 $-C(O)-N-R^{81}_2$ 、 $-S(O)_2-R^{81}$ 和 $-S(O)_2-N-R^{81}_2$, 其中各 R^{81} 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基和芳烷基,

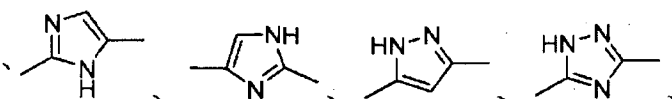
任选地, R^7 和 R^8 一起形成 4 至 7 元环,

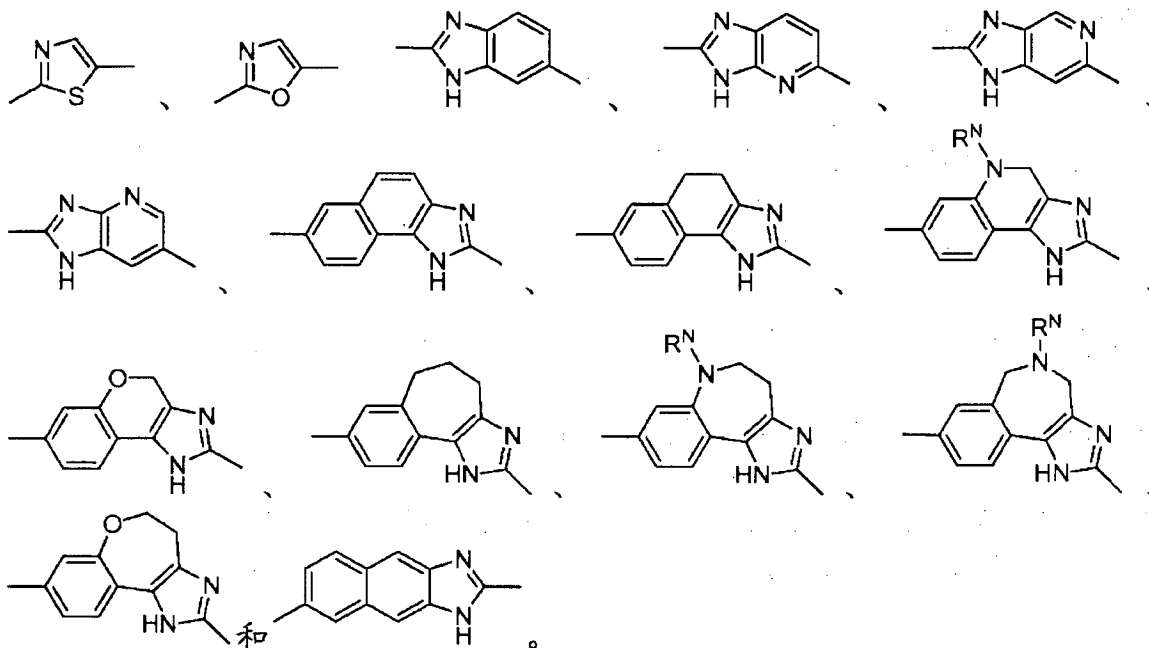
各 t 独立地为 0、1、2、3 或 4, 且

u 为 0、1 或 2。

2. 根据权利要求 1 所述的化合物, 其中 A' 选自单键、 $-(CR_2)_n-O-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$ 和 $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ 以及杂芳基, 所述杂芳基选自



优选地其中 A' 选自单键、



3. 根据前述任一项权利要求所述的化合物, 其中

R^c 、 R^d 、 R^e 和 R^f 各自独立地选自: 氢、 C_1 至 C_8 烷基和 C_1 至 C_8 杂烷基, 其中, 各杂原子在存在时独立地为 N、O 或 S,

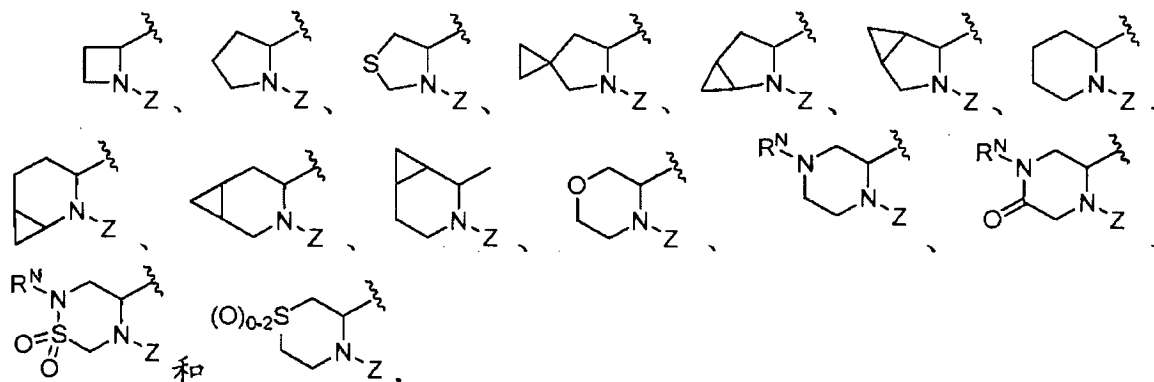
R^e 与 R^d 任选地连接形成 4 至 8 元杂环, 所述杂环任选地与另一个 3 至 6 元杂环稠合,

且

R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 所述杂环任选地与另一个 3 至 6 元杂环稠合;

优选地其中 R^e 与 R^d 或 R^e 与 R^f 中的一者或两者任选地连接形成 4 至 8 元杂环, 所述杂环任选地与另一个 3 至 6 元杂环稠合;

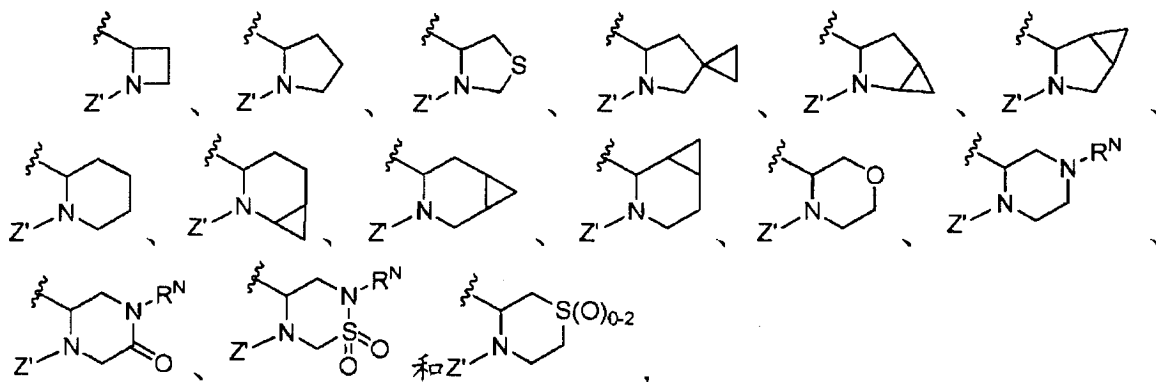
优选地其中 R^e 与 R^d 连接形成选自以下的杂环稠环体系:



其中 R^N 选自氢、 $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基;

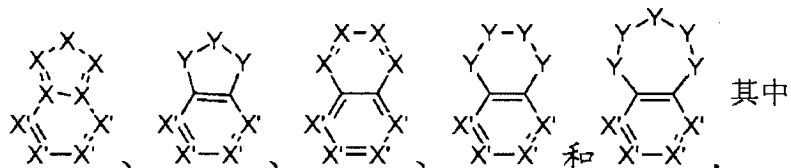
或者

优选地其中 R^e 与 R^f 连接形成选自以下的杂环稠环体系:



其中 R^n 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

4. 根据权利要求1至3中任一项所述的化合物, 其中B和B'一起选自



各 X 独立地为 N 或 C, 且如果为 C, 则在必要时可包括氢以形成完整的价电子层;

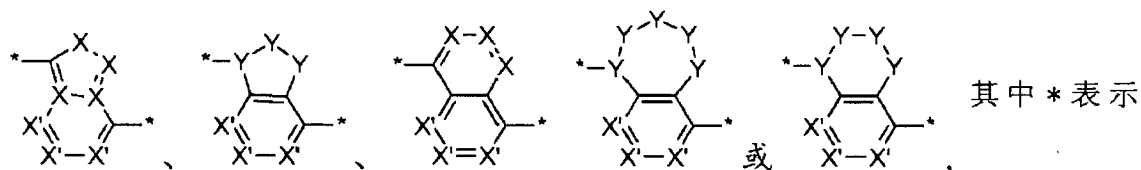
各 X' 独立地为 -N- 或 -CH-, 前提是不超过两个 X' 为 -N-;

各 Y 独立地选自 $-\text{CH}_2-$ 、 $-\text{NH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{C}(\text{O})_2-$ 或 $-\text{S}(\text{O})_{1-2}-$; 且

B 和 B' 在所述分子上的任何可用附接点处与所述化合物的其余部分附接；

并且

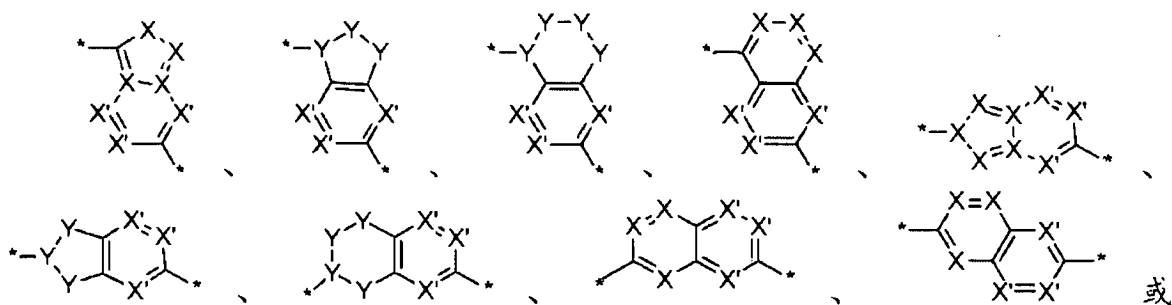
a) 优选地其中 B 和 B' 一起为

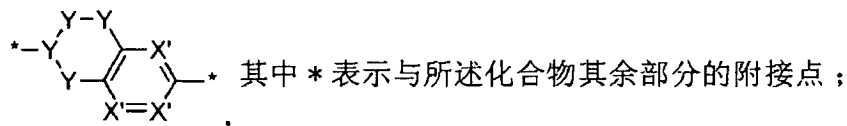


与所述化合物其余部分的附接点；

或者

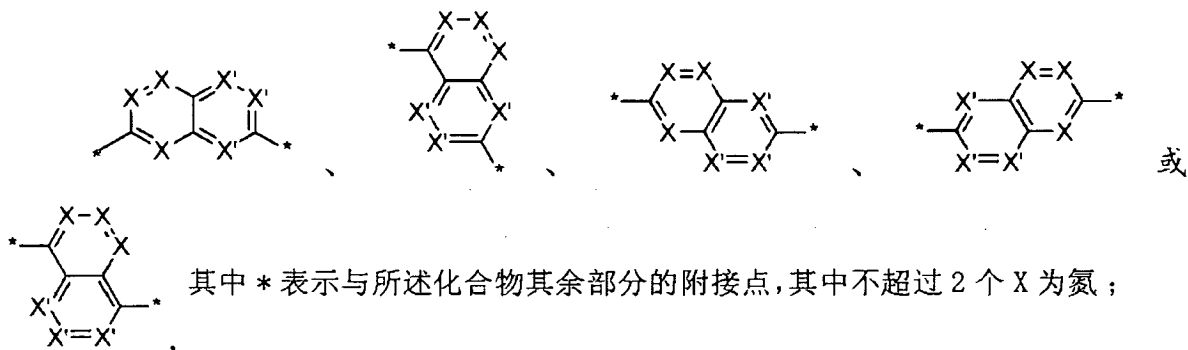
b) 优选地其中 B 和 B' 一起为





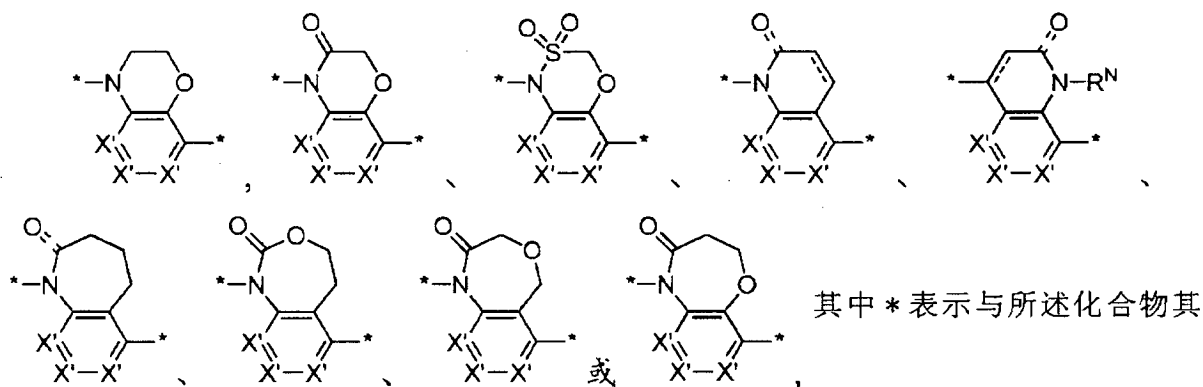
或者

c) 优选地其中 B 和 B' 一起为



或者

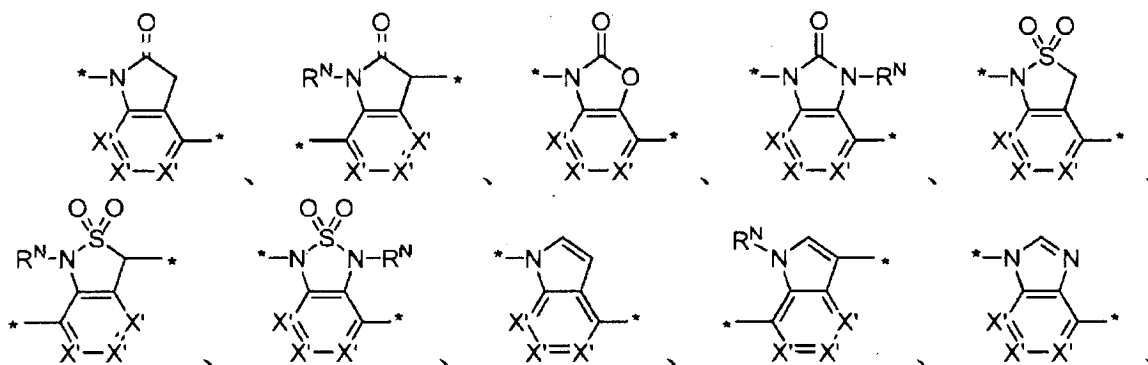
d) 优选地其中 B 和 B' 一起为

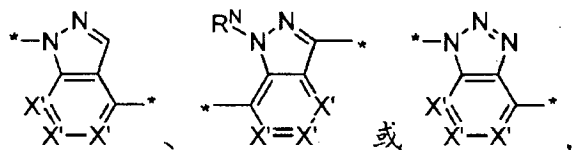


余部分的附接点, 且 R^N 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基；

或者

e) 优选地其中 B 和 B' 一起为



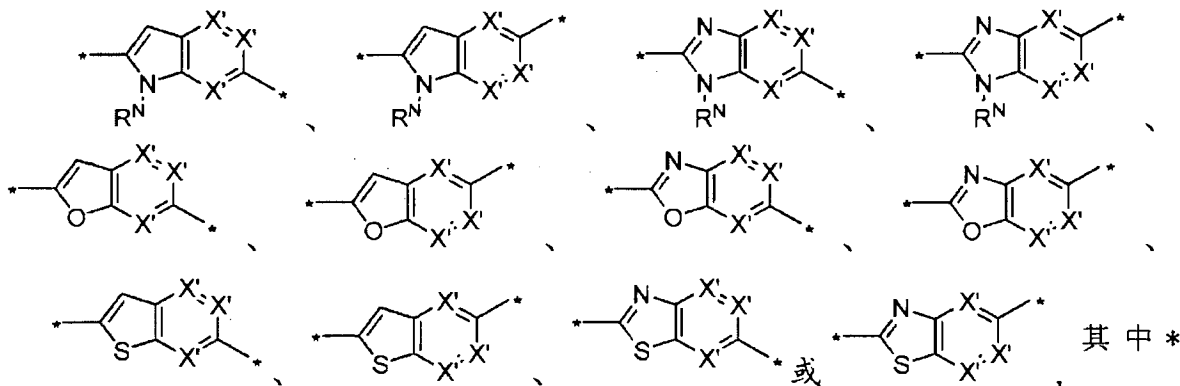


其中 $*$ 表示与所述化合物其余部分的附接点

点, 且 R^N 选自氢、 $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基;

或者

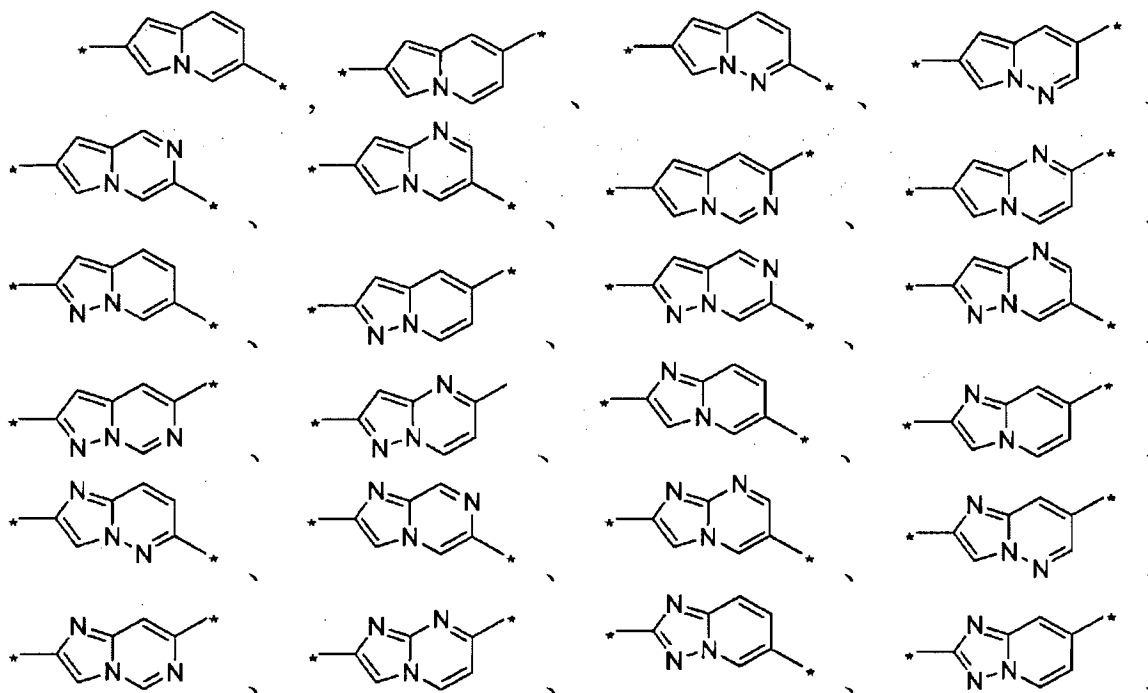
f) 优选地其中 B 和 B' 一起为

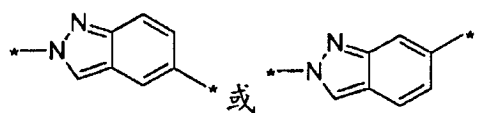


表示与所述化合物其余部分的附接点, 且 R^N 选自氢、 $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基;

或者

g) 优选地其中 B 和 B' 一起为



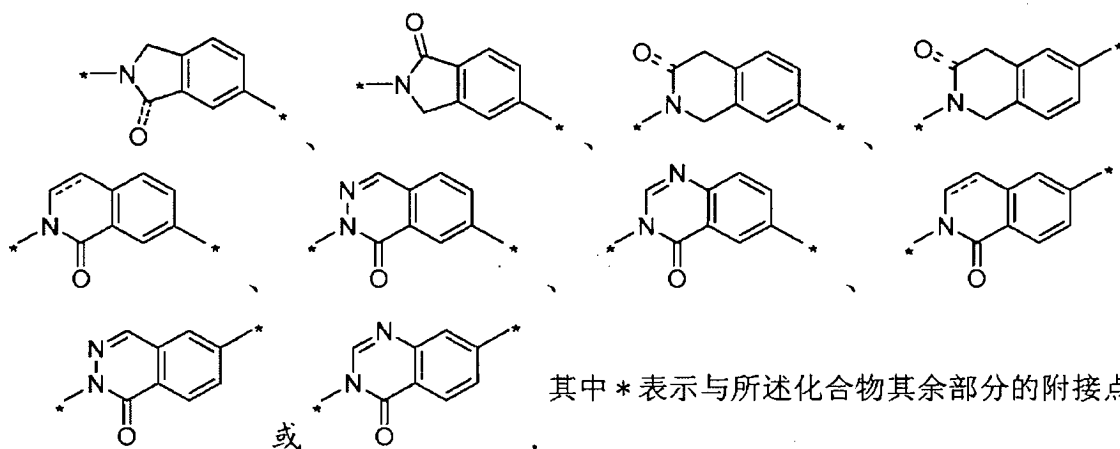


其中 * 表示与所述化合物其余部分的附接点, 且

所述六元环任选地含有一个或两个附加的氮作为杂原子, 前提是所述六元环中的氮的总数不超过 2 个;

或者

h) 优选地其中 B 和 B' 一起为

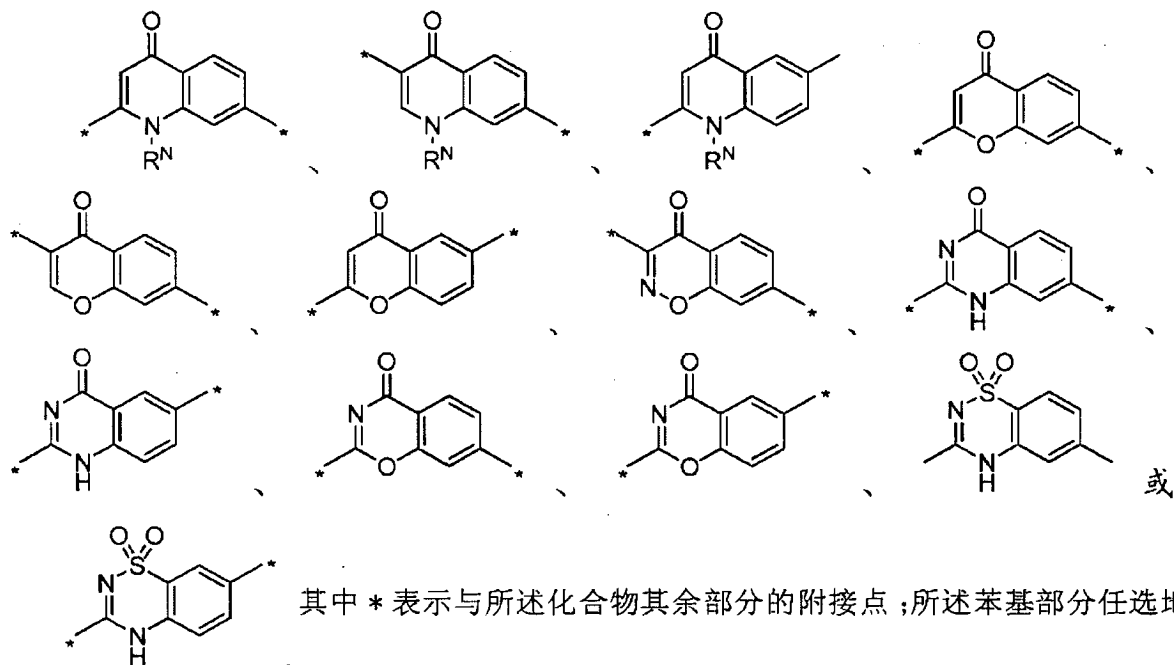


其中 * 表示与所述化合物其余部分的附接点, 且

所述苯基部分任选地含有一个或两个氮作为杂原子;

或者

i) 优选地其中 B 和 B' 一起为

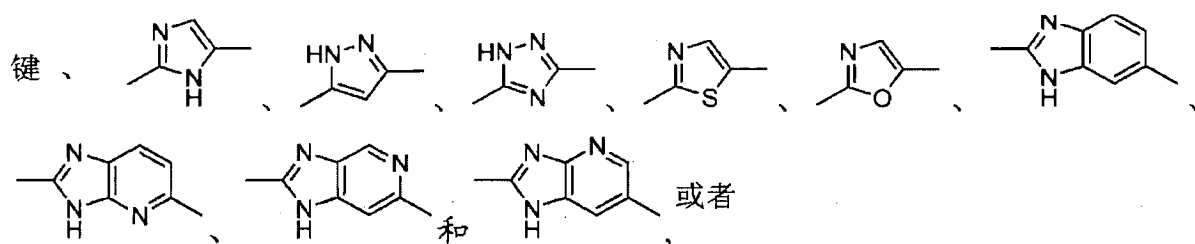
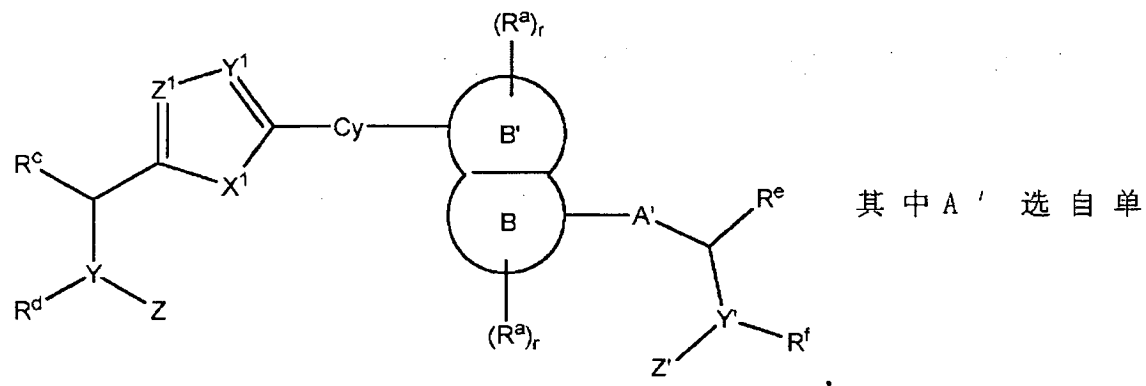


其中 * 表示与所述化合物其余部分的附接点; 所述苯基部分任选地

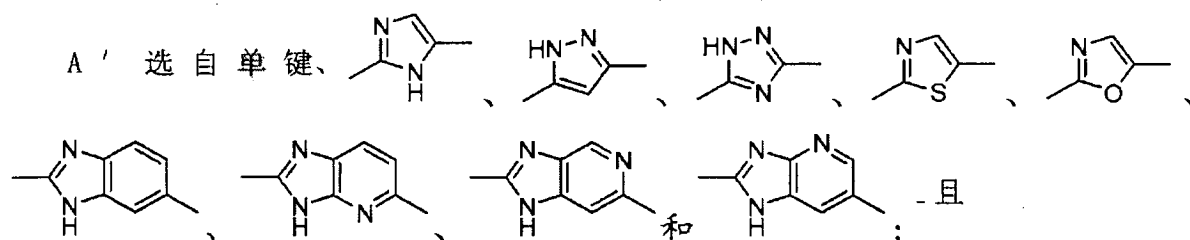
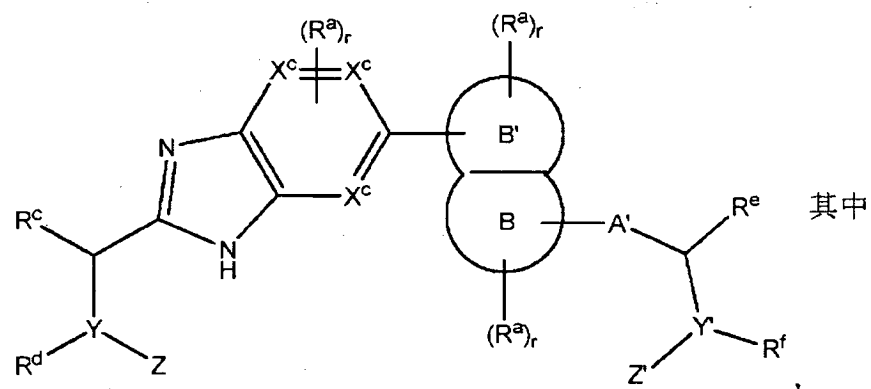
含有一个或两个氮作为杂原子; 且 R^N 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

5. 根据权利要求 1 所述的化合物,

a) 如式 II 所示:

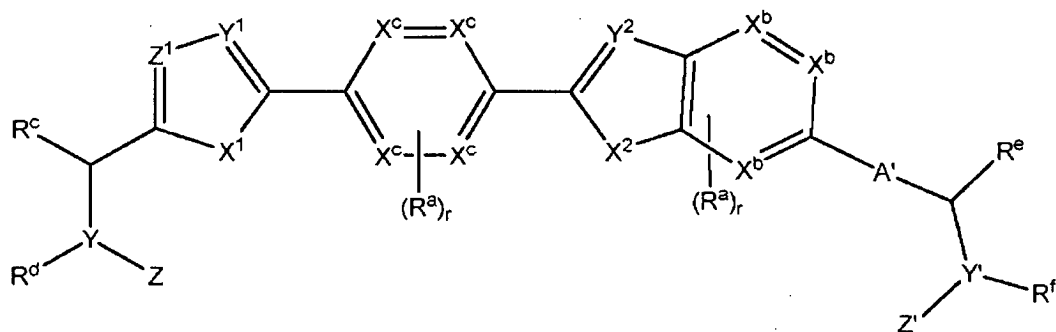


b) 如式 III 所示:

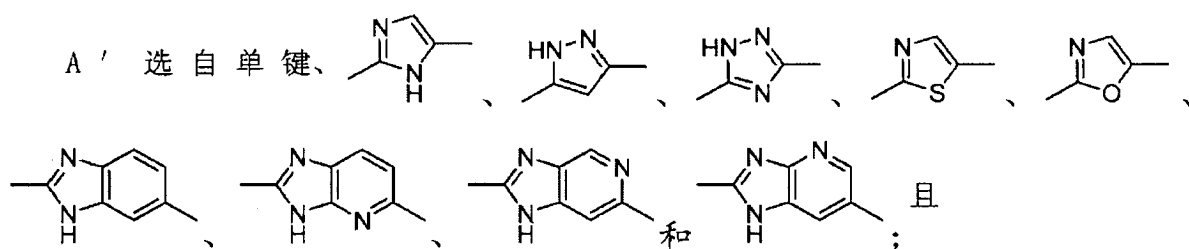


各 X^c 独立地为 C 或 N, 或者

c) 如式 IV 所示:

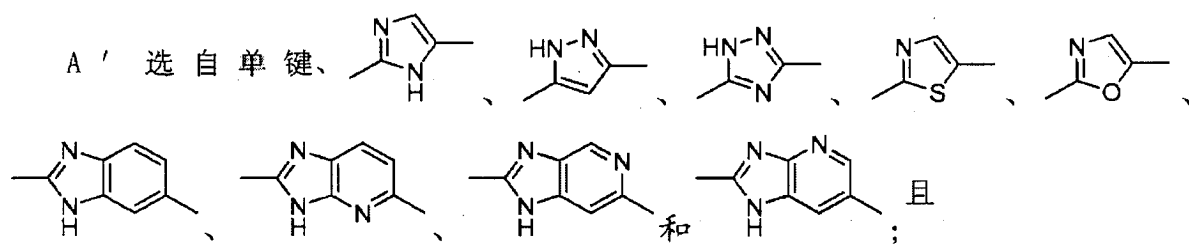
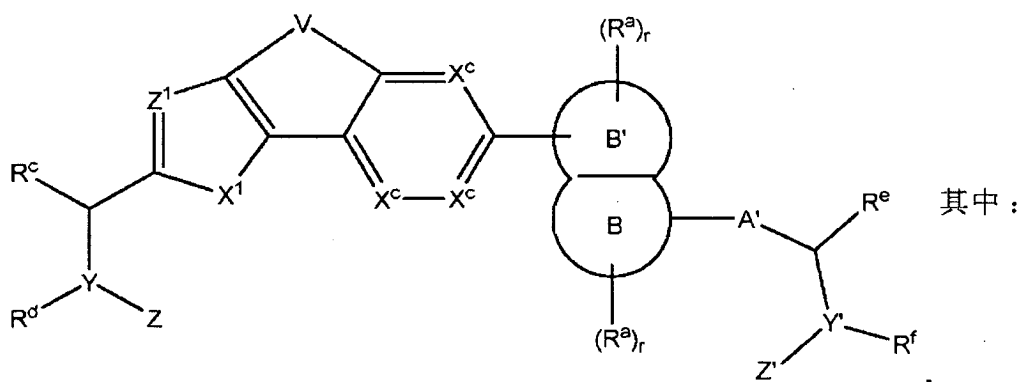


其中：



各 X^b 和 X^c 独立地为 C 或 N, 或者

d) 如式 V 所示：

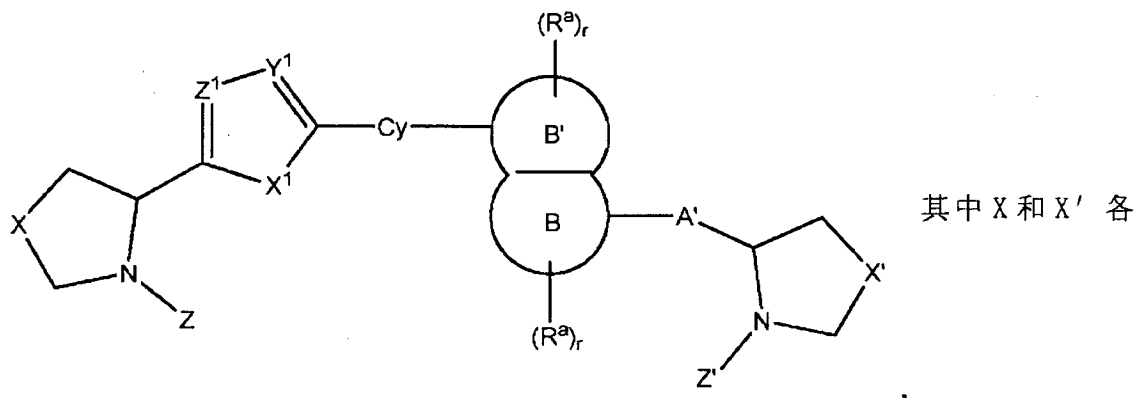


各 X^c 独立地为 C 或 N, 前提是不超过两个 X^c 为 N.

6. 根据权利要求 5 所述的化合物,

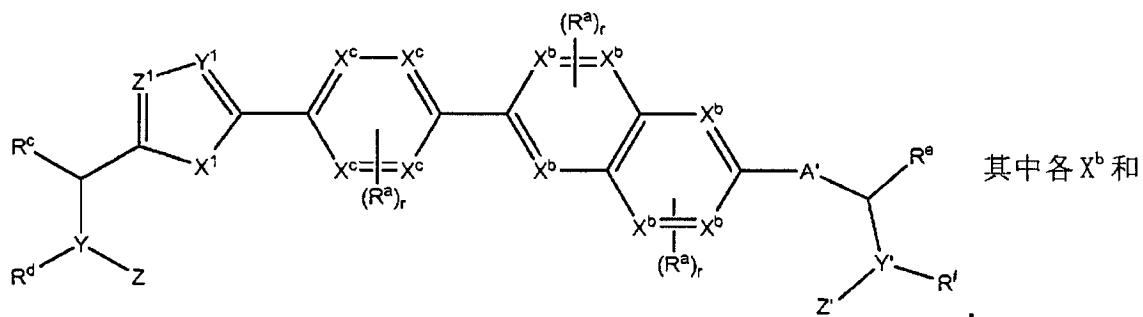
其中 a) 所述如式 II 所示化合物

1) 如式 IIa 所示：



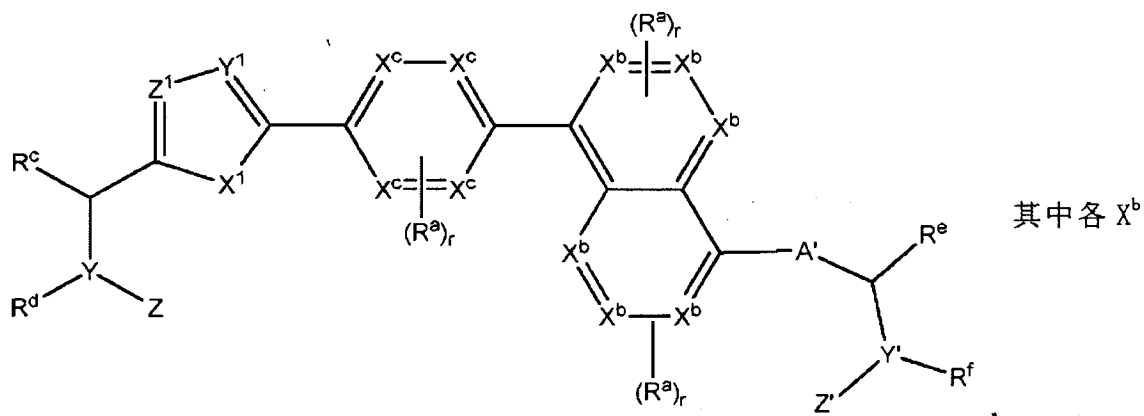
自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

2) 如式 IIb 所示：



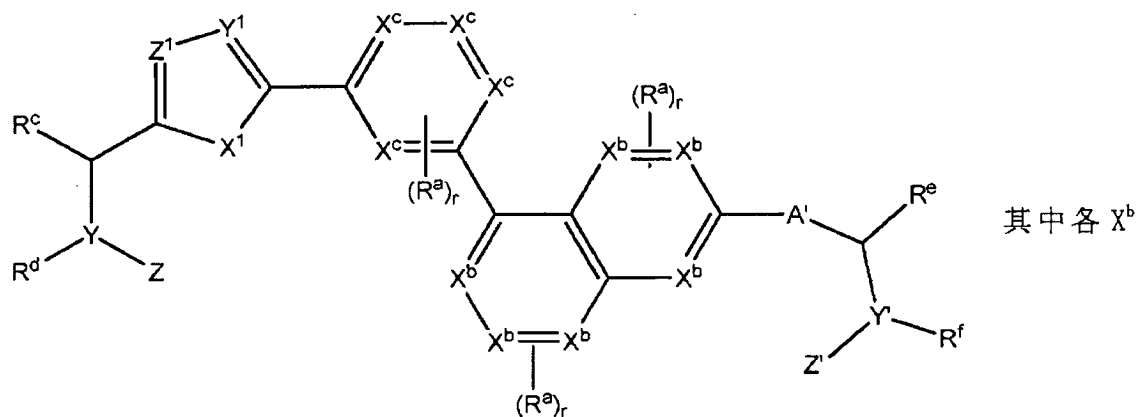
X^c 独立地为 C 或 N；或者

3) 如式 IIId 所示：



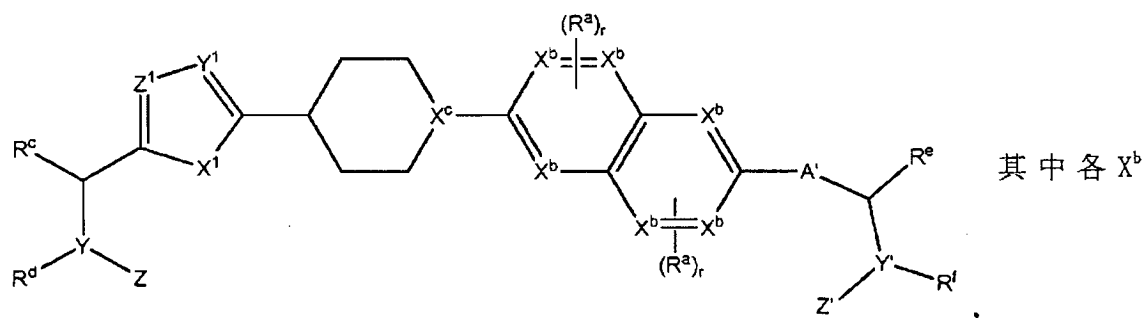
和 X^c 独立地为 C 或 N；或者

4) 如式 IIIf 所示：



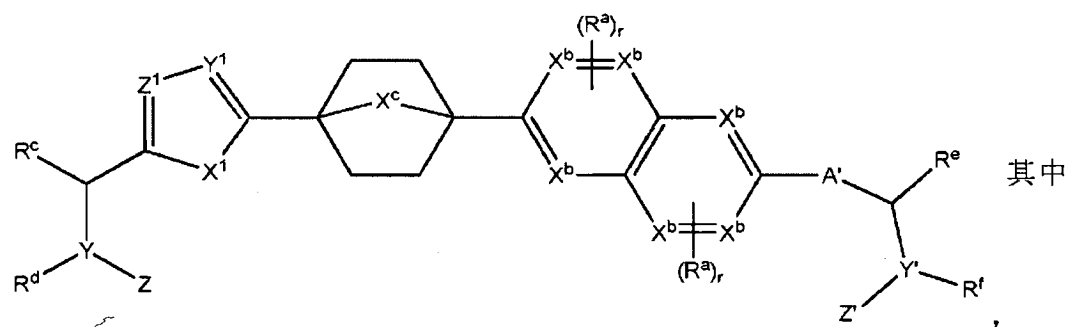
和 X^c 独立地为 C 或 N ;或者

5) 如式 IIh 所示 :



独立地为 C 或 N ;或者

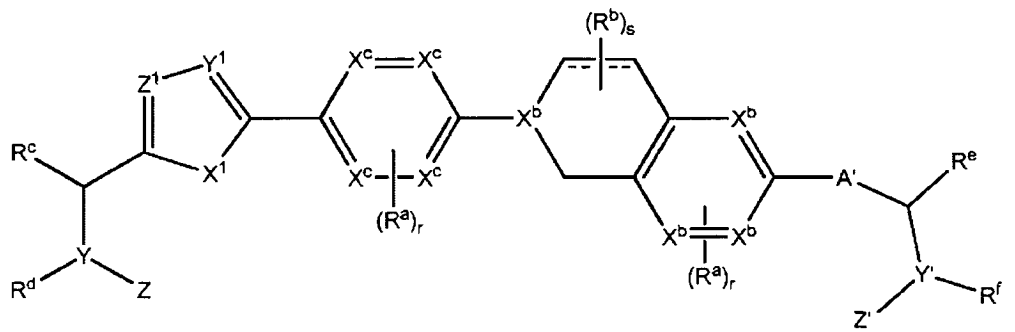
6) 如式 IIj 所示 :



X^c 为 $-\text{CH}_2-$ 、 $-\text{NH}-$ 或 $-\text{CH}_2-\text{CH}_2-$;且

各 X^b 独立地为 C 或 N ;或者

7) 如式 III 所示 :



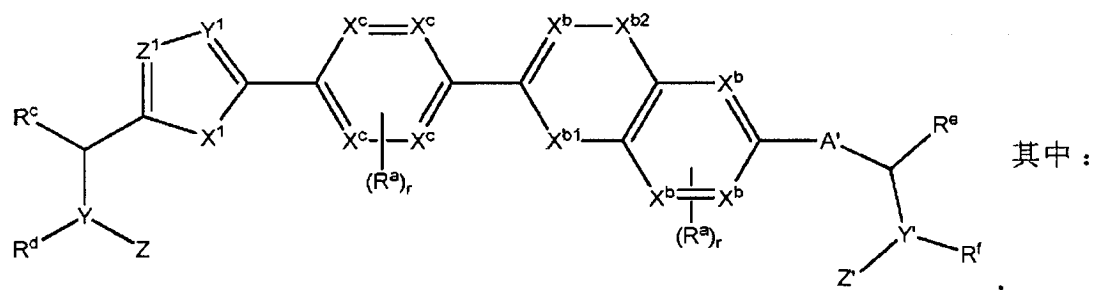
其中：

各 X^b 和 X^c 独立地为 C 或 N；

各 R^b 选自氧代基、-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；且

s 为 0、1、2 或 3；或者

8) 如式 IIn 所示：



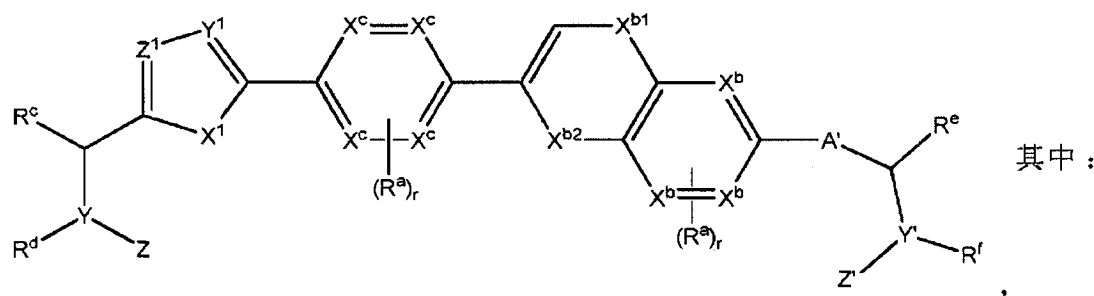
其中：

各 X^b 和 X^c 独立地为 C 或 N；

X^{b1} 为 N 或 O；且

X^{b2} 为 S(O)₂ 或 C(O)；或者

9) 如式 IIp 所示：



其中：

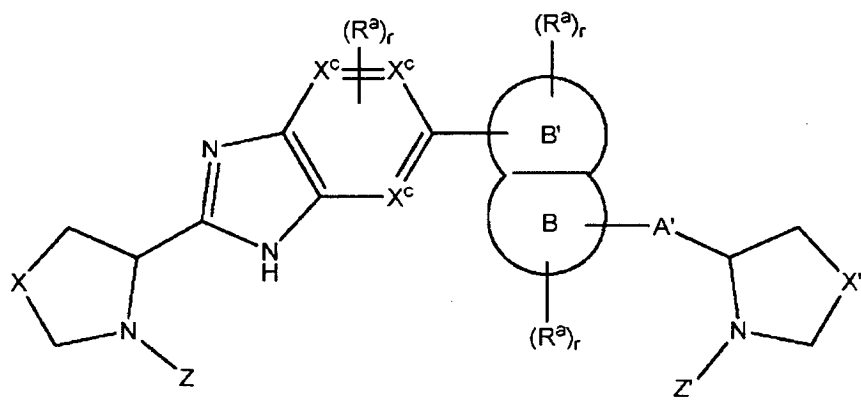
各 X^b 和 X^c 独立地为 C 或 N；

X^{b1} 为 N 或 O；且

X^{b2} 为 S(O)₂ 或 C(O)；或者

其中 b) 所述如式 III 所示化合物

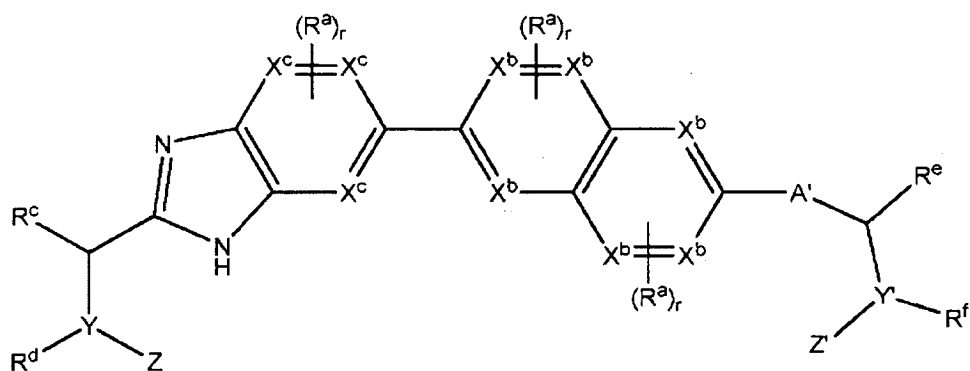
1') 如式 IIIa 所示：



其中 X 和 X' 各自

独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

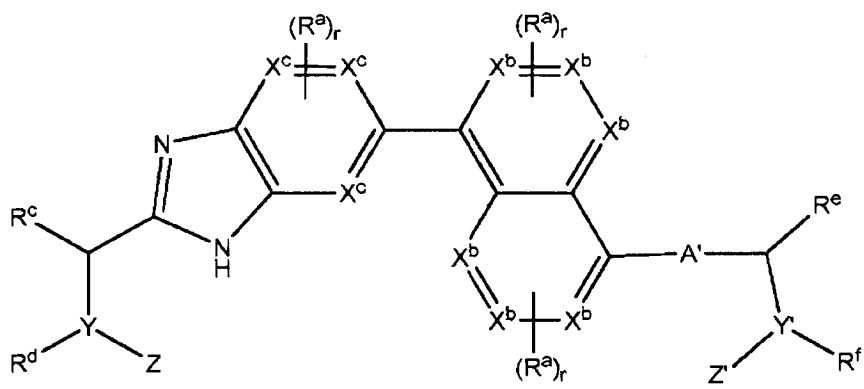
2') 如式 IIIb 所示：



其中各 X^b

独立地为 C 或 N；或者

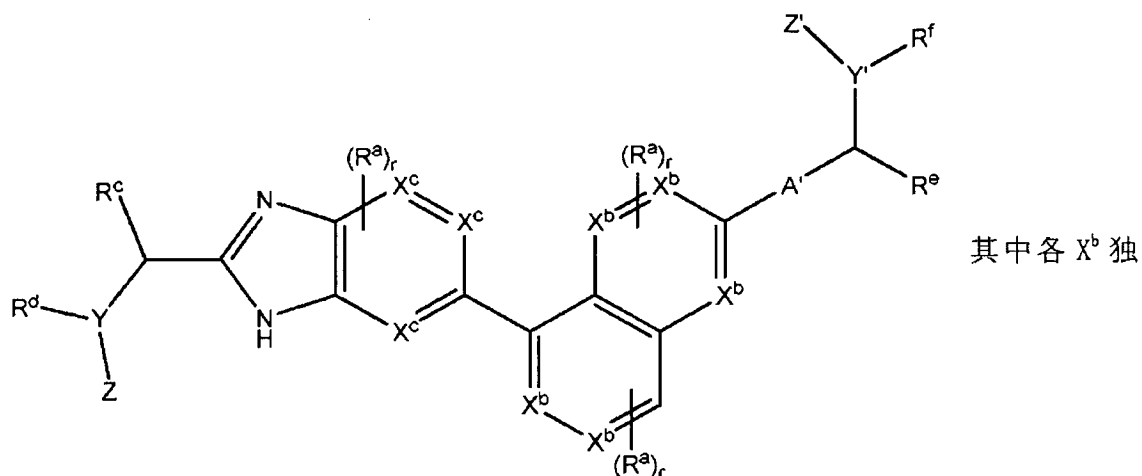
3') 如式 IIIh 所示：



其中各 X^b 独立地为

C 或 N；或者

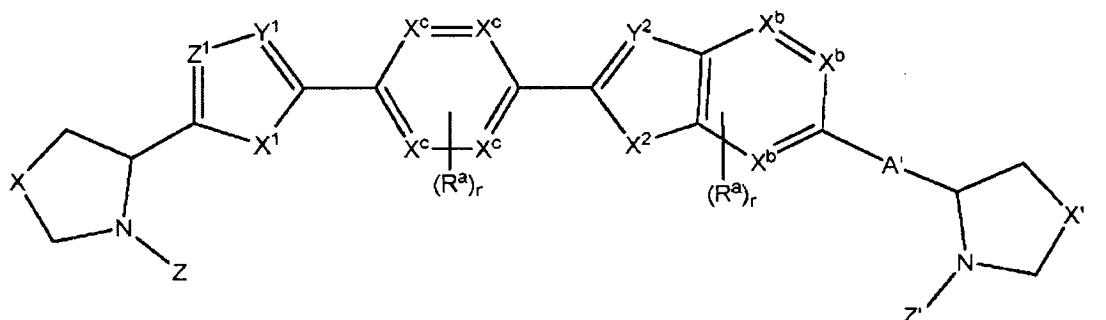
4') 式 IIIIn 所示：



立地为 C 或 N ;或者

其中 c) 所述如式 IV 所示化合物

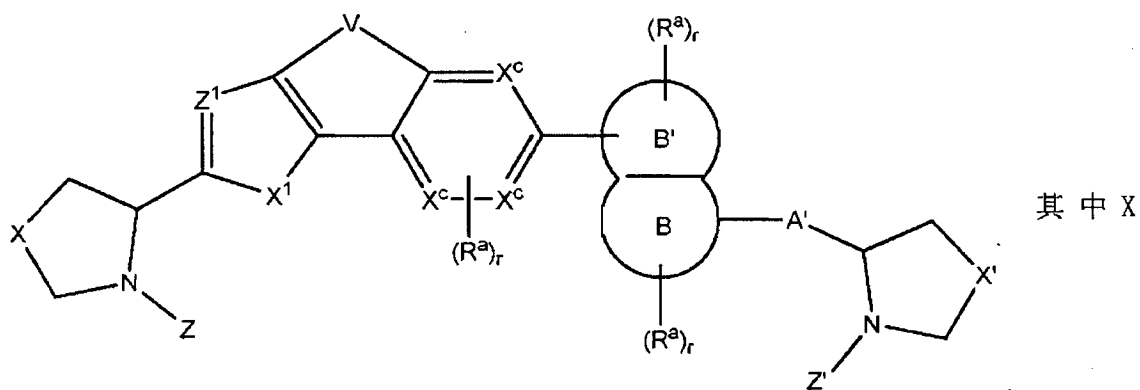
1'') 如式 IVa 所示 :



其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、氧羰基、氨甲酰基和取代的磺酰基 ;或者

其中 d) 所述如式 V 所示化合物具有特征，

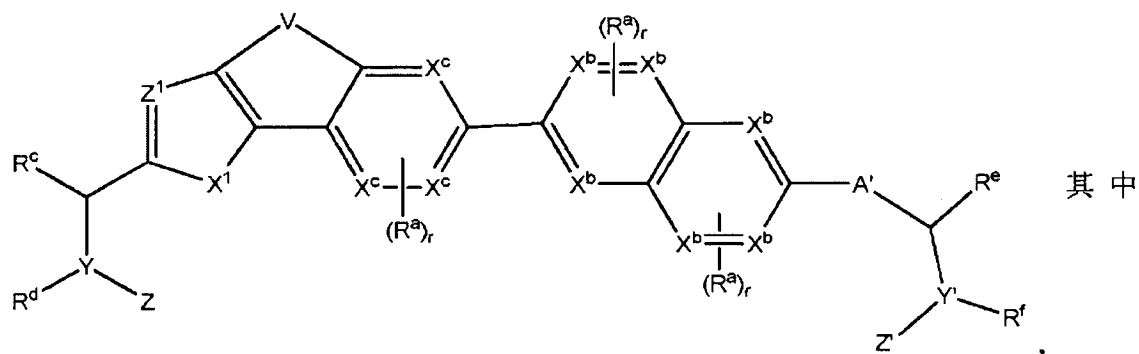
1''') 如式 Va 所示 :



和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{C}\text{H}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基。

、氨甲酰基和取代的磺酰基 ;或者

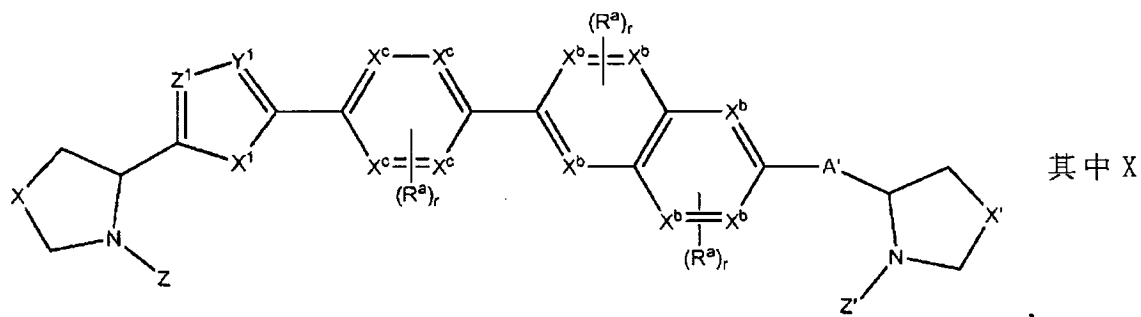
2''') 如式 Vb 所示 :



各 X^b 独立地为 C 或 N。

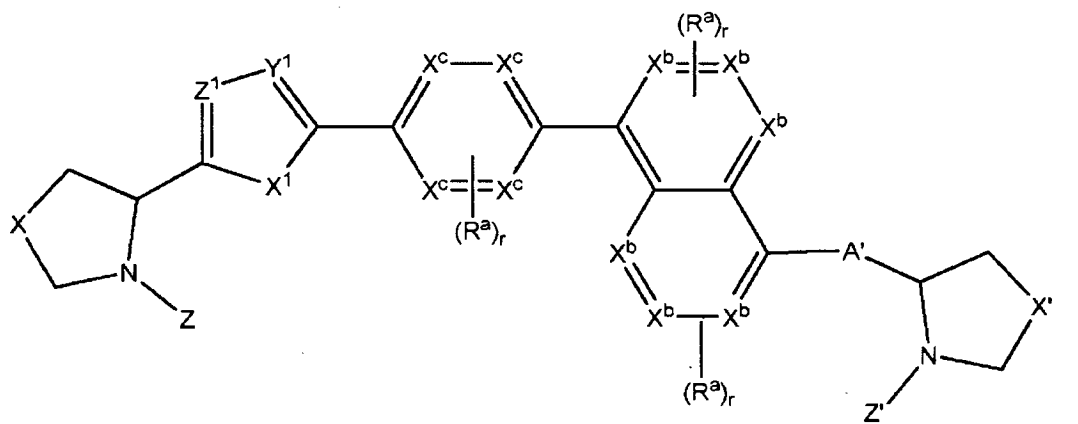
7. 根据权利要求 6 所述的化合物, 其中

1) 所述如式 IIa 所示化合物具有式 IIc 所示的结构,



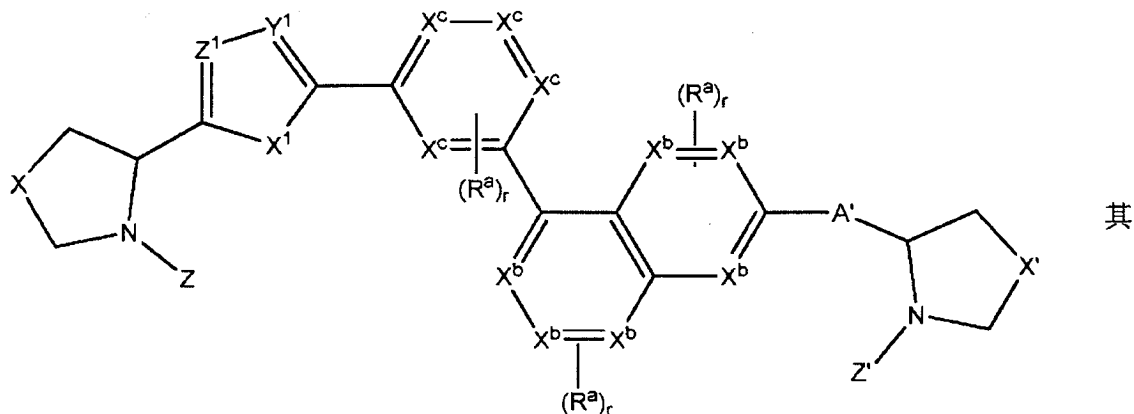
和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基 ;或者

2) 所述如式 IIId 所示化合物具有式 IIe 所示的结构,



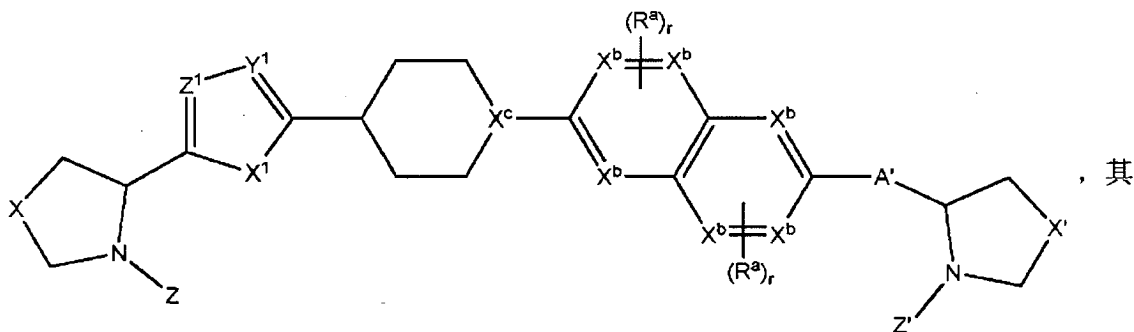
其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基 ;或者

3) 所述如式 IIIf 所示化合物具有式 IIg 所示的结构,



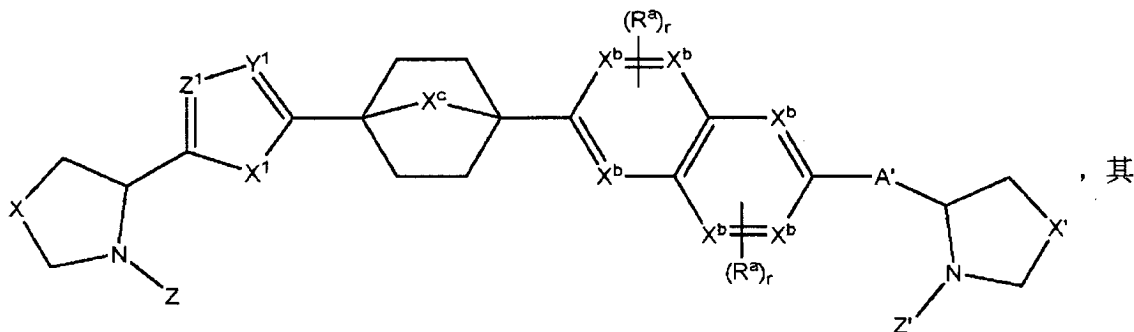
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

4) 所述如式 IIh 所示化合物具有式 IIi 所示的结构，



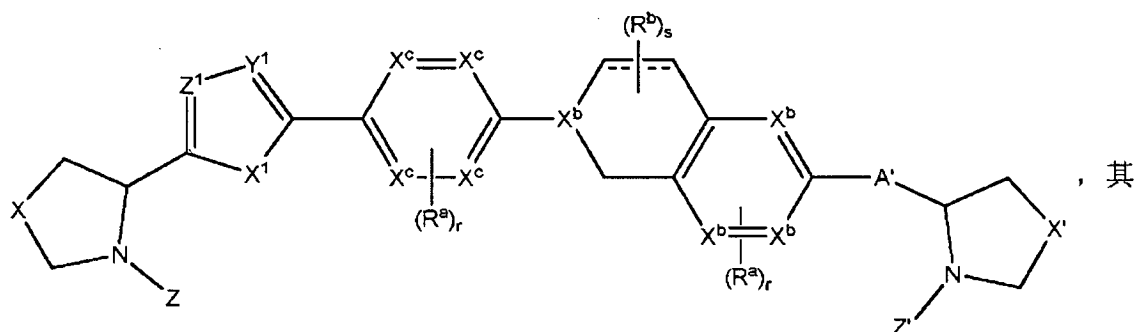
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

5) 所述如式 IIj 所示化合物具有式 IIk 所示的结构，



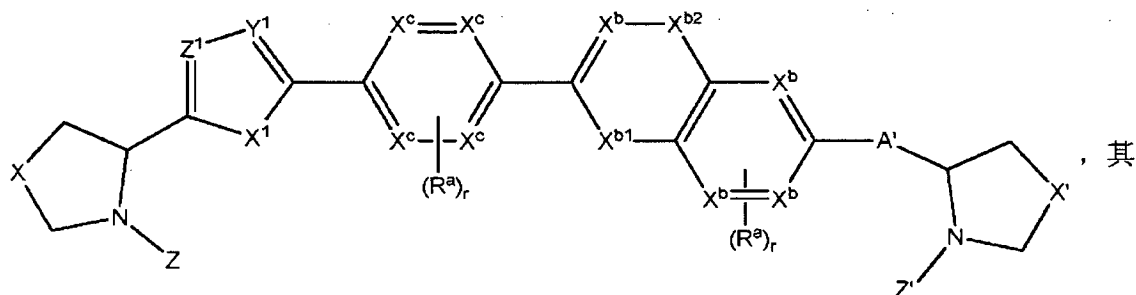
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

6) 所述如式 III 所示化合物具有式 IIIm 所示的结构，



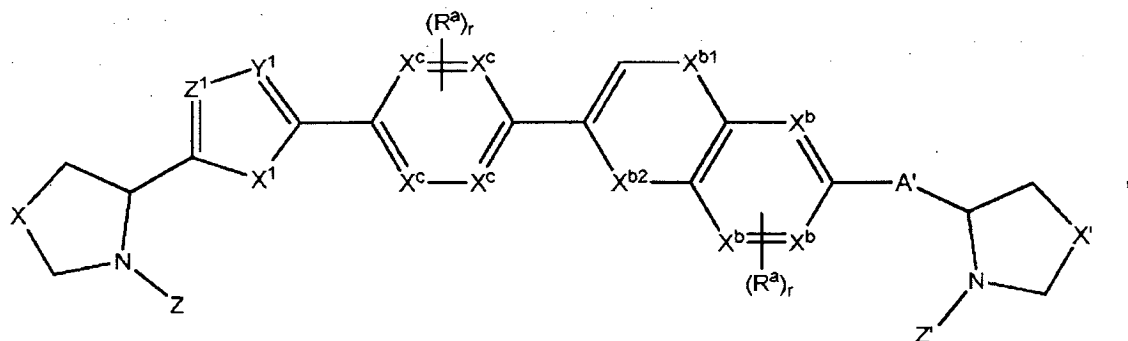
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

7) 所述如式 IIIn 所示化合物具有如式 IIo 所示的结构,



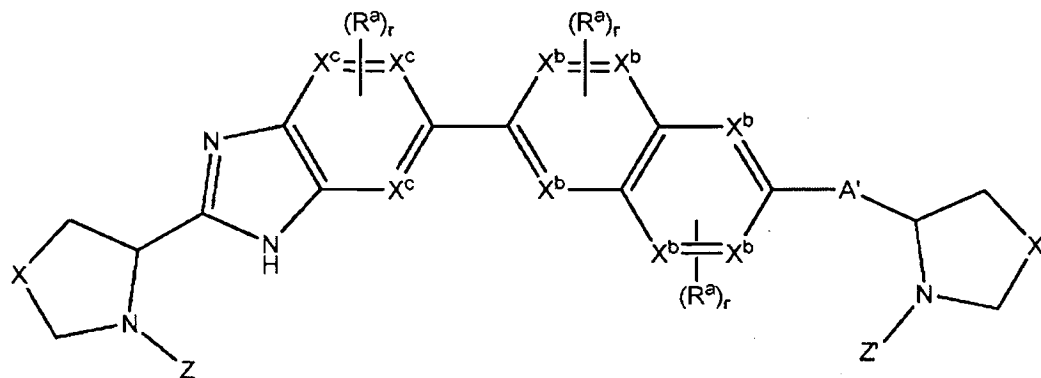
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基; 或者

8) 所述如式 IIp 所示化合物具有式 IIq 所示的结构,



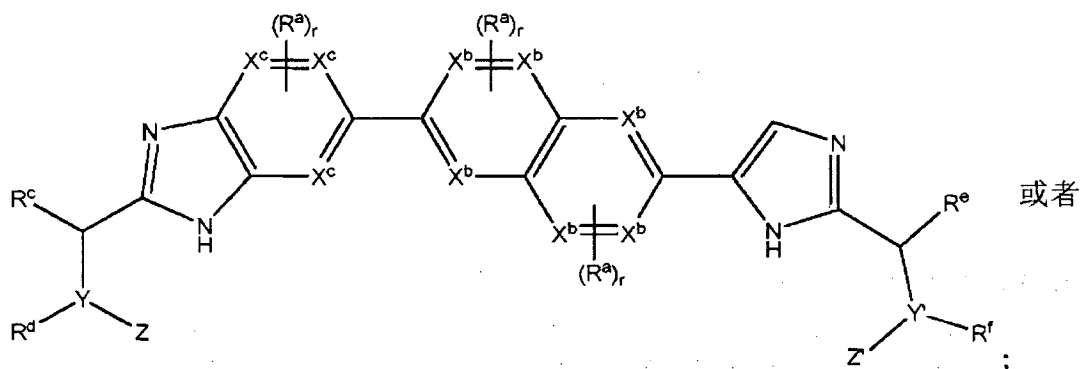
其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{C}(\text{H}_2\text{O})-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨基酰基和取代的磺酰基；或者

9) 所述如式 IIIb 所示化合物具有式 IIIc 所示的结构,

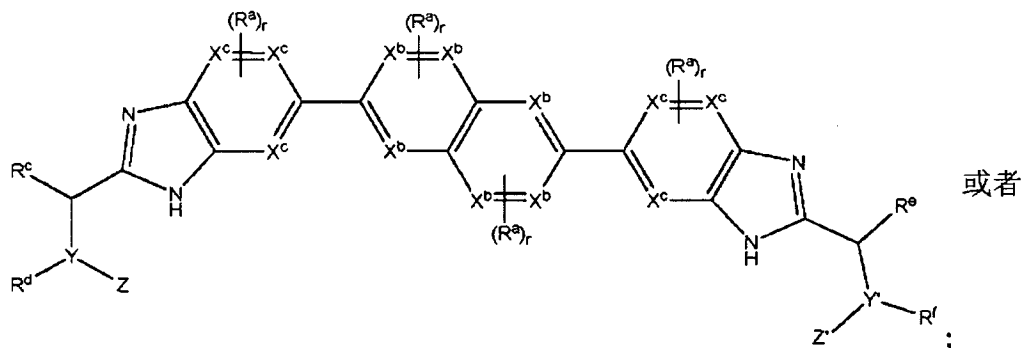


其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

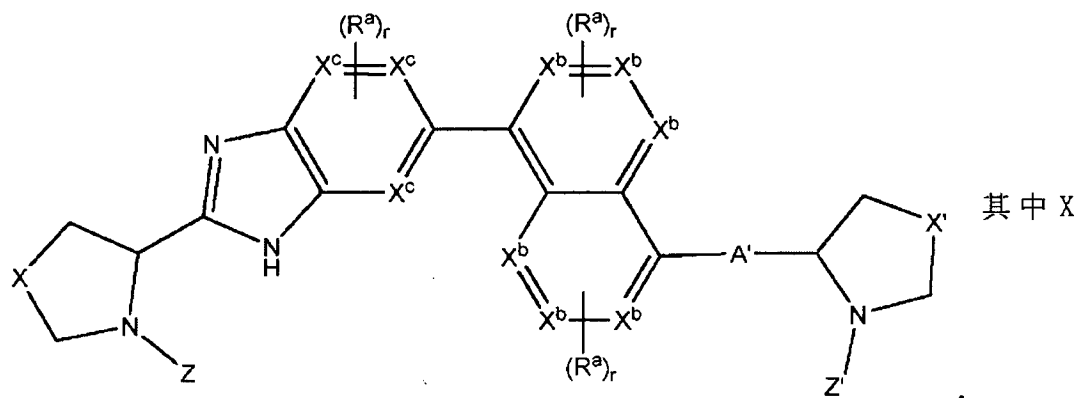
10) 所述如式 IIIb 所示化合物具有式 IIIId 所示的结构，



11) 所述如式 IIIb 所示化合物具有式 IIIIf 所示的结构，

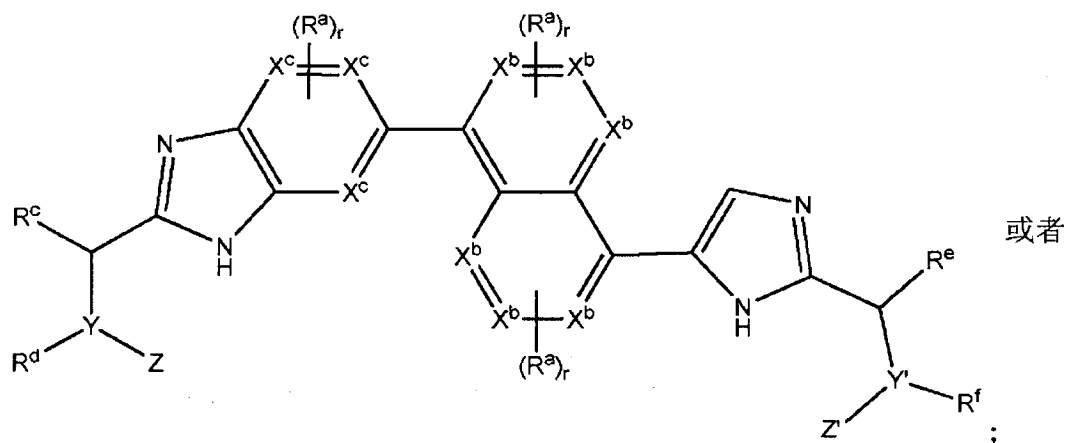


12) 所述如式 IIIh 所示化合物具有式 IIIi 所示的结构，

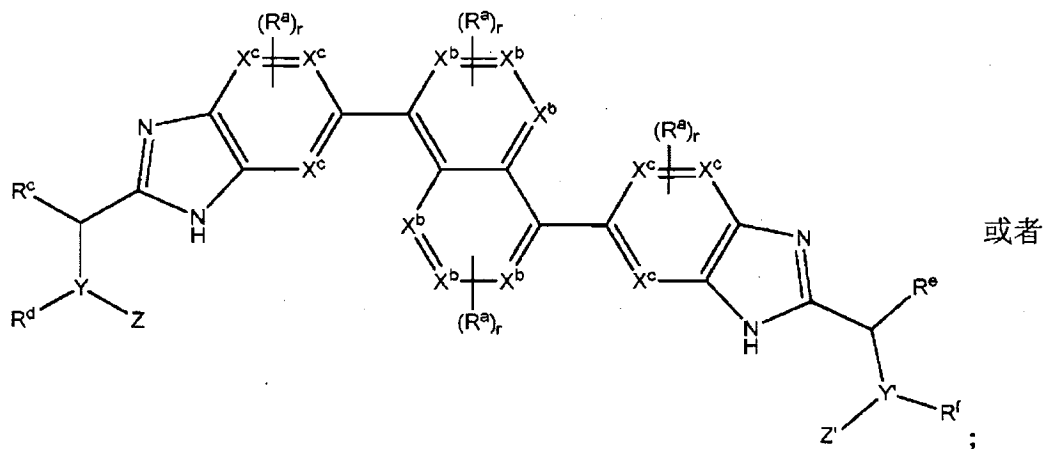


和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{C}\text{H}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

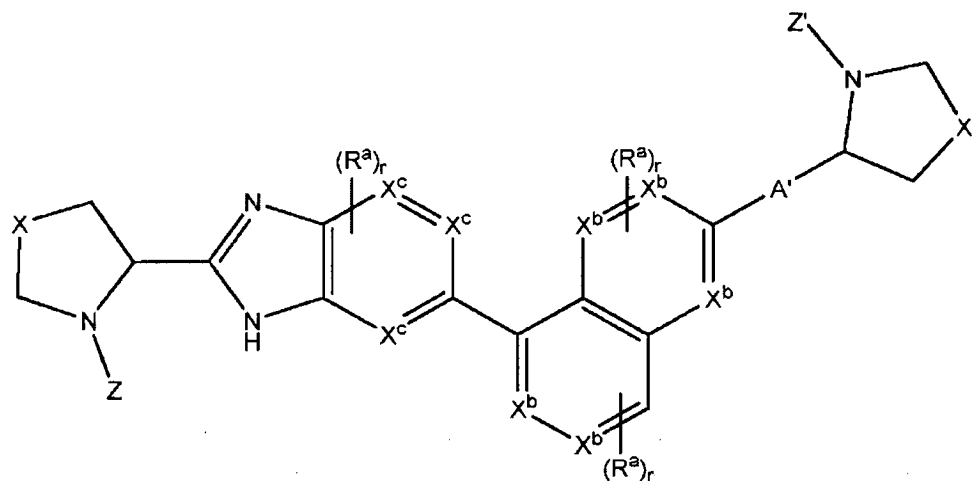
13) 所述如式 IIIIh 所示化合物具有式 IIIIj 所示的结构，



14) 所述如式 IIIIh 所示化合物具有式 IIIIi 所示的结构，



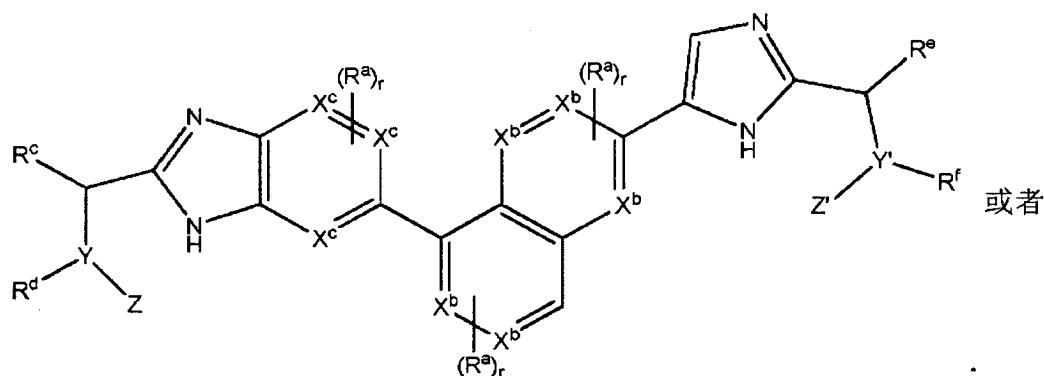
15) 所述如式 IIIIn 所示化合物具有式 IIIIo 所示的结构，



其中 X 和

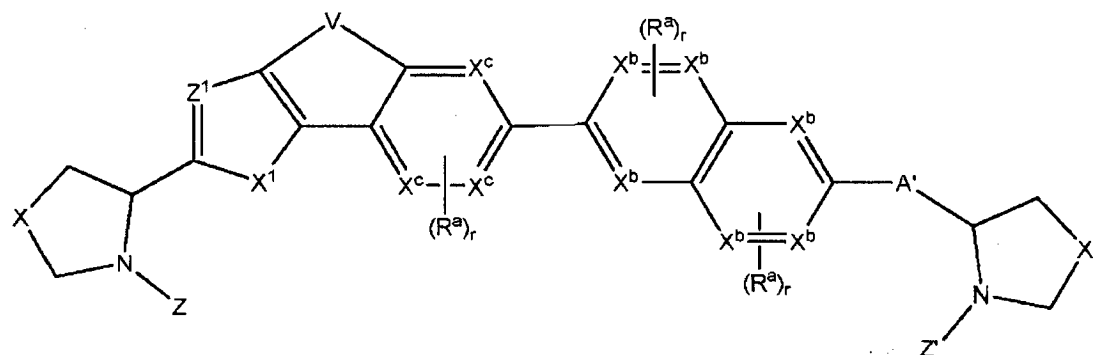
X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

16) 所述如式 IIIIn 所示化合物具有式 IIIIp 所示的结构，



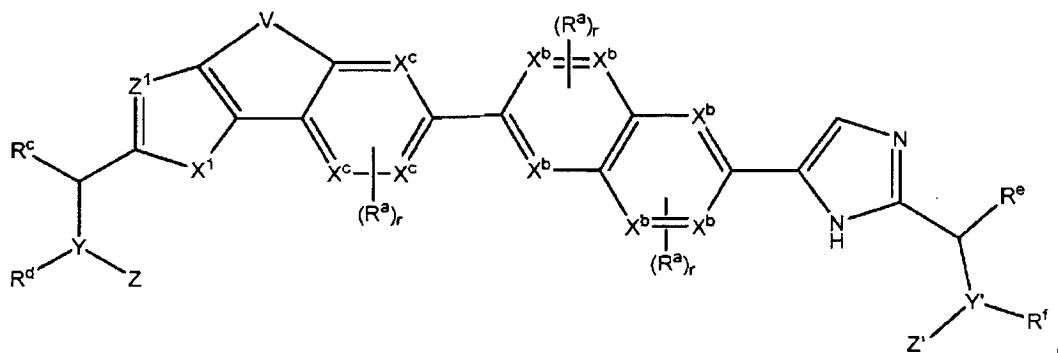
或者

17) 所述如式 Va 所示化合物具有式 Vc 所示的结构，



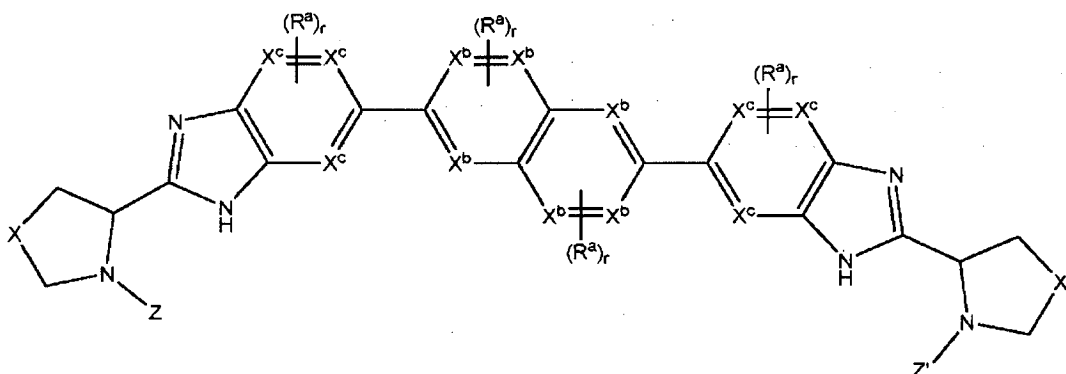
其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

18) 所述如式 Va 所示化合物具有式 Vd 所示的结构，



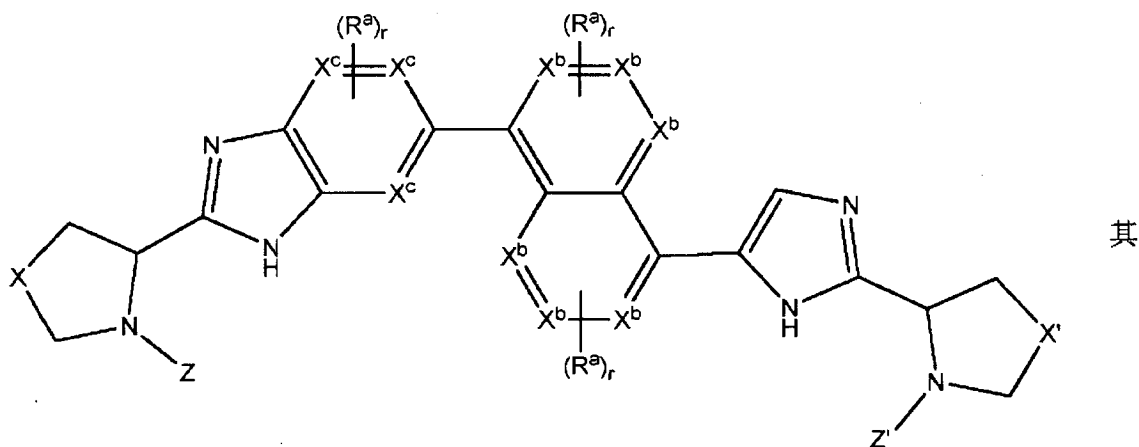
8. 根据权利要求 7 所述的化合物, 其中

- 1) 所述如式 IIh 所示或如式 IIIi 所示的化合物, 其中 X^c 为 C 或者其中 X^c 为 N;
- 2) 所述如式 IIIf 所示化合物具有特征, 如式 IIIg 所示:



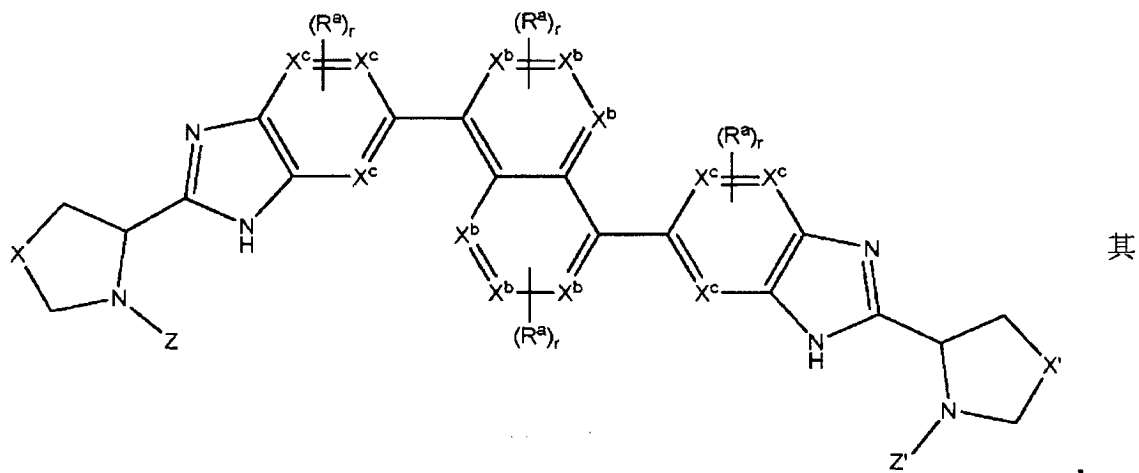
其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基; 或者

- 3) 所述如式 IIIj 所示化合物具有如式 IIIk 所示的结构:



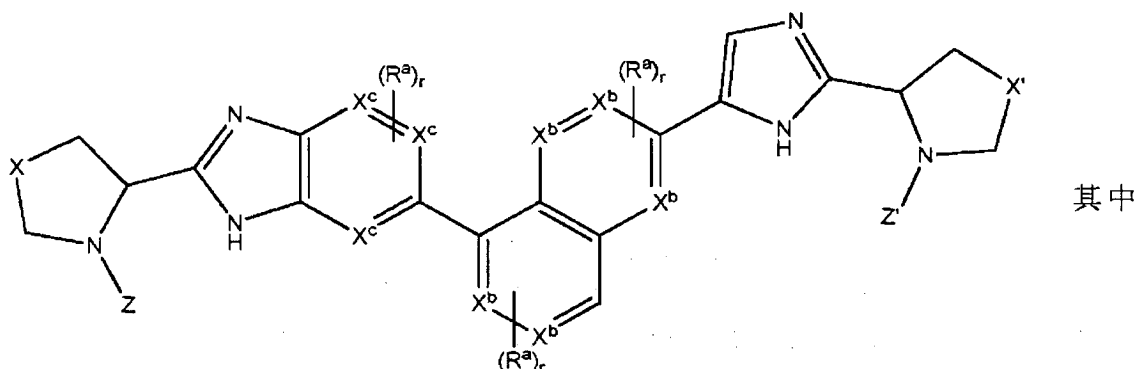
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基; 或者

- 4) 所述如式 IIIl 所示化合物具有如式 IIIm 所示的结构:



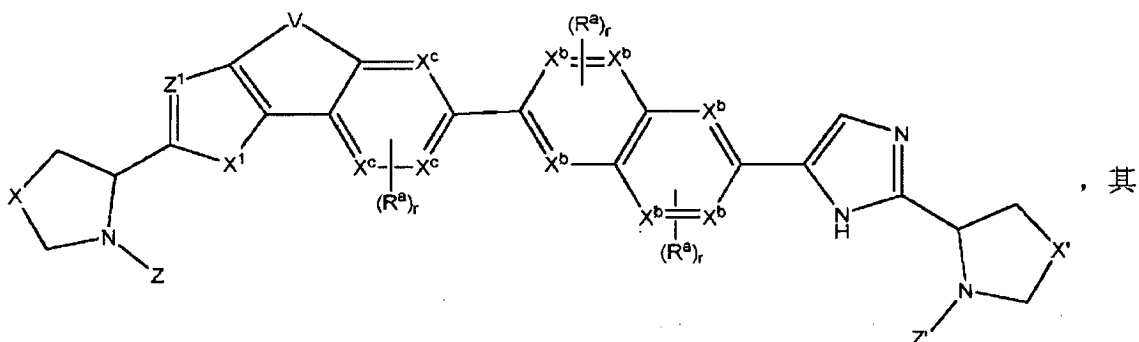
中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

5) 所述如式 IIIp 所示化合物具有如式 IIIq 所示的结构：



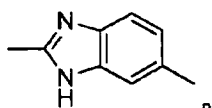
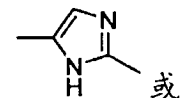
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基；或者

6) 所述如式 Va 所示化合物具有如式 Ve 所示的结构：



中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

9. 根据权利要求 5-8 中任一项所述的化合物, 其中 A' 为



10. 根据权利要求 1-9 中任一项所述的化合物, 其中 Z 和 Z' 各为 1-3 个氨基酸。

11. 根据权利要求 10 所述的化合物, 其中所述氨基酸呈 D 构型。

12. 根据权利要求 1-9 中任一项所述的化合物, 其中 Z 和 Z' 各自独立地选自 $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$ 、 $-U-(CR^4_2)_t-R^8$ 和 $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$ 。

13. 根据权利要求 12 所述的化合物, 其中 Z 和 Z' 中的一者或两者为 $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-[C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_t-NR^7-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_n-NR^7-C(O)-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_n-NR^7-(CR^4_2)_n-C(O)-O-R^8$; 或者

或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_n-NR^7-C(O)-O-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-U-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-[U-(CR^4_2)_t-NR^5-(CR^4_2)_t]_u-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$; 或者

者

其中 Z 和 Z' 中的一者或两者为 $-U-(CR^4_2)_t-NR^5-(CR^4_2)_t-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$; 或者

其中 Z 和 Z' 中的一者或两者为 $-C(O)-(CR^4_2)_t-NR^5-(CR^4_2)_t-C(O)-(CR^4_2)_t-O-(CR^4_2)_t-R^8$; 或者

或者

其中 Z 和 Z' 中的一者或两者为 $-U-(CR^4_2)_t-O-(CR^4_2)_t-R^8$ 。

14. 一种药物组合物, 其包含权利要求 1-9 中的任一种化合物。

15. 权利要求 1-13 中任一项所述的化合物在制备药物中的用途, 其中所述药物用于治疗丙型肝炎。

HCV NS5A 的抑制剂

[0001] 相关申请声明

[0002] 本申请要求 2008 年 12 月 3 日提交的美国临时申请 61/119,723 和 2009 年 4 月 28 日提交的美国临时申请 61/173,590 和 61/214,881 以及 2009 年 6 月 1 日提交的美国临时申请 61/182,958 和 61/182,952 的权益。

技术领域

[0003] 本发明涉及可用于抑制丙型肝炎病毒 (“HCV”) 复制、特别是抑制 HCV 的非结构 5A (“NS5A”) 蛋白功能的化合物。

背景技术

[0004] HCV 为单链 RNA 病毒, 其为黄病毒科 (Flaviviridae) 的一员。该病毒显示出广泛的遗传异质性, 因为目前存在 7 种已鉴别的基因型和 50 种以上已鉴别的亚型。在 HCV 感染的细胞中, 病毒 RNA 转译成多蛋白, 该多蛋白裂解成 10 种个体蛋白。在氨基末端为结构蛋白: 核心 (C) 蛋白以及包膜糖蛋白 E1 和 E2。在 E1 和 E2 之后为整合膜蛋白 p7。另外, 存在六种非结构蛋白: NS2、NS3、NS4A、NS4B、NS5A 和 NS5B, 其在 HCV 生命周期中起功能性作用 (见例如 Lindenbach, B. D. 和 C. M. Rice, Nature. 436:933-938, 2005)。

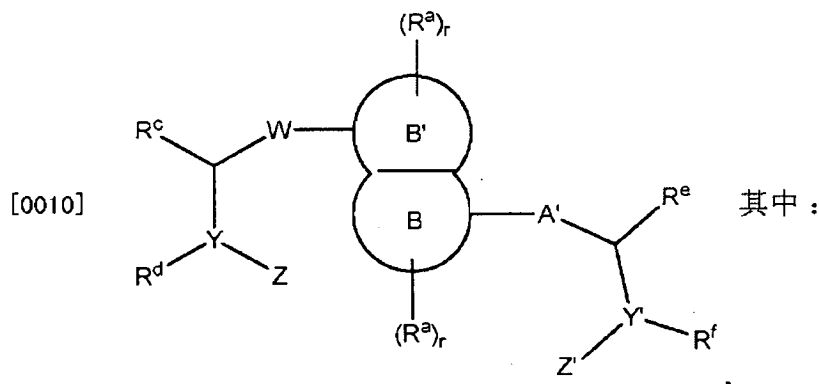
[0005] HCV 感染是严重的健康问题。据估计, 全世界有 1.7 亿人受 HCV 的慢性感染。HCV 感染可导致慢性肝炎、肝硬化、肝衰竭和肝细胞癌。慢性 HCV 感染因此成为世界范围内肝脏相关性过早死亡的主要原因。

[0006] HCV 感染护理治疗方案的现有标准涉及单独或与病毒唑联合使用干扰素- α 。该治疗较为繁琐且有时具有致衰弱或严重的副作用, 并且许多患者对治疗不能持续反应。迫切需要治疗 HCV 感染的新的有效方法。

