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

(57) **Abrégé/Abstract:**
The invention is related to anti-viral compounds, compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

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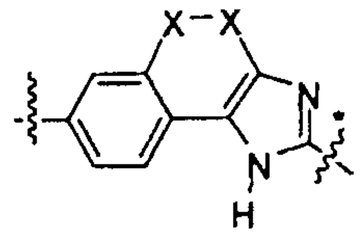
ABSTRACT

The invention is related to anti-viral compounds, compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

In one embodiment the invention provides a compound of formula (Ib20)-(Ib23) wherein L^4 is:



wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; and wherein * designates the site of connection to P.

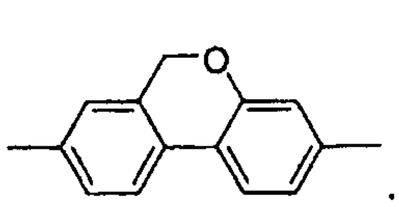
In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ib24):

$$E^0\text{-}V^w\text{-}Z^0\text{-}P^u\text{-}M^0\text{-}A^s\text{-}L^4\text{-}P^{u2}\text{-}Z^0\text{-}V^w\text{-}E^0 \quad \text{(Ib24)}$$

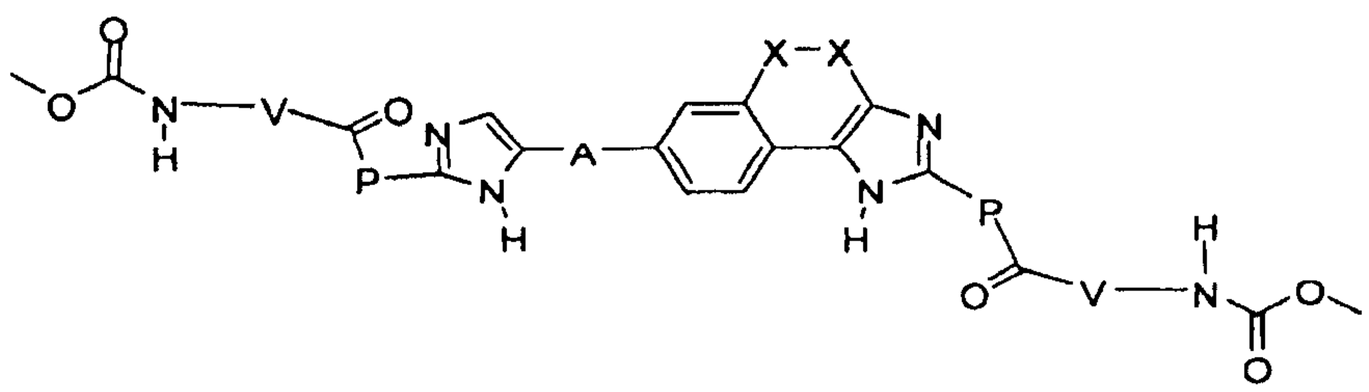
wherein:

each u is independently 0, 1, 3, 5, 7, 8, 10, or 11; each u2 is independently 0, 1, 3, 5, 7, 8, 10, or 11; each w is independently 0, 1, 2, 3, 4, or 5; and s is 5, 6, 13, 14, 15, or 16.

In one embodiment the invention provides a compound of formula (Ib24) wherein s is 16 and A^{16} is:

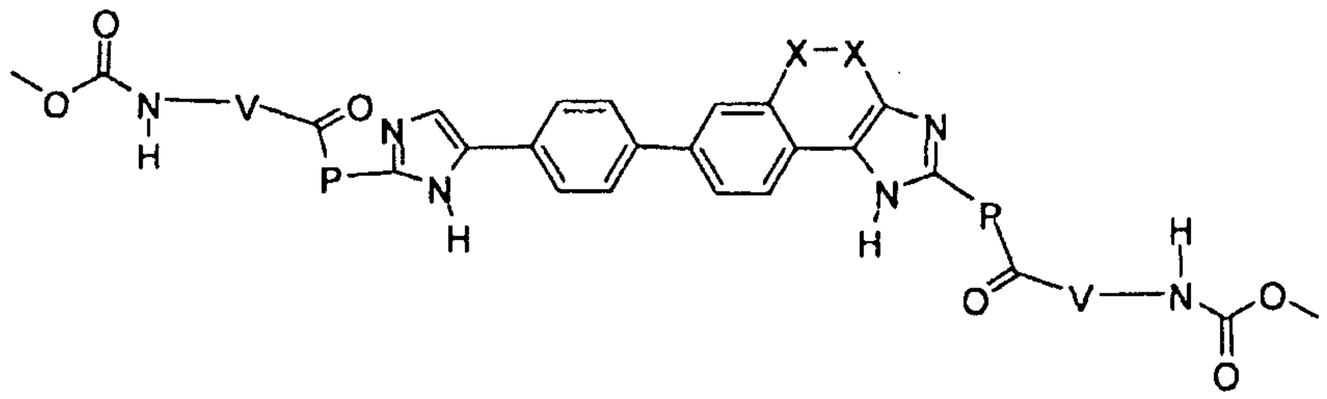


In one embodiment the invention provides a compound of formula:



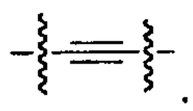
wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; and A is A^0; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula:

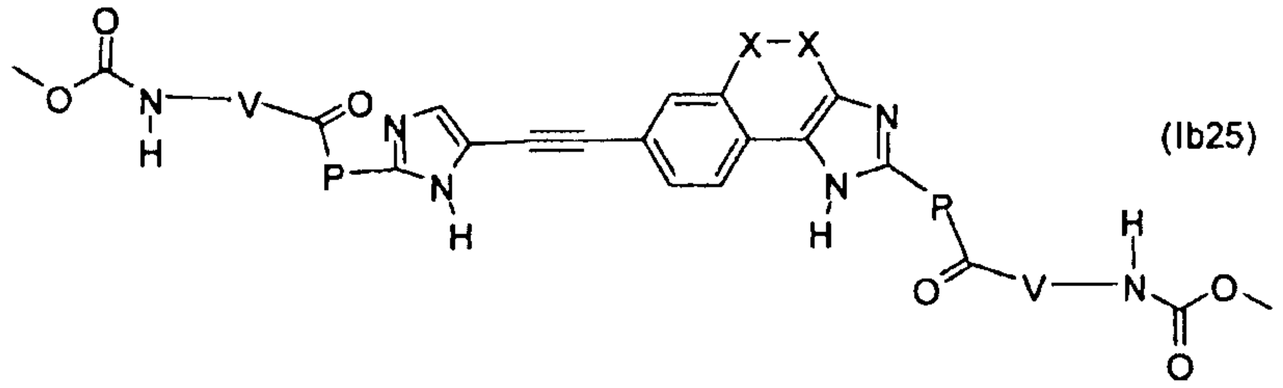


wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ib24) wherein s is 6 and A^6 is:



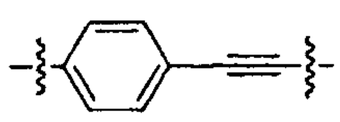
In one embodiment the invention provides a compound of formula (Ib25):



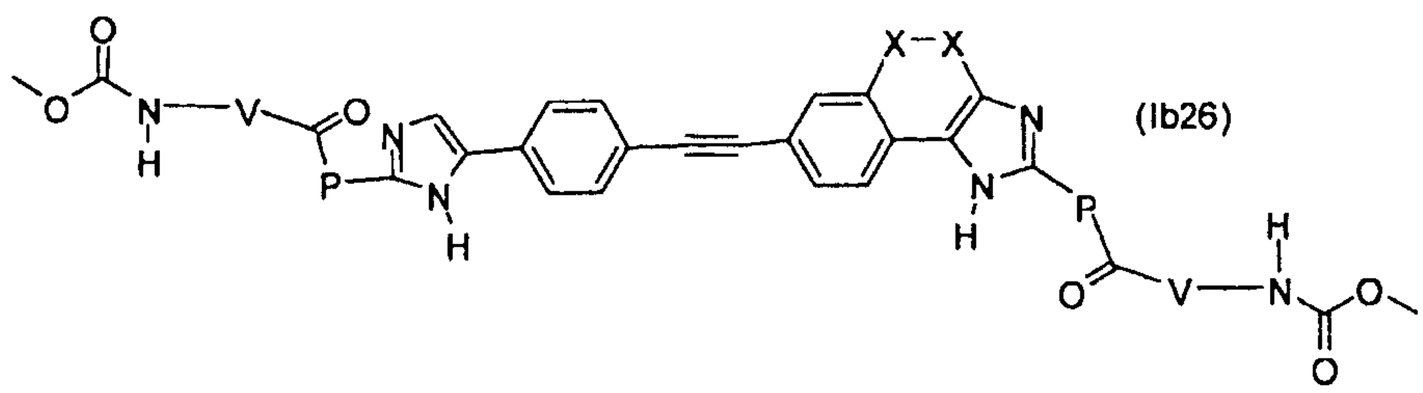
(Ib25)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ib24) wherein s is 5 and A^5 is:



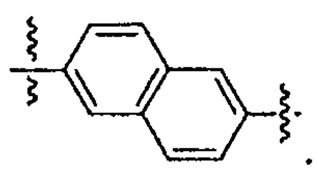
In one embodiment the invention provides a compound of formula (Ib26):



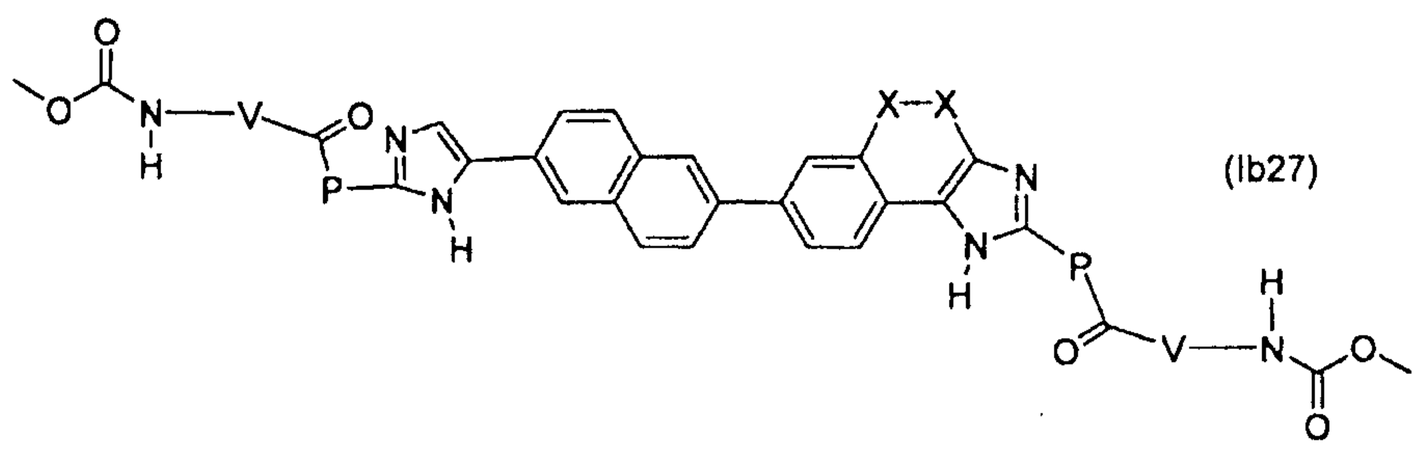
(Ib26)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ib24) wherein s is 13 and A^{13} is:



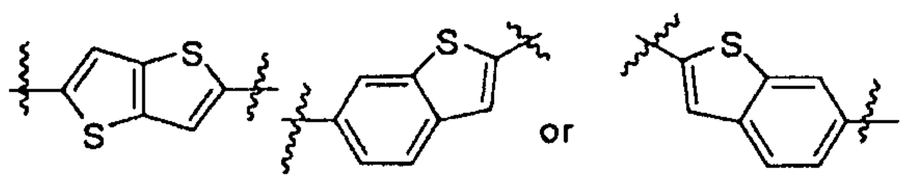
In one embodiment the invention provides a compound of formula (Ib27):