[0007] 发明概述

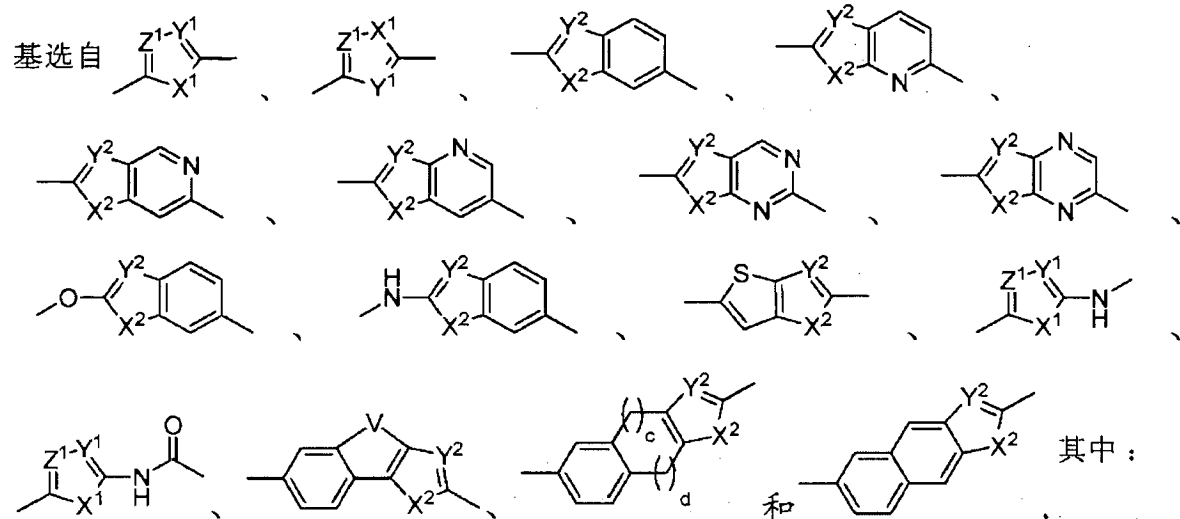
[0008] HCV 的 NS5A 蛋白的基本特征使其成为抑制剂的理想靶标。本公开描述了一类靶向 NS5A 蛋白的化合物, 及其用于治疗人类 HCV 感染的方法。

[0009] 在第一方面, 提供了式 I 化合物:



[0011] A' 选自单键、 $-(CR_2)_n-C(O)-(CR_2)_p-$ 、 $-(CR_2)_n-O-(CR_2)_p-$ 、 $-(CR_2)_n-$

$_n - N(R^N) - (CR_2)_p -$ 、 $-(CR_2)_n - S(O)_k - N(R^N) - (CR_2)_p -$ 、 $-(CR_2)_n - C(O) - N(R^N) - (CR_2)_p -$ 、 $-(CR_2)_n - N(R^N) - C(O) - N(R^N) - (CR_2)_p -$ 、 $-(CR_2)_n - C(O) - O - (CR_2)_p -$ 、 $-(CR_2)_n - N(R^N) - S(O)_k - N(R^N) - (CR_2)_p -$ 和 $-(CR_2)_n - N(R^N) - C(O) - O - (CR_2)_p -$ 以及杂芳基, 该杂芳基



[0012] X^1 为 CH_2 、 NH 、 O 或 S ,

[0013] Y^1 、 Y^2 和 Z^1 各自独立地为 CH 或 N ,

[0014] X^2 为 NH 、 O 或 S ,

[0015] V 为 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-N=CH-$ 、 $-(CH_2)_a-N(R^N)-(CH_2)_b-$ 或 $-(CH_2)_a-O-(CH_2)_b-$, 其中 a 和 b 独立地为 0 、 1 、 2 或 3 , 前提是 a 和 b 不均为 0 ,

[0016] 任选地在苯基残基上包括 1 个或 2 个氮作为杂原子,

[0017] 杂芳基的碳任选各自独立地由选自以下的取代基取代: 卤素、 $-OH$ 、 $-CN$ 、 $-NO_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

[0018] 杂芳基的氮在存在时任选各自独立地由选自以下的取代基取代: $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基,

[0019] a 和 b 独立地为 1 、 2 或 3 ,

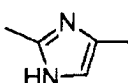
[0020] c 和 d 独立地为 1 或 2 ,

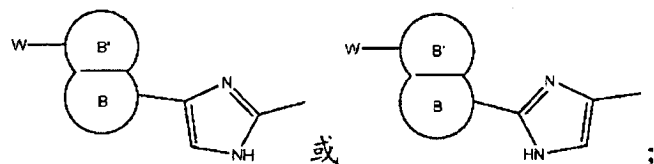
[0021] n 和 p 独立地为 0 、 1 、 2 或 3 ,

[0022] k 为 0 、 1 或 2 ,

[0023] 各 R 独立地选自氢、卤素、 $-OH$ 、 $-CN$ 、 $-NO_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

[0024] 各 R^N 独立地选自氢、 $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基, 且

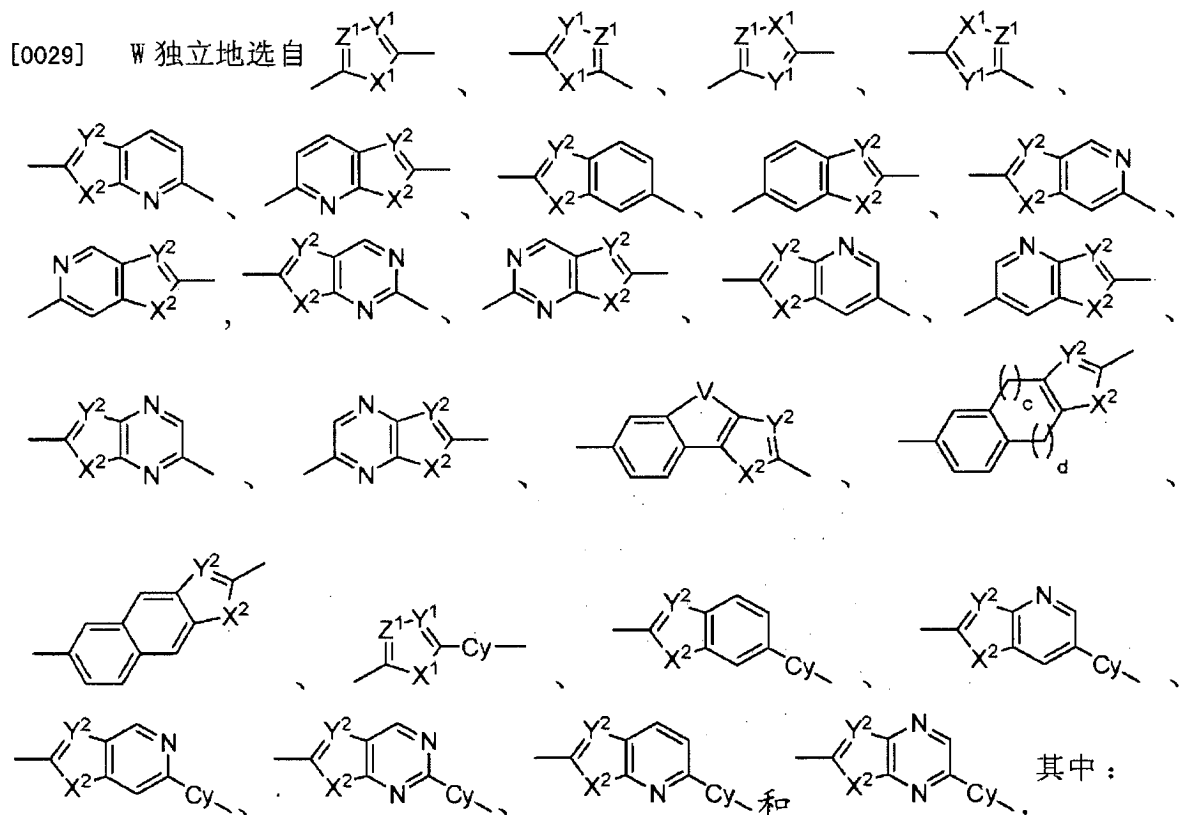
[0025] 其中 B 可附接到 A' 的任一侧上,使得在 A' 为  的实例中, W-B-A' 可为



[0026] B 和 B' 各自独立地为 4 至 8 元环,所述环是芳基、杂芳基、环烷基或杂环基,其中各杂原子在存在时独立地为 N、O 或 S,且其中 B 或 B' 中的至少一者为芳族的;

[0027] 各 R^a 独立地选自 -OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基;且如果 B 或 B' 不为芳族的,则其也可由一个或多个氧代基(oxo)取代;

[0028] 各 r 独立地为 0、1、2 或 3;

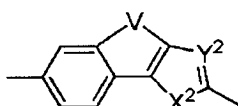


[0030] X¹ 为 CH₂、NH、O 或 S,

[0031] Y¹、Y² 和 Z¹ 各自独立地为 CH 或 N,

[0032] X² 为 NH、O 或 S,

[0033] V 为 -CH₂-CH₂-, -CH=CH-, -N=CH-, -(CH₂)_a-N(R^N)-(CH₂)_b- 或 -(CH₂)_a-O-(CH₂)_b-, 其中 a 和 b 独立地为 0、1、2 或 3,前提是 a 和 b 不均为 0,

[0034]  任选地在苯基残基上包括 1 个或 2 个氮作为杂原子,

[0035] W 任选地由选自以下的一个或多个取代基取代: -OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

[0036] W 和环 B' 可通过 B' 上的碳或氮原子连接, 且

[0037] Cy 为单环、双环或三环 5 至 12 元环烷基、杂环基、芳基或杂芳基, 其中最多三个杂原子独立地为 N、S 或 O, 并且其任选地由选自以下的一个或多个取代基取代: -OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基;

[0038] 各 R^c、R^d、R^e 和 R^f 独立地选自: 氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、芳烷基和可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环, 其中,

[0039] 各杂原子在存在时独立地为 N、O 或 S,

[0040] R^c、R^d、R^e 和 R^f 中的每个可任选地由 C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、芳烷基或可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环取代, 其中各杂原子在存在时独立地为 N、O 或 S,

[0041] R^e 与 R^d 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合; 且

[0042] R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合;

[0043] Y 和 Y' 各自独立地为碳或氮; 且

[0044] Z 和 Z' 独立地选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、1-3 个氨基酸、- [U - (CR⁴)_t - NR⁵ - C(R⁴)_t]_u - U - (CR⁴)_t - NR⁷ - (CR⁴)_t - R⁸、- U - (CR⁴)_t - R⁸ 和 - [U - (CR⁴)_t - NR⁵ - (CR⁴)_t]_u - U - (CR⁴)_t - O - (CR⁴)_t - R⁸, 其中

[0045] U 选自 -C(O)-、-C(S)- 和 -S(O)₂- ,

[0046] 各 R⁴、R⁵ 和 R⁷ 独立地选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基和芳烷基,

[0047] R⁸ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、-C(O)-R⁸¹、-C(S)-R⁸¹、-C(O)-O-R⁸¹、-C(O)-N-R⁸¹、-S(O)₂-R⁸¹ 和 -S(O)₂-N-R⁸¹, 其中各 R⁸¹ 独立地选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基和芳烷基,

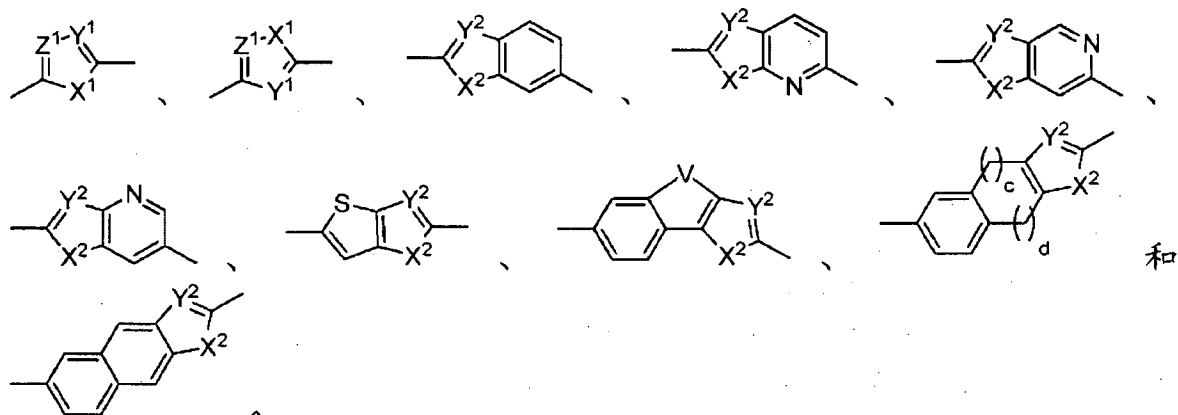
[0048] 任选地, R⁷ 和 R⁸ 一起形成 4 至 7 元环,

[0049] 各 t 独立地为 0、1、2、3 或 4, 且

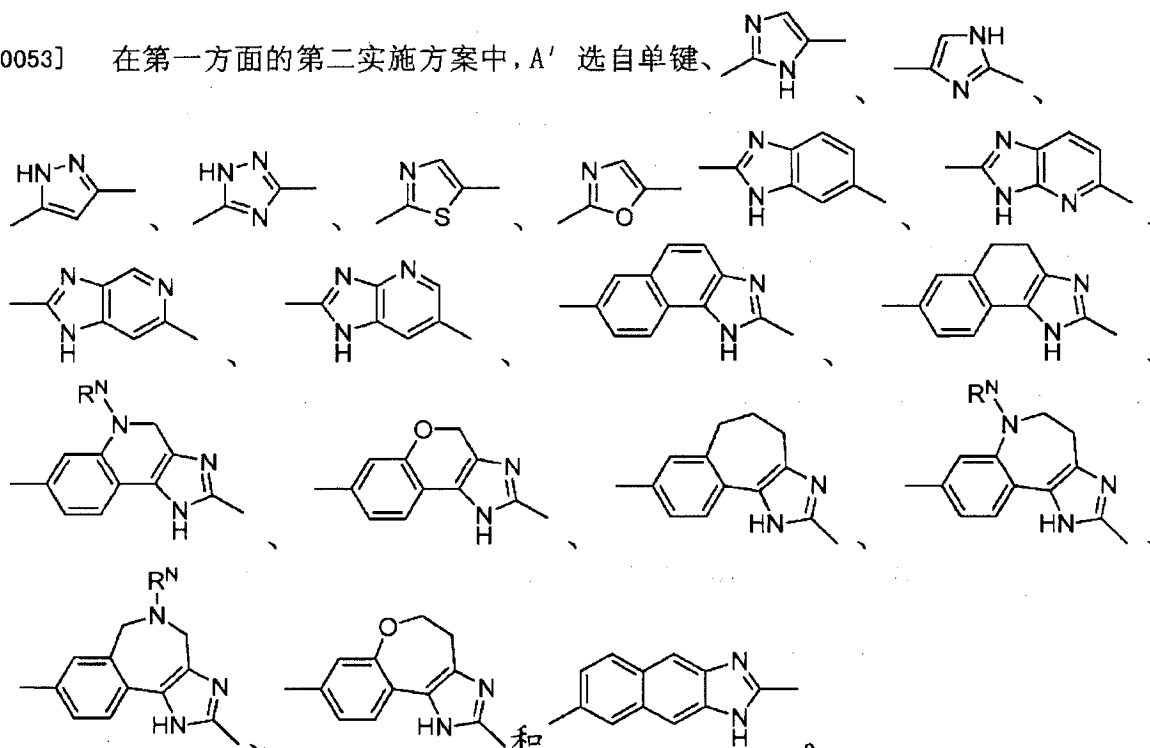
[0050] u 为 0、1 或 2。

[0051] 在第一方面的第一实施方案中, A' 选自单键、- (CR₂)_n - O - (CR₂)_p -、- (CR₂)_n - N(R^N) - (CR₂)_p -、- (CR₂)_n - C(O) - N(R^N) - (CR₂)_p -、- (CR₂)_n - N(R^N) - C(O) - N(R^N) - (CR₂)_p - 和 - (CR₂)_n - N(R^N) - C(O) - O - (CR₂)_p - 以及杂芳基, 该杂芳基选自

[0052]



[0053] 在第一方面的第二实施方案中, A' 选自单键、



[0054] 在第一方面的第三实施方案中, R^c 、 R^d 、 R^e 和 R^f 各自独立地选自: 氢、 C_1 至 C_8 烷基和 C_1 至 C_8 杂烷基, 其中,

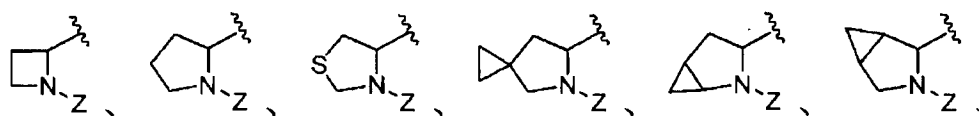
[0055] 各杂原子在存在时独立地为 N、O 或 S,

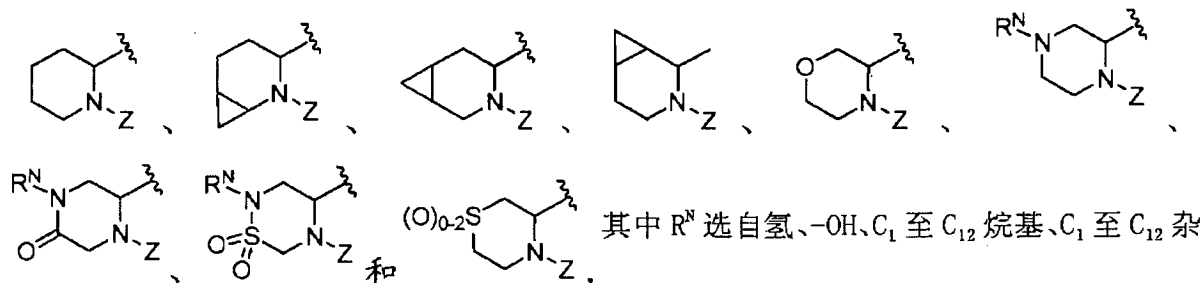
[0056] R^c 与 R^d 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合, 且

[0057] R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合。

[0058] 在第一方面的第四实施方案中, R^c 与 R^d 或 R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合。

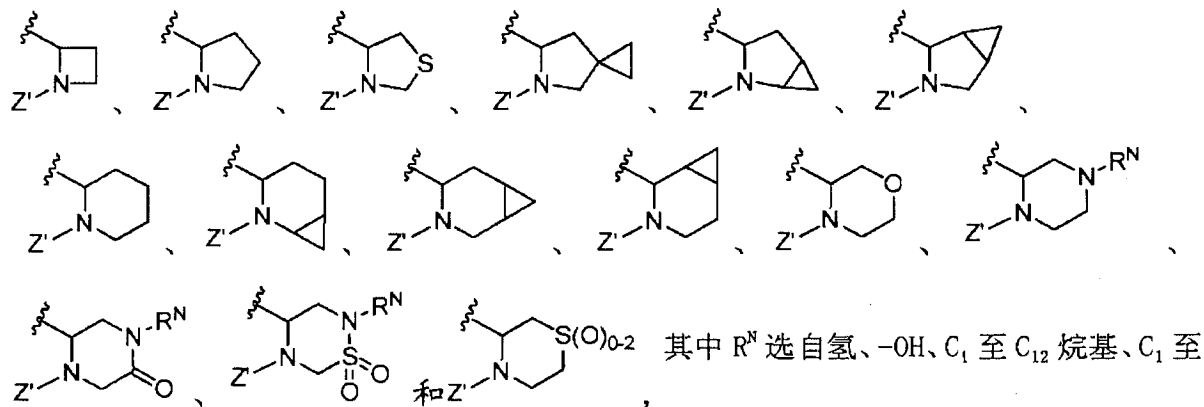
[0059] 在第一方面的第五实施方案中, R^c 与 R^d 连接并形成选自以下的杂环稠环体系:



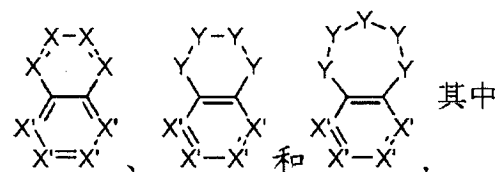
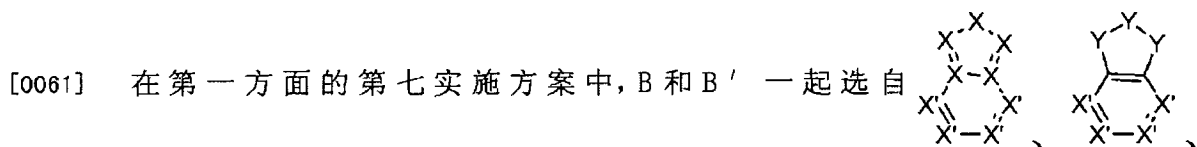


烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

[0060] 在第一方面的第六实施方案中, R^e 与 R^f 连接并形成选自以下的杂环稠环体系:



C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

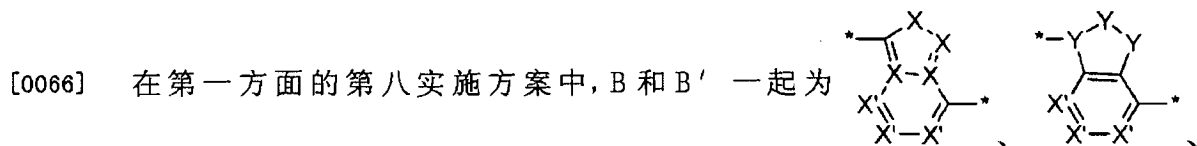


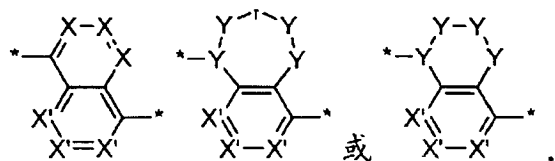
[0062] 各 X 独立地为 N 或 C, 且如果为 C, 则在必要时可包括氢以形成完整的价电子层;

[0063] 各 X' 独立地为 $-N-$ 或 $-CH-$, 前提是不超过两个 X' 为 $-N-$;

[0064] 各 Y 独立地选自 $-CH_2-$ 、 $-NH-$ 、 $-O-$ 、 $-S-$ 、 $-C(O)_2-$ 或 $-S(O)_{1-2}-$; 且

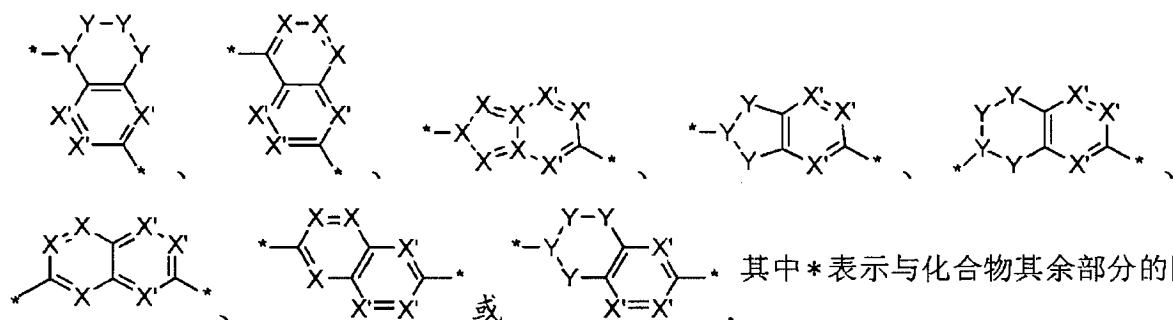
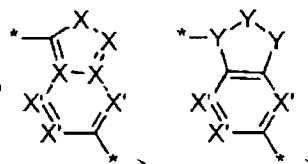
[0065] B 和 B' 在分子上的任何可用附接点处与化合物的其余部分附接。





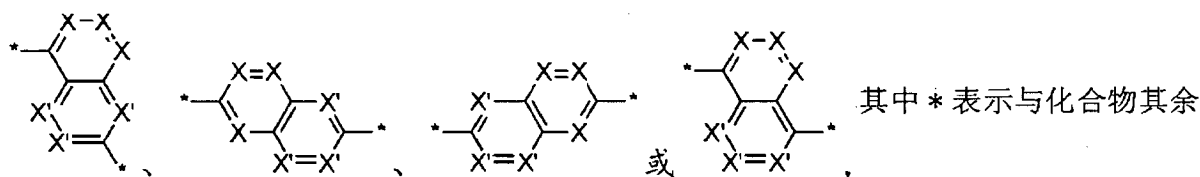
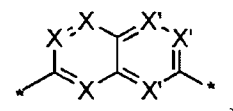
其中 * 表示与化合物其余部分的附接点。

[0067] 在第一方面的第九实施方案中, B 和 B' 一起为



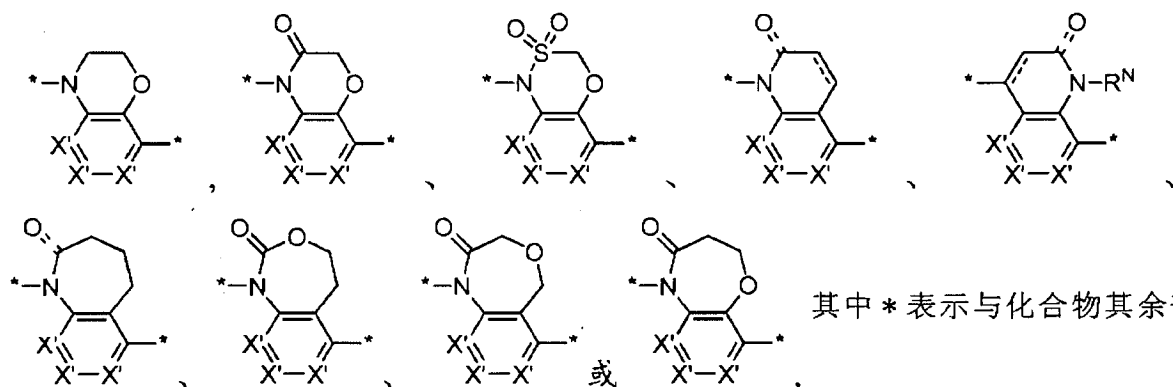
接点。

[0068] 在第一方面的第十实施方案中, B 和 B' 一起为



部分的附接点, 其中不超过 2 个 X 为氮。

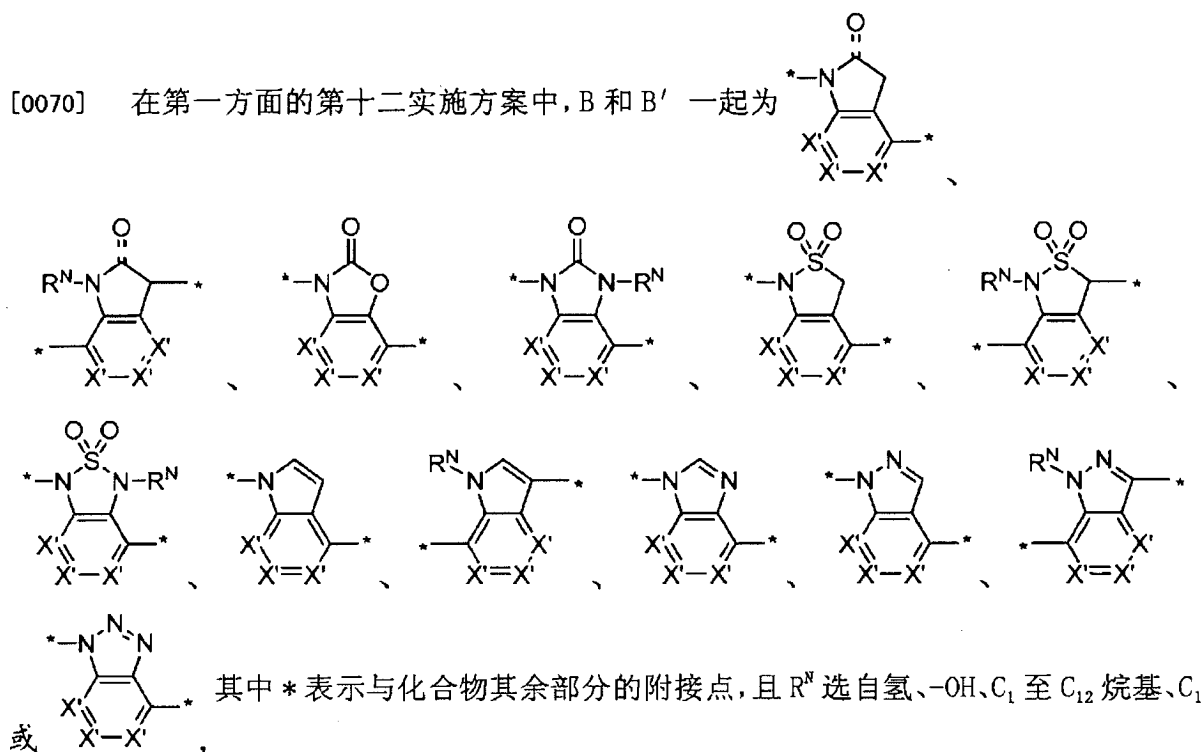
[0069] 在第一方面的第十一实施方案中, B 和 B' 一起为



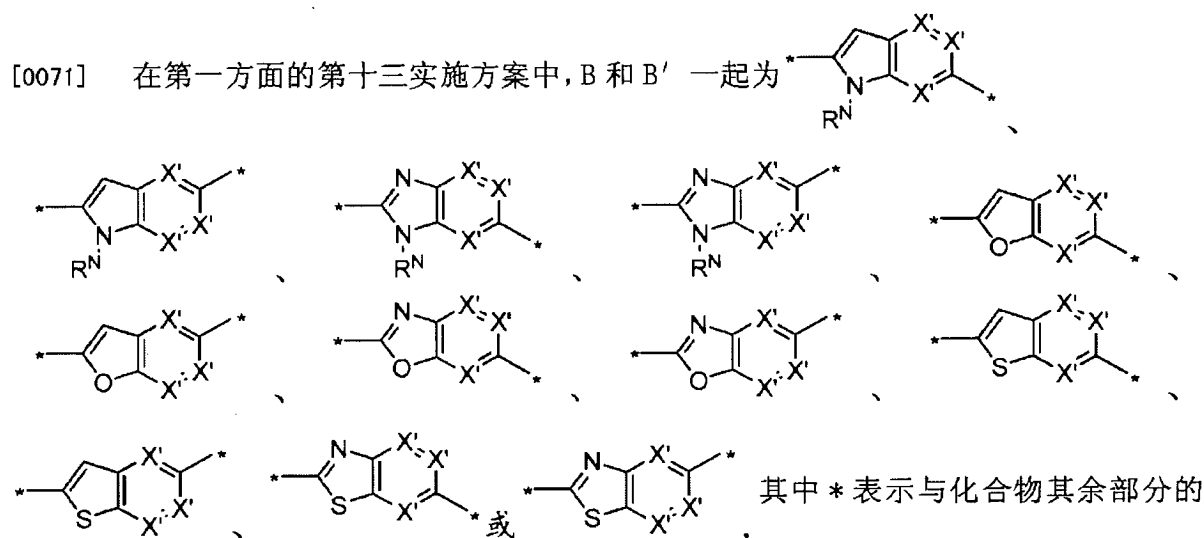
其中 * 表示与化合物其余部

分的附接点, 且 R^N 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

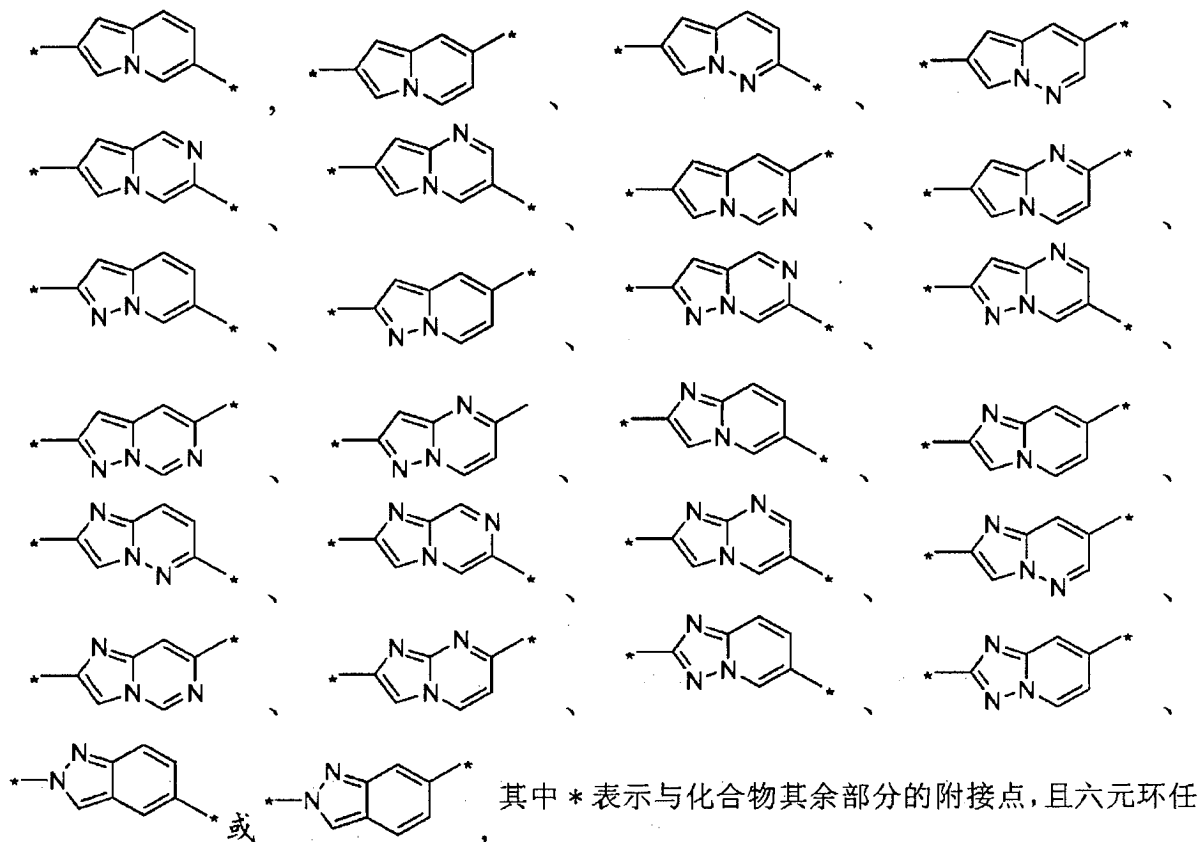
[0070] 在第一方面的第十二实施方案中, B 和 B' 一起为



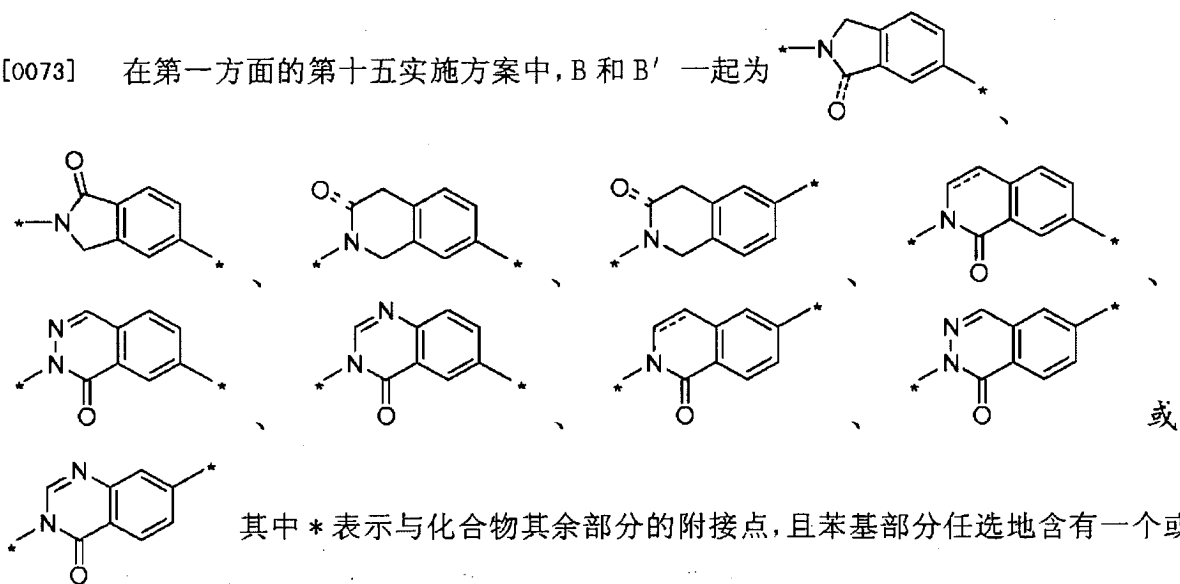
[0071] 在第一方面的第十三实施方案中, B 和 B' 一起为



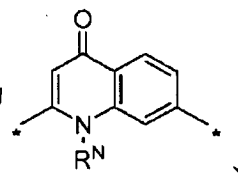
[0072] 在第一方面的第十四实施方案中, B 和 B' 一起为

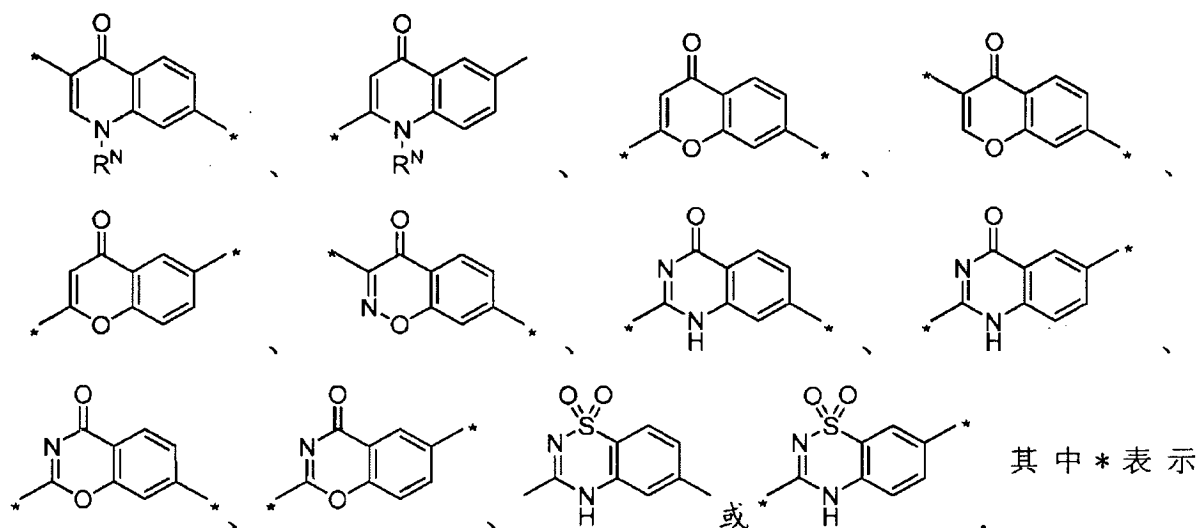


[0073] 在第一方面的第十五实施方案中, B 和 B' 一起为



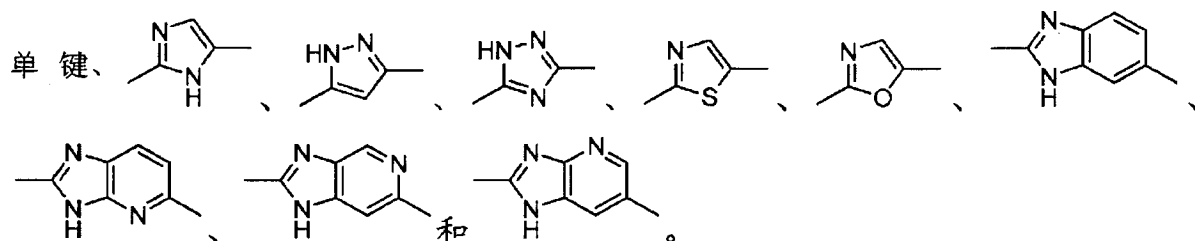
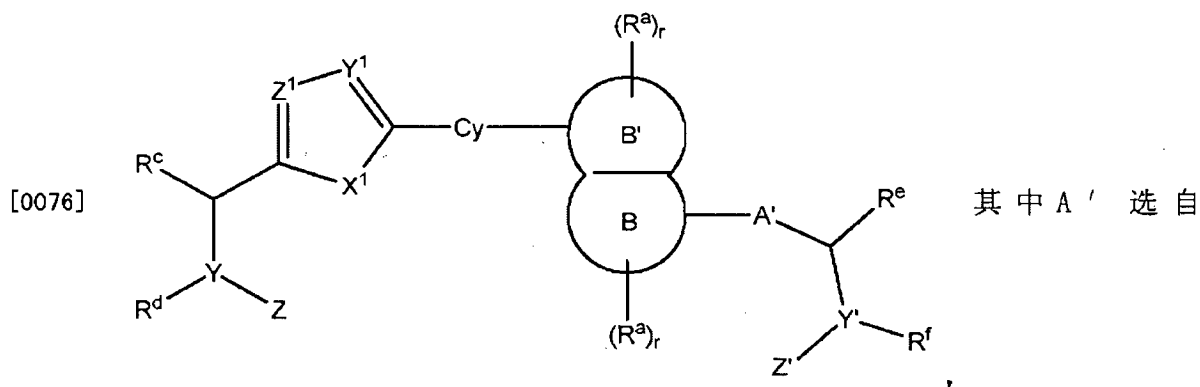
[0074] 在第一方面的第十六实施方案中, B 和 B' 一起为



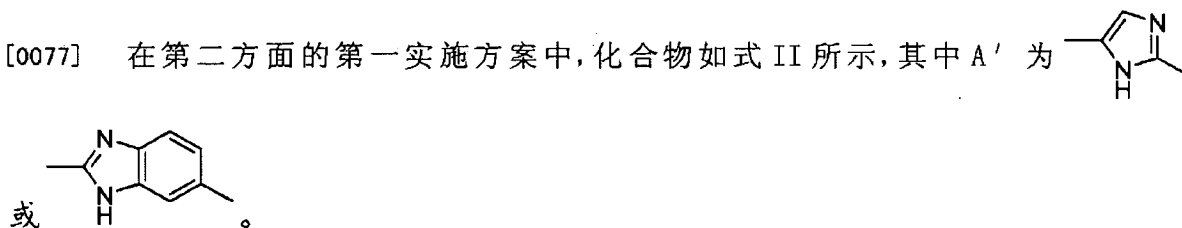


与化合物其余部分的附接点；苯基部分任选地含有一个或两个氮作为杂原子；且 R^N 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

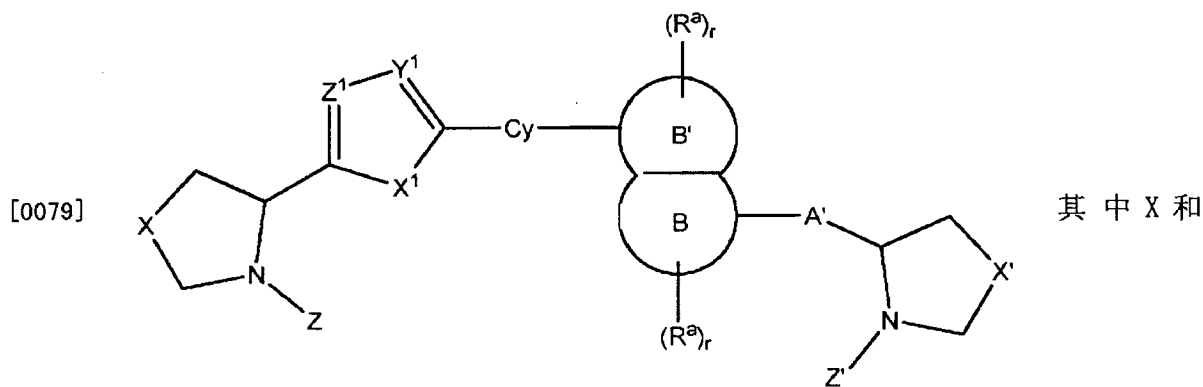
[0075] 在本发明的第二方面, 化合物如式 II 所示:



[0077] 在第二方面的第一实施方案中, 化合物如式 II 所示, 其中 A' 为

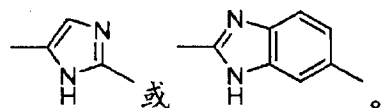


[0078] 在第二方面的第二实施方案中, 化合物如式 IIa 所示:

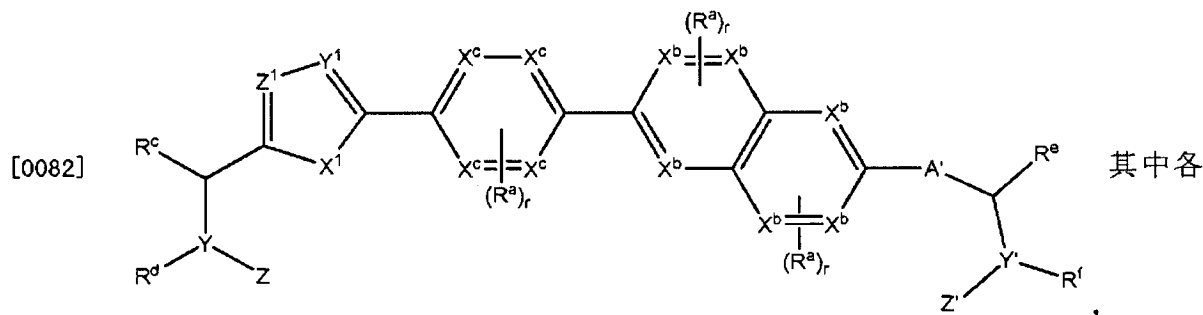


X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0080] 在第二方面的第三实施方案中，化合物如式 IIa 所示，其中 A' 为

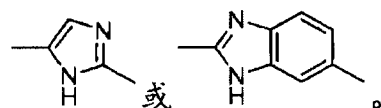


[0081] 在第二方面的第四实施方案中，化合物如式 IIb 所示：

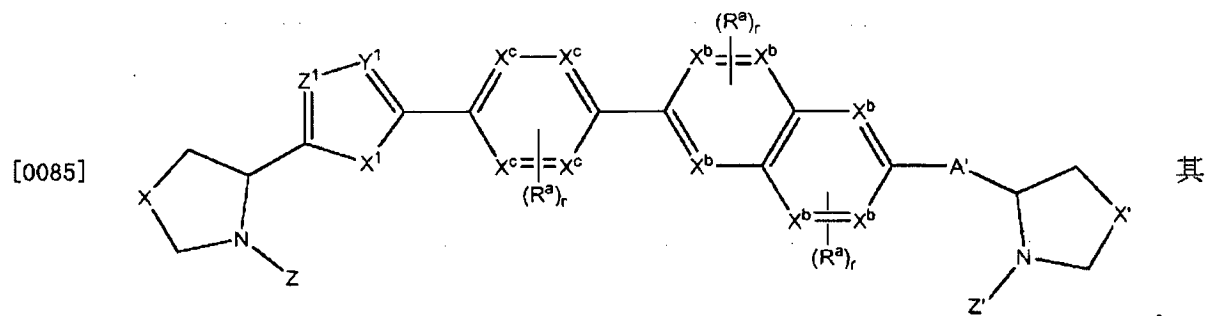


X^b 和 X^c 独立地为 C 或 N。

[0083] 在第二方面的第五实施方案中，化合物如式 IIb 所示，其中 A' 为

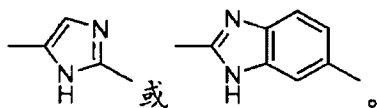


[0084] 在第二方面的第六实施方案中，化合物如式 IIc 所示：

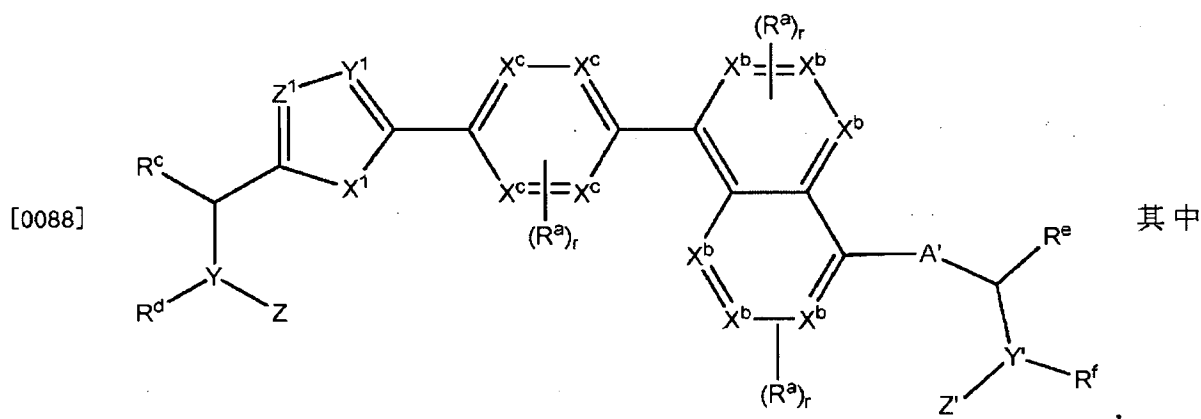


中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0086] 在第二方面的第七实施方案中，化合物如式 IIc 所示，其中 A' 为

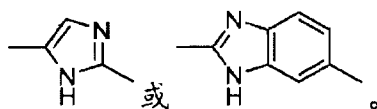


[0087] 在第二方面的第八实施方案中，化合物如式 IIId 所示：



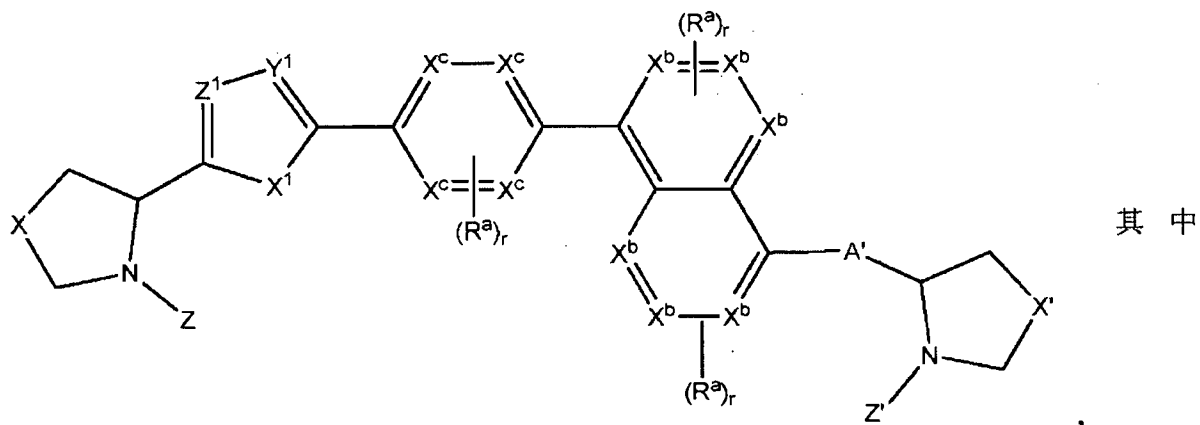
各 X^b 和 X^c 独立地为 C 或 N。

[0089] 在第二方面的第九实施方案中，化合物如式 IIId 所示，其中 A' 为



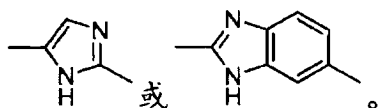
[0090] 在第二方面的第十实施方案中，化合物如式 IIe 所示：

[0091]

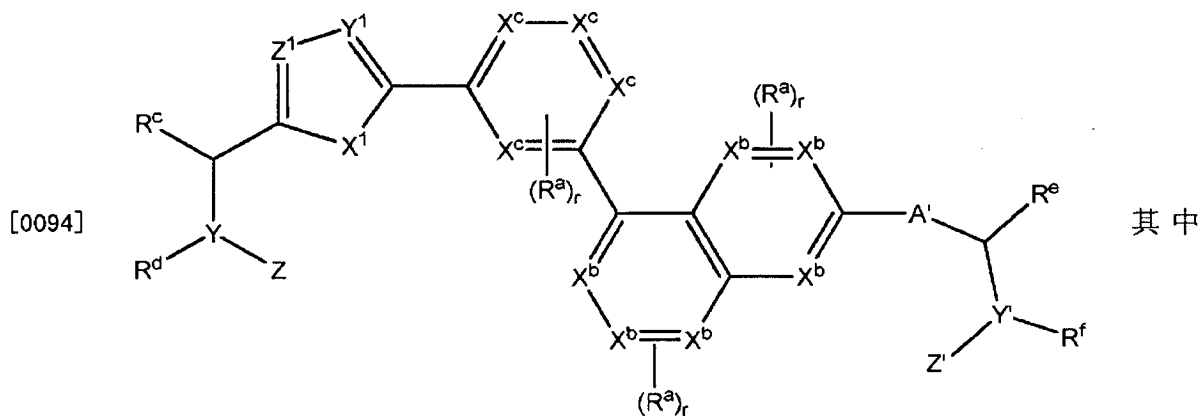


X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0092] 在第二方面的第十一实施方案中, 化合物如式 IIe 所示, 其中 A' 为

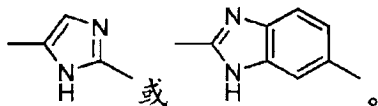


[0093] 在第二方面的第十二实施方案中, 化合物如式 II f 所示:

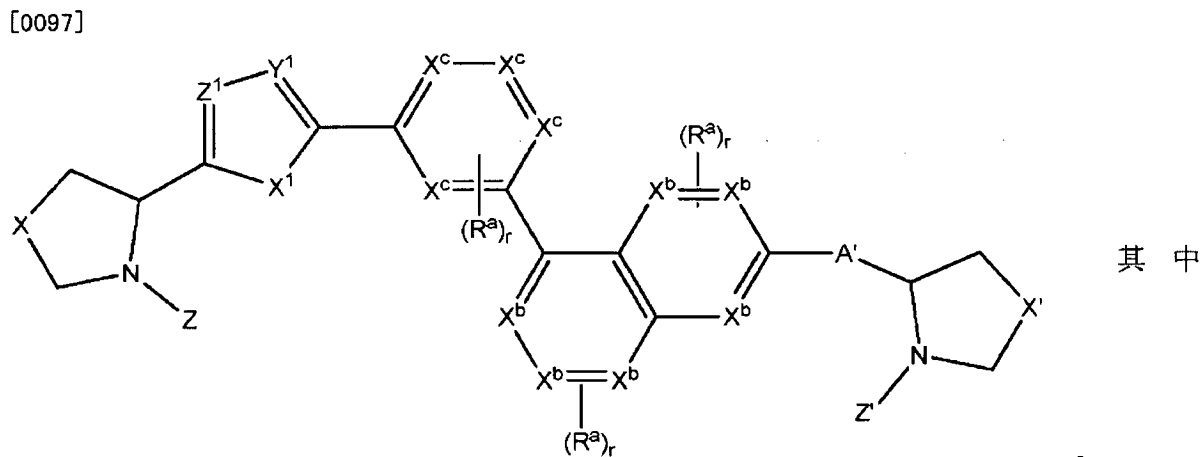


各 X^b 和 X^c 独立地为 C 或 N。

[0095] 在第二方面的第十三实施方案中, 化合物如式 II f 所示, 其中 A' 为

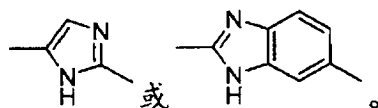


[0096] 在第二方面的第十四实施方案中, 化合物如式 II g 所示:

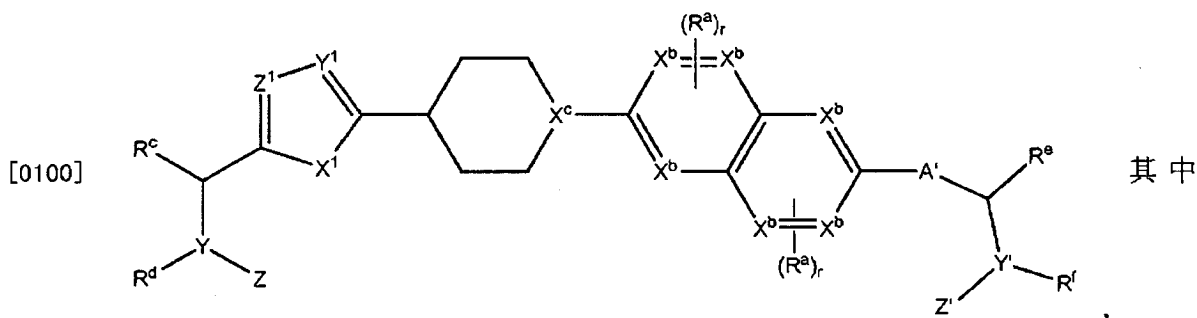


X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0098] 在第二方面的第十五实施方案中, 化合物如式 II g 所示, 其中 A' 为

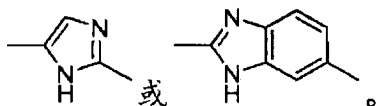


[0099] 在第二方面的第十六实施方案中, 化合物如式 IIh 所示:

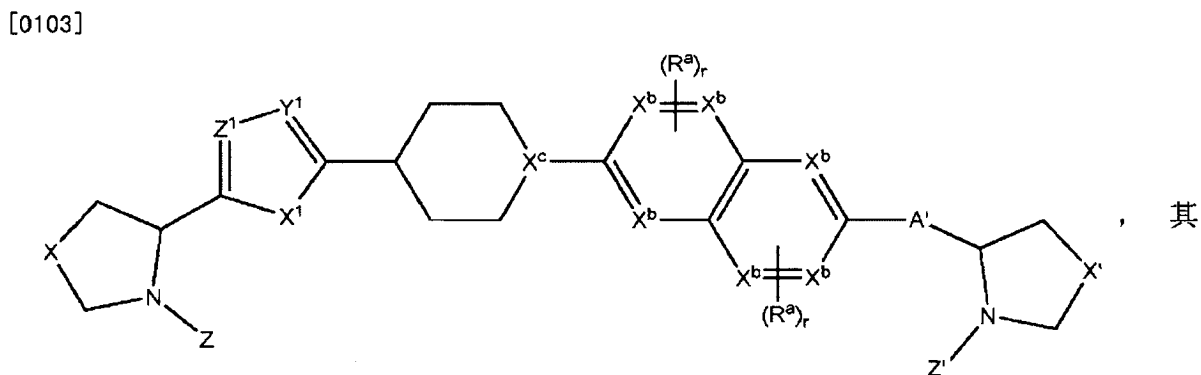


X^c 和各 X^b 独立地为 C 或 N。

[0101] 在第二方面的第十七实施方案中, 化合物如式 IIh 所示, 其中 A' 为

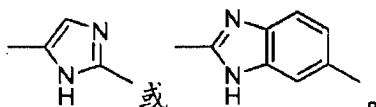


[0102] 在第二方面的第十八实施方案中, 化合物如式 IIi 所示:



中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

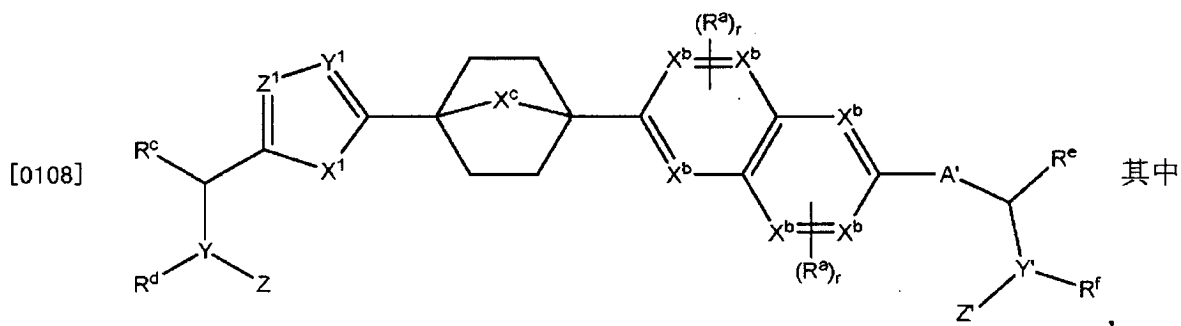
[0104] 在第二方面的第十九实施方案中, 化合物如式 IIi 所示, 其中 A' 为



[0105] 在第二方面的第二十实施方案中, 化合物如式 IIh 或 IIi 所示, 其中 X^c 为 C。

[0106] 在第二方面的第二十一实施方案中, 化合物如式 IIh 或 IIi 所示, 其中 X^c 为 N。

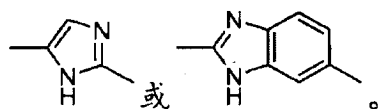
[0107] 在第二方面的第二十二实施方案中, 化合物如式 IIj 所示:



[0109] X^c 为 $-\text{CH}_2-$ 、 $-\text{NH}-$ 或 $-\text{CH}_2-\text{CH}_2-$ ；且

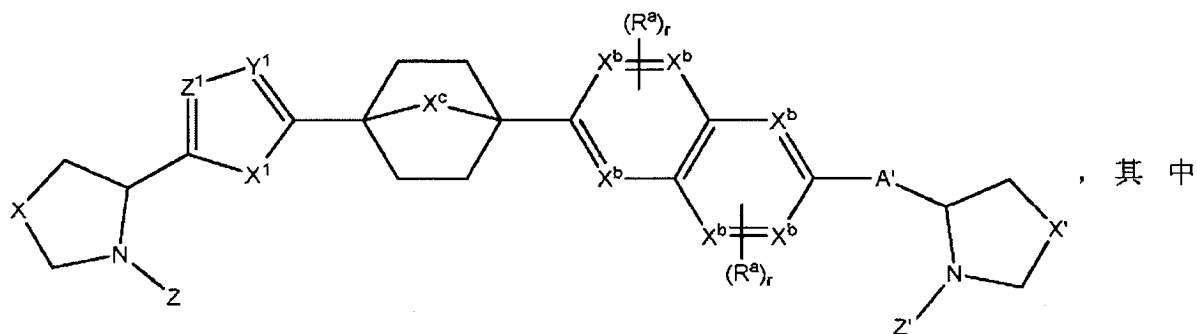
[0110] 各 X^b 独立地为 C 或 N。

[0111] 在第二方面的第二十三实施方案中化合物如式 IIj 所示其中 A' 为



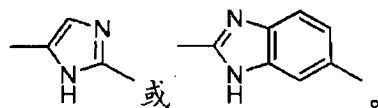
[0112] 在第二方面的第二十四实施方案中, 化合物如式 IIk 所示:

[0113]



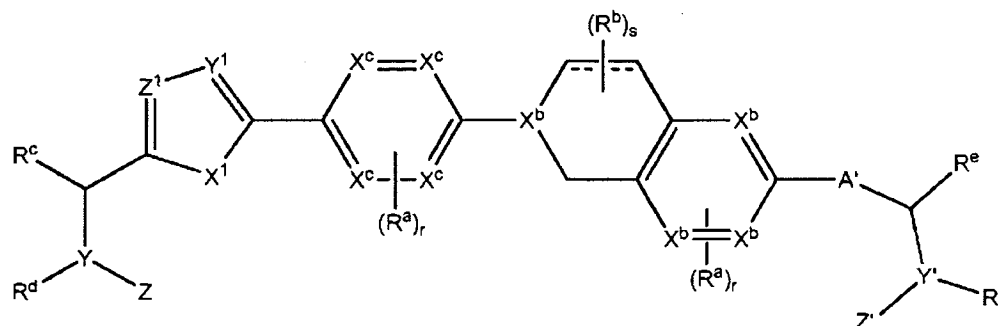
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0114] 在第二方面的第二十五实施方案中, 化合物如式 IIk 所示, 其中 A' 为



[0115] 在第二方面的第二十六实施方案中, 化合物如式 IIIl 所示:

[0116]



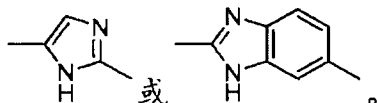
[0117] 其中：

[0118] 各 X^b 和 X^c 独立地为 C 或 N；

[0119] 各 R^b 选自氧代基、-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；且

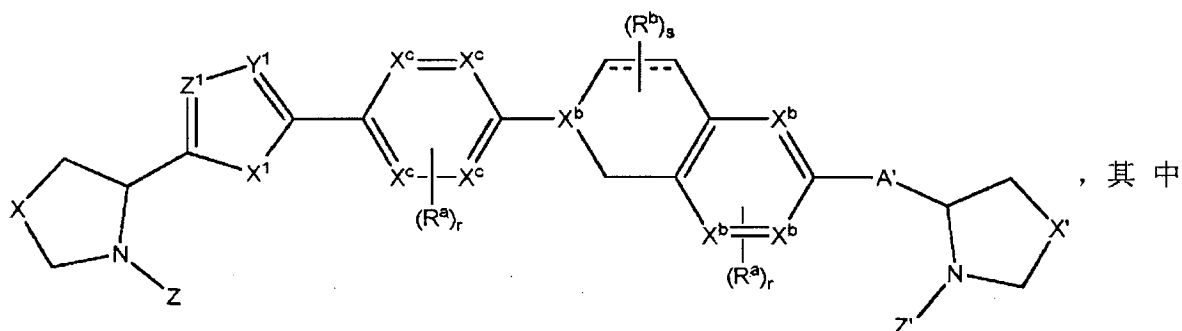
[0120] s 为 0、1、2 或 3。

[0121] 在第二方面的第二十七实施方案中，化合物如式 III 所示，其中 A' 为



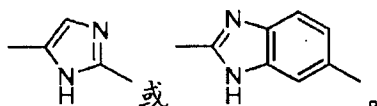
[0122] 在第二方面的第二十八实施方案中，化合物如式 IIIm 所示：

[0123]

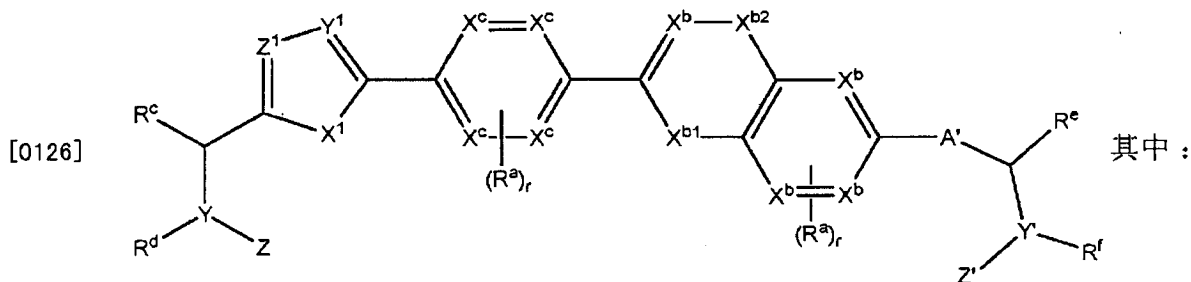


X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-，其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0124] 在第二方面的第二十九实施方案中，化合物如式 IIIm 所示，其中 A' 为



[0125] 在第二方面的第三十实施方案中，化合物如式 IIIn 所示：

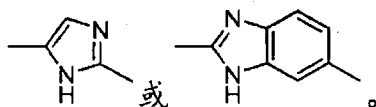


[0127] 各 X^b 和 X^c 独立地为 C 或 N；

[0128] X^{b1} 为 N 或 O；且

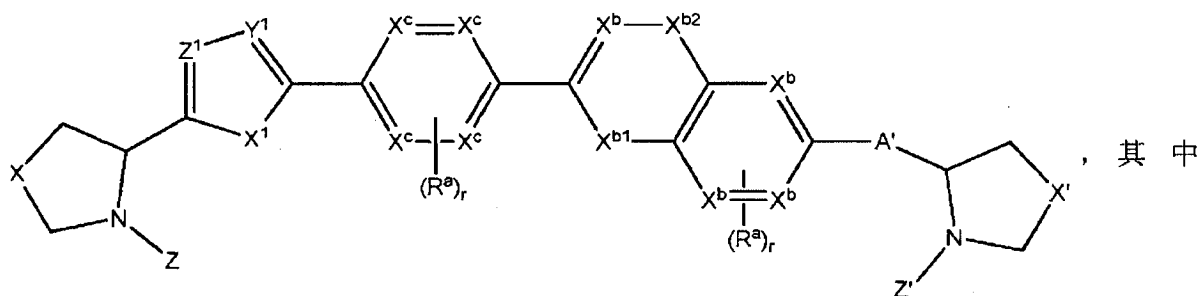
[0129] X^{b2} 为 $S(O)_2$ 或 $C(O)$ 。

[0130] 在第二方面的第三十一实施方案中，化合物如式 IIIn 所示，其中 A' 为



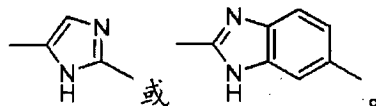
[0131] 在第二方面的第三十二实施方案中，化合物如式 IIo 所示：

[0132]

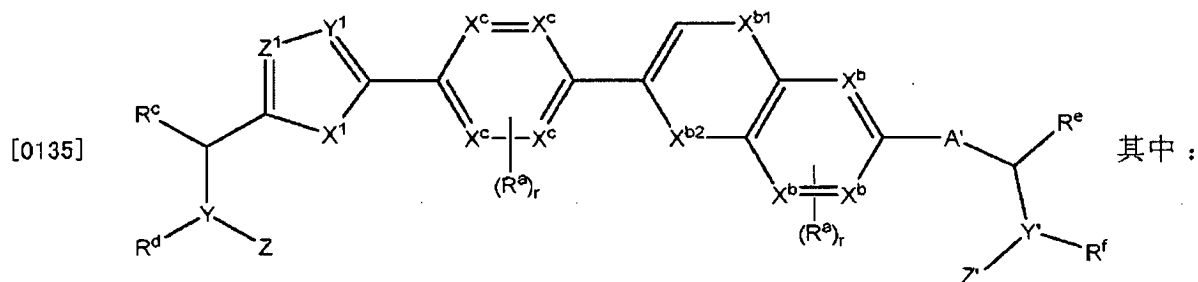


X 和 X' 各自独立地选自化学键、 $-CH_2-$ 、 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-O-$ 、 $-S-$ 、 $-S(O)_{1-2}-$ 、 $-CH_2O-$ 、 $-CH_2S-$ 、 $-CH_2S(O)_{1-2}-$ 和 $-CH_2N(R^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0133] 在第二方面的第三十三实施方案中，化合物如式 IIo 所示，其中 A' 为



[0134] 在第二方面的第三十四实施方案中，化合物如式 IIp 所示：

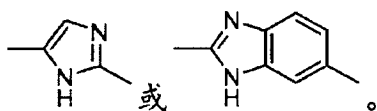


[0136] 各 X^b 和 X^c 独立地为 C 或 N；

[0137] X^{b1} 为 N 或 O ; 且

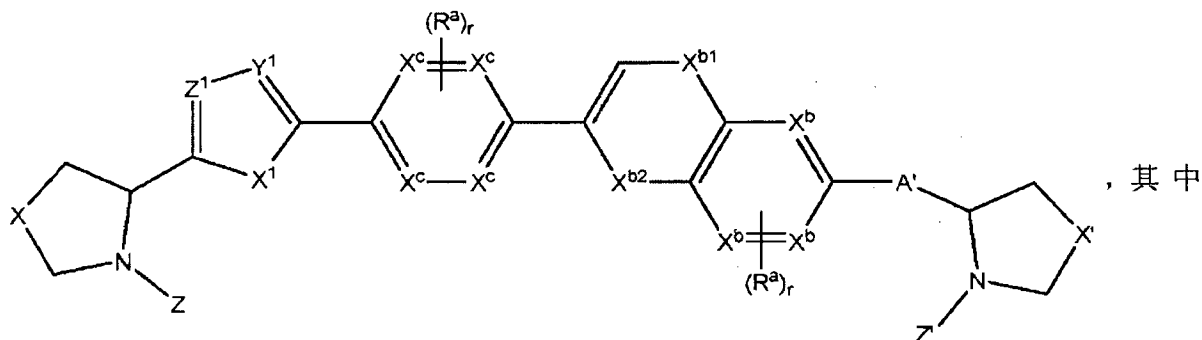
[0138] X^{b2} 为 $S(O)_2$ 或 $C(O)$ 。

[0139] 在第二方面的第三十五实施方案中, 化合物如式 IIp 所示, 其中 A' 为



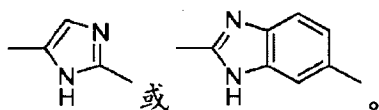
[0140] 在第二方面的第三十六实施方案中, 化合物如式 IIq 所示 :

[0141]

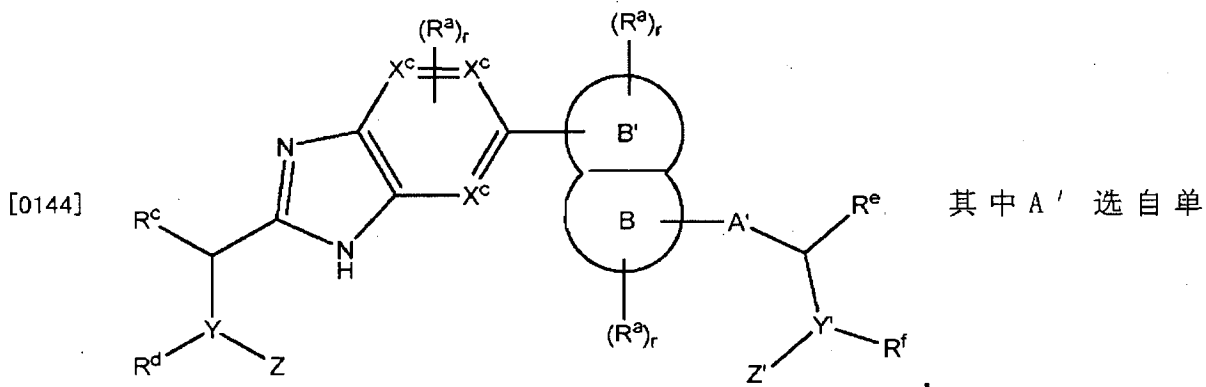


X 和 X' 各自独立地选自化学键、 $-CH_2-$ 、 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-O-$ 、 $-S-$ 、 $-S(O)_{1-2}-$ 、 $-CH_2O-$ 、 $-CH_2S-$ 、 $-CH_2S(O)_{1-2}-$ 和 $-CH_2N(R^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

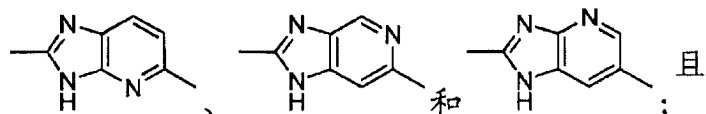
[0142] 在第二方面的第三十七实施方案中, 化合物如式 IIq 所示, 其中 A' 为



[0143] 在本发明的第三方面, 化合物如式 III 所示 :

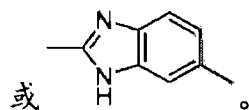


键、 ,

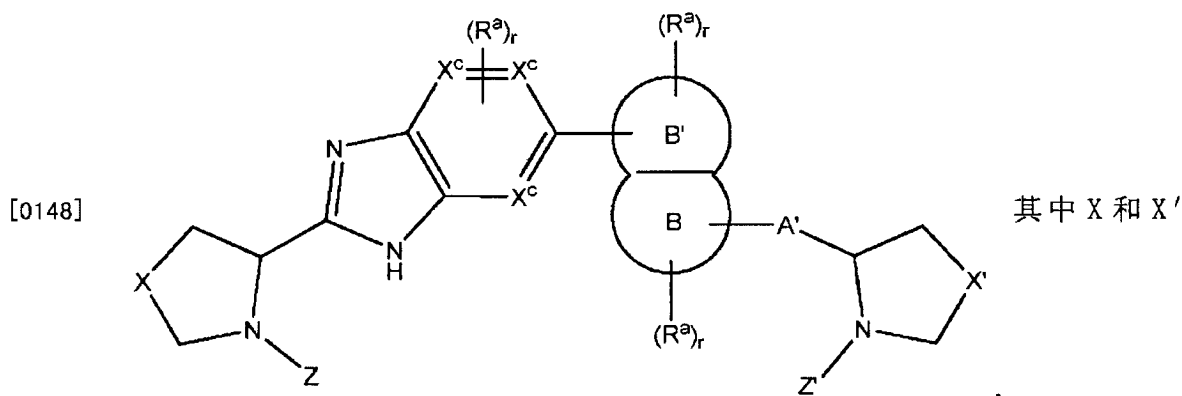


[0145] 各 X^c 独立地为 C 或 N。

[0146] 在第三方面的第一实施方案中, 化合物如式 III 所示, 其中 A' 为

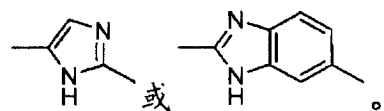


[0147] 在第三方面的第二实施方案中, 化合物如式 IIIa 所示:

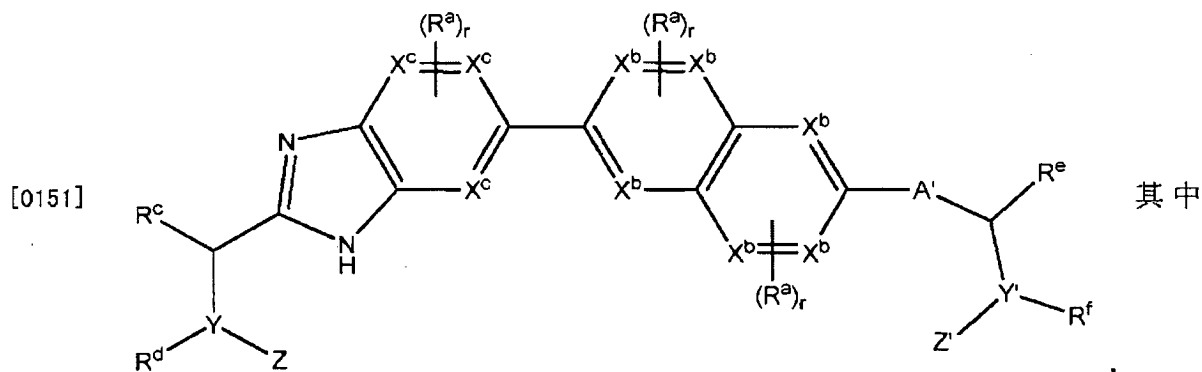


各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0149] 在第三方面的第三实施方案中, 化合物如式 IIIa 所示, 其中 A' 为

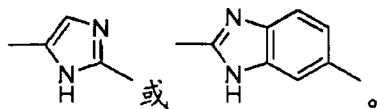


[0150] 在第三方面的第四实施方案中, 化合物如式 IIIb 所示:



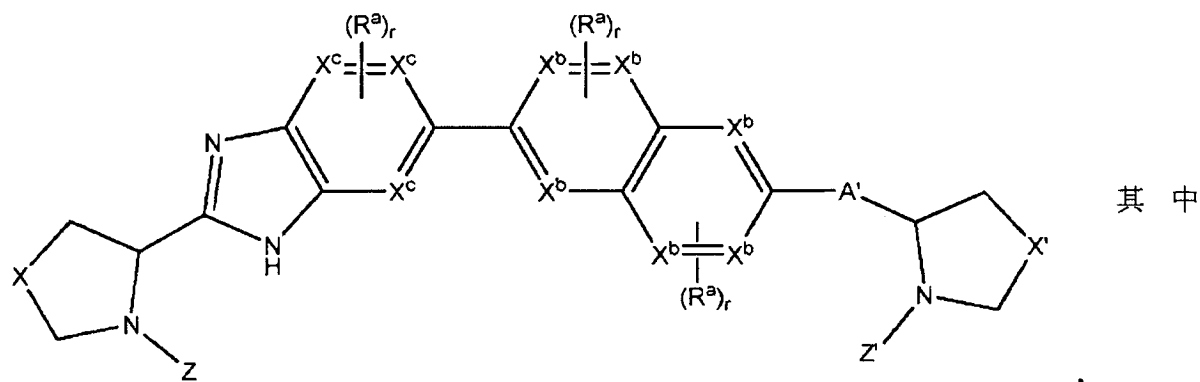
各 X^b 独立地为 C 或 N。

[0152] 在第三方面的第五实施方案中, 化合物如式 IIIb 所示, 其中 A' 为



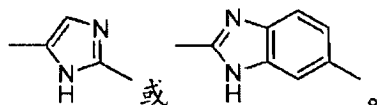
[0153] 在第三方面的第六实施方案中,化合物如式 IIIc 所示:

[0154]



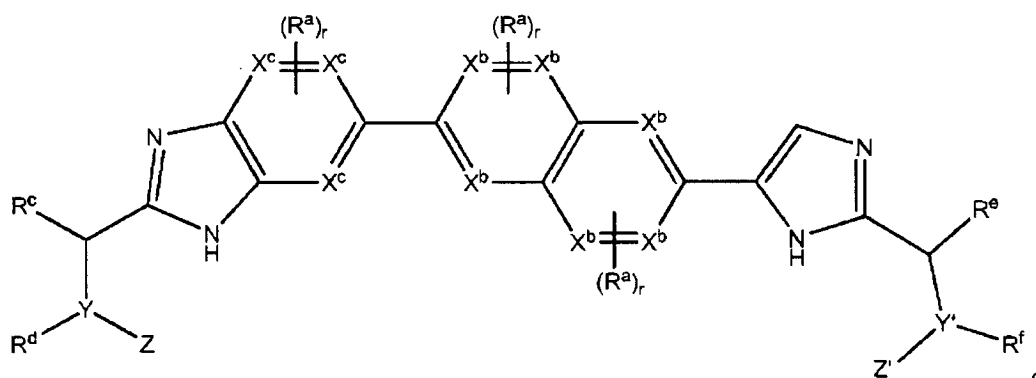
X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0155] 在第三方面的第七实施方案中,化合物如式 IIIc 所示,其中 A' 为



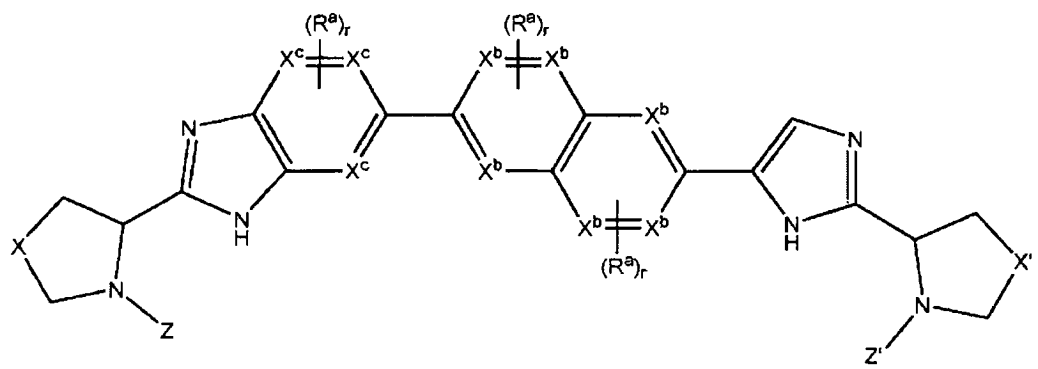
[0156] 在第三方面的第八实施方案中,化合物如式 IIIId 所示:

[0157]



[0158] 在第三方面的第九实施方案中,化合物如式 IIIe 所示:

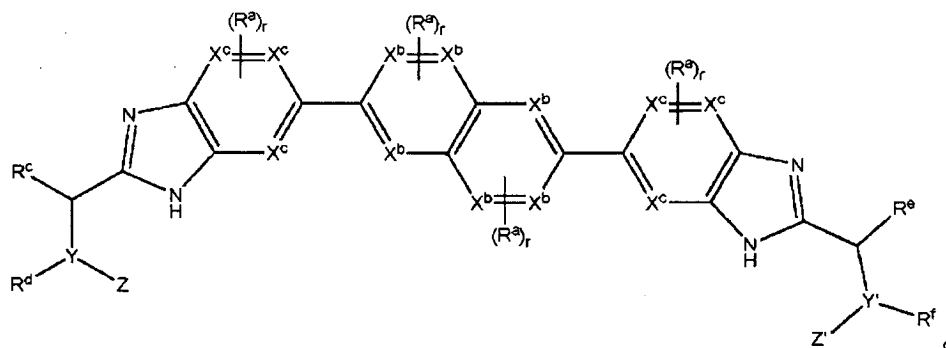
[0159]



[0160] 其中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

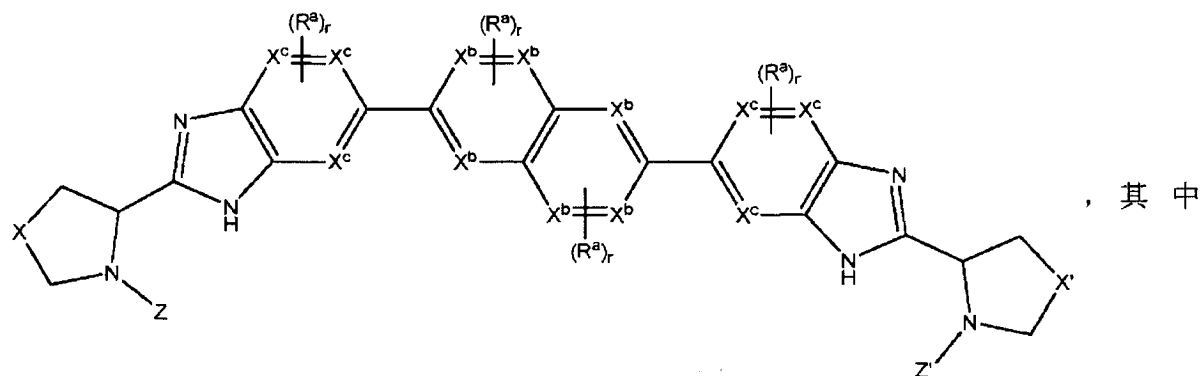
[0161] 在第三方面的第十实施方案中, 化合物如式 IIIIf 所示:

[0162]



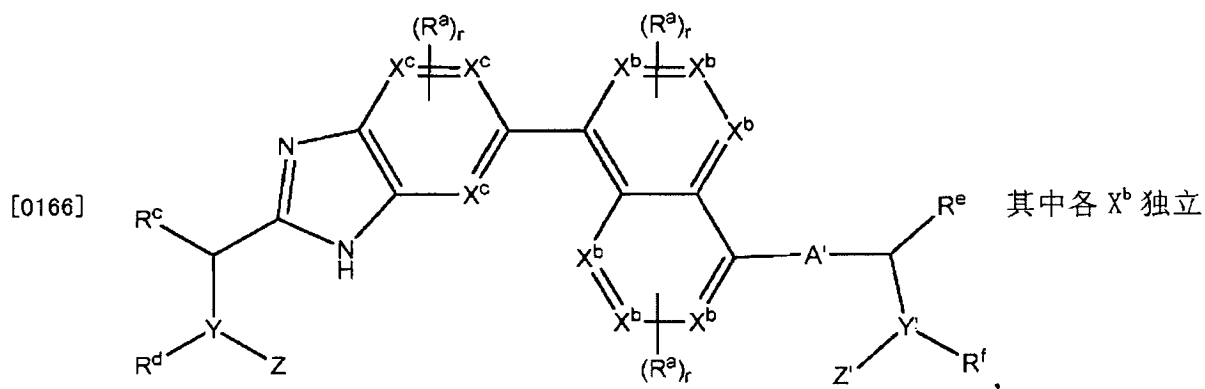
[0163] 在第三方面的第十一实施方案中, 化合物如式 IIIIg 所示:

[0164]



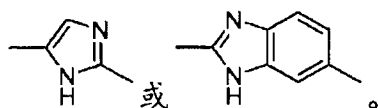
X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0165] 在第三方面的第十二实施方案中, 化合物如式 IIIIh 所示:

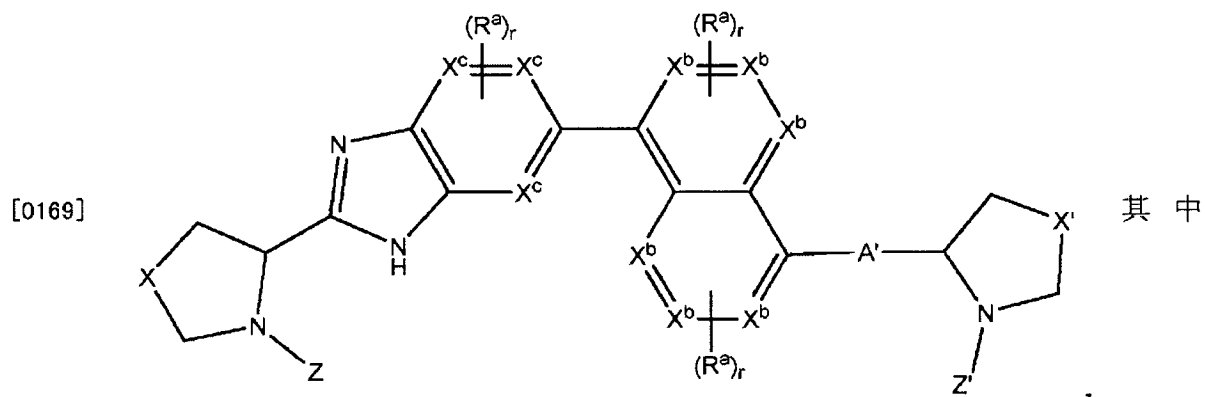


地为 C 或 N。

[0167] 在第三方面的第十三实施方案中, 化合物如式 IIIh 所示, 其中 A' 为

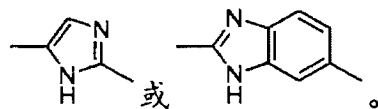


[0168] 在第三方面的第十四实施方案中, 化合物如式 IIIi 所示:



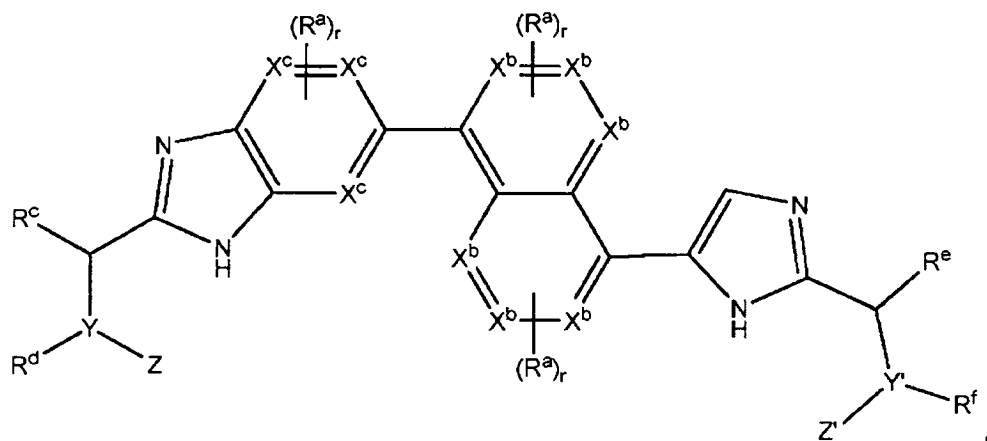
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0170] 在第三方面的第十五实施方案中, 化合物如式 IIIi 所示, 其中 A' 为



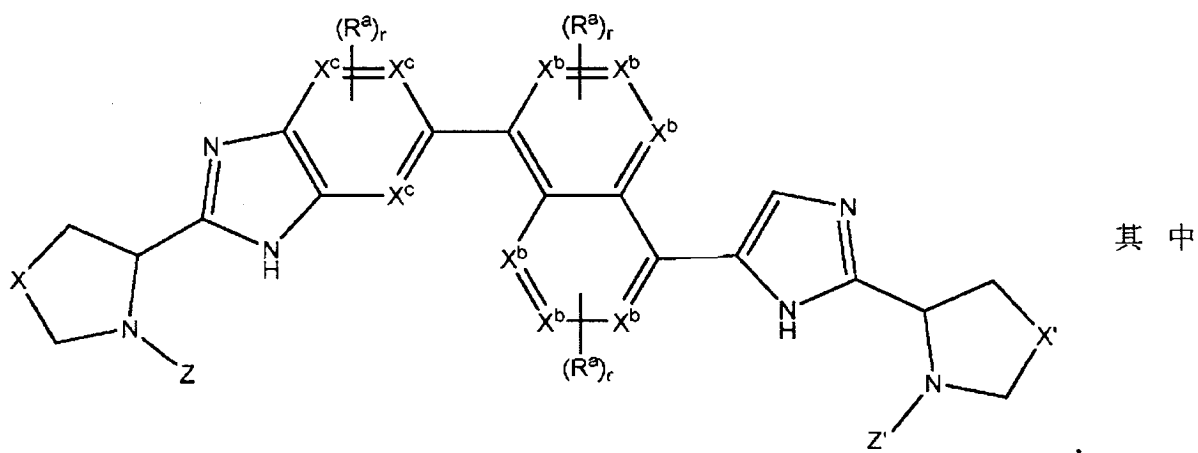
[0171] 在第三方面的第十六实施方案中, 化合物如式 IIIj 所示:

[0172]



[0173] 在第三方面的第十七实施方案中,化合物如式 IIIIk 所示:

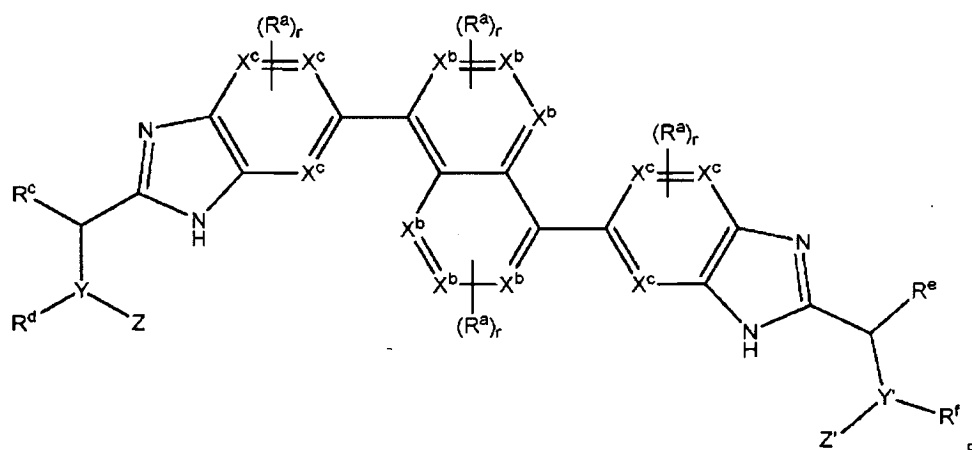
[0174]



X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

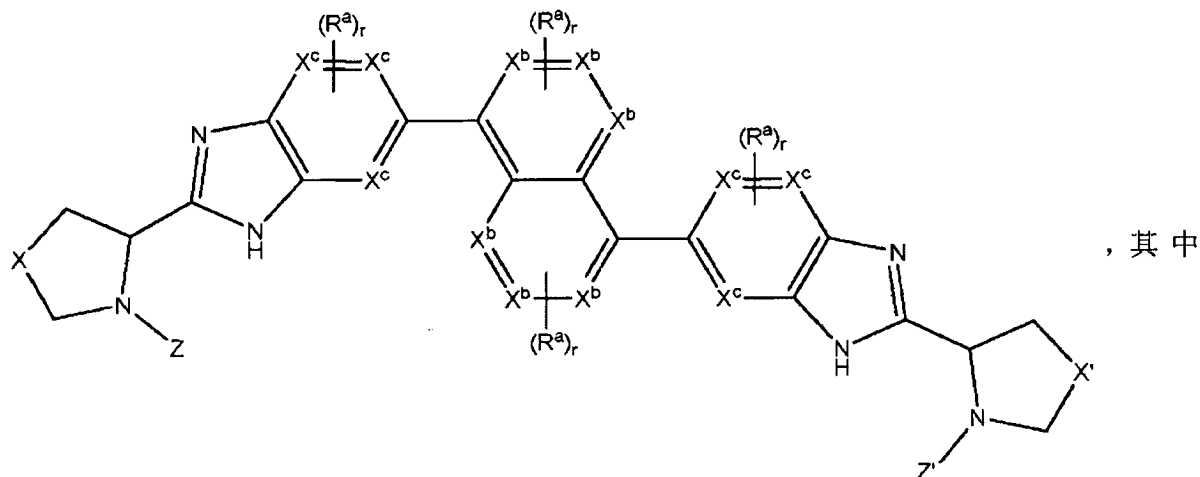
[0175] 在第三方面的第十八实施方案中,化合物如式 IIII1 所示:

[0176]



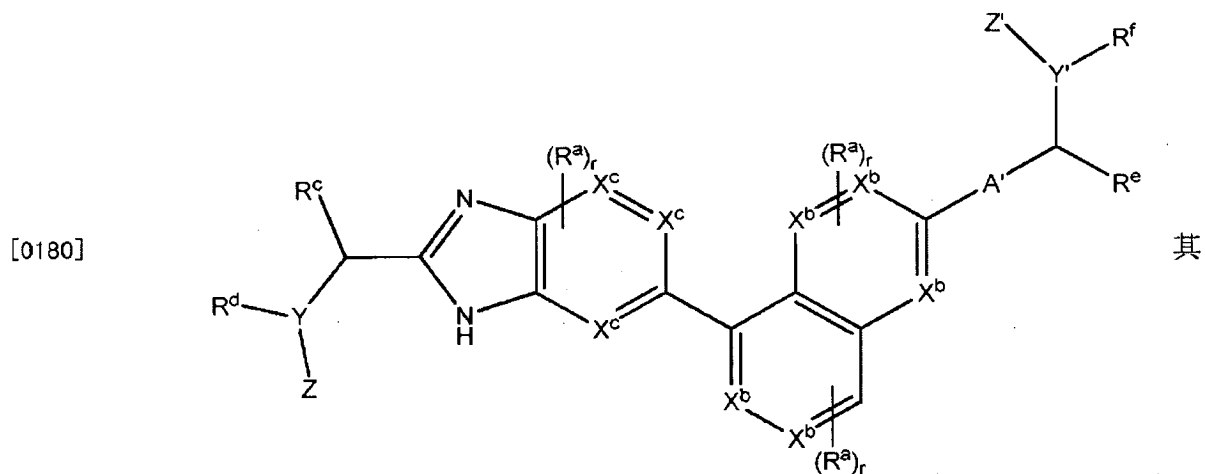
[0177] 在第三方面的第十九实施方案中, 化合物如式 III_m 所示:

[0178]



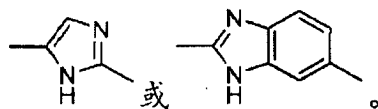
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0179] 在第三方面的第二十实施方案中, 化合物如式 III_n 所示:

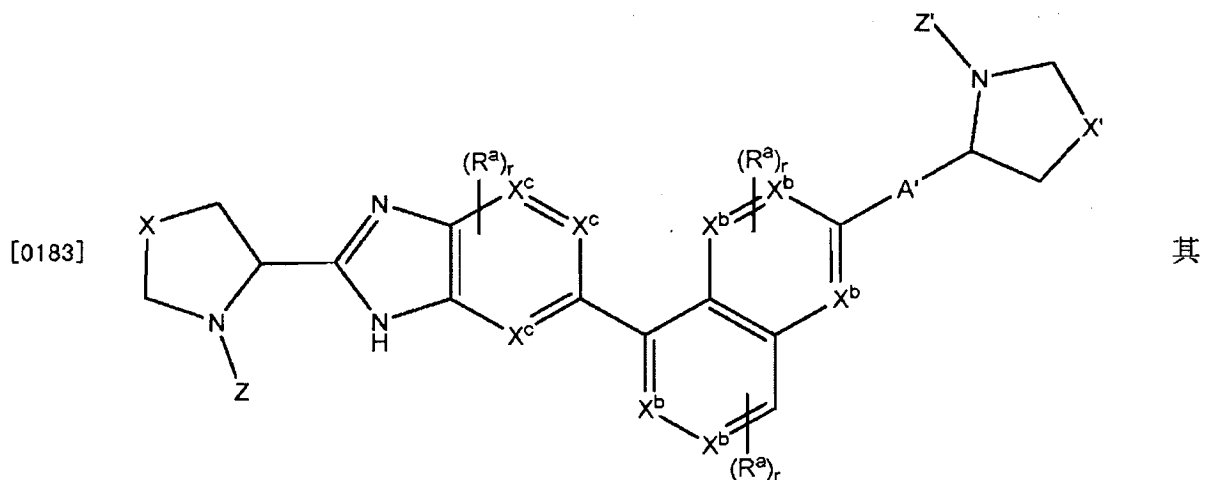


中各 X^b 独立地为 C 或 N。

[0181] 在第三方面的第二十一实施方案中, 化合物如式 IIIIn 所示, 其中 A' 为

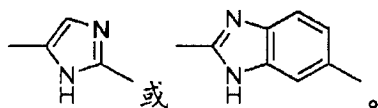


[0182] 在第三方面的第二十二实施方案中, 化合物如式 IIIo 所示:



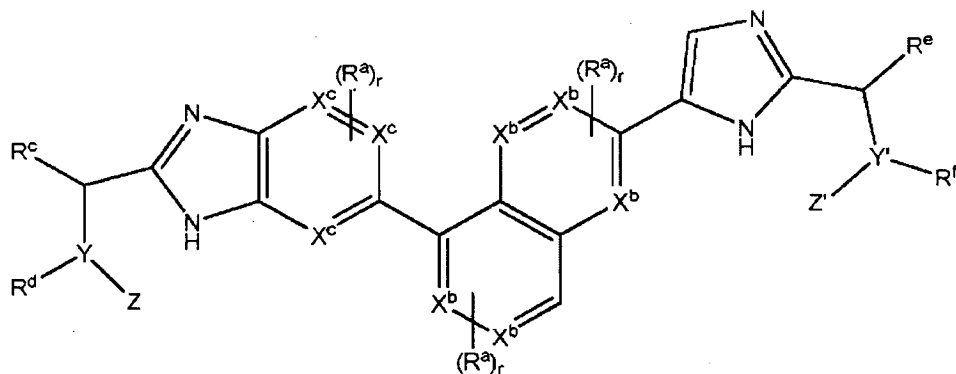
中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0184] 在第三方面的第二十三实施方案中, 化合物如式 IIIo 所示, 其中 A' 为

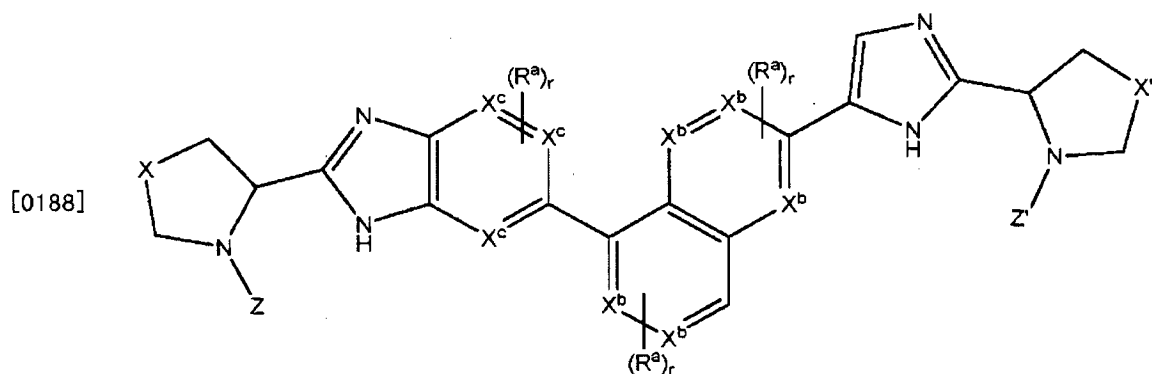


[0185] 在第三方面的第二十四实施方案中, 化合物如式 IIIp 所示:

[0186]

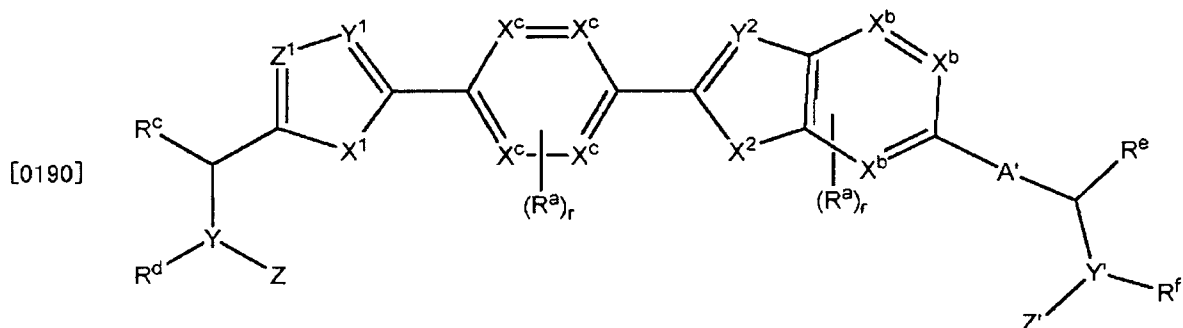


[0187] 在第三方面的第二十五实施方案中, 化合物如式 IIIq 所示:

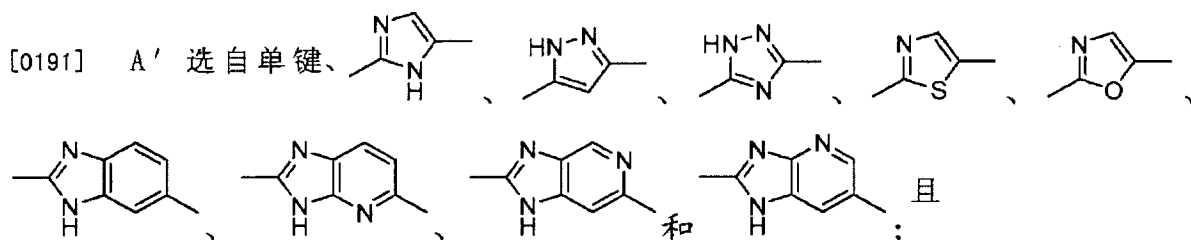


其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0189] 在本发明的第四方面, 化合物如式 IV 所示:

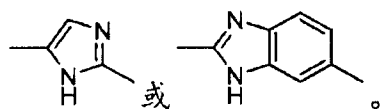


其中：



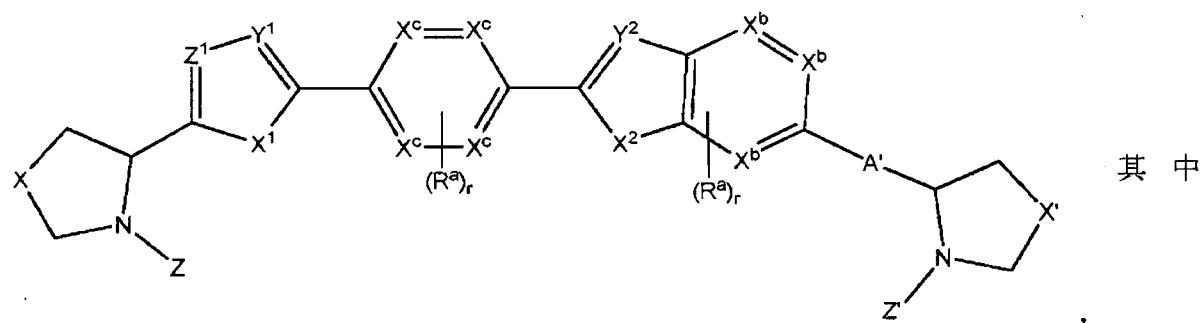
[0192] 各 X^b 和 X^c 独立地为 C 或 N。

[0193] 在第四方面的第一实施方案中, 化合物如式 IV 所示, 其中 A' 为



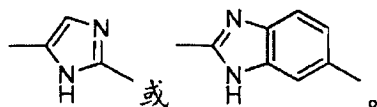
[0194] 在第四方面的第二实施方案中, 化合物如式 IVa 所示:

[0195]

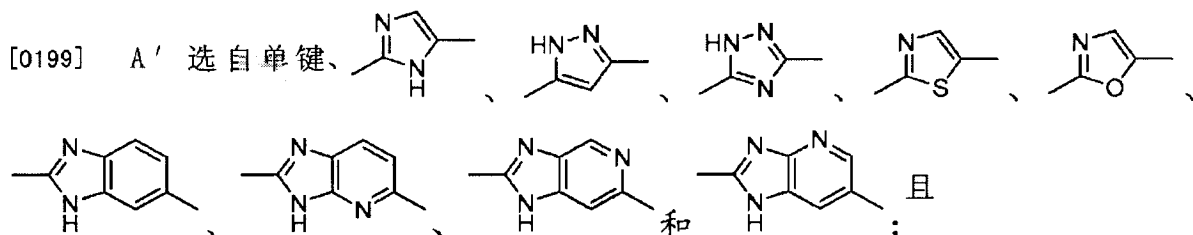
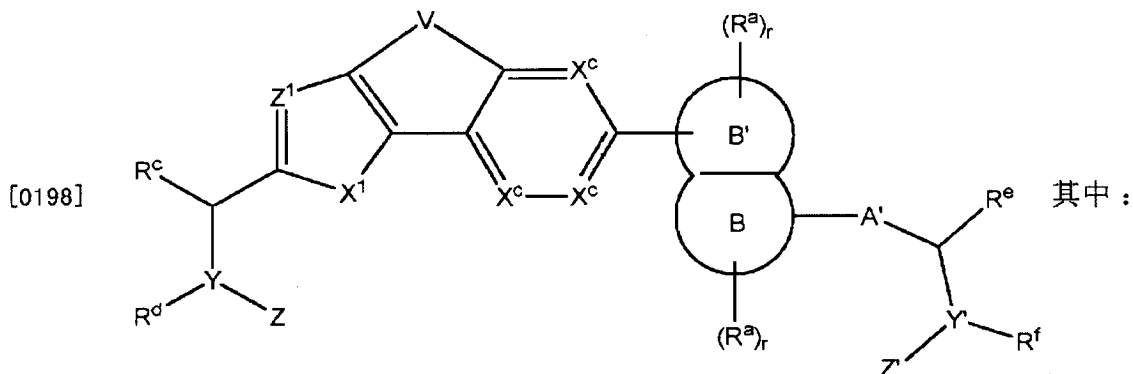


X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磷酰基。

[0196] 在第四方面的第三实施方案中, 化合物如式 IVa 所示, 其中 A' 为

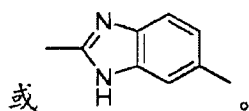


[0197] 在本发明的第五方面, 化合物如式 V 所示:



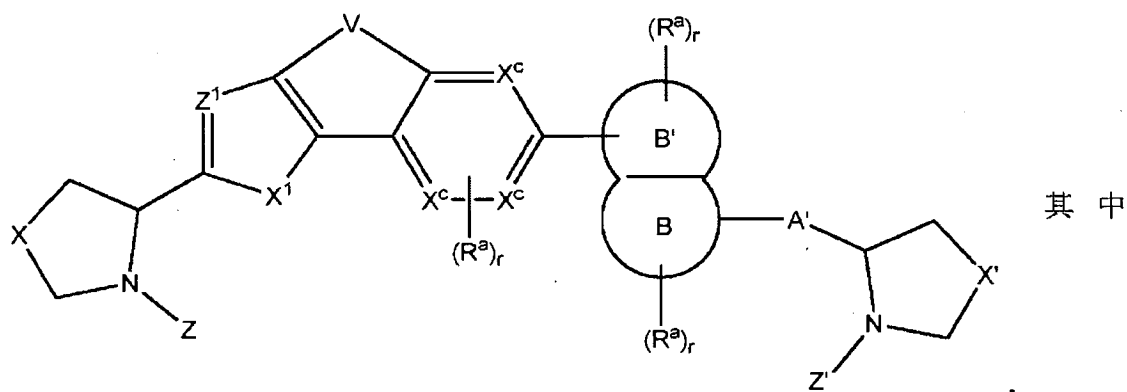
[0200] 各 X^c 独立地为 C 或 N, 前提是不超过两个 X^c 为 N。

[0201] 在第五方面的第一实施方案中, 化合物如式 V 所示, 其中 A' 为 、、



[0202] 在第五方面的第二实施方案中, 化合物如式 Va 所示:

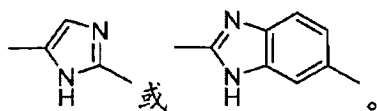
[0203]



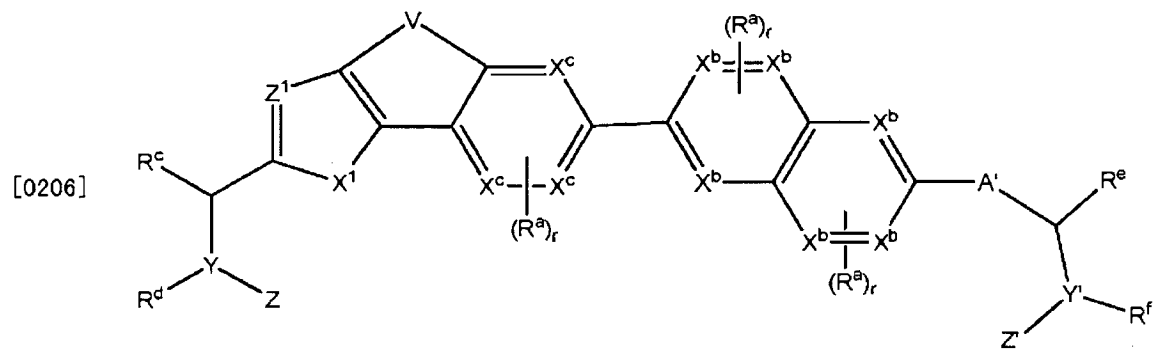
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代

的磺酰基。

[0204] 在第五方面的第三实施方案中, 化合物如式 Va 所示, 其中 A' 为

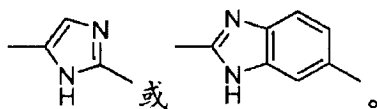


[0205] 在第五方面的第四实施方案中, 化合物如式 Vb 所示:

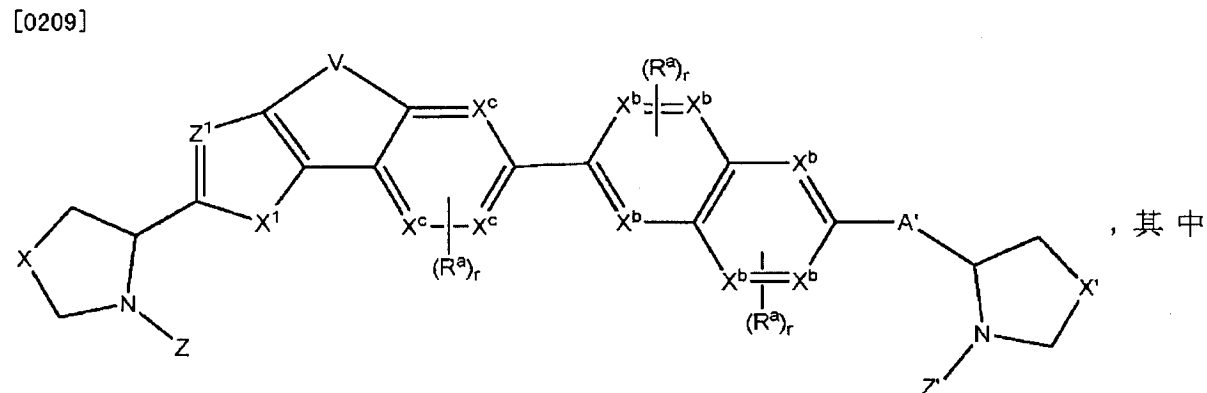


其中各 X^b 独立地为 C 或 N。

[0207] 在第五方面的第五实施方案中化合物如式 Vb 所示其中 A' 为

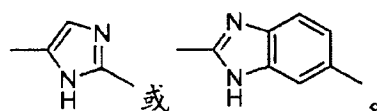


[0208] 在第五方面的第六实施方案中, 化合物如式 Vc 所示:



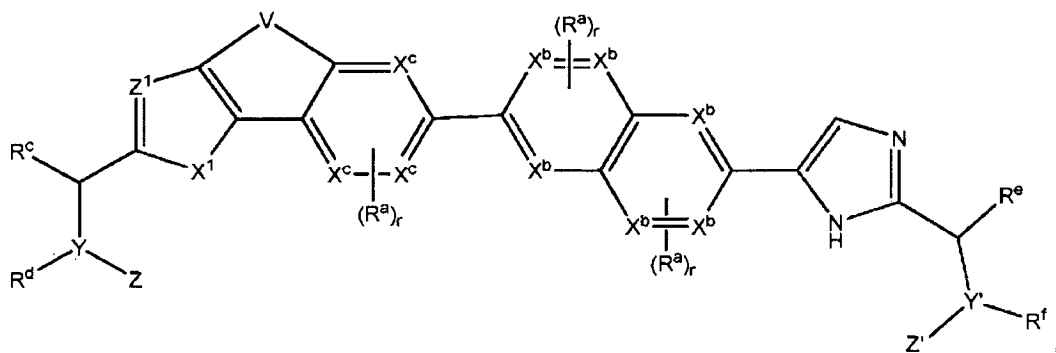
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨基甲酰基和取代的磺酰基。

[0210] 在第五方面的第七实施方案中, 化合物如式 Vc 所示, 其中 A' 为

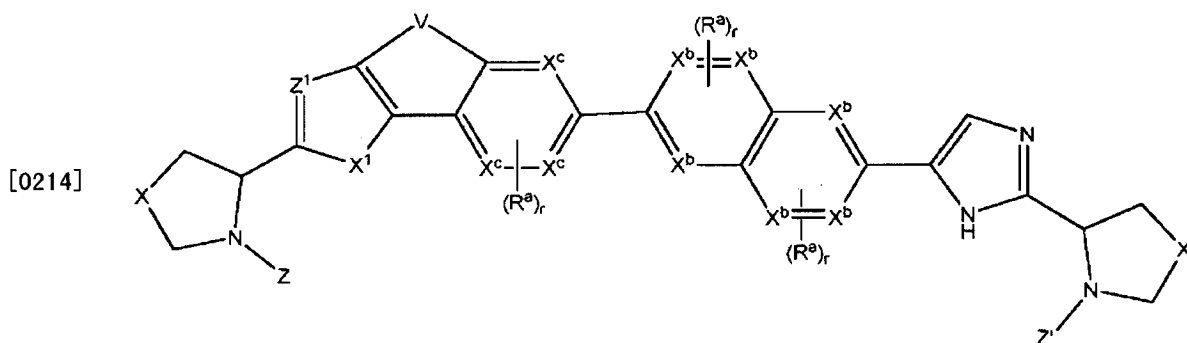


[0211] 在第五方面的第八实施方案中, 化合物如式 Vd 所示:

[0212]



[0213] 在第五方面的第九实施方案中,化合物如式 Ve 所示:



,其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0215] 在本发明的第六方面,在第二方面至第五方面任一者的任何化合物中, R^c 、 R^d 、 R^e 和 R^f 各自独立地选自:氢、 C_1 至 C_8 烷基和 C_1 至 C_8 杂烷基,其中

[0216] 各杂原子在存在时独立地为 N、O 或 S,

[0217] R^e 与 R^d 任选地连接形成 4 至 8 元杂环,该杂环任选地与另一个 3 至 6 元杂环稠合,且

[0218] R^e 与 R^f 任选地连接形成 4 至 8 元杂环,该杂环任选地与另一个 3 至 6 元杂环稠合。

[0219] 在第六方面的第一实施方案中, R^e 与 R^d 或 R^e 与 R^f 连接形成 4 至 8 元杂环,该杂环任选地与另一个 3 至 6 元杂环稠合。

[0220] 在第六方面的第二实施方案中, R^e 与 R^d 以及 R^e 与 R^f 都连接形成 4 至 8 元杂环,该杂环任选地与另一个 3 至 6 元杂环稠合。

[0221] 在本发明的第七方面,如果本发明的任一其它方面中存在 R^a ,则各 R^a 独立地为 $-\text{CN}$ 、 $-\text{OCHF}_2$ 、 $-\text{OCF}_3$ 、 $-\text{CF}_3$ 或 $-\text{F}$ 。

[0222] 在本发明的第八方面,如果存在于任一其它方面的任何化合物中,则 Y 和 Y' 之一为 N。

[0223] 在第八方面的第一实施方案中,Y 和 Y' 均为 N。

[0224] 在本发明的第九方面,任何前述方面中的 Z 和 Z' 各为 1-3 个氨基酸。

[0225] 在第九方面的第一实施方案中,氨基酸呈 D 构型。

[0226] 在本发明的第十方面,任何前述方面中的 Z 和 Z' 各自独立地选自 $-\text{[U-(CR}^4_2\text{)]}$

$t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 、 $-\text{U} - (\text{CR}^4_2)_t - \text{R}^8$ 和 $-[\text{U} - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{U} - (\text{CR}^4_2)_t - \text{O} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0227] 在第十方面的第一实施方案中, Z 和 Z' 均为 $-\text{U} - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0228] 在第十方面的第二实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t - \text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0229] 在第十方面的第三实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0230] 在第十方面的第四实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0231] 在第十方面的第五实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t - \text{U} - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0232] 在第十方面的第六实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0233] 在第十方面的第七实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t - \text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0234] 在第十方面的第八实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^7 - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0235] 在第十方面的第九实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_n - \text{NR}^7 - (\text{CR}^4_2)_n - \text{C}(\text{O}) - \text{R}^{81}$ 。

[0236] 在第十方面的第十实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_n - \text{NR}^7 - \text{C}(\text{O}) - \text{R}^{81}$ 。

[0237] 在第十方面的第十一实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_n - \text{NR}^7 - (\text{CR}^4_2)_n - \text{C}(\text{O}) - \text{O} - \text{R}^{81}$ 。

[0238] 在第十方面的第十二实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_n - \text{NR}^7 - \text{C}(\text{O}) - \text{O} - \text{R}^{81}$ 。

[0239] 在第十方面的第十三实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0240] 在第十方面的第十四实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0241] 在第十方面的第十五实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t]_u - \text{U} - (\text{CR}^4_2)_t - \text{O} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0242] 在第十方面的第十六实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t - \text{U} - (\text{CR}^4_2)_t - \text{O} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0243] 在第十方面的第十七实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{NR}^5 - (\text{CR}^4_2)_t - \text{C}(\text{O}) - (\text{CR}^4_2)_t - \text{O} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0244] 在第十方面的第十八实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U} - (\text{CR}^4_2)_t - \text{O} - (\text{CR}^4_2)_t - \text{R}^8$ 。

[0245] 本发明的第十一方面提供了包含本发明化合物的药物组合物。

[0246] 本发明的第十二方面提供了本发明化合物在制备药物方面的用途。

[0247] 在第十二方面的第一实施方案中,所述药物用于治疗丙型肝炎。

[0248] 本发明的第十三方面提供了治疗丙型肝炎的方法,包括对有需要的受试者施用治疗有效量的任一种本发明的化合物。

[0249] 发明详述

[0250] 除非另外指明,本申请(包括说明书和权利要求书)中所用的下列术语具有下文给出的定义。必须指出的是,除非上下文另外明确规定,否则如本说明书及所附权利要求中所用,单数形式“一”和“所述”包括复数个指示物。可在参考著作中发现标准化学术语的定义,包括 Carey 和 Sundberg(2007) “Advanced Organic Chemistry 第 5 版”卷 A 和卷 B, Springer Science+Business Media LLC, New York。除非另外指明,否则本发明的实施将采用合成有机化学、质谱分析、制备性及分析性色谱法、蛋白质化学、生物化学、重组 DNA 技术以及药理学的常规方法。

[0251] 如本文所用,术语“烷酰基”涵盖以低级烷基作为取代基的羰基。

[0252] 如本文所用,术语“烯基”涵盖取代或未取代的含 2 至 8 个碳原子的直链和支链烯烃基,包括 E 和 Z 两种形式。烯基可任选地由选自以下的一种或多种取代基取代:卤素、-CN、-NO₂、CO₂R、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、SO₂R、-SO₃R、-S(O)₂N(R^N)₂、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

[0253] 如本文所用,术语“烷氧基”涵盖以低级烷基为取代基的氧,包括甲氧基、乙氧基、丁氧基、三氟甲氧基等。其还包括连接至两个单独氧原子的二价取代基,例如但不限于 -O-(CH₂)₁₋₄-O-、-O-CF₂-O-、-O-(CH₂)₁₋₄-O-(CH₂CH₂-O)₁₋₄- 和 -(O-CH₂CH₂-O)₁₋₄-。

[0254] 如本文所用,术语“烷氧羰基”涵盖以烷氧基为取代基的羰基。

[0255] 如本文所用,术语“烷基”涵盖取代或未取代的含 1 至 15 个碳原子的直链和支链烷基。如本文所用,术语“低级烷基”涵盖含 1 至 6 个碳原子的直链和支链烷基,包括甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基等。烷基可任选地由选自以下的一种或多种取代基取代:卤素、-CN、-NO₂、-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、-SO₂R、-SO₃R、-S(O)₂N(R^N)₂、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

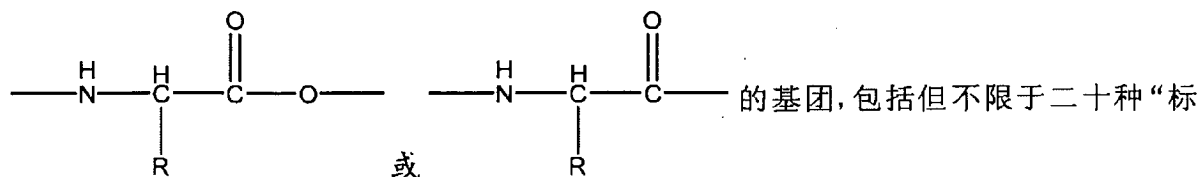
[0256] 如本文所用,术语“亚烷基”、“亚烯基”和“亚炔基”分别指二价(即,附接两个原子)时的“烷基”、“烯基”和“炔基”。

[0257] 如本文所用,术语“烷基磺酰基”涵盖以低级烷基作为取代基的磺酰基。

[0258] 如本文所用,术语“炔基”涵盖取代或未取代的含 2 至 8 个碳原子且具有至少一个碳-碳三键的直链或支链碳链。术语炔基包括例如乙炔基、1-丙炔基、2-丙炔基、1-丁炔基、3-甲基-1-丁炔基等。炔基可任选地由选自以下的一种或多种取代基取代:卤基、-CN、NO₂、CO₂R、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、-SO₂R、-SO₃R、-S(O)₂N(R^N)₂、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

[0259] 如本文所用,术语“氨基”涵盖结构为 -NR^N₂ 的基团。

[0260] 如本文所用,术语“氨基酸”涵盖呈 D 或 L 构型的结构为



的基团,包括但不限于二十种“标准”氨基酸:异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、苯丙氨酸、苏氨酸、色氨酸、缬氨酸、丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸和组氨酸。本发明还包括但不限于D构型氨基酸、β氨基酸、具有侧链的氨基酸以及本领域的技术人员所熟知的所有非天然氨基酸。

[0261] 如本文所用,术语“芳烷基”涵盖以芳族基团为取代基的低级烷基,所述芳族基团可被取代或不被取代。芳烷基可任选地由选自以下的一种或多种取代基取代:卤素、-CN、-NO₂、-CO₂R、-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、-SO₂R、-SO₃R、-S(O)₂N(R^N)₂、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

[0262] 如本文所用,术语“芳基”、“芳族基团”或“芳族环”涵盖取代或未取代的单环和多芳族基团(例如,苯基、吡啶基和吡唑基等)以及多环体系(萘基和喹啉基等)。多环可具有两个或更多个环,其中两个邻接环共用两个原子(这些环经过“稠合”),其中例如至少一个环为芳族的,其它环可为环烷基、环烯基、芳基、杂环基和/或杂芳基。芳基可任选地由选自以下的一种或多种取代基取代:卤素、烷基、-CN、-NO₂、-CO₂R、-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、-SO₂R、-SO₃R、-S(O)₂N(R^N)₂、-SiR₃、-P(O)R、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

[0263] 如本文所用,术语“芳基磺酰基”涵盖以芳基为取代基的磺酰基。该术语意欲包括但不限于单价及多价芳基(例如二价芳基)。

[0264] 如本文所用,术语“氨甲酰基”涵盖结构为 $\text{---}\overset{\text{O}}{\parallel}{\text{C}}\text{---NR}^{\text{N}}_2$ 的基团。

[0265] 如本文所用,术语“羰基”涵盖结构为 $\text{---}\overset{\text{O}}{\parallel}{\text{C}}\text{---}$ 的基团。

[0266] 如本文所用,术语“羧基”涵盖结构为 $\text{---}\overset{\text{O}}{\parallel}{\text{C}}\text{---O---}$ 的基团。

[0267] 如本文所用,术语“环烷基”涵盖取代或未取代的含3至12个碳原子的环烷基,包括环丙基、环戊基、环己基等。术语“环烷基”还包括具有两个环的多环体系,其中两个邻接环共用两个或更多个原子(这些环经过“稠合”)。环烷基可任选地由选自以下的一种或多种取代基取代:卤基、-CN、-NO₂、-CO₂R、-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、-SO₂R、-S(O)₂N(R^N)₂、磷酸酯、膦酸酯、烷基、环烯基、芳基和杂芳基。

[0268] 如本文所用,术语“环烯基”涵盖取代或未取代的含4至12个碳原子的环烯基,其中在两个环碳之间存在至少一个双键,包括环戊烯基、环己烯基等。术语“环烯基”还包括具有两个环的多环体系,其中两个邻接环共用两个或更多个原子(这些环经过“稠

合”)。环烯基可任选地由选自以下的一种或多种取代基取代:卤基、 $-\text{CN}$ 、 $-\text{NO}_2$ 、 $-\text{CO}_2\text{R}$ 、 $-\text{C}(\text{O})\text{R}$ 、 $-\text{O}-\text{R}$ 、 $-\text{N}(\text{R}^N)_2$ 、 $-\text{N}(\text{R}^N)\text{C}(\text{O})\text{R}$ 、 $-\text{N}(\text{R}^N)\text{S}(\text{O})_2\text{R}$ 、 $-\text{SR}$ 、 $-\text{C}(\text{O})\text{N}(\text{R}^N)_2$ 、 $-\text{OC}(\text{O})\text{R}$ 、 $-\text{OC}(\text{O})\text{N}(\text{R}^N)_2$ 、 $-\text{SOR}$ 、 $-\text{SO}_2\text{R}$ 、 $-\text{S}(\text{O})_2\text{N}(\text{R}^N)_2$ 、磷酸酯、膦酸酯、烷基、环烯基、芳基和杂芳基。

[0269] 如本文所用,术语“卤代”或“卤素”包括氟、氯、溴和碘。

[0270] 如本文所用,术语“杂烷基”涵盖具有一个或多个杂原子的烷基。

[0271] 术语“杂原子”(特别是环系内的)是指N、O和S。

[0272] 如本文所用,术语“杂环基”或“杂环”涵盖取代或未取代的芳族和非芳族环状基团,其具有至少一个作为环成员的杂原子。优选的杂环基含5或6个环原子,所述环原子包括至少一个杂原子,所述杂环基包括:环胺(如吗啉基、哌啶基、吡咯烷基等)和环醚(如四氢呋喃、四氢吡喃等)。芳族杂环基也称为“杂芳基”基团,其涵盖可包括1至3个杂原子的单环杂芳族基团,例如吡咯、呋喃、噻吩、咪唑、噁唑、噻唑、三唑、吡唑、噁二唑、噻二唑、吡啶、吡嗪、哒嗪、嘧啶等。术语杂芳基还包括具有两个或更多个环的多环杂芳族体系,其中两个邻接环共用两个或更多个原子(这些环经过“稠合”),其中至少一个环为杂芳基,例如其它环可为环烷基、环烯基、芳基、杂环基和/或杂芳基。多环杂芳族体系的实例包括喹啉、异喹啉、噌啉、四氢异喹啉、喹啶、喹唑啉、苯并咪唑、苯并呋喃、苯并噻吩、苯并噁唑、苯并噻唑、吲唑、嘌呤、苯并三唑、吡咯并吡啶、吡唑并吡啶等。杂环基可任选地由选自以下的一种或多种取代基取代:卤基、烷基、 $-\text{CN}$ 、 $-\text{NO}_2$ 、 $-\text{CO}_2\text{R}$ 、 $-\text{C}(\text{O})\text{R}$ 、 $-\text{O}-\text{R}$ 、 $-\text{N}(\text{R}^N)_2$ 、 $-\text{N}(\text{R}^N)\text{C}(\text{O})\text{R}$ 、 $-\text{N}(\text{R}^N)\text{S}(\text{O})_2\text{R}$ 、 $-\text{SR}$ 、 $-\text{C}(\text{O})\text{N}(\text{R}^N)_2$ 、 $-\text{OC}(\text{O})\text{R}$ 、 $-\text{OC}(\text{O})\text{N}(\text{R}^N)_2$ 、 $-\text{SOR}$ 、 $-\text{SO}_2\text{R}$ 、 $-\text{SO}_3\text{R}$ 、 $-\text{S}(\text{O})_2\text{N}(\text{R}^N)_2$ 、 $-\text{SiR}_3$ 、 $-\text{P}(\text{O})\text{R}$ 、磷酸酯、膦酸酯、环烷基、环烯基、芳基和杂芳基。

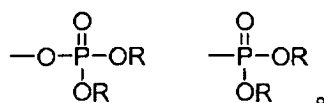
[0273] 如本文所用,术语“氧代基”涵盖用双键连接的氧原子。

[0274] 所谓“药学上可接受”或“药理学上可接受”是指未在生物学或其它方面不合需要的物质,即,可对个体施用该物质而不引起任何不利的生物效应或不会与含有其的组合物的任何组分以有害方式进行相互作用。

[0275] “药学上可接受的盐”是指本发明的化合物的盐,其由本领域中所理解的一般可接受用于药物用途的抗衡离子制成,并具有所需的母体化合物药理活性。此类盐包括:(1)与无机酸(如盐酸、氢溴酸、硫酸、硝酸、磷酸等)形成的酸加成盐;或与有机酸(如乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、酒石酸、柠檬酸、苯甲酸、3-(4-羟基苯甲酰基)苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1,2-乙烷-二磺酸、2-羟基乙磺酸、苯磺酸、4-氯苯磺酸、2-萘磺酸、4-甲苯磺酸、樟脑磺酸、4-甲基双环[2.2.2]-辛-2-烯-1-羧酸、葡庚糖酸、3-苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡萄糖酸、谷氨酸、羟萘甲酸、水杨酸、硬脂酸、粘康酸等;)形成的酸加成盐;或(2)母体化合物中存在的酸性质子由金属离子(例如碱金属离子、碱土金属离子或铝离子)置换;或与有机碱(如乙醇胺、二乙醇胺、三乙醇胺、N-甲基葡萄糖胺、吗啉、哌啶、二甲胺、二乙胺等)配价时所形成的盐。还包括氨基酸的盐(如精氨酸盐等)以及有机酸(如葡萄糖醛酸或半乳糖醛酸等)的盐(见例如Berge等,1977, J. Pharm. Sci. 66:1-19)。

[0276] 如本文所用,术语“磷酸酯”和“膦酸酯”分别指具有下列结构的部分:

[0277]



[0278] 术语“盐”和“水合物”是指将有利地影响化合物的物理和药代动力学性质（如溶解度、可口性、吸收、分布、代谢和排泄）的化合物的水合形式。本领域的技术人员在选择时可考虑的实际上更实用的其它因素，包括所得原料药的原材料成本、结晶容易度、收率、稳定性、溶解度、吸湿性、流动性和可制造性。

[0279] 如本文所用，术语磺酰胺基涵盖具有结构 $\text{—S(=O)}_2\text{—NR}^N_2$ 的基团。

[0280] 如本文所用，术语“磺酸酯基”涵盖具有结构 $\text{—S(=O)}_2\text{—OR}^s$ 的基团，其中 R^s 选自氢、 $\text{C}_1\text{—C}_{10}$ 烷基、 $\text{C}_2\text{—C}_{10}$ 烯基、 $\text{C}_2\text{—C}_{10}$ 炔基、 $\text{C}_1\text{—C}_{10}$ 烷酰基或 $\text{C}_1\text{—C}_{10}$ 烷氧羰基。

[0281] 如本文所用，术语“磺酰基”涵盖具有结构 $\text{—S(=O)}_2\text{—}$ 的基团。

[0282] 如本文所用，“取代的磺酰基”涵盖具有结构 $\text{—S(=O)}_2\text{—R}$ 的基团，包括但不限于烷

基磺酰基和芳基磺酰基。

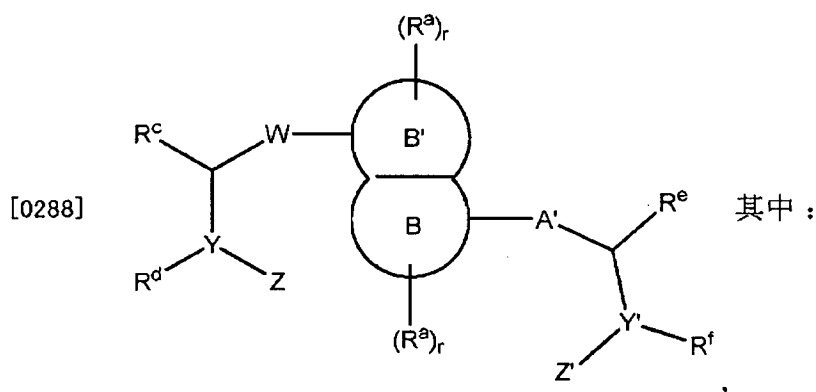
[0283] 如本文所用，术语“硫羰基”是指其中氧原子已经被硫置换的羰基。

[0284] 各 R 独立地选自氢、 $-\text{OH}$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、烯基、炔基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基、氨基和氧代基。

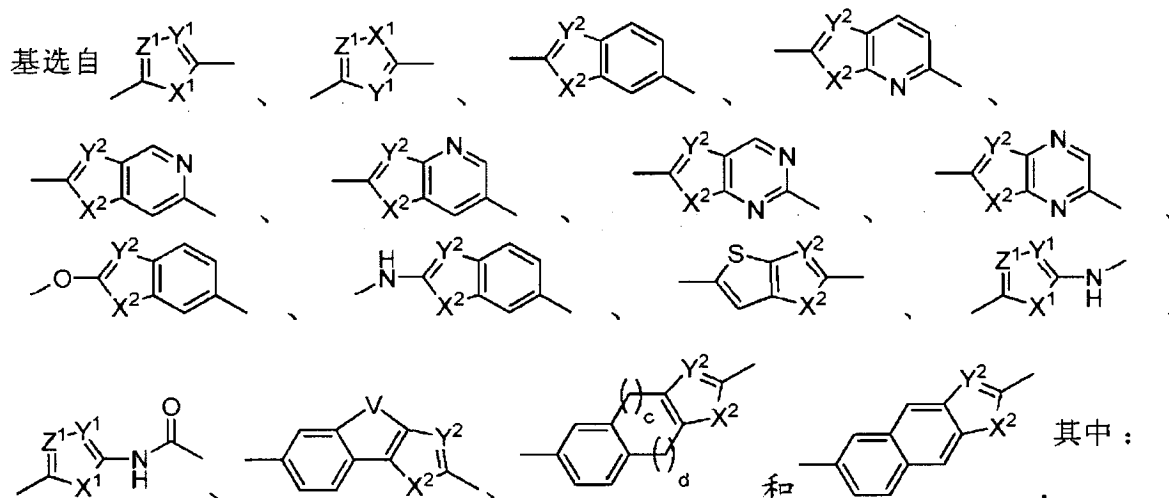
[0285] 各 R^N 独立地选自氢、 $-\text{OH}$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、烯基、炔基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。两个 RN 可与其所附接的 C 、 O 、 N 或 S 一起形成 5 至 7 元环，该环可任选地含另外的杂原子。

[0286] 本发明的化合物可用于抑制或降低 HCV 的活性，特别是 HCV 的 NS5A 蛋白的活性。在这些情况下，NS5A 蛋白活性的抑制和降低是指相对于细胞或受试者未经试验化合物处理的对照实验而言所测得的活性程度较低。在特定的方面中，所测活性的抑制或降低为至少 10% 的降低或抑制。本领域的技术人员将理解，将所测活性降低或抑制至少 20%、50%、75%、90% 或 100% 或其任何数值对于特定应用而言可是优选的。

[0287] 在第一方面, 提供了式 I 化合物:



[0289] A' 选自单键、 $-(CR_2)_n-C(O)-(CR_2)_p-$ 、 $-(CR_2)_n-O-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-S(O)_k-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-C(O)-O-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-S(O)_k-N(R^N)-(CR_2)_p-$ 和 $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ 以及杂芳基, 该杂芳基



[0290] X^1 为 CH_2 、NH、O 或 S,

[0291] Y^1 、 Y^2 和 Z^1 各自独立地为 CH 或 N,

[0292] X^2 为 NH、O 或 S,

[0293] V 为 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-N=CH-$ 、 $(CH_2)_a-N(R^N)-(CH_2)_b-$ 或 $-(CH_2)_a-O-(CH_2)_b-$, 其中 a 和 b 独立地为 0、1、2 或 3, 前提是 a 和 b 不均为 0,

[0294] 任选地在苯基残基上包括 1 个或 2 个氮作为杂原子,

[0295] 杂芳基的碳任选各自独立地由选自以下的取代基取代: 卤素、 $-OH$ 、 $-CN$ 、 $-NO_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基,

[0296] 杂芳基的氮在存在时任选各自独立地由选自以下的取代基取代: $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲

酰基、取代的磺酰基、磺酸酯基和磺酰胺基，

[0297] a 和 b 独立地为 1、2 或 3，

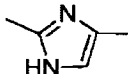
[0298] c 和 d 独立地为 1 或 2，

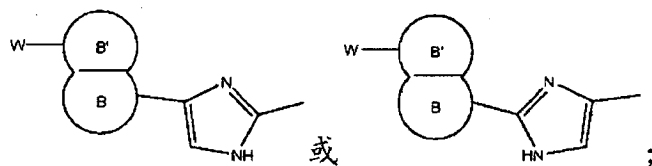
[0299] n 和 p 独立地为 0、1、2 或 3，

[0300] k 为 0、1 或 2，

[0301] 各 R 独立地选自氢、卤素、-OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基，

[0302] 各 R^N 独立地选自氢、-OH、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基，且

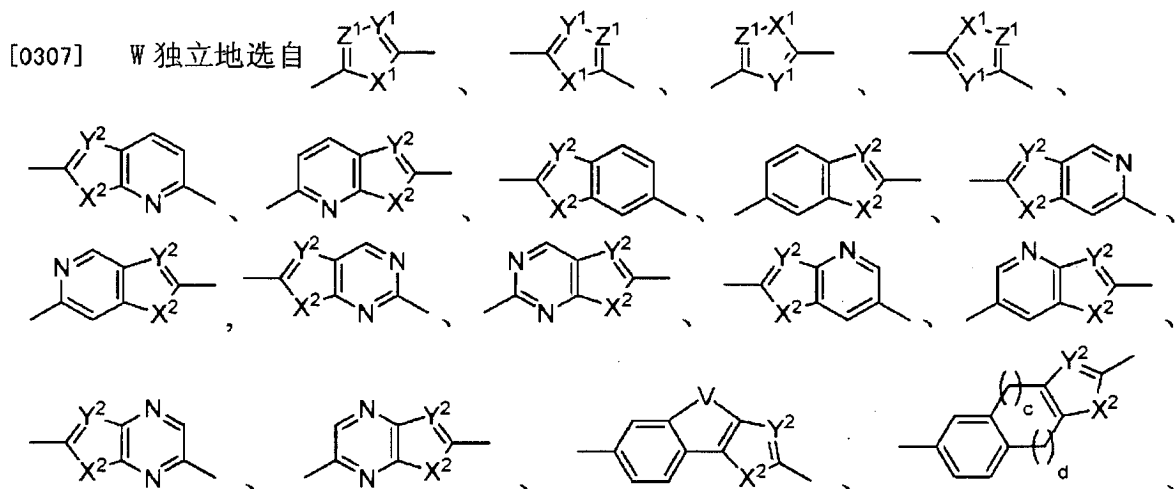
[0303] 其中 B 可附接到 A' 的任一侧上，使得在 A' 为  的实例中，W-B-A' 可为

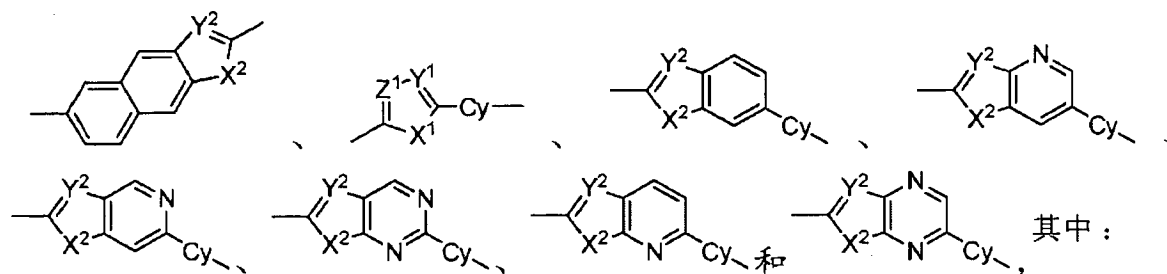


[0304] B 和 B' 各自独立地为 4 至 8 元环，所述环是芳基、杂芳基、环烷基或杂环基，其中各杂原子在存在时独立地为 N、O 或 S，且其中 B 或 B' 中的至少一者为芳族的；

[0305] 各 R^a 独立地选自 -OH、-CN、-NO₂、卤素、C₁ 至 C₁₂ 烷基、C₁ 至 C₁₂ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；如果 B 或 B' 不为芳族的，则其也可由一个或多个氧代基取代；

[0306] 各 r 独立地为 0、1、2 或 3；



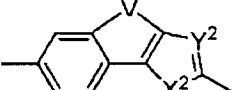


[0308] X^1 为 CH_2 、 NH 、 O 或 S ，

[0309] Y^1 、 Y^2 和 Z^1 各自独立地为 CH 或 N ，

[0310] X^2 为 NH 、 O 或 S ，

[0311] V 为 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-N=CH-$ 、 $(CH_2)_a-N(R^N)-(CH_2)_b-$ 或 $-(CH_2)_a-O-(CH_2)_b-$ ，其中 a 和 b 独立地为 0 、 1 、 2 或 3 ，前提是 a 和 b 不均为 0 ，

[0312]  任选地在苯基残基上包括 1 个或 2 个氮作为杂原子，

[0313] W 任选地由选自以下的一个或多个取代基取代： $-OH$ 、 $-CN$ 、 $-NO_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基，

[0314] W 和环 B' 可通过 B' 上的碳或氮原子连接，且

[0315] Cy 为单环、双环或三环 5 至 12 元环烷基、杂环基、芳基或杂芳基，其中最多三个杂原子独立地为 N 、 S 或 O ，且其任选地由选自以下的一个或多个取代基所取代： $-OH$ 、 $-CN$ 、 $-NO_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；

[0316] 各 R^c 、 R^d 、 R^e 和 R^f 独立地选自：氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、芳烷基和可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环，其中

[0317] 各杂原子在存在时独立地为 N 、 O 或 S ，

[0318] R^c 、 R^d 、 R^e 和 R^f 中的每一者可任选地由 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、芳烷基或可为环烷基、杂环基、杂芳基或芳基的 4 至 8 元环取代，且其中各杂原子在存在时独立地为 N 、 O 或 S ，

[0319] R^c 与 R^d 任选地连接形成 4 至 8 元杂环，该杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合；且

[0320] R^e 与 R^f 任选地连接形成 4 至 8 元杂环，该杂环任选地与另一个 3 至 5 元杂环或杂芳基环稠合；

[0321] Y 和 Y' 各自独立地为碳或氮；且

[0322] Z 和 Z' 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、 $1-3$ 个氨基酸、 $-[U-(CR^4)_t-NR^5-C(R^4)_t]_u-U-(CR^4)_t-NR^7-(CR^4)_t-R^8$ 、 $-U-(CR^4)_t-R^8$ 和 $-[U-(CR^4)_t-NR^5-(CR^4)_t]_u-U-(CR^4)_t-O-(CR^4)_t-R^8$ ，其中

[0323] U 选自 $-C(O)-$ 、 $-C(S)-$ 和 $-S(O)_2-$ ，

[0324] 各 R^4 、 R^5 和 R^7 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、

杂芳基和芳烷基,

[0325] R^8 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、 $-C(O)-R^{81}$ 、 $-C(S)-R^{81}$ 、 $-C(O)-O-R^{81}$ 、 $-C(O)-N-R^{81}_2$ 、 $-S(O)_2-R^{81}$ 和 $-S(O)_2-N-R^{81}_2$, 其中各 R^{81} 独立地选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基和芳烷基,

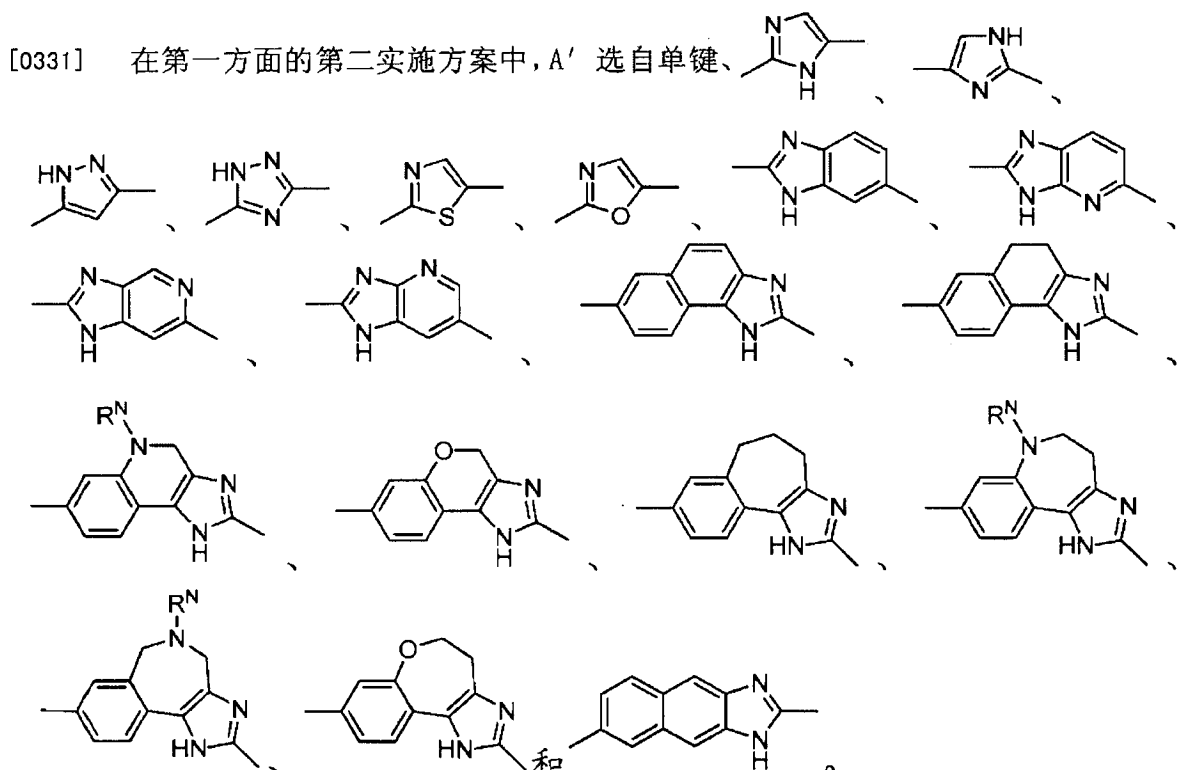
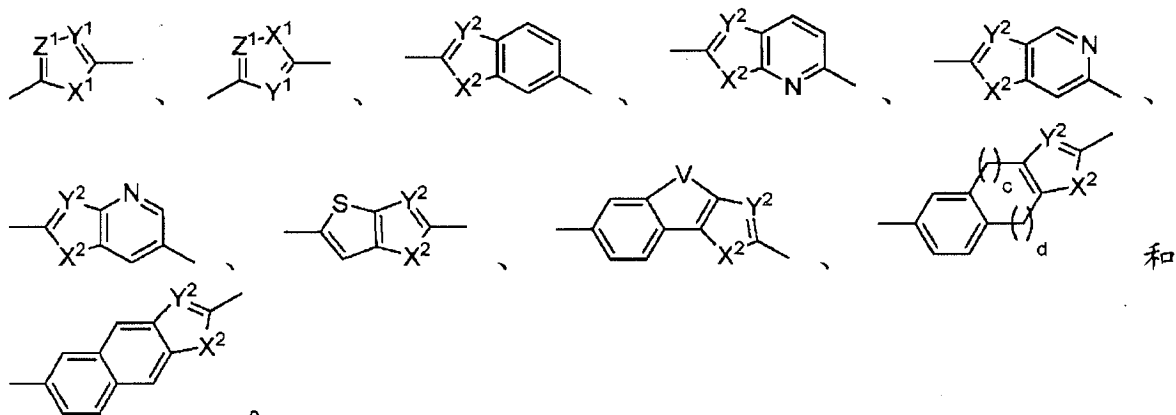
[0326] 任选地, R^7 和 R^8 一起形成 4 至 7 元环,

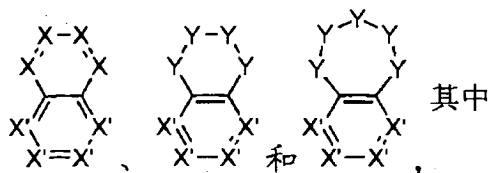
[0327] 各 t 独立地为 0、1、2、3 或 4, 且

[0328] u 为 0、1 或 2。

[0329] 本发明的化合物包括 I 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0330] 在第一方面的第一实施方案中, A' 选自单键、 $-(CR_2)_n-O-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-C(O)-N(R^N)-(CR_2)_p-$ 、 $-(CR_2)_n-N(R^N)-C(O)-N(R^N)-(CR_2)_p-$ 和 $-(CR_2)_n-N(R^N)-C(O)-O-(CR_2)_p-$ 和杂芳基, 该杂芳基选自





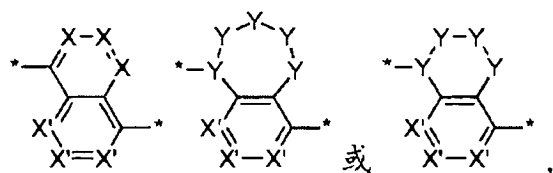
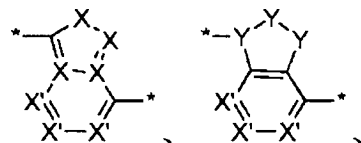
[0340] 各 X 独立地为 N 或 C, 且如果为 C, 则在必要时可包括氢以形成完整的价电子层;

[0341] 各 X' 独立地为 -N- 或 -CH-, 前提是不超过两个 X' 为 -N-;

[0342] 各 Y 独立地选自 -CH₂-, -NH-, -O-, -S-, -C(O)₂- 或 -S(O)₁₋₂-; 且

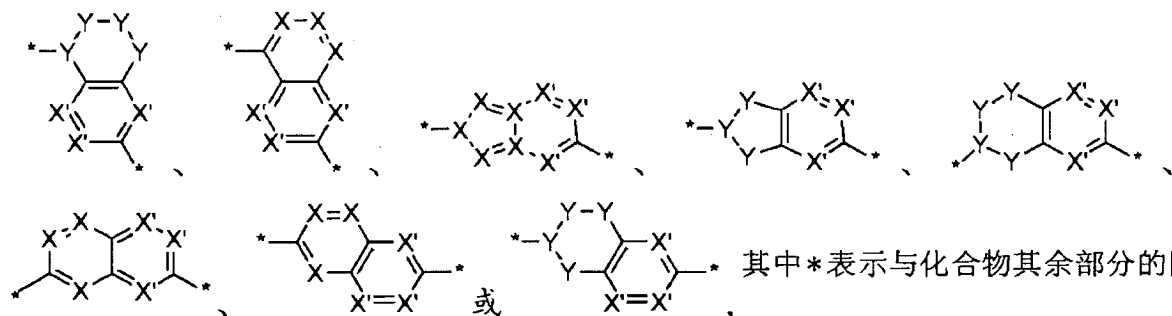
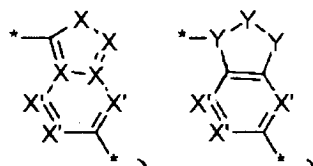
[0343] B 和 B' 在分子上的任何可用附接点处与化合物其余部分附接。

[0344] 在第一方面的第八实施方案中, B 和 B' 一起为



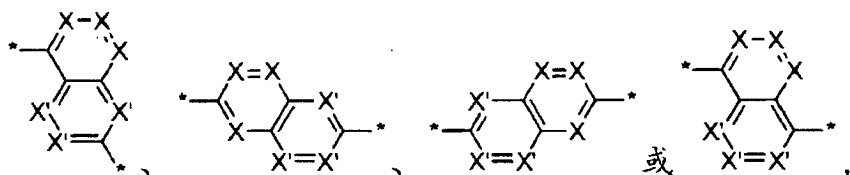
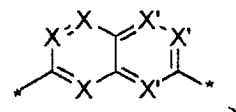
其中 * 表示与化合物其余部分的附接点。

[0345] 在第一方面的第九实施方案中, B 和 B' 一起为



接点。

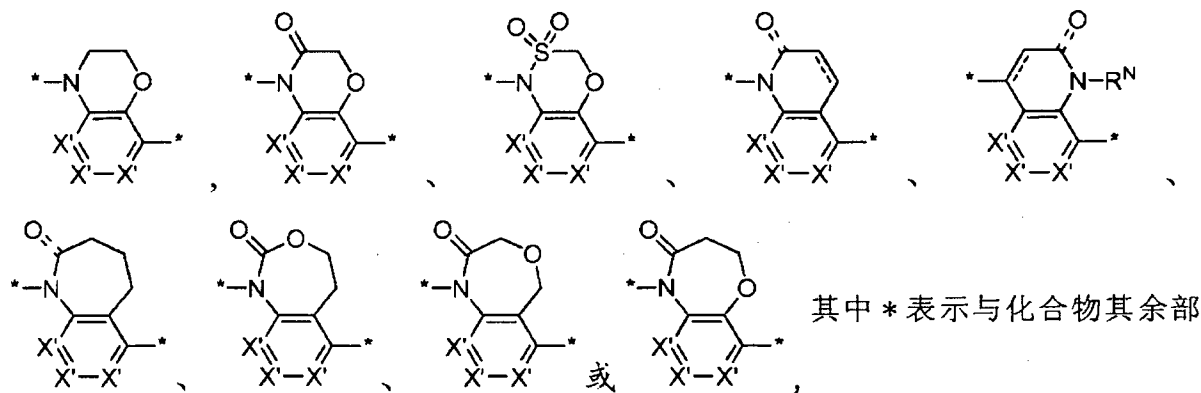
[0346] 在第一方面的第十实施方案中, B 和 B' 一起为



其中 * 表示与化合物其余

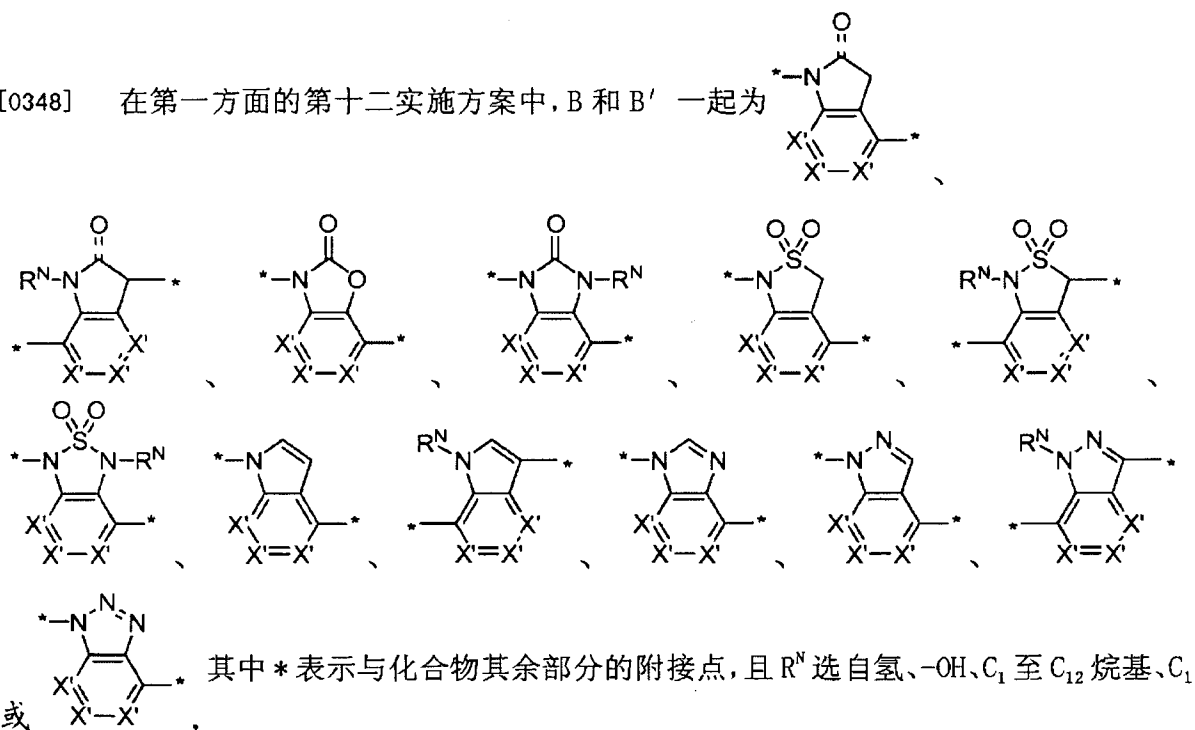
部分的附接点, 其中不超过 2 个 X 为氮。

[0347] 在第一方面的第十一实施方案中, B 和 B' 一起为

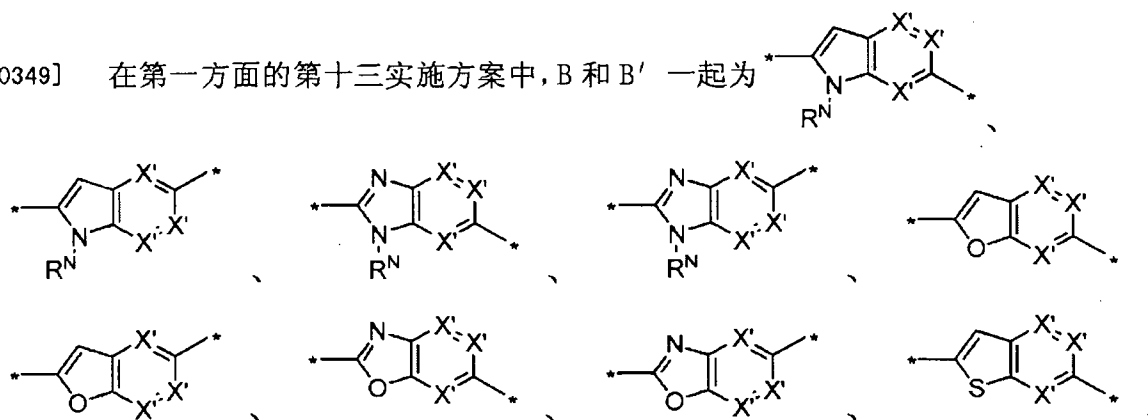


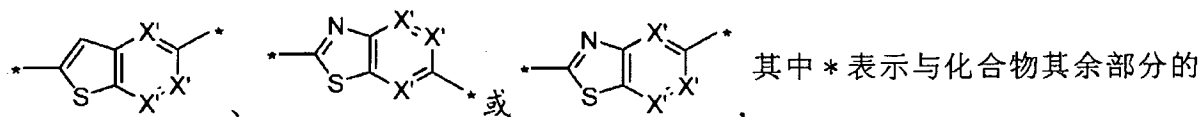
分的附接点, 且 R^N 选自氢、-OH、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

[0348] 在第一方面的第十二实施方案中, B 和 B' 一起为



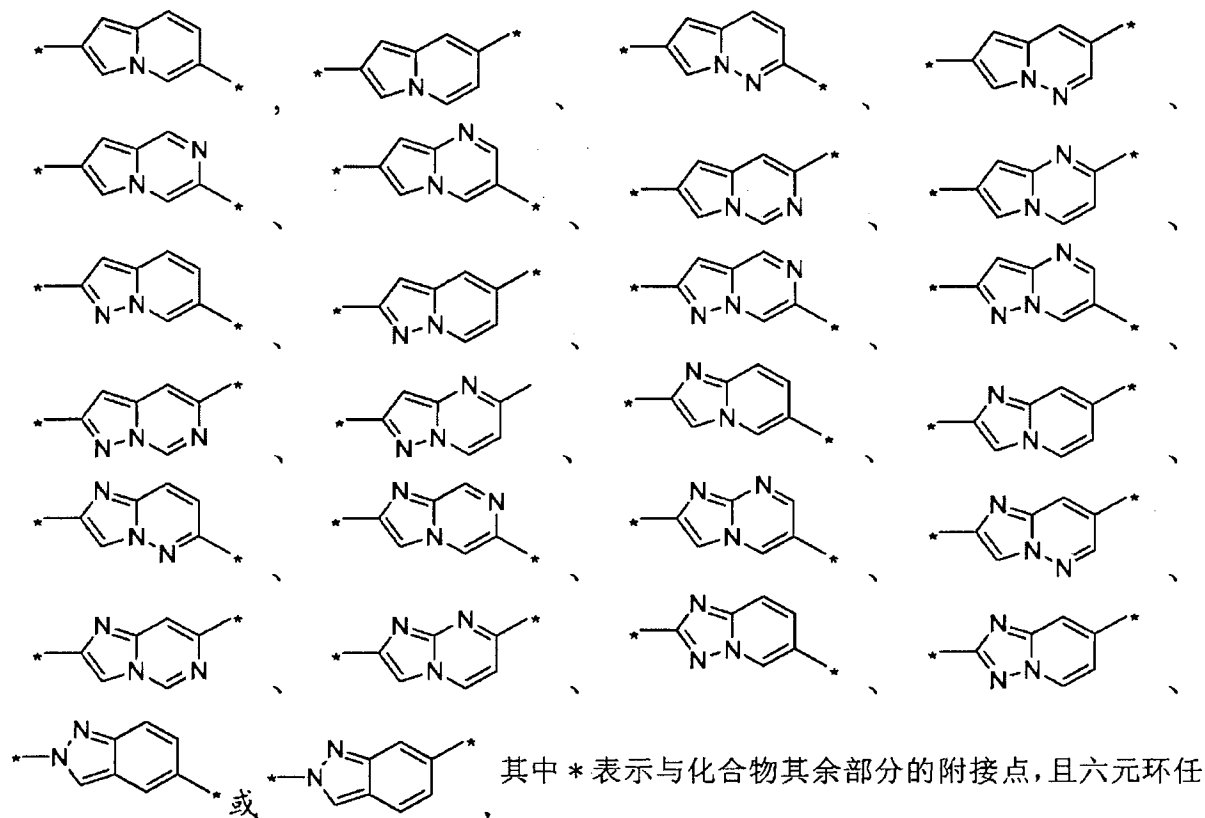
[0349] 在第一方面的第十三实施方案中, B 和 B' 一起为





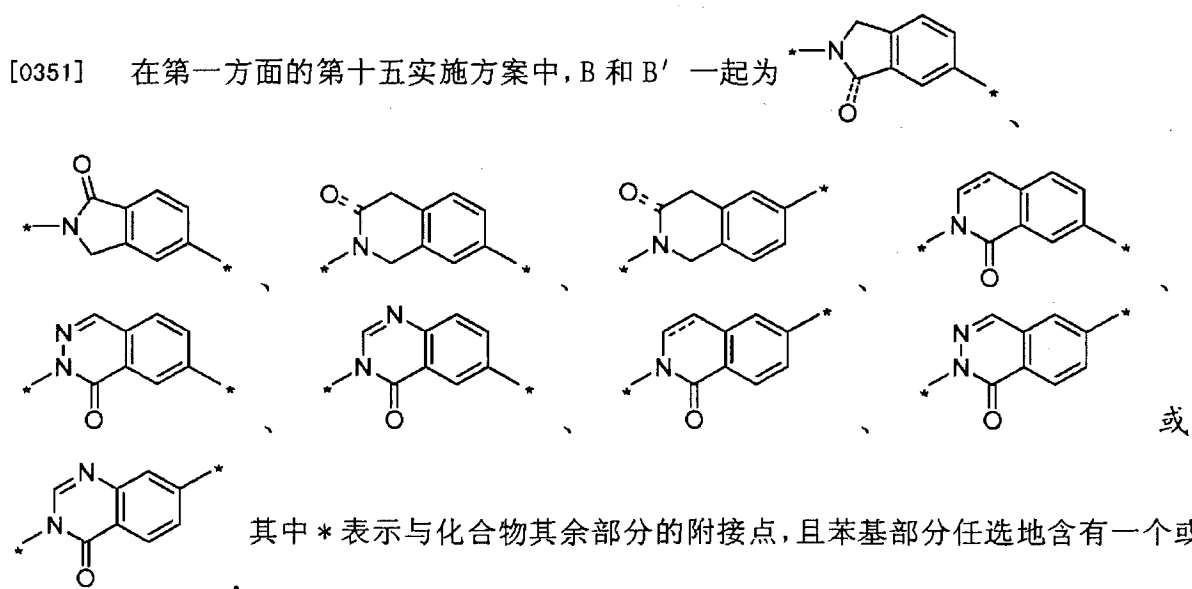
附接点, 且 R^N 选自氢、 $-OH$ 、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基和磺酰胺基。

[0350] 在第一方面的第十四实施方案中, B 和 B' 一起为



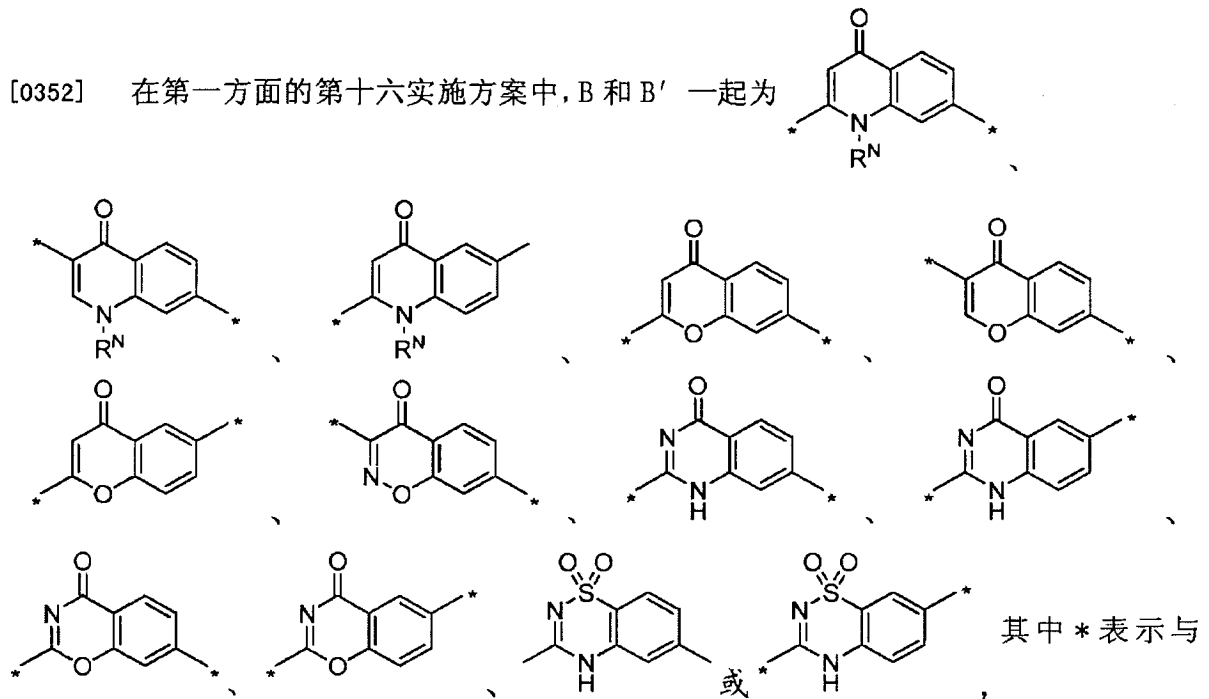
选地含有一个或两个附加的氮作为杂原子, 前提是该六元环中的氮的总数不超过 2 个。

[0351] 在第一方面的第十五实施方案中, B 和 B' 一起为

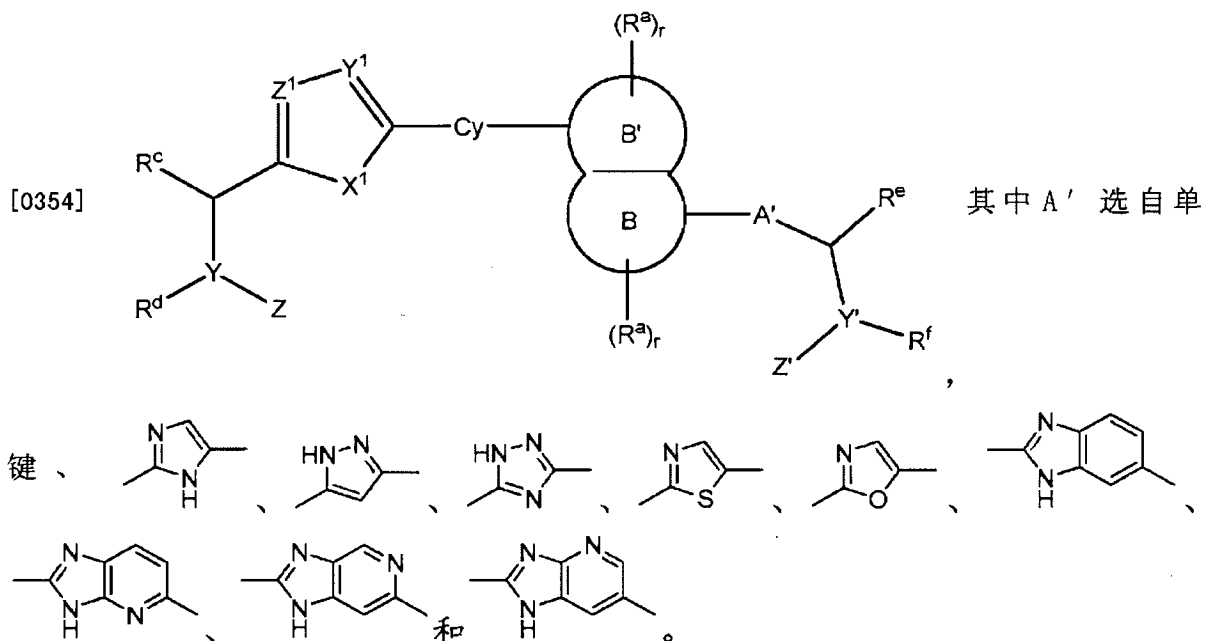


两个氮作为杂原子。

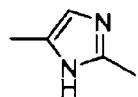
[0352] 在第一方面的第十六实施方案中, B 和 B' 一起为

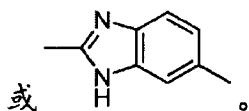


[0353] 在本发明的第二方面, 化合物如式 II 所示:

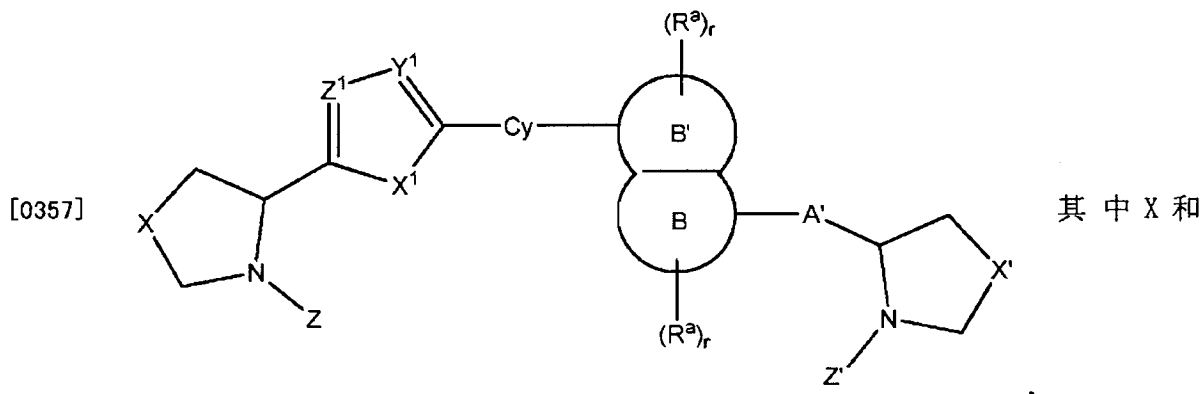


[0355] 在第二方面的第一实施方案中, 化合物如式 II 所示, 其中 A' 为





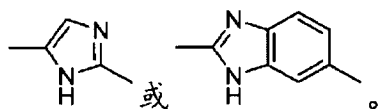
[0356] 在第二方面的第二实施方案中, 化合物如式 IIa 所示:



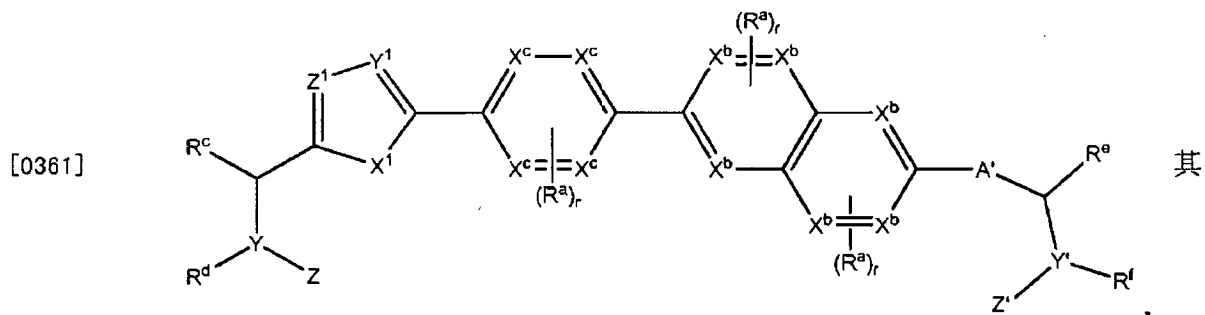
X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0358] 本发明的化合物包括 IIa 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0359] 在第二方面的第三实施方案中, 化合物如式 IIa 所示, 其中 A' 为



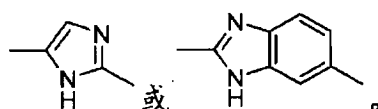
[0360] 在第二方面的第四实施方案中, 化合物如式 IIb 所示:



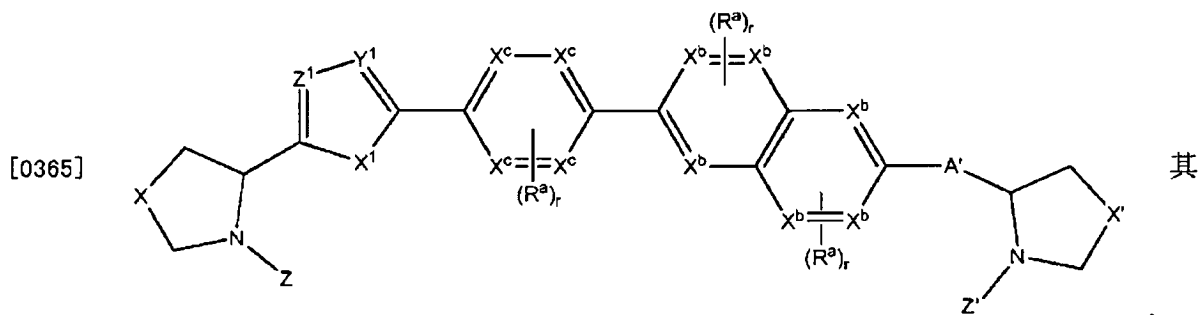
中各 X^b 和 X^c 独立地为 C 或 N。

[0362] 本发明的化合物包括 IIb 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0363] 在第二方面的第五实施方案中, 化合物如式 IIb 所示, 其中 A' 为



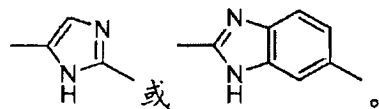
[0364] 在第二方面的第六实施方案中, 化合物如式 IIc 所示:



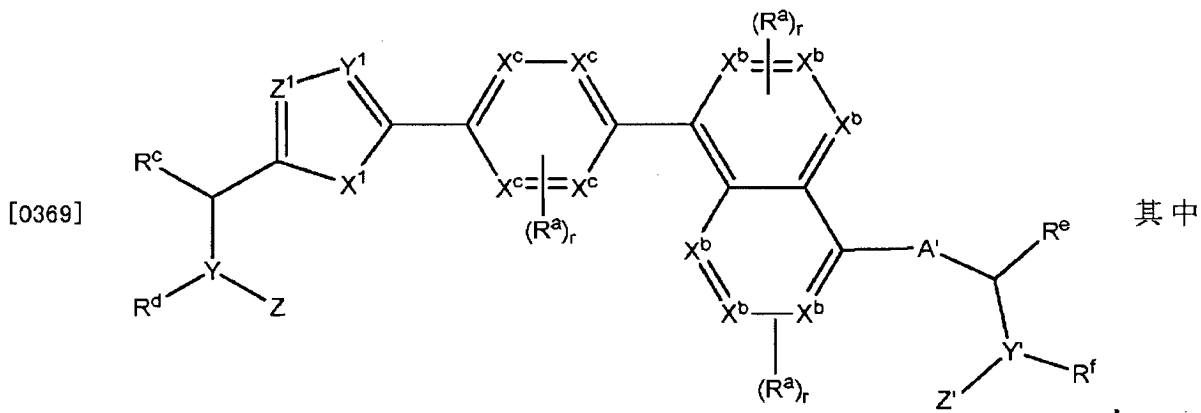
中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0366] 本发明的化合物包括 IIc 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0367] 在第二方面的第七实施方案中, 化合物如式 IIc 所示, 其中 A' 为



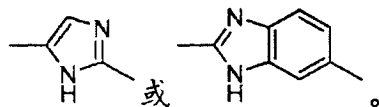
[0368] 在第二方面的第八实施方案中, 化合物如式 IIId 所示:



各 X^b 和 X^c 独立地为 C 或 N。

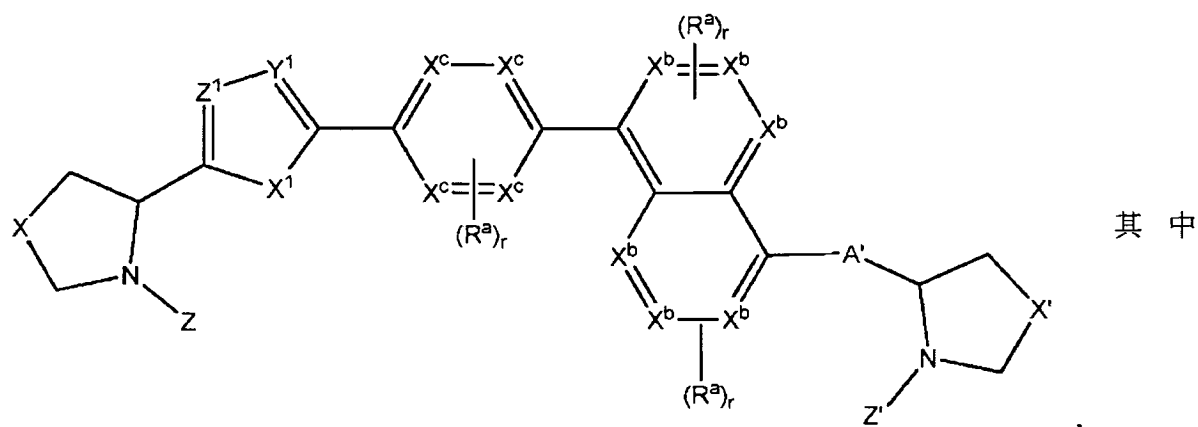
[0370] 本发明的化合物包括 IIId 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0371] 在第二方面的第九实施方案中, 化合物如式 IIId 所示, 其中 A' 为



[0372] 在第二方面的第十实施方案中, 化合物如式 IIe 所示:

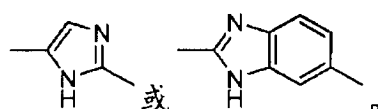
[0373]



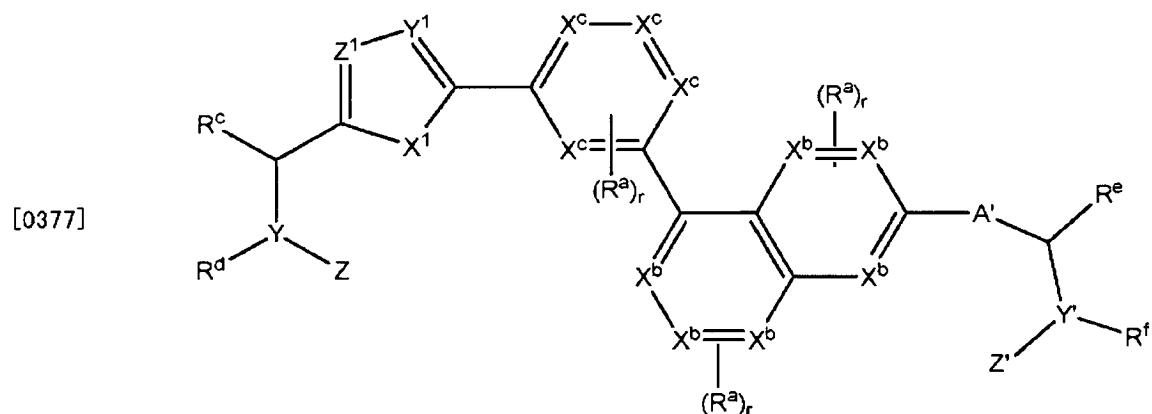
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨基酰基和取代的磺酰基。

[0374] 本发明的化合物包括 IIe 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0375] 在第二方面的第十一实施方案中，化合物如式 IIe 所示，其中 A' 为



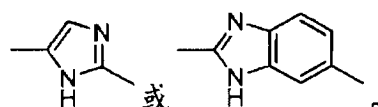
[0376] 在第二方面的第十二实施方案中，化合物如式 IIe 所示：



其中各 X^b 和 X^c 独立地为 C 或 N。

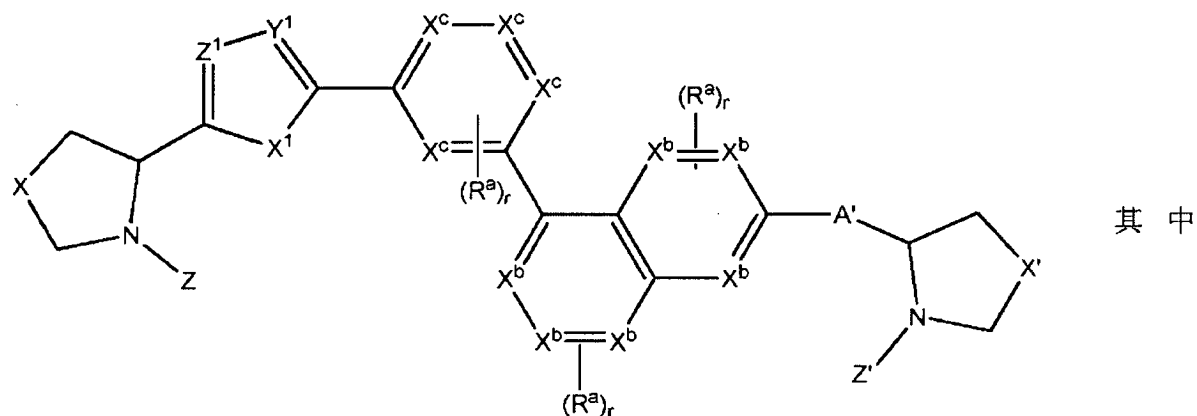
[0378] 本发明的化合物包括 IIe 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0379] 在第二方面的第十三实施方案中，化合物如式 IIe 所示，其中 A' 为



[0380] 在第二方面的第十四实施方案中，化合物如式 IIg 所示：

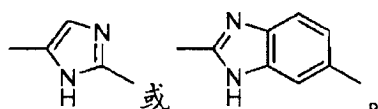
[0381]



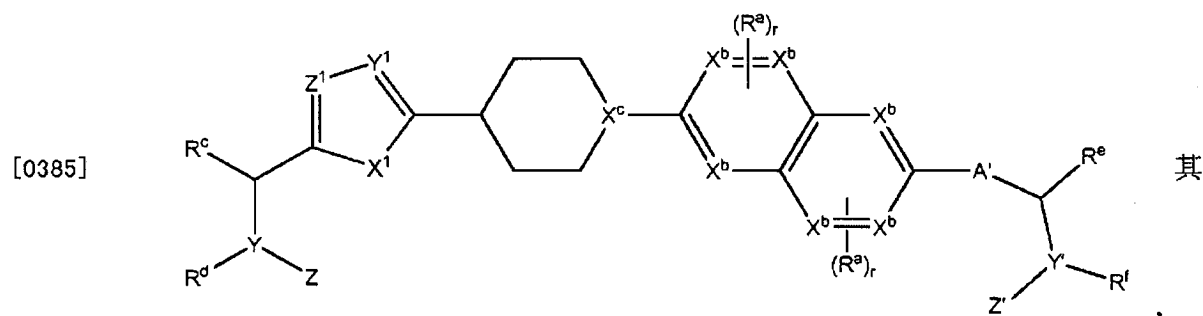
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0382] 本发明的化合物包括 IIg 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0383] 在第二方面的第十五实施方案中，化合物如式 IIg 所示，其中 A' 为