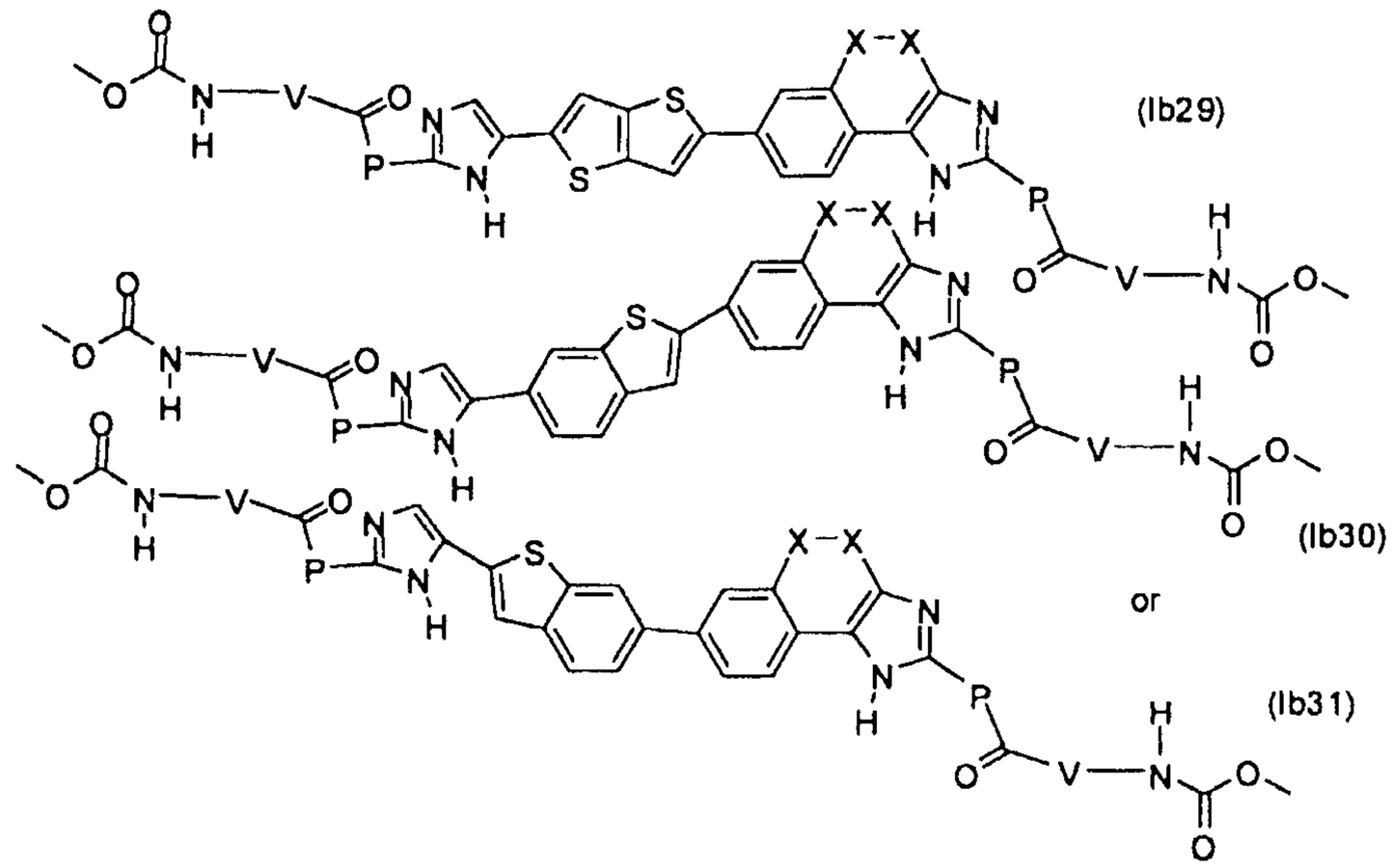
(Ib27)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ib24) wherein s is 14 and A^{14} is:



In one embodiment the invention provides a compound of formula:



(Ib29)

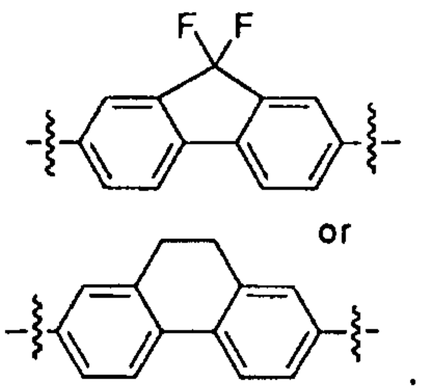
(Ib30)

or

(Ib31)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

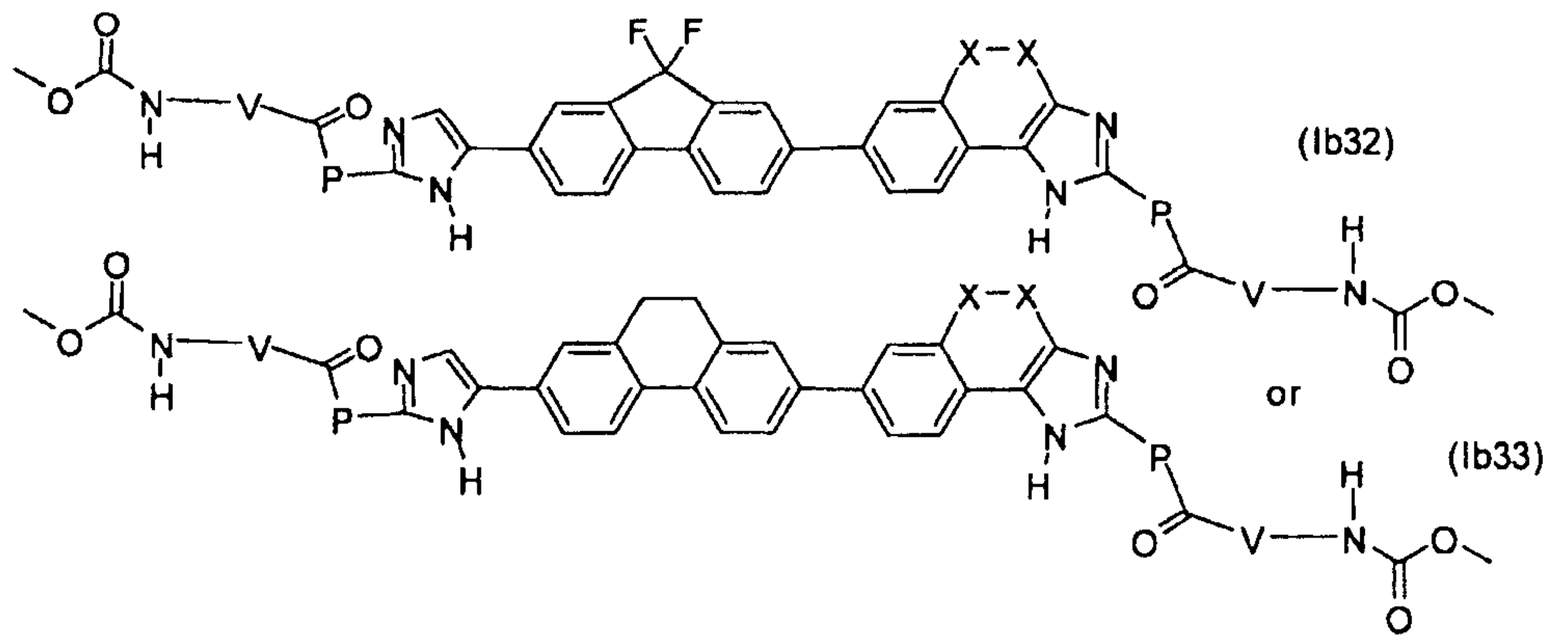
In one embodiment the invention provides a compound of formula (Ib24) wherein s is 15 and A^{15} is:



or

.

In one embodiment the invention provides a compound of formula:



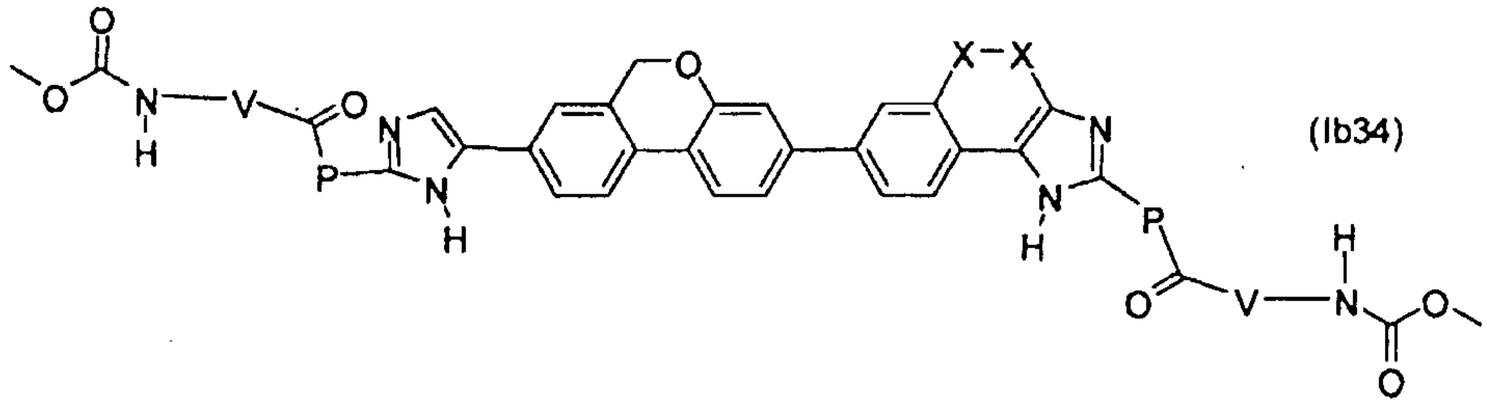
(Ib32)

or

(Ib33)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ib34):



(Ib34)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M-A^{15}-L-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M-A^{15}-L^3-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M^0-A^{15}-L^3-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M-A^{16}-L-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M-A^{16}-L^3-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M^0-A^{16}-L^3-P-Z-R9.

In another specific embodiment of the invention the compound of formula (Ib) is a compound of formula: R9-Z-P-M^9-A^{16}-L^3-P-Z-R9.

In another specific embodiment the invention provides a compound of the following formula (Ib50): E^x-V^w-Z^v-P^u-M^t-A^s-L^n -P^u-Z^v-V^w-E^x (Ib50) wherein the sum of t, s, n, u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least four of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein the sum of n, t, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein the sum of s, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein s, and at least one t, and at least one u are all not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of u, w and t are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of s, u, and w are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of s, u, and w are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least s and both u are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least one of u, or w is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of u are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein at least two of w are not zero.

In another specific embodiment the invention provides a compound of formula (Ib50) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 0 or 10; n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and s is 0, 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 0 or 10; n is 0, 1, 2, 4, 5, 6, 7, 8, 9, or 10; and s is 0, 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 9; n is 3; and s is 3, 4, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 0, 1, 2, 4, 5, 6, 7, 8, 9, 10, or 11; n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and s is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 0; n is 0, 1, 2, 3, 5, 6, 7, 8, 9, or 10; and s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 20.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein t is 1, 2, 4, 5, 6, 7, 8, 9, 10,or 11; n is 4; and s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least three of n, s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least four of n, s, t, u, v, w or x are not zero and at least four of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein the sum of n, t, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein the sum of s, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein s, and at least one t, and at least one u are all not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of u, w and t are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of s, u, and w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of s, u, and w are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least s and both u are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least one of u, or w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of u are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein at least two of w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib50) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the following formula (Ib51): E^x-V^w-Z^v-P^u-M^9-A^s-L^3 -P^u-Z^v-V^w-E^x (Ib51) wherein s is 0, 1, 2, 5, 6, or 7.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least two of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least three of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least four of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least two u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least three of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least three of u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least four of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein the sum of u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least one of u, or w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein both of u are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib51) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of the formula (lb51) wherein both w are not zero.