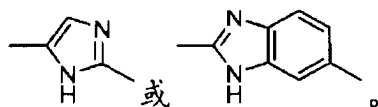
[0384] 在第二方面的第十六实施方案中，化合物如式 IIh 所示：



中 X^c 和各 X^b 独立地为 C 或 N。

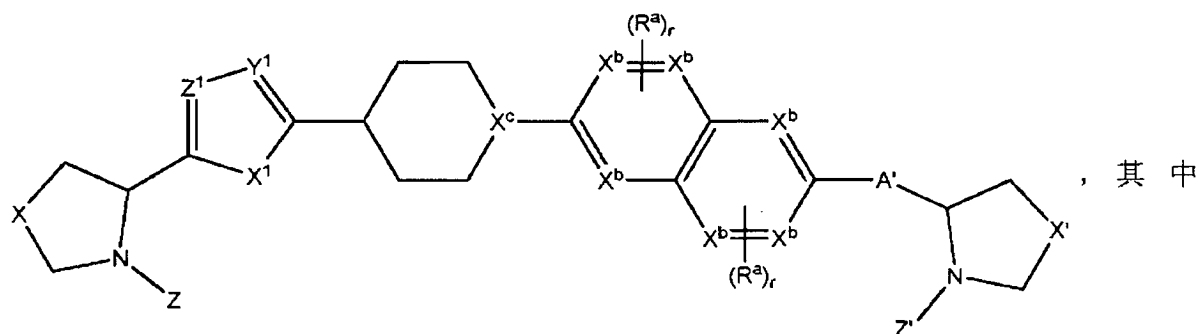
[0386] 本发明的化合物包括 IIh 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0387] 在第二方面的第十七实施方案中，化合物如式 IIh 所示，其中 A' 为



[0388] 在第二方面的第十八实施方案中，化合物如式 IIi 所示：

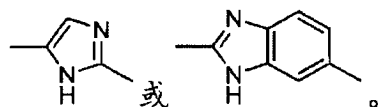
[0389]



X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0390] 本发明的化合物包括 IIi 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

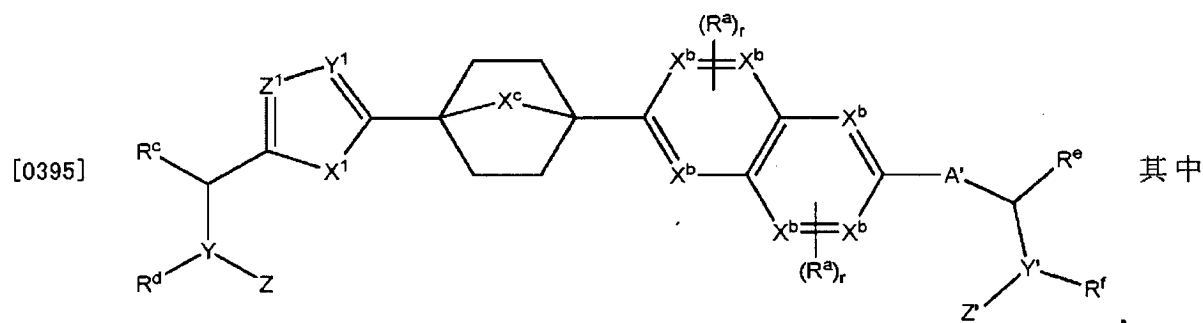
[0391] 在第二方面的第十九实施方案中，化合物如式 IIi 所示，其中 A' 为



[0392] 在第二方面的第二十实施方案中，化合物如式 IIh 或 IIi 所示，其中 X^c 为 C。

[0393] 在第二方面的第二十一实施方案中，化合物如式 IIh 或 IIi 所示，其中 X^c 为 N。

[0394] 在第二方面的第二十二实施方案中，化合物如式 IIj 所示：

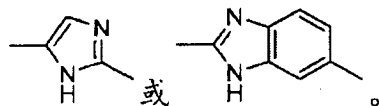


X^c 为 $-\text{CH}_2-$ 、 $-\text{NH}-$ 或 $-\text{CH}_2-\text{CH}_2-$ ；且

[0396] 各 X^b 独立地为 C 或 N。

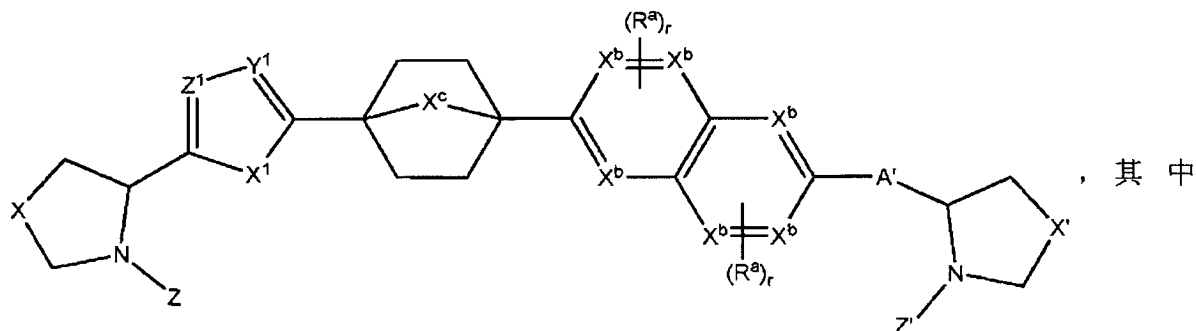
[0397] 本发明的化合物包括 IIj 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0398] 在第二方面的第二十三实施方案中，化合物如式 IIj 所示，其中 A' 为



[0399] 在第二方面的第二十四实施方案中，化合物如式 IIk 所示：

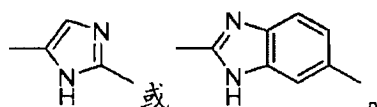
[0400]



X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

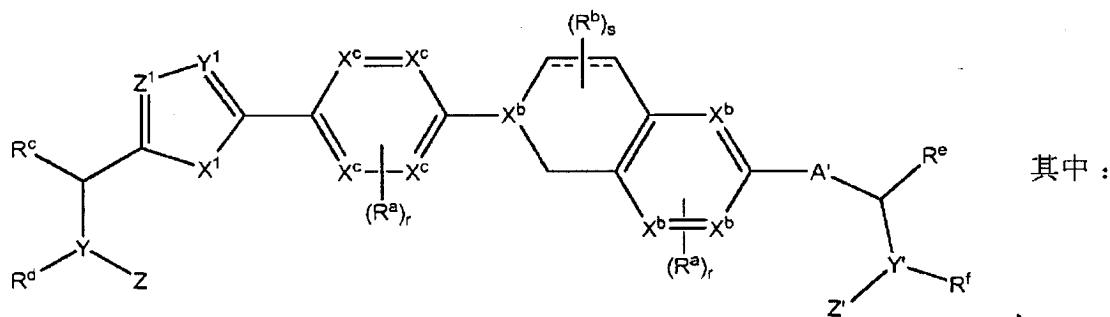
[0401] 本发明的化合物包括 IIk 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0402] 在第二方面的第二十五实施方案中，化合物如式 IIk 所示，其中 A' 为



[0403] 在第二方面的第二十六实施方案中，化合物如式 IIIl 所示：

[0404]



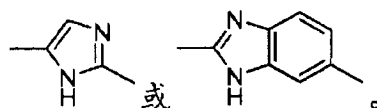
[0405] 各 X^b 和 X^c 独立地为 C 或 N；

[0406] 各 R^b 选自氧代基、 $-\text{OH}$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、卤素、 C_1 至 C_{12} 烷基、 C_1 至 C_{12} 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷氧基、烷氧羰基、烷酰基、氨甲酰基、取代的磺酰基、磺酸酯基、磺酰胺基和氨基；且

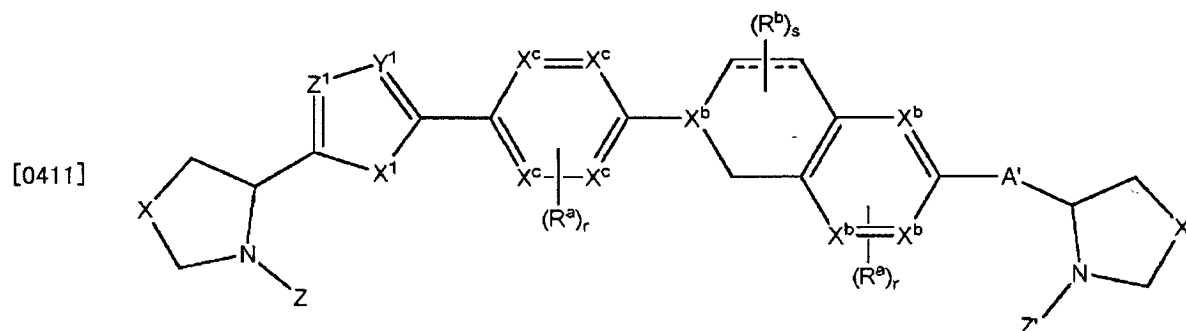
[0407] s 为 0、1、2 或 3。

[0408] 本发明的化合物包括 IIIl 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0409] 在第二方面的第二十七实施方案中，化合物如式 IIIl 所示，其中 A' 为



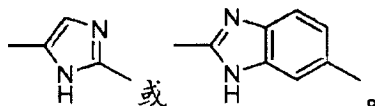
[0410] 在第二方面的第二十八实施方案中，化合物如式 IIIm 所示：



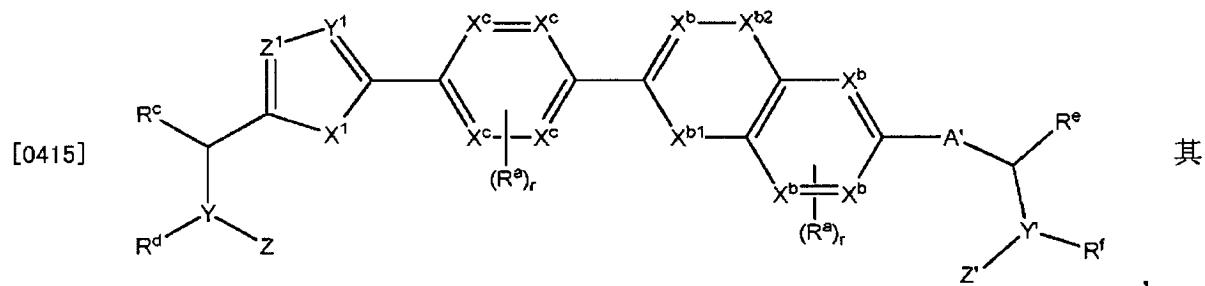
, 其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0412] 本发明的化合物包括 IIIm 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0413] 在第二方面的第二十九实施方案中, 化合物如式 IIIm 所示, 其中 A' 为



[0414] 在第二方面的第三十实施方案中, 化合物如式 IIIn 所示:



中:

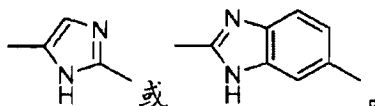
[0416] 各 X^b 和 X^c 独立地为 C 或 N;

[0417] X^{b1} 为 N 或 O; 且

[0418] X^{b2} 为 $\text{S}(\text{O})_2$ 或 $\text{C}(\text{O})$ 。

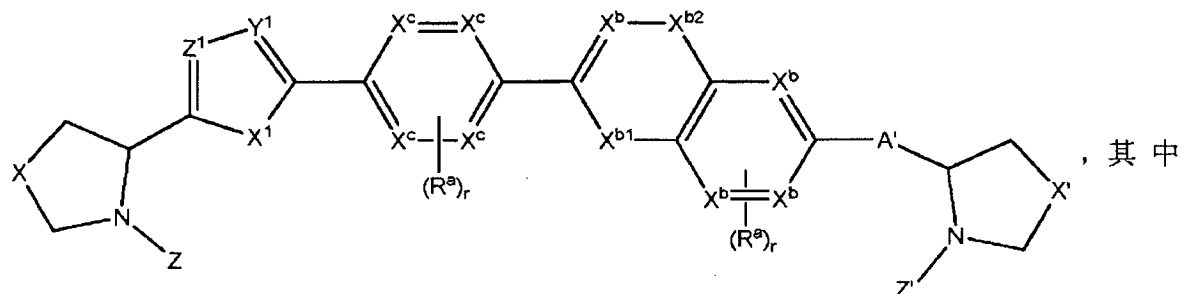
[0419] 本发明的化合物包括 IIIn 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0420] 在第二方面的第三十一实施方案中, 化合物如式 IIIn 所示, 其中 A' 为



[0421] 在第二方面的第三十二实施方案中, 化合物如式 IIo 所示:

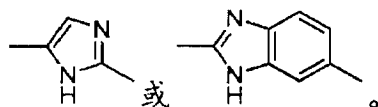
[0422]



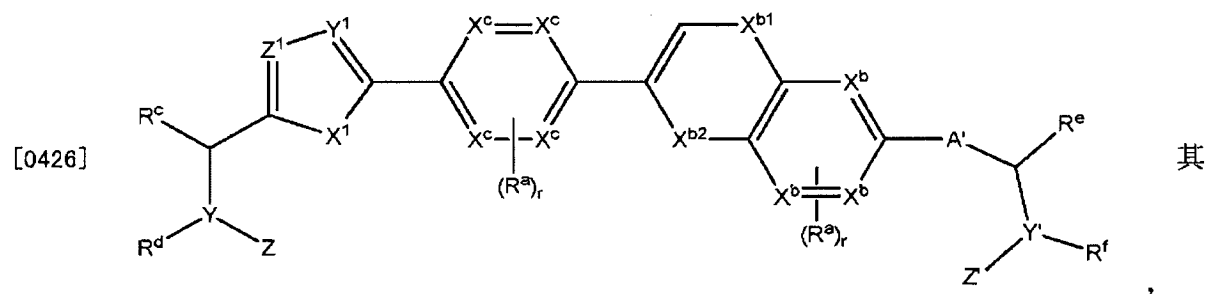
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0423] 本发明的化合物包括 IIo 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0424] 在第二方面的第三十三实施方案中，化合物如式 IIo 所示，其中 A' 为



[0425] 在第二方面的第三十四实施方案中，化合物如式 IIp 所示：



中：

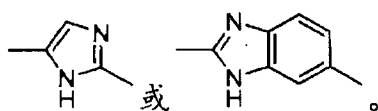
[0427] 各 X^b 和 X^c 独立地为 C 或 N；

[0428] X^{b1} 为 N 或 O；且

[0429] X^{b2} 为 $\text{S}(\text{O})_2$ 或 $\text{C}(\text{O})$ 。

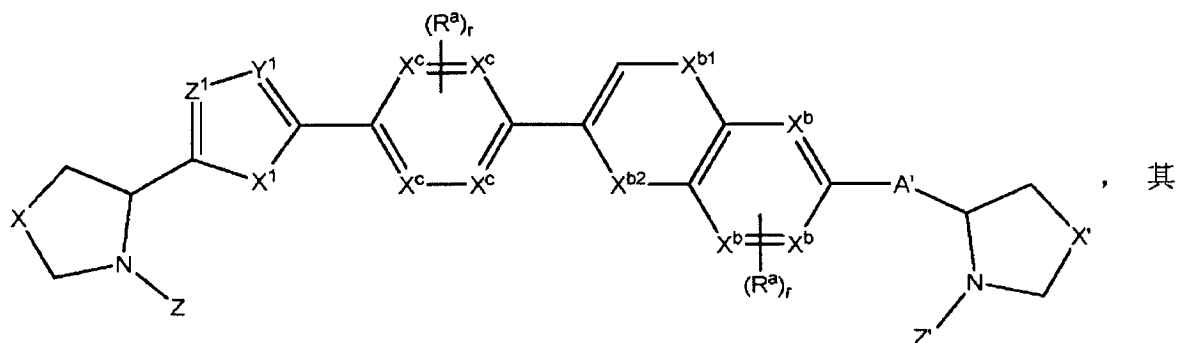
[0430] 本发明的化合物包括 IIp 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0431] 在第二方面的第三十五实施方案中，化合物如式 IIp 所示，其中 A' 为



[0432] 在第二方面的第三十六实施方案中，化合物如式 IIq 所示：

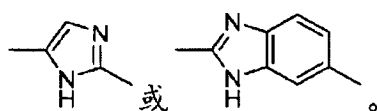
[0433]



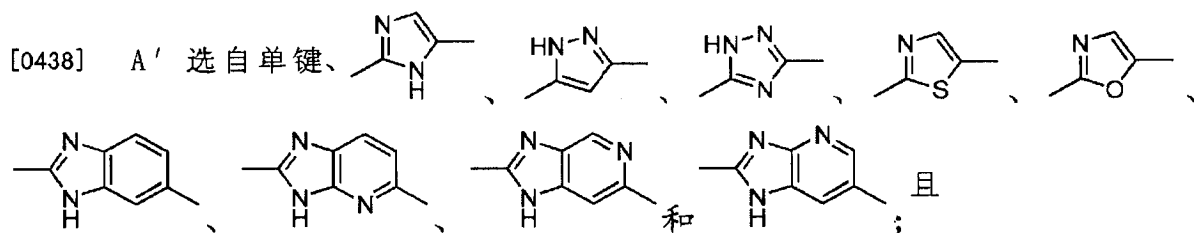
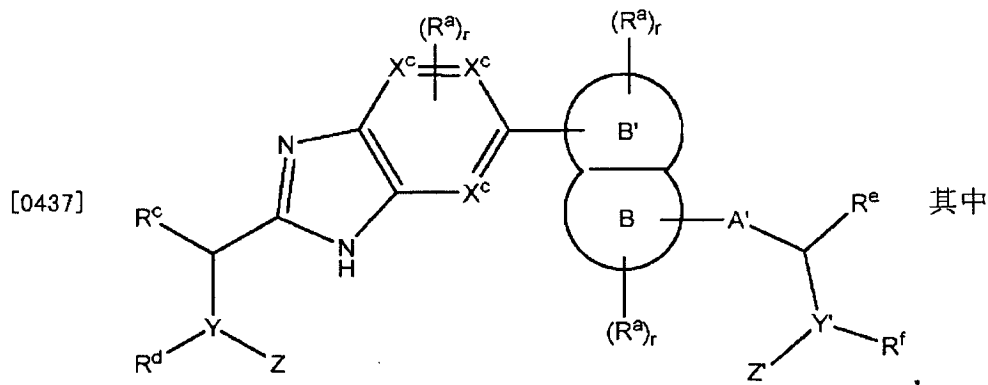
中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0434] 本发明的化合物包括 II_q 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0435] 在第二方面的第三十七实施方案中, 化合物如式 II_q 所示, 其中 A' 为

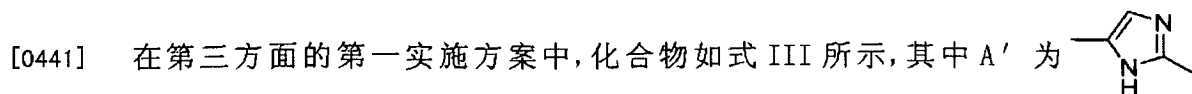


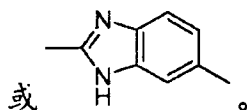
[0436] 在本发明的第三方面, 化合物如式 III 所示:



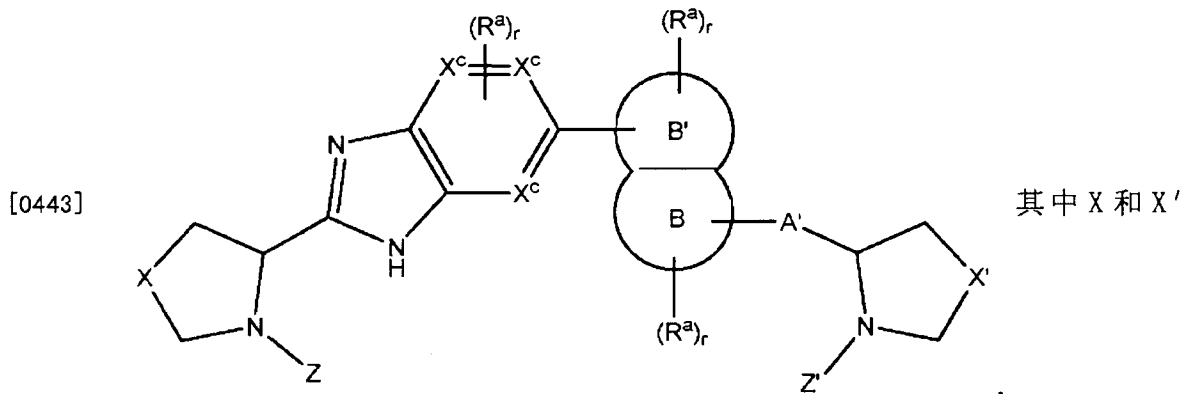
[0439] 各 X^c 独立地为 C 或 N。

[0440] 本发明的化合物包括 III 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。



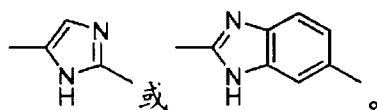


[0442] 在第三方面的第二实施方案中,化合物如式 IIIa 所示:

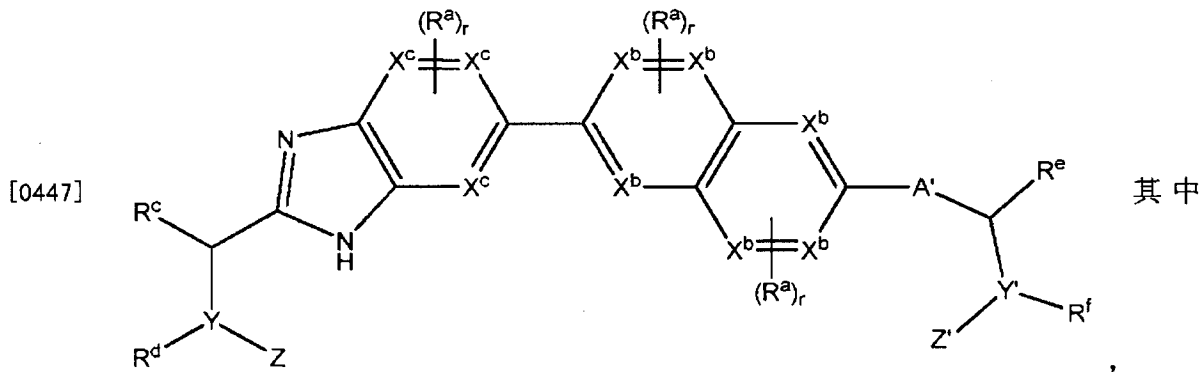


[0444] 本发明的化合物包括 IIIa 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0445] 在第三方面的第三实施方案中,化合物如式 IIIa 所示,其中 A' 为



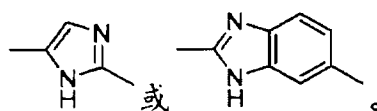
[0446] 在第三方面的第四实施方案中,化合物如式 IIIb 所示:



各 X^b 独立地为 C 或 N。

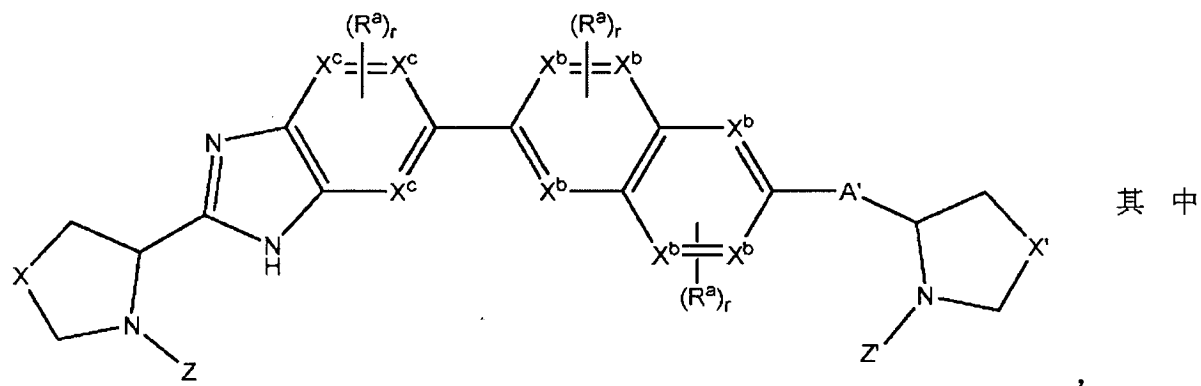
[0448] 本发明的化合物包括 IIIb 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0449] 在第三方面的第五实施方案中,化合物如式 IIIb 所示,其中 A' 为



[0450] 在第三方面的第六实施方案中, 化合物如式 IIIc 所示:

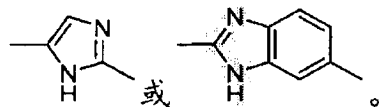
[0451]



X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

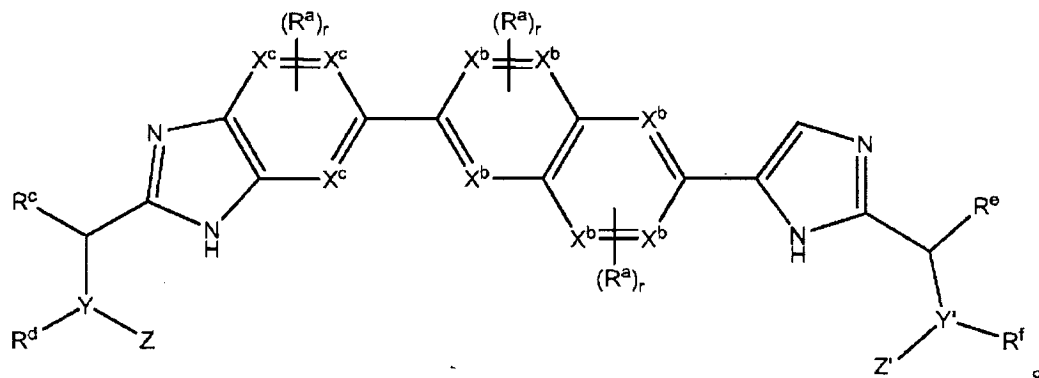
[0452] 本发明的化合物包括 IIIc 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0453] 在第三方面的第七实施方案中, 化合物如式 IIIc 所示, 其中 A' 为



[0454] 在第三方面的第八实施方案中, 化合物如式 IIIId 所示:

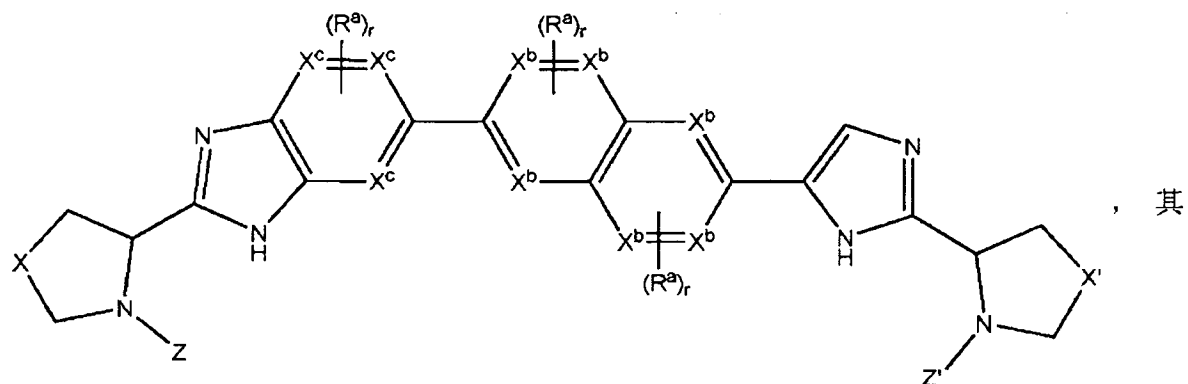
[0455]



[0456] 本发明的化合物包括 IIIId 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0457] 在第三方面的第九实施方案中, 化合物如式 IIIe 所示:

[0458]

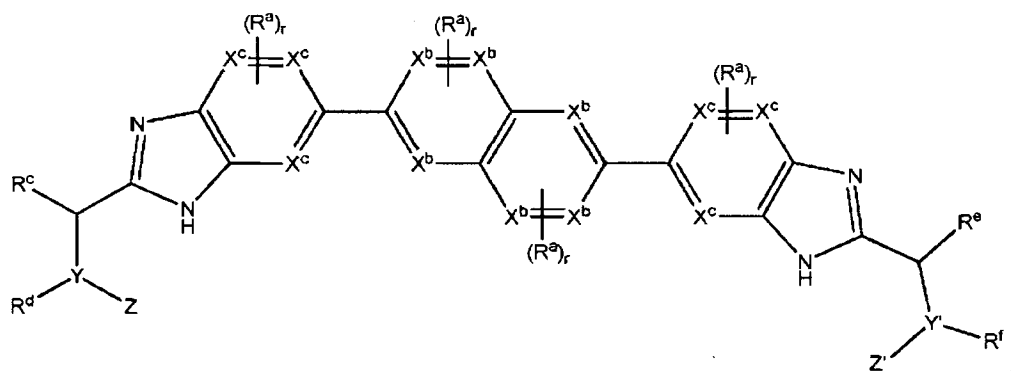


中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0459] 本发明的化合物包括 IIIe 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0460] 在第三方面的第十实施方案中, 化合物如式 IIIf 所示:

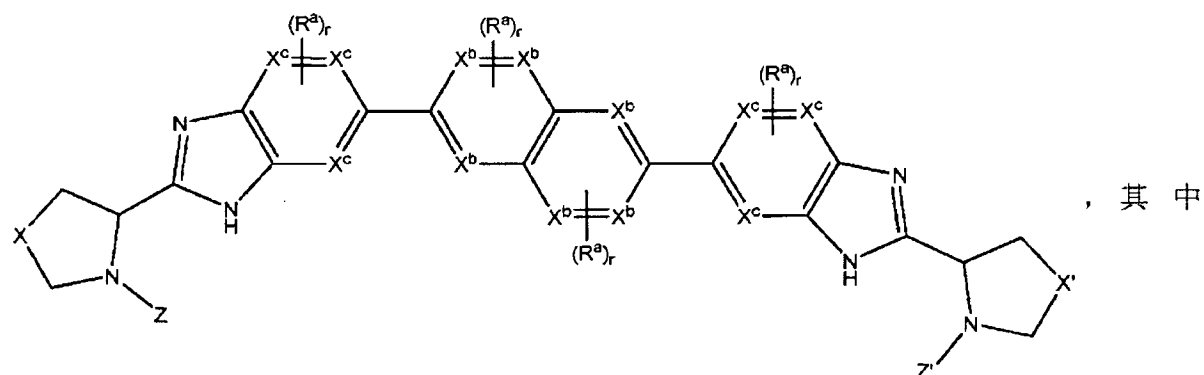
[0461]



[0462] 本发明的化合物包括 IIIf 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0463] 在第三方面的第十一实施方案中, 化合物如式 IIIg 所示:

[0464]

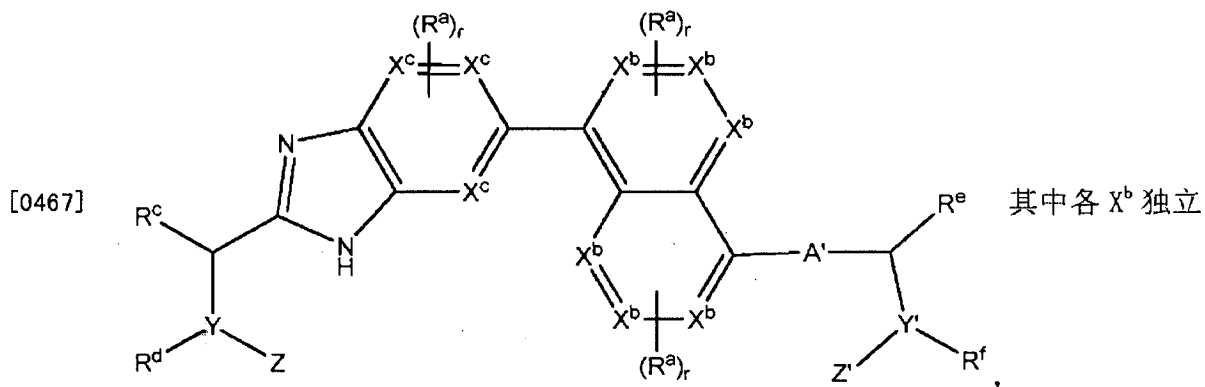


X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-

$S(O)_{1-2}$ -、 $-CH_2O-$ 、 $-CH_2S-$ 、 $-CH_2S(O)_{1-2}-$ 和 $-CH_2N(R^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

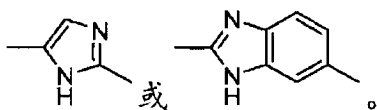
[0465] 本发明的化合物包括 IIIg 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0466] 在第三方面的第十二实施方案中，化合物如式 IIIh 所示：

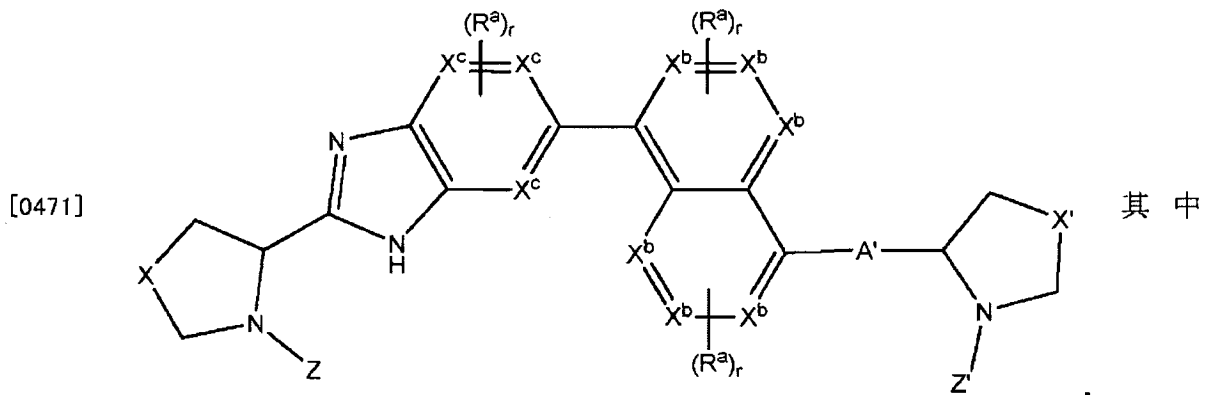


[0468] 本发明的化合物包括 IIIh 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0469] 在第三方面的第十三实施方案中，化合物如式 IIIh 所示，其中 A' 为



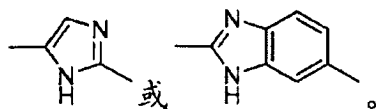
[0470] 在第三方面的第十四实施方案中，化合物如式 IIIi 所示：



X 和 X' 各自独立地选自化学键、 $-CH_2-$ 、 $-CH_2-CH_2-$ 、 $-CH=CH-$ 、 $-O-$ 、 $-S-$ 、 $-S(O)_{1-2}-$ 、 $-CH_2O-$ 、 $-CH_2S-$ 、 $-CH_2S(O)_{1-2}-$ 和 $-CH_2N(R^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

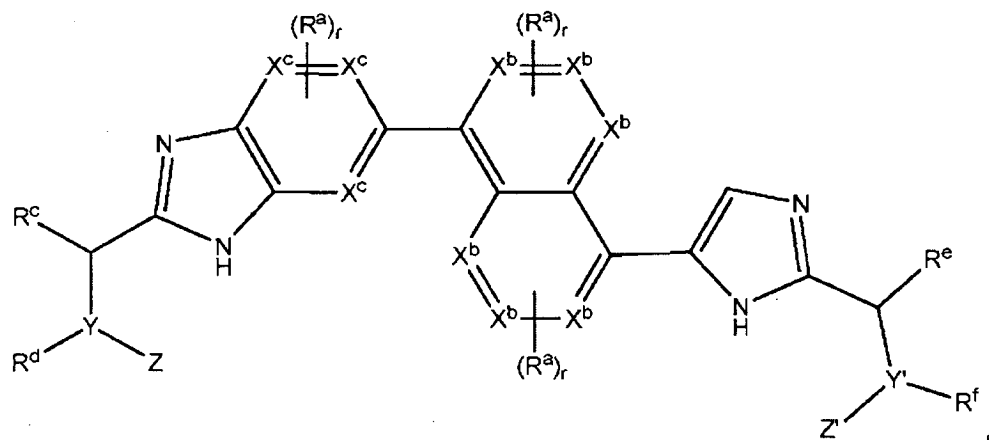
[0472] 本发明的化合物包括 IIIi 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0473] 在第三方面的第十五实施方案中，化合物如式 IIIi 所示，其中 A' 为



[0474] 在第三方面的第十六实施方案中, 化合物如式 IIIj 所示:

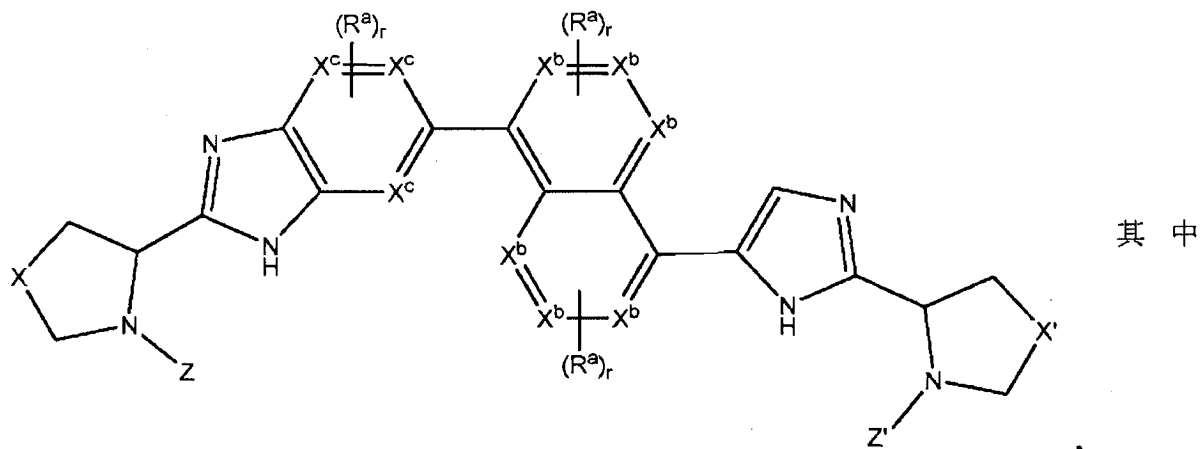
[0475]



[0476] 本发明的化合物包括 IIIj 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0477] 在第三方面的第十七实施方案中, 化合物如式 IIIk 所示:

[0478]

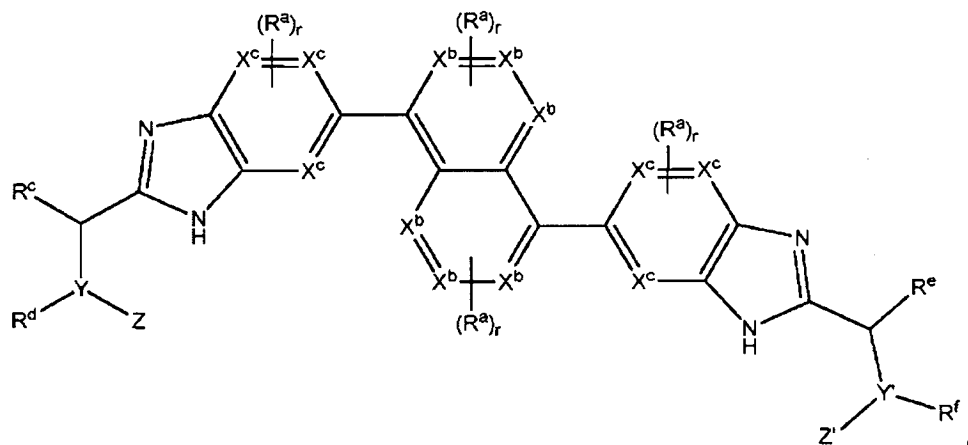


X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0479] 本发明的化合物包括 IIIk 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0480] 在第三方面的第十八实施方案中, 化合物如式 IIIl 所示:

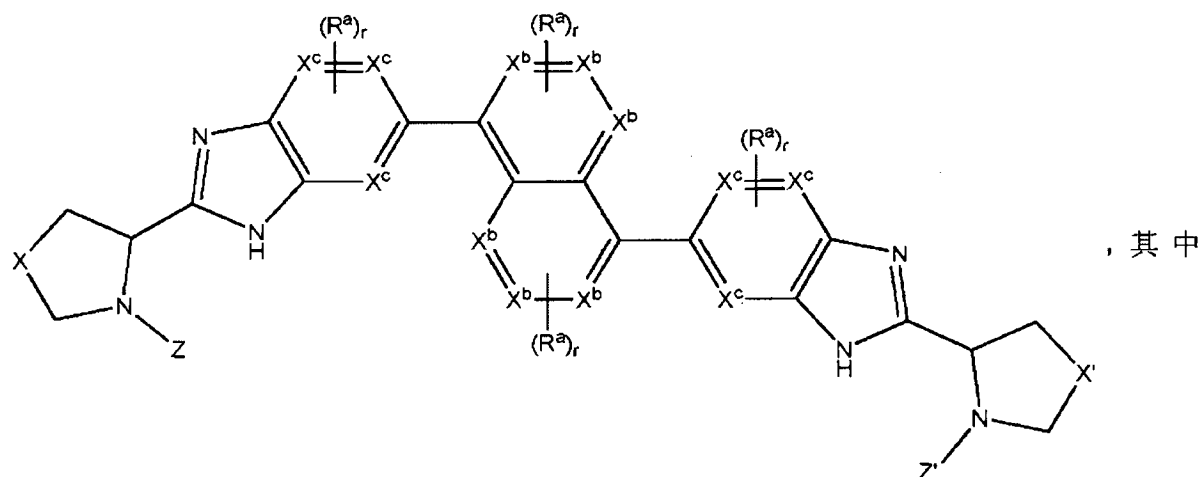
[0481]



[0482] 本发明的化合物包括 IIII1 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0483] 在第三方面的第十九实施方案中, 化合物如式 IIIIm 所示:

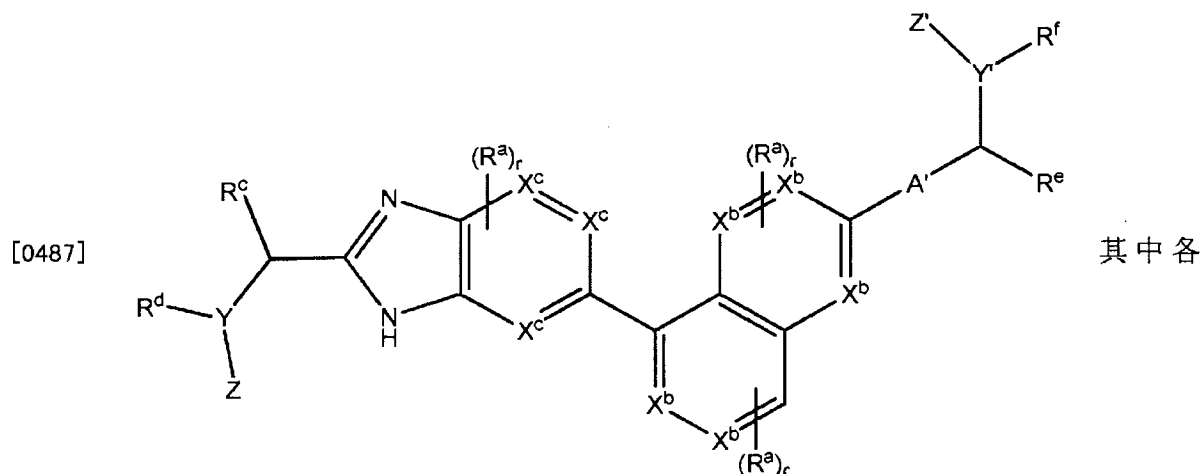
[0484]



X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0485] 本发明的化合物包括 IIIIm 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

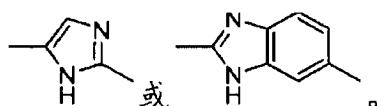
[0486] 在第三方面的第二十实施方案中, 化合物如式 IIIIn 所示:



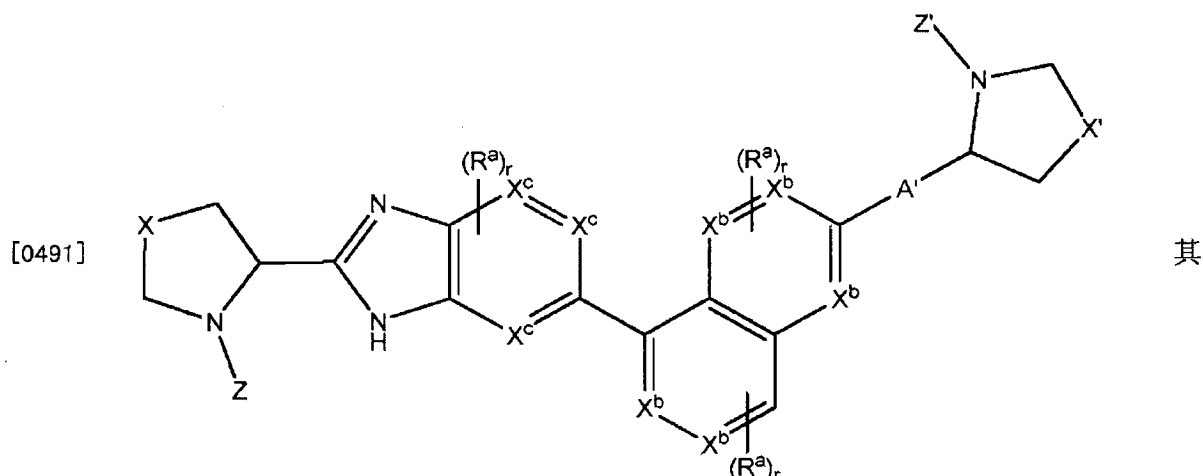
X^b 独立地为 C 或 N。

[0488] 本发明的化合物包括 IIIIn 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0489] 在第三方面的第二十一实施方案中, 化合物如式 IIIIn 所示, 其中 A' 为



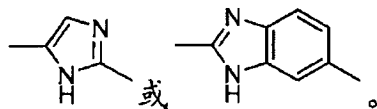
[0490] 在第三方面的第二十二实施方案中, 化合物如式 IIIo 所示:



中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

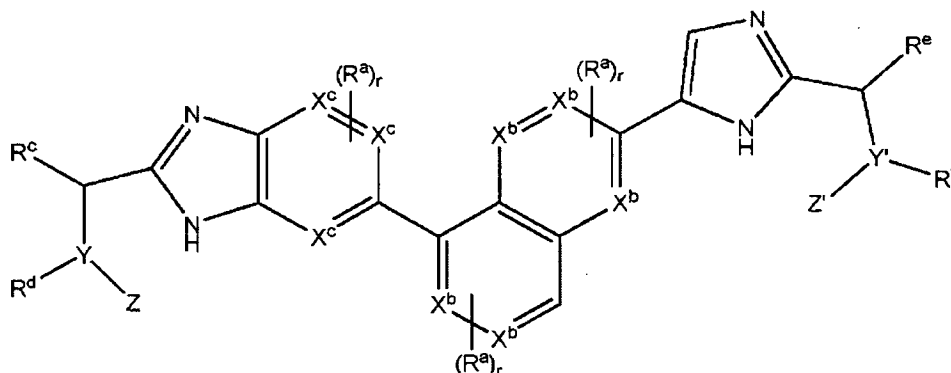
[0492] 本发明的化合物包括 IIIo 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0493] 在第三方面的第二十三实施方案中, 化合物如式 IIIo 所示, 其中 A' 为



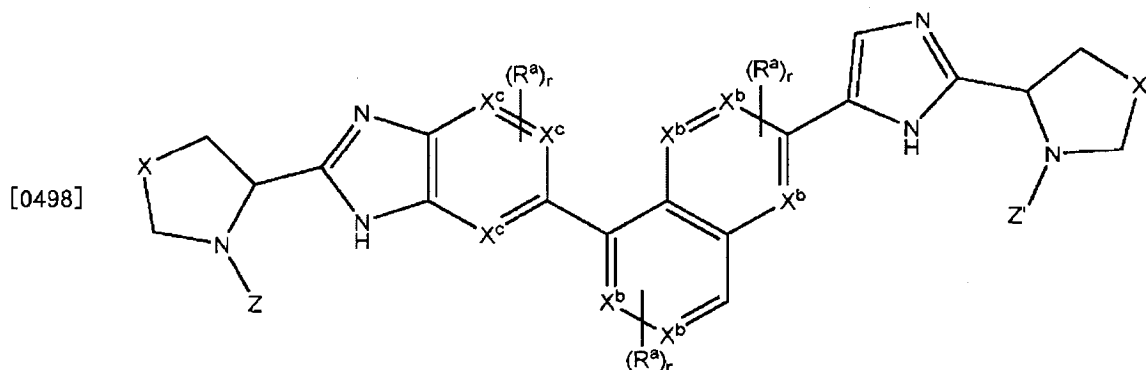
[0494] 在第三方面的第二十四实施方案中,化合物如式 IIIp 所示:

[0495]



[0496] 本发明的化合物包括 IIIp 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0497] 在第三方面的第二十五实施方案中,化合物如式 IIIq 所示:

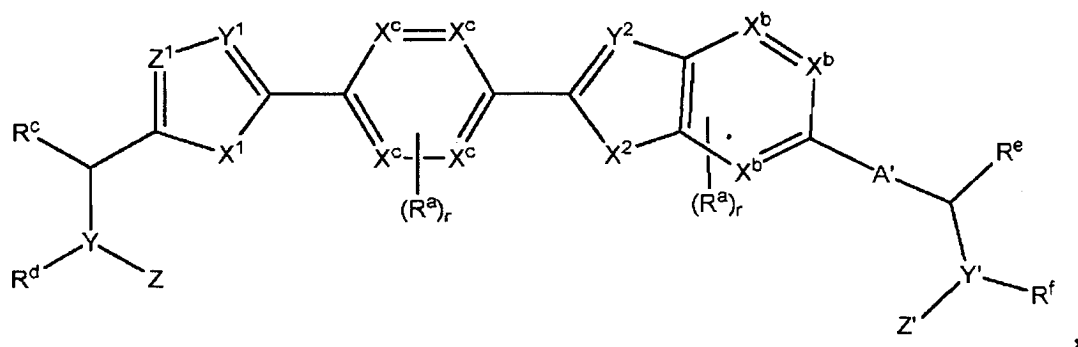


其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

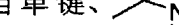
[0499] 本发明的化合物包括 IIIq 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0500] 在本发明的第四方面,化合物如式 IV 所示:

[0501]



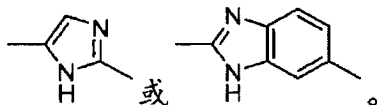
[0502] 其中：

[0503] A' 选自单键、、、、、、
、、和；且

[0504] 各 X^b 和 X^c 独立地为 C 或 N。

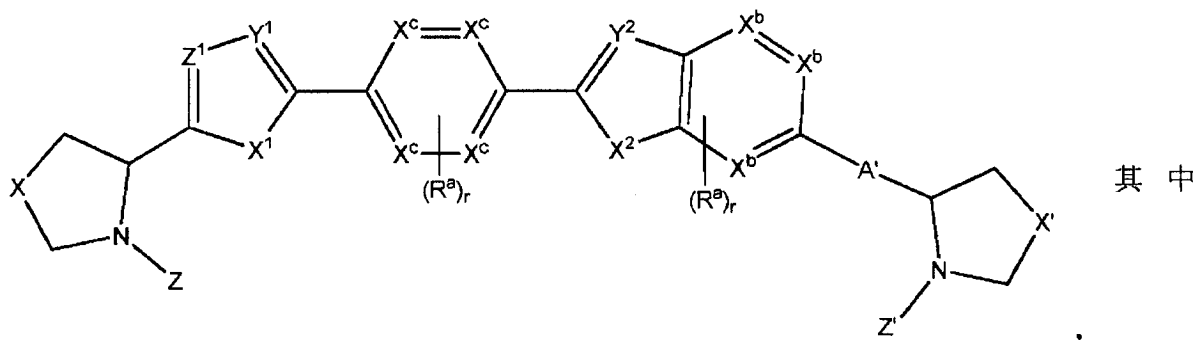
[0505] 本发明的化合物包括 IV 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0506] 在第四方面的第一实施方案中, 化合物如式 IV 所示, 其中 A' 为



[0507] 在第四方面的第二实施方案中, 化合物如式 IVa 所示:

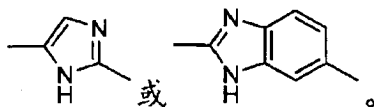
[0508]



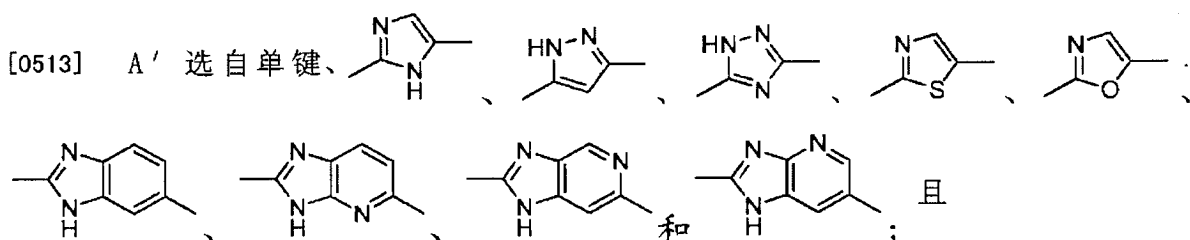
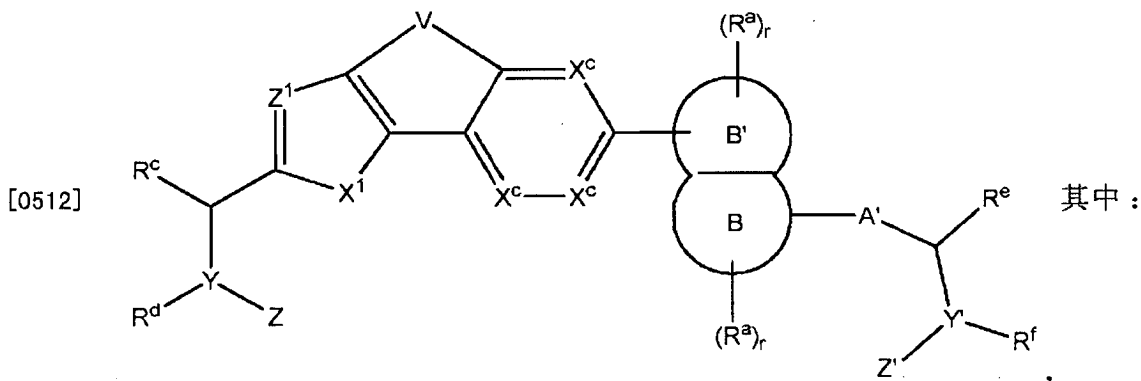
X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$ ，其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0509] 本发明的化合物包括 IVa 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0510] 在第四方面的第三实施方案中, 化合物如式 IVa 所示, 其中 A' 为

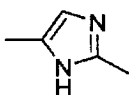


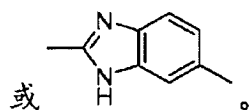
[0511] 在本发明的第五方面, 化合物如式 V 所示:



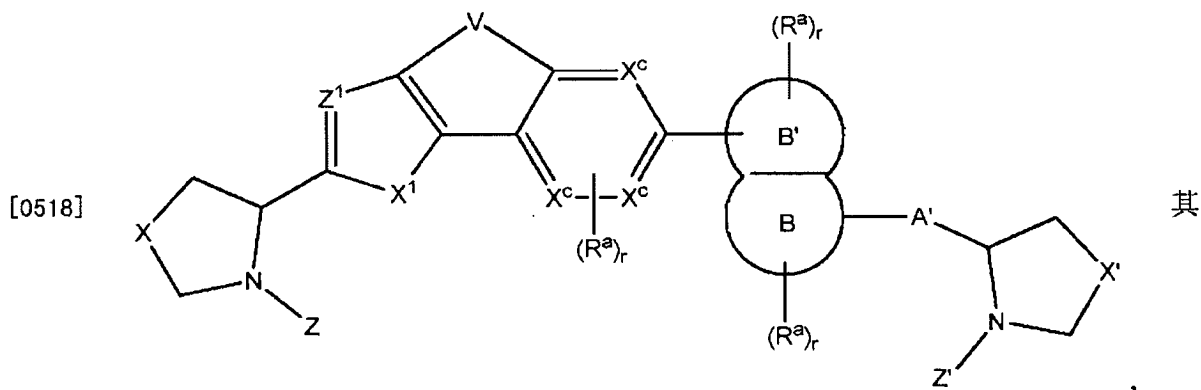
[0514] 各 X^e 独立地为 C 或 N, 前提是不超过两个 X^e 为 N。

[0515] 本发明的化合物包括 V 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0516] 在第五方面的第一实施方案中, 化合物如式 V 所示, 其中 A' 为 



[0517] 在第五方面的第二实施方案中, 化合物如式 Va 所示:

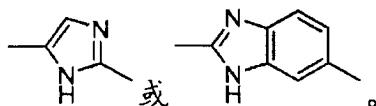


中 X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、

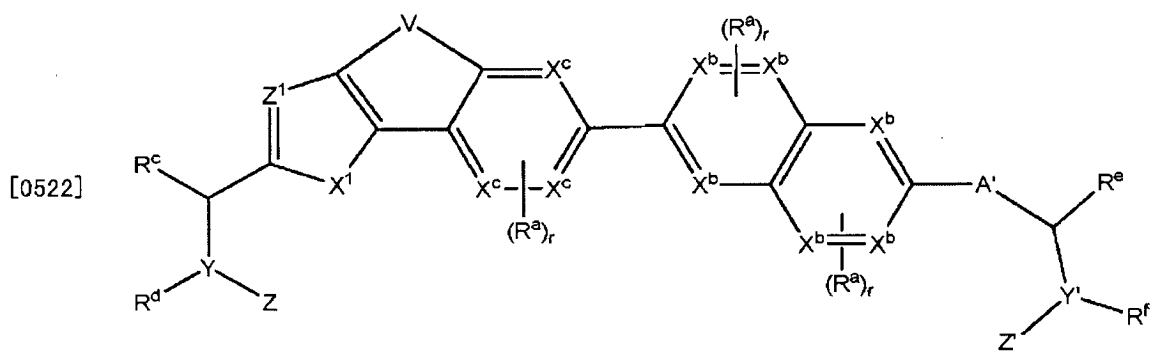
C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0519] 本发明的化合物包括 Va 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0520] 在第五方面的第三实施方案中, 化合物如式 Va 所示, 其中 A' 为



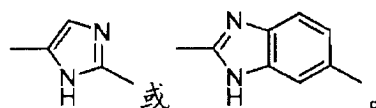
[0521] 在第五方面的第四实施方案中, 化合物如式 Vb 所示:



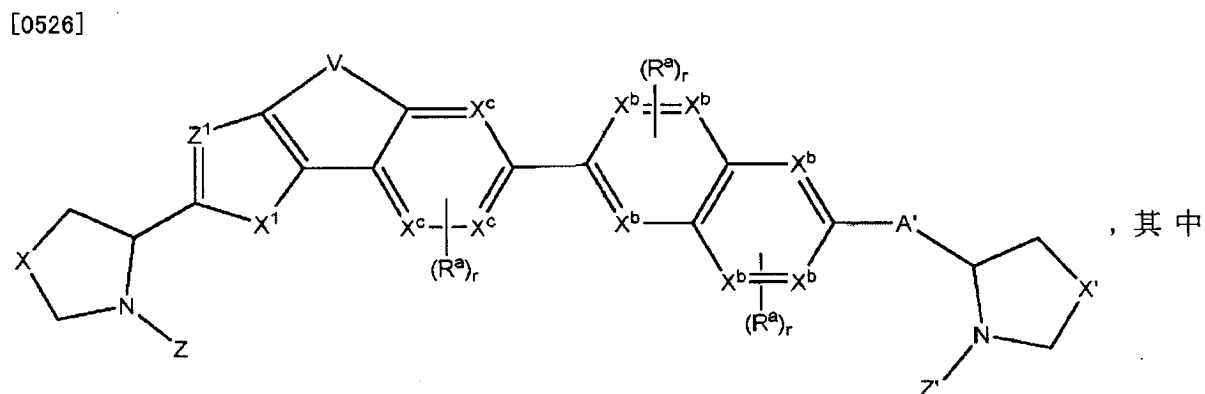
其中各 X^b 独立地为 C 或 N。

[0523] 本发明的化合物包括 Vb 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0524] 在第五方面的第五实施方案中, 化合物如式 Vb 所示, 其中 A' 为



[0525] 在第五方面的第六实施方案中, 化合物如式 Vc 所示:

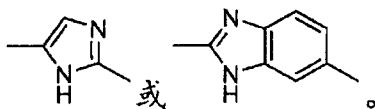


X 和 X' 各自独立地选自化学键、-CH₂-、-CH₂-CH₂-、-CH=CH-、-O-、-S-、-S(O)₁₋₂-、-CH₂O-、-CH₂S-、-CH₂S(O)₁₋₂- 和 -CH₂N(R¹)-, 其中 R¹ 选自氢、C₁ 至 C₈ 烷基、C₁ 至 C₈ 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0527] 本发明的化合物包括 Vc 的药学上可接受的盐及其光学纯对映体、外消旋体或非

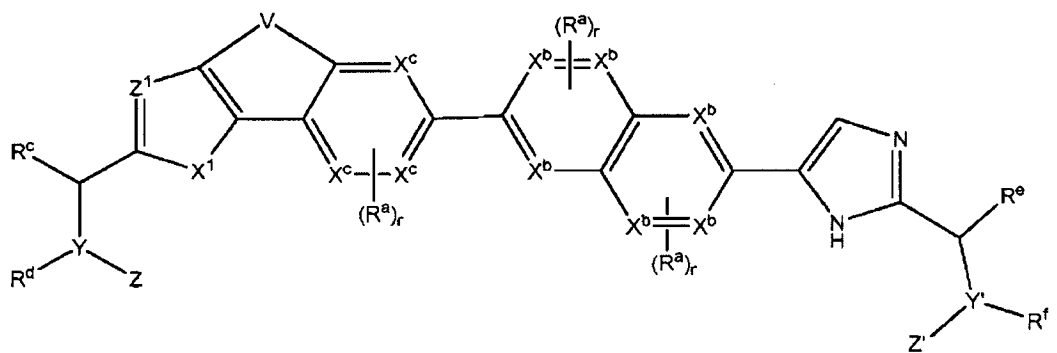
对映混合物。

[0528] 在第五方面的第七实施方案中, 化合物如式 Vc 所示, 其中 A' 为



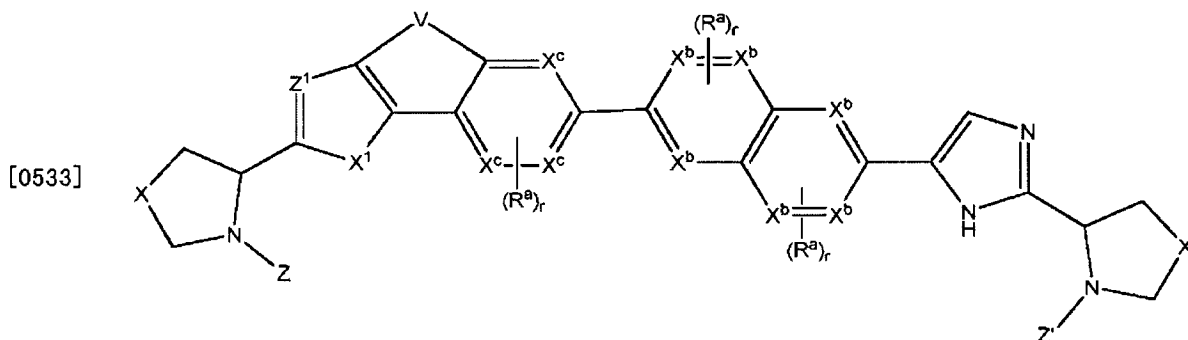
[0529] 在第五方面的第八实施方案中, 化合物如式 Vd 所示:

[0530]



[0531] 本发明的化合物包括 Vd 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0532] 在第五方面的第九实施方案中, 化合物如式 Ve 所示:



, 其中 X 和 X' 各自独立地选自化学键、 $-\text{CH}_2-$ 、 $-\text{CH}_2-\text{CH}_2-$ 、 $-\text{CH}=\text{CH}-$ 、 $-\text{O}-$ 、 $-\text{S}-$ 、 $-\text{S}(\text{O})_{1-2}-$ 、 $-\text{CH}_2\text{O}-$ 、 $-\text{CH}_2\text{S}-$ 、 $-\text{CH}_2\text{S}(\text{O})_{1-2}-$ 和 $-\text{CH}_2\text{N}(\text{R}^1)-$, 其中 R^1 选自氢、 C_1 至 C_8 烷基、 C_1 至 C_8 杂烷基、环烷基、杂环基、芳基、杂芳基、芳烷基、烷酰基、烷氧羰基、氨甲酰基和取代的磺酰基。

[0534] 本发明的化合物包括 Ve 的药学上可接受的盐及其光学纯对映体、外消旋体或非对映混合物。

[0535] 在本发明的第六方面, 在第二至第五方面中任一者的任何化合物中, R^c 、 R^d 、 R^e 和 R^f 各自独立地选自: 氢、 C_1 至 C_8 烷基和 C_1 至 C_8 杂烷基, 其中

[0536] 各杂原子在存在时独立地为 N、O 或 S,

[0537] R^c 与 R^d 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合, 且

[0538] R^e 与 R^f 任选地连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合。

[0539] 在第六方面的第一实施方案中, R^c 与 R^d 或 R^e 与 R^f 连接形成 4 至 8 元杂环, 该杂环

任选地与另一个 3 至 6 元杂环稠合。

[0540] 在第六方面的第二实施方案中, R^c 与 R^d 以及 R^e 与 R^f 均连接形成 4 至 8 元杂环, 该杂环任选地与另一个 3 至 6 元杂环稠合。

[0541] 在本发明的第七方面, 如果本发明的任一其它方面中存在 R^a , 则各 R^a 独立地为 $-\text{CN}$ 、 $-\text{OCHF}_2$ 、 $-\text{OCF}_3$ 、 $-\text{CF}_3$ 或 $-\text{F}$ 。

[0542] 在本发明的第八方面, 如果存在于任一其它方面的任何化合物中, 则 Y 和 Y' 之一为 N 。

[0543] 在第八方面的第一实施方案中, Y 和 Y' 均为 N 。

[0544] 在本发明的第九方面, 任何前述方面中的 Z 和 Z' 各为 1-3 个氨基酸。

[0545] 在第九方面的第一实施方案中, 氨基酸呈 D 构型。

[0546] 在本发明的第十方面, 任何前述方面中的 Z 和 Z' 各自独立地选自 $-\text{[U-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_u-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 、 $-\text{U-(CR}_2^4\text{)]}_t-\text{R}^8$ 和 $-\text{[U-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_u-\text{U-(CR}_2^4\text{)]}_t-\text{O-(CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0547] 在第十方面的第一实施方案中, Z 和 Z' 均为 $-\text{[U-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_u-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0548] 在第十方面的第二实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_t-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0549] 在第十方面的第三实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0550] 在第十方面的第四实施方案中, Z 和 Z' 中的一者或两者为 $-\text{[C(O)-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_u-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0551] 在第十方面的第五实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_t-\text{U-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0552] 在第十方面的第六实施方案中, Z 和 Z' 中的一者或两者为 $-\text{[C(O)-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_u-\text{C(O)-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0553] 在第十方面的第七实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_t-\text{NR}^5-(\text{CR}_2^4\text{)]}_t-\text{C(O)-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0554] 在第十方面的第八实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_t-\text{NR}^7-(\text{CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0555] 在第十方面的第九实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_n-\text{NR}^7-(\text{CR}_2^4\text{)]}_n-\text{C(O)-R}^{81}$ 。

[0556] 在第十方面的第十实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_n-\text{NR}^7-\text{C(O)-R}^{81}$ 。

[0557] 在第十方面的第十一实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_n-\text{NR}^7-(\text{CR}_2^4\text{)]}_n-\text{C(O)-O-R}^{81}$ 。

[0558] 在第十方面的第十二实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_n-\text{NR}^7-\text{C(O)-O-R}^{81}$ 。

[0559] 在第十方面的第十三实施方案中, Z 和 Z' 中的一者或两者为 $-\text{U-(CR}_2^4\text{)]}_t-\text{R}^8$ 。

[0560] 在第十方面的第十四实施方案中, Z 和 Z' 中的一者或两者为 $-\text{C(O)-(CR}_2^4\text{)]}_t$ 。

$_t - R^8$ 。

[0561] 在第十方面的第十五实施方案中, Z 和 Z' 中的一者或两者为 $- [U - (CR^4)_t - NR^5 - (CR^4)_t]_u - U - (CR^4)_t - O - (CR^4)_t - R^8$ 。

[0562] 在第十方面的第十六实施方案中, Z 和 Z' 中的一者或两者为 $- U - (CR^4)_t - NR^5 - (CR^4)_t - U - (CR^4)_t - O - (CR^4)_t - R^8$ 。

[0563] 在第十方面的第十七实施方案中, Z 和 Z' 中的一者或两者为 $- C(O) - (CR^4)_t - NR^5 - (CR^4)_t - C(O) - (CR^4)_t - O - (CR^4)_t - R^8$ 。

[0564] 在第十方面的第十八实施方案中, Z 和 Z' 中的一者或两者为 $- U - (CR^4)_t - O - (CR^4)_t - R^8$ 。

[0565] 一般合成

[0566] 以下方案例示出用于制备本发明包括的化合物及其类似物的一些合成路线。本领域的技术人员应理解, 还可使用替代途径来实现相同及类似的官能化中间体及靶分子。用于指定转化的替代试剂也是可能的。

[0567] 本申请的全文中使用下列缩写:

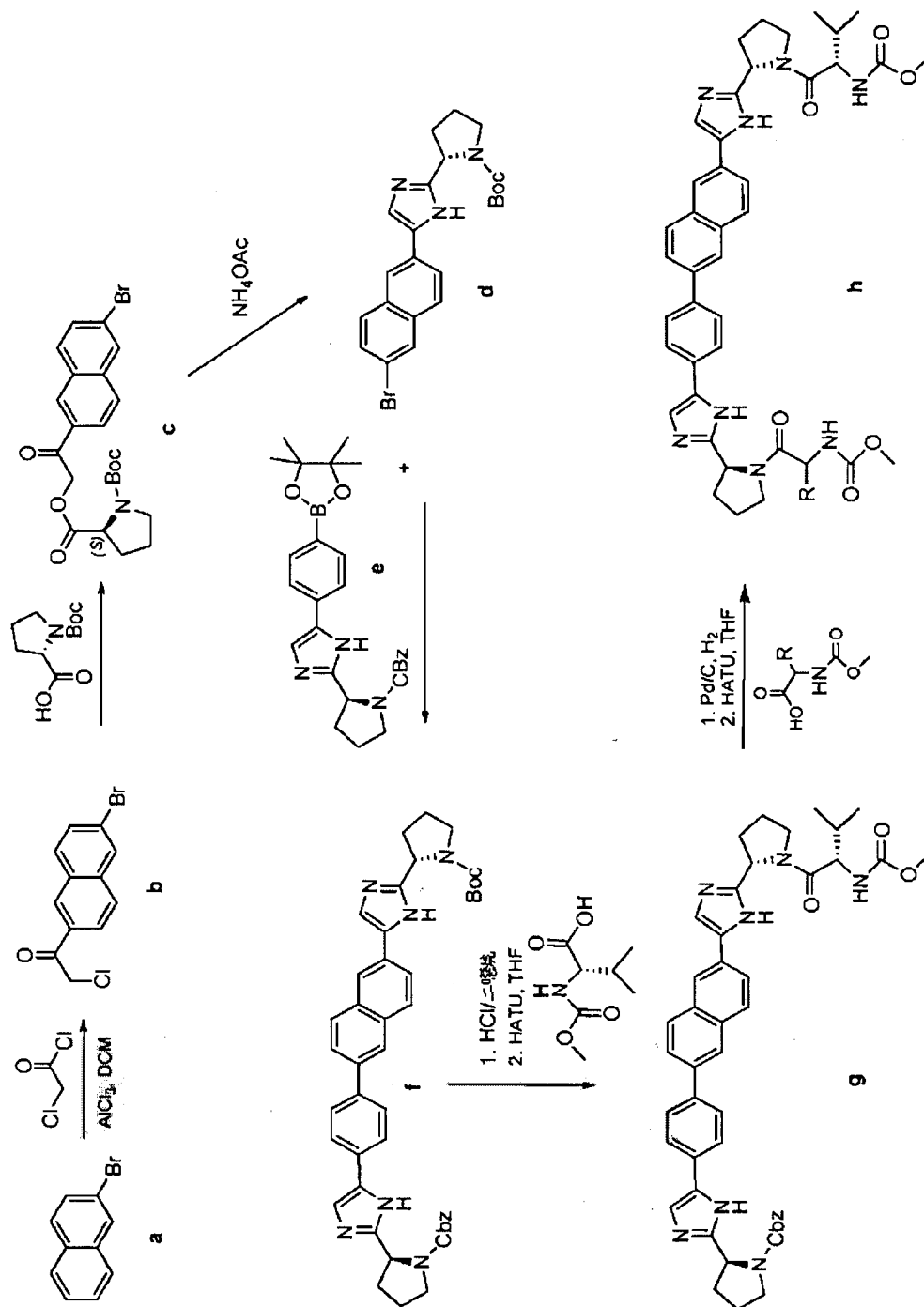
[0568]	ACN	乙腈
[0569]	aq	水溶液
[0570]	Bn	苯甲基
[0571]	BnOH	苯甲醇
[0572]	Boc	叔丁氧羰基
[0573]	DCE	二氯乙烷
[0574]	DCM	二氯甲烷
[0575]	DIEA(DIPEA)	二异丙基乙胺
[0576]	DMA	N, N- 二甲基乙酰胺
[0577]	DME	1, 2- 二甲氧基乙烷
[0578]	DMF	N, N- 二甲基甲酰胺
[0579]	DMSO	二甲基亚砷
[0580]	DMTMM	氯化 4-(4, 6- 二甲氧基 -1, 3, 5- 三嗪 -2- 基) -4- 甲基吗啉鎓
[0581]	DPPA	二苯基磷酰基叠氮化物
[0582]	DTT	二硫苏糖醇
[0583]	EDC	乙基碳二酰亚胺盐酸盐
[0584]	EDCI	1- 乙基 -3-[3-(二甲基氨基) 丙基] 碳二酰亚胺盐酸盐
[0585]	EDTA	乙二胺四乙酸
[0586]	ESI	电喷射离子化
[0587]	Et ₃ N、TEA	三乙胺
[0588]	EtOAc、EtAc	乙酸乙酯
[0589]	EtOH	乙醇
[0590]	g	克
[0591]	h	小时
[0592]	HBTU	O- 苄并三唑 -1- 基 -N, N, N', N' - 四甲基脲六氟磷酸盐

- [0593] HOBt 1- 羟基苯并三唑
- [0594] IC₅₀ 使所测活性降低 50%的抑制剂浓度
- [0595] LAH 氢化锂铝
- [0596] LDA 二异丙基氨基锂
- [0597] LCMS 液相色谱质谱法
- [0598] MeI 碘甲烷
- [0599] MeOH 甲醇
- [0600] min 分钟
- [0601] mmol 毫摩尔
- [0602] NMM 4- 甲基吗啉
- [0603] NMP N- 甲基吡咯烷酮
- [0604] PG 保护基
- [0605] PTT 苯基三甲基三溴化物
- [0606] Py 吡啶
- [0607] rt 室温
- [0608] TEA 三乙胺
- [0609] Tf 三氟甲磺酸盐
- [0610] TFA 三氟乙酸
- [0611] TFAA 三氟乙酸酐
- [0612] THF 四氢呋喃
- [0613] TLC 薄层色谱法

[0614] 下文所用试剂和溶剂可得自诸如 Aldrich Chemical Co. (Milwaukee, Wisconsin, USA) 的商业来源。在 Bruker 400MHz 或 500MHz NMR 波谱仪上记录 ¹H-NMR 谱。将显著的峰以下列顺序列表：多重性 (s, 单峰; d, 双重峰; t, 三重峰; q, 四重峰; m, 多重峰; br s, 宽单峰)、以赫兹 (Hz) 计的耦合常数及质子数。在 Hewlett-Packard 1100MSD 电喷雾质谱仪上采用用于样品递送的 HP1100HPLC 来进行电喷雾离子化 (ESI) 质谱分析。质谱结果以质量与电荷的比率, 然后以各离子的相对丰度 (括号内) 或含最常见原子同位素的 M+H (或如所示 M-H) 离子的单独 m/z 值来报告。在所有情况下, 同位素图谱与预期化学式对应。通常, 将分析物以 0.1mg/mL 溶解于甲醇中, 并将 5 微升与递送溶剂一起注入自 100 至 1500 道尔顿扫描的质谱仪中。所有化合物可使用乙腈 /H₂O 梯度液 (10% -90%) (含 0.1% 甲酸的 H₂O 中的乙腈) 作为递送溶剂, 以正 ESI 模式进行分析。下文提供的化合物也可使用乙腈 /H₂O 中的 2mM NH₄OAc 作为递送溶剂, 以负 ESI 模式进行分析。采用配备有手性 HPLC 柱 (ChiralPak AD, 4.6mm×150mm) 的 Hewlett-Packard Series 1050 系统并采用以 5:95 异丙醇 - 己烷作为流动相的等度洗脱来测定对映体纯度。

[0615] 使用来自 Cambridge Soft Inc. 的 ChemDraw 程序命名化合物。

[0616]



方案 1-1

[0617] 实施例 1 - 式 IIc 化合物的合成

[0618] 方案 1-1 描述具有对称和非对称官能化末端的靶分子及其类似物的制备。

[0619] 步骤 a: 在 0°C 下, 向 2-溴萘 a (62.0g, 300mmol) 在 DCM (1L) 中的溶液里添加 AlCl_3 (44.0g, 330mmol) 和 2-氯乙酰氯 (34.0g, 330mmol)。将反应混合物在 0°C 下搅拌 1 小时, 然后添加 H_2O (500mL) 并萃取。将有机层用 H_2O 洗涤, 经无水 Na_2SO_4 干燥, 在减压下蒸发得到 80g 粗产物, 将其从 10% EtOAc-己烷 (v/v) 中再结晶纯化得到白色固体 b (28g, 36% 收率): ^1H NMR (500MHz, CDCl_3) δ 8.44 (s, 1H)、8.07 (s, 1H)、8.04 (d, $J = 11.0\text{Hz}$, 1H)、7.84 (d, $J = 8.5\text{Hz}$, 2H)、7.66 (d, $J = 8.5\text{Hz}$, 1H)、4.81 (s, 2H) ppm; LCMS (ESI) m/z 282.9 ($\text{M}+\text{H}$) $^+$ 。

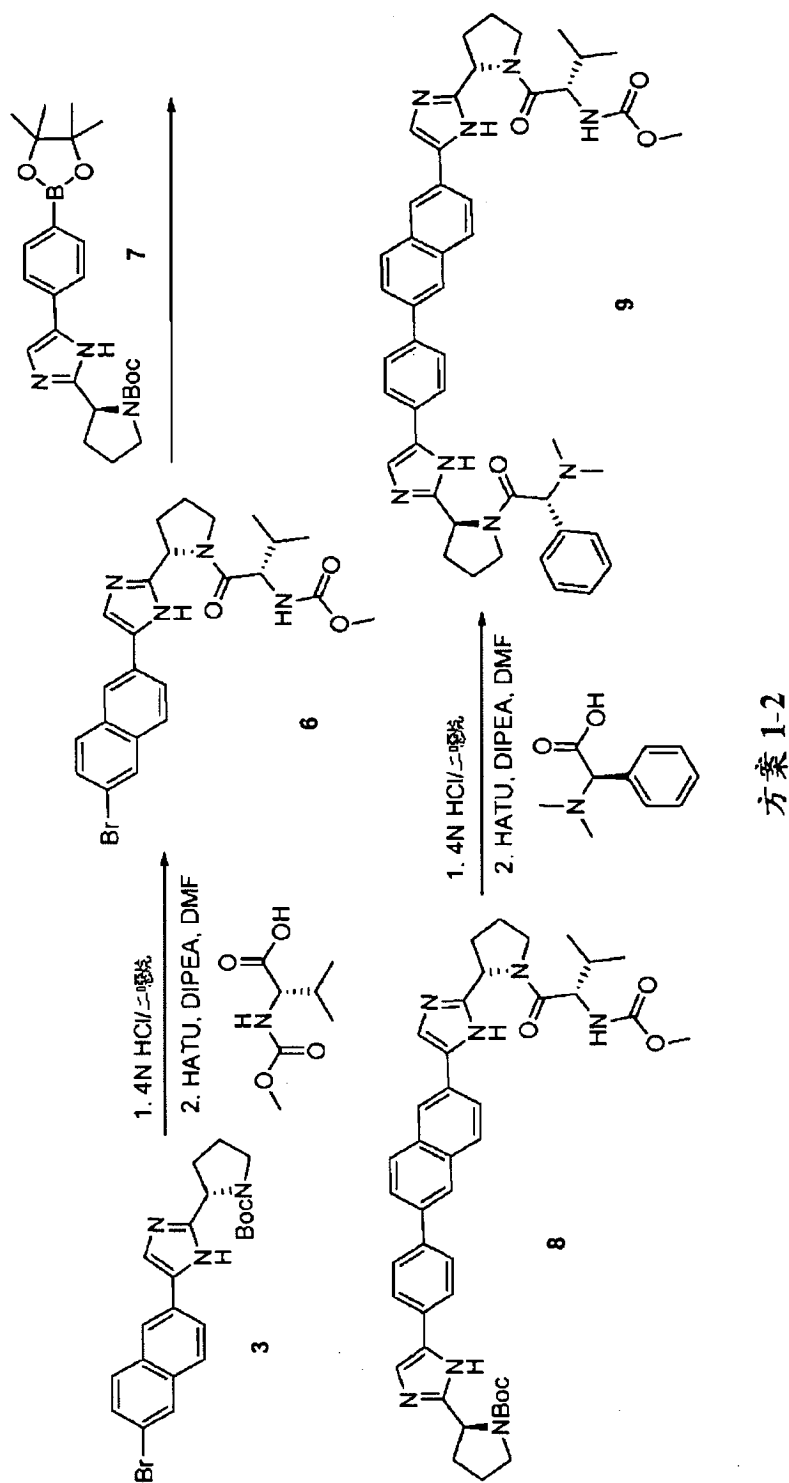
[0620] 步骤 b: 向 b(28.0g, 100mmol) 在 DCM(500mL) 中的溶液里添加 N-Boc-L-Pro-OH(24.7g, 115mmol) 和 Et_3N (70.0mL, 500mmol), 并将混合物在室温下搅拌 2 小时。将混合物在减压下浓缩得到粗产物 c, 其不经进一步纯化便用于下一步骤中。LC-MS(ESI) m/z 462.1 (M+H)⁺。

[0621] 步骤 c: 向 c(46.0g, 100mmol) 在甲苯(500mL) 中的溶液里添加 NH_4OAc (77g, 1.0mol), 并将混合物在 110°C 下搅拌过夜, 且在减压下浓缩。将所得残留物通过硅胶柱色谱法(石油醚/EtOAc 1:1(v/v)) 纯化, 得到黄色固体 d(30g, 68% 收率): LC-MS(ESI) m/z 442.1 (M+H)⁺。

[0622] 步骤 d: 向 d(10.0g, 23.0mmol) 在无水 DME(200mL) 和等摩尔硼酸酯 e 中的溶液里添加 PPh_3 (1.2g, 4.6mmol)、 $\text{Pd}(\text{PPh}_3)_4$ (1.6g, 2.3mmol) 和 2.0M Na_2CO_3 溶液。将混合物在氩气下回流过夜。将有机溶剂在减压下移除, 并将残留物用 H_2O 处理, 用 EtOAc (2×200mL) 进行萃取。干燥合并的有机相, 过滤并在真空中浓缩以得到残留物, 将其通过硅胶柱色谱法(石油醚/EtOAc 3:1(v/v)) 纯化, 得到黄色固体 f(10g, 96% 收率)。LC-MS(ESI) m/z 709.3 (M+H)⁺。

[0623] 步骤 e: 向 f(150mg, 0.29mmol) 在二噁烷(3mL) 的搅拌溶液中滴加二噁烷(3mL) 中的 4.0N HCl。将混合物在室温下搅拌 4 小时, 然后浓缩得到略带黄色的固体(134mg), 将其直接用于下一步骤。将残留物(134mg, 0.290mmol) 悬浮于 THF(5mL) 中, 并添加 DIPEA(0.32mL), 随后添加 N-甲氧羰基-L-Val-OH(151mg, 0.860mmol)。搅拌 15 分钟后, 添加 HATU(328mg, 0.860mmol), 并将混合物在室温下再搅拌 2 小时, 然后浓缩。将残留物通过制备性 HPLC 纯化, 得到 g(40mg, 19% 收率)。

[0624]



[0625] 步骤a:参见方案1-2,向化合物3(2.0g, 4.5mmol)在二噁烷(25mL)中的溶液里添加二噁烷(25mL)中的4.0N HCl。在室温下搅拌4小时后,将反应混合物浓缩,并将残留物在真空中干燥,得到略带黄色的固体(2.1g),其不经进一步纯化便直接用于下一步骤。

[0626] 步骤 b: 向步骤 a(4.5mmol) 中的残留物中添加 DMF(25mL), 然后添加 DIPEA(3.7mL, 22.5mmol) 和 N-氨基甲酸甲酯-L-缬氨酸(945mg, 5.4mmol)。在室温下搅拌 15 分钟后, 向 H₂O(400mL) 中缓慢添加反应混合物。过滤沉淀的白色固体并干燥, 得到化合

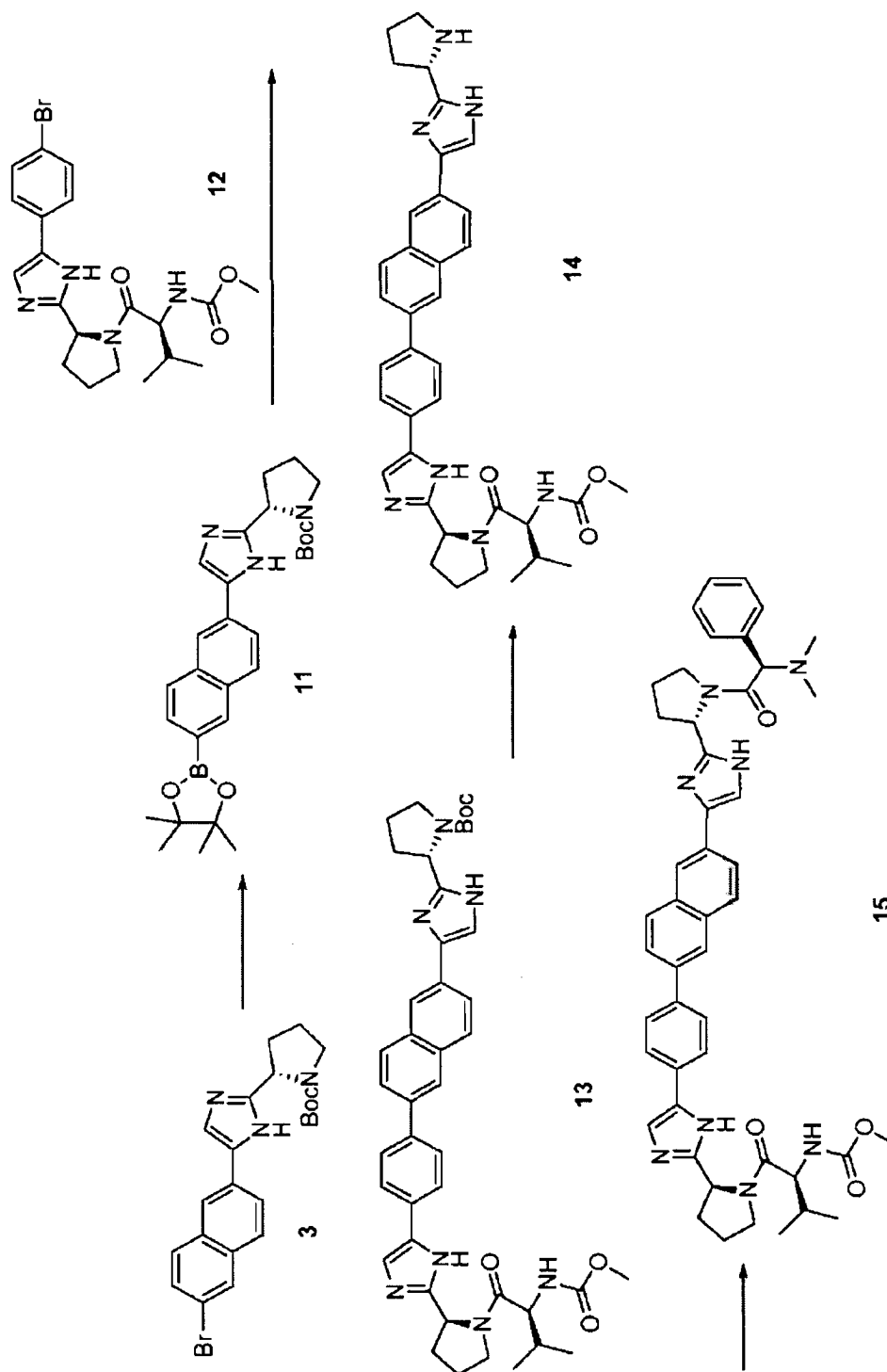
物 6 (2.2g, 98% 收率)。LC-MS (ESI) :m/z 499.1 (M+H)⁺。

[0627] 步骤 c: 向化合物 6 (800mg, 1.6mmol)、化合物 7 (718mg, 1.6mmol) 和 NaHCO₃ (480mg, 5.7mmol) 在 1,2-二甲氧基乙烷 (15mL) 和 H₂O (5mL) 中的混合物里添加 Pd(dppf)Cl₂ (59mg, 0.08mmol)。在 N₂ 气氛中于 80°C 下搅拌过夜后, 浓缩反应混合物。使残留物在 20% 甲醇 / CHCl₃ (100mL) 与 H₂O (100mL) 之间分开。将有机相分离, 并用 20% 甲醇 / CHCl₃ (100mL) 再次萃取水相。将合并的有机相随后用盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 15:1 (v/v)) 纯化, 得到黄色固体化合物 8 (1.0g, 85% 收率)。LC-MS (ESI) :m/z 732.4 (M+H)⁺。

[0628] 步骤 d: 向化合物 8 (200mg, 0.27mmol) 在二噁烷 (3.0mL) 中的溶液里添加二噁烷 (3.0mL) 中的 4N HCl。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 从而以定量收率得到 HCl 盐, 其不经进一步纯化便直接用于下一步骤。

[0629] 步骤 e: 向所述盐 (0.27mmol) 在 DMF (5.0mL) 中的溶液里添加 DIPEA (0.47mL, 2.7mmol), 然后添加 N,N-二甲基-D-苯基甘氨酸 (59mg, 0.33mmol) 和 HATU (125mg, 0.33mmol)。在室温下搅拌 1 小时后, 使反应混合物在 H₂O 与 DCM 之间分开。将有机相随后用 H₂O 和盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过制备性 HPLC 纯化, 得到化合物 9。LC-MS (ESI) :m/z 793.4 (M+H)⁺。

[0630]



方案 1-3

[0631] 步骤a: 向化合物3(3.2g, 7.2mmol)、双(频哪醇合)二硼(3.86g, 15.2mmol)和KOAc(1.85g, 18.8mmol)在1,4-二噁烷(100mL)中的混合物里添加Pd(dppf)Cl₂(440mg, 0.6mmol)。在N₂气氛中于80℃下搅拌3小时后, 浓缩反应混合物。将残留物通过硅胶柱色谱法(石油醚/EtOAc = 2/1(v/v))纯化, 得到白色固体化合物11(2.8g, 80%收率)。LC-MS(ESI): m/z 490.3 (M+H)⁺。

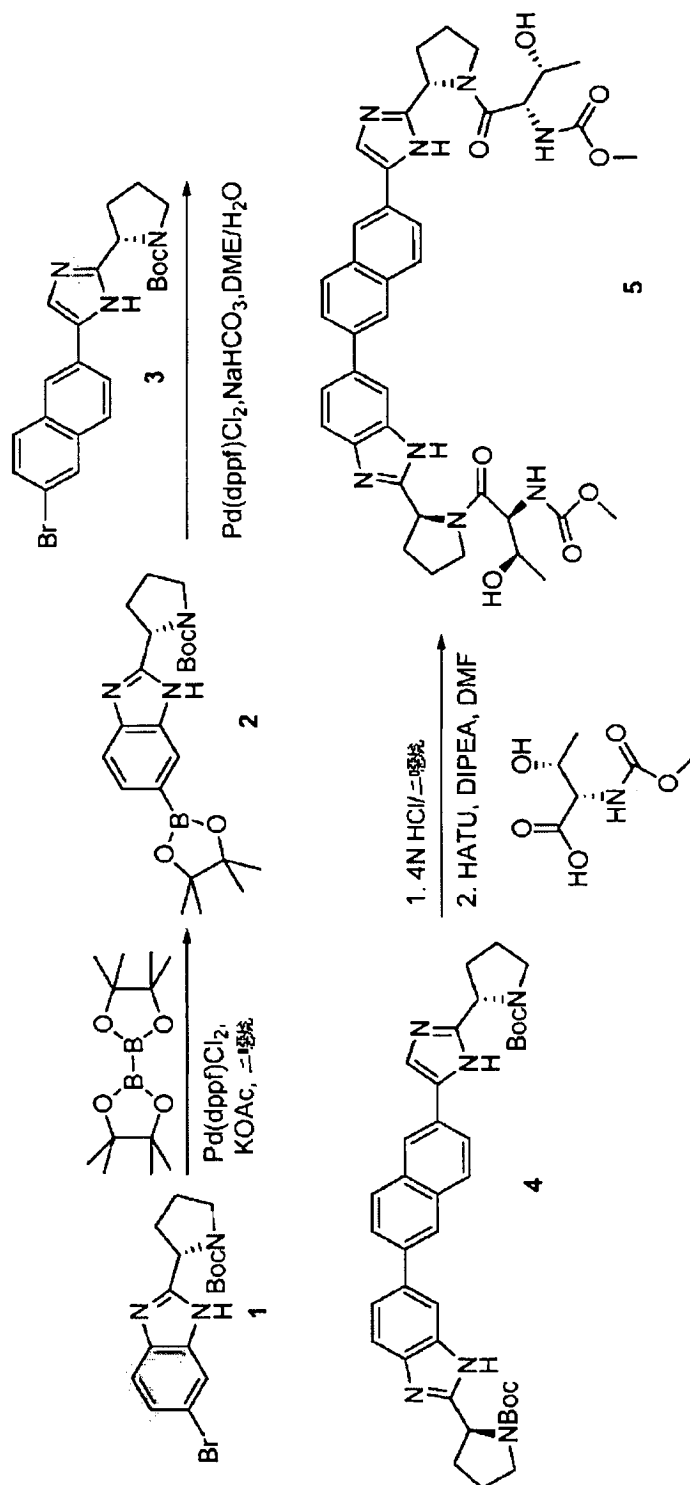
[0632] 步骤 b: 向化合物 11 (626mg, 1.27mmol)、化合物 12 (570mg, 1.27mmol) 和

NaHCO_3 (420mg, 4.99mmol) 在 1,2-二甲氧基乙烷 (30mL) 和 H_2O (10mL) 中的混合物里添加 Pd(dppf)Cl_2 (139mg, 0.19mmol)。在 N_2 气氛中于 80°C 下搅拌过夜后, 浓缩反应混合物。使残留物在 20% 甲醇/ CHCl_3 (100mL) 与 H_2O (100mL) 之间分开。用 20% 甲醇/ CHCl_3 (100mL) 再次萃取水相。将合并的有机相随后用盐水洗涤, 用无水 Na_2SO_4 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法 (石油醚/ $\text{EtOAc} = 2/1$ (v/v)) 纯化, 得到黄色固体化合物 13 (635mg, 68% 收率)。LC-MS (ESI) : m/z 732.4 ($\text{M}+\text{H}$)⁺。

[0633] 步骤 c: 向化合物 13 (200mg, 0.27mmol) 在二噁烷 (3.0mL) 中的溶液里添加二噁烷 (3.0mL) 中的 4N HCl 。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 从而以定量收率得到化合物 14 的 HCl 盐, 其不经进一步纯化便直接用于下一步骤。

[0634] 步骤 d: 向所述盐 (0.27mmol) 在 DMF (5.0mL) 中的溶液里添加 DIPEA (0.47mL, 2.7mmol), 然后添加 N,N-二甲基-D-苯基甘氨酸 (59mg, 0.33mmol) 和 HATU (125mg, 0.33mmol)。在室温下搅拌 1 小时后, 将反应混合物在 H_2O 与 DCM 之间分开。将有机相随后用 H_2O 和盐水洗涤, 用无水 Na_2SO_4 干燥, 过滤并浓缩。将残留物通过制备性 HPLC 纯化, 得到化合物 15。LC-MS (ESI) : m/z 793.4 ($\text{M}+\text{H}$)⁺。

[0635]



方案 2-1

[0636] 实施例 2 - 式 IIIe 化合物的合成

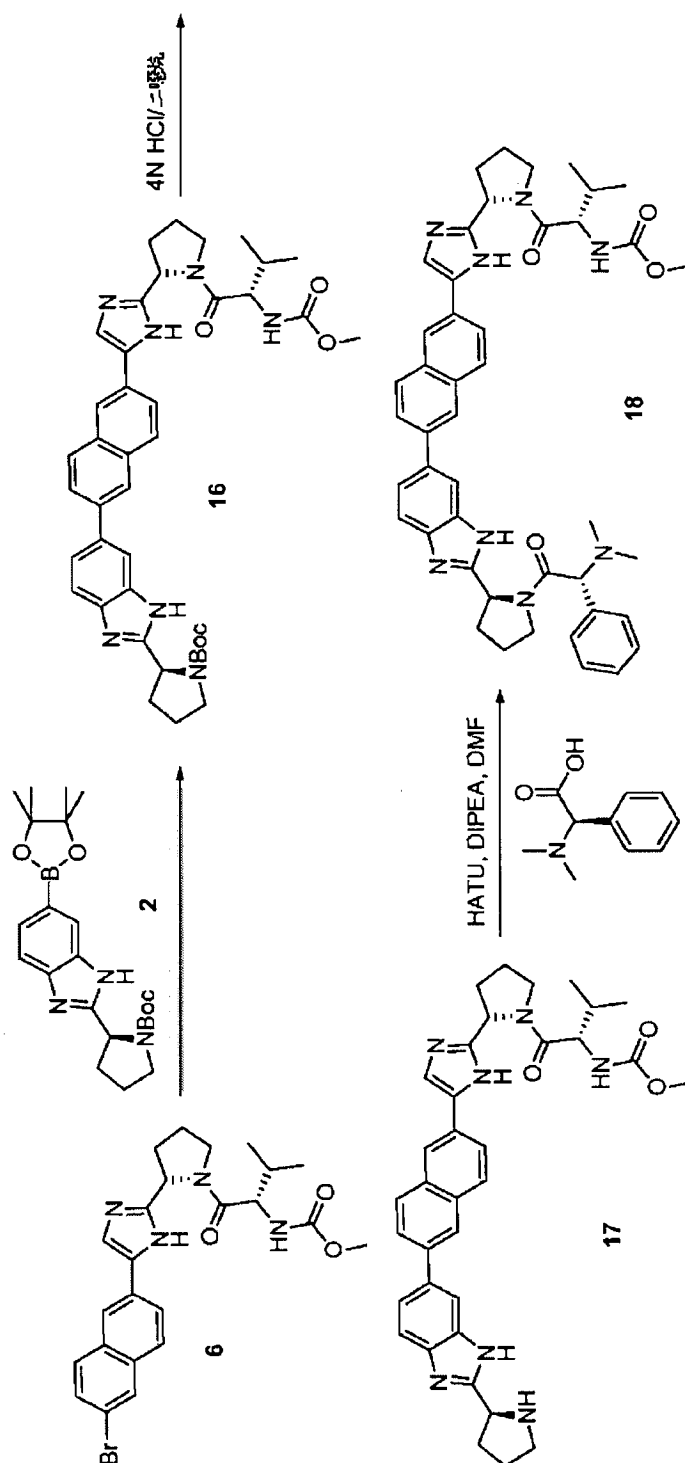
[0637] 步骤 a: 参见方案 2-1, 向化合物 1 (5.05g, 13.8mmol)、双(频哪醇合)二硼 (7.1g, 27.9mmol) 和 KOAc (3.2g, 32.5mmol) 在 1,4-二噁烷 (100mL) 中的混合物里添加 Pd(dppf)Cl_2 (400mg, 0.5mmol)。在 N_2 气氛中于 80°C 下搅拌 3 小时后, 浓缩反应混合物。将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 2/1 (v/v)) 纯化, 得到灰色固体化合物 2 (3.0g, 53% 收率)。LC-MS (ESI): m/z 414.2 ($\text{M}+\text{H}$)⁺。

[0638] 步骤 b: 向化合物 2(522mg, 1.26mmol)、化合物 3(500mg, 1.13mmol) 和 NaHCO_3 (333mg, 3.96mmol) 在 1,2-二甲氧基乙烷(30mL) 和 H_2O (10mL) 中的混合物里添加 $\text{Pd}(\text{dppf})\text{Cl}_2$ (74mg, 0.1mmol)。在 N_2 气氛中于 80°C 下搅拌过夜后, 浓缩反应混合物。将残留物在 20% 甲醇/ CHCl_3 (100mL) 与 H_2O (100mL) 之间分开。将有机相分离, 并用 20% 甲醇/ CHCl_3 (100mL) 再次萃取水相。将合并的有机相随后用盐水洗涤, 用无水 Na_2SO_4 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法($\text{DCM}/\text{MeOH} = 50:1(\text{v/v})$) 纯化, 得到黄色固体化合物 4(450mg, 55% 收率)。LC-MS(ESI) : m/z 649.3 ($\text{M}+\text{H}$)⁺。

[0639] 步骤 c: 向化合物 4(160mg, 0.25mmol) 在二噁烷(2.0mL) 中的溶液里添加二噁烷中的 4N HCl (2.0mL)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 从而以定量收率得到 HCl 盐, 其不经进一步纯化便直接用于下一步骤。

[0640] 步骤 d: 向上述盐(0.25mmol) 在 DMF(4.0mL) 中的溶液里添加 DIPEA(0.44mL, 2.5mmol), 然后添加 N-氨基甲酸甲酯-L-苏氨酸(110mg, 0.62mmol) 和 HATU(240mg, 0.63mmol)。在室温下搅拌 1 小时后, 将反应混合物在 H_2O 与 DCM 之间分开。将有机相随后用 H_2O 和盐水洗涤, 用无水 Na_2SO_4 干燥, 过滤并浓缩。将残留物通过制备性 HPLC 纯化, 得到白色粉末化合物 5。LC-MS(ESI) : m/z 767.3 ($\text{M}+\text{H}$)⁺。

[0641]



方案 2-2

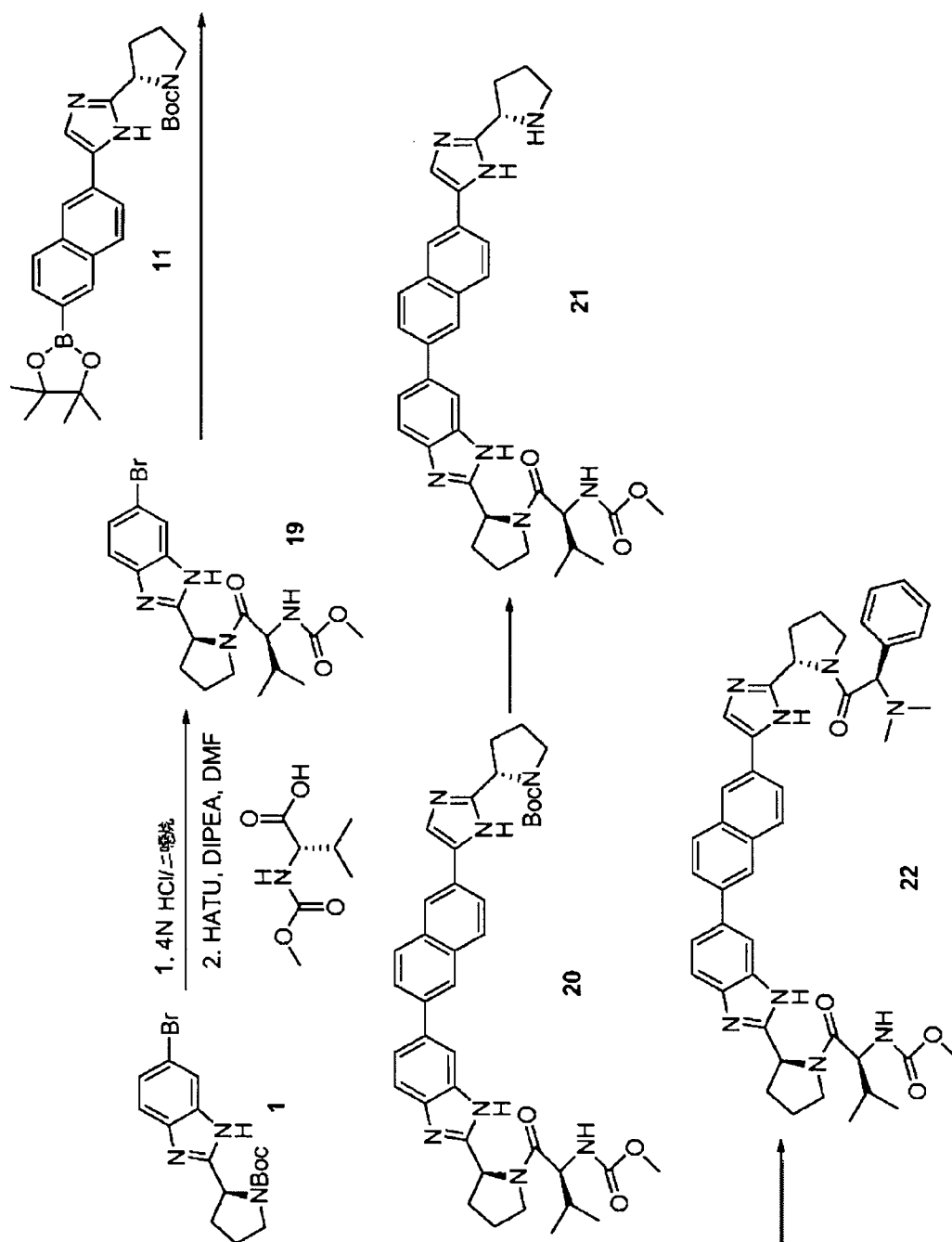
[0642] 步骤 a: 参见方案 2-2, 向化合物 2 (1.16g, 2.32mmol)、化合物 6 (1.40g, 3.39mmol) 和 NaHCO_3 (823mg, 9.8mmol) 在 1, 2-二甲氧基乙烷 (30mL) 和 H_2O (10mL) 中的混合物里添加 $\text{Pd}(\text{dppf})\text{Cl}_2$ (103mg, 0.14mmol)。在 N_2 气氛中于 80°C 下搅拌过夜后, 浓缩反应混合物。将残留物在 20% 甲醇/ CHCl_3 (150mL) 与 H_2O (150mL) 之间分开。用 20% 甲醇/ CHCl_3 (150mL) 再次萃取水相。将合并的有机相随后用盐水洗涤, 用无水 Na_2SO_4 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 1.5/1 (v/v)) 纯化, 得到黄色固体化合物 16 (1.32g, 80%)

收率)。LC-MS (ESI) :m/z 706.4 (M+H)⁺。

[0643] 步骤 b: 向化合物 16 (200mg, 0.28mmol) 在二噁烷 (3.0mL) 中的溶液里添加二噁烷 (3.0mL) 中的 4N HCl。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 从而以定量收率得到化合物 17 的 HCl 盐, 将其直接用于下一步骤。

[0644] 步骤 c: 向所述盐 (0.28mmol) 在 DMF (5.0mL) 中的溶液里添加 DIPEA (0.49mL, 2.8mmol), 然后添加 N,N-二甲基-D-苯基甘氨酸 (61mg, 0.34mmol) 和 HATU (129mg, 0.34mmol)。在室温下搅拌 1 小时后, 将反应混合物在 H₂O 与 DCM 之间分开。将有机相随后用 H₂O 和盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过制备性 HPLC 纯化, 得到化合物 18。LC-MS (ESI) :m/z 767.4 (M+H)⁺。

[0645]



方案 2-3

[0646] 步骤 a: 参见方案 2-3, 向化合物 1 (4.0g, 10.9mmol) 在二噁烷 (40mL) 中的溶液里添加二噁烷 (40mL) 中的 4N HCl。在室温下搅拌过夜后, 浓缩反应混合物。将残留物用 DCM 洗涤, 过滤并在真空中干燥, 从而以定量收率得到盐酸盐, 其不经进一步纯化便用于下一步骤。

[0647] 步骤 b: 向所述盐 (10.9mmol) 在 DMF (30mL) 中的溶液里添加 DIPEA (5.8mL, 33.0mmol), 然后添加 N-甲氧羰基-L-缬氨酸 (2.1g, 12.1mmol) 和 HATU (4.6g, 12.1mmol)。在室温下搅拌 1 小时后, 将反应混合物在 H₂O 与 DCM 之间分开。将有机相随后用 H₂O 和盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法 (DCM/石油醚 = 4/1(v/v)) 纯化, 得到化合物 19 (3.0g, 65% 收率)。LC-MS (ESI) :m/

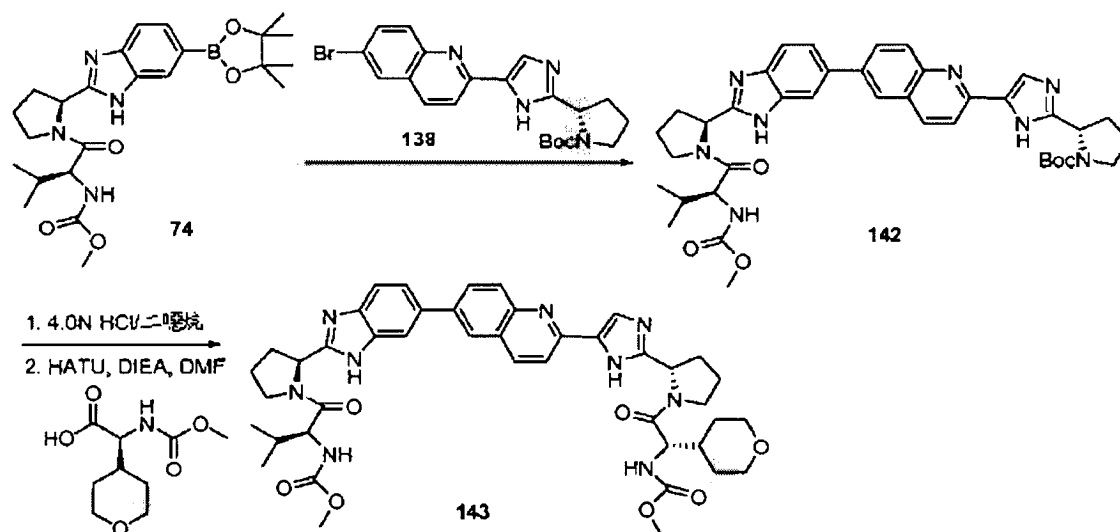
z423.1 (M+H)⁺。

[0648] 步骤 c: 向化合物 11 (800mg, 1.9mmol)、化合物 19 (700mg, 1.7mmol) 和 NaHCO₃ (561mg, 6.6mmol) 在 1,2-二甲氧基乙烷 (60mL) 和 H₂O (20mL) 中的混合物里添加 Pd(dppf)Cl₂ (183mg, 0.25mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后, 浓缩反应混合物。然后将残留物在 20% 甲醇 / CHCl₃ (100mL) 与 H₂O (100mL) 之间分开。用 20% 甲醇 / CHCl₃ (100mL) 再次萃取水相。将合并的有机相随后用盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 2/1 (v/v)) 纯化, 得到黄色固体化合物 20 (600mg, 52% 收率)。LC-MS (ESI) : m/z 706.4 (M+H)⁺。

[0649] 步骤 d: 向化合物 20 (200mg, 0.28mmol) 在二噁烷 (3.0mL) 中的溶液里添加二噁烷 (3.0mL) 中的 4N HCl。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 从而以定量收率得到化合物 21 的 HCl 盐, 其不经进一步纯化便直接用于下一步骤。

[0650] 步骤 e: 向化合物 21 (0.28mmol) 在 DMF (5.0mL) 中的溶液里添加 DIPEA (0.49mL, 2.8mmol), 然后添加 N,N-二甲基-D-苯基甘氨酸 (64mg, 0.36mmol) 和 HATU (129mg, 0.34mmol)。在室温下搅拌 1 小时后, 将反应混合物在 H₂O 与 DCM 之间分开。将有机相随后用 H₂O 和盐水洗涤, 用无水 Na₂SO₄ 干燥, 过滤并浓缩。将残留物通过制备性 HPLC 纯化, 得到化合物 22。LC-MS (ESI) : m/z 767.4 (M+H)⁺。

[0651]



方案 2-4

[0652] 步骤 a: 在 N₂ 气氛中于室温下, 向化合物 74 (510mg, 1.09mmol)、化合物 138 (300mg, 0.68mmol)、NaHCO₃ (228mg, 2.72mmol) 在 1,2-二甲氧基乙烷 (20mL) 和 H₂O (5mL) 中的混合物里添加 Pd(dppf)Cl₂·CH₂Cl₂ (111mg, 0.140mmol)。在 80℃ 下于 N₂ 气氛中搅拌过夜后, 将反应混合物浓缩, 并将残留物用 EtOAc (100mL) 和 H₂O (25mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 1/2 (v/v)) 纯化, 得到黄色固体化合物 142 (360mg, 75% 收率)。LC-MS (ESI) : m/z 707.4 (M+H)⁺。

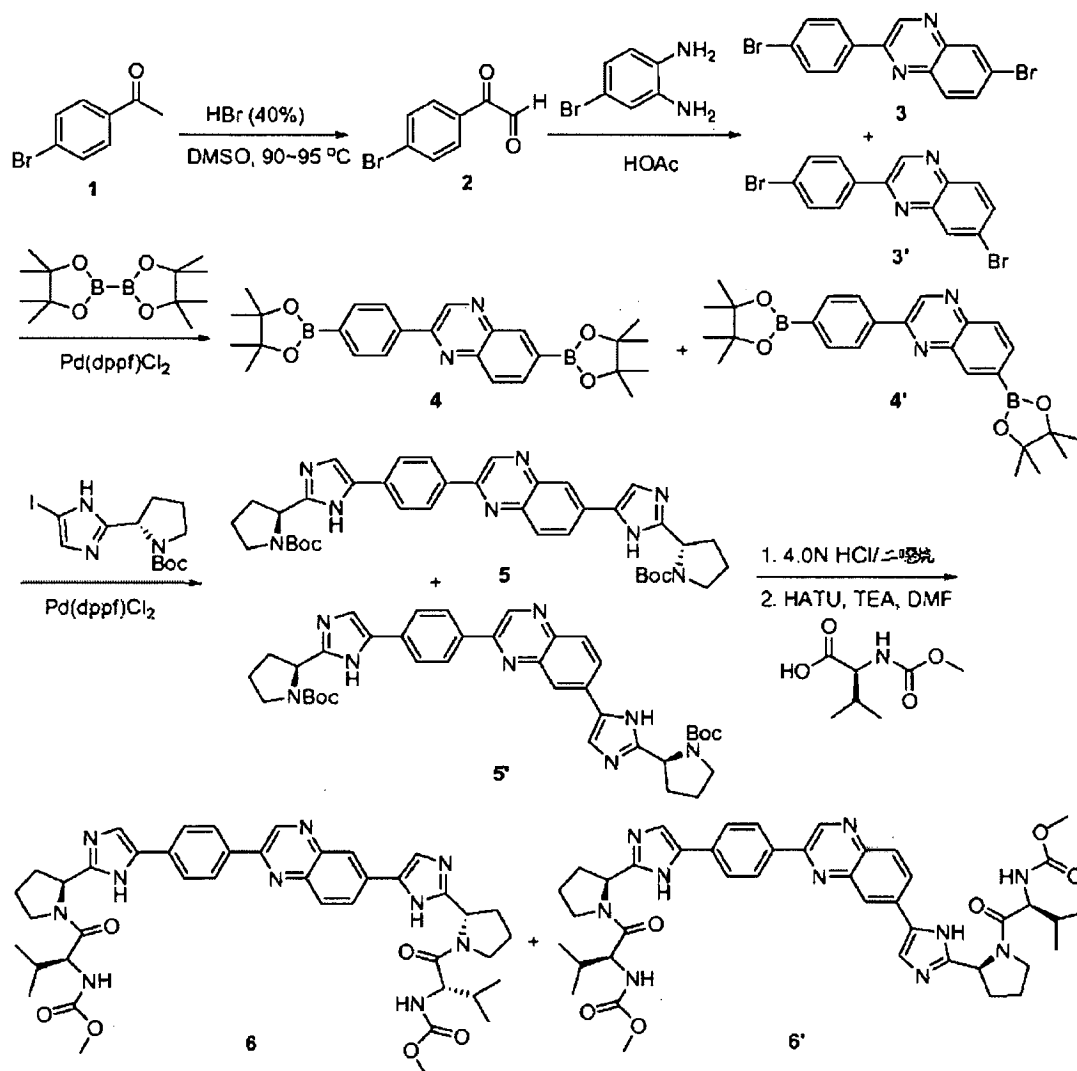
[0653] 步骤 b: 在室温下, 向化合物 142 (115mg, 0.16mmol) 在二噁烷 (2.0mL) 中的溶液里

添加二噁烷中的 4N HCl (2.0mL)。在室温下搅拌过夜后,将反应混合物浓缩,并将残留物在真空中干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS (ESI) m/z 607. 3 (M+H) $^{+}$ 。

[0654] 步骤 c: 随后,将所述 HCl 盐溶解于 DMF (2mL) 中,并向所得混合物中添加 DIEA (0.28mL, 1.6mmol)、N-Moc-L-(四氢-2H-吡喃-4-基)甘氨酸 (41mg, 0.19mmol) 和 HATU (73mg, 0.19mmol)。在室温下搅拌 15 分钟后,将反应混合物浓缩,并将残留物通过制备性 HPLC 纯化,得到化合物 143。LC-MS : (ESI) m/z 806. 4 (M+H) $^{+}$ 。

[0655] 实施例 3 - 其它式 IIc 化合物的合成

[0656]



方案 3-1

[0657] 步骤 a: 参见方案 3-1, 在室温下, 向化合物 1 (49.7g, 0.25mol) 在 DMSO 中的溶液里滴加 40% 的 HBr (0.50mol) 水溶液。在 90℃ 下搅拌 3 小时后, 将反应混合物倒入 H₂O 中, 并将所得混合物保持在 50 ~ 60℃ 下。将黄色固体通过过滤收集, 并在丙酮/H₂O (1/19 (v/v)) 中再结晶两次, 得到化合物 2 (50g, 87% 收率)。LC-MS (ESI) : m/z 212. 9 (M+H) $^{+}$ 。

[0658] 步骤 b: 将 2 (19.0g, 80.0mmol) 和 4-溴苯-1,2-二胺 (15.0g, 80.0mmol) 在

H₂OAc(180mL) 中的混合物回流过夜。随后,将反应混合物倒入冰 H₂O 中。将固体通过过滤收集,并通过硅胶柱色谱法纯化,得到一对区域异构体化合物 3 和 3' (2.8g, 10% 收率)。LC-MS (ESI) :m/z362.9 (M+H)⁺。

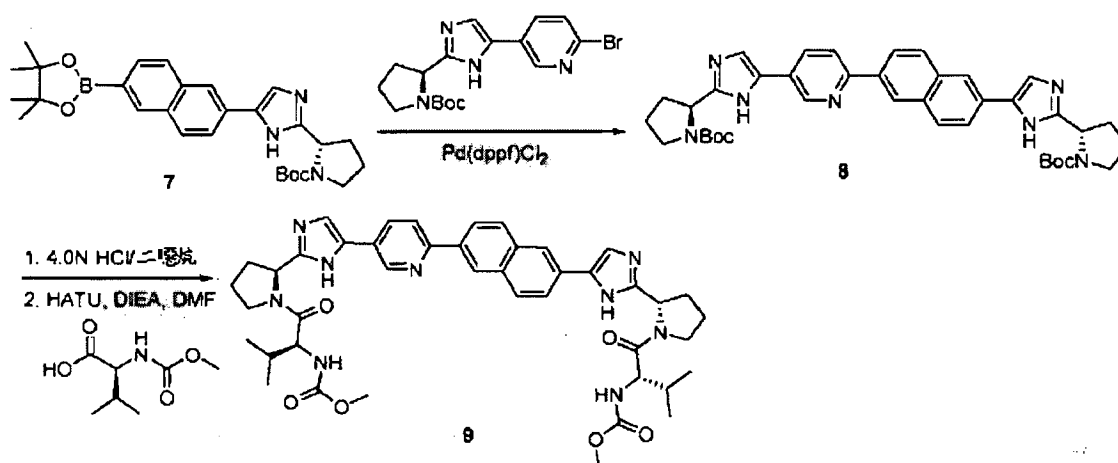
[0659] 步骤 c:将化合物 3 (4.8g, 5.4mmol)、双(频哪醇合)二硼(9.6g, 38mmol)、醋酸钾(3.8g, 38mmol) 和 Pd(dppf)Cl₂·CH₂Cl₂(524mg, 0.54mmol) 在二噁烷(100mL) 中的混合物在氩气氛中于 80℃ 下搅拌 17 小时。随后,过滤反应混合物。将滤饼用 EtOAc(50mL×3) 洗涤若干次。将滤液用 H₂O 洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法(PE/ 丙酮= 10:1(v/v)) 纯化,得到一对区域异构体化合物 4 和 4' (2.2g, 89% 收率)。LC-MS (ESI) :m/z459.3 (M+H)⁺。(还将相应的硼酸分离,并用作下一步骤的活性中间体)。

[0660] 步骤 d:将化合物 4 和 4' (1.0g, 2.2mmol)、(S)-2-(5-碘-1H-咪唑-2-基)吡咯烷-1-羧酸叔丁酯(2.0g, 5.4mmol)、碳酸氢钠(1.5g, 18mmol) 和 Pd(dppf)Cl₂·CH₂Cl₂(427mg, 0.44mmol) 在 DME/H₂O(3/1(v/v)) (80mL) 中的混合物在氩气氛中于 80℃ 下搅拌 17 小时。随后,将反应混合物浓缩,并将残留物用 EtOAc(100mL) 稀释。将有机层用盐水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法(PE/ 丙酮= 10:1(v/v)) 纯化,得到一对区域异构体化合物 5 和 5' (590mg, 40% 收率)。LC-MS (ESI) :m/z677.3 (M+H)⁺。

[0661] 步骤 e:将化合物 5 和 5' (200mg, 0.3mmol) 在二噁烷中的 4.0N HCl(10mL) 中的混合物在室温下搅拌过夜。将溶剂移除,并将残留物在真空中干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z477.2 (M+H)⁺。

[0662] 步骤 f:随后,将所述 HCl 盐溶解于 DMF(2mL) 中,并向所得混合物中依次添加 Et₃N(304mg, 3.0mmol)、N-Moc-L-Val-OH(116mg, 0.66mmol) 和 HATU(251mg, 0.66mmol)。在室温下搅拌 2 小时后,将反应混合物倒入 H₂O(50mL) 中,并将所得悬浮液用 DCM 萃取若干次(20mL×3)。将萃取物合并,用盐水洗涤,并用无水 MgSO₄ 干燥。将溶剂移除,并将残留物通过制备性 HPLC 纯化,得到一对区域异构体化合物 6 和 6'。LC-MS (ESI) :m/z791.4 (M+H)⁺。

[0663]



方案 3-2

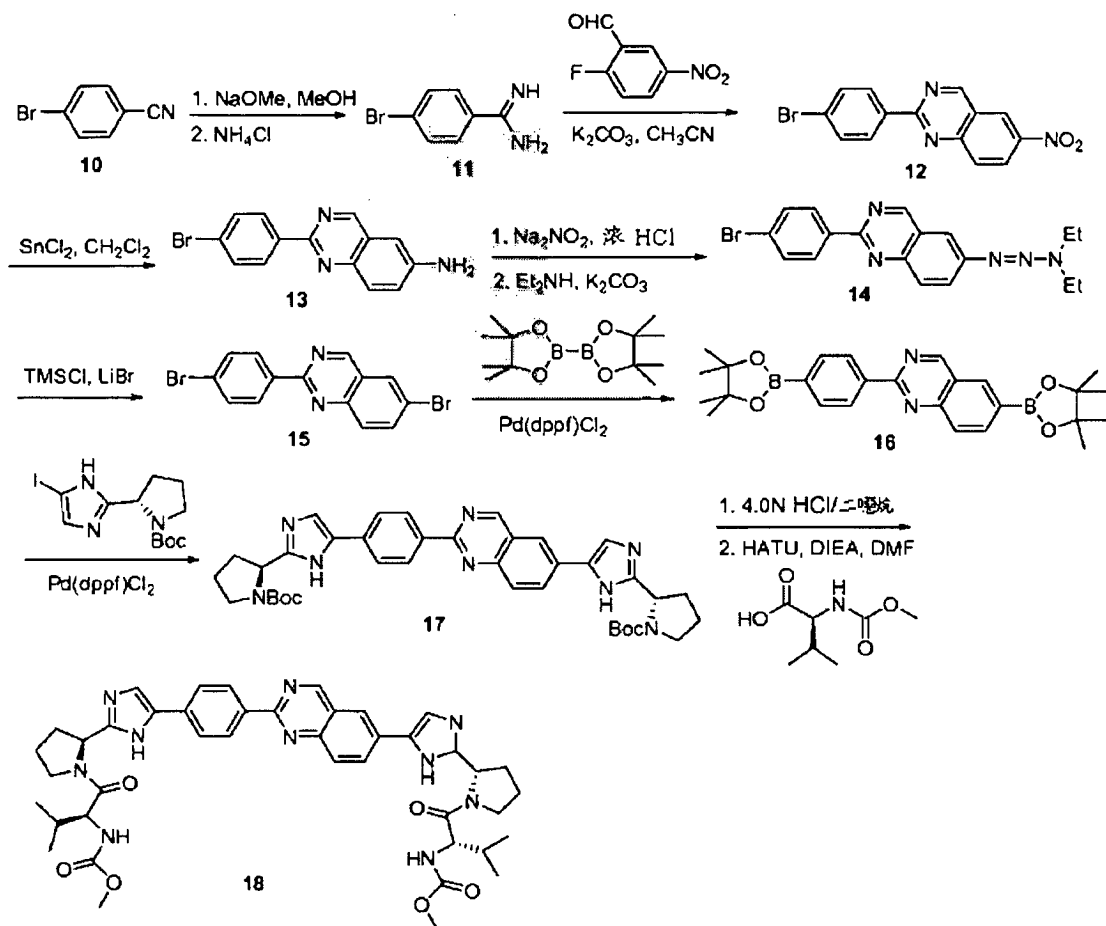
[0664] 步骤 a:参见方案 3-2,在氩气氛中于室温下,向化合物 7(909mg, 1.86mmol)、

(S)-2-(5-(6-溴吡啶-3-基)吡咯烷-1-羧酸叔丁酯 (800mg, 2.04mmol) 和 NaHCO_3 (625mg, 7.44mmol) 在 1,2-二甲氧基乙烷 (100mL) 和 H_2O (30mL) 的溶液中添加 Pd(dppf)Cl_2 (152mg, 0.186mmol)。在 80°C 下于氩气氛中搅拌过夜后, 浓缩反应混合物。将残留物用 CH_2Cl_2 (200mL) 稀释。将有机层用 H_2O 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 ($\text{DCM}/\text{MeOH} = 50:1 (\text{v/v})$) 纯化, 得到化合物 8 (700mg, 55% 收率)。LC-MS (ESI) : m/z : 676.4 ($\text{M}+\text{H}$)⁺。

[0665] 步骤 b: 向化合物 8 (200mg, 0.296mmol) 在二噁烷 (3mL) 中的搅拌溶液里添加二噁烷中的 4.0N HCl (3mL)。在室温下搅拌 4 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z : 476.2 ($\text{M}+\text{H}$)⁺。

[0666] 步骤 c: 随后, 将所述 HCl 盐溶解于 DMF (3mL) 中, 并向所得混合物中依次添加 DIEA (388mg, 3.0mmol)、N-Moc-L-Val-OH (116mg, 0.66mmol) 和 HATU (251mg, 0.66mmol)。在室温下搅拌 2 小时后, 将反应混合物倒入 H_2O (50mL) 中, 并将所得悬浮液用 DCM 萃取若干次 ($20\text{mL} \times 3$)。将萃取物合并, 用盐水洗涤, 并用无水 MgSO_4 干燥。将溶剂移除, 并将残留物通过制备性 HPLC 纯化, 得到化合物 9。¹H NMR (500MHz, 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 ($\text{M}+\text{H}$)⁺。

[0667]



方案 3-3

[0668] 步骤 a: 参见方案 3-3, 在室温下, 向 10 (45.0g, 247mmol) 在 MeOH (500mL) 中的溶液里添加 NaOMe (1.4g, 25mmol)。在室温下搅拌 48 小时后, 向反应混合物中添加 NH₄Cl (13.4g, 250mmol), 并将所得混合物再搅拌 24 小时。将溶剂移除, 并将残留物在真空中干燥, 得到化合物 11, 其不经进一步纯化便用于下一步骤。LC-MS: (ESI) :m/z = 199.0 (M+H)⁺。

[0669] 步骤 b: 向 11 (15g, 75mmol) 在 CH₃CN (500mL) 中的溶液里添加 K₂CO₃ (11.4g, 83.0mmol), 然后添加 2-氟-5-硝基苯甲醛 (12.7g, 75.0mmol)。回流 12 小时后, 将反应混合物浓缩, 并将残留物用 MeOH 洗涤, 得到粗化合物 12 (12g), 其不经进一步纯化便用于下一步骤。LC-MS: (ESI) :m/z = 330.0 (M+H)⁺。

[0670] 步骤 c: 向 12 (5.0g, 15mmol) 在 MeOH (500mL) 中的溶液里添加氯化锡 (II) (14.3g, 75.0mmol) 和浓缩的盐酸 (17mL)。在室温下搅拌 3.5 小时后, 向反应混合物中小心添加饱和 NaHCO₃ 水溶液 (470mL)。将所得混合物用乙酸乙酯 (100mL×3) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 13 (2.5g)。LC-MS: (ESI) :m/z = 300.0 (M+H)⁺。

[0671] 步骤 d: 在 0℃ 下, 向 13 (300mg, 1.0mmol) 在浓缩的 HCl (0.25mL) 中的溶液里滴加 NaNO₂ (76mg, 1.1mmol) 在 H₂O (1mL) 中的溶液。在 0℃ 下搅拌 30 分钟后, 向反应混合物中添加

加 K_2CO_3 (207mg, 1.5mmol) 和 Et_2NH (0.11g, 1.5mmol) 在冰 H_2O (1mL) 中的溶液。随后, 将乙醚 (100mL) 添加到混合物中。将有机层分离, 用 H_2O (15mL) 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 14 (350mg), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 384.1 (M+H)⁺。

[0672] 步骤 e: 在室温下, 向化合物 14 (1.8g, 4.7mmol) 和 LiBr (834mg, 9.6mmol) 在乙腈 (10mL) 中的溶液里添加 TMSCl (782mg, 7.2mmol)。在 60℃ 下搅拌 15 分钟后, 将反应混合物冷却至室温, 并用 5% 的 $NaHCO_3$ 水溶液 (30mL) 处理。将混合物浓缩, 并将残留物用 CH_2Cl_2 (50mL $\times$ 3) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (戊烷/乙醚 = 1/19 (v/v)) 纯化, 得到化合物 15 (1.0g, 59% 收率)。LC-MS : (ESI) : m/z = 362.9 (M+H)⁺。

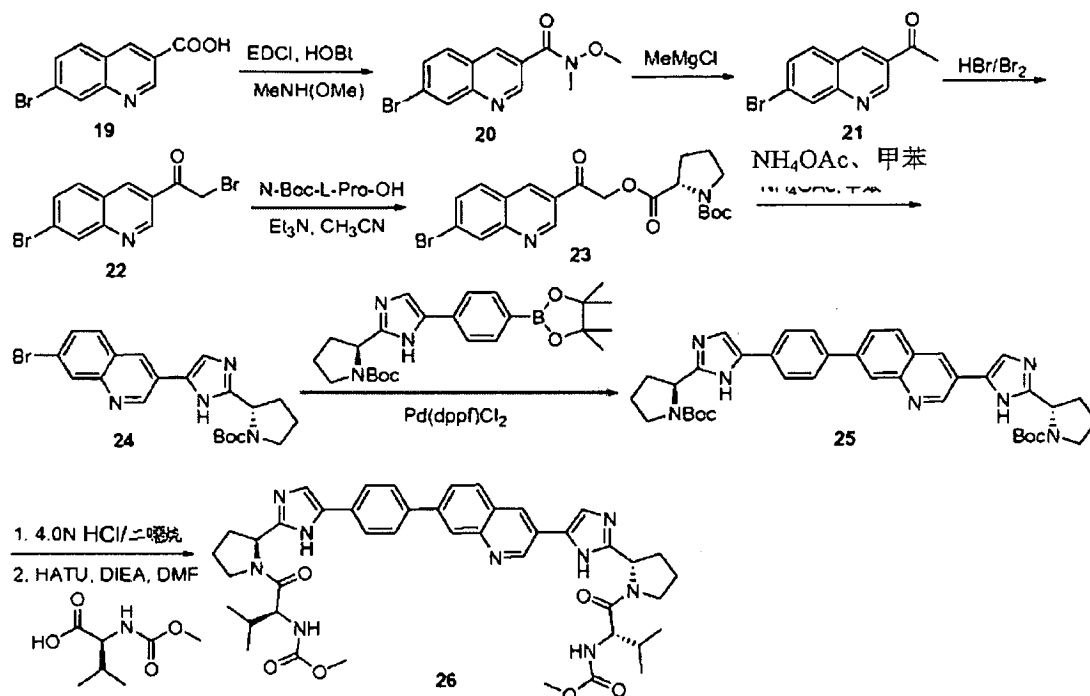
[0673] 步骤 f: 在氩气氛中于室温下, 向 15 (300mg, 0.82mmol) 于二噁烷 (20mL) 中的溶液里依次添加双 (频哪醇合) 二硼 (915mg, 3.63mmol)、醋酸钾 (403mg, 4.12mmol) 和 $Pd(dppf)Cl_2$ (134mg, 0.160mmol)。在氩气氛中于 80℃ 下搅拌 17 小时后, 将反应混合物用 EtOAc (100mL) 稀释。将所得混合物用 H_2O 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (PE/丙酮 = 3/1 (v/v)) 纯化, 得到化合物 16 (227mg, 60% 收率)。LC-MS (ESI) : m/z 459.3 (M+H)⁺。(还将相应的硼酸分离, 并用作下一步骤的活性中间体)。

[0674] 步骤 g: 在氩气氛中于室温下, 向 16 (300mg, 0.65mmol) 在 DME/ H_2O (3/1 (v/v) ; 30mL) 中的溶液里依次添加 (S)-2-(5-碘-1H-咪唑-2-基) 吡咯烷-1-羧酸叔丁酯 (595mg, 1.64mmol)、 $NaHCO_3$ (443mg, 5.28mmol) 和 $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (126mg, 0.13mmol)。在氩气氛中于 80℃ 下搅拌 17 小时后, 将反应混合物用 EtOAc (150mL) 稀释。将有机层分离, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (PE/丙酮 = 2/1 (v/v)) 纯化, 得到略带黄色的固体化合物 17 (151mg, 34% 收率)。LC-MS (ESI) : m/z 677.3 (M+H)⁺。

[0675] 步骤 h: 在室温下, 向化合物 17 (100mg, 0.15mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌过夜后, 将溶剂移除, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 477.2 (M+H)⁺。

[0676] 步骤 i: 向所述 HCl 盐在 DMF (2mL) 中的溶液里添加 DIPEA (0.24mL, 1.5mmol), 然后添加 N-Moc-L-Val-OH (65mg, 0.37mmol) 和 HATU (141mg, 0.37mmol)。在室温下搅拌 30 分钟后, 将反应溶液倒入 H_2O (50mL) 中。过滤悬浮液, 并将固体通过制备性 HPLC 纯化, 得到化合物 18。¹H NMR (500MHz, 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)⁺。

[0677]



方案 3-4

[0678] 步骤 a: 参见方案 3-4, 在室温下, 向 19 (5.00g, 19.8mmol) 在 CH_3CN (200mL) 中的溶液里分别添加 EDCI (9.10g, 47.6mmol)、HOBT (1.34g, 5.95mmol)、 $\text{MeNH}(\text{OMe}) \cdot \text{HCl}$ (2.93g, 30mmol) 和 Et_3N (6.6g, 65.3mmol)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物通过硅胶柱色谱法 (石油醚/ EtOAc = 5/1 (v/v)) 纯化, 得到白色固体化合物 20 (5.1g, 87% 收率)。LC-MS (ESI) : m/z 295.0 ($\text{M}+\text{H}$)⁺。

[0679] 步骤 b: 在 N_2 气氛中于 0℃ 下, 向化合物 20 (2.0g, 6.8mmol) 在 THF (200mL) 中的溶液里缓慢添加 THF 中的 3M MeMgCl (4.5mL)。在 0℃ 下搅拌 1 小时, 然后在室温下搅拌 1 小时后, 通过添加数滴 NH_4Cl 水溶液使反应淬灭。将反应混合物浓缩, 并将残留物用 NaHCO_3 水溶液 (5mL) 和 EtOAc (100mL) 稀释。将有机相用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/ AcOEt = 10:1 (v/v)) 纯化, 得到白色固体化合物 21 (1.0g, 59%)。LC-MS (ESI) : m/z 250.0 ($\text{M}+\text{H}$)⁺。

[0680] 步骤 c: 在室温下, 向化合物 21 (500mg, 2.0mmol) 在 HOAc (20mL) 和 48% HBr 水溶液 (0.5mL) 中的溶液里缓慢添加 48% HBr 水溶液 (0.5mL) 中的 Br_2 (320mg, 2.0mmol)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物用 H_2O (100mL) 稀释。将混合物用 EtOAc (100mL $\times$ 3) 萃取。将萃取物合并, 用饱和 NaHCO_3 (30mL $\times$ 3) 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到白色固体粗化合物 22 (440mg), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 327.9 ($\text{M}+\text{H}$)⁺。

[0681] 步骤 d: 在室温下, 向化合物 22 (415mg, 1.26mmol) 在 CH_3CN (15mL) 中的溶液里分别添加 N-Boc-L-Pro-OH (300mg, 1.36mmol) 和 Et_3N (382mg, 3.78mmol)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到粗化合物 23 (580mg), 其不经进一步纯化便用于下一步骤; LC-MS (ESI) : m/z 463.1 ($\text{M}+\text{H}$)⁺。

[0682] 步骤 e: 将化合物 23 (580mg, 1.25mmol) 和 NH_4OAc (962mg, 12.5mmol) 在甲苯 (25mL)

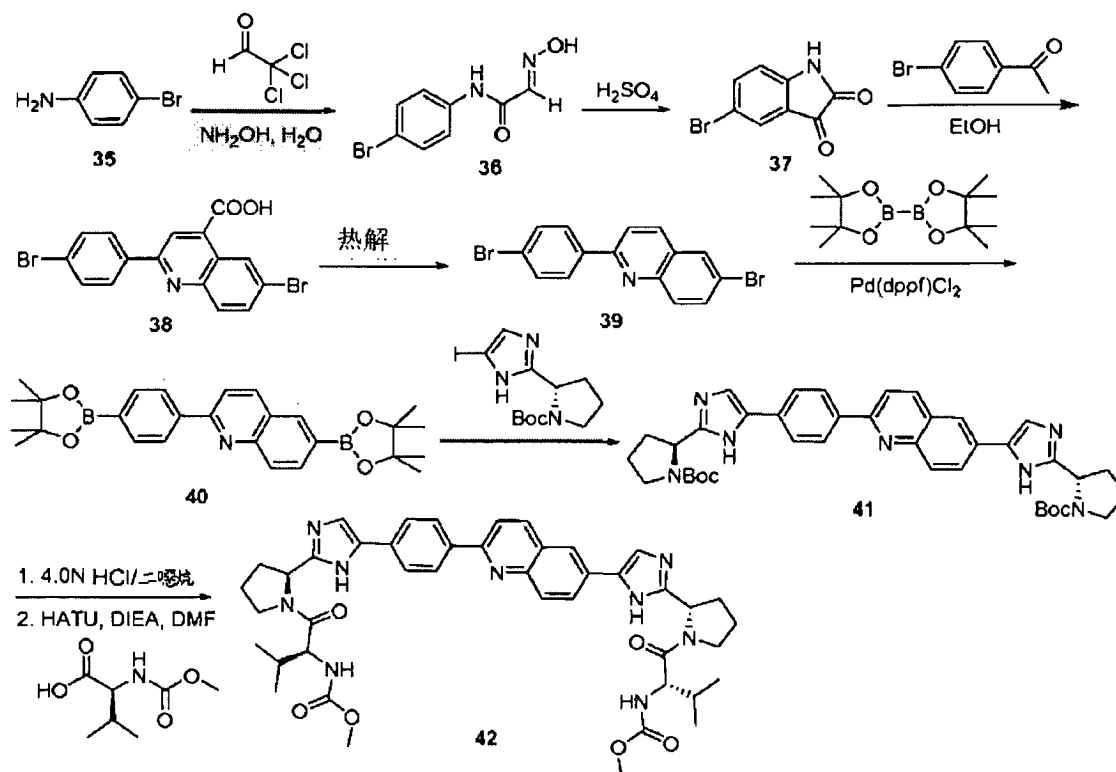
中的混合物在 110℃ 下搅拌过夜。将反应混合物浓缩,并将残留物通过硅胶柱色谱法(石油醚/EtOAc = 9/1(v/v))纯化,得到白色固体化合物 24(400mg, 72%)。LC-MS(ESI):m/z 443.1(M+H)⁺。

[0683] 步骤 f:在 N₂ 气氛中,向化合物 24(380mg, 0.86mmol)、(S)-2-(5-(4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-1H-咪唑-2-基)吡咯烷-1-羧酸叔丁酯(378mg, 0.860mmol)和 NaHCO₃(253mg, 3.01mmol)在 1,2-二甲氧基乙烷(15mL)和 H₂O(5mL)中的混合物里添加 Pd(dppf)Cl₂(35mg, 0.04mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后,浓缩反应混合物。将残留物用 H₂O(50mL)稀释,并用 EtOAc(50mL×3)萃取。将萃取物合并,用盐水洗涤,并用无水 Na₂SO₄干燥。将溶剂移除,并将残留物通过硅胶柱色谱法(石油醚/EtOAc = 5/2(v/v))纯化,得到黄色固体化合物 25(550mg, 95%收率)。LC-MS(ESI):m/z 676.4(M+H)⁺。

[0684] 步骤 g:在室温下,向化合物 26(150mg, 0.22mmol)在二噁烷(2mL)中的溶液里添加二噁烷中的 4N HCl(2mL)。在室温下搅拌过夜后,将溶剂移除并将残留物在真空中干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS(ESI):m/z 476.2(M+H)⁺。

[0685] 步骤 h:向所述 HCl 盐在 DMF(2mL)中的混合物里添加 DIPEA(0.37mL, 2.3mmol),然后添加 N-Moc-L-Val-OH(101mg, 0.58mmol)和 HATU(218mg, 0.58mmol)。在室温下搅拌 30 分钟后,将反应混合物浓缩,并将残留物通过制备性 HPLC 纯化,得到化合物 26。¹H NMR(500MHz, CD₃OD) 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)⁺。

[0686]



方案 3-5

[0687] 步骤 a: 参见方案 3-5, 向三氯乙醛 (7.2g, 48mmol) 在水 (120mL) 中的混合物里添加 Na_2SO_4 (104g), 然后添加浓缩的 HCl 水溶液 (10mL) 中的 4-溴苯胺 (35) 和 H_2O (100mL) 中的 $\text{NH}_2\text{OH} \cdot \text{HCl}$ (8.8g, 0.13mol)。回流 1 小时后, 将反应混合物冷却至室温。将固体通过过滤收集, 并在真空中干燥, 得到黄色固体化合物 36 (8.0g, 91%)。LC-MS (ESI): m/z : 243.0 ($\text{M}+\text{H}$)⁺。

[0688] 步骤 b: 向圆底烧瓶装入 20mL H_2SO_4 (98%), 并将溶液暖至 50℃。随后, 以将温度保持在 60℃ 和 70℃ 之间的速率添加化合物 36 (4.8g, 20mmol)。完成化合物 36 的添加后, 将所得混合物加热至 80℃ 并再搅拌 10 分钟。将混合物冷却至室温并倒入冰 (200g) 中。将固体通过过滤收集, 用水洗涤若干次, 并在真空中干燥, 得到橙色固体化合物 37 (3.6g, 80% 收率)。LC-MS (ESI): m/z : 225.9 ($\text{M}+\text{H}$)⁺。

[0689] 步骤 c: 将化合物 37 (1.35g, 6.0mmol)、1-(4-溴苯基)乙酮 (1.14g, 5.7mmol) 和氢氧化钾 (1.02g, 18.3mmol) 在乙醇 (50mL) 中的混合物回流过夜。将反应混合物浓缩, 并将残留物用石油醚 (100mL) 和水 (200mL) 稀释。将水相分离, 通过添加 1N HCl 酸化, 然后用乙酸乙酯 (50mL × 3) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到红色固体粗化合物 38 (1.2g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI): m/z : 405.9 ($\text{M}+\text{H}$)⁺。

[0690] 步骤 d: 在氩气氛中, 将装有化合物 5 (1.2g, 2.95mmol) 的烧瓶加热至 300℃ 达 30 分钟。然后将固体通过硅胶柱色谱法 (石油醚/EtOAc = 19:1 (v/v)) 纯化, 得到黄色固体化合物 39 (160mg, 15% 收率)。LC-MS (ESI): m/z : 361.9 ($\text{M}+\text{H}$)⁺。

[0691] 步骤 e: 将化合物 39 (0.11g, 0.30mmol)、双(频哪醇合)二硼 (0.34g, 1.3mmol)、

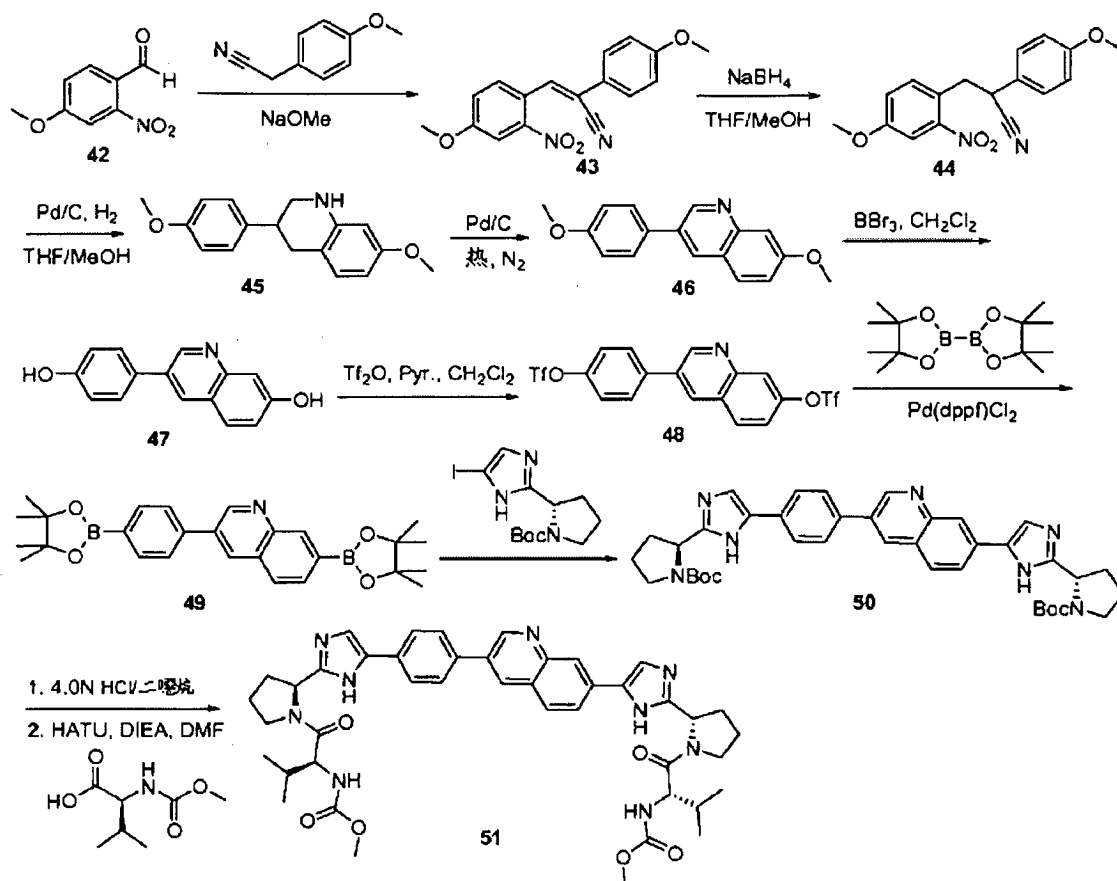
醋酸钾 (0.15g, 1.5mmol) 和 Pd(dppf)Cl_2 (50mg, 0.06mmol) 与二噁烷 (20mL) 的混合物在氩气氛中于 80℃ 下搅拌过夜。随后, 将反应混合物用 EtOAc (100mL) 稀释。将所得混合物用 H_2O (50mL) 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 10/1 (v/v)) 纯化, 得到化合物 40 (0.12g, 86% 收率)。LC-MS (ESI) : m/z : 458.3 (M+H)⁺。(还将相应的硼酸分离, 并用作下一步骤的活性中间体)。

[0692] 步骤 f: 在氩气氛中于室温下, 向化合物 40 (120mg, 0.26mmol) 在 DME/ H_2O (3/1 (v/v); 24mL) 中的溶液里依次添加 (S)-2-(5-碘-1H-咪唑-2-基) 吡咯烷-1-羧酸叔丁酯 (290mg, 0.80mmol)、 NaHCO_3 (220mg, 2.6mmol) 和 $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (62mg, 0.064mmol)。在氩气氛中于 80℃ 下搅拌过夜后, 将反应混合物用 EtOAc (100mL) 稀释。将有机层分离, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (PE/丙酮 = 2/1 (v/v)) 纯化, 得到黄色固体化合物 17 (151mg, 86% 收率)。LC-MS (ESI) : m/z : 676.4 (M+H)⁺。

[0693] 步骤 g: 向化合物 41 (120mg, 0.18mmol) 在二噁烷 (2mL) 中的搅拌溶液里添加 4N HCl / 二噁烷 (2mL)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z : 476.2 (M+H)⁺。

[0694] 步骤 h: 向所述 HCl 盐在 DMF (2mL) 中的混合物里添加 DIPEA (0.3mL, 1.8mmol), 然后添加 N-Moc-L-Val-OH (79mg, 0.45mmol) 和 HATU (169mg, 0.45mmol)。在室温下搅拌 30 分钟后, 将反应混合物缓慢倒入 H_2O 。将固体通过过滤收集, 并通过制备性 HPLC 纯化, 得到化合物 42。¹H NMR (500MHz, CD_3OD) δ 8.96 (d, 2H, J = 9.5Hz)、8.63 (s, 1H)、8.53 (d, 2H, J = 10.0Hz)、8.40 - 8.39 (m, 3H)、8.18 (s, 1H)、8.08 (d, 2H, J = 13Hz)、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)⁺。

[0695]



方案 3-6

[0696] 步骤 a: 参见方案 3-6, 在室温下, 将 4-甲氧基-2-硝基苯甲醛 (42) (1.4g, 7.7mmol) 和 4-甲氧基苯基乙腈 (1.13g, 7.7mmol) 添加到甲醇钠 (0.4g, 7.7mmol) 在甲醇 (10mL) 中的溶液里。在室温下搅拌 5 小时后, 将反应混合物过滤。将固体分别用水和 95% 乙醇洗涤, 并在真空中干燥, 得到黄色粉末化合物 43 (1.82g, 77% 收率)。¹H NMR (500MHz, CDCl₃) δ 7.90 (d, J = 8.5Hz, 1H)、7.85 (s, 1H)、7.70 (d, J = 2.0Hz, 1H)、7.63 (d, J = 9.0Hz, 2H)、7.28 (m, 1H)、6.98 (d, J = 9.0Hz, 2H)、3.94 (s, 3H)、3.87 (s, 3H) ppm. LC-MS (ESI) :m/z 311.1 (M+H)⁺。

[0697] 步骤 b: 在室温下, 向化合物 43 (15.5g, 50mmol) 在 THF/ 甲醇 (5/1 (v/v), 240mL) 中的溶液里添加 NaBH₄ (2.8g, 75mmol)。在室温下搅拌 4 小时后, 将反应混合物倒入冰水中, 并用 1N HCl 水溶液处理。将所得混合物用 EtOAc (50mL × 2) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 44 (9.8g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 335.1 (M+Na)⁺。

[0698] 步骤 c: 将化合物 44 (9.0g, 29mmol) 和 10% Pd/C (4.5g) 在 THF (240mL) 和 MeOH (60mL) 中的混合物在 H₂ 气氛中于 45℃ 下搅拌 48 小时。将所得混合物通过 CELITE™ 545 过滤; 将滤饼用 MeOH (50mL × 3) 洗涤。将滤液浓缩, 并将残留物通过硅胶柱色谱法 (石油醚/ 乙酸乙酯 9:1) 纯化, 得到白色固体化合物 45 (5.5g, 71% 收率)。¹H NMR (500MHz, CDCl₃) δ 7.16 (d, J = 8.5Hz, 2H)、6.91–6.87 (m, 3H)、6.25 (d, J = 8.5Hz, 1H)、6.12 (s, 1H)、3.80 (s, 3H)、3.75 (s, 3H)、3.41 (d, J = 11.0Hz, 1H)、3.27 (t, J = 11.0Hz, 1H)、

3.11-3.05(m, 1H)、2.90(d, $J = 8.0\text{Hz}$, 2H) ppm; LC-MS (ESI) :m/z 270.1 (M+H)⁺。

[0699] 步骤 d: 将化合物 45 (2.7g, 10mmol) 和 10% Pd/C (1.4g) 的混合物在氩气氛中于 270 ~ 280℃ 下搅拌 30 分钟。将混合物通过硅胶柱色谱法 (石油醚/EtOAc = 6/1 (v/v)) 纯化, 得到白色固体化合物 46 (1.8g, 68%)。LC-MS (ESI) :m/z 266.1 (M+H)⁺。

[0700] 步骤 e: 在 -40℃ 下, 向化合物 46 (0.80g, 3.0mmol) 在 CH₂Cl₂ (30mL) 中的溶液里添加 4N BBr₃/CH₂Cl₂ (4.5mL, 18mmol)。在室温下搅拌过夜后, 将反应混合物用水 (30mL) 稀释。将所得混合物用 1N NaOH 溶液处理, 以将 pH 调节至 8, 并用 EtOAc (60mL × 2) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶色谱法 (石油醚/EtOAc = 2/1 (v/v)) 纯化, 得到白色固体化合物 47 (0.7g, 99%)。LC-MS (ESI) :m/z 238.1 (M+H)⁺。

[0701] 步骤 f: 在 0℃ 下, 向化合物 47 (0.82g, 3.5mmol) 和吡啶 (1.3g, 16mmol) 在 CH₂Cl₂ (45mL) 中的溶液里添加 Tf₂O (3.6g, 13mmol)。在室温下搅拌 30 分钟后, 将反应混合物浓缩, 并将残留物通过硅胶色谱法 (石油醚/EtOAc = 10/1 (v/v)) 纯化, 得到黄色固体化合物 48 (0.40g, 23%)。LC-MS (ESI) :m/z 502.1 (M+H)⁺。

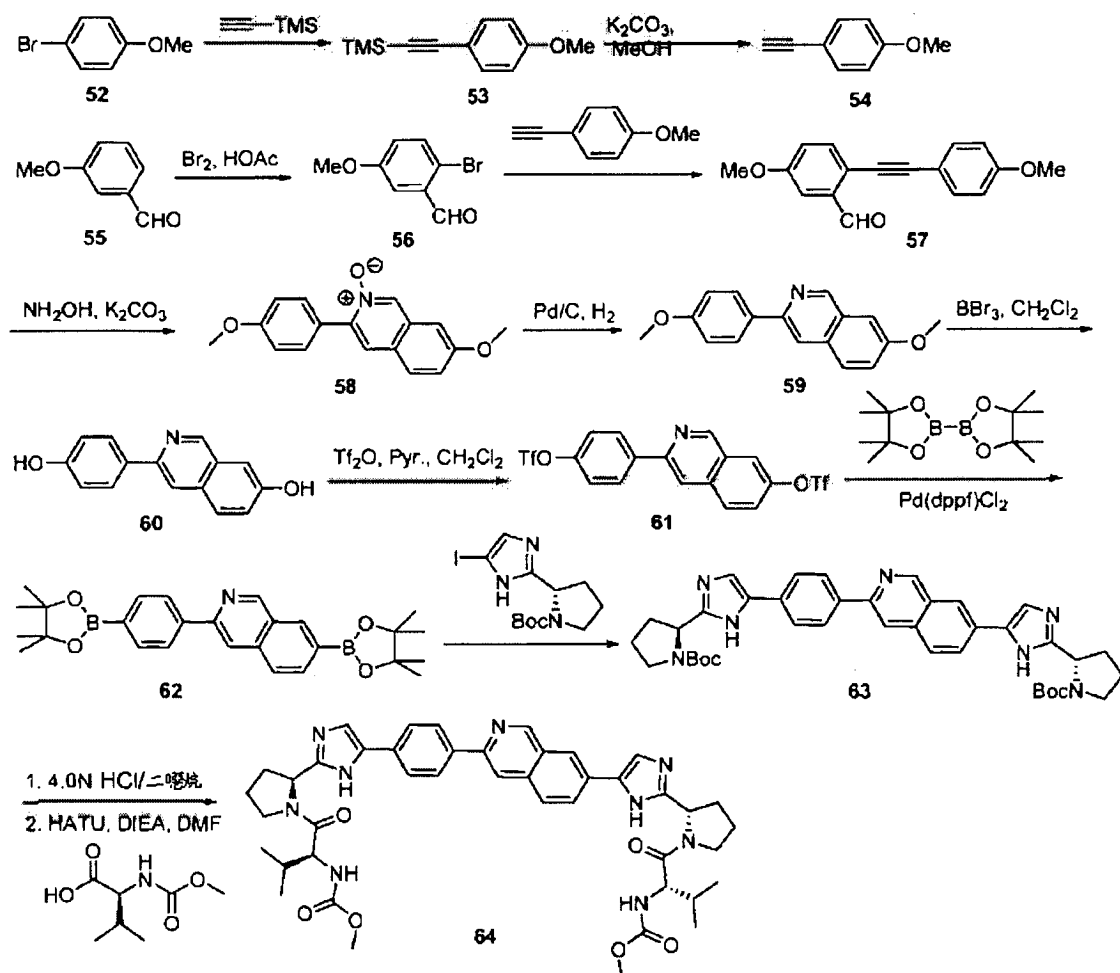
[0702] 步骤 g: 将化合物 48 (0.40g, 0.80mmol)、双 (频哪醇合) 二硼 (1.0g, 4.0mmol)、醋酸钾 (0.55g, 5.6mmol) 和 Pd(dppf)Cl₂ (200mg, 0.24mmol) 与二噁烷 (20mL) 的混合物在氩气氛中于 80℃ 下搅拌过夜。随后, 将反应混合物用 EtOAc (100mL) 稀释。将所得混合物用 H₂O (50mL) 洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 10/1 (v/v)) 纯化, 得到化合物 49 (0.20g, 54% 收率)。LC-MS (ESI) :m/z : 458.3 (M+H)⁺。(还将相应的硼酸分离, 并用作下一步骤的活性中间体)。

[0703] 步骤 h: 在氩气氛中于室温下, 向化合物 49 (160mg, 0.35mmol) 在 DME/H₂O (3/1 (v/v); 40mL) 中的溶液里依次添加 (S)-2-(5-碘-1H-咪唑-2-基) 吡咯烷-1-羧酸叔丁酯 (388mg, 1.07mmol)、NaHCO₃ (289mg, 3.44mmol) 和 Pd(dppf)Cl₂ · CH₂Cl₂ (71mg, 0.090mmol)。在氩气氛中于 80℃ 下搅拌过夜后, 将反应混合物用 EtOAc (100mL) 稀释。将有机层分离, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 2/1 (v/v)) 纯化, 得到黄色固体化合物 50 (151mg, 64% 收率)。LC-MS (ESI) :m/z 676.4 (M+H)⁺。

[0704] 步骤 i: 在室温下, 向化合物 50 (140mg, 0.21mmol) 在二噁烷 (2mL) 中的搅拌溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 476.2 (M+H)⁺。

[0705] 步骤 j: 向所述 HCl 盐在 DMF (2mL) 中的混合物里添加 DIPEA (0.35mL, 2.1mmol), 然后添加 N-Boc-L-Val-OH (92mg, 0.53mmol) 和 HATU (200mg, 0.530mmol)。在室温下搅拌 30 分钟后, 将反应混合物倒入水中。将固体通过过滤收集, 并通过制备性 HPLC 纯化, 得到化合物 51。¹H NMR (500MHz, CD₃OD) 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)⁺。

[0706]



方案 3-7

[0707] 步骤 a: 参见方案 3-7, 在氩气氛中, 将化合物 52 (9.35g, 50mmol)、TMS-乙炔 (7.35g, 75mmol)、DIEA (21.0mL, 150mmol)、CuI (475mg, 2.50mmol)、 $Pd(PPh_3)_2Cl_2$ (3.51g, 5.0mmol) 和 PPh_3 (2.62g, 10.0mmol) 在无水 THF (100mL) 中的混合物回流过夜。将反应混合物浓缩, 并将残留物用水 (50mL) 和 EtOAc (150mL) 稀释。将有机层用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 10/1 (v/v)) 纯化, 得到黄色油状化合物 53 (10.0g, 98%)。LC-MS (ESI) : m/z 205.1 (M+H) $^+$ 。

[0708] 步骤 b: 在室温下, 将化合物 53 (2.4g, 11.7mmol) 和 K_2CO_3 (4.9g, 35.3mmol) 在 THF (20mL) 和 MeOH (20mL) 中的混合物搅拌 3 小时。将溶剂移除, 并将残留物用 EtOAc (150mL) 稀释, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 10/1 (v/v)) 纯化, 得到黄色油状化合物 54 (1.3g, 84%)。LC-MS (ESI) : m/z 133.1 (M+H) $^+$ 。

[0709] 步骤 c: 向化合物 55 (25.0g, 184mmol) 在 AcOH (125mL) 中的溶液里添加 Br_2 (11.0mL, 220mmol)。在室温下搅拌 4 小时后, 过滤反应混合物。将固体用 H_2O 洗涤, 并在真空中干燥, 得到白色固体化合物 56 (38g, 96%)。LC-MS (ESI) : m/z 215.0 (M+H) $^+$ 。

[0710] 步骤 d: 在 N_2 气氛中于 40 $^{\circ}C$ 下, 将化合物 54 (17.9g, 83.3mmol)、化合

物 56 (11.0g, 83.3mmol)、CuI (1.59g, 0.25mmol)、Et₃N (23.00mL, 166.6mmol)、Pd(PPh₃)₂Cl₂ (2.95g, 4.20mmol) 和 PPh₃ (4.40g, 16.7mmol) 在 DMF (100mL) 中的混合物搅拌过夜。将反应混合物浓缩, 并将残留物用 EtOAc (500mL) 稀释。将所得混合物用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 10/1 (v/v)) 纯化, 得到化合物 57 (9.8g, 45%)。LC-MS (ESI) :m/z 267.1 (M+H)⁺。

[0711] 步骤 e: 向化合物 57 (5.5g, 21mmol) 在 EtOH (100mL) 中的溶液里分别添加盐酸羟胺 (1.73g, 25.0mmol) 和 NaOAc (2.05g, 25.0mmol)。在 60℃ 下搅拌 2 小时后, 向反应混合物中添加 K₂CO₃ (4.3g, 31mmol) 和 H₂O (15mL)。将所得混合物回流 12 小时, 然后浓缩。将残留物溶解于 EtOAc 中, 将所得混合物用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 58 (5.8g)。LC-MS (ESI) :m/z 282.1 (M+H)⁺。

[0712] 步骤 f: 在 H₂ 气氛中于室温下, 将化合物 58 (100mg, 0.36mmol) 和 5% Pd/C (75mg) 在 EtOH (25mL) 中的混合物搅拌过夜。将反应混合物通过 CELITE™545 过滤。将滤饼用 MeOH (25mL×3) 洗涤。将滤液浓缩, 并将残留物通过硅胶柱色谱法纯化, 得到化合物 59 (50mg, 53%)。LC-MS (ESI) :m/z 266.1 (M+H)⁺。

[0713] 步骤 g: 在 N₂ 气氛中于 -40℃ 下, 向化合物 59 (2.0g, 7.5mmol) 在 CH₂Cl₂ (75mL) 中的溶液里添加 CH₂Cl₂ 中的 4N BBr₃ (12mL, 45mmol)。在室温下搅拌过夜后, 通过添加水 (10mL) 使反应淬灭。随后, 将混合物用饱和 NaHCO₃ 水溶液处理, 以将 pH 值调节至 8。将有机层用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 2/1 (v/v)) 纯化, 得到白色固体化合物 60 (1.36g, 76%)。LC-MS (ESI) :m/z 238.1 (M+H)⁺。

[0714] 步骤 h: 在 0℃ 下, 向基质 7 (1.36g, 5.7mmol) 和 吡啶 (2.03g, 25.7mmol) 在 CH₂Cl₂ (120mL) 中的溶液里添加 CH₂Cl₂ (30mL) 中的 Tf₂O (5.84g, 20.7mmol)。在 0℃ 下搅拌 30 分钟后, 将反应混合物浓缩, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 10/1 (v/v)) 纯化, 得到黄色固体化合物 61 (2.4g, 84%)。LC-MS (ESI) :m/z 502.0 (M+H)⁺。

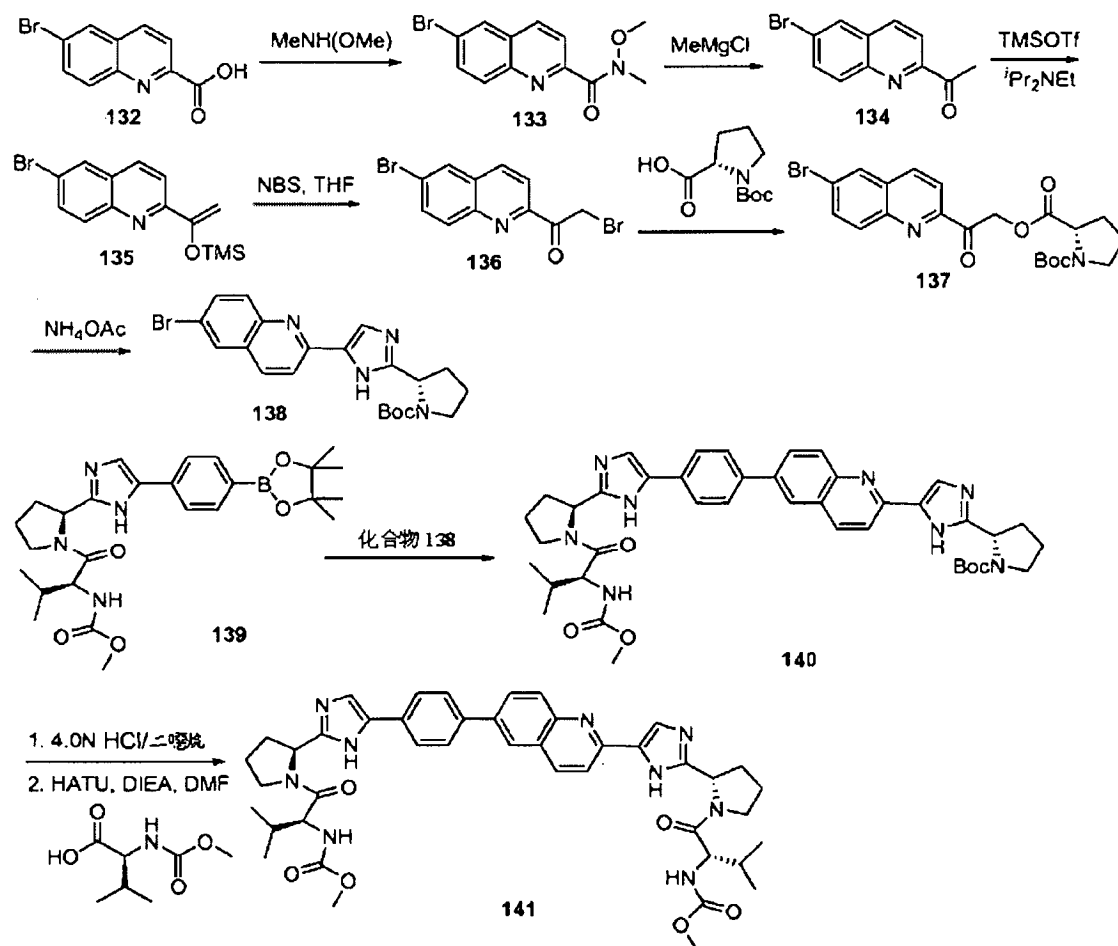
[0715] 步骤 i: 在氩气氛中于 80℃ 下, 将化合物 61 (2.0g, 4.0mmol)、双 (频哪醇合) 二硼 (5.1g, 20mmol)、醋酸钾 (2.7g, 28mmol) 和 Pd(dppf)Cl₂ (0.98g, 1.2mmol) 与二噁烷 (80mL) 的混合物搅拌过夜。随后, 将反应混合物用 EtOAc (100mL) 稀释。将所得混合物用 H₂O (50mL) 洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 10/1 (v/v)) 纯化, 得到化合物 62 (986mg, 54% 收率)。LC-MS (ESI) :m/z :458.3 (M+H)⁺。(还将相应的硼酸分离, 并用作下一步骤的活性中间体)。

[0716] 步骤 j: 在氩气氛中于室温下, 向化合物 62 (1.7g, 3.7mmol) 在 DME/H₂O (3/1 (v/v); 40mL) 中的溶液里依次添加 (S)-2-(5-碘-1H-咪唑-2-基) 吡咯烷-1-羧酸叔丁酯 (3.70g, 10.0mmol)、NaHCO₃ (2.7g, 32mmol) 和 Pd(dppf)Cl₂ (0.65mg, 0.80mmol)。在氩气氛中于 80℃ 下搅拌过夜后, 将反应混合物用 EtOAc (150mL) 稀释。将有机层分离, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 2/1 (v/v)) 纯化, 得到黄色固体化合物 63 (650mg, 26%)。LC-MS (ESI) :m/z 676.4 (M+H)⁺。

[0717] 步骤 k: 在室温下, 向化合物 63 (140mg, 0.21mmol) 在二噁烷 (3mL) 中的搅拌溶液里添加二噁烷中的 4N HCl (3mL)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 476.2 (M+H)⁺。

[0718] 步骤1: 随后, 向所述HCl盐在DMF(3mL)中的混合物里添加DIPEA(0.5mL, 3.0mmol), 然后添加N-Moc-L-Val-OH(130mg, 0.740mmol)和HATU(281mg, 0.740mmol)。在室温下搅拌30分钟后, 将反应混合物倒入H₂O中。将固体通过过滤收集, 并通过制备性HPLC纯化, 得到化合物64。¹H NMR(500MHz, CD₃OD) 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)⁺。

[0719]



方案 3-8

[0720] 步骤a: 参见方案3-8, 在室温下, 向132(3.70g, 14.7mmol)在DMF(50mL)中的溶液里添加N,O-二甲基羟胺盐酸盐(1.46g, 15.0mmol)、HATU(6.15g, 16.2mmol)和Et₃N(2.22g, 22.0mmol)。在室温下搅拌24小时后, 将反应混合物浓缩, 并将残留物用DCM(150mL)稀释。将混合物分别用饱和NH₄Cl水溶液和盐水洗涤, 用无水Na₂SO₄干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法(石油醚/EtOAc = 4/1(v/v))纯化, 得到黄色固体化合物133(3.78g, 87%收率)。LC-MS(ESI): m/z 295.0(M+H)⁺。

[0721] 步骤b: 在0℃下, 向化合物133(3.53g, 12.0mmol)在THF(80mL)中的溶液里缓慢添加THF中的3M MeMgCl(6mL)。在0℃下搅拌1小时, 然后在室温下再搅拌1小时后, 通过

添加饱和 NH_4Cl 水溶液使反应淬灭。将反应混合物浓缩,向残留物中添加饱和 NaHCO_3 水溶液 (25mL) 和 EtOAc (100mL)。将有机相用盐水洗涤,并用无水 Na_2SO_4 干燥。将溶剂移除,并将残留物在真空中干燥,得到白色固体化合物 134 (3.0g, 100%)。LC-MS (ESI) : m/z 250.0 ($\text{M}+\text{H}$)⁺。

[0722] 步骤 c: 向化合物 134 (2.80g, 11.2mmol) 在 DCM (80mL) 中的溶液里添加 $^i\text{Pr}_2\text{NEt}$ (5.79g, 44.8mmol)。将混合物冷却至 0°C, 并滴加 TMSOTf (7.47g, 33.6mmol)。在 0°C 下搅拌 30 分钟, 然后在室温下再搅拌 1 小时后, 将反应混合物分别用饱和 NaHCO_3 水溶液和盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 135 (3.6g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 322.0 ($\text{M}+\text{H}$)⁺。

[0723] 步骤 d: 在 0°C 下, 向化合物 135 (3.60g, 11.2mmol) 在 THF (60mL) 中的溶液里滴加 NBS (1.79g, 10.1mmol) 在 THF (20mL) 中的溶液。在 10°C 下搅拌 1 小时后, 将反应混合物浓缩, 并将残留物用 DCM (150mL) 稀释。将混合物用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 136 (3.6g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 327.9 ($\text{M}+\text{H}$)⁺。

[0724] 步骤 e: 在室温下, 向化合物 136 (3.6g, 10.9mmol) 在 EtOAc (100mL) 中的溶液里添加 (S)-N-Boc-Pro-OH (2.47g, 11.5mmol) 和 Et_3N (3.31g, 32.7mmol)。在室温下搅拌 5 小时后, 将反应混合物分别用饱和 NaHCO_3 水溶液和盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 137 (5.0g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 463.1 ($\text{M}+\text{H}$)⁺。

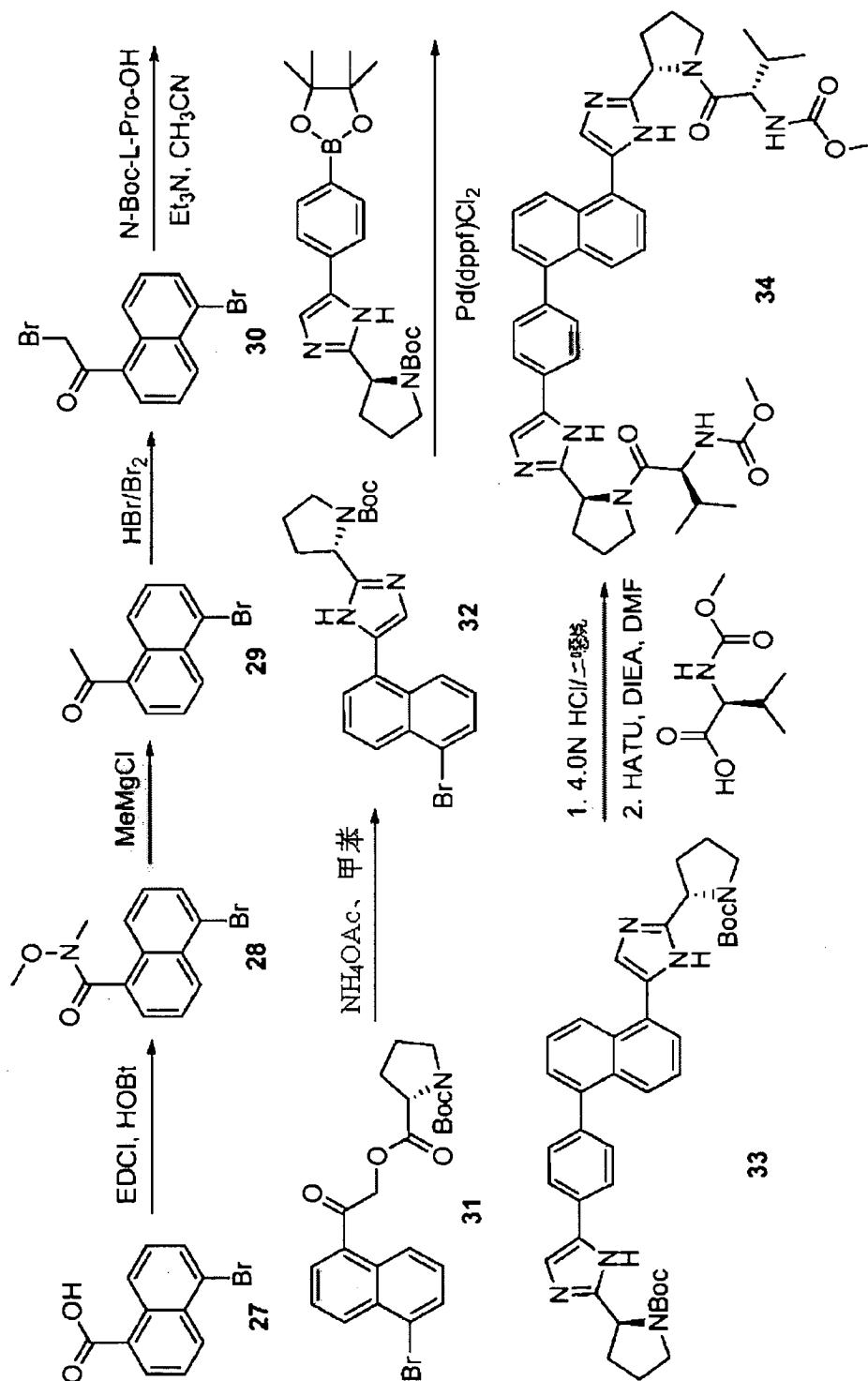
[0725] 步骤 f: 在 115°C 下, 将粗化合物 137 (5.0g) 和 NH_4OAc (8.39g, 109mmol) 在甲苯 (100mL) 中的混合物搅拌过夜。将溶剂移除, 并将残留物用 EtOAc (200mL) 稀释。将混合物用水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/ EtOAc = 3/1 (v/v)) 纯化, 得到白色固体化合物 138 (1.2g, 25%)。LC-MS (ESI) : m/z 443.1 ($\text{M}+\text{H}$)⁺。

[0726] 步骤 g: 在 N_2 气氛中, 向化合物 138 (442mg, 1.00mmol)、化合物 139 (546mg, 1.10mmol) 和 NaHCO_3 (336mg, 4.00mmol) 在 1,2-二甲氧基乙烷 (8mL) 和 H_2O (2mL) 中的混合物里添加 $\text{Pd}(\text{dppf})\text{Cl}_2\text{CH}_2\text{Cl}_2$ (163mg, 0.20mmol)。在 80°C 下搅拌过夜后, 将反应混合物浓缩, 并将残留物用 EtOAc (50mL) 和 H_2O (10mL) 稀释。将有机相用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/ EtOAc = 1/2 (v/v)) 纯化, 得到黄色固体化合物 140 (500mg, 68% 收率)。LC-MS (ESI) : m/z 733.4 ($\text{M}+\text{H}$)⁺。

[0727] 步骤 h: 向化合物 140 (139mg, 0.19mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2.0mL)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物溶解于水 (5mL) 中, 并添加饱和 NaHCO_3 水溶液, 以将 pH 值调节至 8。将所得混合物用 NaCl 饱和, 并用 DCM (15mL $\times$ 5) 萃取。将萃取物合并, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到游离碱, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 633.3 ($\text{M}+\text{H}$)⁺。

[0728] 步骤 i: 随后, 将游离碱溶解于 DCM (5mL) 中, 并向混合物中添加 N-Moc-L-Val-OH (40mg, 0.23mmol) 和 DIC (29mg, 0.23mmol)。在室温下搅拌 20 分钟后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到化合物 141。LC-MS (ESI) : m/z 790.4 ($\text{M}+\text{H}$)⁺。

[0729]



方案 4-1

[0730] 实施例 4 - 式 IIe 化合物的合成

[0731] 步骤 a. 参见方案 4-1, 在室温下, 向化合物 27 (5.0g, 20mmol) 在 CH_3CN (200mL) 中的溶液里添加 EDCI (5.8g, 30mmol)、HOBt (675mg, 30mmol)、 $\text{MeNH(OMe)} \cdot \text{HCl}$ (2.93g, 30mmol) 和 Et_3N (6.1g, 60mmol)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 5/1 (v/v)) 纯化, 得到白色固体化合物 28 (5.4g, 92% 收率)。LC-MS (ESI) : m/z 294.0 ($\text{M}+\text{H}$)⁺。

[0732] 步骤 b: 在 N_2 气氛中于 0°C 下, 向化合物 28 (2.9g, 10mmol) 在 THF (100mL) 中的溶液里缓慢添加 THF (20mmol) 中的 3M MeMgCl (20mmol)。在 0°C 下搅拌 1 小时后, 然后在室温下搅拌 1 小时后, 通过添加数滴 NH_4Cl 水溶液使反应淬灭。将反应混合物浓缩, 并将残留物用 EtOAc (100mL) 稀释。将有机相用饱和 $NaHCO_3$ 水溶液洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / AcOEt = 10:1 (v/v)) 纯化, 得到化合物 29 (2.3g, 92% 收率)。LC-MS (ESI) : m/z 249.0 (M+H)⁺。

[0733] 步骤 c: 在 0°C 下, 向 29 (1.84g, 7.4mmol) 在 DCM (100mL) 中的溶液里滴加 Br_2 (18.8g, 14.7mmol)。在 0°C 下搅拌 30 分钟后, 将反应混合物暖至室温, 同时再搅拌 2 小时。随后, 将反应混合物分别用水和饱和 $NaHCO_3$ 水溶液洗涤, 将有机相用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到黄色固体粗化合物 30 (2.0g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 326.9 (M+H)⁺。

[0734] 步骤 d: 在室温下, 向化合物 30 (1.95g, 5.9mmol) 在 DCM (50mL) 中的溶液里添加 N-Boc-L-Pro-OH (1.6g, 7.3mmol) 和 Et_3N (1.7mL, 12.2mmol)。在室温下搅拌 2 小时后, 将反应混合物分别用饱和 NH_4Cl 和盐水洗涤; 并将有机相用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 31 (2.4g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 462.1 (M+H)⁺。

[0735] 步骤 e: 在 110°C 下, 将化合物 31 (2.4g, 5.2mmol) 和 NH_4OAc (4.0g, 52mmol) 在甲苯 (52mL) 中的混合物搅拌过夜。随后, 将反应混合物冷却至室温, 并用 EtOAc (100mL) 稀释。将混合物分别用饱和 Na_2CO_3 水溶液 (50mL $\times$ 2) 和盐水洗涤; 将有机相用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 1/1 (v/v)) 纯化, 得到黄色固体化合物 32 (1.4g, 62%)。LC-MS (ESI) : m/z 442.1 (M+H)⁺。

[0736] 步骤 f: 在 N_2 气氛中, 向化合物 32 (1.0g, 2.3mmol)、(S)-2-(5-(4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基))-1H-咪唑-2-基)吡咯烷-1-羧酸叔丁酯 (1.0g, 2.3mmol) 和 $NaHCO_3$ (0.76g, 9.0mmol) 在 1,2-二甲氧基乙烷 (30mL) 和 H_2O (10mL) 中的混合物里添加 $Pd(dppf)Cl_2$ (277mg, 0.34mmol)。在 N_2 气氛中于 80°C 下搅拌过夜后, 浓缩反应混合物。将残留物 H_2O (50mL) 稀释, 并将水相用 EtOAc (50mL $\times$ 3) 萃取。将萃取物合并, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 5/2 (v/v)) 纯化, 得到黄色固体化合物 33 (1.0g, 78% 收率)。LC-MS (ESI) : m/z 675.4 (M+H)⁺。

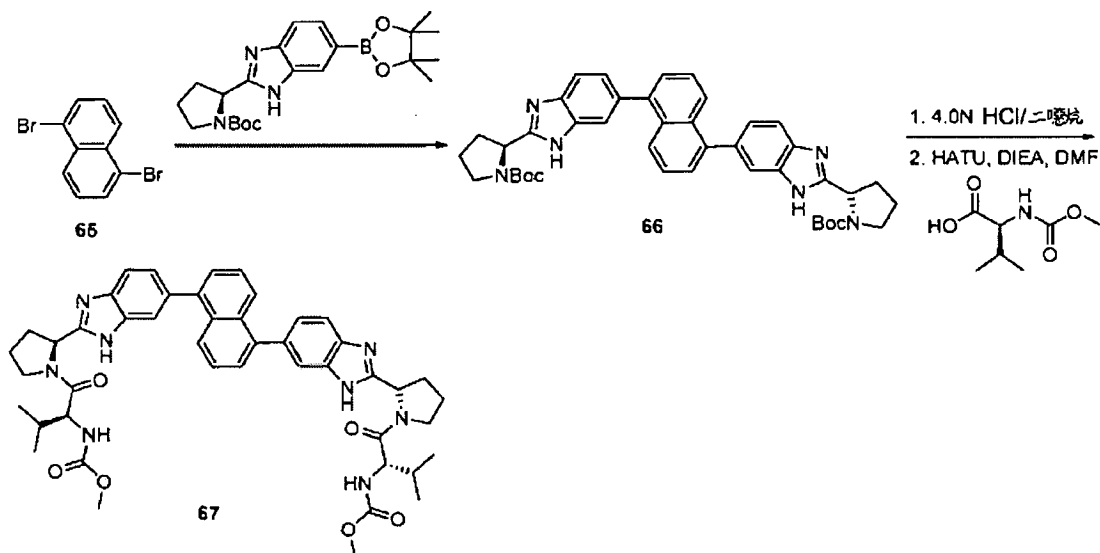
[0737] 步骤 g: 在室温下, 向化合物 33 (250mg, 0.37mmol) 在二噁烷 (3mL) 中的搅拌溶液里滴加二噁烷中的 4.0N HCl (3mL)。在室温下搅拌 4 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 475.3 (M+H)⁺。

[0738] 步骤 h: 随后, 在室温下, 将所述 HCl 盐悬浮于 THF (5mL) 和 DIPEA (0.35mL) 以及 N-Moc-L-Val-OH (130mg, 0.74mmol) 中。在室温下搅拌 15 分钟后, 添加 HATU (340mg, 0.89mmol), 并将所得反应混合物在室温下再搅拌 2 小时。将溶剂移除, 并将残留物通过制备性 HPLC 纯化, 得到化合物 34。¹H NMR (500MHz, $CDCl_3$) 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)⁺。

[0739] 实施例 5 - - 式 IIII1 化合物的合成

[0740]