In another specific embodiment the invention provides a compound of the following formula (Ib52): E^x-V^w-Z^v-P^u-M^0-A^0-L^4 -P^u-Z^v-V^w-E^x (Ib52).

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least two of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least three of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least four of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least two u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least three of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least three of u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least four of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein the sum of u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least one of u, or w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ib52) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein both of u are not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of the formula (Ib52) wherein both w are not zero.

Compounds of formula (Ic)

In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ic):

E-V-Z-P-M-A-A-M-P-Z-V-E (Ic)

wherein:

each A is selected from $-A^5$;

each M is selected from $-M^t$;

each P is selected from $-P^u$;

each Z is selected from $-Z^v$;

each V is selected from $-V^w$;

each E is selected from $-E^x$;

each s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21;

each t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, or 14;

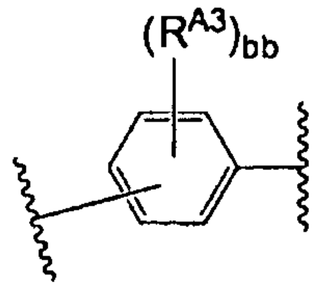
each v is 0, 1, 2, 3, 4, 5, or 6;

each w is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21;

each x is 0 or 1;

wherein the sum of s, t, u, v, w, and x is not 0;

each A^0 is independently:



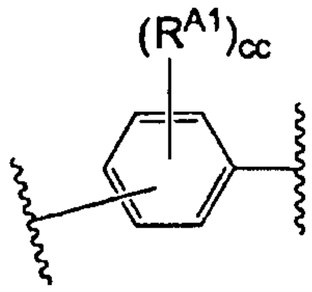
wherein:

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

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

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

each A^1 is independently:



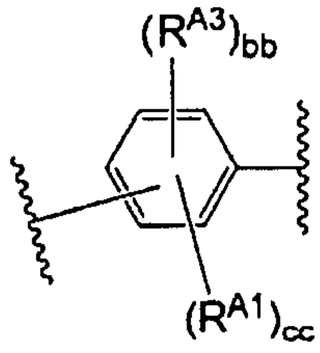
wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

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

each A^2 is independently:



wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group

consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

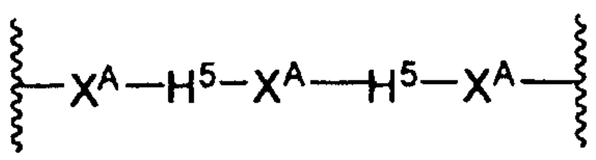
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

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

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

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

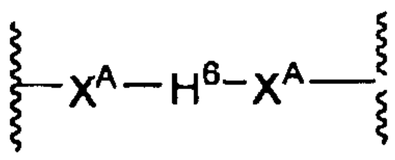
each A^4 is independently:



wherein:

each H^5 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^5 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent

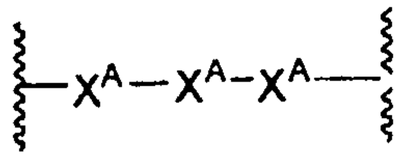
each A^5 is independently:



wherein:

each H^6 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^6 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; provided that at least one X^A is present;

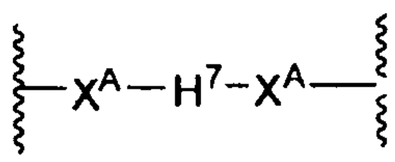
each A^6 is independently:



wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, allenyl, alkynyl, or absent; provided that at least one X^A is present;

each A^7 is independently:

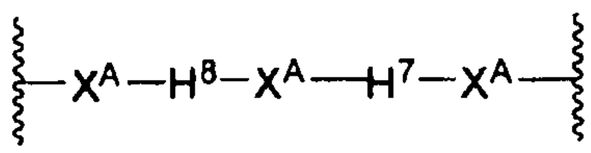


wherein:

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

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^8 is independently:



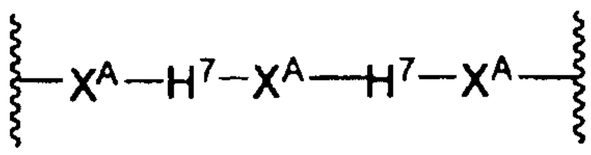
wherein:

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

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^9 is independently:

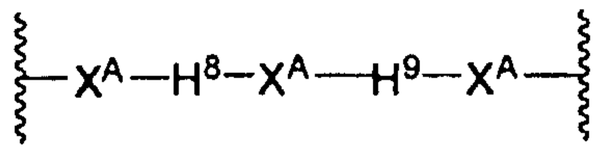


wherein:

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

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{10} is independently:



wherein:

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^9 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent

each A^{11} is independently:

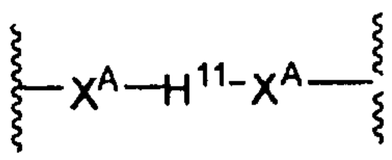
wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each H^{10} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that is optionally fused to an aryl, which H^{10} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{12} is independently:



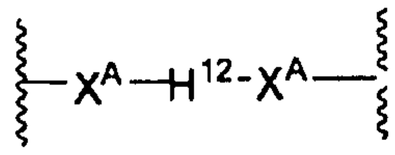
wherein:

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each H^{11} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms that is optionally fused to an aryl, which H^{11} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{13} is independently:

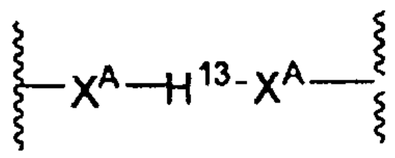


wherein:

each H^{12} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{14} is independently:

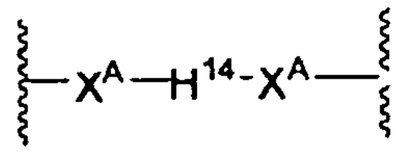


wherein:

each H^{13} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{15} is independently:

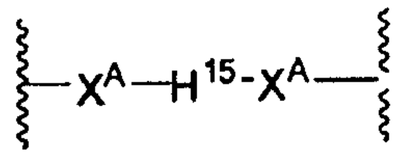


wherein:

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

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{16} is independently:

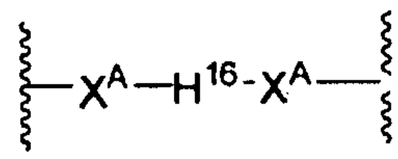


wherein:

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

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{17} is independently:



wherein:

each H^{16} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

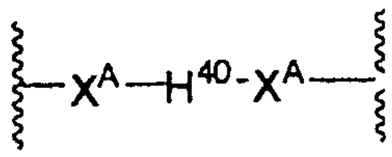
each A^{18} is independently:

wherein:

each H^{17} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each A^{21} is independently:



wherein:

each H^{40} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

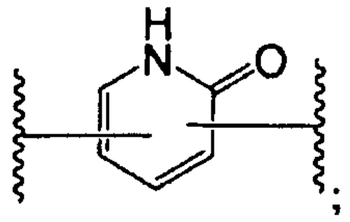
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent;

each M^0 is independently a five membered heteroaryl group optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl and trialkylsilylalkoxyalkyl;

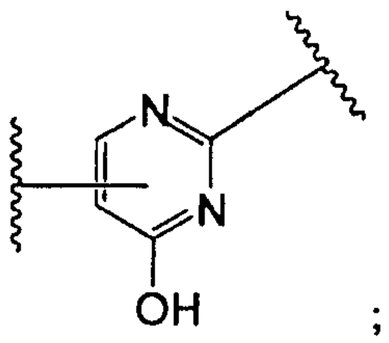
each M^1 is independently selected from –C(=O)NH-, –C(=O)NH-$C(R^M)_2$-, -NHC(=O) -, -$C(R^M)_2$NHC(=O)-, –NHC(=O)NR^M-, –NHC(=O)O -; wherein each R^M is independently selected from H and alkyl;

each M^2 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

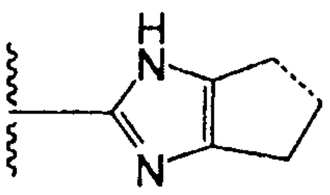
each M^3 is independently:



each M^4 is independently:



each M^5 is independently:



wherein the bond designated with --- is fused to a ring defined for P;

each M^6 is independently a bicyclic bridged ring system comprising 5-15 atoms wherein at least one of the atoms is a heteroatom;

each M^7 is independently a pyrid-di-yl;

each M^8 is independently partially saturated or a saturated five-membered ring that comprises one or more heteroatoms and that is optionally substituted with one or two oxo;

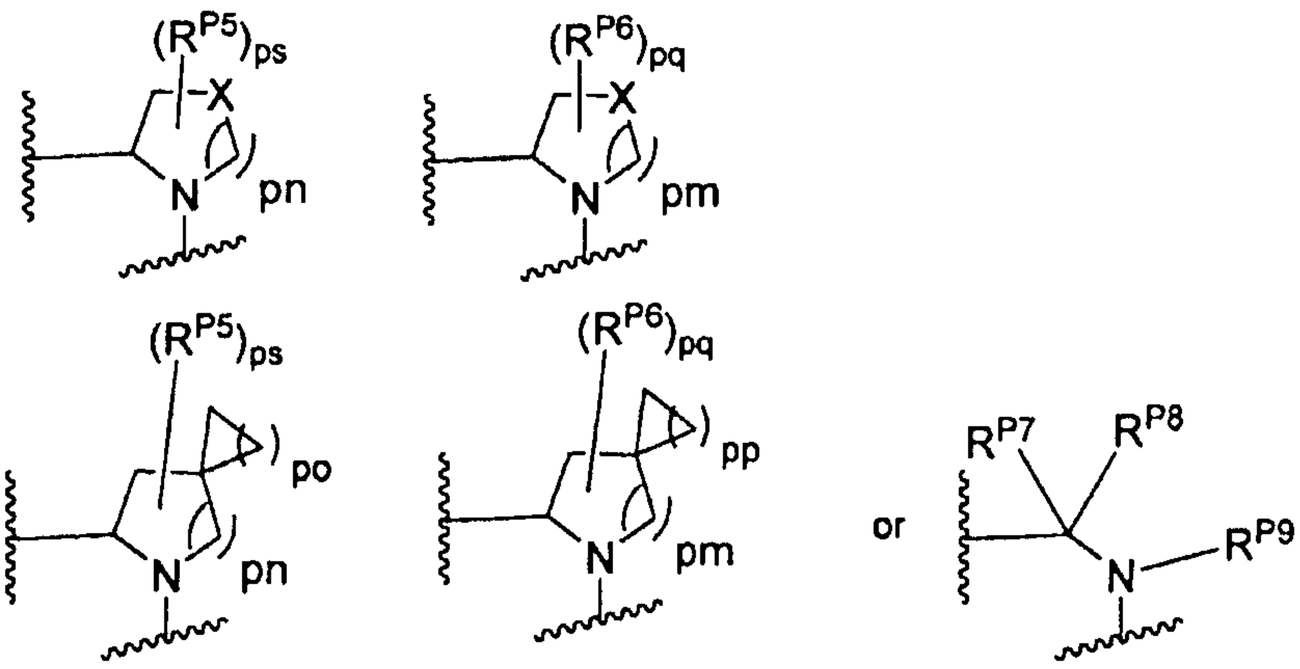
each M^9 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^{P11};

each M^{10} is independently a five membered heteroaryl group;

each M^{11} is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$;

each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each P^0 is independently:



wherein:

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

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

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

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

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

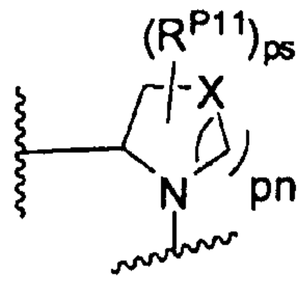
pm and pn are independently 0, 1, or 2;

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

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

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

each P^1 is independently:



wherein:

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

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

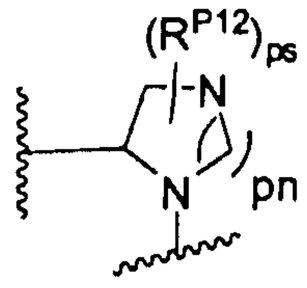
at least one R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy,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

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

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^2 is independently:



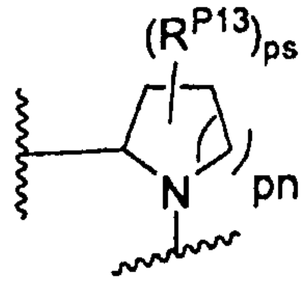
wherein:

each R^{P12} is independently selected from R^{P5}, R^{P11},-C(=O)OR^h, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

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



wherein:

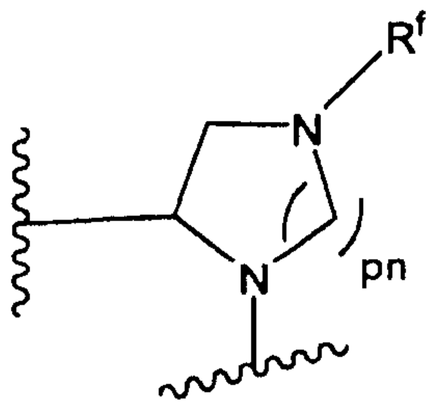
the ring is substituted with one or more oxo groups;

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

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

pn is 0, 1, or 2;

each P^4 is independently a ring of the formula:



wherein:

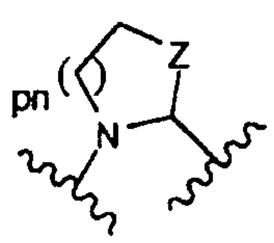
the ring is optionally substituted with one or more groups R^{P14} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P14} that are attached to the same carbon

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

pn is 0, 1, or 2;

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

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



wherein:

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

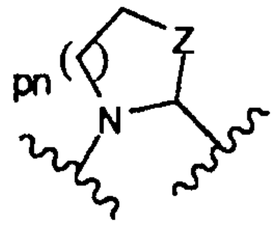
pn is 0, 1, or 2;

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

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

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

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



wherein:

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

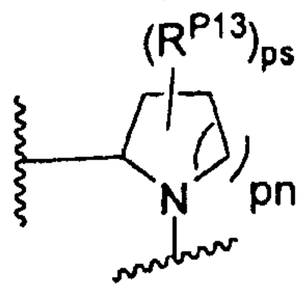
Z is O, S, S(=O), $S(=O)_2$, or NR^f;

pn is 0, 1, or 2;

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

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

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



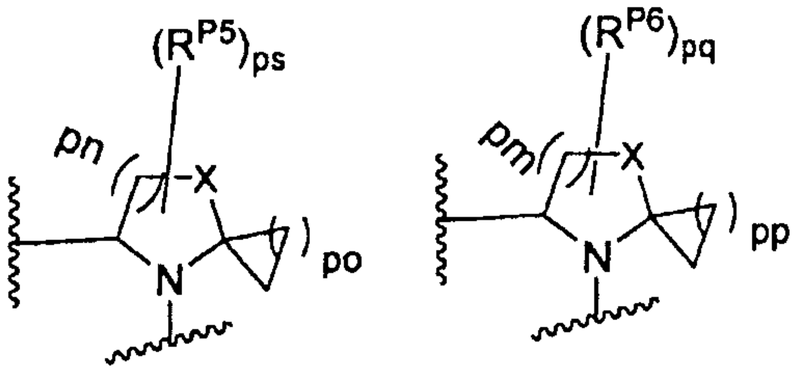
wherein:

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

pn is 0, 1 or 2;

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

each P^{10} is independently:



wherein:

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

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

each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused

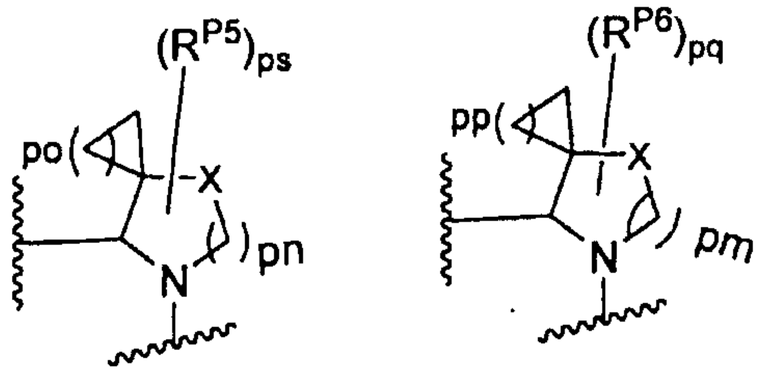
three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

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

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

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

each P^{11} is independently:



wherein:

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

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

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

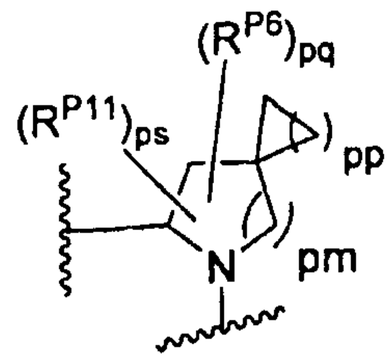
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{12} is independently:



wherein:

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

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

pm is independently 0, 1, or 2;

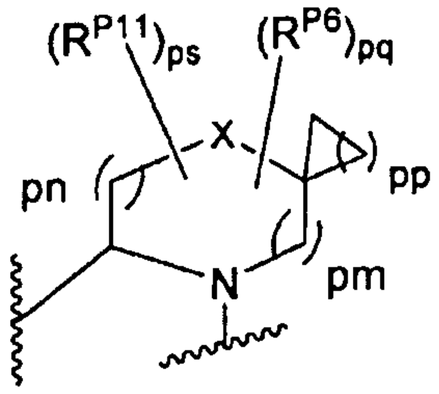
pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

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

each P^{13} is independently:



wherein:

X is selected from O, S, S(O), SO_2, or NR^h;

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

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

pm and pn are independently 0, 1, or 2 but the sum of pn and pm is greater than zero;

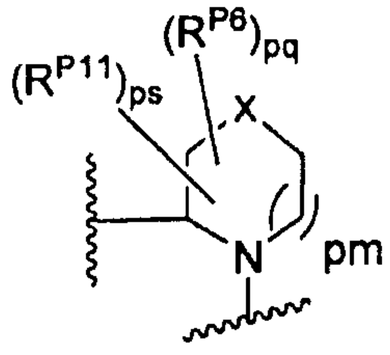
pp are independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

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

each P^{14} is independently:



wherein:

the ring is substituted with one or more oxo group;

X is NR^f;

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

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

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

pm is independently 0, 1, or 2;

ps is 1, 2, 3, or 4;

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

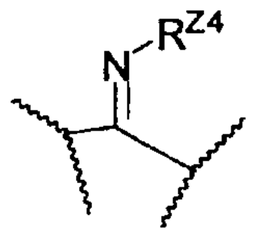
each $-Z^0-$ is –C(=O)- or –C(=S)-;

each $-Z^1-$ is independently a bond, or $-C(R^{Z1})_2-$; wherein each R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each $-Z^2-$ is independently saturated or partially unsaturated (C_3-C_8)cycloalkyl that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

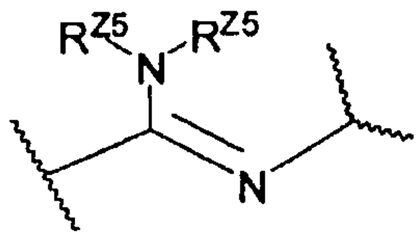
each $-Z^3-$ is independently saturated, partially unsaturated, or aromatic 4-8 membered heterocyclic or heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^4-$ is independently:



wherein each R^{Z4} is independently H, alkyl, cyano, aryl, or heteroaryl;

each $-Z^5-$ is independently:



wherein each R^{Z5} is independently H, alkyl, cyano, aryl, or heteroaryl; or two R^{Z5}s together with the nitrogen to which they are attached form a 4-8 membered heterocyclic ring that is optionally substituted with one or more oxo and with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^6-$ is independently $-C(R^{Z1})-$ and is doublebonded to P; wherein R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

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

each E^1 is independently $-OC(=O)NR^{Ee}R^{Ef}$ wherein each R^{Ee} and R^{Ef} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl,

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

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

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

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and NRaRbC(=O)O-; Ra and Rb are each independently selected from hydrogen, alkenyl, and alkyl;

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^6 is independently arylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^7 is independently heterocyclosulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^8 is independently spirocycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^9 is independently spirocycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{10} is independently fusedbicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{11} is independently fusedbicycliccycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{12} is independently bridged-bicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{13} is independently bridged-bicyclic-cycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{14} is independently aryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{15} is independently arylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{16} is independently cycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{17} is independently cycloalkylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{18} is independently heterocyclooxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{19} is independently heterocycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{20} is independently heteroaryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl; and

each V^{21} is independently heteroarylalkylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl.

In another specific embodiment of the invention the compound of formula (Ic) comprises: M^0-A-A-M^0, M^0-A-A-M^9, M^9-A-A-M^0, or M^9-A-A-M^9, M^{10}-A-A-M^0, M^0-A-A-M^{10}, M^{10}-A-A-M^9, M^9-A-A-M^{10}, or M^{10}-A-A-M^{10}.

In another specific embodiment of the invention –A-A- is –A^0-A^5-.

In another specific embodiment of the invention –A-A- is –A^0-A^{13}-.

In another specific embodiment of the invention –A-A- is –A^{13}-A^{13}-.

In another specific embodiment of the invention –A-A- is –A^0-A^{11}-.

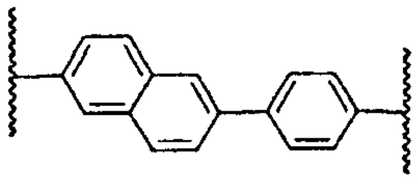
In another specific embodiment of the invention –A-A- is –A^{13}-A^6-.

In another specific embodiment of the invention one A is A^0 and one A is A^5, wherein one X^A in the A^5 is absent and the other X^A in the A^5 is alkynyl.

In another specific embodiment of the invention –A^0-A^5- has the following structure:

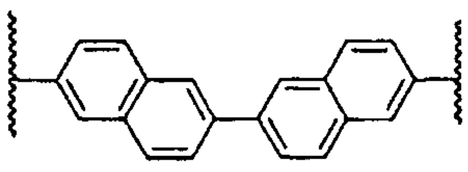
In another specific embodiment of the invention one A is A^0 and one A is A^{13}, wherein both X^A in the A^{13} are absent.

In another specific embodiment of the invention –A^0-A^{13}- has the following structure:



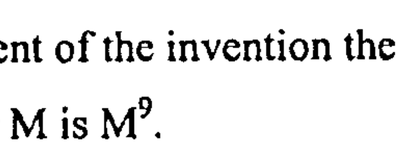
In another specific embodiment of the invention A-A is A^{13}- A^{13}, wherein all X^A in both A^{13} are absent.