方案 5-1

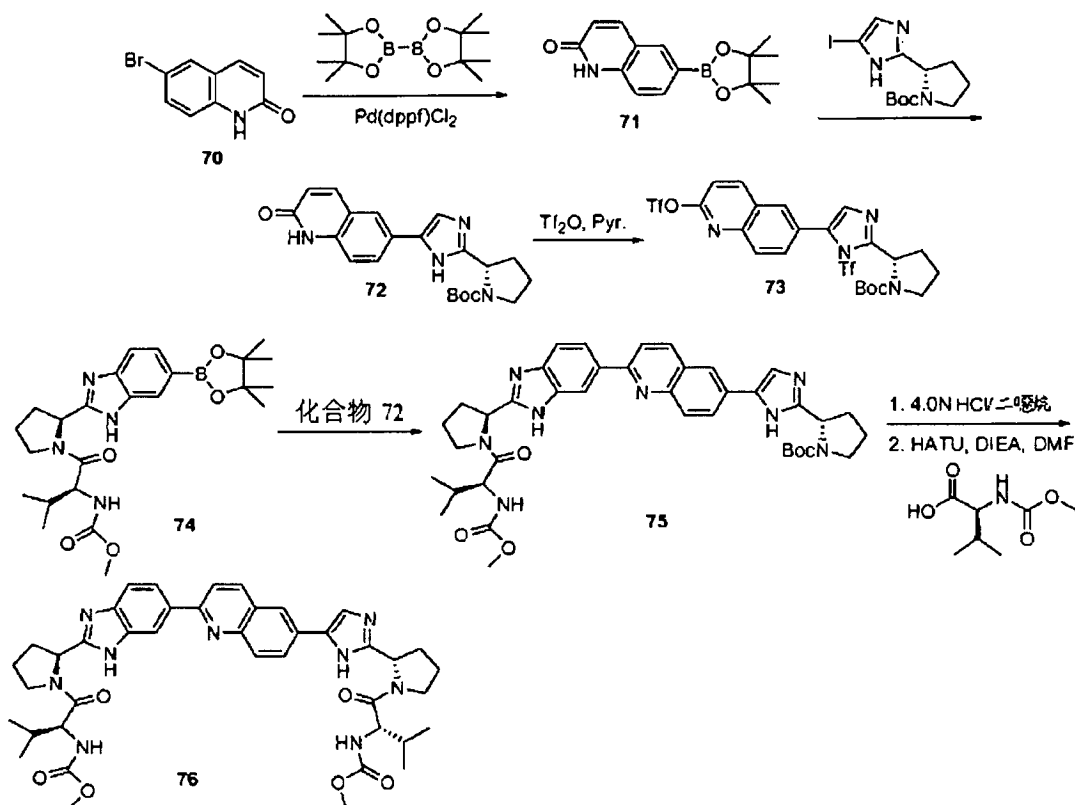
[0741] 步骤 a: 参见方案 5-1, 在 N₂ 气氛中于室温下, 向化合物 65 (300mg, 1. 05mmol)、(S)-2-(6-(4, 4, 5, 5- 四甲基 -1, 3, 2- 二氧杂环戊硼烷 -2- 基)-1H- 苯并 [d] 咪唑 -2- 基) 吡咯烷 -1- 羧酸叔丁酯 (1. 14g, 2. 75mmol) 和 NaHCO₃ (740mg, 8. 80mmol) 在 1, 2- 二甲氧基乙烷 (30mL) 和水 (10mL) 中的混合物里添加 Pd(dppf)Cl₂ (179mg, 0. 220mmol)。在 80℃ 下搅拌过夜后, 浓缩反应混合物。将残留物用 DCM (100mL) 和水 (25mL) 稀释。将有机层用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 2/1 (v/v)) 纯化, 得到化合物 66 (650mg, 86%)。LC-MS (ESI) :m/z 699. 4 (M+H)⁺。

[0742] 步骤 b: 在室温下, 向化合物 66 (110mg, 0. 16mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便直接用于下一步骤。LC-MS (ESI) :m/z 499. 3 (M+H)⁺。

[0743] 步骤 c: 随后, 在室温下, 将所述 HCl 盐溶解于 DMF (2mL) 中, 然后添加 DIPEA (207mg, 16mmol)、N-Moc-L-Val-OH (68mg, 0. 39mmol) 和 HATU (148mg, 0. 39mmol)。在室温下搅拌 15 分钟后, 将反应混合物添加到水中。将固体通过过滤收集, 并通过制备性 HPLC 纯化, 得到化合物 67。LC-MS (ESI) :m/z 813. 4 (M+H)⁺。

[0744] 实施例 6 - 式 IIIId 化合物的合成

[0745]



方案 6-1

[0746] 步骤 a: 参见方案 6-1, 在 N_2 气氛中于室温下, 向化合物 70 (8.00g, 35.7mmol, 购自 Aldrich Chemicals, Milwaukee, Wisconsin, USA)、双(频哪醇合)二硼 (10.9g, 42.8mmol)、 K_2CO_3 (10.50g, 107.1mmol) 在 1,4-二噁烷 (600mL) 中的混合物里添加 $Pd(dppf)Cl_2$ (2.9g, 3.6mmol)。在 N_2 气氛中于 $80^\circ C$ 下搅拌 3 小时后, 将反应混合物冷却至室温, 并通过 Celiart[®] 545 过滤。将滤饼用 EtOAc (100mL $\times$ 3) 洗涤。将滤液浓缩, 并将残留物用 EtOAc (500mL) 稀释。将所得混合物用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 1/1 (v/v)) 纯化, 得到淡褐色固体化合物 71 (8.28g, 86% 收率)。LC-MS (ESI): m/z 272.1 (M+H)⁺。

[0747] 步骤 b: 在 N_2 气氛中, 向化合物 71 (5.90g, 21.8mmol)、(S)-2-(5-碘-1H-咪唑-2-基)吡咯烷-1-羧酸叔丁酯 (9.50g, 26.2mmol)、 $NaHCO_3$ (7.30g, 87.2mmol) 在 1,2-二甲氧基乙烷 (500mL) 和水 (150mL) 中的混合物里添加 $Pd(dppf)Cl_2$ (3.6g, 4.4mmol)。在 $80^\circ C$ 下搅拌过夜后, 将反应混合物浓缩, 并将残留物用 EtOAc (250mL) 和水 (50mL) 稀释。将有机层用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (DCM/MeOH = 5/1 (v/v)) 纯化, 得到黄色固体化合物 72 (5.30g, 64% 收率)。LC-MS (ESI): m/z 381.2 (M+H)⁺。

[0748] 步骤 c: 在 $0^\circ C$ 下, 向化合物 72 (2.0g, 5.26mmol) 在 40mL 吡啶中的溶液里滴加 Tf_2O (3.71g, 13.1mmol)。在 $0^\circ C$ 下搅拌 1 小时并在室温下搅拌 3 小时后, 浓缩反应混合物。残留物通过硅胶柱色谱法 (石油醚/丙酮 = 4/1 (v/v)) 纯化, 得到黄色固体化合物 73 (2.04g,

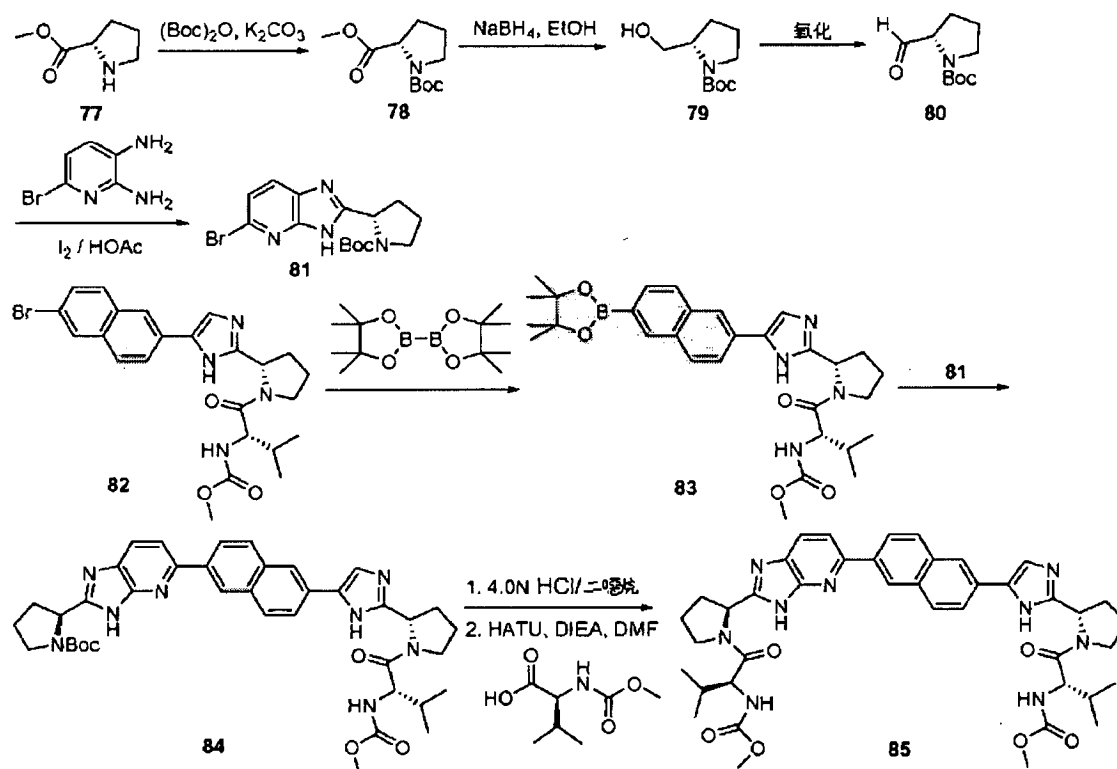
60%收率)。LC-MS(ESI): m/z 645.1 (M+H)⁺。

[0749] 步骤 d: 在 N₂ 气氛中于室温下, 向化合物 73 (500mg, 0.78mmol)、(S)-3-甲基-1-氧代-1-((S)-2-(6-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-1H-苯并[d]咪唑-2-基)丁-2-基)氨基甲酸甲酯 (74) (419mg, 0.89mmol) 和 NaHCO₃ (299g, 3.56mmol) 在 1,2-二甲氧基乙烷 (60mL) 和水 (20mL) 中的混合物里添加 Pd(dppf)Cl₂ (147mg, 0.18mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后, 浓缩反应混合物。将残留物用 EtOAc (100mL) 和水 (25mL) 稀释。将有机层用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 1:1 (v/v)) 纯化, 得到黄色固体化合物 75 (0.40g, 64% 收率)。LC-MS(ESI): m/z 707.4 (M+H)⁺。

[0750] 步骤 e: 在室温下, 向化合物 75 (150mg, 0.22mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS(ESI): m/z 607.3 (M+H)⁺。

[0751] 步骤 f: 随后, 在室温下, 将所述 HCl 盐溶解于 DMF (2mL) 中, 然后添加 Et₃N (0.11mL, 0.81mmol)、N-Moc-L-Val-OH (32mg, 0.18mmol) 和 HATU (69mg, 0.18mmol)。在室温下搅拌 1 小时后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到化合物 76。LC-MS(ESI): m/z 764.4 (M+H)⁺。

[0752]



方案 6-2

[0753] 步骤 a: 参见方案 6-2, 向化合物 78 (50.0g, 0.30mol) 在 THF (500mL) 和 H₂O (500mL) 中的溶液里添加 K₂CO₃ (83g, 0.60mol) 和 (Boc)₂O (73.0g, 0.330mol)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物用 EtOAc (250mL × 3) 萃取。将萃取物合并, 用盐水洗涤, 并

用无水 Na_2SO_4 干燥。将溶剂移除,并将残留物在真空中干燥,得到粗化合物 78 (62g),其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 230.1 (M+H)⁺。

[0754] 步骤 b:在室温下,向化合物 78 (60.0g, 260mmol) 在 EtOH (1L) 中的溶液里缓慢添加 NaBH_4 (50.0g, 1.30mol)。在室温下搅拌过夜后,通过添加丙酮 (10mL) 使反应淬灭。将所得混合物浓缩,并将残留物用 EtOAc (500mL) 稀释。将混合物用盐水洗涤,并在真空中干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 1/1 (v/v)) 纯化,得到白色固体化合物 79 (42.0g, 80% 收率)。LC-MS (ESI) :m/z 202.1 (M+H)⁺。

[0755] 步骤 c:在 -78℃ 下,向化合物 79 (30.0g, 150mmol) 和 DMSO (35.0g, 450mmol) 于 DCM (1L) 的溶液中添加乙二酰氯 (28.0g, 220mmol)。在 -78℃ 下搅拌 4 小时后,向反应混合物中添加 Et_3N (60.0g, 600mmol),并将所得混合物在 -78℃ 下再搅拌 1 小时。随后,通过添加 H_2O 使反应淬灭。将有机层分离,并将水层用 DCM (200mL × 2) 萃取。将萃取物合并,用盐水洗涤,并用 Na_2SO_4 干燥。将溶剂移除,并将残留物在真空中干燥,得到无色油状粗化合物 80 (22.0g),其不经进一步纯化便立即使用。LC-MS (ESI) :m/z 200.1 (M+H)⁺。

[0756] 步骤 d:在室温下,将化合物 80 (7.7g, 38.5mmol)、6-溴吡啶-2,3-二胺 (8.0g, 42.8mmol) (PCT 国际申请 W02008021851) 和碘 (1.08g, 4.28mmol) 在 AcOH (30mL) 中的混合物搅拌过夜。通过添加饱和 NaHCO_3 水溶液中和反应混合物。将所得混合物用 EtOAc (200mL × 3) 萃取。将萃取物合并,用盐水洗涤,并用无水 Na_2SO_4 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (DCM/MeOH = 80/1 (v/v)) 纯化,得到化合物 81 (7.8g, 55% 收率)。LC-MS (ESI) :m/z 367.1 (M+H)⁺。

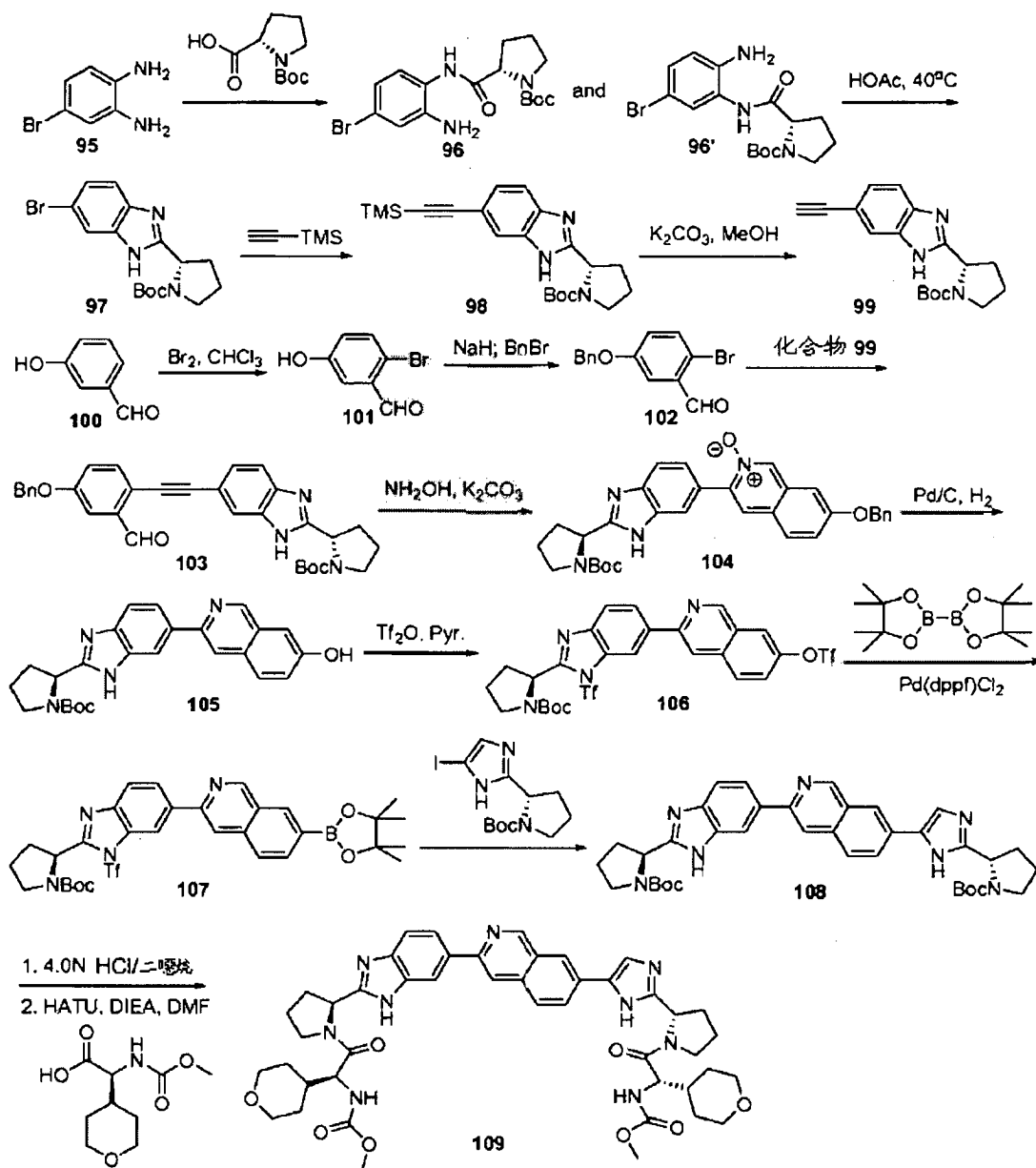
[0757] 步骤 e:在 N_2 气氛中于 80℃ 下,将化合物 82 (10.0g, 20.1mmol)、双(频哪醇合)二硼 (7.65g, 30.1mmol)、醋酸钾 (6.89g, 70.3mmol) 和 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (886mg, 1.0mmol) 在 1,4-二噁烷 (200mL) 中的混合物搅拌 3 小时。将反应混合物通过 CELITE™545 过滤,并将滤饼用 EtOAc (200mL × 3) 洗涤。将滤液用盐水洗涤,并用无水 Na_2SO_4 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (DCM/MeOH = 50/1 (v/v)) 纯化,得到白色固体化合物 83 (9.8g, 89% 收率):LC-MS (ESI) :m/z 547.3 (M+H)⁺。

[0758] 步骤 f:在 N_2 气氛中于 80℃ 下,将化合物 81 (2.0g, 5.4mmol)、化合物 83 (2.9g, 5.4mmol)、 NaHCO_3 (1.60g, 18.9mmol) 和 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (239mg, 0.27mmol) 在 1,2-二甲氧基乙烷 (90mL) 和水 (30mL) 中的混合物搅拌过夜。将反应混合物浓缩,并向残留物中添加 DCM (200mL) 和水 (50mL)。将有机相用盐水洗涤,并用无水 Na_2SO_4 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (DCM/MeOH = 80/1 (v/v)) 纯化,得到黄色固体化合物 84 (1.5g, 40% 收率)。LC-MS (ESI) :m/z 707.4 (M+H)⁺。

[0759] 步骤 g:向化合物 84 (200mg, 0.28mmol) 在 3mL 二噁烷中的溶液里添加二噁烷中的 4N HCl (3mL)。在室温下搅拌 3 小时后,将反应混合物浓缩,并将残留物在真空中干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 607.3 (M+H)⁺。

[0760] 步骤 h:随后,将所述 HCl 盐溶解于 DMF (3mL) 中,并向所得混合物中添加 Et_3N (0.20mL, 1.4mmol)、N-Moc-L-Val-OH (55mg, 0.31mmol) 和 HATU (118mg, 0.31mmol)。在室温下搅拌 1 小时后,将反应混合物浓缩,并将残留物通过制备性 HPLC 纯化,得到化合物 85。LC-MS (ESI) :m/z 764.4 (M+H)⁺。

[0761]



方案 6-3

[0762] 步骤 a: 参见方案 6-3, 在室温下, 向 N-Boc-L-Pro-OH (29g, 135mmol) 和 DIPEA (29g, 225mmol) 在 THF (500mL) 中的溶液里添加 HATU (51g, 135mmol)。在室温下搅拌 10 分钟后, 添加 4-溴苯-1,2-二胺 (95) (25g, 135mmol), 并将所得溶液在室温下再搅拌数小时。随后, 将反应混合物浓缩, 并将残留物用 EtOAc (500mL) 稀释。将所得混合物用水 (100mL×3) 洗涤若干次, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 96 和 96' 的混合物, 其不经进一步纯化便用于下一步骤。LC-MS (ESI): m/z 384.1 (M+H)⁺。

[0763] 步骤 b: 在 40°C 下, 将得自上述反应的粗化合物 96 和 96' 在 AcOH (1000mL) 中的混合物搅拌 12 小时。随后, 通过添加饱和碳酸氢钠水溶液小心中和反应混合物, 以将 pH 值

调节至 8。将所得混合物用 EtOAc 萃取若干次 (250mL×3)。将萃取物合并,用水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物通过硅胶色谱法 (石油醚 /EtOAc = 4/1(v/v)) 纯化,得到黄色固体 97 (35g, 71% 收率, 自 95 经两个步骤)。LC-MS (ESI) :m/z366. 1 (M+H)⁺。

[0764] 步骤 c: 在 N₂ 气氛中, 将化合物 97 (10. 0g, 27. 3mmol)、三甲基甲硅烷基乙炔 (4. 0g, 41. 0mmol)、DIPEA (3. 5g, 27. 3mmol)、CuI (220mg, 1. 15mmol)、PPh₃ (1. 2g, 4. 6mmol) 和 Pd(PPh₃)₂Cl₂ (1. 6g, 2. 3mmol) 在无水 THF (200mL) 中的混合物回流过夜。将反应混合物浓缩, 并将残留物用 EtOAc (250mL) 稀释。将混合物用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 /EtOAc = 3/1(v/v)) 纯化, 得到化合物 98 (7. 8g, 85% 收率)。LC-MS (ESI) :m/z384. 2 (M+H)⁺。

[0765] 步骤 d: 在室温下, 将化合物 98 (7. 7g, 20mmol) 和 K₂CO₃ (27. 6g, 0. 2mol) 在 THF (150mL) 和 MeOH (150mL) 中的混合物搅拌 3 小时。将反应混合物通过 CELITE™545 过滤, 并将滤饼用 EtOAc (100mL×3) 洗涤。将滤液浓缩, 并将残留物用 DCM (250mL) 稀释。将混合物用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 2/1(v/v)) 纯化, 得到化合物 99 (4. 7g, 75% 收率)。LC-MS (ESI) :m/z312. 2 (M+H)⁺。

[0766] 步骤 e: 在室温下, 经 40-45 分钟向间羟基苯甲醛 (100) (30. 0g, 0. 24mol) 在干燥 CHCl₃ (245mL) 中的溶液里缓慢添加溴 (12. 36mL, 0. 24mol)。添加结束后, 将反应混合物在室温下搅拌 3 小时。随后, 小心添加饱和 NaHCO₃ 水溶液以中和混合物。将有机层用盐水洗涤, 并用 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到褐色固体粗化合物 101 (37g)。LC-MS (ESI) :m/z200. 9 (M+H)⁺。

[0767] 步骤 f: 在 N₂ 气氛中于 0 °C 下, 向化合物 101 (10g, 49. 8mmol) 在无水 THF / DMF (5/1(v/v), 120mL) 中的溶液里添加 NaH (2. 0g, 51mmol ; 矿物油中 60% 的分散体)。在室温下搅拌 30 分钟后, 经 20-25 分钟向混合物中添加苄基溴 (8. 7mL, 73mmol)。将所得混合物在室温下搅拌过夜, 并通过添加饱和 NH₄Cl 水溶液 (50mL) 使反应淬灭。将反应混合物浓缩, 并将残留物用 EtOAc (150mL) 和水 (50mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 /EtOAc = 10/1(v/v)) 纯化, 得到化合物 102 (11g, 77% 收率)。LC-MS (ESI) :m/z291. 0 (M+H)⁺。

[0768] 步骤 g: 在 60 °C 下, 将化合物 99 (2. 80g, 9. 0mmol)、化合物 102 (2. 6g, 9. 0mmol)、Pd(PPh₃)₂Cl₂ (6. 3g, 0. 9mmol)、CuI (2. 55g, 1. 34mmol)、Et₃N (2. 5mL, 18mmol) 和 PPh₃ (4. 7g, 1. 8mmol) 在 DMF (100mL) 中的混合物搅拌 12 小时。随后, 浓缩反应混合物。将残留物用 EtOAc (150mL) 和水 (50mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 /EtOAc = 10/1(v/v)) 纯化, 得到化合物 103 (4. 0g, 86% 收率)。LC-MS (ESI) :m/z522. 2 (M+H)⁺。

[0769] 步骤 h: 在室温下, 向化合物 103 (4. 1g, 7. 9mmol) 在 EtOH (100mL) 中的溶液里分别添加盐酸羟胺 (650mg, 9. 4mmol) 和 NaOAc (770mg, 9. 4mmol)。在 60 °C 下搅拌 2 小时后, 向反应混合物中添加 K₂CO₃ (1. 64g, 11. 85mmol) 和水 (20mL)。将所得混合物回流 12 小时。随后, 将反应混合物浓缩, 并将残留物用 EtOAc (200mL) 和水 (20mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 5/1(v/v) 至 DCM/MeOH = 5/1(v/v)) 纯化, 得到化合物 104 (1. 5g, 36% 收率)。LC-MS (ESI) : m/z537. 2 (M+H)⁺。

[0770] 步骤 i: 在 H_2 气氛中于室温下, 将化合物 104 和 10% Pd/C (1.5g) 在 MeOH (50mL) 中的混合物搅拌过夜。随后, 将反应混合物通过 CELITE™545 过滤, 并将滤饼用 MeOH (50mL × 3) 洗涤。将滤液浓缩, 并将残留物通过硅胶柱色谱法纯化, 得到化合物 105 (670mg, 56% 收率)。LC-MS (ESI) : m/z 431.2 (M+H)⁺。

[0771] 步骤 j: 在 0°C 下, 向化合物 105 (650mg, 1.5mmol) 在无水吡啶 (711mg, 9.0mmol) 中的溶液里添加 Tf_2O (1.07g, 3.8mmol)。在室温下搅拌过夜, 将反应混合物浓缩, 并将残留物用 EtOAc (100mL) 稀释。将混合物用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 5/1 (v/v)) 纯化, 得到化合物 106 (720mg, 69% 收率)。LC-MS (ESI) : m/z 695.1 (M+H)⁺。

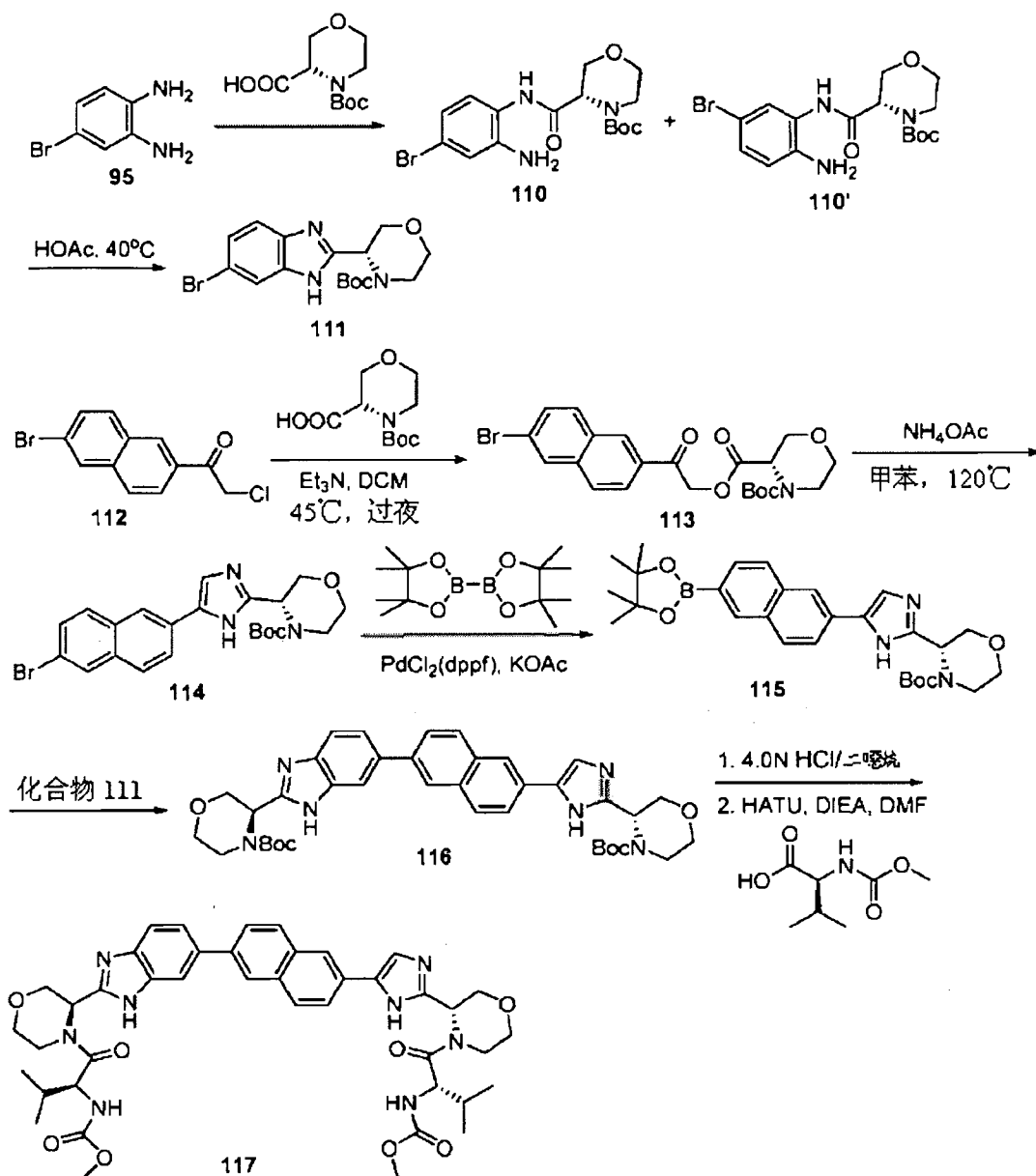
[0772] 步骤 k: 在 N_2 气氛中于 80°C 下, 将化合物 106 (410mg, 0.6mmol)、双 (频哪醇合) 二硼 (227mg, 0.9mmol)、 $PdCl_2(dppf) \cdot CH_2Cl_2$ (100mg, 0.12mmol) 和 KOAc (235mg, 2.4mmol) 在二噁烷 (15mL) 中的混合物搅拌 1 小时。反应混合物未经任何处理便用于下一步骤。LC-MS (ESI) : m/z 673.2 (M+H)⁺。

[0773] 步骤 l: 在 N_2 气氛中, 向上述反应混合物中添加 (S)-2-(5-碘-1H-咪唑-2-基) 吡咯烷-1-羧酸叔丁酯 (370mg, 1.02mmol), 然后添加 $NaHCO_3$ (201mg, 2.4mmol)、1,2-二甲氧基乙烷 (4mL)、水 (2mL) 和 $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (100mg, 0.12mmol)。在 N_2 气氛中于 80°C 下搅拌 2 小时后, 向反应混合物中添加 K_2CO_3 (691mg, 5mmol) 和 MeOH (20mL)。在室温下搅拌 30 分钟后, 浓缩混合物。将残留物用 EtOAc (150mL) 和水 (50mL) 稀释。将有机层用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 5/1 (v/v)) 纯化, 得到化合物 108 (140mg, 36% 收率; 自化合物 107 经两个步骤)。LC-MS (ESI) : m/z 650.3 (M+H)⁺。

[0774] 步骤 m: 在室温下, 向 108 (135mg, 0.2mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LCMS (ESI) : m/z 450.2 (M+H)⁺。

[0775] 步骤 n: 随后, 将所述 HCl 盐溶解于 DMF (2mL) 中, 并向所得混合物中添加 DIPEA (0.33mL, 2.0mmol)、N-THPoc-L-Val-OH (108mg, 0.50mmol) 和 HATU (190mg, 0.50mmol)。在室温下搅拌 15 分钟后, 将反应混合物添加到冰水中。将固体通过过滤收集, 并通过制备性 HPLC 纯化, 得到化合物 109。LC-MS (ESI) : m/z 848.4 (M+H)⁺。

[0776]



方案 6-4

[0777] 步骤 a: 参见方案 6-4。在室温下, 向 (S)-4-(叔丁氧羰基)吗啡-3-羧酸 (4.1g, 22.0mmol) 和 DIPEA (4.3g, 33.0mmol) 在 THF (100mL) 中的溶液里添加化合物 95 (4.6g, 20.0mmol)。搅拌 5 分钟后, 向反应混合物中添加 HATU (7.6g, 20.0mmol), 并将所得反应混合物在室温下搅拌 2 小时。将反应混合物浓缩, 并将残留物用 EtOAc (200mL) 和水 (50mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到化合物 110 和 110' 的粗混合物 (10g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI): m/z 400.1 (M+H)⁺。

[0778] 步骤 b: 在 40°C 下, 将化合物 110 和 110' (10g) 在 AcOH (50mL) 中的混合物搅拌 16 小时。随后, 将反应混合物添加到冰水 (200mL) 中, 并通过添加饱和 Na₂CO₃ 水溶液来中和, 以

将 pH 值调节至 pH8。将所得混合物用 EtOAc (100mL×3) 萃取, 将萃取物合并, 用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 1/3 (v/v)) 纯化, 得到黄色固体化合物 111 (4.5g, 60% 收率; 自 95 经两个步骤)。LC-MS (ESI) : m/z 382.1 (M+H)⁺。

[0779] 步骤 c: 向 1-(6-溴萘-2-基)-2-氯乙酮 (112) (27.0g, 95.2mmol) 在 DCM (200mL) 中的溶液里分别添加 (S)-4-(叔丁氧羰基) 吗啡-3-羧酸 (20.0g, 86.6mmol) 和 Et₃N (60.0mL, 433mmol)。在 45℃ 下搅拌过夜后, 将反应混合物分别用饱和 NaHCO₃ 水溶液 (50mL)、饱和 NH₄Cl 水溶液 (50mL) 和盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 113 (41.4g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 478.1 (M+H)⁺。

[0780] 步骤 d: 在 120℃ 下, 将粗化合物 113 (41.4g) 和 NH₄OAc (100g, 1.30mol) 在甲苯 (300mL) 中的混合物搅拌过夜。将反应混合物浓缩, 并将残留物用 EtOAc (500mL) 稀释。将混合物用水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 6/1 to 1/1 (v/v)) 纯化, 得到黄色固体化合物 114 (24g, 61% 收率; 自 112 经两个步骤)。LC-MS (ESI) : m/z 458.1 (M+H)⁺。

[0781] 步骤 e: 在 N₂ 气氛中, 向化合物 114 (3g, 6.55mmol)、双(频哪醇合)二硼 (1.83g, 7.2mmol) 和 K₂CO₃ (1.67g, 17.03mmol) 在 1,4-二噁烷 (100mL) 中的混合物里添加 Pd(dppf)Cl₂·DCM (0.8g, 0.98mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后, 将反应混合物通过 CELITE™545 过滤, 并将滤饼用 EtOAc (100mL×3) 洗涤。将滤液用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (DCM/MeOH = 50/1 (v/v)) 纯化, 得到化合物 115 (2.0g, 61% 收率)。LC-MS (ESI) : m/z 506.3 (M+H)⁺。

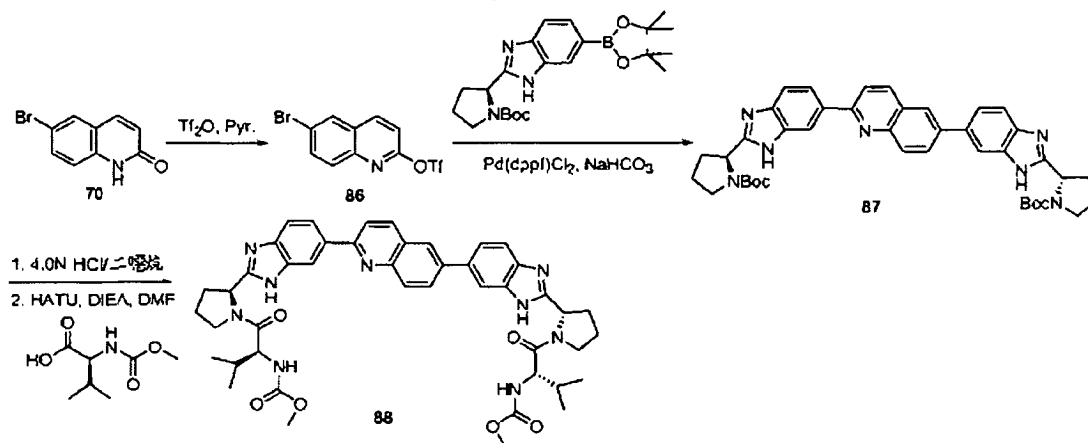
[0782] 步骤 f: 在 N₂ 气氛中, 向化合物 111 (500mg, 1.3mmol)、化合物 115 (900mg, 1.78mmol) 和 NaHCO₃ (328mg, 3.9mmol) 在 DME (15mL) 和水 (5mL) 中的混合物里添加 Pd(dppf)Cl₂·DCM (106mg, 0.13mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后, 将反应混合物浓缩, 并将残留物用 EtOAc (100mL) 和水 (25mL) 稀释。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/丙酮 = 4/1 (v/v)) 纯化, 得到黄色固体化合物 116 (310mg, 35% 收率)。LC-MS (ESI) : m/z 703.3 (M+Na)⁺。

[0783] 步骤 g: 在室温下, 向化合物 116 (150mg, 0.31mmol) 在二噁烷 (3.0mL) 中的搅拌溶液里添加二噁烷中的 4N HCl (3.0mL)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。

[0784] 步骤 h: 随后, 将所述 HCl 盐溶解于 DMF (3.0mL) 中, 并向所得混合物中分别添加 DIPEA (0.43mL, 2.5mmol)、N-Moc-L-Val-OH (136mg, 0.78mmol) 和 HATU (353mg, 0.93mmol)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到化合物 117。LC-MS (ESI) : m/z 795.4 (M+H)⁺。

[0785] 实施例 7 - 式 IIIg 化合物的合成

[0786]



方案 7-1

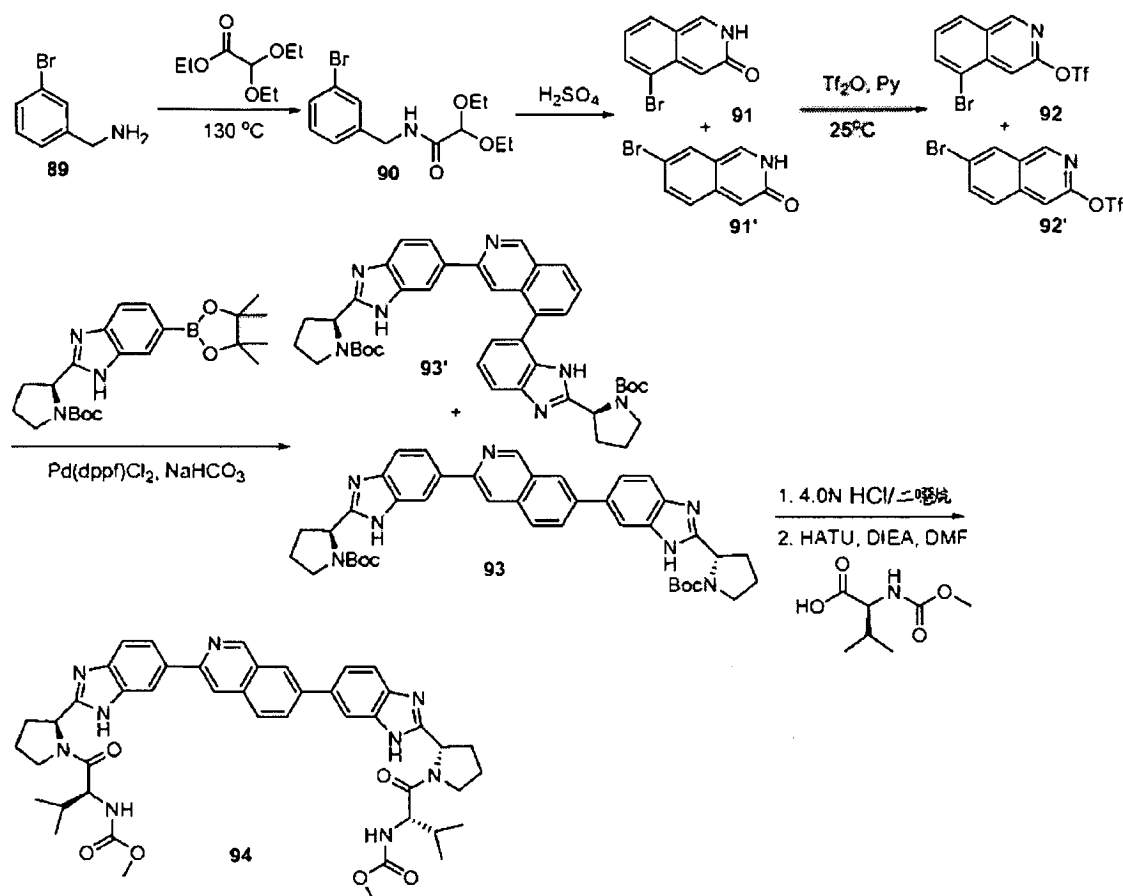
[0787] 步骤 a: 参见方案 7-1, 在 0℃ 下, 向 6-溴喹啉-2(1H)-酮 (70) (0.40g, 1.8mmol) 在无水吡啶 (12mL) 中的溶液里滴加 TiF_2O (0.81g, 2.9mmol)。在 0℃ 下搅拌 1 小时并在室温下搅拌 3 小时后, 浓缩反应混合物。将残留物溶解于 DCM (100mL); 将所得混合物用水 (25mL $\times$ 3) 洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 2/1 (v/v)) 纯化, 得到黄色固体化合物 86 (0.54g, 84% 收率)。LC-MS (ESI): m/z 355.9 ($\text{M}+\text{H}$)⁺。

[0788] 步骤 b: 在 N_2 气氛中于室温下, 向化合物 86 (0.54g, 1.5mmol)、(S)-2-(6-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)-1H-苯并[d]咪唑-2-基)吡咯烷-1-羧酸叔丁酯 (1.24g, 3.0mmol) 和 NaHCO_3 (1.01g, 12.0mmol) 在 1,2-二甲氧基乙烷 (30mL) 和水 (10mL) 中的混合物里添加 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (0.27g, 0.3mmol)。在 80℃ 下搅拌过夜后, 浓缩反应混合物。将残留物用 EtOAc (100mL) 和水 (25mL) 稀释。将有机相分离, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 1/1 (v/v)) 纯化, 得到黄色固体化合物 87 (1.0g, 95% 收率)。LC-MS (ESI): m/z 700.4 ($\text{M}+\text{H}$)⁺。

[0789] 步骤 c: 在室温下, 向化合物 87 (100mg, 0.14mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌 4 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便直接用于下一步骤。LC-MS (ESI): m/z 500.2 ($\text{M}+\text{H}$)⁺。

[0790] 步骤 d: 随后, 将所述 HCl 盐溶解于 DMF (2mL) 中, 并向所得混合物中分别添加 Et_3N (0.20mL, 1.4mmol)、N-Moc-L-Val-OH (55mg, 0.32mmol) 和 HATU (122mg, 0.32mmol)。在室温下搅拌 30 分钟后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到化合物 88。LC-MS (ESI): m/z 814.3 ($\text{M}+\text{H}$)⁺。

[0791]



方案 7-2

[0792] 步骤 a: 参见方案 7-2, 在 130 °C 下, 将化合物 89 (7.44g, 40.0mmol) 和 2, 2- 二乙氧基乙酸乙酯 (9.15g, 52.0mmol) 的混合物搅拌 7 小时。将反应混合物溶解于石油醚 (250mL) 中。将所得混合物分别用饱和 NH₄Cl 水溶液和盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到黄色油状粗化合物 90 (11.4g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 316.0 (M+H)⁺。

[0793] 步骤 b: 在室温下, 将化合物 90 (12.4g, 40mmol) 在浓 H₂SO₄ (50mL) 中的混合物搅拌 5 小时。随后, 将反应混合物倒入冰水中。将悬浮液过滤, 并将滤液用 10% NH₄OH 中和。将固体通过过滤收集, 用水洗涤, 并在真空中干燥, 得到化合物 91 和 91' 的混合物。LCMS (ESI) : m/z 224.0 (M+H)⁺。

[0794] 步骤 c: 在 0 °C 下, 向化合物 92 和 92' (222mg, 1.0mmol) 在无水吡啶 (5mL) 中的混合物里添加 Tf₂O (0.5mL)。在室温下搅拌 8 小时后, 将反应混合物浓缩, 并将残留物溶解于 DCM (50mL) 中。将混合物用水 (25mL × 3) 洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (EtOAc/ 石油醚 = 5/1 (v/v)) 纯化, 得到化合物 92 和 92' 的黄色油状混合物 (160mg, 45% 收率)。LC-MS (ESI) : m/z 355.9 (M+H)⁺。

[0795] 步骤 d: 在 N₂ 气氛中于室温下, 向化合物 92 和 92' (160mg, 0.45mmol)、(S)-2-(6-(4, 4, 5, 5- 四甲基 -1, 3, 2- 二氧杂环戊硼烷 -2- 基) -1H- 苯并 [d] 咪唑 -2- 基) 吡咯烷 -1- 羧酸叔丁酯 (463mg, 1.12mmol) 和 NaHCO₃ (227mg, 2.7mmol) 在 1, 2- 二甲氧基乙

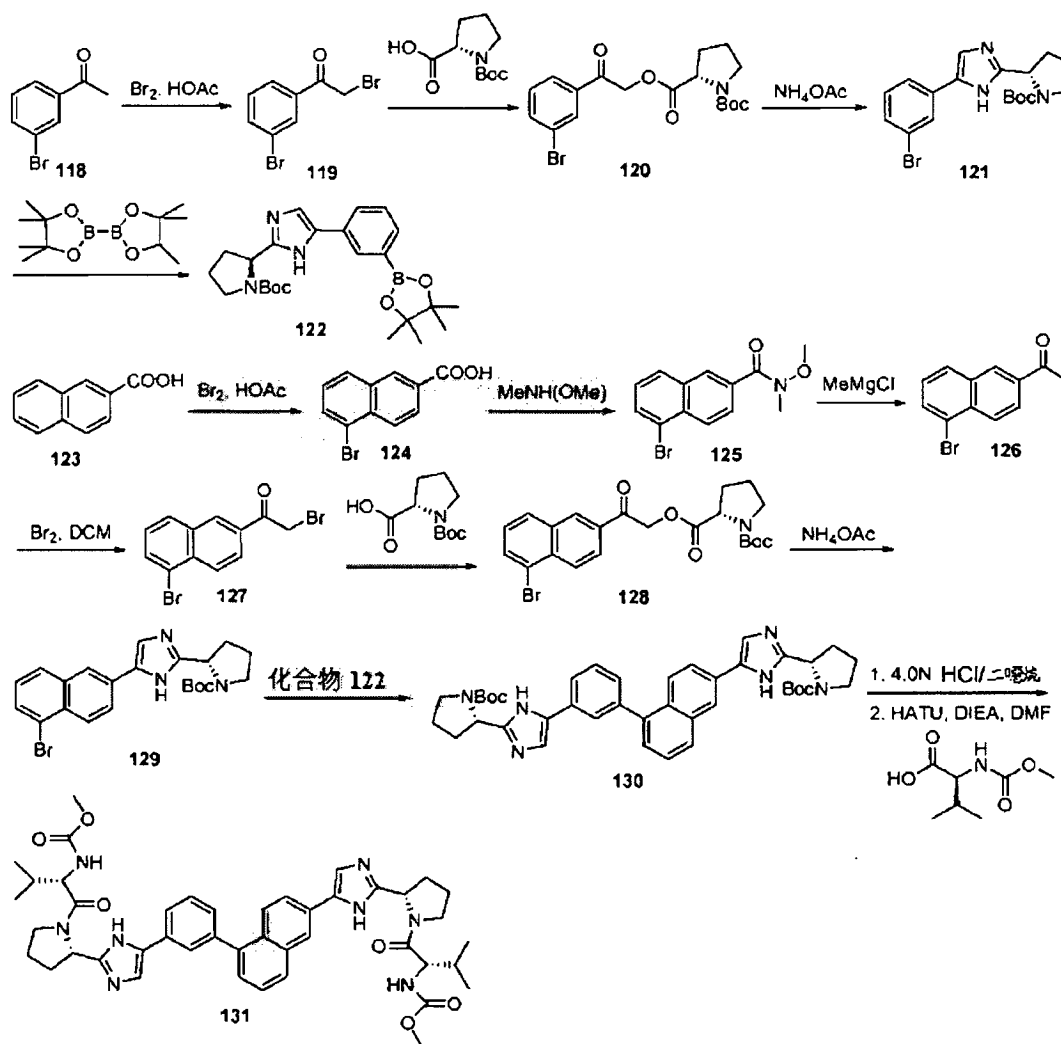
烷 (30mL) 和水 (10mL) 中的混合物里添加 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (80mg, 0.09mmol)。在 80°C 下搅拌过夜后, 将反应混合物浓缩, 并向残留物中添加 EtOAc (100mL) 和水 (20mL)。将有机相分离, 用盐水洗涤, 并用无水 Na_2SO_4 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚/ EtOAc = 1/1 (v/v)) 纯化, 得到化合物 93 (180mg, 57% 收率) 和化合物 93' (60mg, 19% 收率)。LC-MS (ESI) : m/z 700. 4 ($\text{M}+\text{H}$)⁺。

[0796] 步骤 e: 向化合物 93 (100mg, 0.14mmol) 在二噁烷 (2mL) 中的溶液里添加二噁烷中的 4N HCl (2mL)。在室温下搅拌 3 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 500. 2 ($\text{M}+\text{H}$)⁺。

[0797] 步骤 f: 随后, 将所述 HCl 盐溶解于 DMF (2mL) 中, 并向混合物中分别添加 Et_3N (0.20mL, 1.4mmol)、 N-Moc-L-Val-OH (55mg, 0.32mmol) 和 HATU (122mg, 0.32mmol)。在室温下搅拌 1 小时后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到化合物 94。LC-MS (ESI) : m/z 814. 4 ($\text{M}+\text{H}$)⁺。

[0798] 实施例 8 - 式 11g 化合物的合成

[0799]



方案 8-1

[0800] 步骤 a: 参见方案 8-1, 在室温下, 向化合物 118 (57.5g, 290mmol) 在 HOAc (100mL) 中的溶液里缓慢添加 Br₂ (49.0g, 290mmol)。在室温下搅拌 2 小时后, 向反应混合物中缓慢添加饱和 NaHCO₃ 水溶液。将有机相用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到粗化合物 119 (60g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 276.9 (M+H)⁺。

[0801] 步骤 b: 在室温下, 向化合物 119 (25.0g, 89.9mmol) 在 CH₃CN (100mL) 中的溶液里添加 (S)-N-Boc-Pro-OH (19.4g, 89.9mmol), 然后添加 Et₃N (37.35mL, 269.7mmol)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物用 DCM (250mL) 稀释。将混合物用水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物在真空中干燥, 得到化合物 120 (37g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 313.2 (M-100+H)⁺。

[0802] 步骤 c: 在 140℃ 下, 将粗化合物 120 (37g) 和 NH₄OAc (69.2g, 899mmol) 在二甲苯 (100mL) 中的混合物搅拌过夜。将反应混合物浓缩, 并将残留物用 DCM (500mL) 稀释。将混合物用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 10/1 (v/v)) 纯化, 得到白色固体化合物 121 (12g, 40% 收率; 自化合物 119 经三个步骤)。LC-MS (ESI) : m/z 392.1 (M+H)⁺。

[0803] 步骤 d: 在 N₂ 气氛中, 向化合物 121 (3g, 7.65mmol)、双 (频哪醇合) 二硼 (4.24g, 16.8mmol)、KOAc (1.87g, 19.1mmol) 在 1,4-二噁烷 (200mL) 中的混合物里添加 Pd(dppf)Cl₂ (624mg, 0.765mmol)。在 N₂ 气氛中于 80℃ 下搅拌过夜后, 将反应混合物通过 CELITE™545 过滤, 并将滤饼用 EtOAc (100mL × 3) 洗涤。将滤液用盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / 丙酮 = 8/1 (v/v)) 纯化, 得到灰色固体化合物 122 (2.9g, 86% 收率)。LC-MS (ESI) : m/z 440.3 (M+H)⁺。

[0804] 步骤 e: 向 2-萘甲酸 (123) (50.0g, 290mmol) 在 HOAc (100mL) 中的沸腾溶液中缓慢添加 Br₂ (46.3g, 290mmol) 和 I₂ (1.25g, 43.5mmol) 的混合物。添加完成后, 将反应混合物回流 30 分钟。将反应混合物冷却至室温并过滤。将固体用 HOAc 洗涤, 并在真空中干燥, 得到粗化合物 124 (50g), 其不经进一步纯化便用于下一步骤。LC-MS (ESI) : m/z 251.0 (M+H)⁺。

[0805] 步骤 f: 在室温下, 向化合物 124 (10.0g, 39.8mmol) 在 CH₃CN (200mL) 中的混合物里添加 EDCI (18.3g, 95.5mmol)、Et₃N (16.08mL, 159.2mmol) 和 N,O-二甲基羟胺盐酸盐 (4.8g, 50mmol)。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物用 DCM (250mL) 稀释。将混合物分别用饱和 NH₄Cl 水溶液、饱和 NaHCO₃ 水溶液和盐水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / EtOAc = 8/1 (v/v)) 纯化, 得到白色固体化合物 125 (3.6g, 31% 收率)。LC-MS (ESI) : m/z 294.0 (M+H)⁺。

[0806] 步骤 g: 在 0℃ 下, 向化合物 125 (3.60g, 12.2mmol) 在 THF (150mL) 中的溶液里缓慢添加 THF 中的 3M MeMgCl (8.31mL)。在 0℃ 下搅拌 1 小时并在室温下搅拌 1 小时后, 通过添加饱和 NH₄Cl 水溶液 (5mL) 使反应淬灭。将溶剂移除, 并将残留物用 DCM 稀释。将混合物用水洗涤, 并用无水 Na₂SO₄ 干燥。将溶剂移除, 并将残留物通过硅胶柱色谱法 (石油醚 / AcOEt = 10/1 (v/v)) 纯化, 得到白色固体化合物 126 (3.05g, 100% 收率)。LC-MS (ESI) : m/z 249.0 (M+H)⁺。

[0807] 步骤 h: 在室温下, 向化合物 126 (3.05g, 12.2mmol) 在 DCM (100mL) 中的溶液里缓慢添加 DCM (10mL) 中的 Br₂ (1.93g, 12.2mmol)。在室温下搅拌 2 小时后, 通过添加饱和

NaHCO₃ 水溶液 (10mL) 使反应淬灭。将有机层用盐水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物在真空中干燥,得到粗化合物 127 (4.0g),其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 326.9 (M+H)⁺。

[0808] 步骤 i: 向粗化合物 127 (4.0g) 在 CH₃CN (15mL) 中的溶液里添加 (S)-N-Boc-Pro-OH (3.14g, 14.6mmol) 和 Et₃N (3.70g, 36.6mmol)。在室温下搅拌 2 小时后,将反应混合物浓缩,并将残留物用 DCM (200mL) 稀释。随后,将混合物分别用饱和 NH₄Cl 水溶液和水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物在真空中干燥,得到粗化合物 128 (5.6g),其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 462.1 (M+H)⁺。

[0809] 步骤 j: 在 110℃ 下,将粗化合物 128 (5.6g) 和 NH₄OAc (9.36g, 122mmol) 在甲苯 (80mL) 中的混合物搅拌过夜。将反应混合物浓缩,并将残留物用 DCM (250mL) 稀释。将混合物用水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 5/1 (v/v)) 纯化,得到白色固体化合物 129 (3.0g, 56 收率)。LC-MS (ESI) :m/z 442.1 (M+H)⁺。

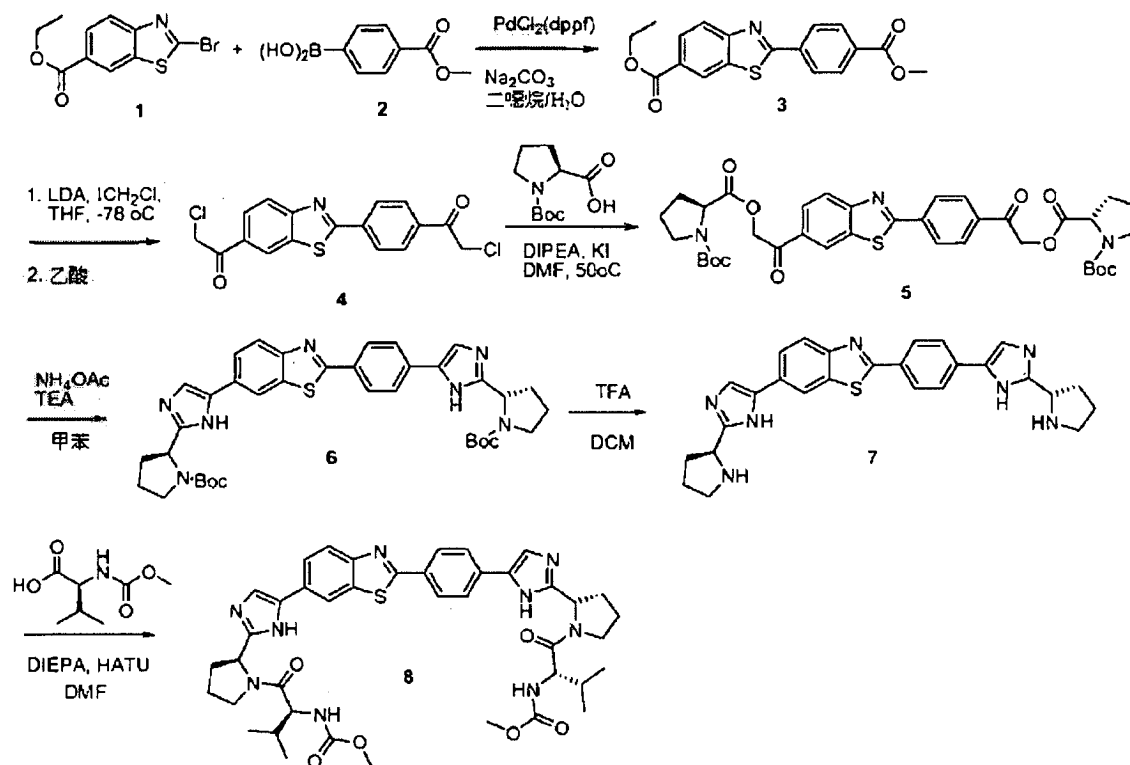
[0810] 步骤 k: 在 N₂ 气氛中,向化合物 122 (633mg, 1.44mmol)、化合物 129 (500mg, 1.31mmol) 和 NaHCO₃ (330mg, 3.01mmol) 在 1,2-二甲氧基乙烷 (15mL) 和水 (5mL) 中的混合物里添加 Pd(dppf)Cl₂ (107mg, 0.131mmol)。在 80℃ 下搅拌过夜后,将反应混合物浓缩,并将残留物用 EtOAc (50mL) 和水 (20mL) 稀释。将有机相用盐水洗涤,并用无水 Na₂SO₄ 干燥。将溶剂移除,并将残留物通过硅胶柱色谱法 (石油醚/EtOAc = 10/1 (v/v)) 纯化,得到黄色固体化合物 130 (400mg, 45% 收率)。LC-MS (ESI) :m/z 675.4 (M+H)⁺。

[0811] 步骤 l: 在室温下,向化合物 130 (150mg, 0.22mmol) 在二噁烷 (2.0mL) 中的溶液里添加二噁烷中的 4N HCl (2.0mL)。在室温下搅拌 3 小时后,将反应混合物浓缩,并将残留物在真空中干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z 475.3 (M+H)⁺。

[0812] 步骤 m: 随后,在室温下,将所述 HCl 盐溶解于 DMF (2.0mL) 中,并向混合物中添加 DIPEA (0.36mL, 2.2mmol)、N-Moc-L-Val-OH (86mg, 0.49mmol) 和 HATU (202mg, 0.49mmol)。在室温下搅拌 1 小时后,将反应混合物浓缩,并将残留物通过制备性 HPLC 纯化,得到化合物 131。LC-MS (ESI) :m/z 789.4 (M+H)⁺。

[0813] 实施例 9 - - 式 IVa 化合物的合成

[0814]



方案 9-1

[0815] 步骤 a: 参见方案 9-1, 通过将脱气并用氮再填充的过程重复三次来处理 2-溴苯并噻唑 1 (2.72g, 9.5mmol)、4-甲氧羰基苯基硼酸 (2) (1.80g, 10mmol)、Pd(dppf)Cl₂ (388mg, 0.475mmol) 在 2M Na₂CO₃ (10mL) 和二噁烷 (20mL) 中的混合物。然后将反应混合物在氮气氛围中于 95℃ 下搅拌 4 小时。冷却后, 将混合物用 THF 稀释, 然后通过 CELITE™545 垫过滤。将滤液浓缩, 并通过快速色谱法 (使用二氯甲烷作为洗脱液) 直接纯化粗产物, 得到白色固体化合物 3 (1.96g, 60% 收率)。

[0816] 步骤 b: 在 -78°C 下, 经 15 分钟将正丁基锂 (己烷中 2.5M, 25.3mL, 63.1mmol) 的溶液缓慢添加到二异丙胺 (6.97g, 68.8mmol) 在 THF (20mL) 中的溶液里。添加后, 将溶液在 -78°C 下搅拌 30 分钟, 然后暖至 0°C 。将 LDA 溶液冷却至 -78°C 以用于下一步骤中。

[0817] 步骤c:将3(1.96g, 5.74mmol)和氯碘甲烷(7.30g, 41.2mmol)在THF(15mL)中的溶液冷却至-78℃。经20分钟将上文制备的LDA溶液经套管缓慢输入此溶液中。将所得混合物再搅拌1小时。通过在-78℃下缓慢添加乙酸在THF中的溶液(1/1(v/v), 40mL)使反应淬灭。将反应混合物暖至室温,然后用水和乙酸乙酯稀释。将水层用乙酸乙酯萃取。将合并的有机层经无水硫酸钠干燥,过滤并浓缩。将粗产物4(1.80g)在真空中干燥,并将残留物直接用于下一缩合反应。

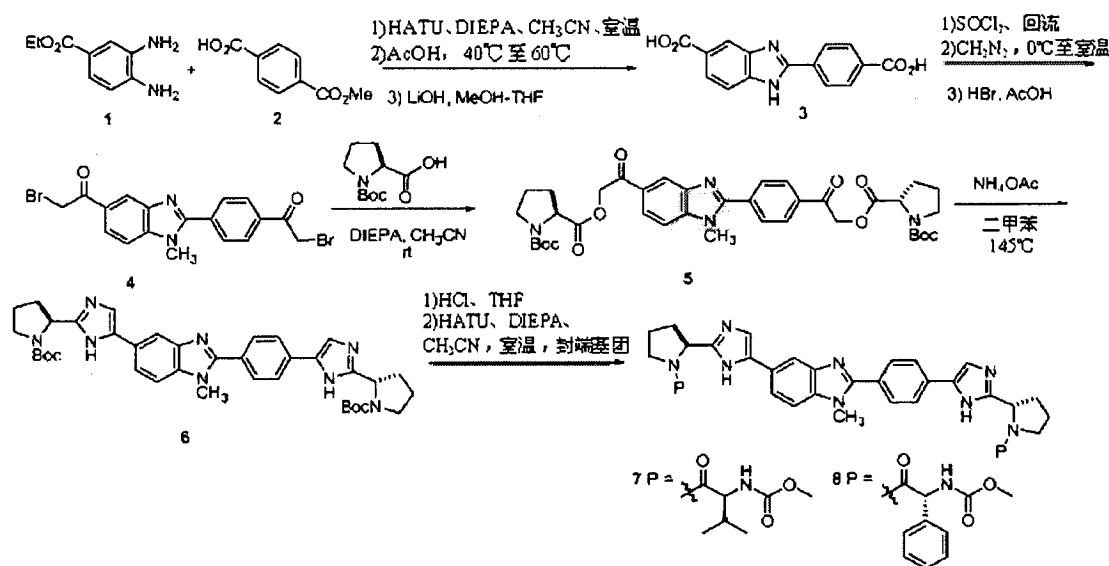
[0818] 步骤 d: 在 50℃ 下, 将 4 (0.59g, 1.61mmol)、N-Boc-L-Proline (0.83g, 3.85mmol)、KI (0.64g, 3.85mmol) 和二异丙基乙胺 (0.64g, 3.85mmol) 在 DMF (40mL) 中的混合物搅拌 4 小时。蒸发溶剂, 并将残留物用水处理。将固体通过过滤收集, 并用水洗涤两次。在真空中干燥后, 将粗产物通过快速色谱法 (乙酸乙酯 / 己烷 = 1/9 至 1/5 (v/v)) 纯化, 得到白色固体 5 (0.92g, 67% 收率)。

[0819] 步骤 e: 在 140 °C 下, 将在密封管中的二酯 5 (0.81g, 1.12mmol)、乙酸铵 (2.59g, 33.5mmol) 和三乙胺 (3.39g, 33.5mmol) 在甲苯 (100mL) 中的混合物搅拌 90 分钟。冷却后, 将反应混合物转移到烧瓶中, 并浓缩至干燥。将残留物在氯仿与水之间分开, 并将有机层用水和盐水洗涤并浓缩。将粗产物通过快速色谱法 (NH_4OH / 丙酮 / 乙酸乙酯 = 1/2/100 (v/v/v)) 纯化, 得到白色固体化合物 6 (0.51g, 67% 收率)。

[0820] 步骤 f: 在室温下, 将三氟乙酸 (3mL) 缓慢添加到 6 在二氯甲烷 (10mL) 中的溶液里。将所得混合物在该温度下搅拌 1 小时, 并浓缩至干燥。将残留物溶解于水中, 并将水溶液碱化至 pH11。将产物用氯仿萃取 5 次。移除溶剂后, 得到呈 TFA 盐形式的 7 (274mg, 76%)。

[0821] 步骤 g: 在室温下, 将 N-甲氧羰基-L-缬氨酸 (40mg, 0.23mmol)、DIPEA (98mg, 0.76mmol) 和 HATU (87mg, 0.23mmol) 在 DMF 中的混合物搅拌 30 分钟。添加固体 7 (80mg, 0.076mmol)。将反应混合物在室温下搅拌 2 小时, 然后滴入水中。形成沉淀, 并通过过滤收集。将粗产物通过制备性 HPLC 纯化, 得到化合物 8 (16mg)。 ^1H NMR (CDCl_3 , 300MHz) 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 ($\text{M}+\text{H}$) $^+$ 。

[0822]



方案 9-2

[0823] 步骤 a: 参见方案 9-2, 向化合物 2 (6.31g, 35mmol) 和 HATU (14.63g, 38.5mmol) 在 CH_3CN (150mL) 中的混合物里缓慢添加 DIPEA (9.05g, 11.35mL, 70mmol)。将所得混合物在室温下搅拌 15 分钟。在室温下向混合物中添加 3,4-二氨基-苯甲酸乙酯 1 (6.31g, 35mmol), 并在室温下持续搅拌 17 小时。将反应用饱和 NaHCO_3 溶液淬灭, 并用 EtOAc ($3 \times 150\text{mL}$) 萃取。将合并的有机相用 H_2O ($2 \times 200\text{mL}$) 和盐水 (200mL) 洗涤, 经 Na_2SO_4 干燥, 过滤, 并在旋转蒸发器上浓缩。将粗混合物通过柱色谱法 (以己烷/ EtOAc = 3/1 至 2/1 (v/v) 洗脱) 纯化, 得到黄褐色固体酰胺 (11.2g, 94%)。LC-MS (ESI): m/z ($\text{M}+\text{H}$) $^+$: 343; ($\text{M}-\text{H}$) $^-$: 341。

[0824] 步骤 b: 在 40°C 下, 将得自上述反应的产物 (11.2g, 33mmol) 在 AcOH (100mL) 中的混合物加热 18 小时。使温度暖至 60°C, 并进一步将混合物加热 24 小时。根据 LC-MS 分析,

所有起始物质均已消耗。在旋转蒸发器上移除过量溶剂,得到粗混合物,将该混合物通过柱色谱法(以己烷/EtOAc = 3/1(v/v)洗脱)纯化,得到官能化苯并咪唑(10.2g, 96% 收率)。LC-MS(ESI): m/z 325.1 (M+H)⁺。

[0825] 步骤 c: 将得自上述反应的产物(10.2g, 31mmol)和 LiOH(7.54g, 0.31mol)在 MeOH(200mL)中的混合物在回流条件下加热 60 小时。将乳状混合物用 10% HCl 溶液酸化,以将 pH 调节为 1,得到白色沉淀物。将沉淀物通过过滤收集,然后在真空中干燥,得到化合物 3(8.9g, 定量收率),其不经进一步纯化便用于下一步骤。LC-MS(ESI): m/z 283.1 (M+H)⁺。

[0826] 步骤 d: 将 3(8.9g, 31mmol)在亚硫酰氯(60mL)中的混合物回流 3 小时。将反应混合物浓缩,并将残留物在真空中干燥,得到酰氯,将其悬浮于无水二乙醚(200mL)/THF(50mL)的混合物中。在 0℃下,向悬浮液中滴加快速生成的重氮甲烷溶液(由 251mmol 4-N, N-三甲基-苯磺酰胺生成的约 166mmol 重氮甲烷溶液),然后在 0℃至室温下搅拌过夜(20 小时)。在旋转蒸发器上移除所有挥发物,得到残留物。将残留物通过柱色谱法(以己烷/EtOAc = 3/1(v/v)洗脱)纯化,得到黄色固体(1.89g, 17% 收率)。

[0827] 步骤 e: 在室温下,向得自上述的 2-重氮基-1-{2-[4-(2-重氮基-乙酰基)-苯基]-1-甲基-1H-苯并咪唑-5-基}-乙酮(1.89g, 5.49mmol)在 AcOH(50mL)中的混合物里缓慢添加 HBr(AcOH 中 48%, 1.62mL, 14.31mmol)。将所得混合物在室温下搅拌 13 小时,然后在旋转蒸发器上移除所有挥发物,得到粗混合物。在旋转蒸发器上用甲苯(2×25mL)进一步干燥粗混合物,得到黄色固体化合物 4,其不经进一步纯化便用于下一步骤。LC-MS(ESI): m/z 448.9 (M+H)⁺。

[0828] 步骤 f: 在室温下,向化合物 4(~5.49mmol)在 CH₃CN(50mL)中的粗混合物里添加 N-Boc-L-脯氨酸(2.59g, 12.01mmol),然后添加 DIEPA(3.71mL, 22.9mmol)。将所得混合物在室温下搅拌 5 小时,并用 H₂O 淬灭。将混合物用 EtOAc(3×50mL)萃取。将合并的有机相用 H₂O(50mL)和盐水(50mL)洗涤,经 Na₂SO₄ 干燥,过滤,并在旋转蒸发器上浓缩。粗混合物不经进一步纯化便用于下一步骤。LC-MS(ESI): m/z 719.3 (M+H)⁺。

[0829] 步骤 g: 向 5(~5.72mmol)在二甲苯(50mL)中的粗溶液中添加 NH₄OAc(6.61g, 85.8mmol)。将所得混合物在 145℃下加热 1.5 小时,然后在旋转蒸发器上移除所有溶剂,得到粗混合物,使其经受柱色谱法(以己烷:EtOAc = 1:3 至仅 EtOAc 洗脱)。得到呈黄褐色固体的化合物 6(717mg)。LC-MS(ESI): m/z 679.4 (M+H)⁺。

[0830] 步骤 h: 在室温下,向 6(717mg, 1.06mmol)在 THF(7.5mL)中的粗溶液中添加 HCl(二噁烷中 4.0M, 10mL)。将所得混合物在室温下搅拌 16 小时,然后在旋转蒸发器上移除所有挥发物,得到黄色固体。将黄色固体用二乙醚(2×10mL)洗涤,然后在真空中进一步干燥,得到 HCl 盐,其不经进一步纯化便用于下一步骤。LC-MS(ESI): m/z 479.3。¹H NMR 波谱显示了粗产物为 1:1 比例的两种区域异构体的混合物。(M+H)⁺。

[0831] 步骤 i: 向所述 HCl 盐(48mg, ~0.1mmol)、N-Boc-L-Val-OH(35mg, 0.2mmol)和 HATU(76mg, 0.2mmol)在 CH₃CN(1.0mL)中的粗溶液里添加 DIEPA(65L, 0.4mmol)。将所得混合物在室温下搅拌 2.5 小时,然后在旋转蒸发器上移除所有溶剂,得到粗混合物。将粗混合物通过制备性 HPLC(以 H₂O 至 CH₃CN 洗脱)纯化。分别获得 10.0mg(黄色固体, 7)和 8.7mg(黄色固体, 7')的两种区域异构体。7 的表征:¹H NMR(300MHz, CDCl₃) 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)、

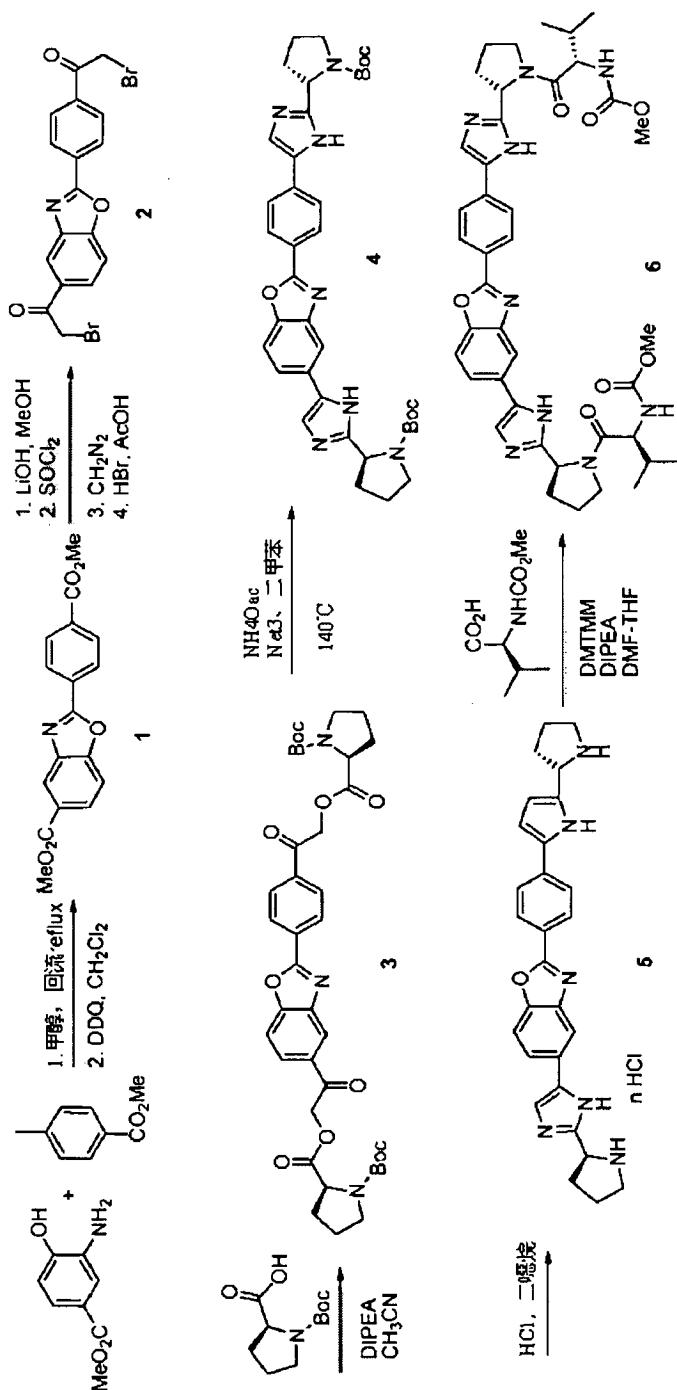
3.60-3.78(m, 12H)、2.76(br s, 1H)、2.20-2.44(m, 4H)、1.98-2.18(m, 4H)、0.89-1.12(m, 12H) ppm。LC-MS(ESI) :m/z (M+2)/2⁺:397, (M+1)⁺:794。

[0832] 化合物 7' 的表征:¹H NMR(300MHz, CDCl₃) δ8.30(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 = 6.6Hz, 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)⁺。

[0833] 按照用于合成化合物 7 和 7' 的相同的程序并用 N-Moc-D-Phg-OH 代替 N-Moc-L-Val-OH 作为酰胺试剂获得 N-Moc-D-Phg-OH 封端的类似物 8。¹H NMR(300MHz, CDCl₃) δ8.32(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。

[0834] 按照用于合成化合物 7 和 7' 的相同的程序并用 N-Moc-D-Phg-OH 代替 N-Moc-L-Val-OH 作为酰胺试剂获得 N-Moc-D-Phg-OH 封端的类似物 8。¹H NMR(300MHz, CDCl₃) δ8.32(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。

[0835]



方案 9-3

[0836] 步骤 a: 在室温下, 将 3-氨基-4-羟基苯甲酸甲酯 (2.5g, 15mmol) 和 4-甲酰基苯甲酸甲酯 (2.46g, 15mmol) 在甲醇 (75mL) 中的混合物搅拌过夜。将溶剂在减压下蒸发, 并将剩余的残留物溶解于二氯甲烷 (150mL) 中。添加 DDQ (3.5g, 15.4mmol), 并将反应混合物在室温下搅拌 1 小时。添加饱和 NaHCO₃ (200mL)。将悬浮液滤除, 将所得固体用饱和 NaHCO₃ (50mL)、水 (50mL) 和乙酸乙酯 (100mL) 洗涤, 并在真空中干燥, 得到黄色固体化合物 1 (4g, 86% 收率)。

[0837] 步骤 b: 将二酯 1 (4g, 12.8mmol) 和一水合氢氧化锂 (2.7g, 64mmol) 在甲醇和水的混合溶剂 (60mL, 甲醇/水 = 1/5) 中的混合物回流 6 小时。将甲醇蒸发, 并通过 HCl (浓)

中和剩余的水溶液。将所得悬浮液滤除,将固体用水(50mL)洗涤,并在真空中干燥,得到相应的二羧酸(3.3g,95%收率),为黄色固体。

[0838] 步骤 c:将二羧酸样品(2.88g, 10.2mmol) 悬浮在亚硫酰氯(30mL)中,将混合物回流 6 小时。将反应混合物在减压下蒸发,并在真空中干燥,得到相应的黄色固体二酰氯(3.25g)。

[0839] 步骤 d:在 0℃下,将所得二酰氯(1.5g, 4.7mmol) 在乙醚中的悬浮液用重氮甲烷(71mL, 乙醚中 0.33N, 23mmol) 处理 2 小时。将溶剂在减压下蒸发,并在真空中干燥,得到相应的重氮酮(1.55g),为黄色固体。LC-MS(ESI):m/z332.1[M+H]⁺。

[0840] 步骤 e:在 0℃下,将所得重氮酮(1.55g, 4.7mmol) 悬浮于乙酸(10mL)中,并向混合物中滴加 AcOH 中的 48% HBr(3.93g, 23.3mmol)。然后将反应混合物暖至室温并搅拌 1 小时。将饱和 Na₂CO₃ 缓慢添加到反应混合物中以中和酸。将所得悬浮液滤除,将固体用水洗涤,并在真空中干燥,得到黄色固体溴酮 2(1.38g, 69%收率)。

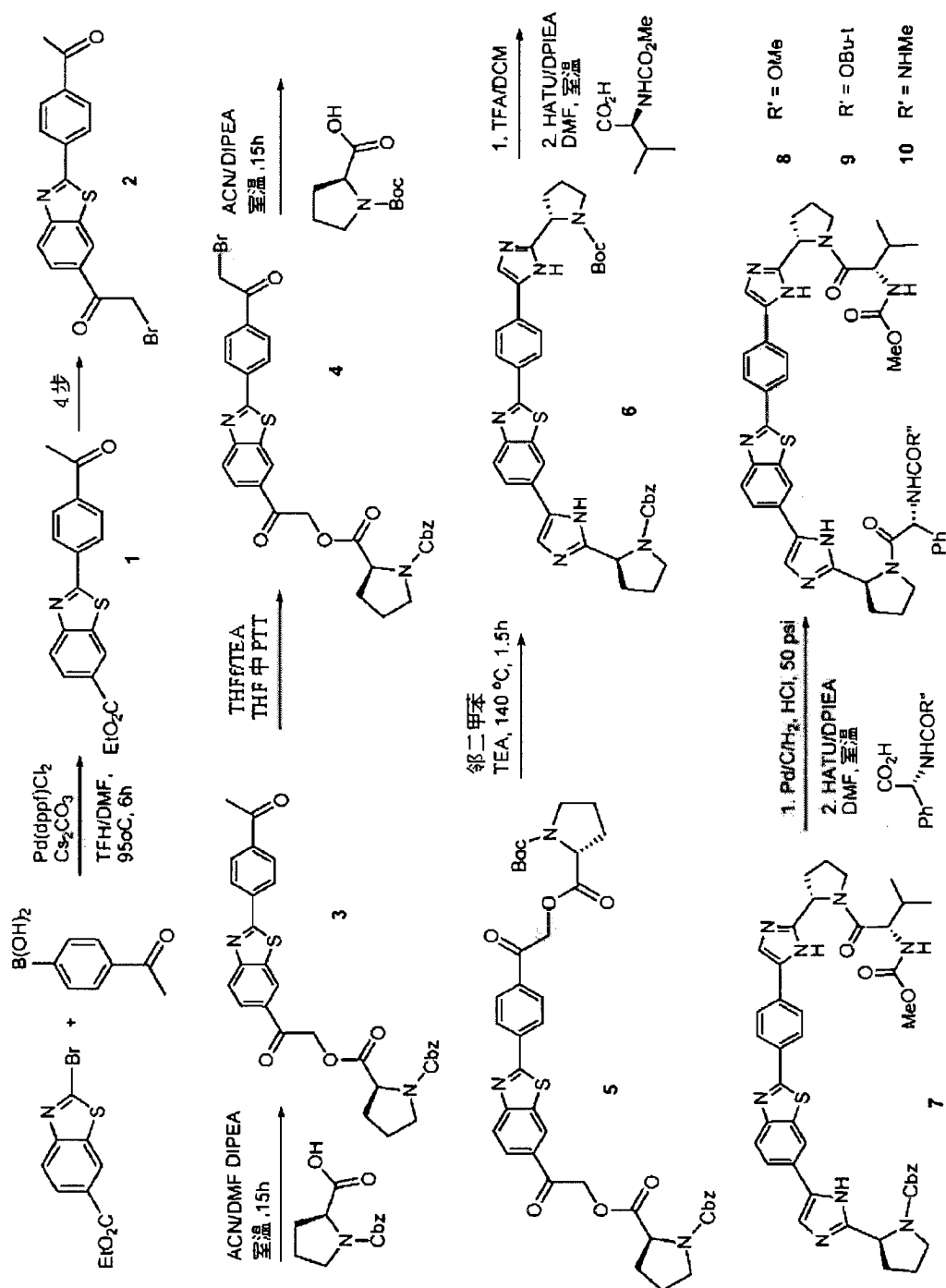
[0841] 步骤 f:在室温下,将溴酮 2(1.38g, 3.2mmol)、N-Boc-L 脯氨酸(2.7g, 12.6mmol) 和 DIPEA(2.2mL, 12.6mmol) 在乙腈(3mL)中的溶液搅拌过夜。将乙腈蒸发,并将剩余的残留物在乙酸乙酯(50mL)与水(25mL)之间分开。然后收集有机相,并经 Na₂SO₄ 干燥。在减压下浓缩后,将粗产物经硅胶(乙酸乙酯/己烷=35/65)纯化,得到黄色固体酯 3(0.56g, 25%收率)。LC-MS(ESI):m/z706.3[M+H]⁺。

[0842] 步骤 g:在 140℃下,在密封 parr 瓶中,将酯 3(560mg, 0.8mmol) 和乙酸铵(1.84g, 24mmol) 在脱气二甲苯(3.3mL)中的混合物搅拌 90 分钟。移除挥发性溶剂后,将残留物通过硅胶色谱法(乙酸乙酯 100%,然后为乙酸乙酯/甲醇=90/10(v/v))纯化,得到黄色固体双咪唑 4(474mg, 89%收率)。LC-MS(ESI):m/z666.3[M+H]⁺。

[0843] 步骤 h:在室温下,向双咪唑 4(474mg, 0.71mmol) 在 THF(20mL)中的溶液里添加二噁烷中的 4N HCl(3.6mL, 14mmol)。将反应混合物在室温下搅拌 2 小时。蒸发溶剂,并将残留物在真空中干燥,得到黄色 HCl 盐 5(约 330mg),其不经进一步纯化便用于下一步骤。LC-MS(ESI):m/z465.2[M+H]⁺。

[0844] 步骤 i:在室温下,向 5(135mg, 0.29mmol)、N-Moc-L-Val-OH(152.6mg, 0.87mmol) 和 DMTMM(240.5mg, 0.87mmol) 在 DMF-THF 混合溶剂(2mL, DMF/THF = 1/3(v/v))中的溶液里添加 DIPEA(0.5mL, 2.9mmol)。将反应混合物在室温下搅拌 2 小时。将 THF 蒸发,并将剩余的反应混合物经制备性 HPLC 纯化,得到白色固体化合物 6。¹H NMR(300MHz, CD₃OD) δ 0.92(m, 12H)、2.05(m, 4H)、2.26(m, 4H)、3.65(s, 6H)、3.9(m, 2H)、3.99(m, 2H)、4.22(m, 2H)、5.18(m, 2H)、7.33(s, 1H)、7.48(s, 1H)、7.64(d, J = 8.7Hz, 1H)、7.73(d, J = 8.1Hz, 1H)、7.88(d, J = 8.1Hz, 2H)、7.99(s, 1H)、8.21(d, J = 8.7Hz, 2H) ppm。LC-MS(ESI):m/z780.4[M+H]⁺。

[0845]



方案 9-4

[0846] 步骤 a: 参见方案 9-4, 在 Schlenk 烧瓶中, 将 2-溴-6-苯并噻唑羧酸乙酯 (100mg, 0.35mmol)、4-乙酰基苯基硼酸 (69mg, 0.42mmol)、 Pd(dppf)Cl_2 (14mg, 0.05mmol) 和 Cs_2CO_3 (228mg, 0.70mmol) 溶解于混合溶剂 (THF/DMF = 3:2, 5mL) 中。将反应混合物脱气, 并用氮气再填充三次。将烧瓶在氮气下加热至 95°C 达 6 小时, 然后冷却至室温。将溶剂在减压下移除, 并将残留物再溶解于二氯甲烷 (DCM) 中。将 DCM 溶液用饱和 NaHCO_3 、盐水洗涤, 并用 Na_2SO_4 干燥, 浓缩, 通过硅胶柱 (DCM/MeOH = 9.8/0.2 (v/v)) 纯化, 得到浅黄色的固体 1 (70mg, 62% 收率)。 ^1H NMR (300MHz, 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/

z326.1(M+H)⁺。

[0847] 步骤 b: 向 1(4.0g, 12.3mmol) 在 THF/MeOH/H₂O 混合溶剂(100mL) 中的悬浮液里添加 LiOH·H₂O(2.58g, 61.5mmol)。将反应混合物在室温下搅拌过夜。将挥发物移除, 加水(50mL), 并用 2N HCl 将 pH 调节至 1-2。将沉淀物过滤并干燥, 得到白色固体游离酸(3.6g, 100%)。LC-MS(ESI): m/z: 298.0(M+H)⁺。

[0848] 步骤 c: 将酸样品(3g, 10mmol) 悬浮在亚硫酸氯(50mL) 中, 加热回流 2 小时。将挥发物在减压下移除, 并将残留物(3.2g) 在真空中干燥, 得到相应的酰基氯。

[0849] 步骤 d: 在 0℃ 下, 向上述的酰基氯(3g, 9.5mmol) 在 DCM/THF 混合溶剂(7/3(v/v), 100mL) 中的悬浮液里添加新制备的二乙醚中的重氮甲烷(5.0 当量)。将反应混合物在 0℃ 至室温下搅拌 1 小时。LC-MS and ¹H NMR 显示反应完成。将溶剂移除, 得到粗产物重氮酮。¹H NMR(300MHz, CDCl₃) δ: 4.3(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。

[0850] 步骤 e: 将重氮酮溶解于乙酸(50mL), 并添加 HBr(1.1 当量, 48% 水溶液), 在室温下搅拌 1 小时, 浓缩得到化合物 2(4.5g)。

[0851] 步骤 f: 向 N-Cbz-L-脯氨酸(3.59g, 14.4mmol) 在乙腈(100mL) 和 DMF(50mL) 中的溶液里添加乙腈(50mL) 中的二异丙基乙胺(6.0mL, 36mmol) 和 2(4.5g, 12mmol)。将反应混合物在室温下搅拌过夜。将溶剂移除, 并将产物用二氯甲烷(3×) 萃取, 用 NaHCO₃(200mL) 和盐水洗涤, 经 Na₂SO₄ 干燥。移除溶剂后, 将粗产物通过硅胶柱(己烷/EtOAc = 1/1(v/v)) 纯化, 得到 3(1.2g)。LC-MS(ESI): m/z 543.2(M+H)⁺。

[0852] 步骤 g: 在 -78℃ 下, 向 3(1.2g, 2.2mmol) 和 TEA(2.18mL, 13.2mmol) 在 DCM 中的溶液里添加 TMS-OTf(0.8mL, 4.4mmol)。将反应物搅拌至室温过夜后, 添加 PTT(910mg, 2.42mmol)。将反应物在室温下搅拌 2 小时, 并用 NaHCO₃ 溶液淬灭。将混合物在水与 CH₂Cl₂(3×) 之间分开, 将有机相用盐水洗涤, 干燥, 过滤, 并在真空中浓缩, 得到粗化合物 4(1.37g)。

[0853] 步骤 h: 向 N-Boc-L-脯氨酸(568mg, 2.6mmol) 在乙腈(10mL) 中的溶液里添加乙腈(10mL) 中的 DIPEA(0.54mL, 3.3mmol) 和 4(1.37g, 2.2mmol)。将反应混合物在室温下搅拌过夜。将溶剂移除, 并将产物用二氯甲烷(3×) 萃取, 用 NaHCO₃(200mL) 和盐水洗涤, 用 Na₂SO₄ 干燥。移除溶剂后, 将粗产物通过硅胶柱(己烷/EtOAc = 1/1(v/v)) 纯化, 得到 5(900mg, 54% 收率)。LC-MS(ESI): m/z 756.3(M+H)⁺。

[0854] 步骤 i: 向压力管中的 5(900mg, 1.19mmol) 在邻二甲苯(20mL) 中的溶液里添加乙酸铵(2.75g, 35.7mmol) 和三乙胺(5mL, 35.7mmol)。将管密封, 加热至 140℃ 达 1.5 小时, 冷却至室温。将挥发性组分在真空中移除, 并将残留物在水与 CH₂Cl₂ 之间分开, 将有机相干燥, 过滤, 并在真空中浓缩。将所得粗料通过快速色谱法(己烷:EA:MeOH = 5:5:1) 纯化, 得到黄色残留物 6(630mg, 74% 收率)。LC-MS(ESI): m/z 716.3(M+H)⁺。

[0855] 步骤 j: 向 6(630mg, 0.88mmol) 在 DCM(20mL) 中的溶液里添加 TFA(5mL)。将反应混合物在室温下搅拌 2 小时; 移除 TFA, 得到 TFA 盐, 其不经进一步纯化便用于下一步骤。

[0856] 步骤 k: 向 TFA 盐(550mg, 0.88mmol) 在 DMF(10mL) 中的溶液里添加 N-Moc-L-Val-OH(308mg, 1.76mmol)、HATU(502mg, 1.32mmol) 和 DIPEA(871 μL, 5.28mmol)。将反应物在室温下搅拌过夜。将溶剂在减压下移除。将粗产物通过硅胶柱(CH₂Cl₂/MeOH =

9.8/0.2(v/v)) 纯化,得到 7(500mg,74%收率)。LC-MS(ESI): m/z 773.3(M+H)⁺。

[0857] 步骤 1:向 7(500mg,0.647mmol) 在 MeOH(20mL) 中的溶液里添加 Pd/C(50mg) 和数滴浓 HCl,用 H₂ 吹扫。将反应混合物在摇动器中于 60psi 下摇动 48 小时。将混合物通过 CELITE™ 过滤并浓缩;将残留物通过硅胶柱(DCM/MeOH = 8/2(v/v)) 纯化,得到游离胺(300mg)。

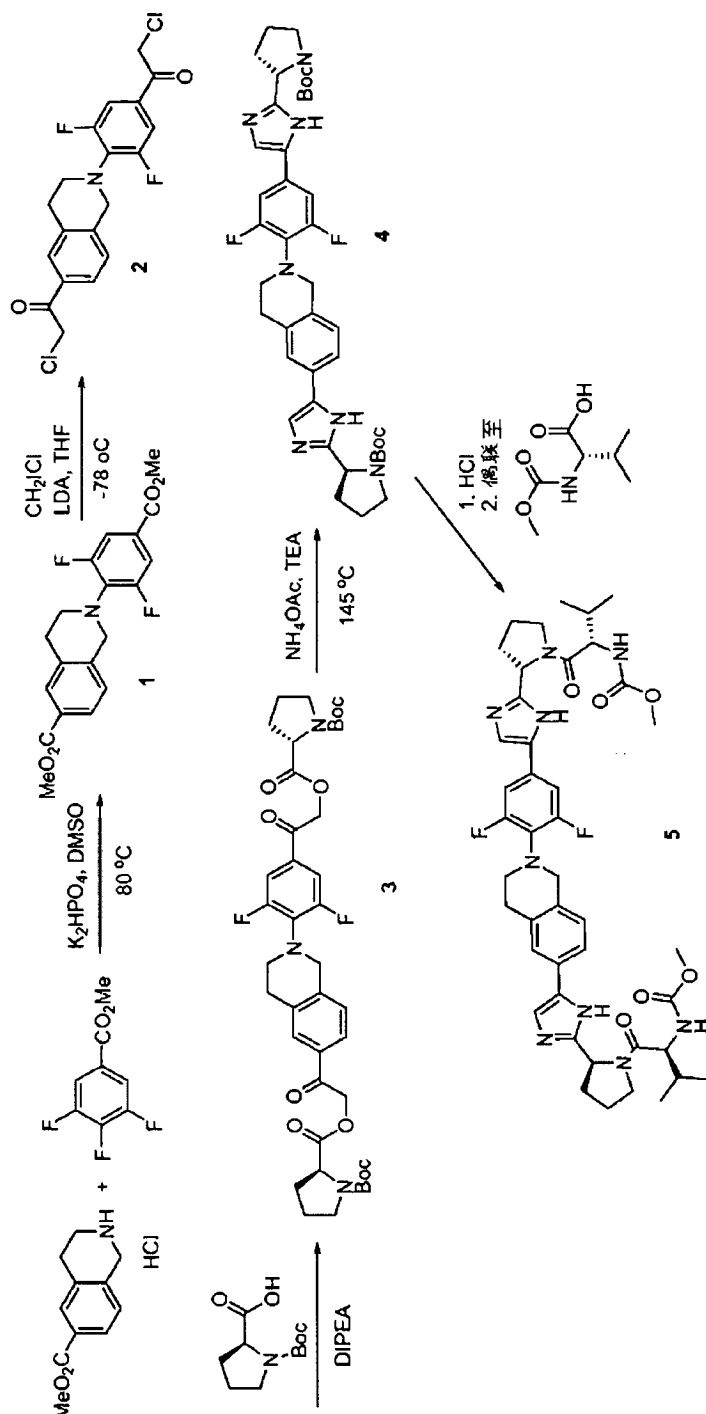
[0858] 步骤 m:向得自步骤 8a 的游离胺(100mg,0.16mmol) 在 DMF(5mL) 中的溶液里添加 N-Moc-D-Phg-OH(43mg,0.204mmol)、HATU(60mg,0.157mmol) 和 DIPEA(155 μL,0.942mmol)。将反应物在室温下搅拌过夜。将溶剂在减压下移除。将粗产物通过制备性 HPLC 纯化,得到 8(33mg),其中 R'' 为甲基。LC-MS(ESI): m/z 830.3(M+H)⁺。

[0859] 其它实施例。类似地,取得自步骤 8a 中的游离胺样品并在上述步骤 b 中用 N-Boc-D-Phg-OH 代替 N-Moc-D-Phg-OH,得到相应的 N-Boc 类似物 9(75mg)。LC-MS(ESI): m/z :872.4(M+H)]⁺。

[0860] 取 9(70mg,0.08mmol) 在 DCM(15mL) 中的样品并以 TFA(4mL) 处理。得到相应的脱 Boc 产物,为 TFA 盐。

[0861] 向 TFA 盐在 THF(10mL) 中的溶液里添加 DIPEA(132 μL,0.8mmol) 和 CDI(39mg,0.24mmol)。将反应物在室温下搅拌,直至反应完成(通过 LC-MS 监测)。向溶液中添加甲胺盐酸盐(54mg,0.8mmol)。将反应物在室温下搅拌过夜。将溶剂移除,并将残留物通过制备性 HPLC 纯化,得到化合物 10(12mg)。LC-MS(ESI): m/z 829.4(M+H)⁺。

[0862]



方案 10-1

[0863] 实施例 10 - - 式 IIIm 化合物的合成

[0864] 步骤 a: 参见方案 10-1, 在 80°C 下, 将 1, 2, 3, 4-四氢异喹啉-6-羧酸甲酯盐酸盐 (4.28g, 18.8mmol)、3, 4, 5-三氟苯甲酰氯 (3.8g, 20mmol) 和 K_2HPO_4 (17.0g, 98mmol) 在 60mL DMSO 中的混合物搅拌 8 小时。冷却后, 将所得混合物在 800mL EtOAc 与 800mL H_2O 之间分开。将有机层先后用 H_2O 和盐水洗涤, 并干燥 (Na_2SO_4)。浓缩后, 将残留物通过硅胶柱色谱法 (己烷 / 乙酸乙酯 (v/v), 3/1 至 1/1) 纯化, 得到浅黄色的固体化合物 1 (4.1g, 60% 收率)。 ^1H NMR (300MHz, 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。

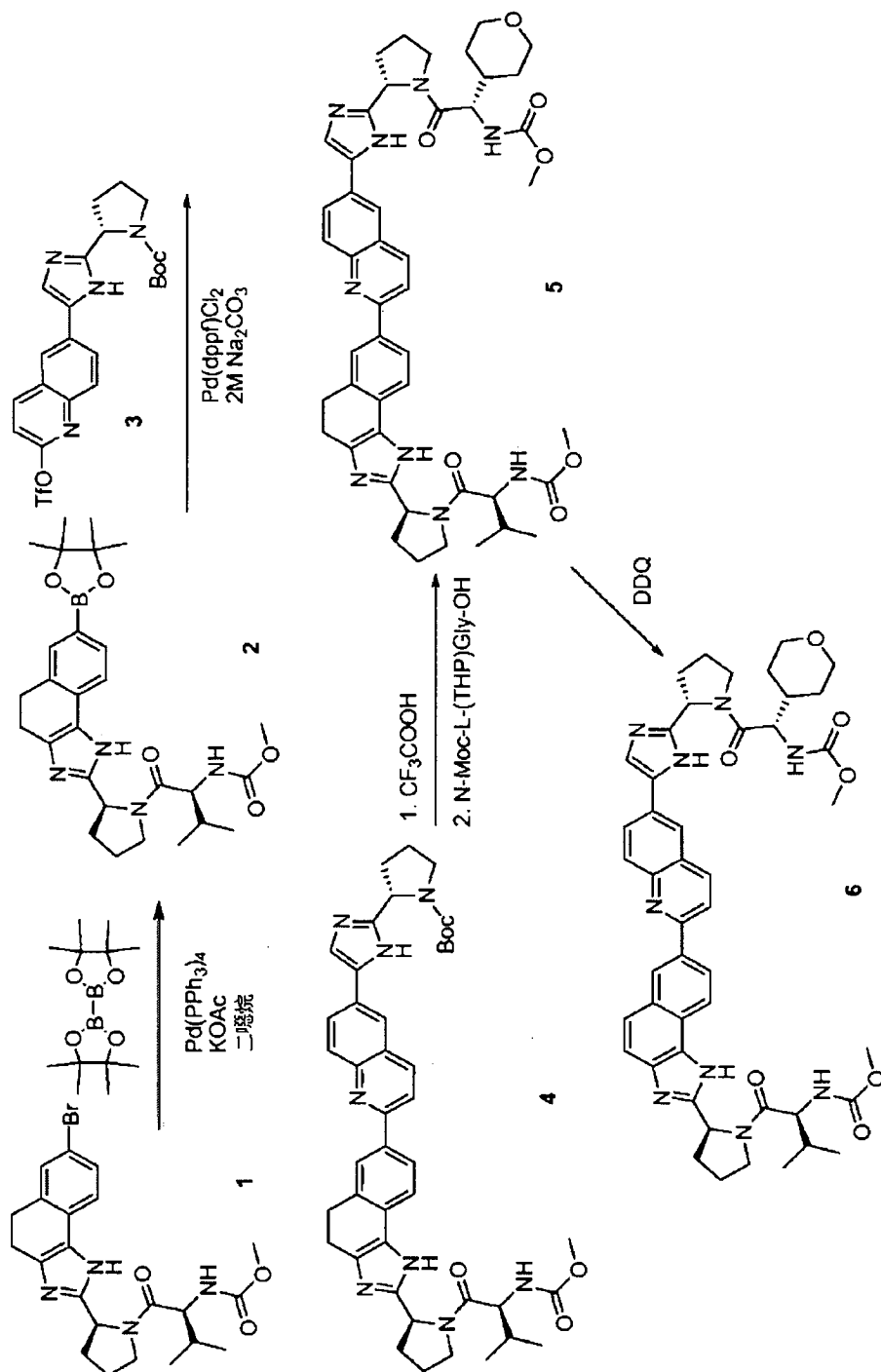
[0865] 步骤 b: 在 -78°C 下, 通过套管经 20 分钟向 1 (2.0g, 5.53mmol) 和氯碘甲烷 (5.86g, 33.2mmol) 在 THF (40mL) 中的溶液里添加 LDA (预冷却至 -78°C , 由 40mL THF 中的 10mL 二异丙胺和 26.5mL 己烷中的 2.5M *n*-BuLi 新制备)。将反应混合物在 -78°C 下搅拌两小时, 然后通过滴加 12mL AcOH/THF (v/v, 1/1) 使其淬灭。使所得混合物升温, 并将其在 EtOAc 与饱和 NaHCO_3 之间分开。将有机层用 H_2O 洗涤, 并经 Na_2SO_4 干燥。浓缩后, 将残留物通过快速柱色谱法 (硅胶、己烷/乙酸乙酯, v/v, 4/1) 纯化, 得到褐色固体化合物 2 (1.19g, 54% 收率)。 ^1H NMR (300MHz, 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。

[0866] 步骤 c: 将化合物 2 (1.19g, 2.99mmol)、N-Boc-L-脯氨酸 (1.65g, 7.64mmol)、KI (1.27g, 7.65mmol) 和 DIPEA (1.32mL, 7.63mmol) 溶解于 CH_3CN (15.3mL) 中。然后将反应混合物在油浴中加热至 50°C 达 4 小时, 然后冷却至室温。将溶剂在真空中移除, 并将粗产物在 EtOAc (20mL) 与 H_2O (10mL) 之间分开。将有机层分离, 并将水层用 EtOAc ($2 \times 20\text{mL}$) 萃取。将合并的 EtOAc 层经 Na_2SO_4 干燥, 过滤, 并在真空中浓缩。将粗料通过快速柱色谱法 (用己烷/乙酸乙酯 (2/1 至 1/1 (v/v)) 洗脱) 纯化, 得到黄色固体 3 (1.1g, 49% 收率)。

[0867] 步骤 d: 将化合物 3 (1.0g, 1.32mmol)、 NH_4OAc (2.89g, 39.6mmol)、TEA (5.52mL, 96.6mmol) 溶解于二甲苯 (6.6mL) 中。然后将密封管中的反应混合物在油浴中加热至 140°C 达 2 小时, 然后冷却至室温。添加 EtOAc 和 H_2O , 并有机层分离。将水层用 EtOAc ($3 \times 50\text{mL}$) 萃取。将合并的 EtOAc 层经 Na_2SO_4 干燥, 过滤, 并在真空中浓缩。将粗料通过快速柱色谱法 (用己烷/乙酸乙酯 (1/2 至 0/1 (v/v))) 纯化, 得到黄色固体 4 (0.7g, 74% 收率)。

[0868] 步骤 5。用二噁烷中的 4M HCl (14.3mL, 57.3mmol) 处理在搅拌下溶解于二噁烷 (2mL) 中的化合物 4 的样品 (0.50g, 0.70mmol)。在室温下搅拌 2 小时后, 将反应混合物浓缩, 并将残留物在真空中干燥, 得到 HCl 盐, 其不经进一步纯化便用于下一步骤。将所述 HCl 盐 (50mg, 0.097mmol) 和 N-Moc-L-缬氨酸 (34mg, 0.194mmol) 溶解于 DMF (2mL) 中。将 DIPEA (0.2mL, 1.16mmol) 和 DMTMM (53.6mg, 0.19mmol) 添加到混合物中。在室温下搅拌过夜后, 将反应混合物浓缩, 并将残留物通过制备性 HPLC 纯化, 得到浅黄色的固体化合物 5 (9.3mg)。 ^1H NMR (CD_3OD , 300MHz) 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 ($\text{M}+\text{H}$) $^{+}$ 。

[0869]



方案 11-1

[0870] 实施例 11 - - 式 Vc 化合物的合成

[0871] 步骤 a: 参见方案 11-1, 在氮气氛围中, 向溴化物 1 (2.0g, 4.2mmol, 根据已公开的条件制备) 在二噁烷 (60mL) 中的溶液里添加双(频哪醇合)二硼 (4.32g, 17mmol)、 $\text{Pd(PPh}_3)_4$ (0.49g, 0.42mmol) 和醋酸钾 (2.06g, 21mmol)。将反应混合物在 80°C 下搅拌 5 小时, 然后用乙酸乙酯 (150mL) 稀释。将有机相用 H_2O (20mL) 洗涤, 经硫酸钠干燥, 并在真空中浓缩。将残留物进一步通过硅胶柱色谱法 (己烷 / 乙酸乙酯 = 1/4 至 0/1 (v/v)) 纯化, 得到 2 (1.73g, 79% 收率)。LC-MS (ESI) : m/z 523.3 ($\text{M}+\text{H}$) $^+$ 。

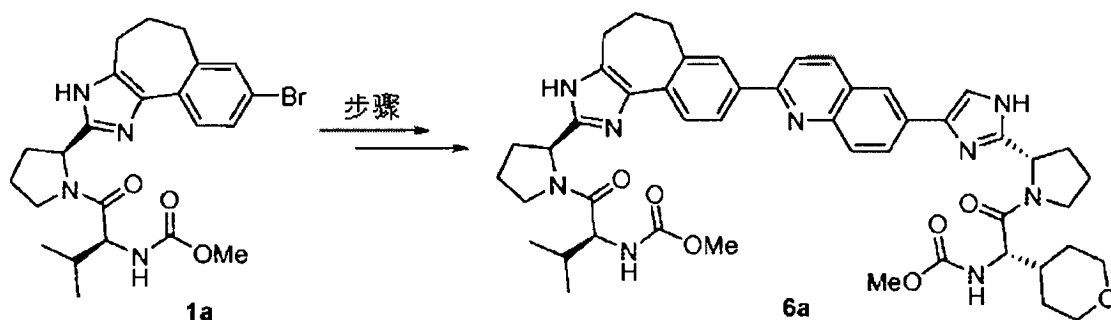
[0872] 步骤 b: 通过将脱气并用氮再填充的过程重复三次来处理 2-羟基喹啉三氟甲磺酸酯 3 (0.72g, 1.4mmol)、硼酸酯 2 (0.73g, 1.4mmol)、Pd(dppf)Cl₂-DCM (114mg, 0.14mmol) 在 2M Na₂CO₃ (2.8mL) 和二噁烷 (5.6mL) 中的混合物。然后将反应混合物在氮气氛围中于 90℃ 下搅拌 4 小时。冷却后, 将混合物用 THF 稀释, 然后通过 CELITE™ 垫过滤。将滤液浓缩, 将粗产物通过快速色谱法 (NH₄OH/ 乙腈/ 乙酸乙酯, 1:8:100) 纯化, 得到白色固体纯产物 4 (0.80g, 75% 收率)。LC-MS (ESI) : m/z 759.4 (M+H)⁺。

[0873] 步骤 c: 在室温下, 将三氟乙酸 (2.5mL) 缓慢添加到 4 (0.80g, 1.5mmol) 在 CH₂Cl₂ (5.0mL) 中的溶液里。将所得混合物在室温下搅拌 2 小时, 然后浓缩至干燥。将粗产物在真空中干燥, 得到 TFA 盐, 其不经进一步纯化便用于下一步骤。LCMS (ESI) : m/z 659.3 (M+H)⁺。

[0874] 步骤 d: 向得自上述反应的 TFA 盐 (69.1mg, 0.11mmol) 在 DMF (3mL) 中的混合物里添加 DIPEA (0.23mL, 1.4mmol), 然后添加 L-N-甲氧羰基-(4-四氢-2H-吡喃-4-基)甘氨酸 (30mg, 0.14mmol) 和 HATU (52g, 0.14mmol)。在室温下搅拌 2 小时后, 将反应混合物在搅拌的同时缓慢滴加到 H₂O 中。通过过滤收集所得沉淀物。将粗产物通过制备性 HPLC 纯化, 得到产物 5 (34.5mg)。¹H NMR (CDCl₃, 300MHz) 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)⁺。

[0875] 步骤 e: 将化合物 5 (37.7mg, 0.044mmol)、DDQ (10.0mg, 0.044mmol) 在 6mL 苯中的溶液回流 2.5 小时。移除溶剂后, 将粗产物通过制备性 HPLC 纯化, 得到黄色粉末 6 (23mg)。¹H NMR (CDCl₃, 300MHz) 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)⁺。

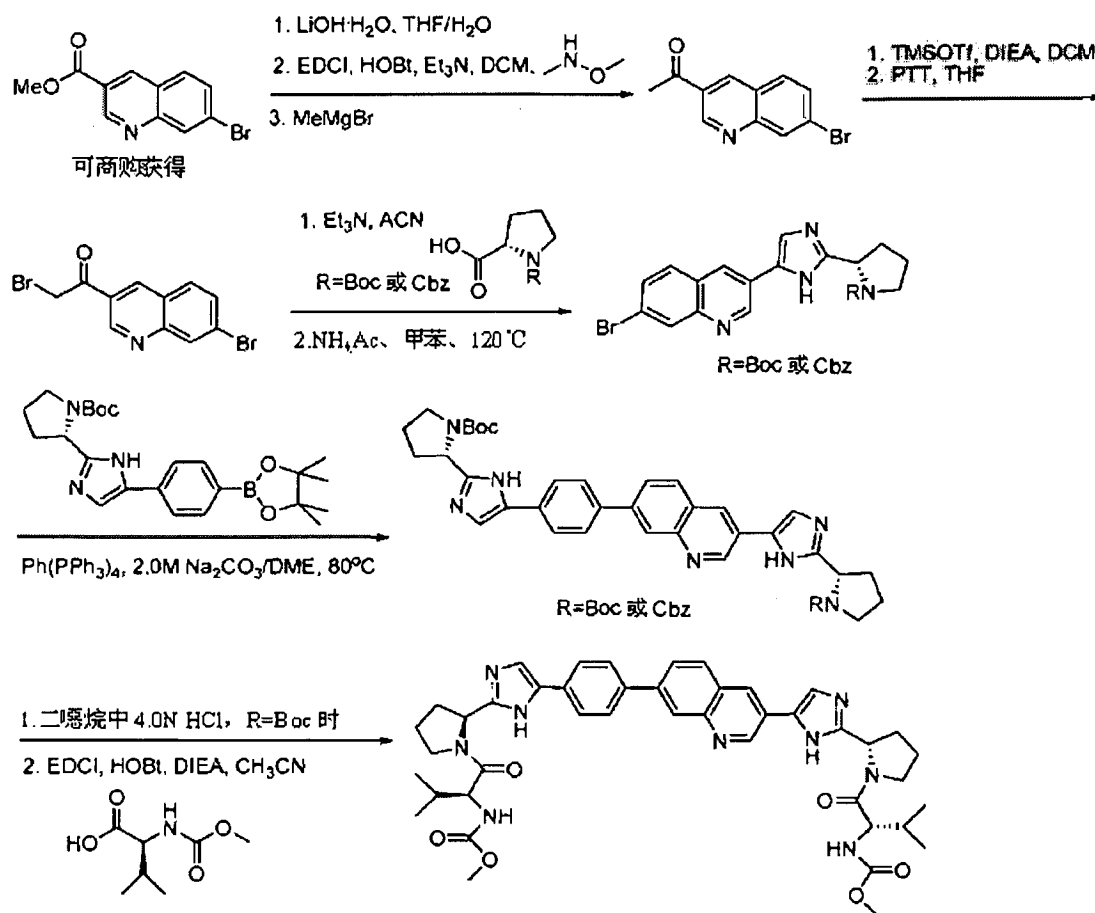
[0876]



[0877] 根据方案 11-1 中所述的程序和条件, 并用化合物 1a 代替化合物 1, 制备化合物 6a。¹H NMR (300MHz, CD₃OD) 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)⁺。

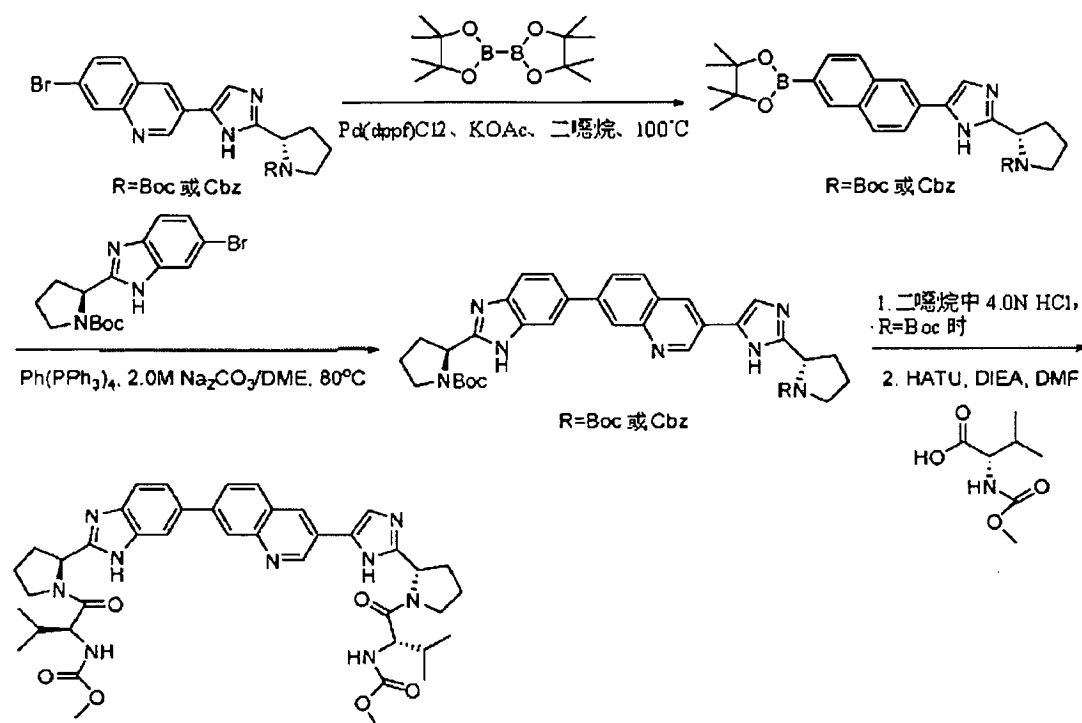
[0878] 实施例 12 - - 本发明化合物的其它合成方案

[0879]



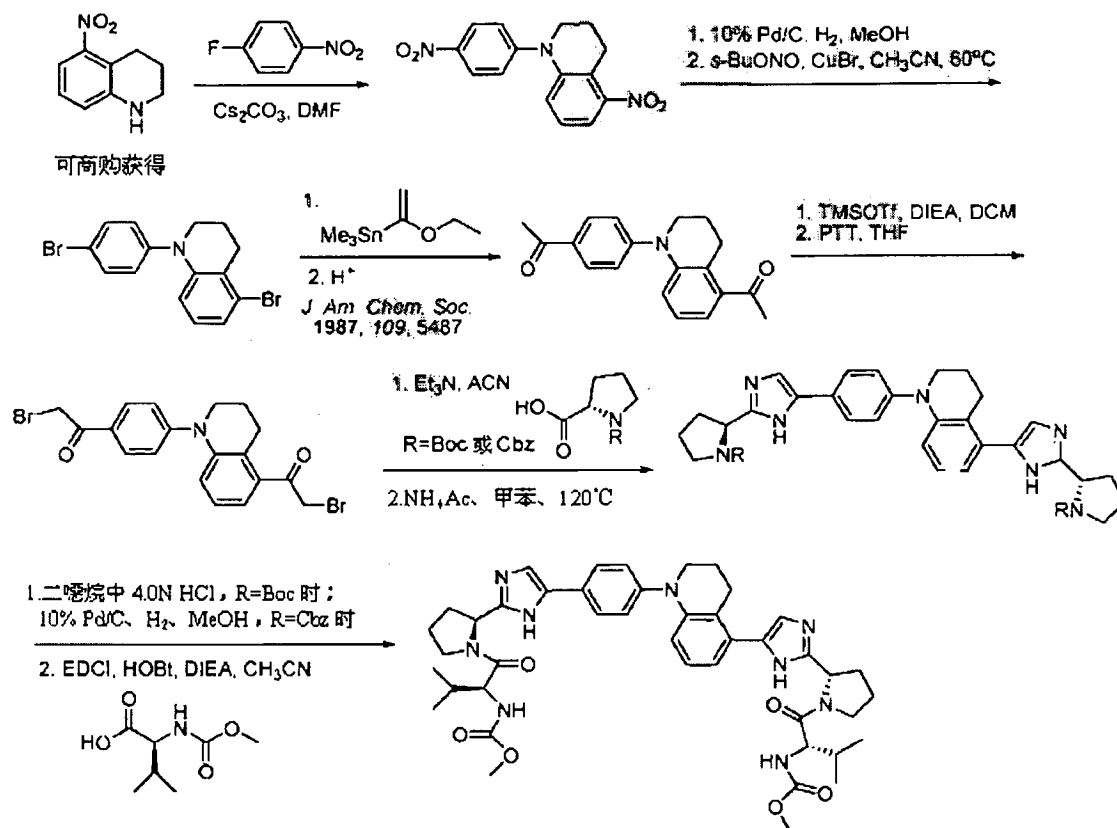
方案 12-1

[0880]



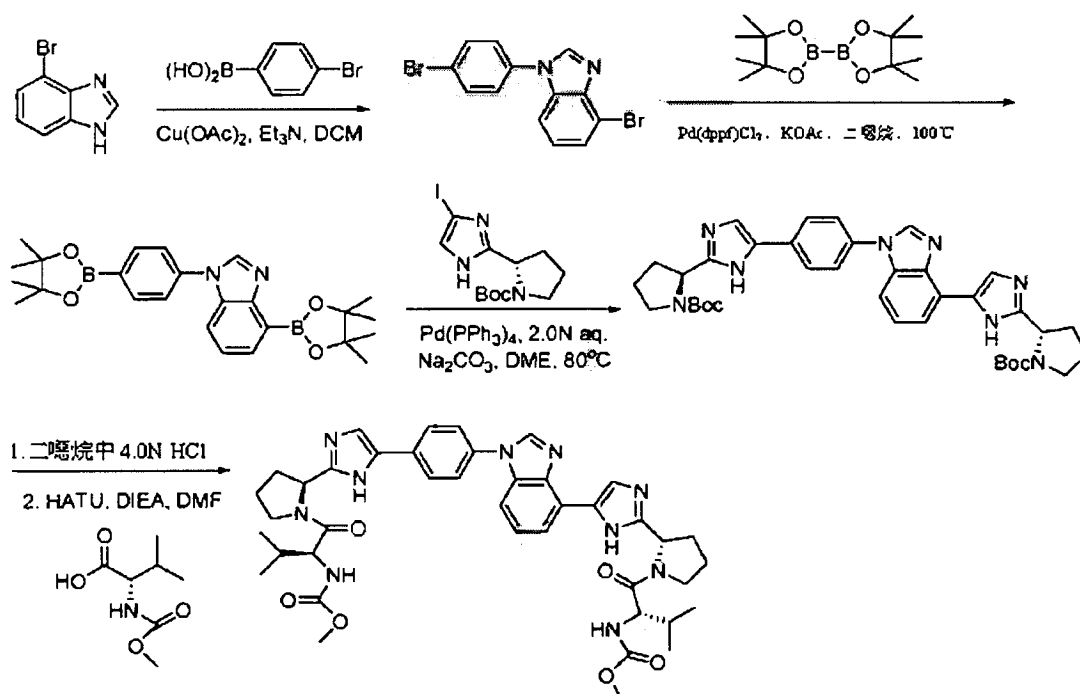
方案 12-2

[0881]



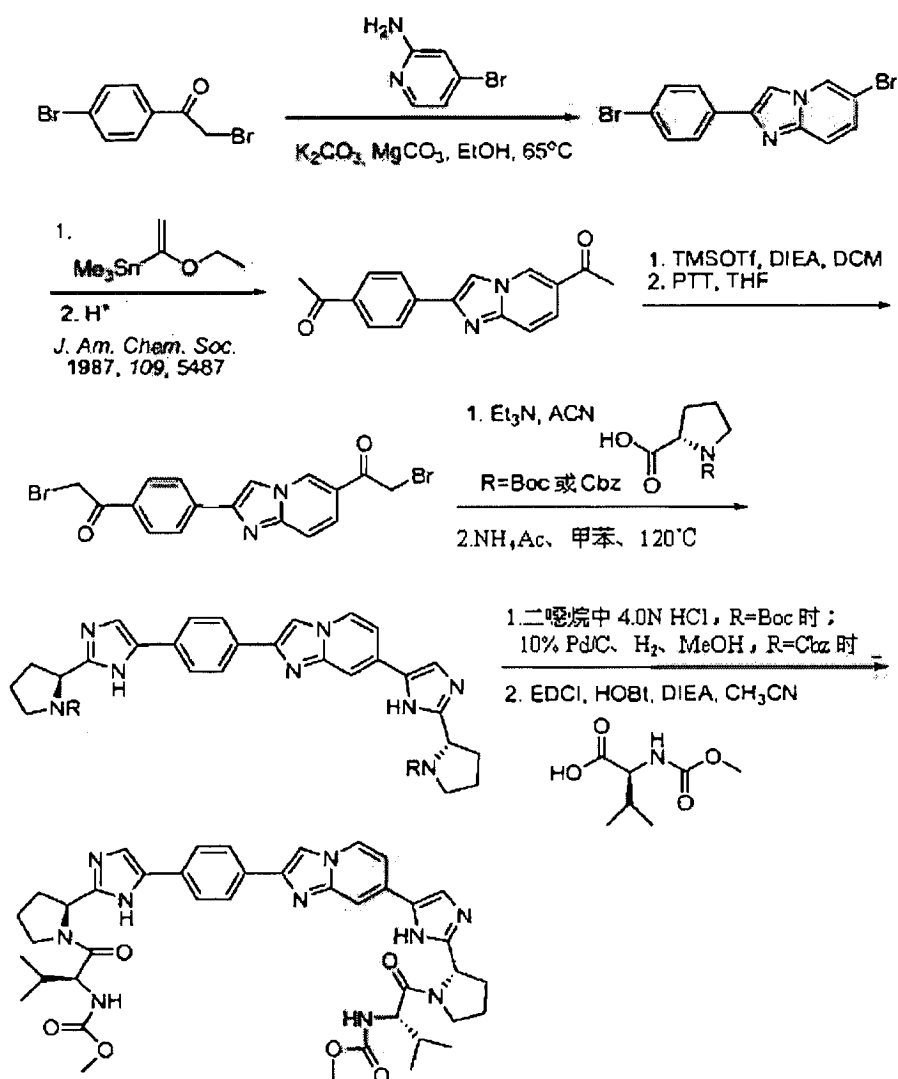
方案 12-3

[0882]



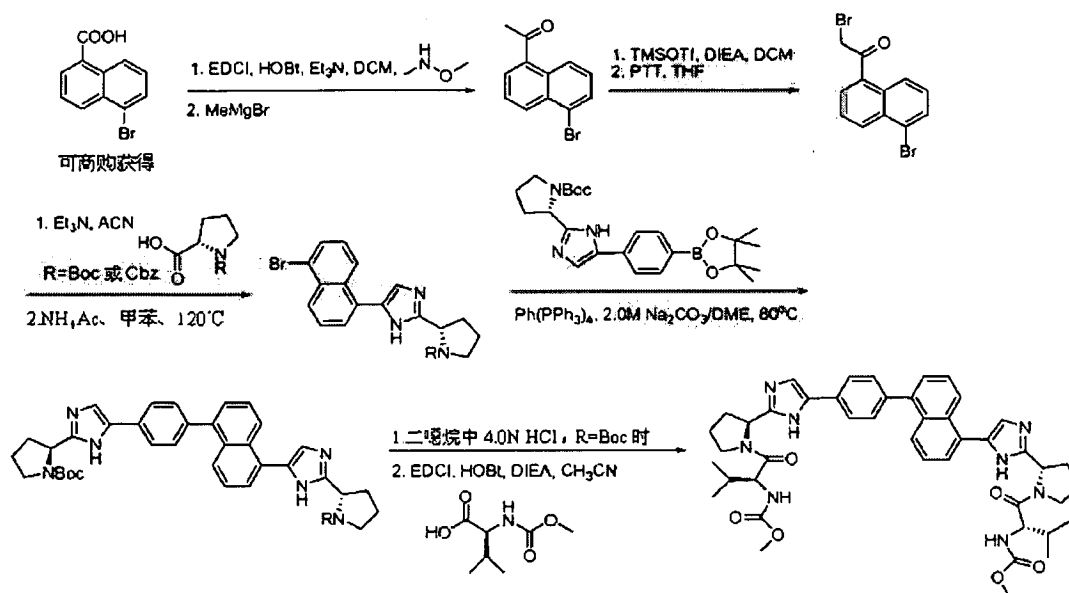
方案 12-4

[0883]

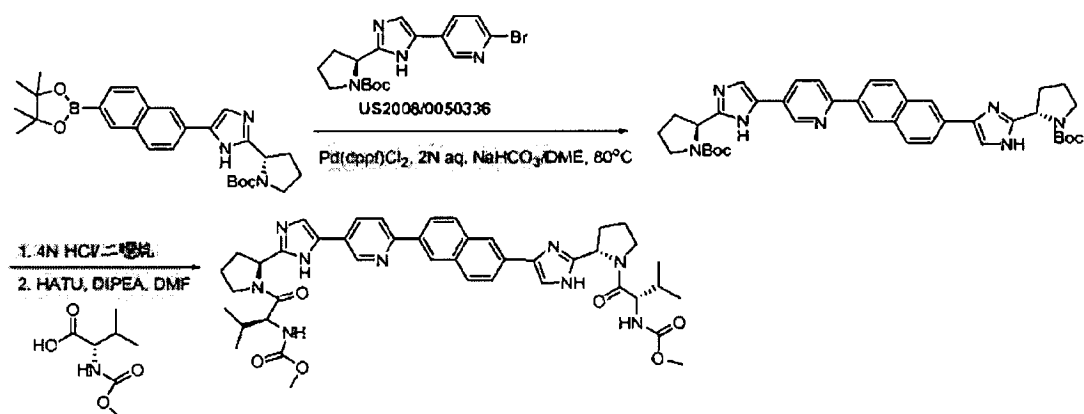


方案 12-5

[0884]

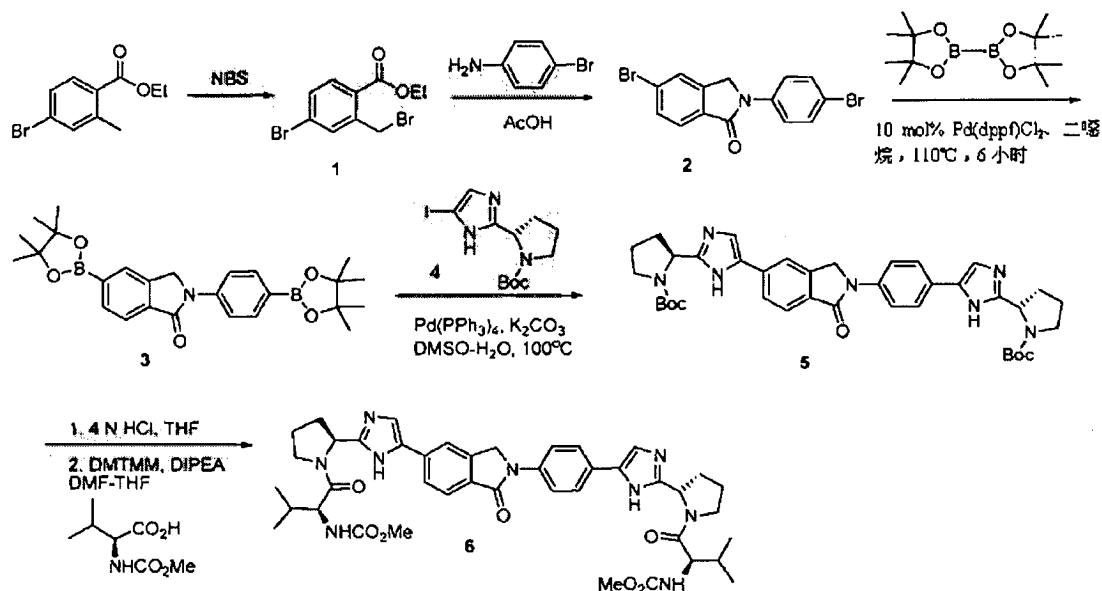


方案 12-6



方案 12-7

[0885]



方案 12-8

[0886] 步骤 a: 参见方案 12-8, 将 4-溴-2-甲基苯甲酸乙酯 (1.0g, 4.11mmol) 和 NBS (1.15g, 6.46mmol) 在 CCl₄ (13.7mL) 中的混合物加热回流 6 小时。将白色沉淀物滤除, 并在减压下浓缩滤液, 得到黄色油状物 1 (1.47g), 根据 LC/MS, 其含大约 25% 的未反应的起始物质。粗料不经进一步纯化便进行使用。

[0887] 步骤 b: 将粗酯 1 (4.11mmol) 溶解于冰醋酸 (13.7mL) 中, 并向溶液中添加 4-溴苯胺 (0.85g, 4.93mmol)。然后将反应混合物加热回流 12 小时, 并冷却至室温。添加 H₂O (150mL), 并用固体 Na₂CO₃ 中和至 pH7。将水溶液用乙酸乙酯 (3×100mL) 萃取, 并将有机层经 Na₂SO₄ 干燥, 过滤, 并在真空中浓缩。将粗料通过快速柱色谱法 (用己烷/乙酸乙酯 (12/1 至 10/1) 洗脱以移除副产物), 然后用纯乙酸乙酯洗脱纯化, 得到褐色固体 2 (0.54g, 36% 收率)。¹H NMR (300MHz, CDCl₃) δ 7.79-7.69 (m, 3H)、7.68-7.67 (m, 2H)、7.65-7.52 (m, 2H)、4.82 (m, 2H) ppm。

[0888] 步骤 c: 在 110 °C 下, 将化合物 2 (0.54g, 1.46mmol)、频哪醇硼烷 (0.82g, 3.22mmol)、KOAc (0.86g, 8.76mmol) 和 Pd 催化剂 (0.12g, 0.15mmol) 在二噁烷 (28mL) 中的混合物加热 30 小时。将反应混合物冷却至室温, 并用 H₂O 稀释。将水层用乙酸乙酯萃取, 将有机层经 Na₂SO₄ 干燥, 过滤, 并在真空中浓缩。将粗料通过快速柱色谱法 (用乙酸乙酯洗脱) 纯化, 得到深黄色固体 3 (0.49g, 73% 收率)。¹H NMR (300MHz, CDCl₃) δ 7.90-7.70 (m, 7H)、4.81 (s, 2H)、1.40-1.20 (m, 24H) ppm。

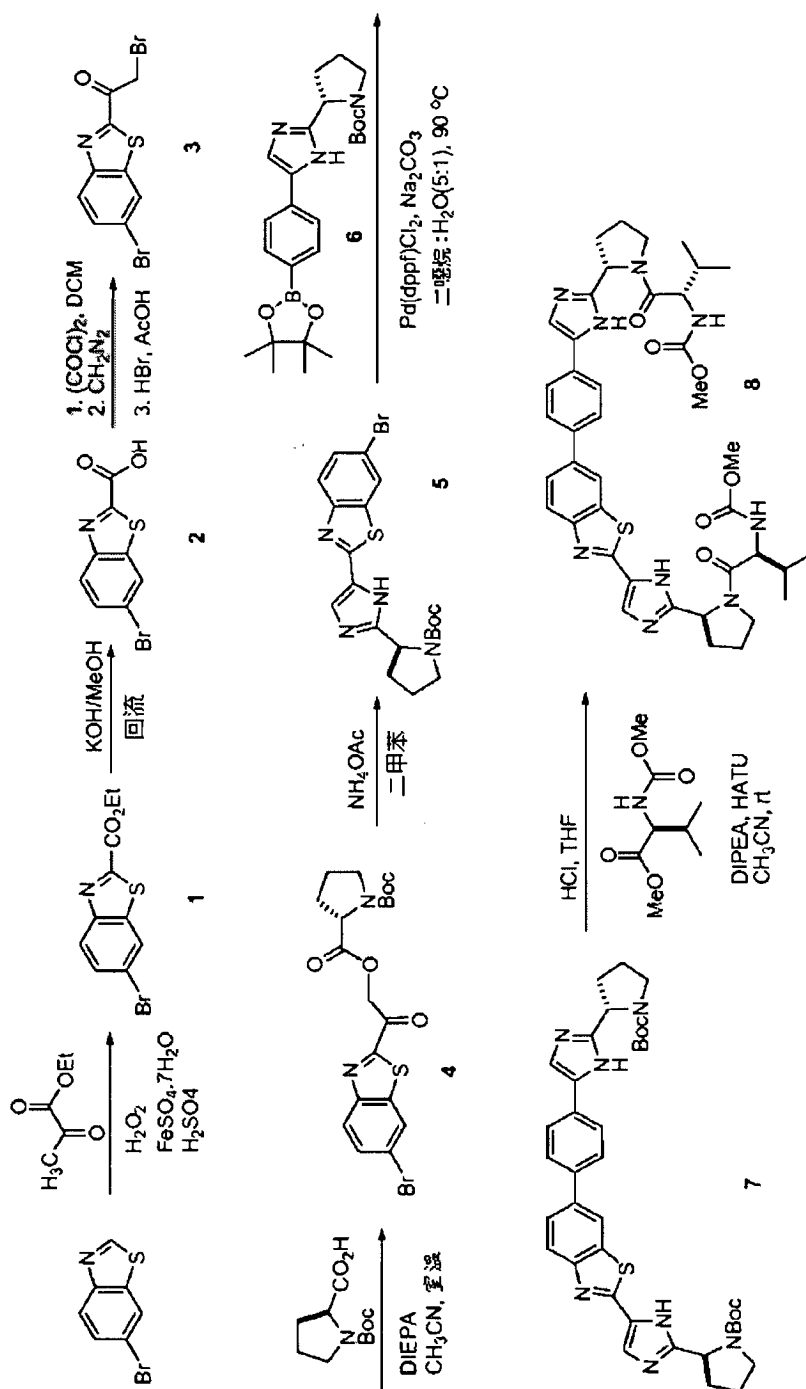
[0889] 步骤 d: 在 100°C 下, 将 3 (400mg, 0.87mmol)、咪唑化合物 4 (630mg, 1.73mmol) 和 Pd(PPh₃)₄ (200mg, 0.17mmol) 及碳酸钾 (311mg, 2.25mmol) 在 DMSO (10mL) 和 H₂O (3.5mL) 中的混合物加热 14 小时。将反应混合物冷却至室温, 用 H₂O 稀释, 并用二氯甲烷萃取。将合并的有机层经 Na₂SO₄ 干燥, 过滤, 并在真空中浓缩。将粗料通过快速柱色谱法 (用乙酸乙酯/甲醇 = 97/3 (v/v)) 纯化, 得到浅黄色的固体 5 (357mg, 61% 收率)。¹H NMR (CDCl₃, 300MHz) 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。

[0890] 步骤 e: 在室温下, 向 5 (40mg, 0.059mmol) 在 THF (0.6mL) 中的搅拌悬浮液中添加 1,4-二噁烷中的 4N HCl 溶液 (0.6mL), 并将混合物在室温下搅拌 4 小时。将反应混合物在真空中浓缩, 得到 HCl 盐 (37mg, 100% 收率), 其未经纯化便用于下一步骤。LC-MS (ESI) :m/z : $[(M+2H)/2]^+$ 478.5。

[0891] 步骤 f: 向上述 HCl 盐 (37mg, 0.059mmol) 和 N-甲氧羰基-L-缬氨酸 (22.6mg, 0.13mmol) 在 DMF (2mL) 中的搅拌溶液里添加 HATU (49mg, 0.13mmol), 然后添加二异丙基乙胺 (0.1mL, 0.59mmol)。在室温下搅拌 4 小时后, 将反应混合物用 H₂O 稀释, 并用二氯甲烷萃取。将合并的有机层经 Na₂SO₄ 干燥, 过滤, 并在真空中浓缩, 得到粗产物, 将其通过制备性 HPLC 纯化, 得到白色固体 6 (6.4mg, 14% 收率)。¹H NMR (CDCl₃, 300MHz) 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。

[0892] 步骤 g: 类似地, 根据公开的程序制备化合物 2 的六元类似物 (2a、2b、2c)。根据上述相同的合成顺序和条件进一步转化化合物 2a、2b 和 2c, 得到化合物 6 的各自类似物。

[0893]



方案 12-9

[0894] 步骤 a: 参见方案 12-9, 在 0°C 下, 向丙酮酸乙酯 (24.4g, 23.4mmol) 中滴加 H_2O_2 (35%, 13.6g, 13.6mL, 140mmol), 然后搅拌 5 分钟。在 0°C 下, 向 6-溴-苯并噻唑 (10.0g, 46.7mmol) 在 H_2O (45mL) 和 H_2SO_4 (13.7g, 7.5mL, 140mmol) 中的混合物里同时添加新制备的丙酮酸乙酯混合物和 H_2O (90mL) 中的 $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (38.9g, 140mmol)。将所得混合物保持在 0°C 下, 并在室温下搅拌过夜。在 0°C 下, 向混合物中添加另外的 H_2SO_4 (27.4g, 15.0mL, 280mmol), 然后添加新制备的丙酮酸乙酯混合物 (28.8g 丙酮酸乙酯, 46.8mL, 420mmol, 与 35% 的 H_2O_2 , 27.2g, 27.2mL, 280mmol) 和 H_2O (180mL) 中的 $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (77.8g, 280mmol)。在 0°C 下搅拌 7.5 小时后, 向反应混合物中添加过量的冰, 并用

2.0M KOH 溶液将 pH 调节至 10-11。将碱性混合物用 EtOAc (5×300mL) 萃取,并将合并的有机层经 Na₂SO₄ 干燥,过滤,并在旋转蒸发器上浓缩,得到黄色油状物。粗产物 1 不经进一步纯化便用于下一步骤。LC-MS (ESI) :m/z : (M+1)⁺288。

[0895] 步骤 b: 向 1 (~ 46.7mmol) 在 MeOH (250mL) 中的粗混合物里添加 KOH (25.2g, 450mmol)。将混合物在回流条件下加热 3 小时后,将所有挥发物在旋转蒸发器上移除,得到褐色固体。将褐色固体溶解于 H₂O (200mL) 中,然后用 EtOAc (3×200mL) 萃取。将水相的 pH 用 10% HCl 溶液调节至 3-4,并用 EtOAc (5×200mL) 萃取。将合并的有机层经 Na₂SO₄ 干燥,过滤,并在旋转蒸发器上浓缩,得到黄色固体 2 (9.66g, 80% 收率)。LC-MS (ESI) :m/z (M+1)⁺260。

[0896] 步骤 c: 在室温下,向 2 (1.43g, 5.5mmol) 在 DCM (50mL) 中的混合物里缓慢添加乙二酰氯 (14.0g, 9.5mL, 110mmol), 然后添加一滴 DMF。将所得混合物在室温下搅拌过夜 (15 小时) 后,在旋转蒸发器上移除所有挥发物。粗混合物不经纯化便用于下一步骤。

[0897] 步骤 d: 在 0℃ 下,向 6-溴-苯并噻唑-2-羰基氯 2 (~ 5.5mmol) 在 THF (50mL) 中的溶液里滴加快速生成的重氮甲烷溶液 (由 25.1mmol 4-N, N-三甲基-苯磺酰胺生成大约 16.6mmol 重氮甲烷溶液)。将所得混合物在 0℃ 下搅拌 30 分钟,然后将温度升至室温。在室温下持续搅拌 2.5 小时后,将所有挥发物在旋转蒸发器上移除。粗混合物不经进一步纯化便用于下一步骤。

[0898] 步骤 e: 在室温下,向得自上述的 1-(6-溴-苯并噻唑-2-基)-2-重氮基-乙酮 (~ 5.5mol) 在 AcOH (30mL) 中的混合物里缓慢添加 HBr 水溶液 (48%, 0.69mL, 6.1mmol)。将所得混合物在室温下再搅拌 2 小时。在旋转蒸发器上移除所有挥发物,得到深色固体。通过在旋转蒸发器上与甲苯 (15mL×2) 一起共沸蒸发进一步干燥粗混合物。得到深褐色固体化合物 3,其不经进一步纯化便用于下一步骤。

[0899] 步骤 f: 向 2-溴-1-(6-溴-苯并噻唑-2-基)-乙酮 A7 (~ 5.5mmol) 于 CH₃CN (50mL) 中的粗混合物里添加吡咯烷-1,2-二羧酸 1-叔丁酯 (1.31g, 6.1mmol), 然后添加 DIPEA (2.14g, 2.69mL, 16.6mmol)。将所得混合物在室温下搅拌 5 小时,并用 H₂O 淬灭。将混合物用 EtOAc (3×50mL) 萃取,然后将合并的有机相用 H₂O (50mL) 和盐水 (50mL) 洗涤,经 Na₂SO₄ 干燥,过滤,并在旋转蒸发器上干燥。将粗混合物通过柱色谱法 (用己烷/EtOAc = 6:1 至 4:1 (v/v) 洗脱),得到呈褐色固体的标题化合物 (297mg, 自 2 经总共 4 个步骤为 12%)。LC-MS (ESI) :m/z : (M+H)⁺493。

[0900] 步骤 g: 向 (S)-2-(2-(6-溴苯并[d]噻唑-2-基)-2-氧代乙基)吡咯烷-1,2-二羧酸 1-叔丁酯 4 (297mg, 0.63mmol) 于二甲苯 (5.0mL) 中的溶液里添加 NH₄OAc (488mg, 6.32mmol)。将所得混合物在 145℃ 下加热 2 小时,然后在旋转蒸发器上移除所有溶剂,得到粗混合物,使其经受柱色谱法 (以己烷:EtOAc (1:1 至 0:1 比例) 洗脱)。得到褐色固体化合物 5 (65mg, 23%)。LC-MS (ESI) :m/z : (M+H)⁺451。

[0901] 步骤 h: 用 N₂ 净化 5 (43mg, 0.1mmol)、6 (44mg, 0.1mmol) (如前所述制备)、Pd(dppf) Cl₂ (4mg, 5 μmol) 和 Na₂CO₃ (35mg, 0.33mmol) 于二噁烷/H₂O (2.0mL/0.4mL) 中的混合物。将所得混合物在 90℃ 搅拌 8 小时,然后用 H₂O 稀释。将反应混合物用 EtOAc 萃取,并将合并的有机层经 Na₂SO₄ 干燥,过滤,并在旋转蒸发器上浓缩。将粗混合物通过柱色谱法 (用己烷:EtOAc = 1:3 (v/v) 洗脱) 纯化,得到黄色固体 7 (60mg, 60% 收率)。LC-MS (ESI) :m/z :

(M+H)⁺683 ; (M-H) -681。

[0902] 步骤 i :在室温下,向化合物 7(717mg, 1.056mmol) 于 THF (7.5mL) 的粗溶液里添加 HCl (二噁烷中 4.0M, 10mL)。将所得混合物在室温下搅拌 16 小时,然后在旋转蒸发器上移除所有挥发物,得到黄色固体。将黄色固体用二乙醚 (2×10mL) 洗涤,然后在旋转蒸发器进一步干燥,得到黄色固体。粗固体不经进一步纯化便用于下一步骤。将得自上述脱保护的游离胺 (48mg, ~0.1mmol) 溶解于 CH₃CN (1.0mL) 中,用 N-甲氧羰基-L-缬氨酸 (35mg, 0.2mmol)、HATU (76mg, 0.2mmol) 和 DIEPA (52mg, 65L, 0.4mmol) 处理。将所得混合物在室温下搅拌 2.5 小时,然后在旋转蒸发器上移除所有溶剂,得到粗混合物。将粗混合物通过制备性 HPLC (用 H₂O 至 CH₃CN 洗脱),所分离的化合物为~80%纯度。将产物通过制备性 TLC (用含 5% NH₄OH 的 EtOAc 洗脱) 进一步纯化,得到白色固体产物 8 (4.5mg)。¹H NMR (300MHz, CDCl₃) δ: 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。

[0903] 生物活性

[0904] 采用 HCV 复制子检测法来测定本发明化合物的生物活性。在 Huh7 细胞中持续表达双顺反子基因型 1b 复制子的 1b_Huh-Luc/Neo-ET 细胞系得自 ReBLikon GMBH。此细胞系用于将荧光素酶活性读数用作化合物对复制子含量抑制的量度,由此测试化合物的抑制作用。

[0905] 第 1 天 (接种的第二天),将每种化合物一式三份添加到细胞中。将培养盘温育 72 小时,然后进行荧光素酶检测。使用 Promega Corporation 制造的 Bright-Glo 试剂盒 (目录号 E2620) 测量酶活性。使用下列等式得到每种化合物的对照百分比值。

[0906] 对照% = (平均化合物值 / 平均对照) * 100

[0907] 使用 GraphPad Prism 和下列等式确定 EC₅₀ :

[0908] $Y = \text{底部} + (\text{顶部} - \text{底部}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{Hill 斜率}))}$

[0909] 在复制子检测中将化合物的 EC₅₀ 值重复若干次。

[0910] 本发明的实施例化合物在表 1 和表 2 中示出。表 1 包括许多化合物对 HCV1b 的抑制活性。另外,还提供了质谱结果。表 2 提供了本发明的其它实施例化合物。将生物活性表示为 *、**、*** 或 ****,其分别对应 >1000nM、999nM 至 10nM、9.9nM 至 1nM 或 <1nM 的 EC₅₀ 范围。

[0911] 药物组合物

[0912] 本发明的第十一方面提供包含本发明化合物的药物组合物。在第一实施方案中,该药物组合物还包含一种或多种药学上可接受的赋形剂或载体,以及任选的其它治疗和 / 或预防成分。此类赋形剂对于本领域的技术人员而言是已知的。本发明的化合物包括但不限于碱性化合物,如游离碱。在 Remington's Pharmaceutical Sciences,第 18 版 (Easton, Pennsylvania :Mack Publishing Company, 1990) 中可获得药学上可接受的赋形剂的详细论述。

[0913] 根据预定的施用模式,药物组合物可呈固体、半固体或液体剂型形式,如片剂、栓剂、丸剂、胶囊、粉末、液体、悬浮液、霜膏、油膏、洗剂等,优选地为适于单次施用精确剂量的单位剂型。组合物将包括有效量的所选药物与药学上可接受的载体的组合,另外还可包括

其它药剂、辅剂、稀释剂、缓冲剂等。

[0914] 本发明包括药物组合物,其包含本发明的化合物(包括其异构体、异构体的外消旋或非外消旋混合物或药学上可接受的盐或溶剂化物)以及一种或多种药学上可接受的载体和任选的其它治疗和/或预防成分。

[0915] 就固体组合物而言,常规的无毒性固体载体包括(例如)医药级甘露糖醇、乳糖、淀粉、硬脂酸镁、糖精钠、滑石粉、纤维素、葡萄糖、蔗糖、碳酸镁等。

[0916] 就口服施用而言,组合物通常呈片剂、胶囊、软凝胶胶囊非水性溶液、悬浮液或糖浆的形式。片剂和胶囊为优选的口服施用形式。用于口服的片剂和胶囊通常包括一种或多种常用载体,如乳糖和玉米淀粉。通常还添加润滑剂,如硬脂酸镁。当使用液体悬浮液时,活性剂可与乳化剂和悬浮剂组合。如果需要,还可添加调味剂、着色剂和/或甜味剂。掺入本文口服制剂的其它任选组分包括但不限于防腐剂、悬浮剂、增稠剂等。

[0917] 本发明的第十二方面提供了本发明化合物在制备药物方面的用途。

[0918] 在第十二方面的第一实施方案中,所述药物用于治疗丙型肝炎。

[0919] 本发明的第十三方面提供治疗丙型肝炎的方法,其包括对有需要的受试者施用治疗有效量的本发明化合物,该化合物任选地在药物组合物中。向受试者递送药学或治疗有效量的组合物。精确有效量将随受试者而变化,并将取决于物种、年龄、受试者体型及健康状况、所治疗病症的性质和程度、主治医师的建议以及选择用于施用的治疗剂或治疗剂组合。因此,可通过常规实验测定用于指定情形的有效量。可向受试者施用所需要的剂量,以减轻和/或缓解病征、症状或所考虑的疾病起因,或导致生物系统发生任何其它所需的改变。本领域中治疗此类疾病的普通技术人员可根据个人知识以及本申请的公开内容而无需过多实验即可确定用于治疗指定疾病的本发明化合物的治疗有效量。

[0920] 组合法

[0921] 本发明化合物、其异构形式及其药学上可接受的盐可用于单独或与靶向 HCV 生命周期中所涉及的病毒或细胞单元或功能的其它化合物组合使用来治疗和预防 HCV 感染。适用于本发明的化合物类别可包括但不限于所有类别的 HCV 抗病毒剂。就组合法而言,可用于与本发明化合物组合的机制类别 (mechanistic classes) 的药剂包括例如 HCV 聚合酶的核苷和非核苷抑制剂、蛋白酶抑制剂、解旋酶抑制剂、NS4B 抑制剂,以及在功能上抑制内部核糖体进入位点 (IRES) 的药剂和抑制 HCV 细胞附着或病毒进入、HCV RNA 转译、HCV RNA 转录、复制或 HCV 突变、组装或病毒释放的其它药物。属于这些类别并可用于本发明的特定化合物包括但不限于大环、杂环的和线性 HCV 蛋白酶抑制剂,如 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 蛋白酶辅因子抑制剂)、VX-500、VX-813、PHX-1766、PHX2054、IDX-136、IDX-316、ABT-450EP-013420 (和同源物) 以及 VBY-376; 可用于本发明的核苷 HCV 聚合酶 (复制酶) 抑制剂包括但不限于 R7128、PSI-7851、IDX-184、IDX-102、R1479、UNX-08189、PSI-6130、PSI-938 和 PSI-879 以及各种其它核苷和核苷酸类似物和 HCV 抑制剂,包括 (但不限于) 以 2' -C- 甲基修饰的核苷 (酸)、4' - 氮杂修饰的核苷 (酸) 和 7' - 脱氮修饰的核苷 (酸) 衍生的那些。可用于本发明的非核苷 HCV 聚合酶 (复制酶) 抑制剂包括但不限于 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 和 GL-60667。

[0922] 此外,本发明 NS5A 抑制剂可与下列组合使用:亲环素(cyclophyllin)和亲免疫素(immunophyllin)拮抗剂(例如但不限于 DEBIO 化合物、nM-811 以及环孢霉素及其衍生物)、激酶抑制剂、热休克蛋白(例如 HSP90 和 HSP70)的抑制剂;其它免疫调节剂,可包括但不限于干扰素($-\alpha$ 、 $-\beta$ 、 $-\Omega$ 、 $-\gamma$ 、 $-\lambda$ 或合成干扰素),如 Intron ATM、Roferon-ATM、Canferon-A300TM、AdvaferonTM、InfergenTM、HumoferonTM、Sumiferon MPTM、AlfaferoneTM、IFN- β TM、FeronTM等;聚乙二醇衍化(聚乙二醇化)的干扰素化合物,如 PEG 干扰素- α -2a(PegasysTM)、PEG 干扰素- α -2b(PEGIntronTM)、聚乙二醇化 IFN- α -con1 等;干扰素化合物的长效制剂及衍生物,如白蛋白融合干扰素、AlbuferonTM、LocteronTM等;具有多种类型的可控递送体系的干扰素(例如 ITCA-638、DUROSTM 皮下递送体系递送的 ω -干扰素);刺激干扰素在细胞中合成的化合物,如瑞喹莫德(resiquimod)等;白介素;增强 I 型辅助 T 细胞应答进展的化合物,如 SCV-07 等;TOLL 样受体激动剂,如 CpG-10101(actilon)、艾沙托立宾(isotorabine)、ANA773 等;胸腺素 α -1;ANA-245 和 ANA-246;二盐酸组胺;丙帕锗(propagermanium);十氧化四氯;安普利近(ampligen);IMP-321;KRN-7000;抗体,如 civacir、XTL-6865 等;以及预防性和治疗性疫苗,如 InnoVac C、HCV E1E2/MF59 等。此外,涉及施用 NS5A 抑制剂、I 型干扰素受体激动剂(例如 IFN- α)和 II 型干扰素受体激动剂(例如 IFN- γ)的任何上述方法均可通过施用有效量的 TNF- α 拮抗剂来加强。适用于此类组合疗法的示例性非限制性 TNF- α 拮抗剂包括 ENBRELTM、REMICADETM 和 HUMIRATM。

[0923] 此外,本发明的 NS5A 抑制剂可与抗原动物剂和被认为可有效治疗 HCV 感染的其它抗病毒剂组合使用,例如但不限于前药硝唑尼特(nitazoxanide)。硝唑尼特可用作与本发明所公开的化合物以及可用于治疗 HCV 感染的其它药剂(如聚乙二醇干扰素 α -2a 和病毒唑(Ribavarin))组合的药剂(参见例如 Rossignol, JF and Keefte, EB, Future Microbiol. 3:539-545, 2008)。

[0924] 本发明的 NS5A 抑制剂还可与干扰素和聚乙二醇化干扰素、病毒唑或其类似物(例如 tarabavarin、levoviron)、微小 RNA、小干扰 RNA 化合物(例如 SIRPLEX-140-N 等)、核苷酸或核苷类似物、免疫球蛋白、肝保护剂、抗炎剂和其它 NS5A 抑制剂的替代形式一起使用。HCV 生命周期中的其它靶标的抑制剂包括 NS3 解旋酶抑制剂;NS4A 辅因子抑制剂;反义寡核苷酸抑制剂,如 ISIS-14803、AVI-4065 等;载体编码的短发夹 RNA(shRNA);HCV 特异性核酶,如 heptazyme、RPI-13919 等;进入抑制剂,如 HepeX-C、HuMax-HepC 等; α -葡萄糖苷酶抑制剂,如西戈斯韦(celgosivir)、UT-231B 等;KPE-02003002 和 BIVN401 以及 IMPDH 抑制剂。其它示例性 HCV 抑制剂化合物包括下列专利公开中公布的化合物:美国专利 No. 5,807,876;美国专利 No. 6,498,178;美国专利 No. 6,344,465;美国专利 No. 6,054,472;W097/40028;W098/40381;W000/56331、W002/04425;W003/007945;W003/010141;W003/000254;W001/32153;W000/06529;W000/18231;W000/10573;W000/13708;W001/85172;W003/037893;W003/037894;W003/037895;W002/100851;W002/100846;EP1256628;W099/01582;W000/09543;W002/18369;W098/17679、W000/056331;W098/22496;W099/07734;W005/073216、W005/073195 和 W008/021927。

[0925] 另外,例如病毒唑和干扰素的组合可与至少一种本发明的化合物以多种组合疗法形式施用。本发明不限于上述类别或化合物,并涵盖已知的和新颖的化合物及生物活性剂

的组合(参见 Strader, D. B.、Wright, T.、Thomas, D. L. 和 Seeff, L. B., AASLD Practice Guidelines. 1-22, 2009; 和 Manns, M. P.、Foster, G. R.、Rockstroh, J. K.、Zeuzem, S.、Zoulim, F. 以及 Houghton, M., Nature Reviews Drug Discovery. 6:991-1000, 2007; Pawlotsky, J-M.、Chevaliez, S. 和 McHutchinson, J. G., Gastroenterology. 132:179-1998, 2007; Lindenbach, B. D. 和 Rice, C. M., Nature 436:933-938, 2005; Klebl, B. M.、Kurtenbach, A.、Salassidis, K.、Daub, H. 和 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. 和 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. 和 Matsuura, Y., The EMBO Journal. 1-11, 2006; Soriano, V., Peters, M. G. 和 Zeuzem, S. Clinical Infectious Diseases. 48:313-320, 2009; Huang, Z.、Murray, M. G. 和 Secrist, J. A., Antiviral Research. 71:351-362, 2006; 以及 Neyts, J., Antiviral Research. 71:363-371, 2006, 每个文献的全文都以引用的方式并入本文)。希望本发明的组合疗法包括本发明群组的化合物与本发明群组的其它化合物或本发明群组外的其它化合物的任何化学上相容的组合, 前提是该组合不消除本发明群组化合物的抗病毒活性或药物组合物本身的抗病毒活性。

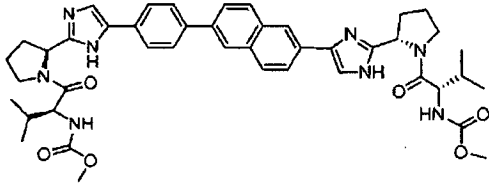
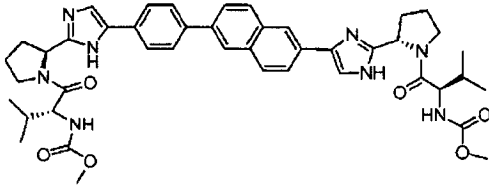
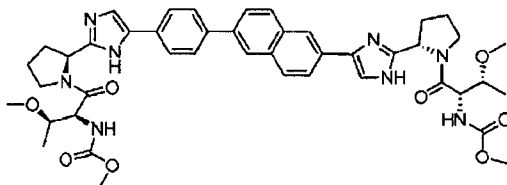
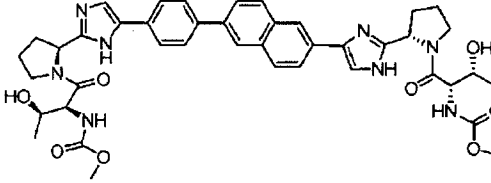
[0926] 组合疗法可按次序进行, 即首先以一种药剂治疗, 然后以第二种药剂治疗(例如, 各治疗包括本发明的不同化合物的情形或一种治疗包括本发明化合物以及另一种治疗包括一种或多种生物活性剂的情形)或其可用两种药剂同时(同时进行)治疗。依序治疗可包括第一治疗结束后与第二治疗开始前的合理时间。用两种药剂同时治疗可以相同的日剂量或单独剂量进行。组合疗法不必限于两种药剂, 并可包括三种或更多种药剂。用于同时和依序组合疗法的剂量将取决于组合疗法的组分的吸收、分布、代谢和排泄速率以及本领域的技术人员已知的其它因素。剂量值还将随着待缓解病症的严重程度而变化。应进一步理解, 对于任何特定受试者而言, 可根据个体的需要和施用或监督组合疗法施用的个人的专业判断, 随时间调整特定剂量方案和时程。

[0927] 本说明书引用的所有专利公开和专利申请均以引用的方式并入本文, 如同具体且单独地指出将每个专利公开和专利申请以引用的方式并入。

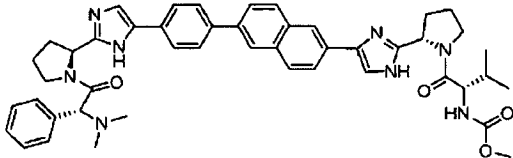
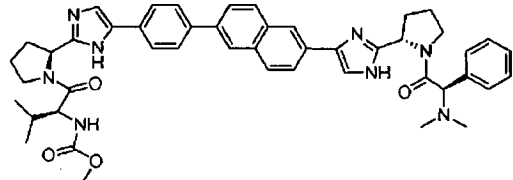
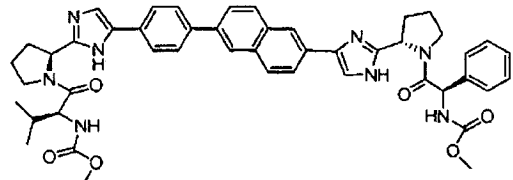
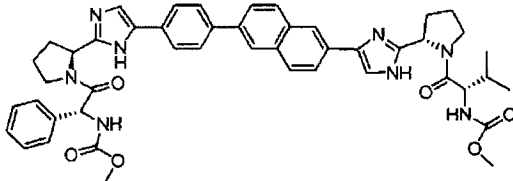
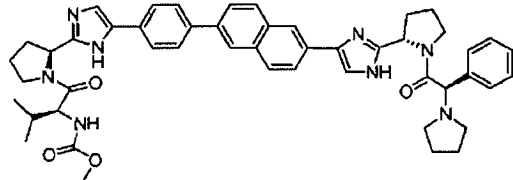
[0928] 尽管为了清楚理解的目的, 已经通过举例说明和实施例的方式对上述本发明进行了一定程度的详细描述, 但根据本发明的教导, 对于本领域的普通技术人员将显而易见的是, 可在不脱离如所附权利要求限定的本发明的实质或范围的情况下对本发明作出一些改变和修改。

[0929] 表 1

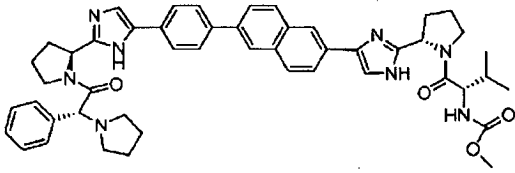
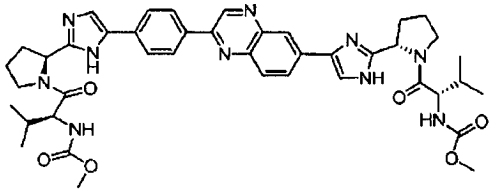
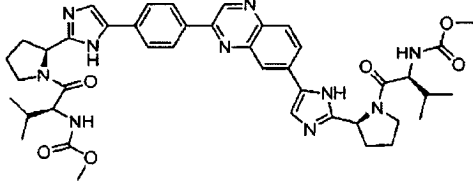
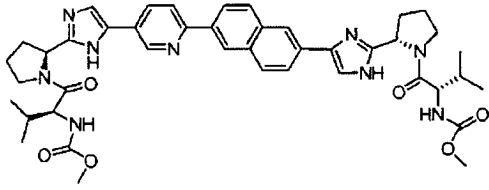
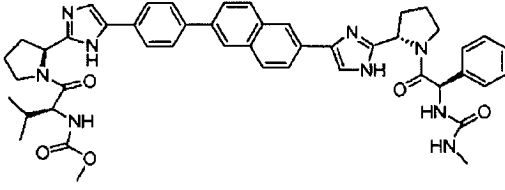
[0930]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
1		****	789.4
2		***	789.4
3		****	821.4
4		****	793.4

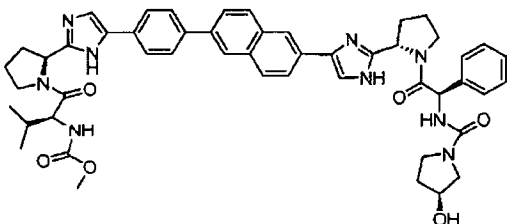
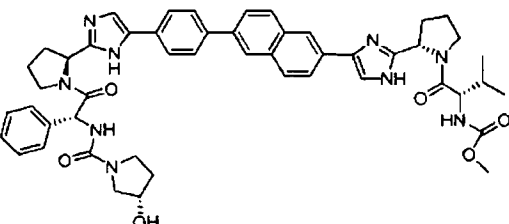
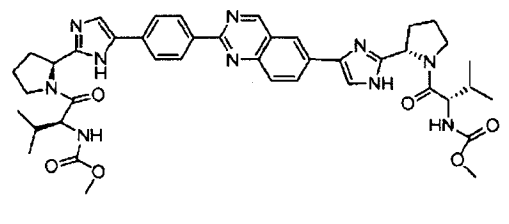
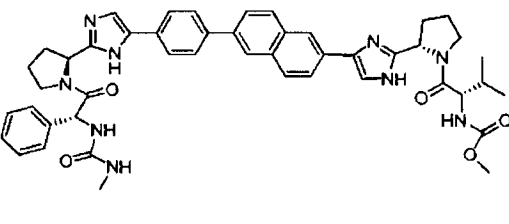
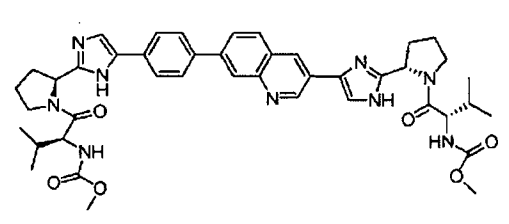
[0931]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
5		****	793.4
6		****	793.4
7		****	823.4
8		****	823.4
9		****	819.4

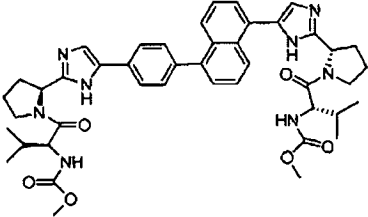
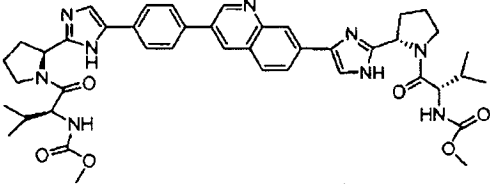
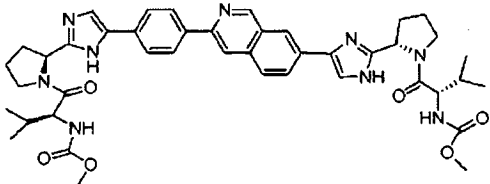
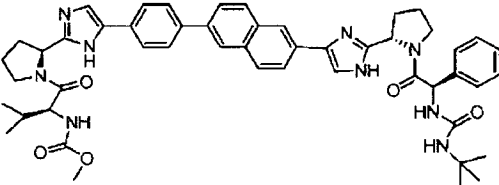
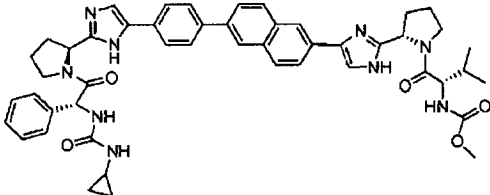
[0932]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
10		****	819.4
11		****	791.4
12		***	791.4
13		****	790.4
14s		****	822.4

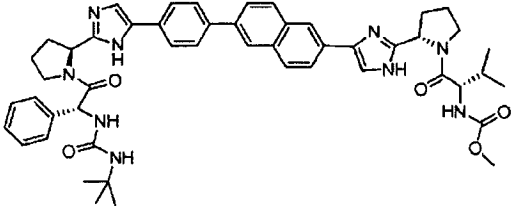
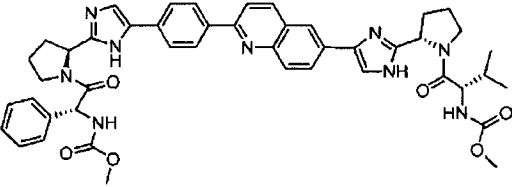
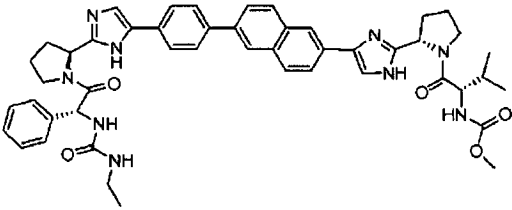
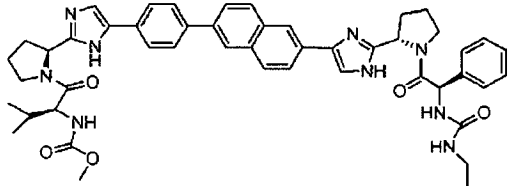
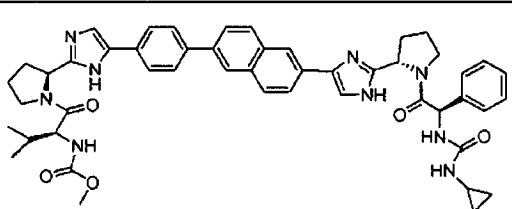
[0933]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
15		****	878.4
16		****	878.4
17		****	791.4
18		****	822.4
19		****	790.4

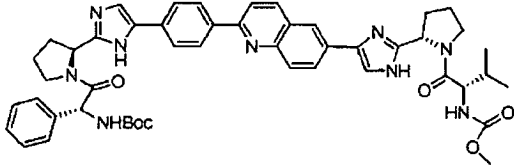
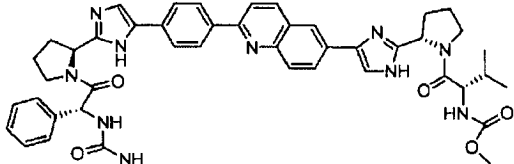
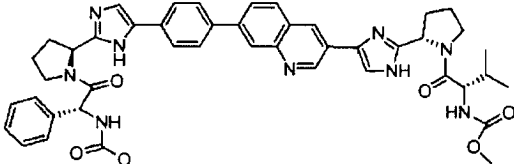
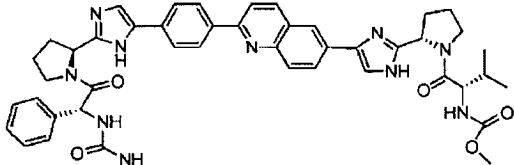
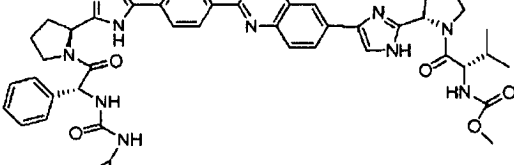
[0934]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
20		****	789.4
21		****	790.4
22		****	790.4
23		****	864.4
24		****	848.4

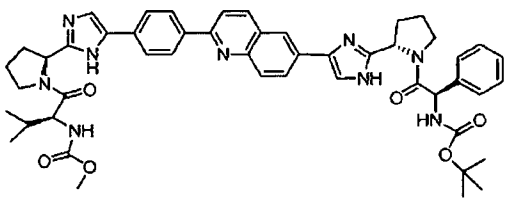
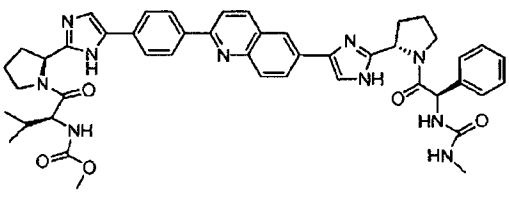
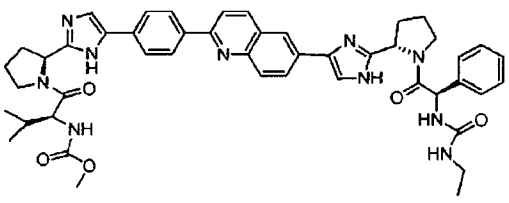
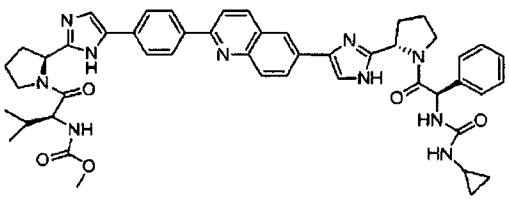
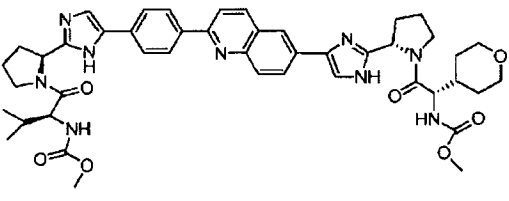
[0935]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
25		****	864.4
26		****	824.4
27		****	836.4
28		****	836.4
29		****	848.4

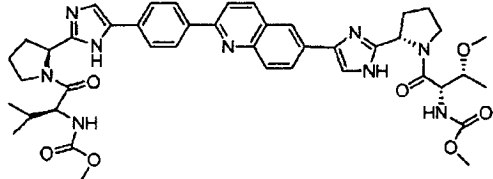
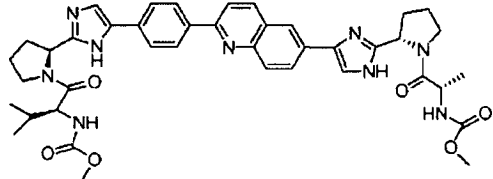
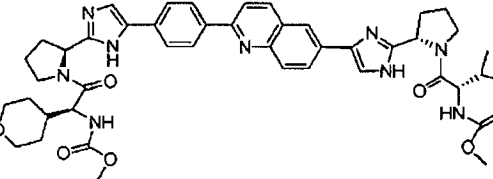
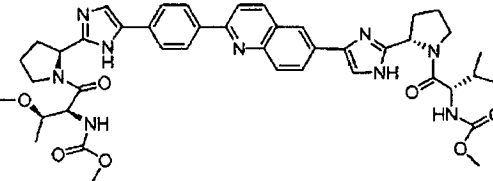
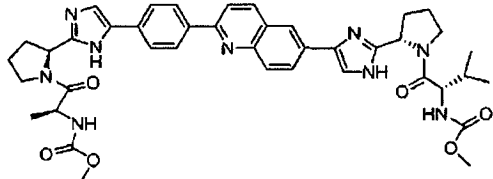
[0936]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
30		****	866.4
31		****	823.4
32		****	824.4
33		****	837.4
34		****	849.4

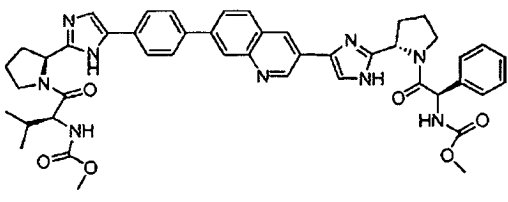
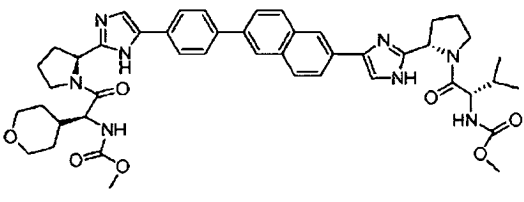
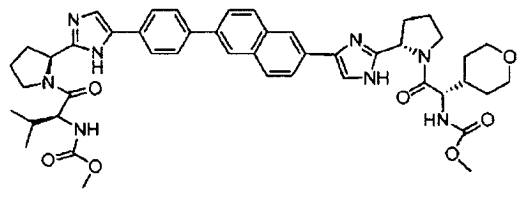
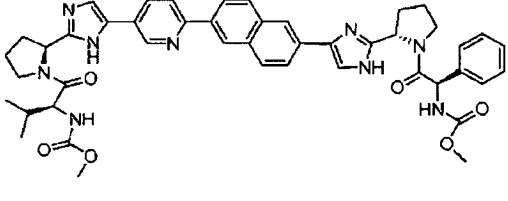
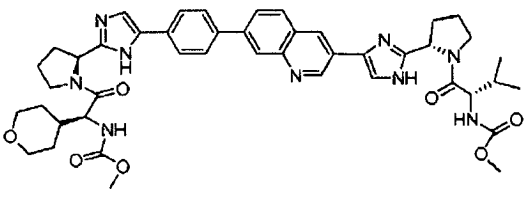
[0937]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
35		****	866.4
36		****	823.4
37		****	837.4
38		****	849.4
39		****	832.4

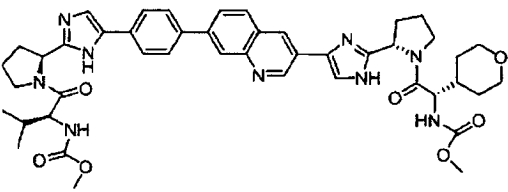
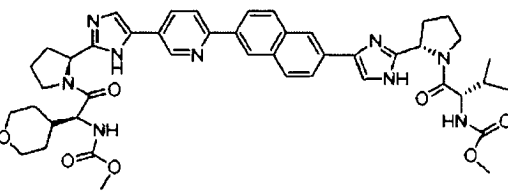
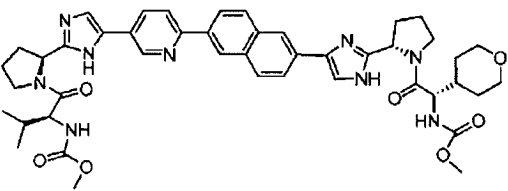
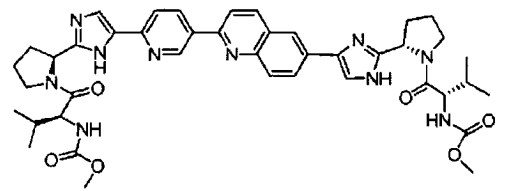
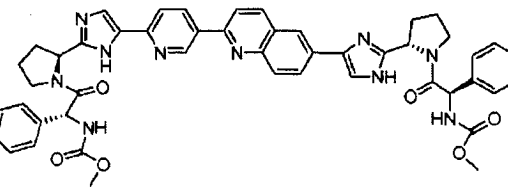
[0938]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
40		****	806.4
41		****	762.4
42		****	832.4
43		****	806.4
44		****	762.4

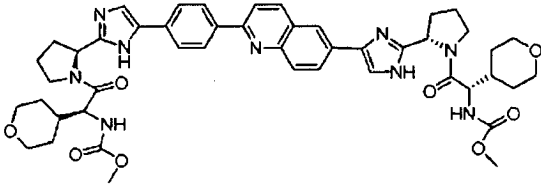
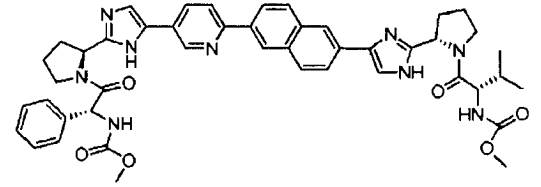
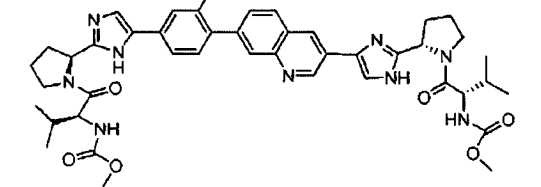
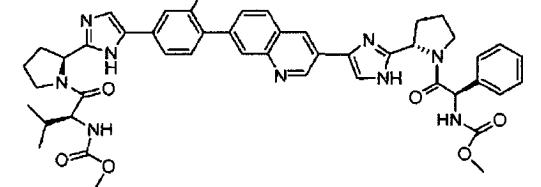
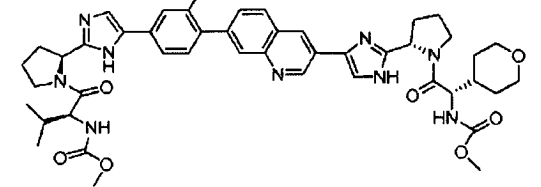
[0939]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
45		****	824.4
46		****	831.4
47		****	831.4
48		****	824.4
49		****	832.4

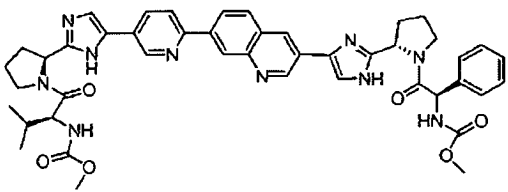
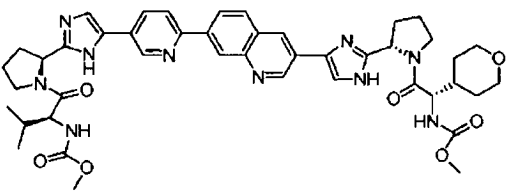
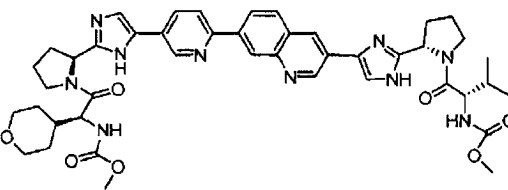
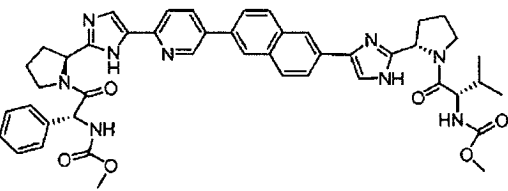
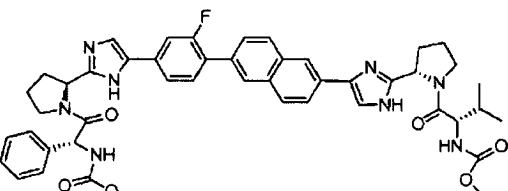
[0940]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
50		****	832.4
51		****	832.4
52		****	832.4
53		****	791.4
54		****	859.4

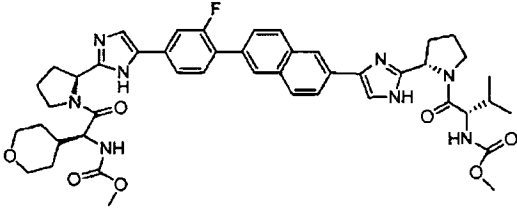
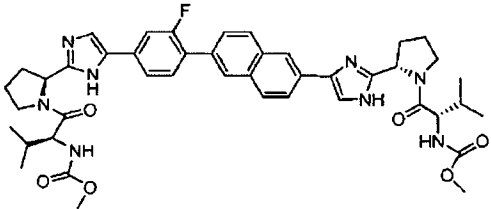
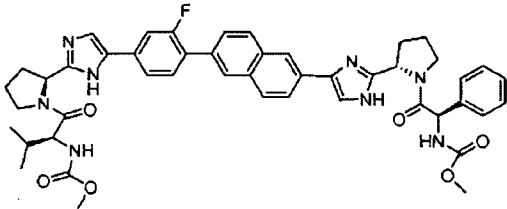
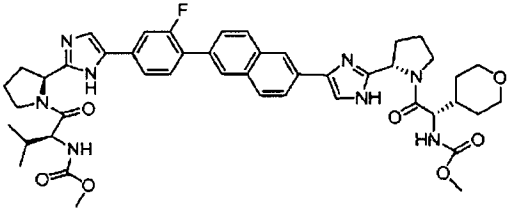
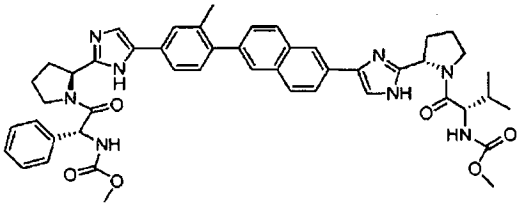
[0941]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
55		****	877.4
56		****	824.4
57		****	808.4
58		****	842.4
59		****	850.4

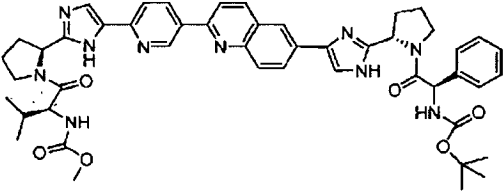
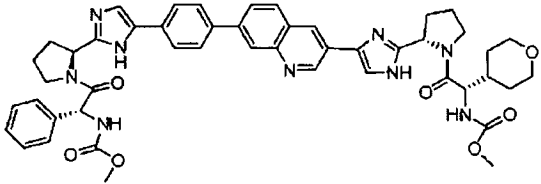
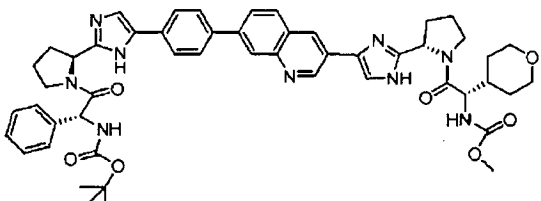
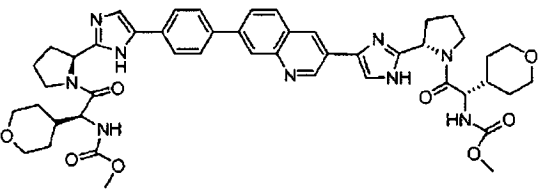
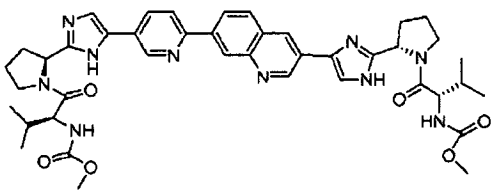
[0942]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
60		****	825.4
61		****	833.4
62		****	833.4
63		****	824.4
64		****	841.4

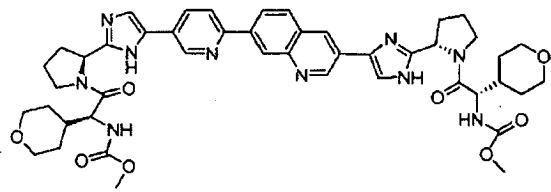
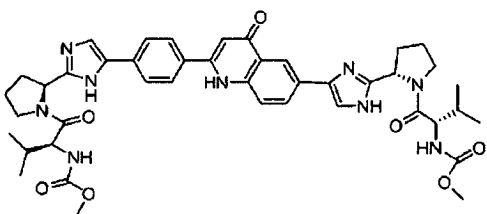
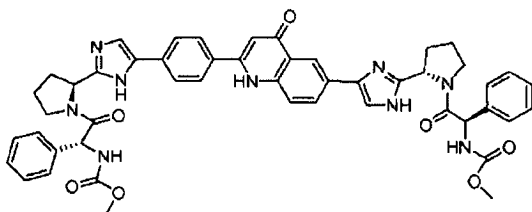
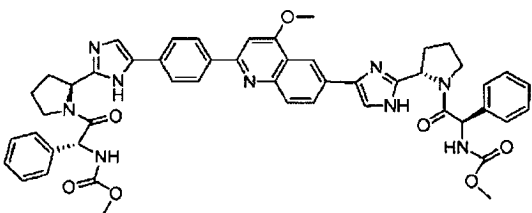
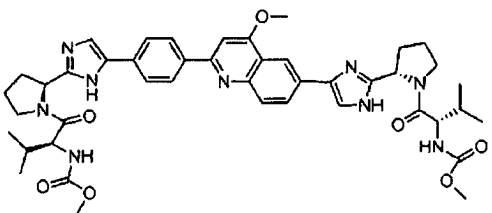
[0943]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
65		****	849.4
66		****	807.4
67		****	841.4
68		****	849.4
69		****	837.4

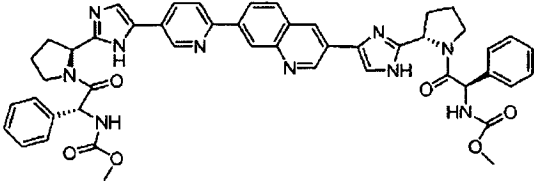
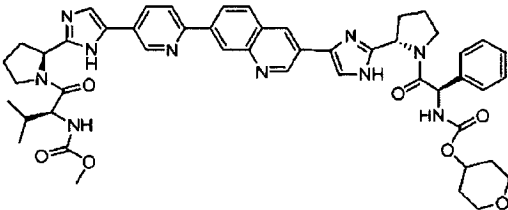
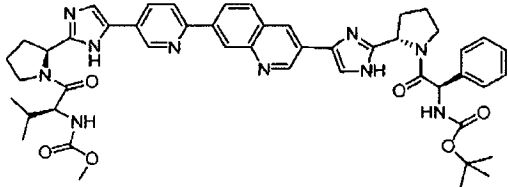
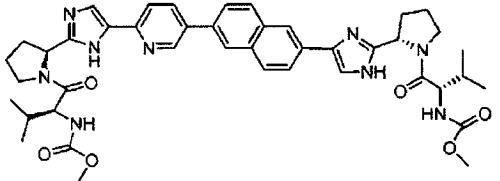
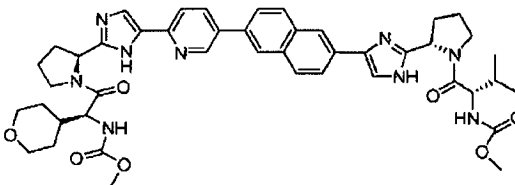
[0944]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
70		****	867.4
71		****	866.4
72		****	908.4
73		****	874.4
74		****	791.4