In another specific embodiment of the invention –A^{13}-A^{13}- has the following structure:



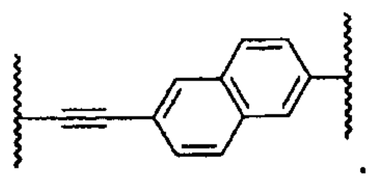
In another specific embodiment of the invention A-A- is A^0- A^{11} wherein all X^A in both the A^0 and the A^{11}, are absent or alkynyl.

In another specific embodiment of the invention $-A^0$-A^{11}- has the following structure:



In another specific embodiment of the invention the compound of formula (Ic) comprises one A^{13} and one A^6 wherein all X^A in the A^{13} are absent.

In another specific embodiment of the invention–A^{13}-A^6- has the following structure:

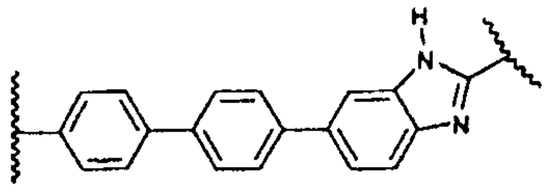


In another specific embodiment of the invention M^0 is imidazolyl and M^9 is benzimidazolyl.

In another specific embodiment of the invention the compound of formula (Ic) comprises two A^0 and one M is M^9.

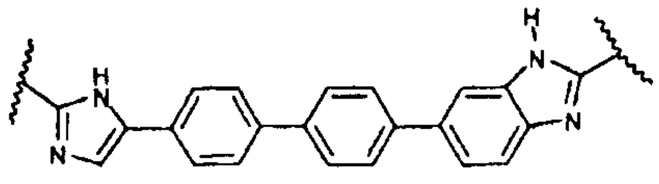
In another specific embodiment of the invention the compound of formula (Ic) comprises two A^0 and one M is M^0 and another M is M^9.

In another specific embodiment of the invention the compound of formula (Ic) comprises A^0-A^0-M^9 which has the following structure:



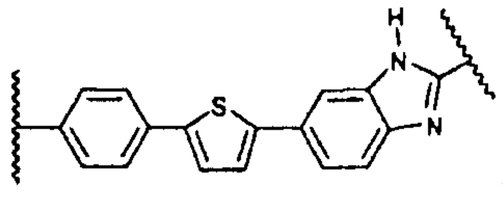
In another specific embodiment of the invention the compound of formula (Ic) comprises M^0-A^0-A^0-M^9.

In another specific embodiment of the invention M^0-A^0-A^0-M^9 has the following structure:



In another specific embodiment of the invention the compound of formula (Ic) comprises A^0-A^7-M^9.

In another specific embodiment of the invention A^0-A^7-M^9 has the following structure:



In another specific embodiment of the invention the compound of formula (Ic) comprises one or two M and each M is M^0.

In another specific embodiment of the invention the compound of formula (Ic) comprises one or two M and each M is imidazolyl.

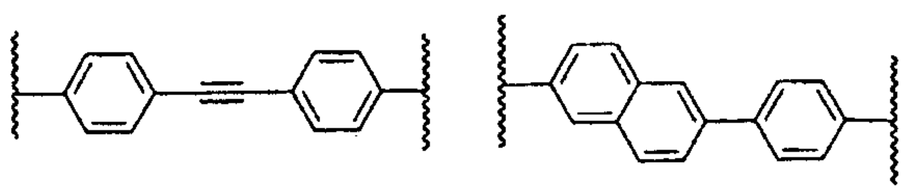
In another specific embodiment of the invention the compound of formula (Ic) comprises one or two M and each M is M^9.

In another specific embodiment of the invention the compound of formula (Ic) comprises one or two M and each M is benzimidazolyl.

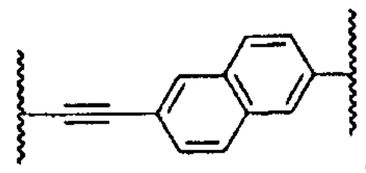
In another specific embodiment of the invention the compound of formula (Ic) comprises two M wherein one M is M^0 and one M is M^9.

In another specific embodiment of the invention the compound of formula (Ic) comprises two M wherein one M is imidazolyl and one M is benzimidazolyl.

In another specific embodiment of the invention A-A is selected from:



and



In another specific embodiment of the invention –M-A-A-M- is selected from M^0-A-A-M^0, M^0-A-A-M^9, M^9-A-A-M^0, and M^9-A-A-M^9.

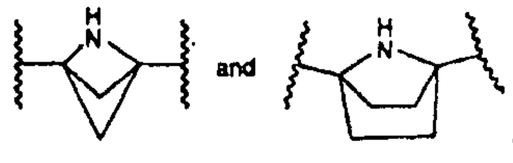
In another specific embodiment of the invention the compound of formula (Ic) M-A-A-M is selected from M^{10}-A-A-M^0, M^0-A-A-M^{10}, M^{10}-A-A-M^9, M^9-A-A-M^{10}, and M^{10}-A-A-M^{10}.

In another specific embodiment of the invention each M is independently a 5-membered heteroaryl ring.

In another specific embodiment of the invention each M is 2,4-imidazoldiyl.

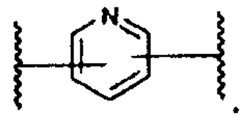
In another specific embodiment of the invention M is M^6.

In another specific embodiment of the invention M is selected from:



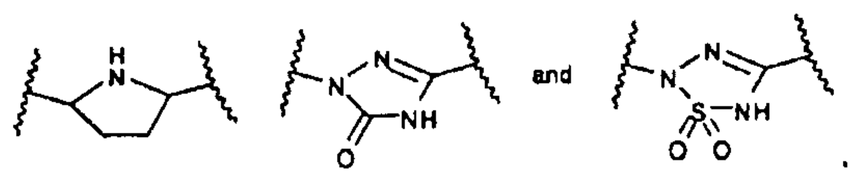
In another specific embodiment of the invention M is M^7.

In another specific embodiment of the invention M is:

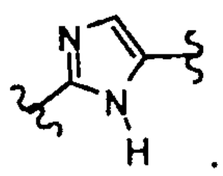


In another specific embodiment of the invention M is M^8.

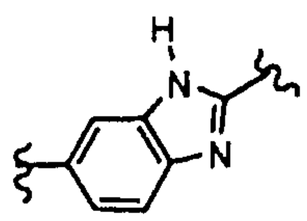
In another specific embodiment of the invention M is selected from the group consisting of:



In another specific embodiment of the invention M^0 is:



In another specific embodiment of the invention M is M^9 which is:



In another specific embodiment of the invention the sum of s, t, u, v, w, and x is not 0;

In another specific embodiment of the invention at least two of s, t, u, v, w, and x are other than 0.

In another specific embodiment of the invention at least three of s, t, u, v, w, and x are other than 0.

In another specific embodiment of the invention at least four of s, t, u, v, w, and x are other than 0.

In another specific embodiment of the invention at least five of s, t, u, v, w, and x are other than 0.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic1): E^0-V^0-Z^0-P-M^0-A^{13}-A^6-M-P-Z^0-V^0-E^0 (Ic1) or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic2): E^0-V^0-Z^0-P-M^9-A^{13}-A^6-M-P-Z^0-V^0-E^0 (Ic2) or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic3): E^0-V^0-Z^0-P-M^{10}-A^{13}-A^6-M-P-Z^0-V^0-E^0 (Ic3) or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic4): E^0-V^0-Z^0-P-M^{11}-A^{13}-A^6-M-P-Z^0-V^0-E^0 (Ic4) or a pharmaceutically acceptable salt, or prodrug thereof.

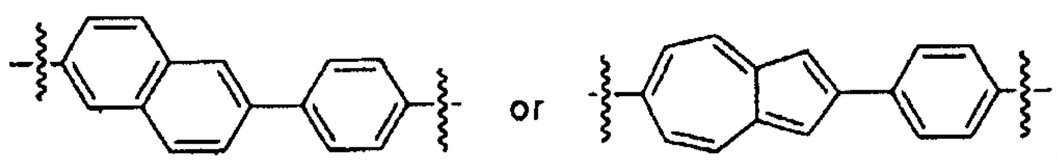
In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic5): E^0-V^0-Z^0-P-M^0-A^{13}-A^0-M-P-Z^0-V^0-E^0 (Ic5) or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic6): E^0-V^0-Z^0-P-M^9-A^{13}-A^0-M-P-Z^0-V^0-E^0 (Ic6) or a pharmaceutically acceptable salt, or prodrug thereof.

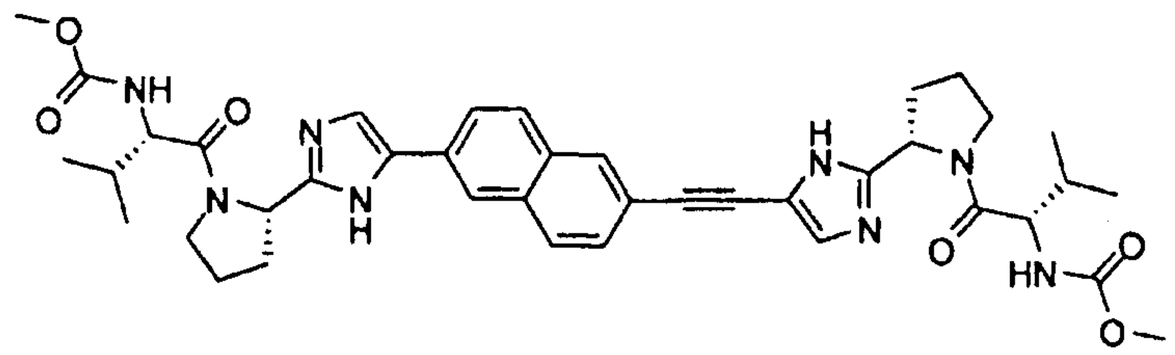
In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic7): E^0-V^0-Z^0-P-M^{10}-A^{13}-A^0-M-P-Z^0-V^0-E^0 (Ic7) or a pharmaceutically acceptable salt, or prodrug thereof.

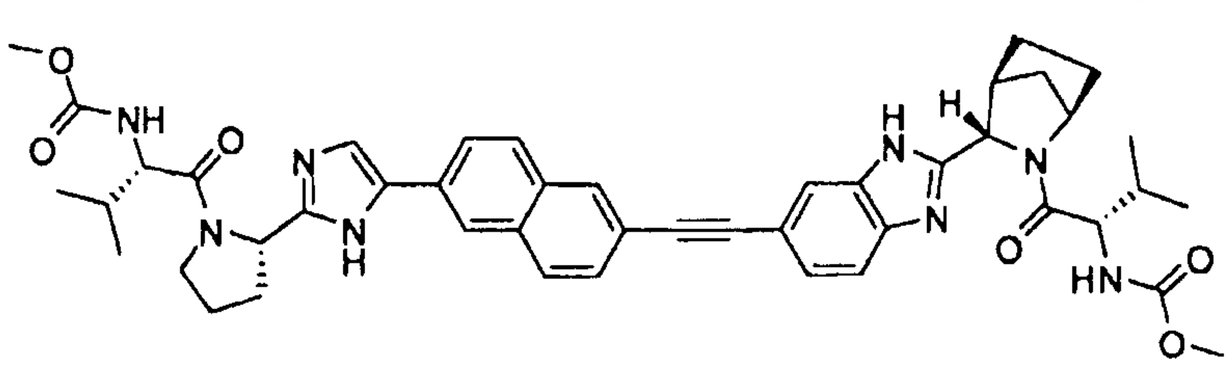
In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic8): E^0-V^0-Z^0-P-M^{11}-A^{13}-A^0-M-P-Z^0-V^0-E^0 (Ic8) or a pharmaceutically acceptable salt, or prodrug thereof.