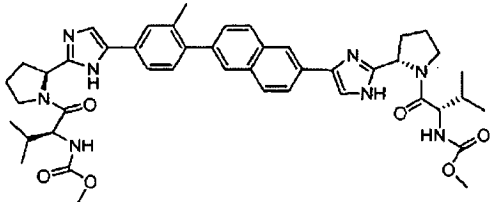
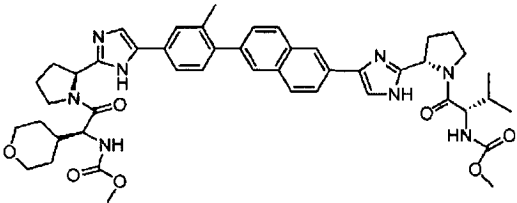
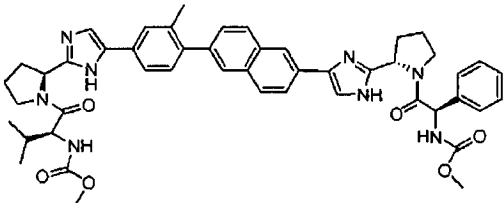
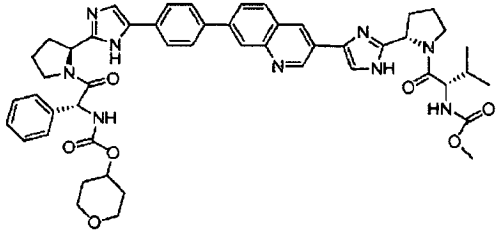
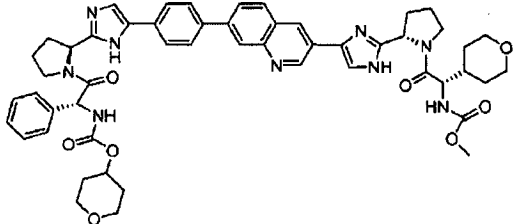
[0945]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
75		****	875.5
76		****	806.4
77		**	874.4
78		****	888.4
79		****	820.4

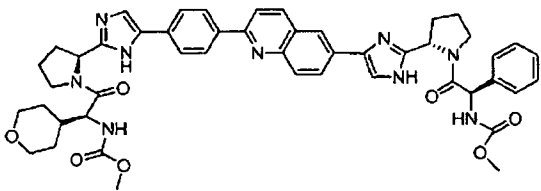
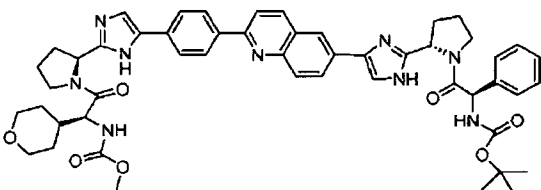
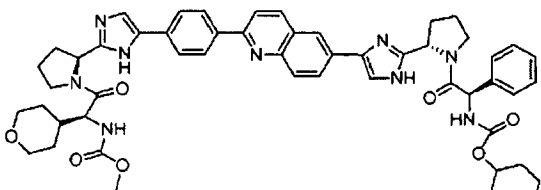
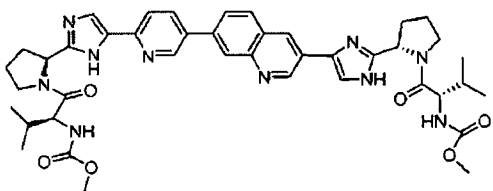
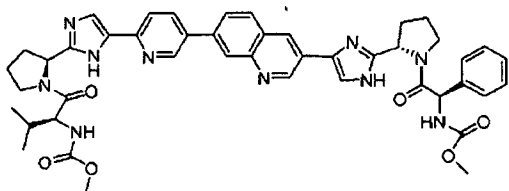
[0946]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
80		****	859.4
81		****	895.4
82		****	867.4
83		****	790.4
84		****	832.4

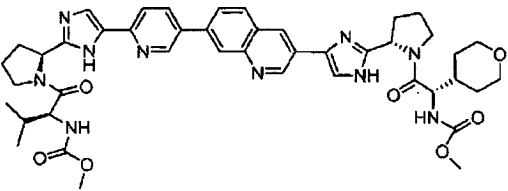
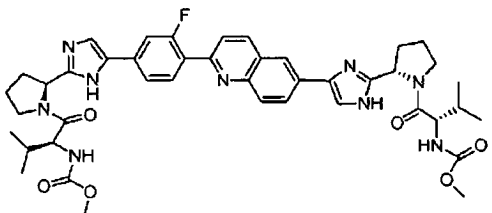
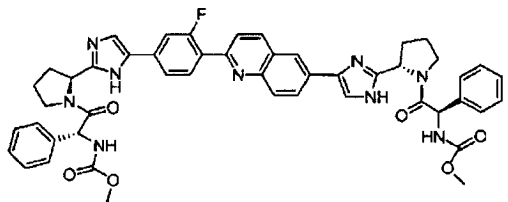
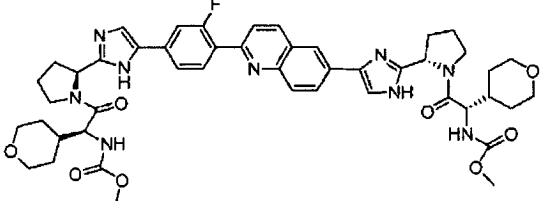
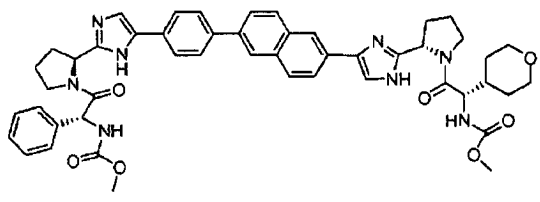
[0947]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
85		****	803.4
86		****	845.4
87		****	837.4
88		****	894.4
89		****	936.4

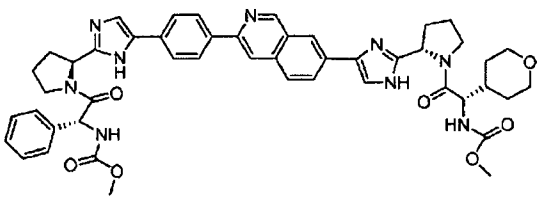
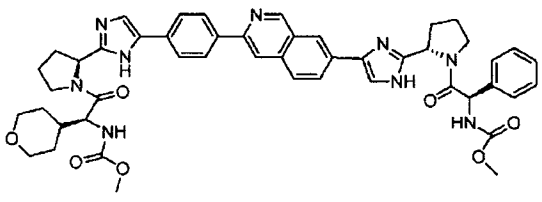
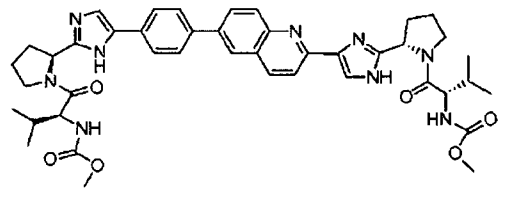
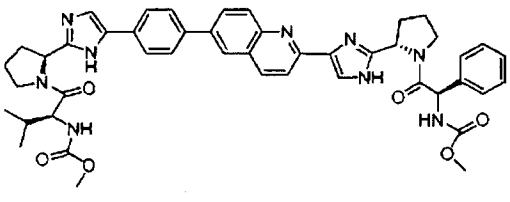
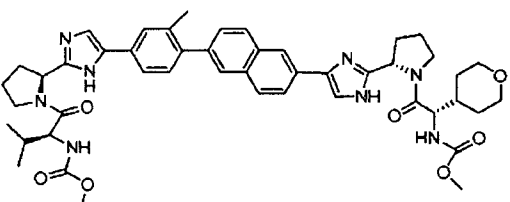
[0948]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
90		****	866.4
91		****	908.4
92		****	936.4
93		****	791.4
94		****	825.4

[0949]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
95		****	833.4
96		****	808.4
97		****	876.4
98		****	892.4
99		****	865.4

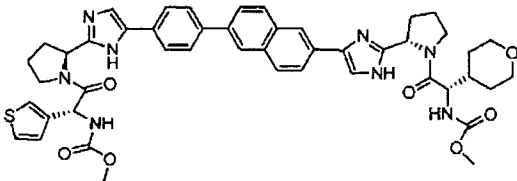
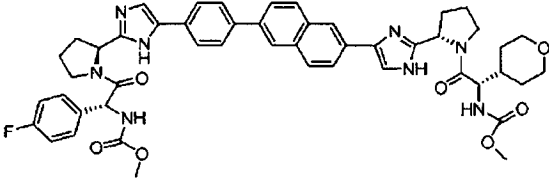
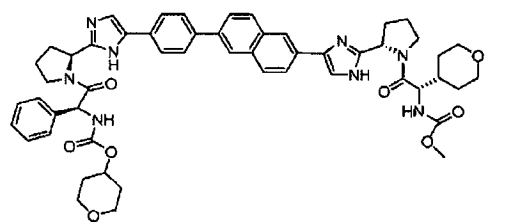
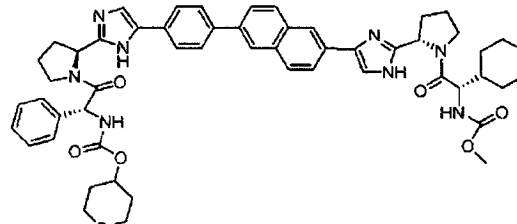
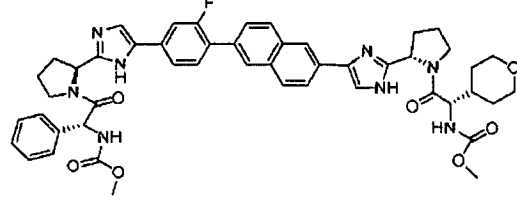
[0950]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
100		****	866.4
101		****	866.4
102		****	790.4
103		****	824.4
104		****	845.4

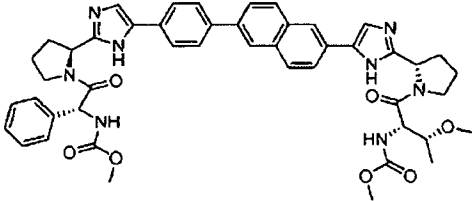
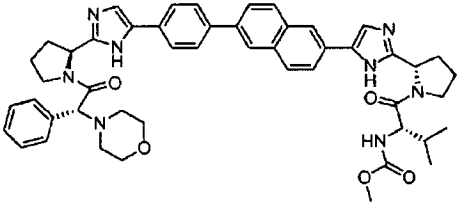
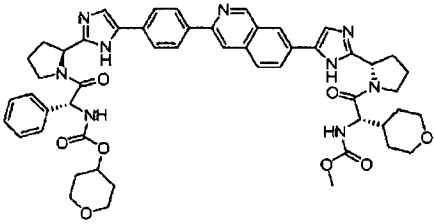
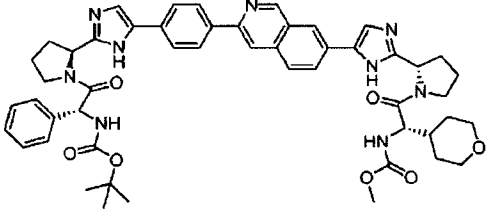
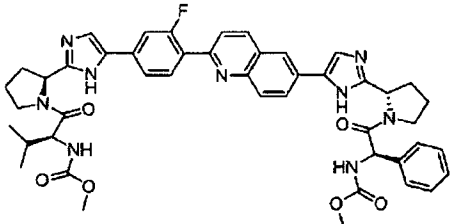
[0951]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
105		****	865.4
106		****	883.4
107		****	842.4
108		****	892.4
109		****	876.4

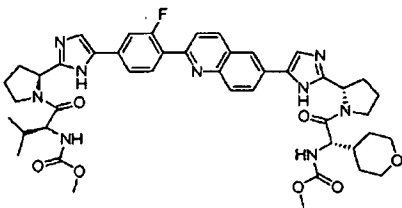
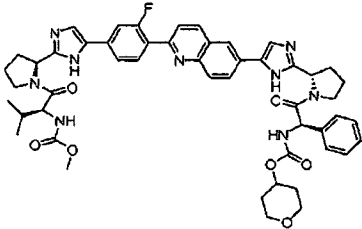
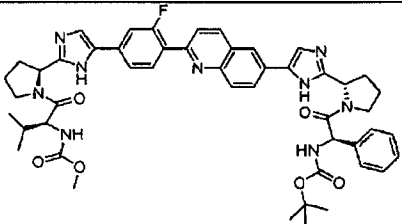
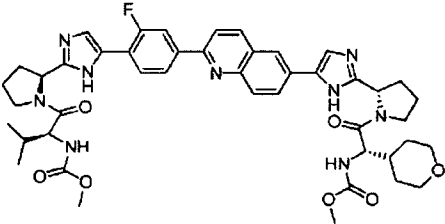
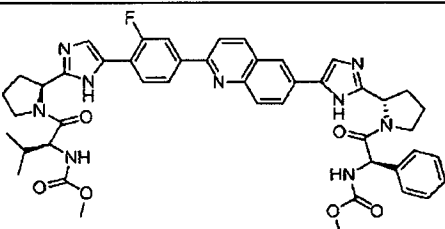
[0952]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
110		****	871.4
111		****	883.4
112		****	935.4
113		****	935.4
114		****	883.4

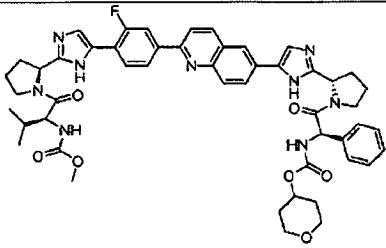
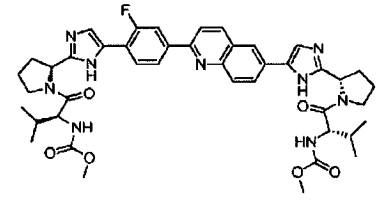
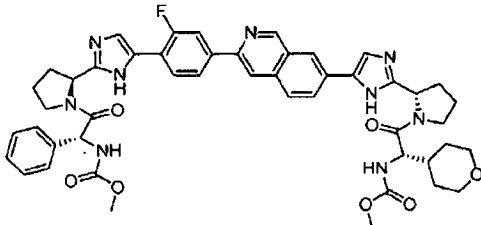
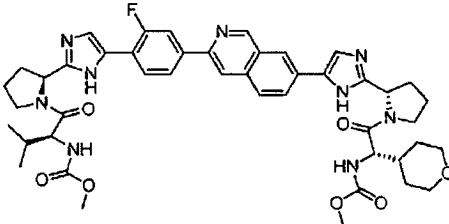
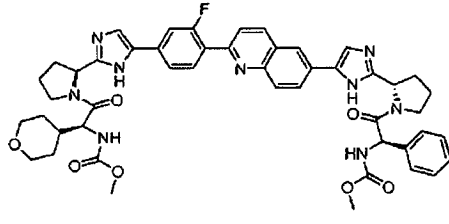
[0953]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
115		****	839.4
116		****	835.4
117		****	936.4
118		****	908.4
119		****	842.4

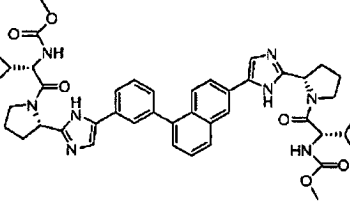
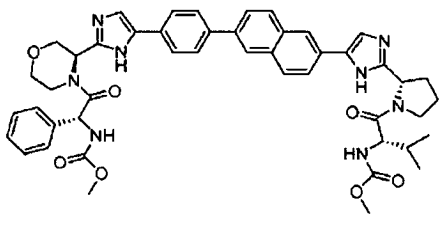
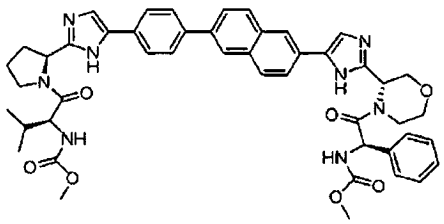
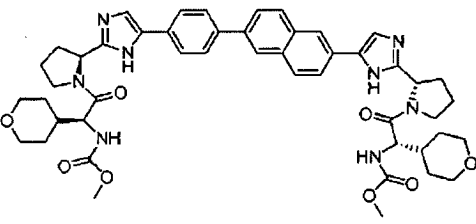
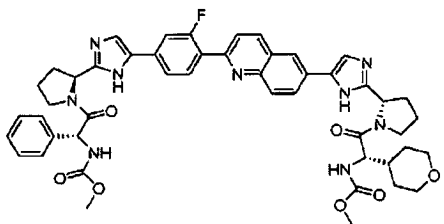
[0954]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
120		****	850.4
121		****	912.4
122		****	884.4
123		****	850.4
124		****	842.4

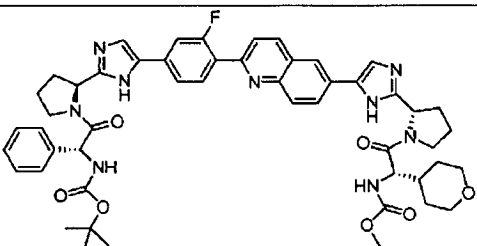
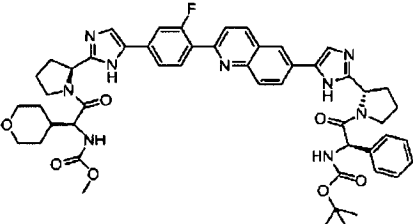
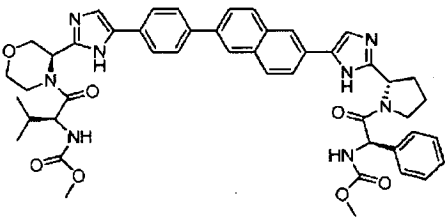
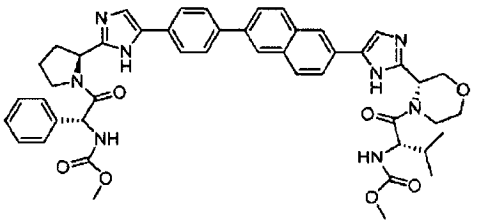
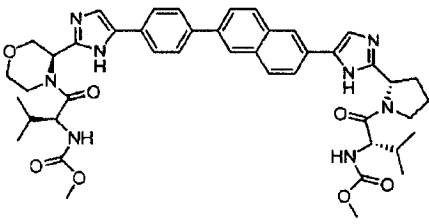
[0955]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
125		****	912.4
126		****	808.4
127		****	884.4
128		****	850.4
129		****	884.4

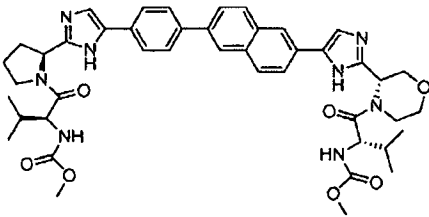
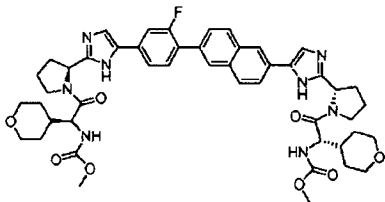
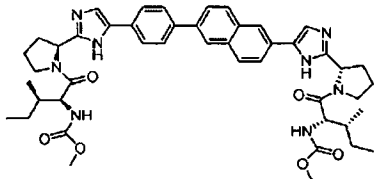
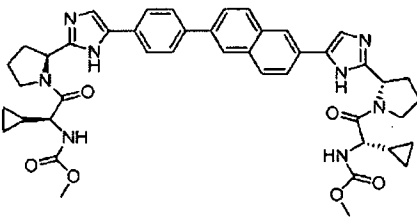
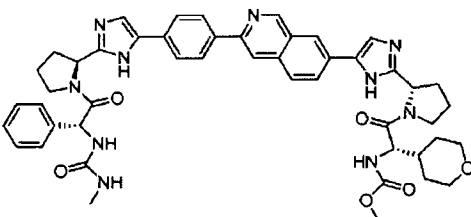
[0956]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
130		****	789.4
131		****	839.4
132		****	839.4
133		****	873.4
134		****	884.4

[0957]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
135		****	926.4
136		****	926.4
137		****	839.4
138		****	839.4
139		****	805.4

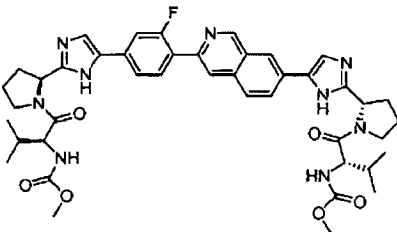
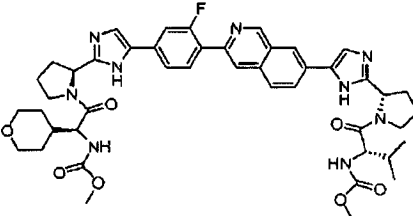
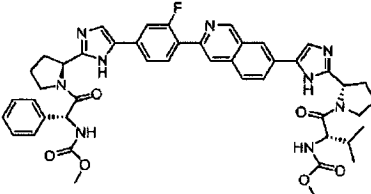
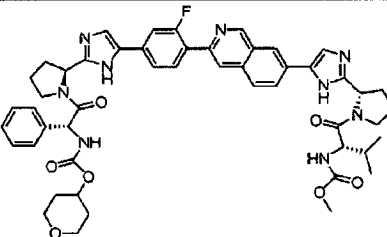
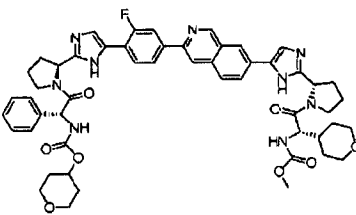
[0958]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
140		****	805.4
141		****	891.4
142		****	817.4
143		****	785.4
144		****	865.4

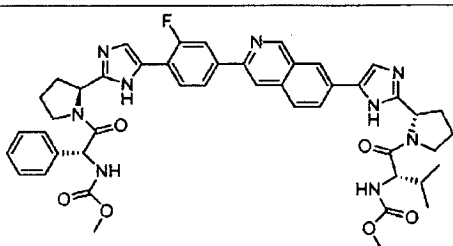
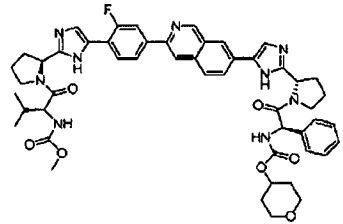
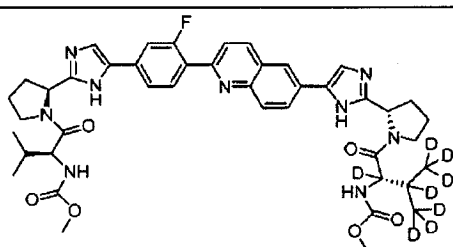
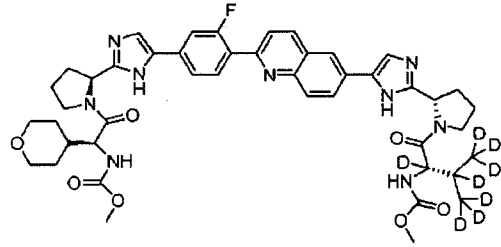
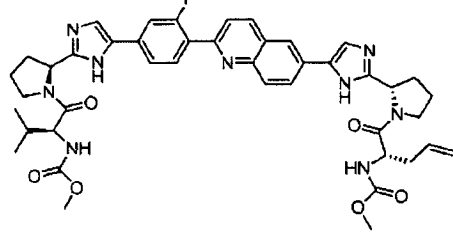
[0959]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
145		****	891.4
146		****	806.4
147		****	848.4
148		****	840.4
149		****	910.4

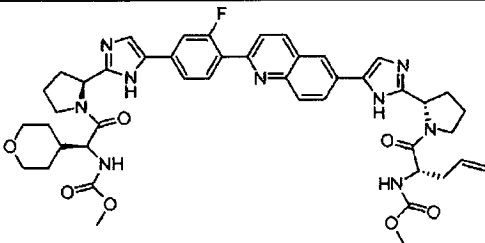
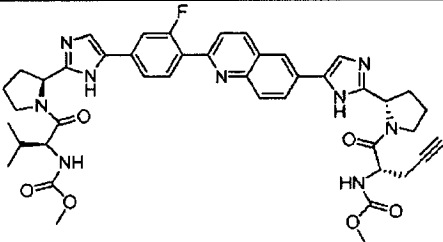
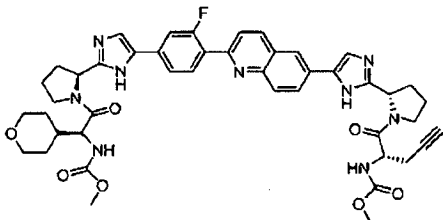
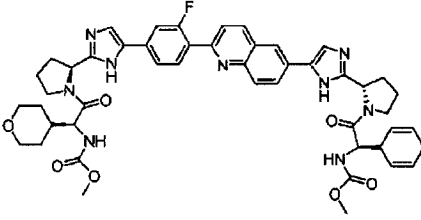
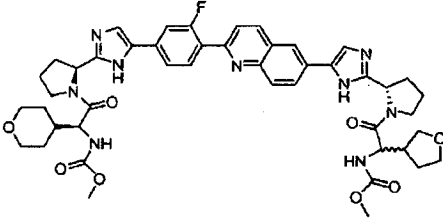
[0960]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
150		****	808.4
151		****	850.4
152		****	842.4
153		****	912.4
154		****	954.4

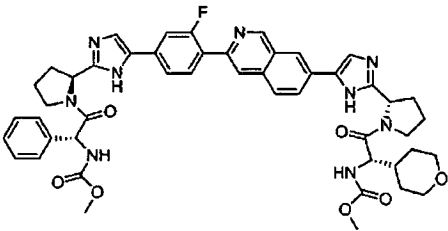
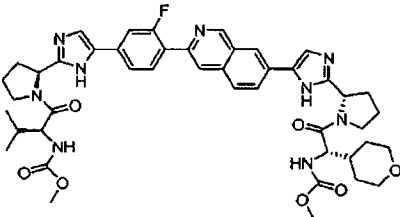
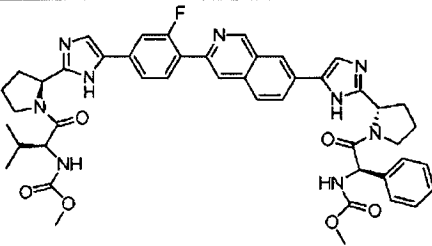
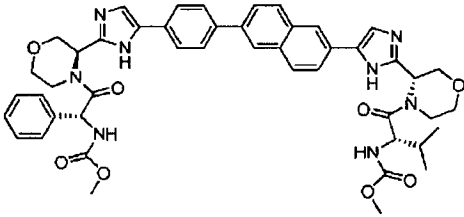
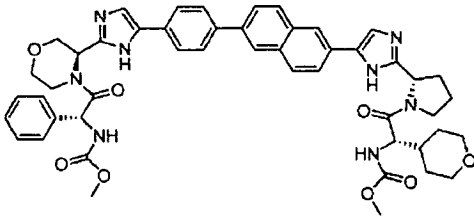
[0961]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
155		****	842.4
156		****	912.4
157			816.4
158			858.4
159			806.4

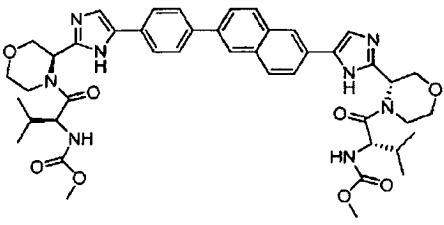
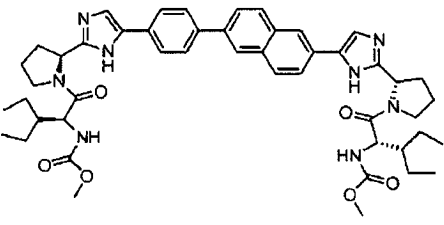
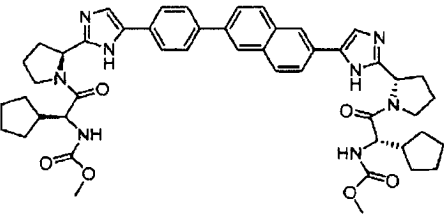
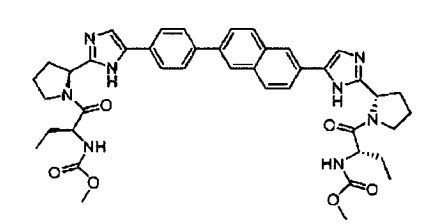
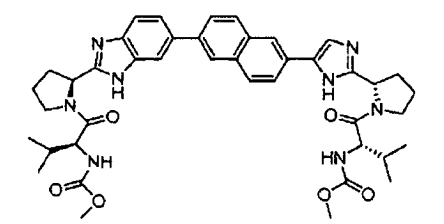
[0962]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
160			848.4
161			804.4
162			846.4
163			886.4
164			878.4

[0963]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
165			884.4
166			850.4
167			842.4
168			855.4
169			881.4

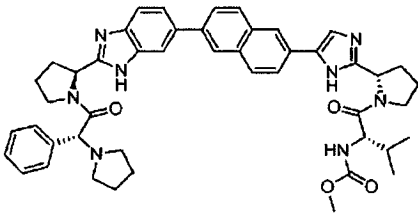
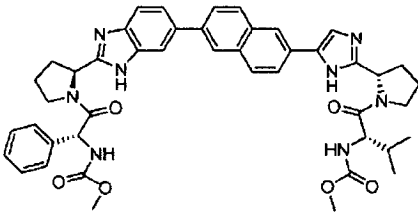
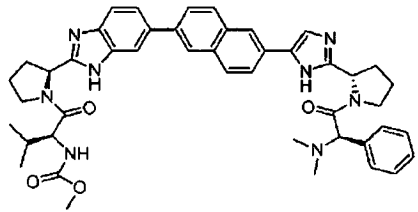
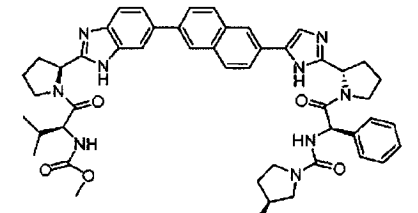
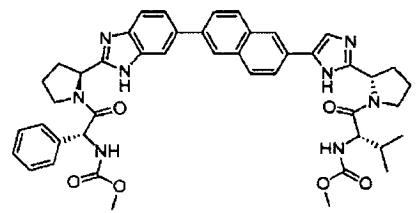
[0964]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
170			821.4
171			845.4
172			841.4
173			761.4
174		****	763.4

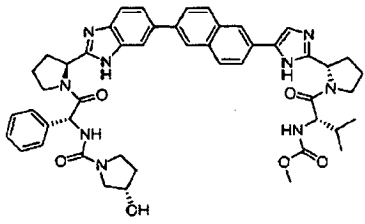
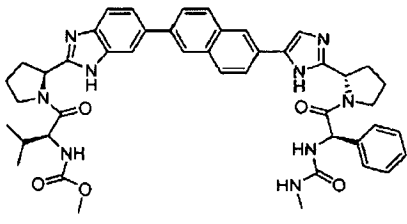
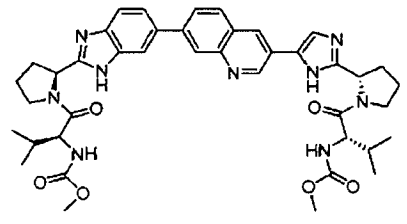
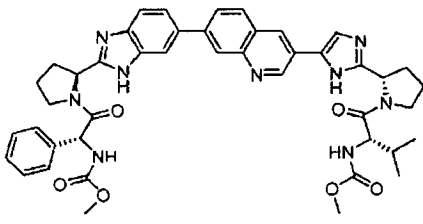
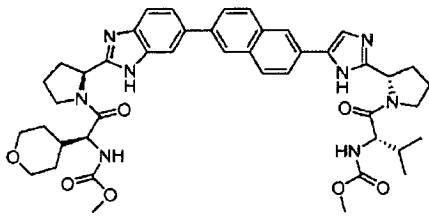
[0965]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
175		****	767.3
176		****	795.4
177		****	767.4
178		****	793.4
179		****	797.4

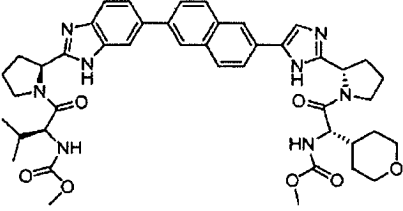
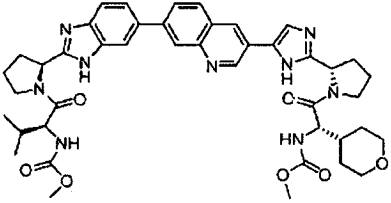
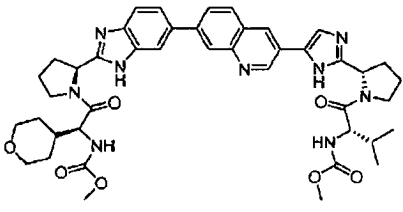
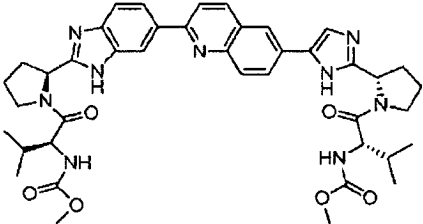
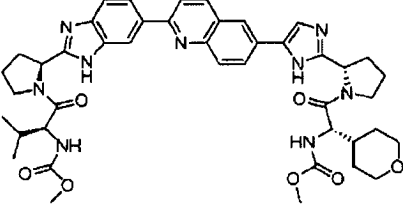
[0966]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H)+
180		****	793.4
181		****	797.4
182		****	767.4
183		****	852.4
184		****	797.4

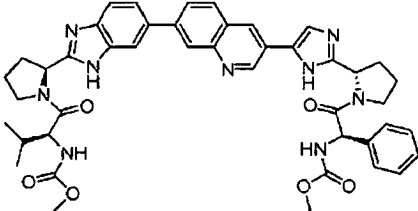
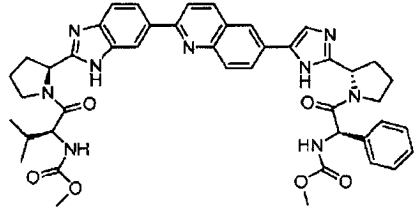
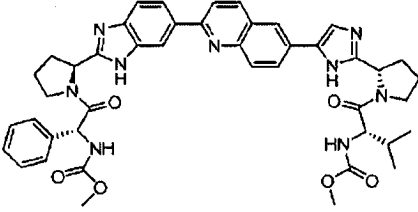
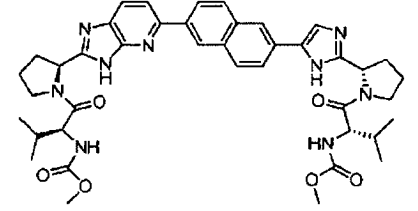
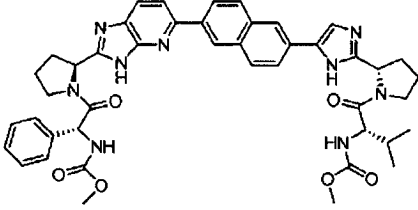
[0967]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
185		****	852.4
186		****	796.4
187		****	764.4
188		***	798.4
189		****	805.4

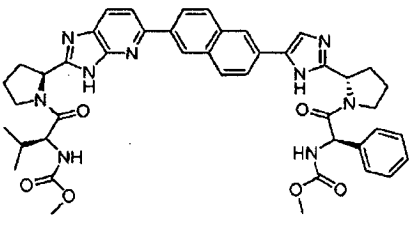
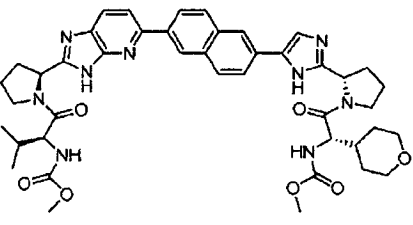
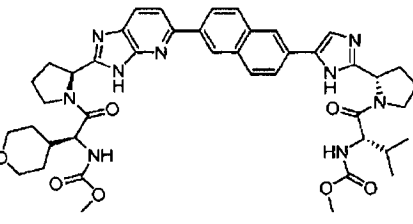
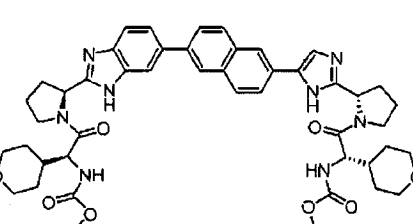
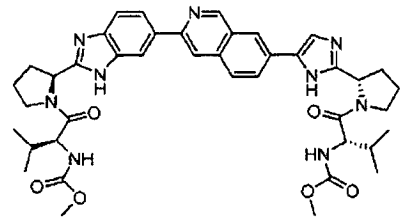
[0968]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
190		****	805.4
191		****	806.4
192		****	806.4
193		****	764.4
194		****	806.4

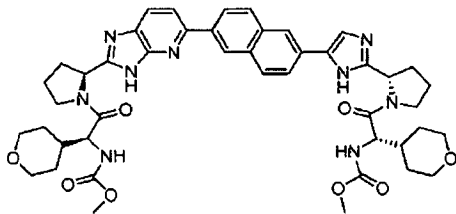
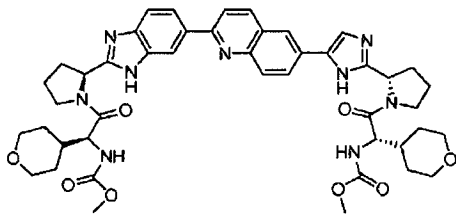
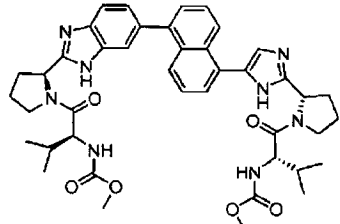
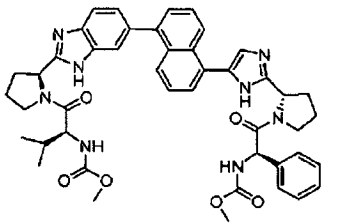
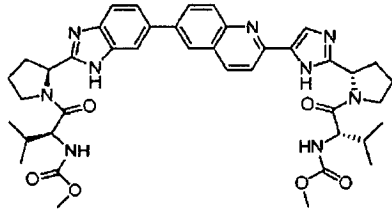
[0969]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
195		****	798.4
196		****	798.4
197		****	798.4
198		****	764.4
199		****	798.4

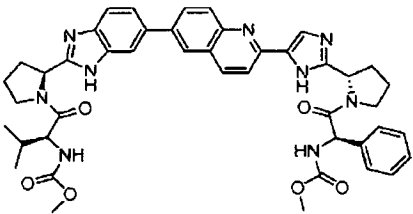
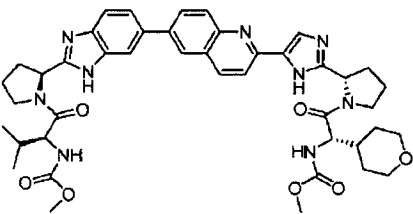
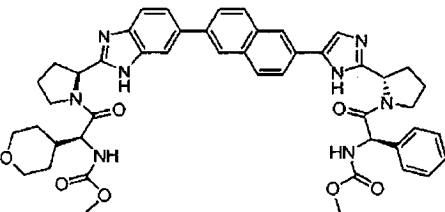
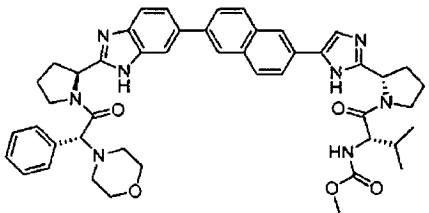
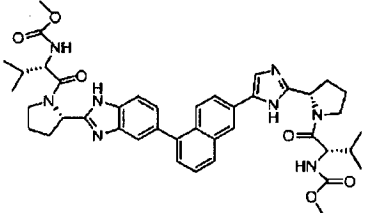
[0970]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
200		****	798.4
201		****	806.4
202		****	806.4
203		****	847.4
204		****	764.4

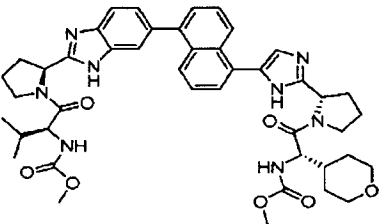
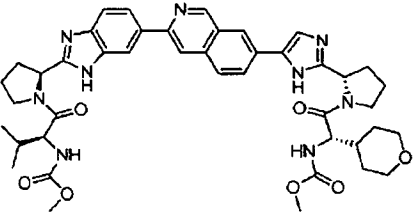
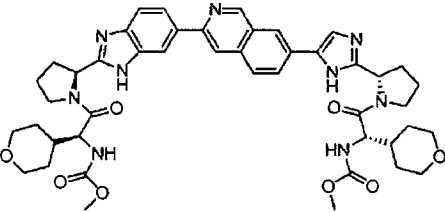
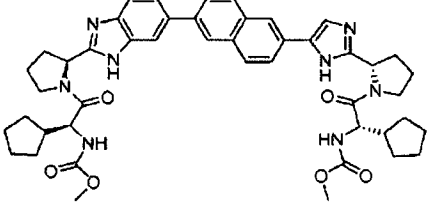
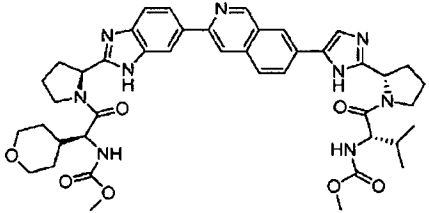
[0971]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
205		****	848.4
206		***	848.4
207		****	763.4
208		****	797.4
209		****	764.4

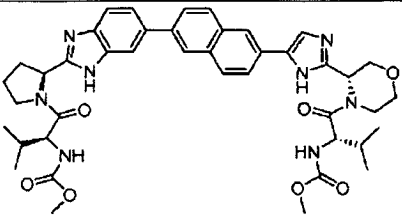
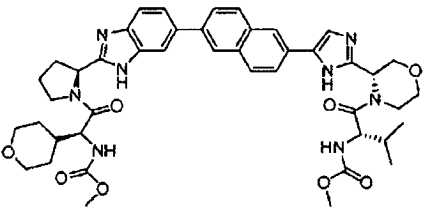
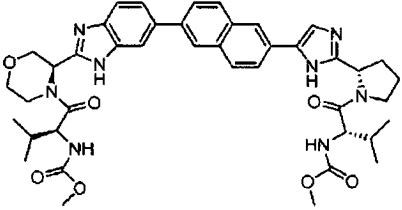
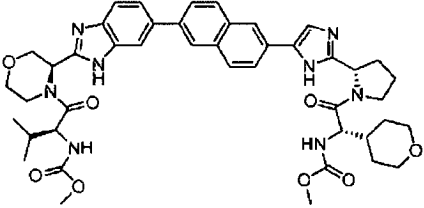
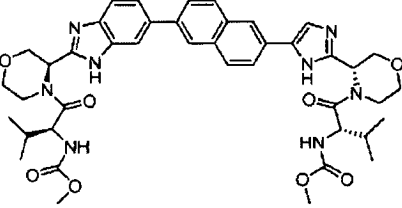
[0972]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
210		****	798.4
211		****	806.4
212		****	839.4
213		****	809.4
214		**	763.4

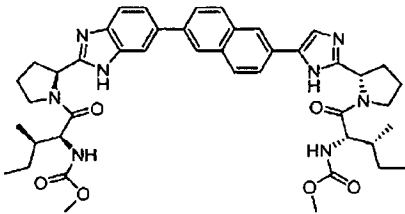
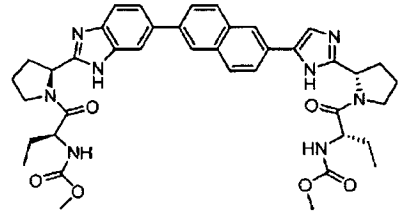
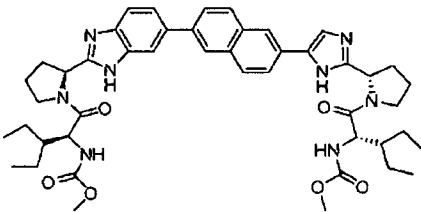
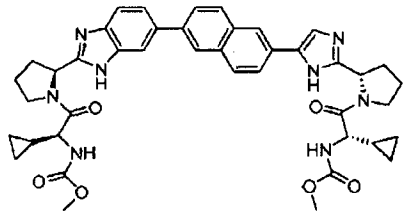
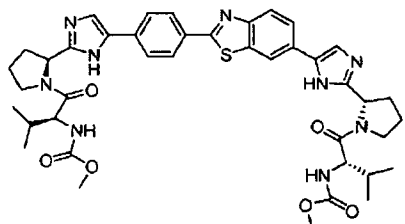
[0973]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
215		****	805.4
216		****	806.4
217		***	848.4
218		****	815.4
219			806.4

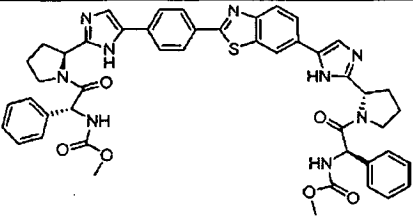
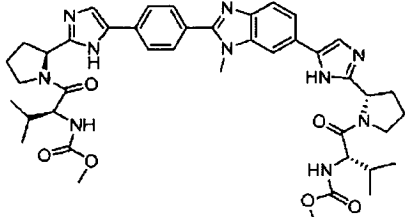
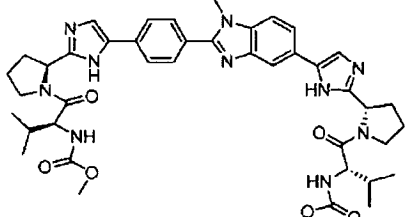
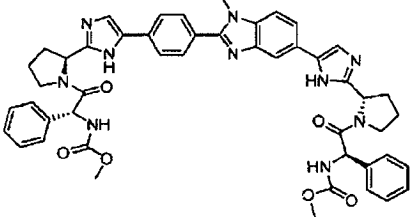
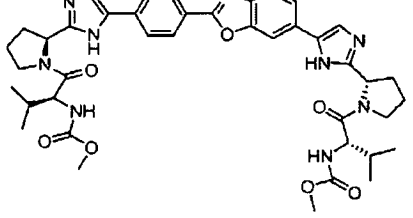
[0974]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
220			779.4
221			821.4
222			779.4
223			821.4
224			795.4

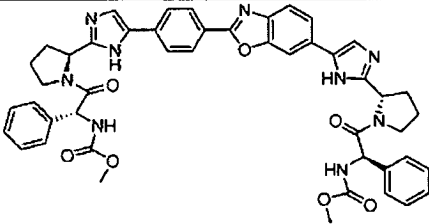
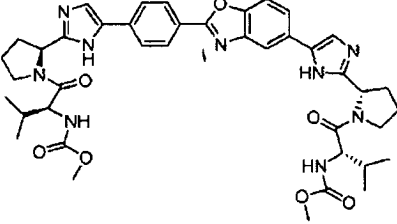
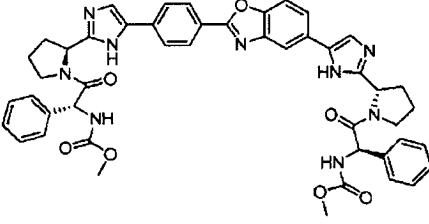
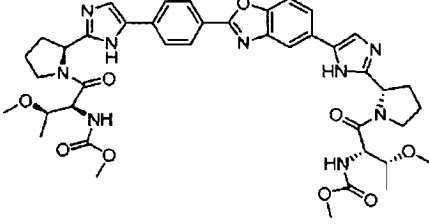
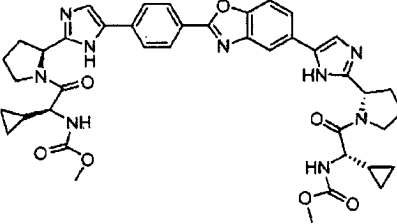
[0975]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
225			791.4
226			735.4
227			819.4
228			759.4
229		****	796.4

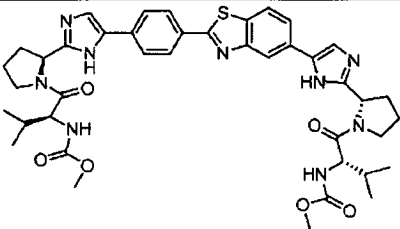
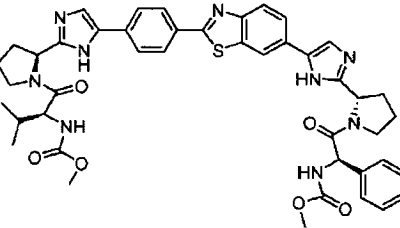
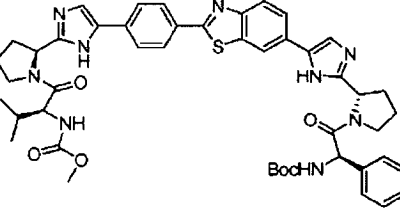
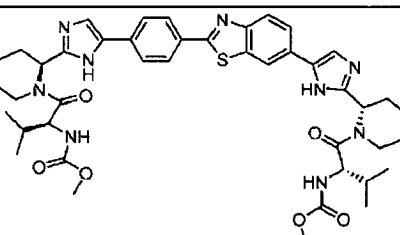
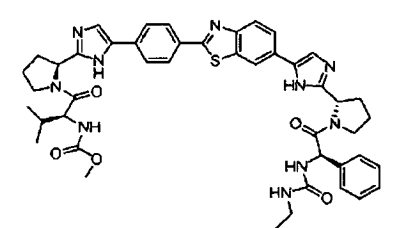
[0976]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
230		****	864.3
231		****	793.4
232		****	793.4
233		****	861.4
234		****	780.4

[0977]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
235		****	848.3
236		****	780.4
237		****	848.3
238		****	812.4
239		****	776.3

[0978]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
240		****	796.4
241		****	830.3
242		****	872.4
243		****	824.4
244		****	843.4

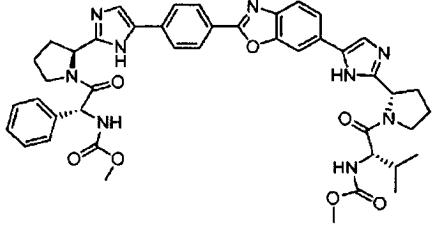
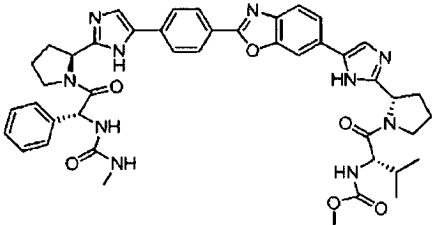
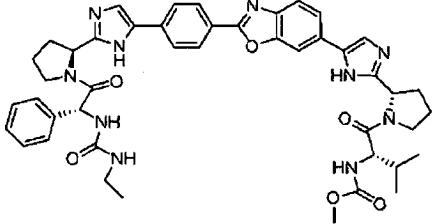
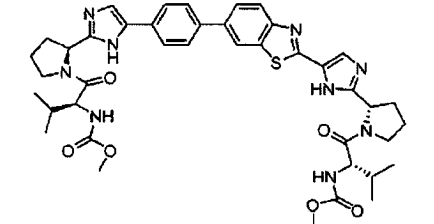
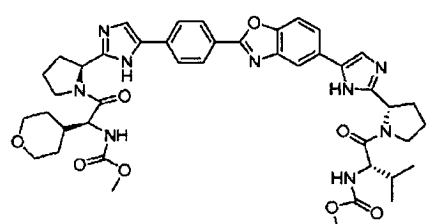
[0979]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
245		****	829.4
246		****	773.3
247		****	856.4
248		****	892.4
249		****	814.4

[0980]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
250		**	716.3
251		****	813.4
252		****	827.4
253		****	796.4
254		****	856.4

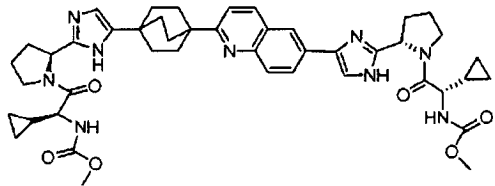
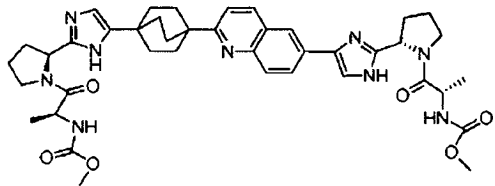
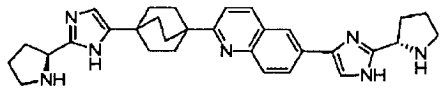
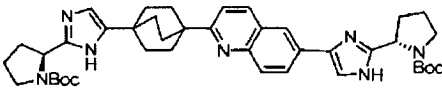
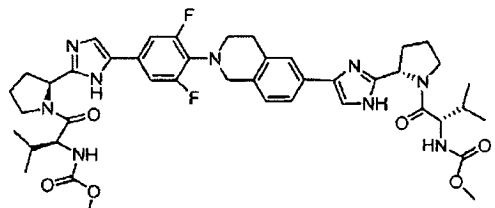
[0981]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
255		****	814.4
256		****	813.4
257		****	827.4
258		****	796.4
259		****	822.4

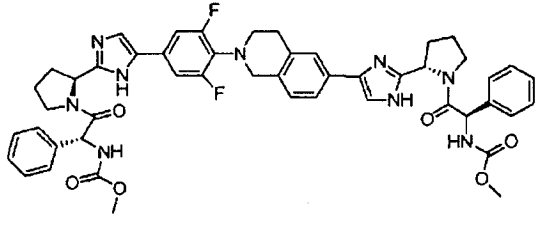
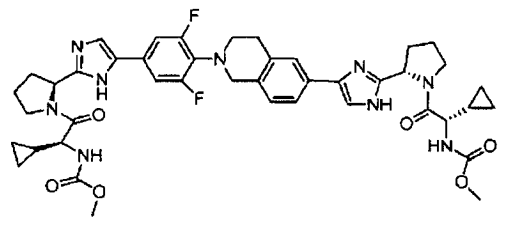
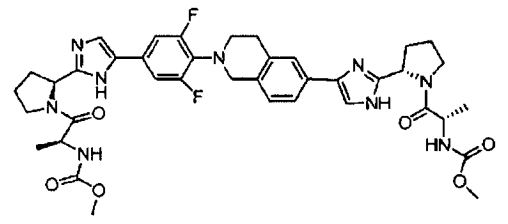
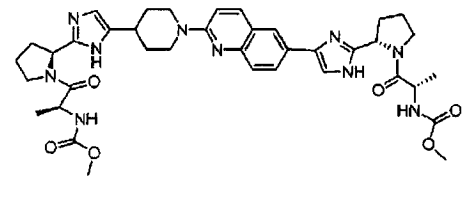
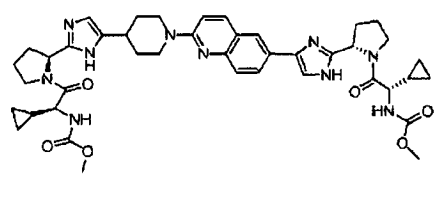
[0982]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
260		****	814.4
261		***	821.5
262		****	822.5
263		****	890.4
264		***	830.5

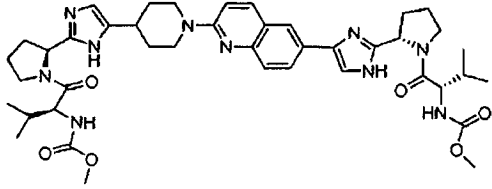
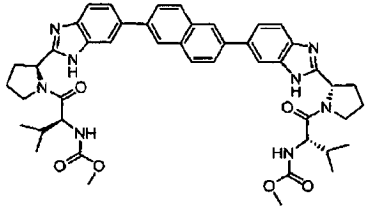
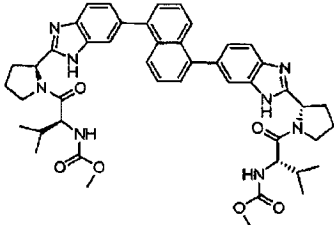
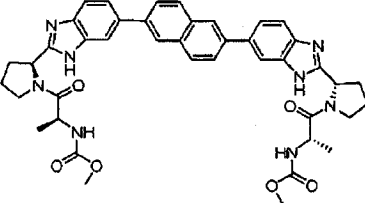
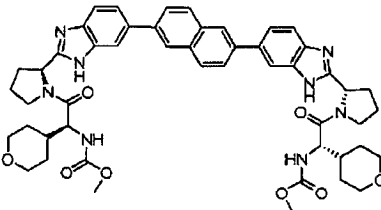
[0983]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
265		****	818.4
266		****	766.4
267		*	508.3
268		**	708.4
269		****	830.4

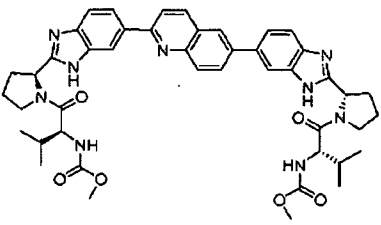
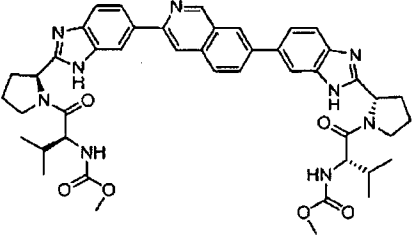
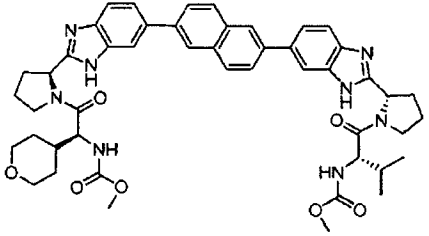
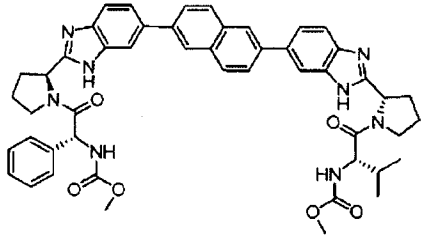
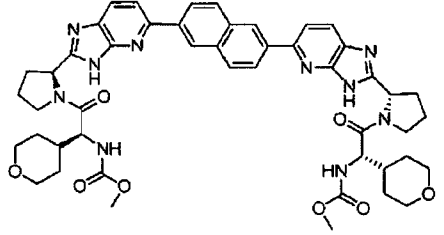
[0984]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
270		****	898.4
271		****	826.4
272		****	774.3
273		***	741.4
274		***	793.4

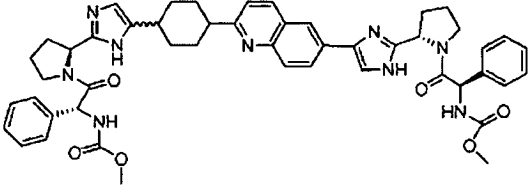
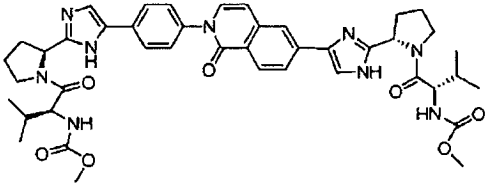
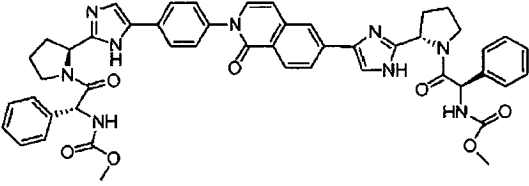
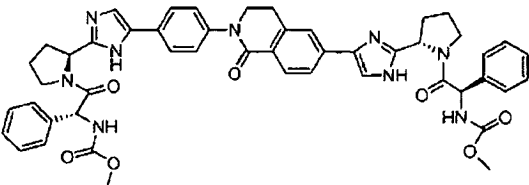
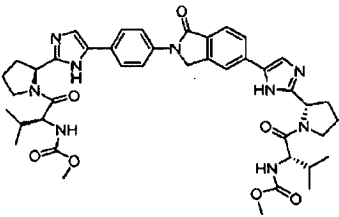
[0985]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
275		****	797.4
276		****	813.4
277		****	813.4
278		****	757.3
279		****	897.4

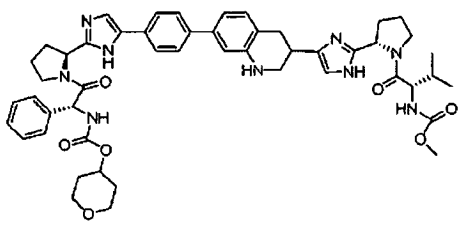
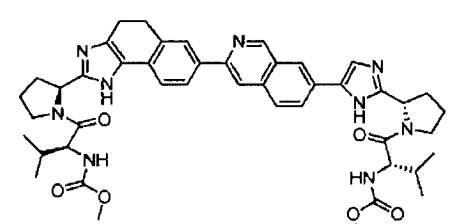
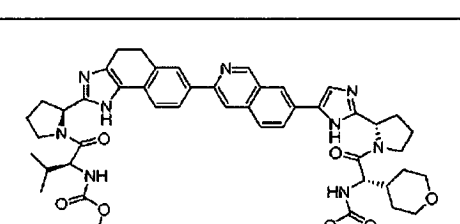
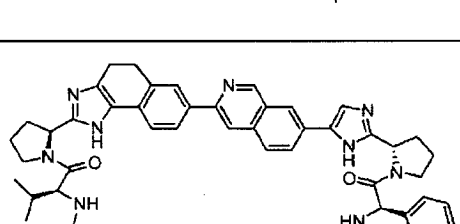
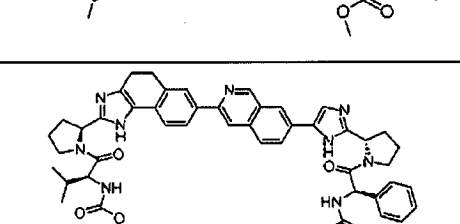
[0986]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
280		****	814.4
281		****	814.4
282		****	855.4
283		****	847.4
284			899.4

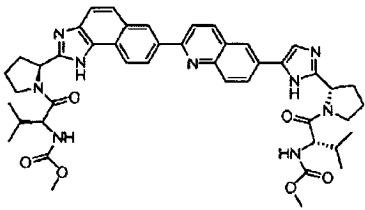
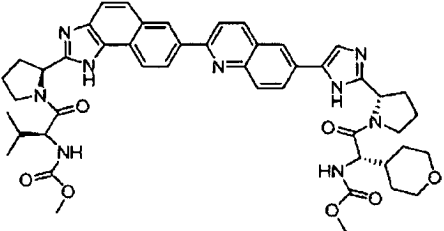
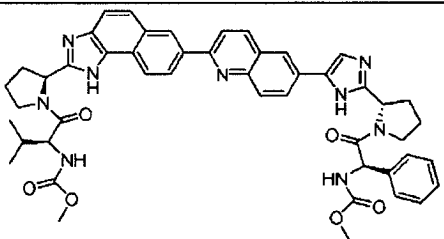
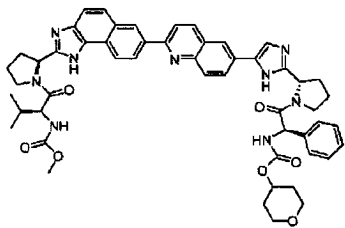
[0987]

化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
286		****	864.4
287		****	806.4
288		****	874.4
289		****	876.4
290		****	794.4

[0988]

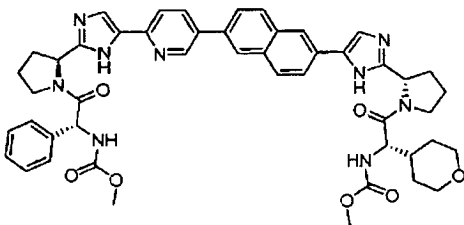
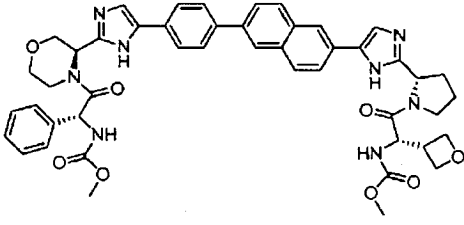
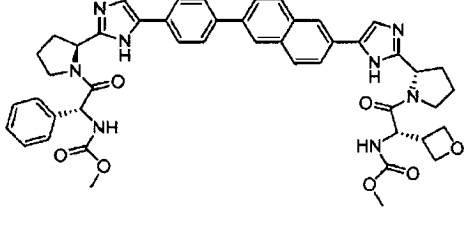
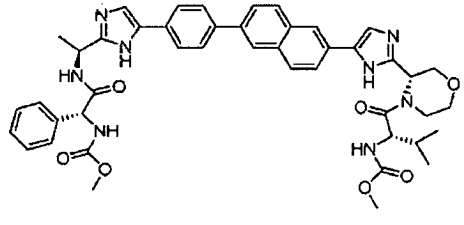
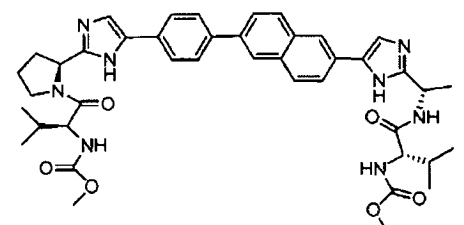
化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
291		****	898.5
292		****	816.4
293		****	858.4
294		****	850.4
295		****	920.4

[0989]

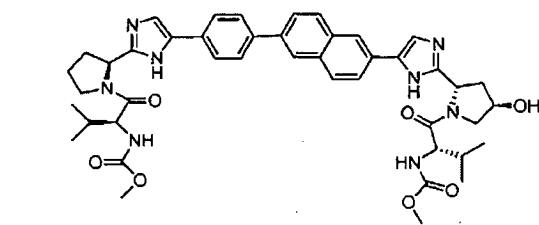
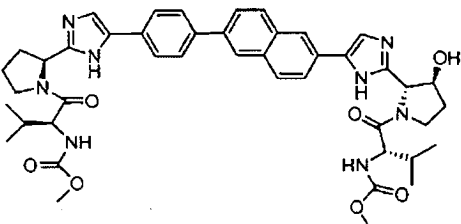
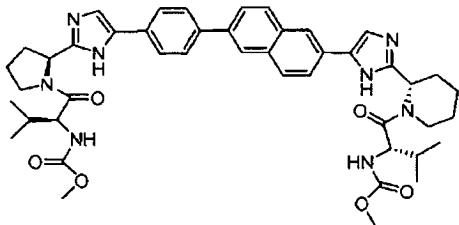
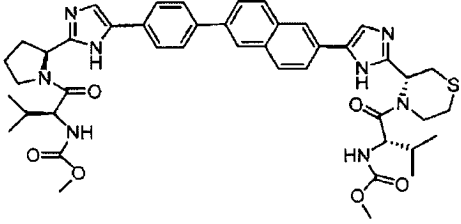
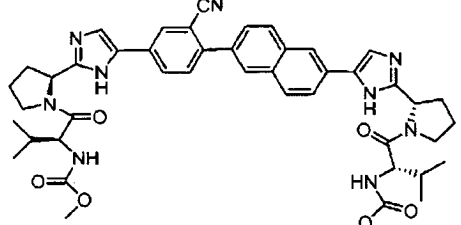
化合物	结构	对 HCV 基因型 1b 的抑制	MS (M+H) ⁺
296		****	814.4
297		****	856.4
298		****	848.4
299		****	918.4

[0990] 表 2

[0991]

化合物	结构
300	
301	
302	
303	
304	

[0992]

化合物	结构
305	
306	
307	
308	
309	

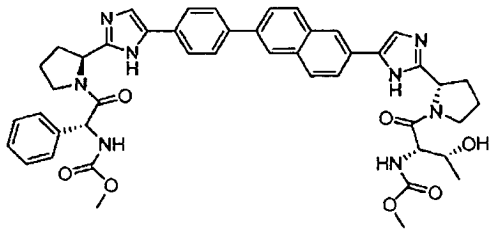
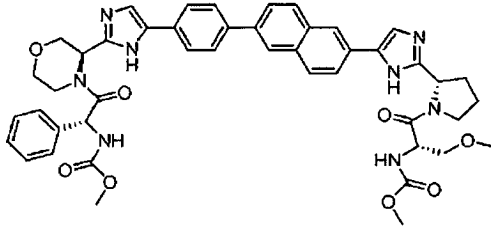
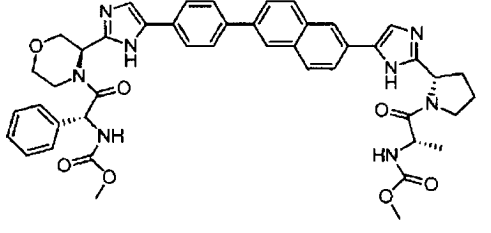
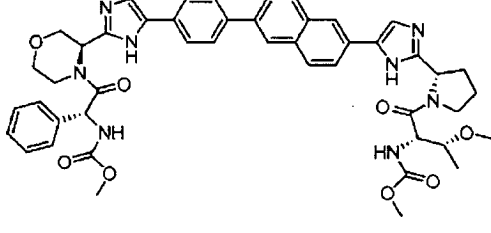
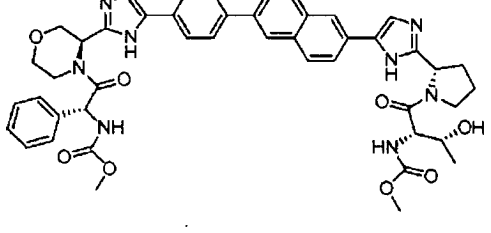
[0993]

化合物	结构
310	
311	
312	
313	
314	

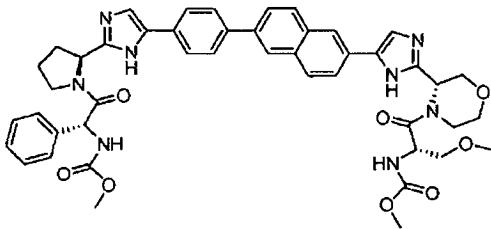
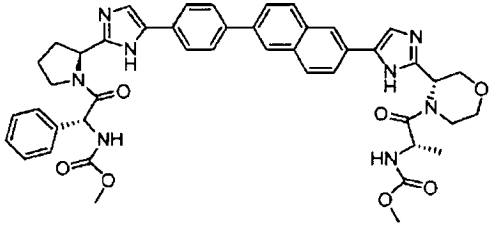
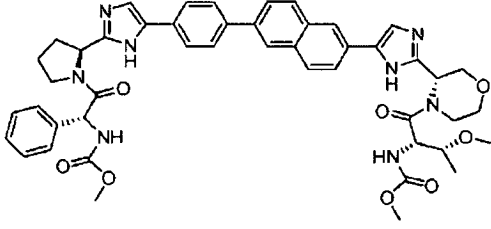
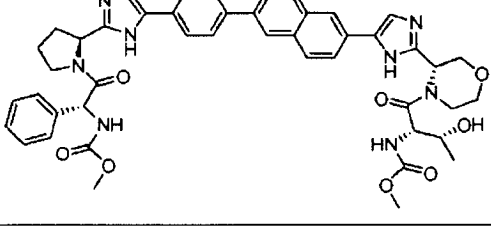
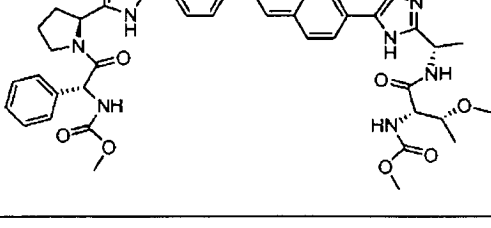
[0994]

化合物	结构
315	
316	
317	
318	
319	

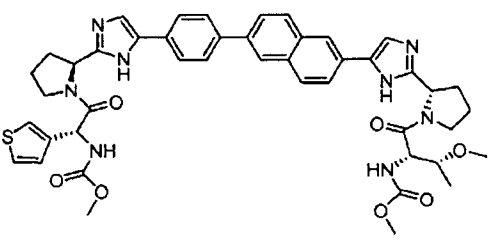
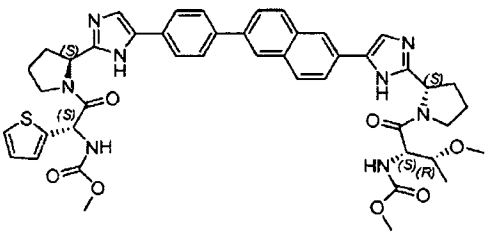
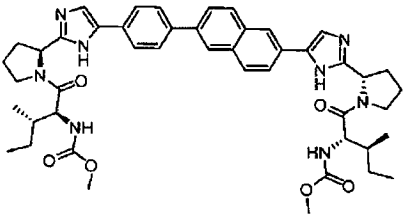
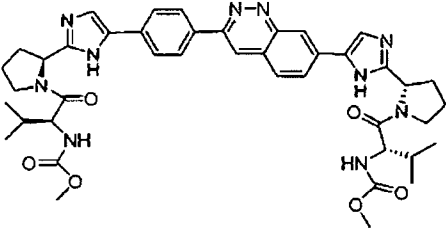
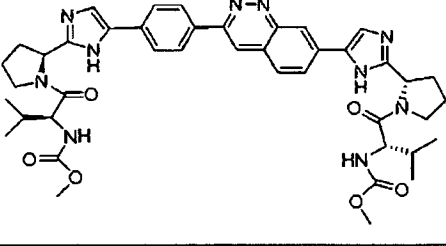
[0995]

化合物	结构
320	
321	
322	
323	
324	

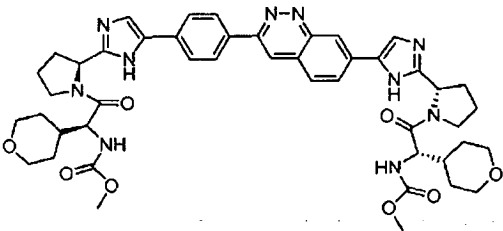
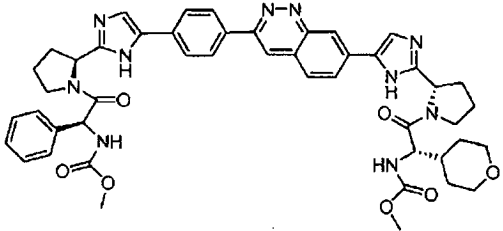
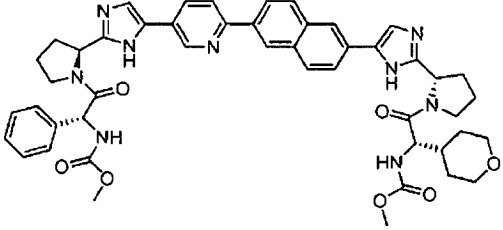
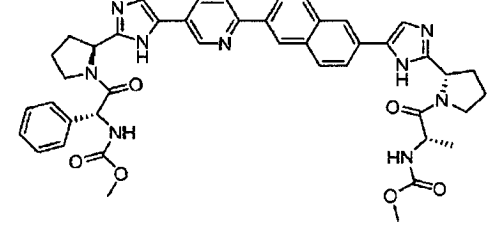
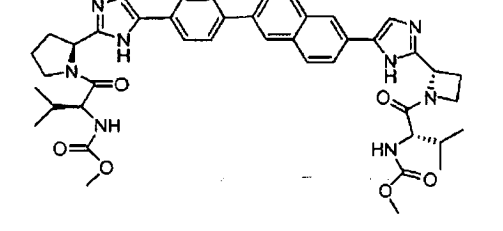
[0996]

化合物	结构
325	
326	
327	
328	
329	

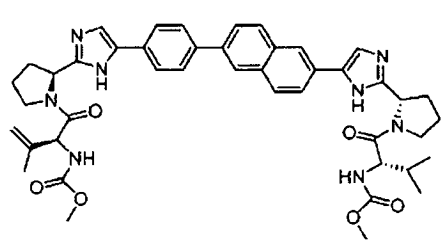
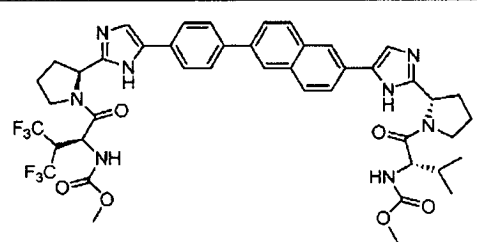
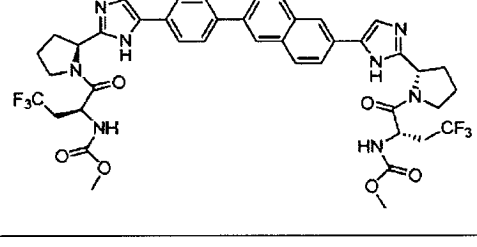
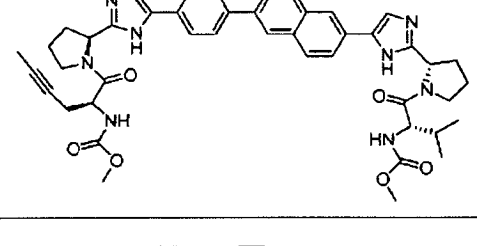
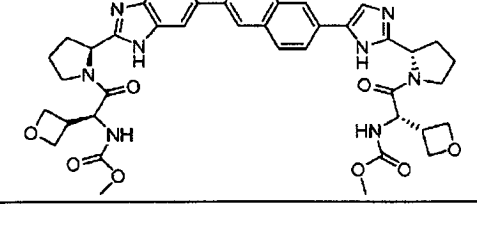
[0997]

化合物	结构
330	
331	
332	
333	
334	

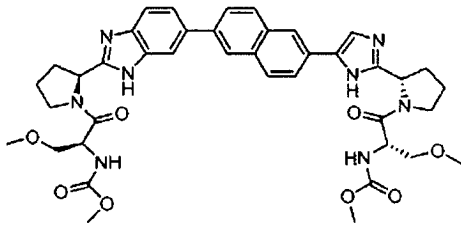
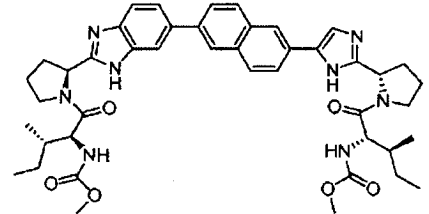
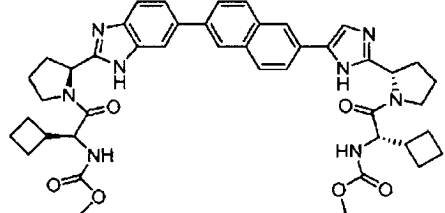
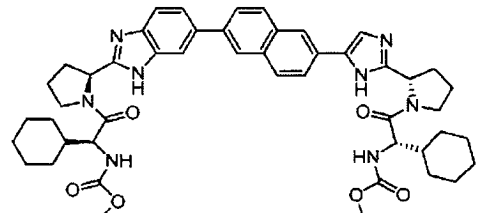
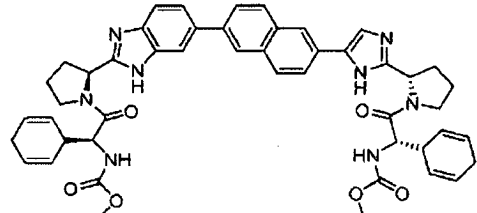
[0998]

化合物	结构
335	
336	
337	
338	
339	

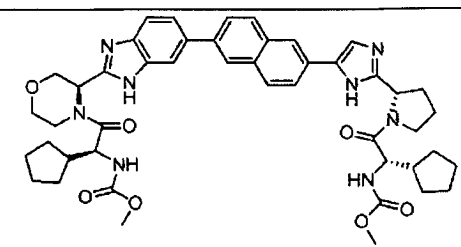
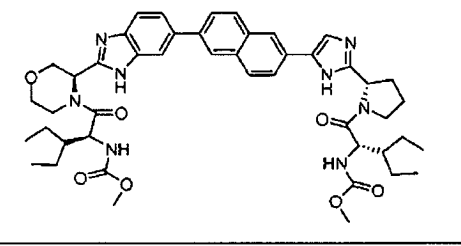
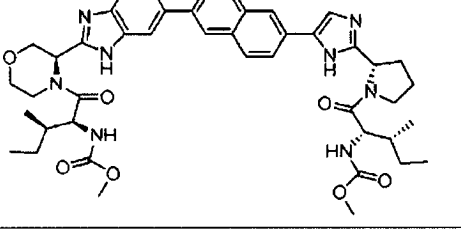
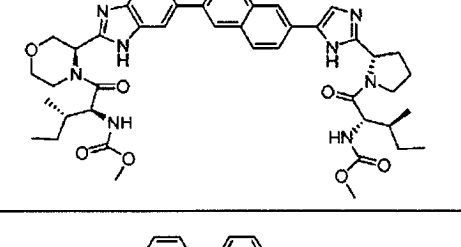
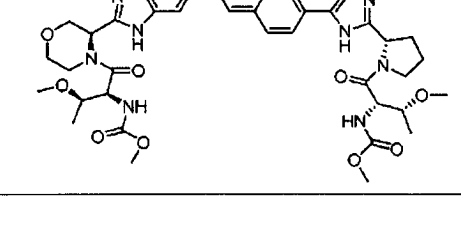
[0999]

化合物	结构
340	
341	
342	
343	
344	

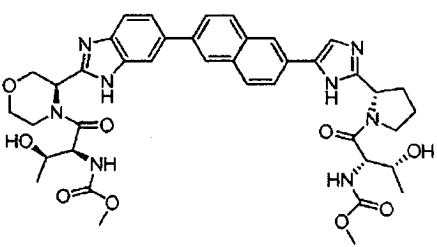
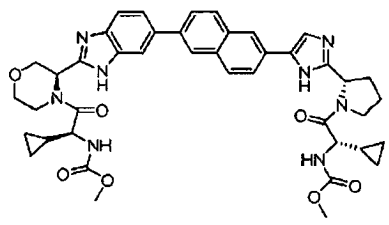
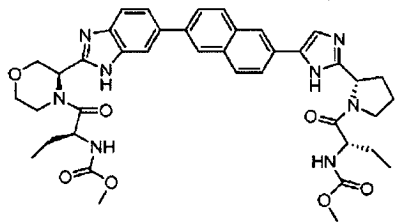
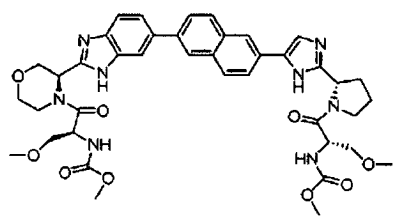
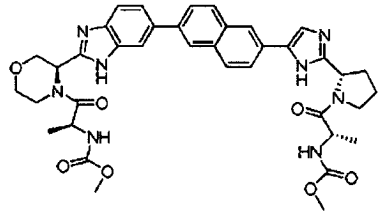
[1000]

化合物	结构
345	
346	
347	
348	
349	

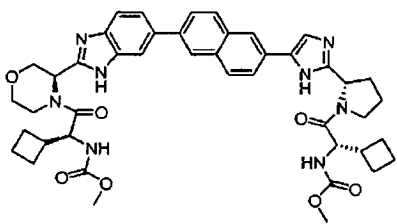
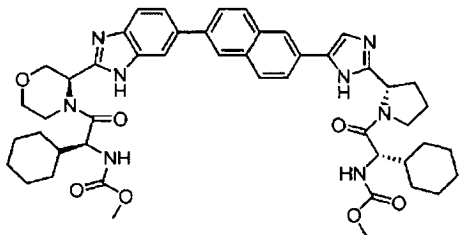
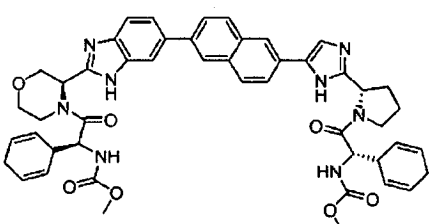
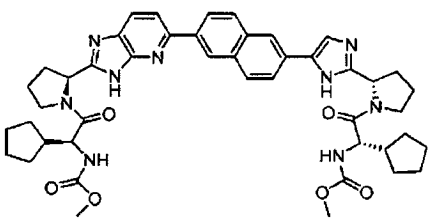
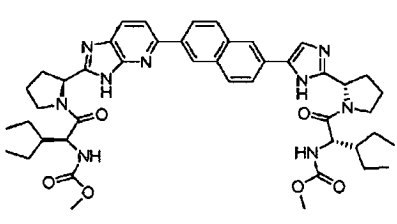
[1001]

化合物	结构
350	
351	
352	
353	
354	

[1002]

化合物	结构
355	
356	
357	
358	
359	

[1003]

化合物	结构
360	
361	
362	
363	
364	

[1004]

化合物	结构
365	
366	
367	
368	
369	

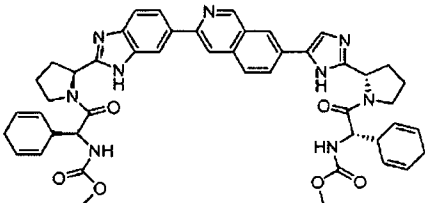
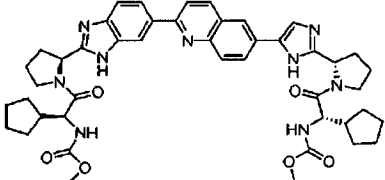
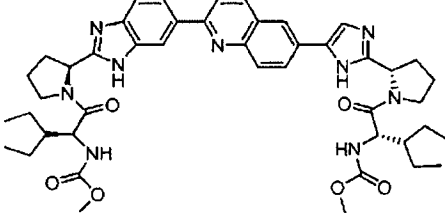
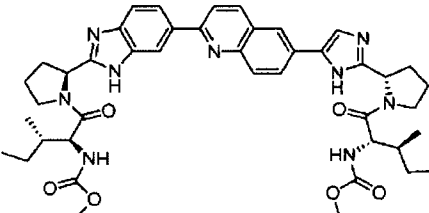
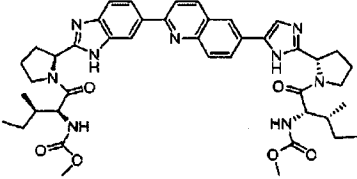
[1005]

化合物	结构
370	
371	
372	
373	
374	

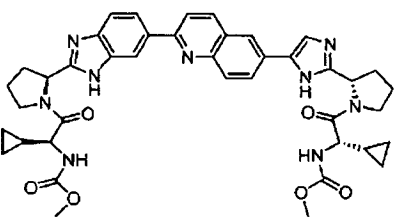
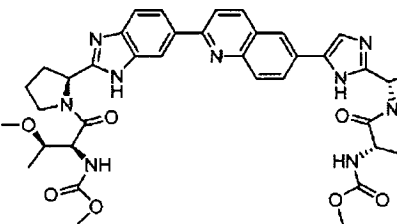
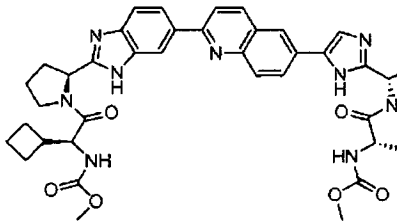
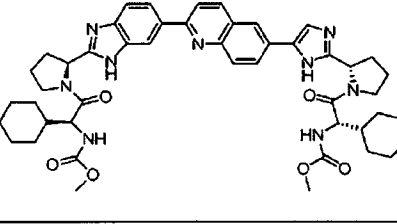
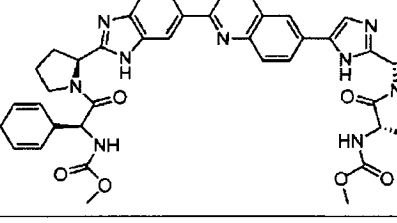
[1006]

化合物	结构
375	
376	
377	
378	
379	

[1007]

化合物	结构
380	
381	
382	
383	
384	

[1008]

化合物	结构
385	
386	
387	
388	
389	

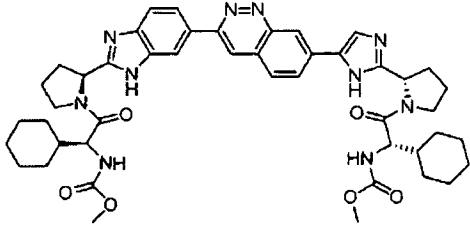
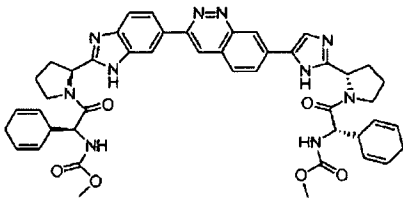
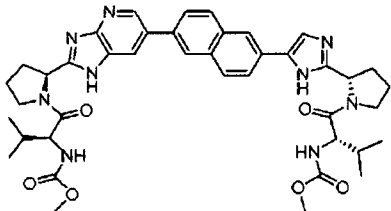
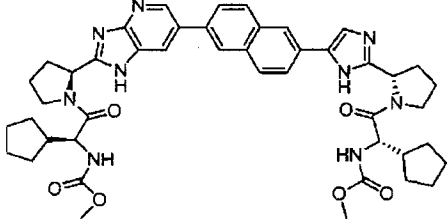
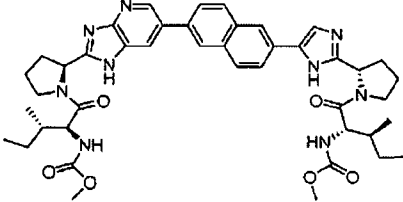
[1009]

化合物	结构
390	
391	
392	
393	
394	

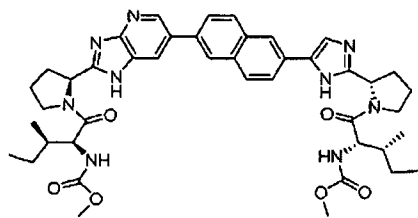
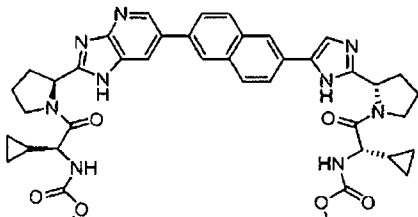
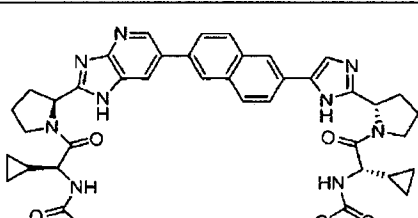
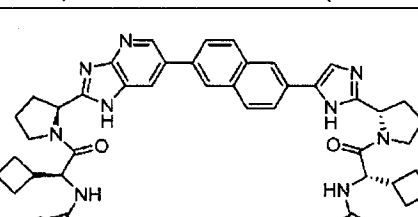
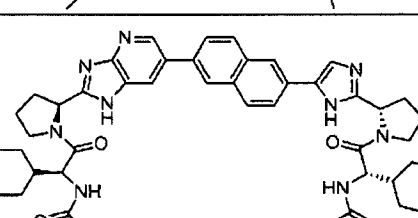
[1010]

化合物	结构
395	
396	
397	
398	
399	

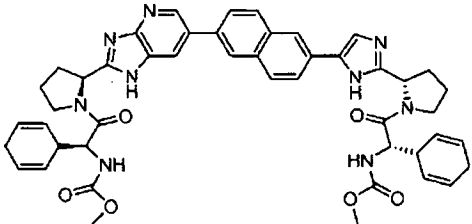
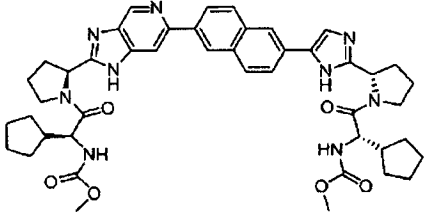
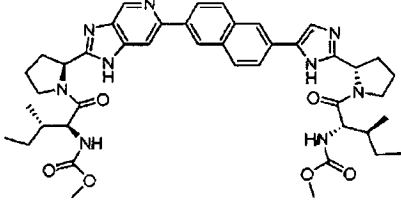
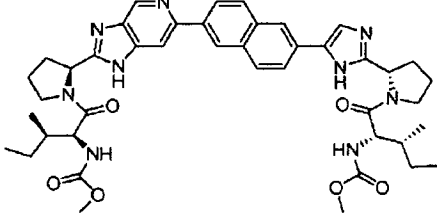
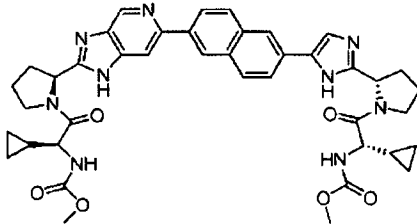
[1011]

化合物	结构
400	
401	
402	
403	
404	

[1012]

化合物	结构
405	
406	
407	
408	
409	

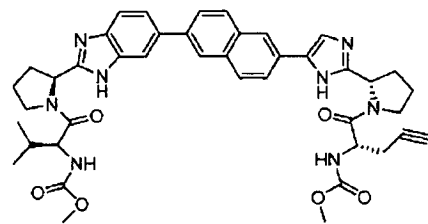
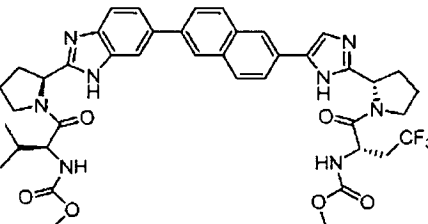
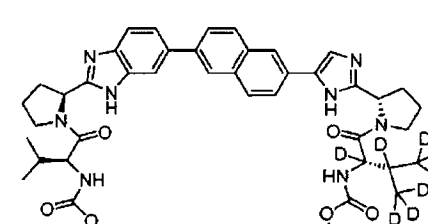
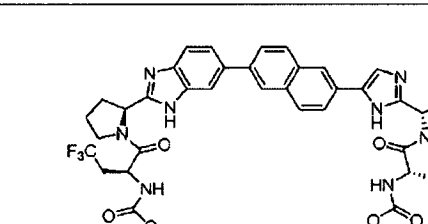
[1013]

化合物	结构
410	
411	
412	
413	
414	

[1014]

化合物	结构
415	
416	
417	
418	
419	

[1015]

化合物	结构
420	
421	
422	
423	
424	