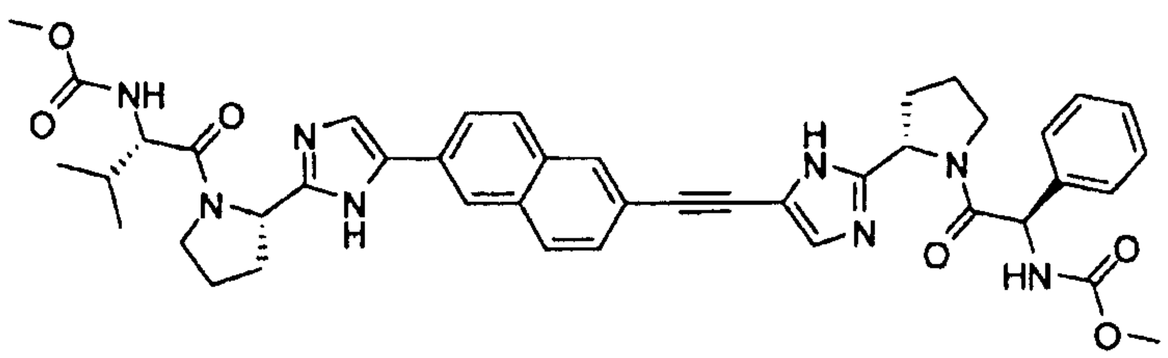
In another specific embodiment of the invention A^{13}-A^0 is:

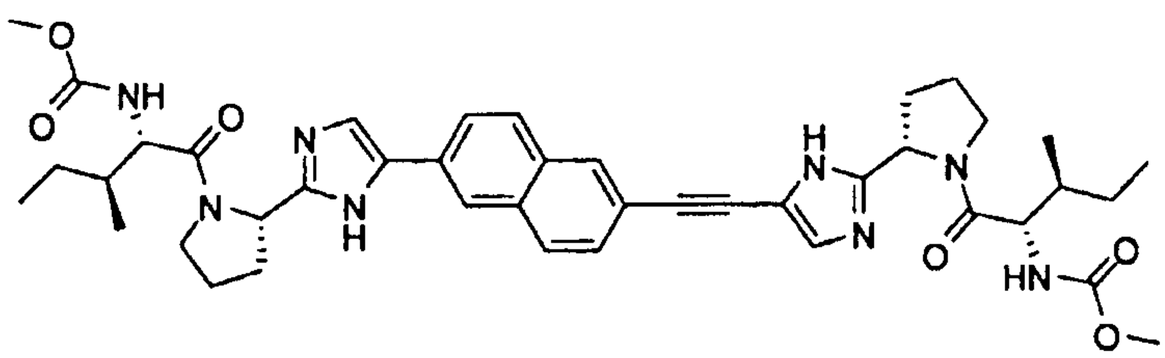


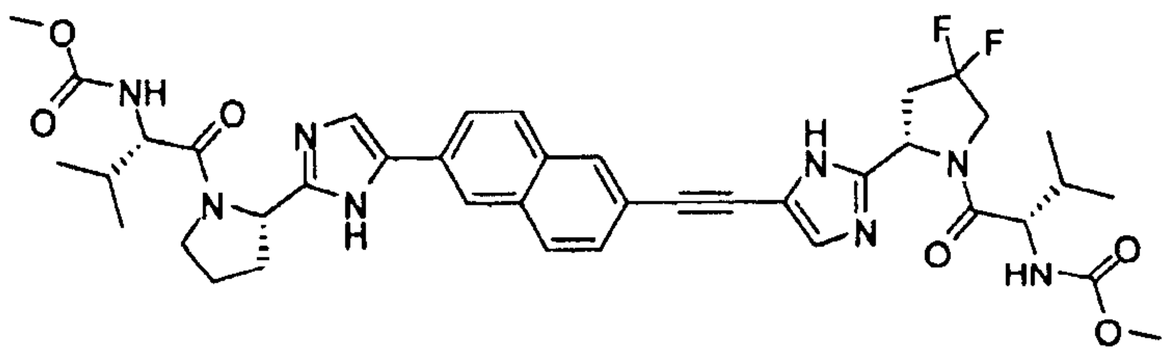
In another specific embodiment of the invention the compound of formula (Ic) is:

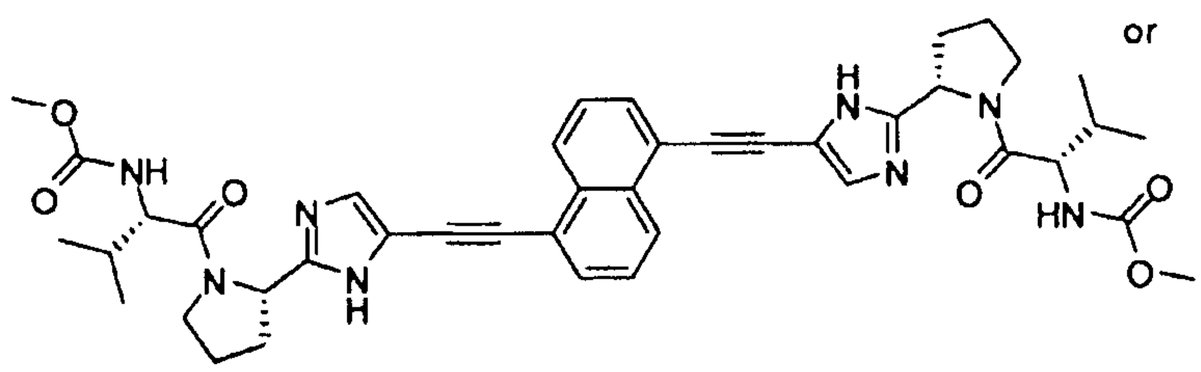






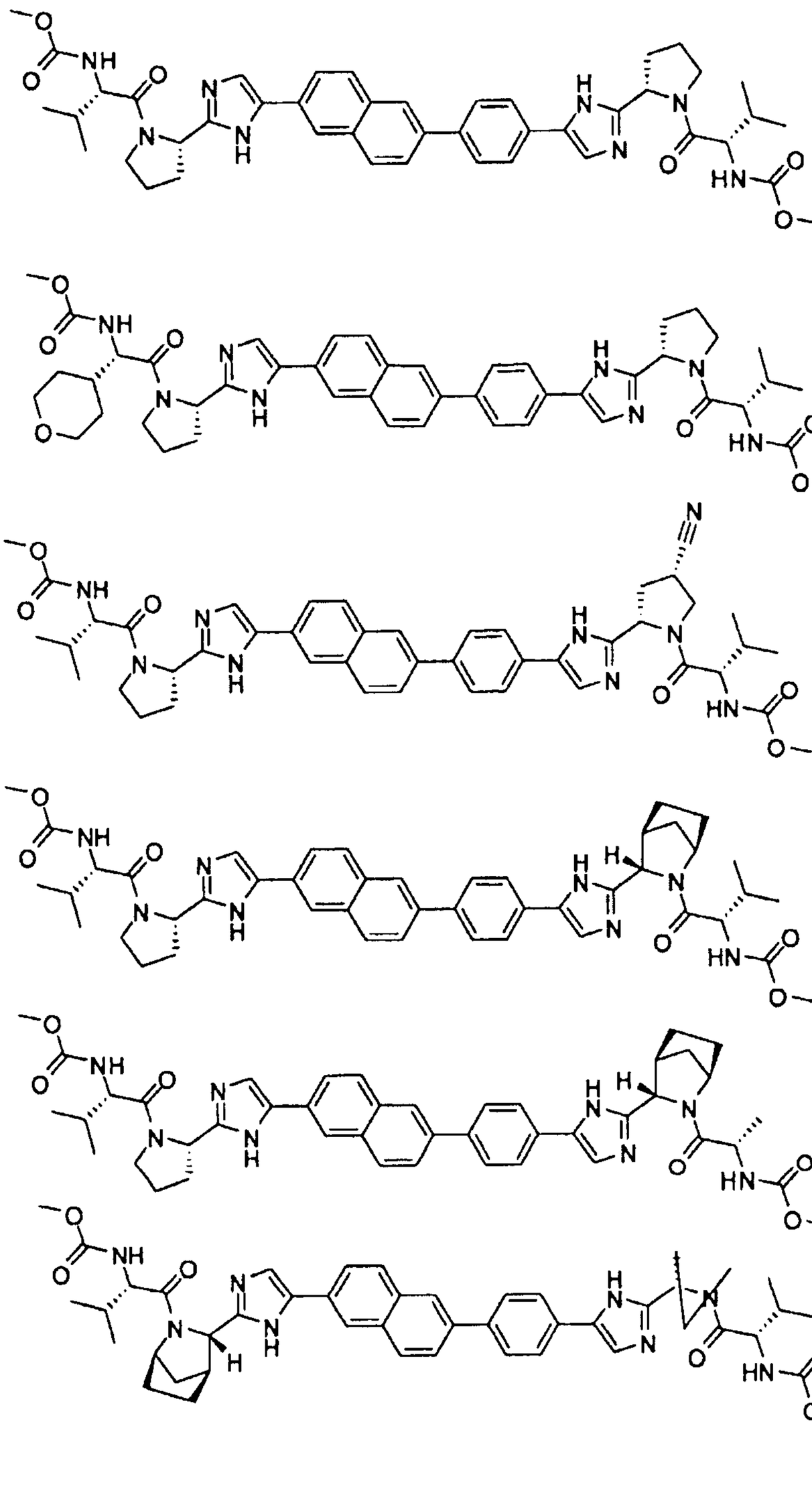


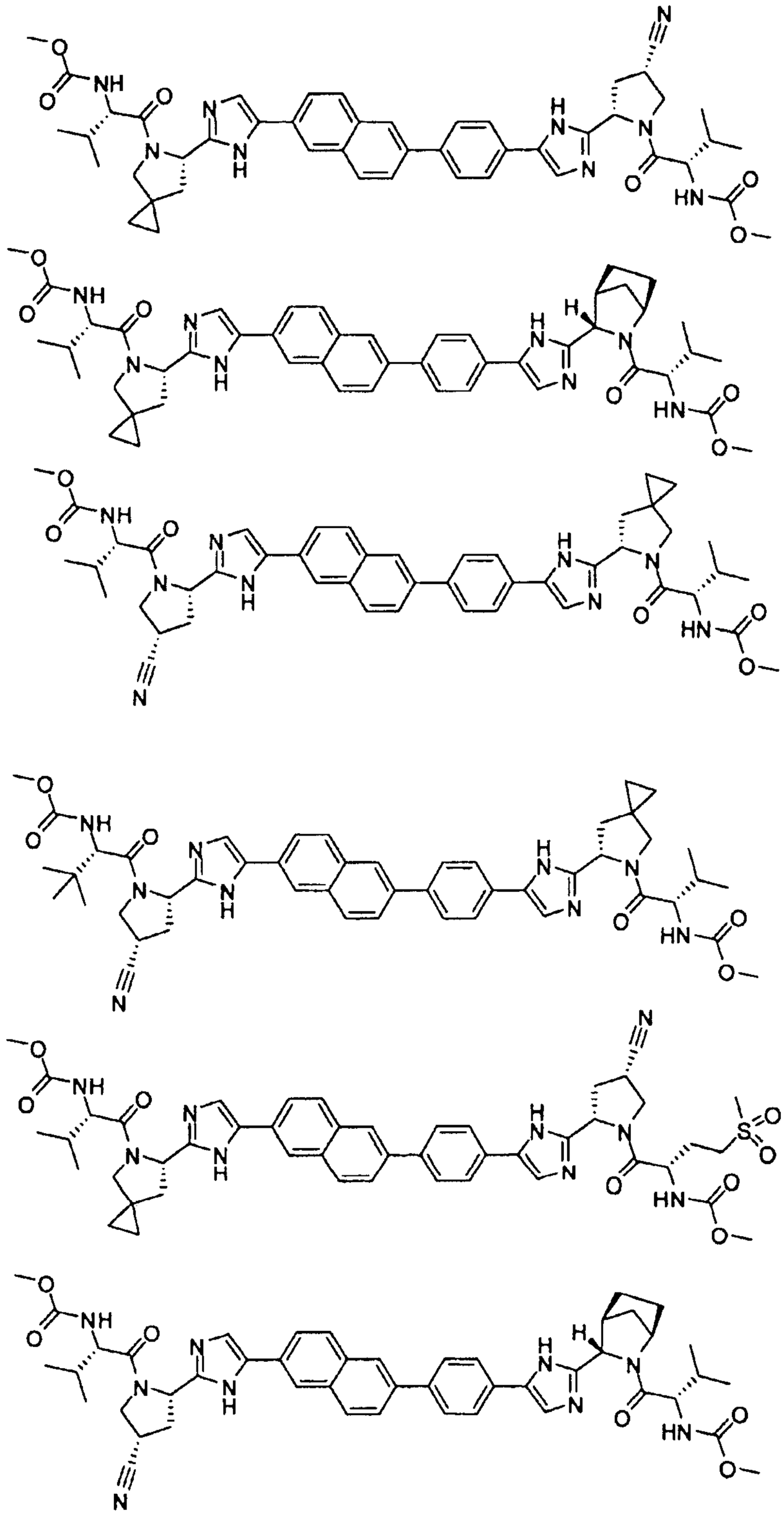


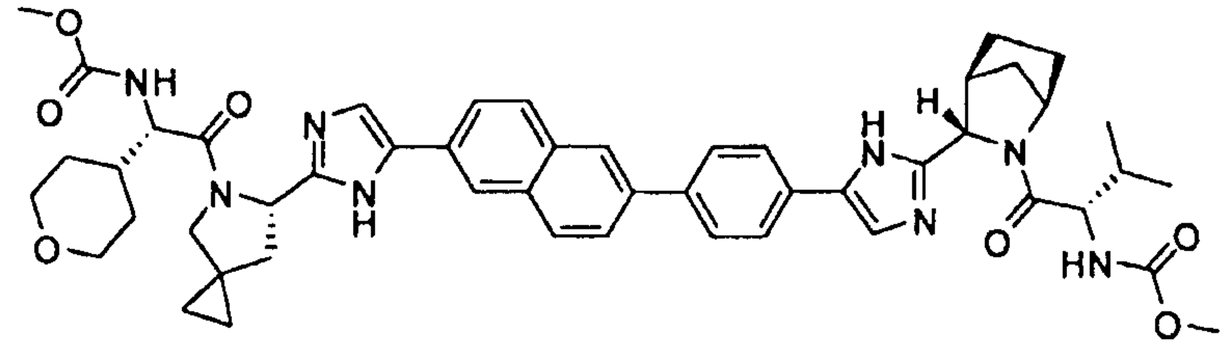


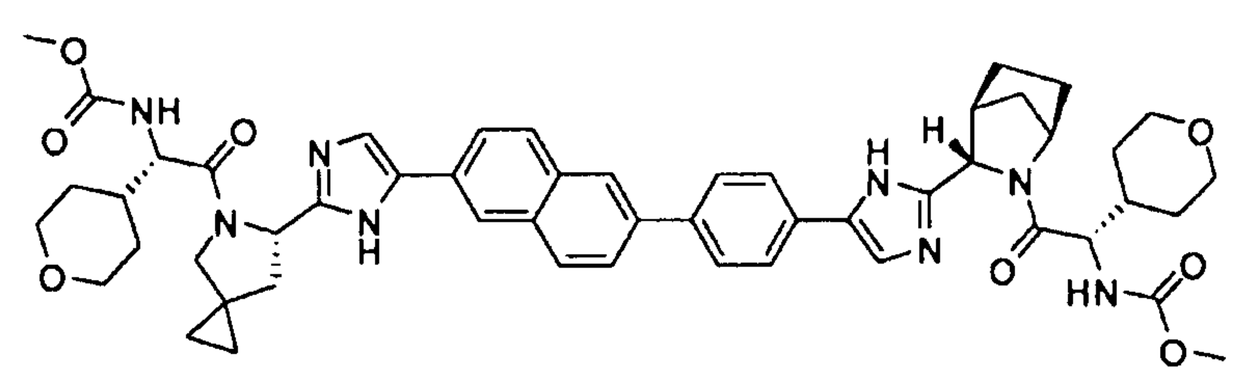
or a pharmaceutically acceptable salt, or prodrug thereof.

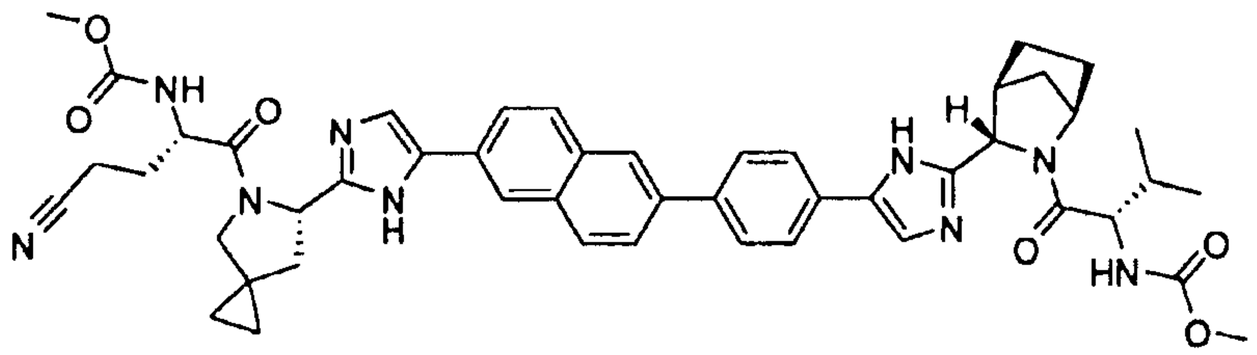
In another specific embodiment of the invention the compound of formula (Ic) is:

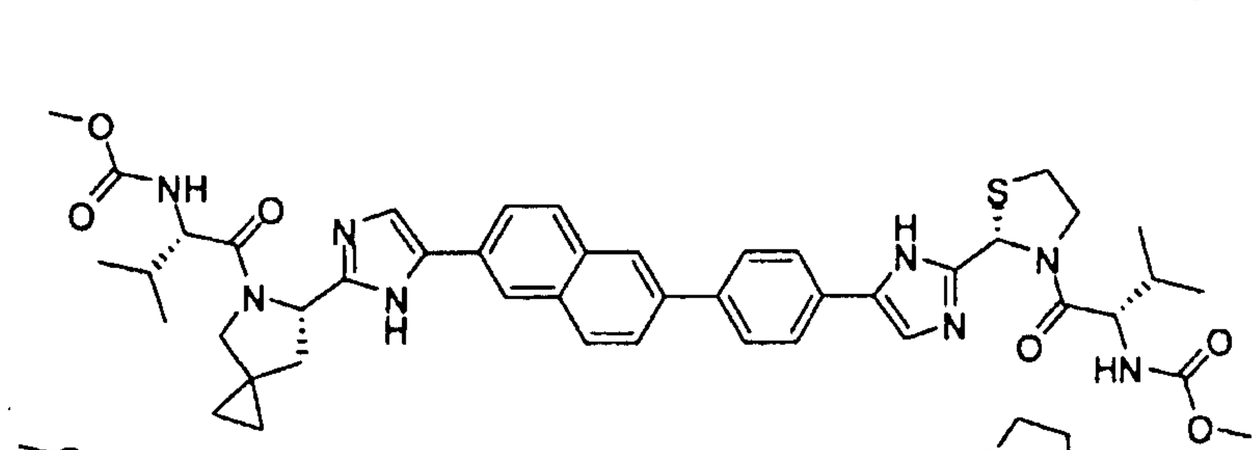


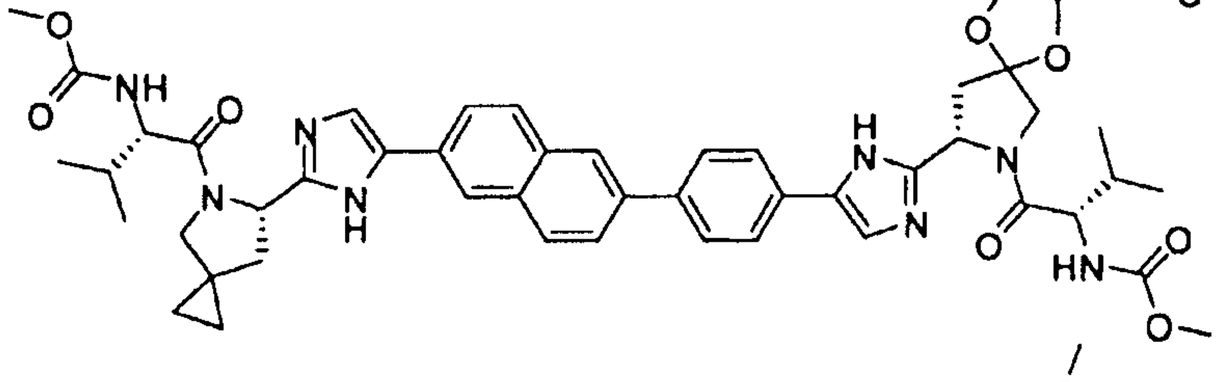


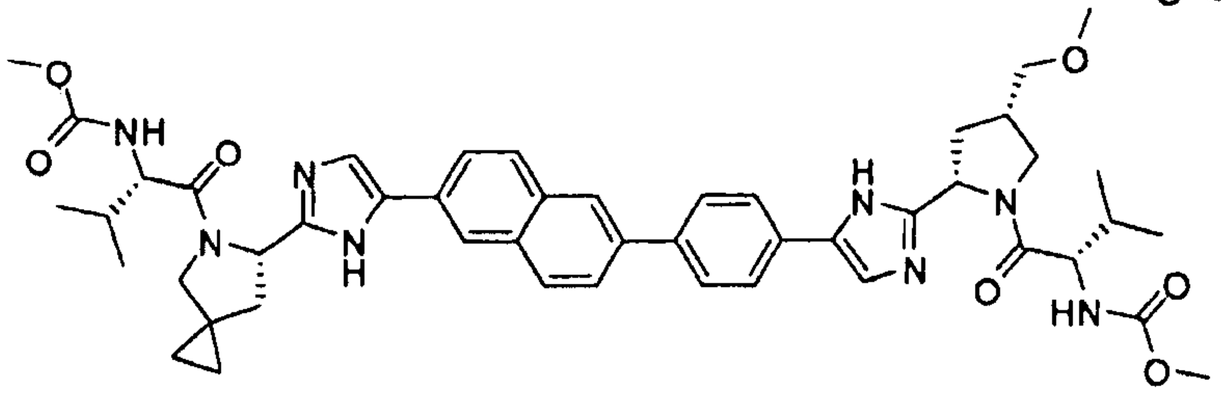


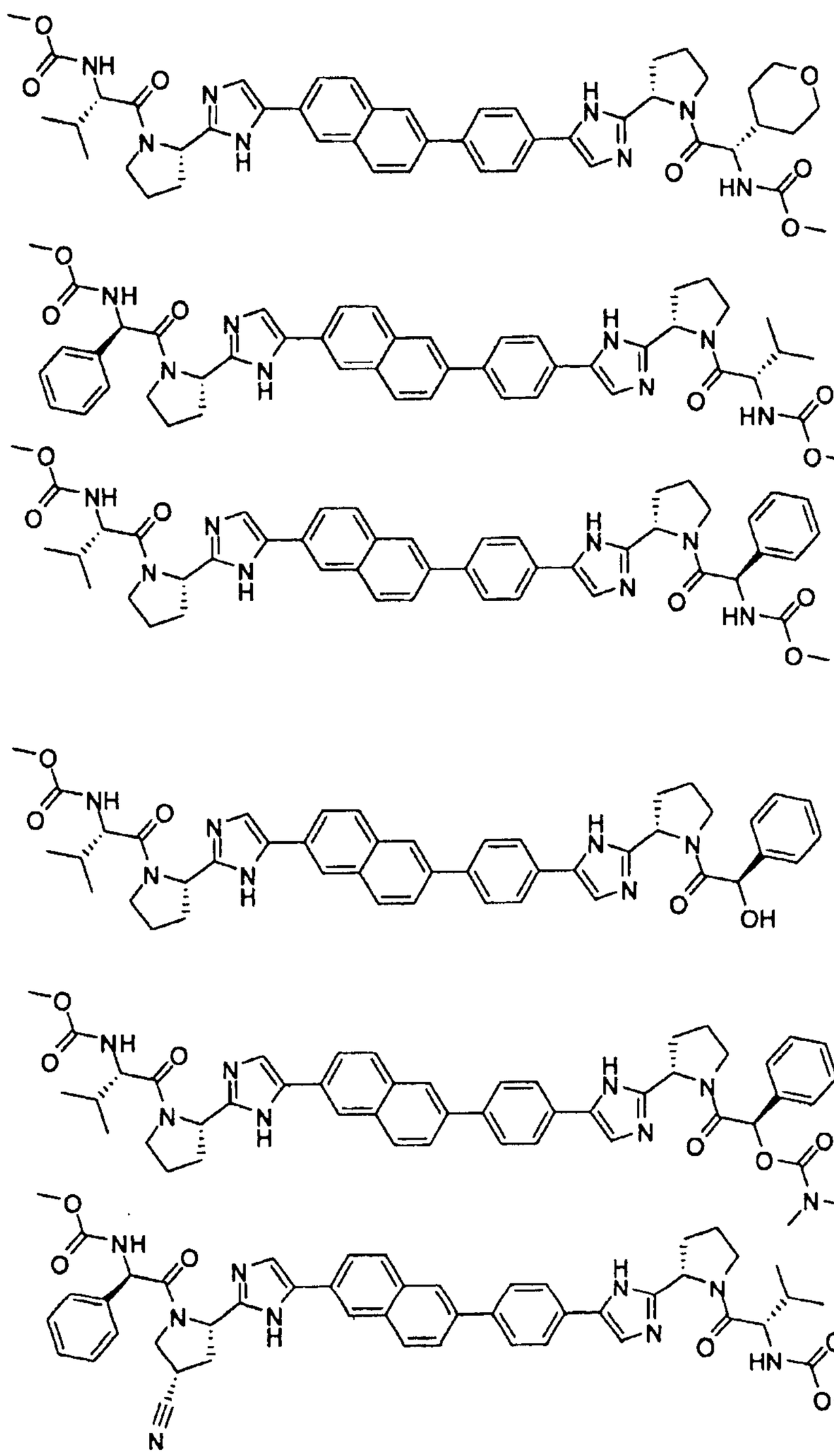


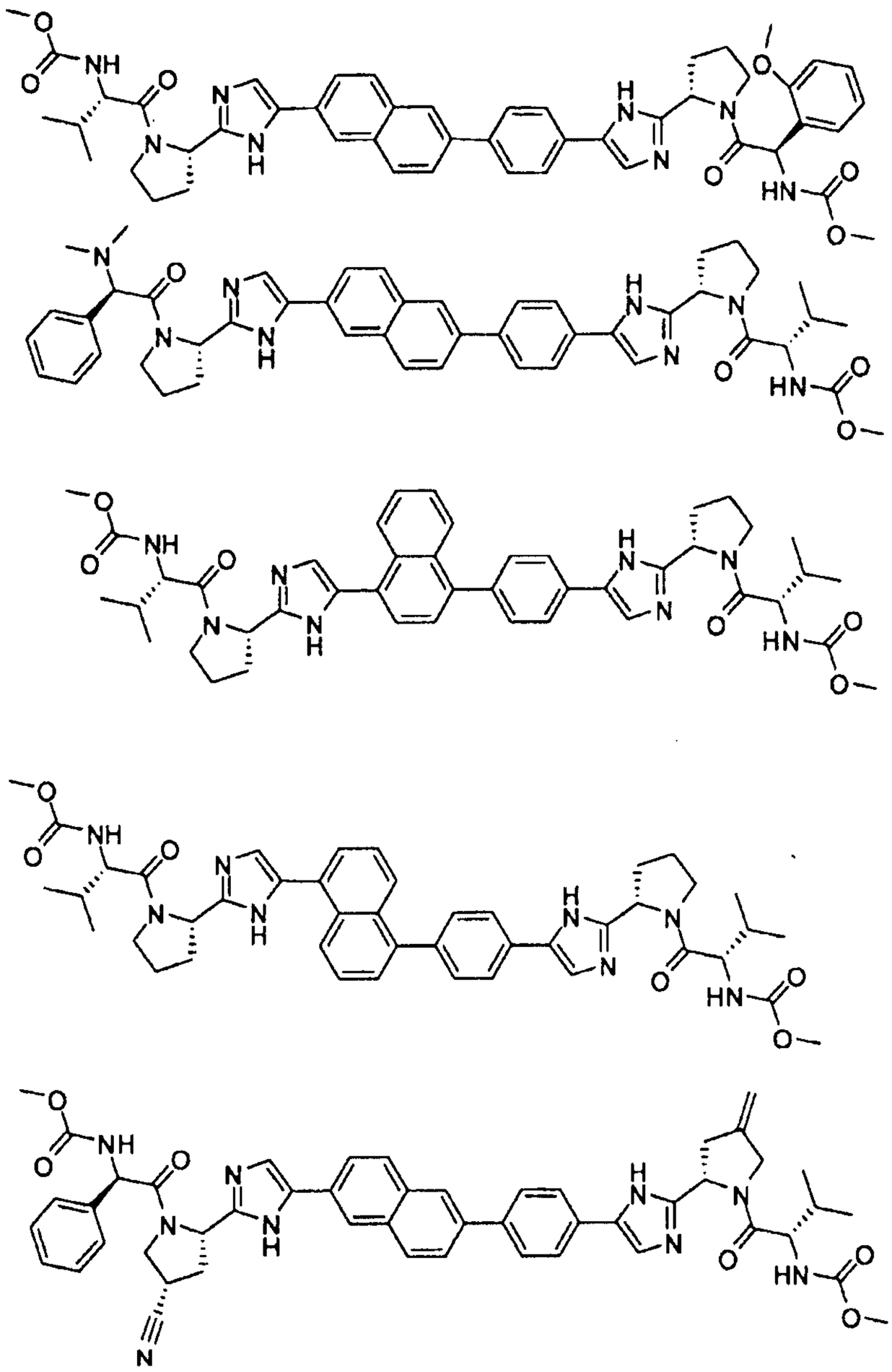


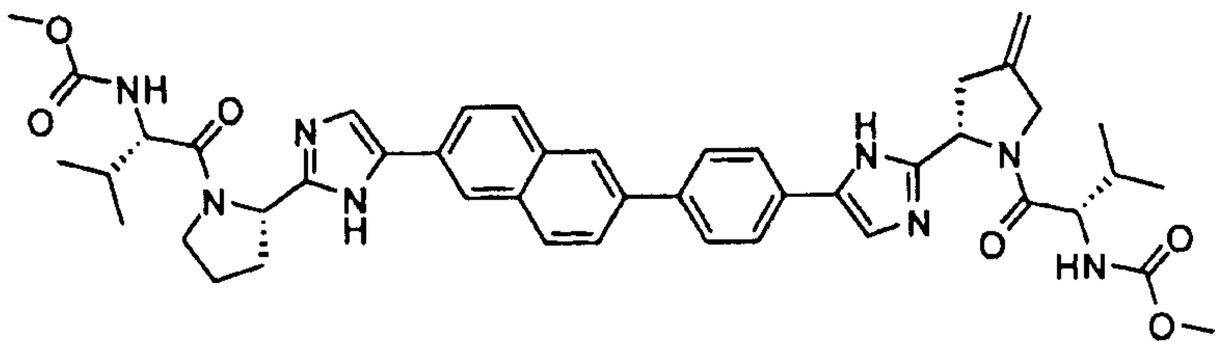




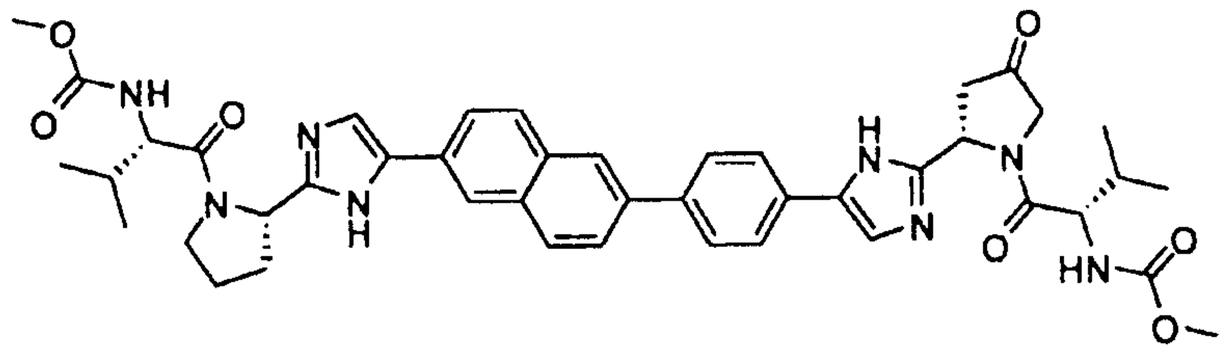






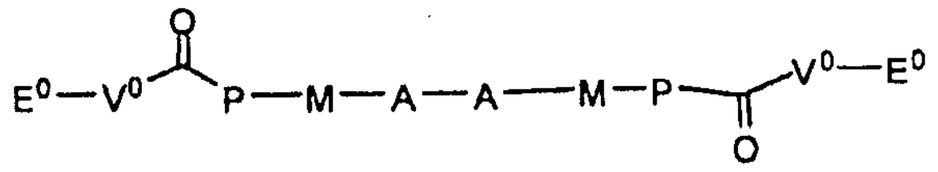


or



or a pharmaceutically acceptable salt, or prodrug thereof.

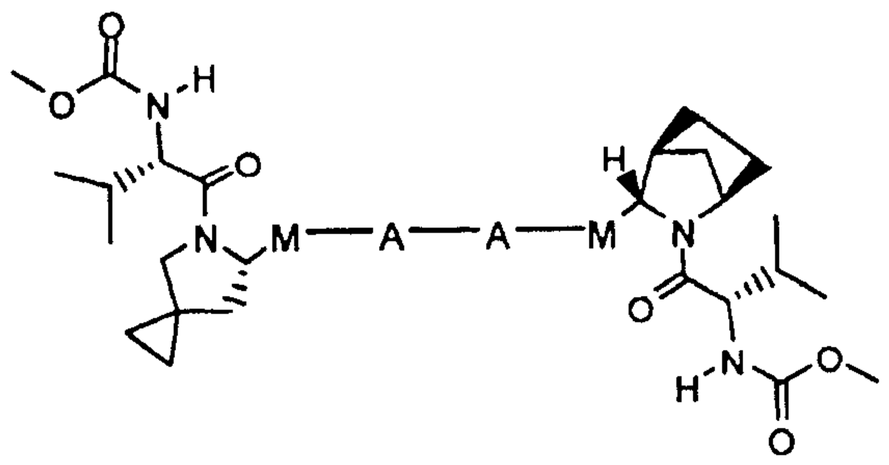
In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic9):



(Ic9)

or a pharmaceutically acceptable salt, or prodrug thereof.

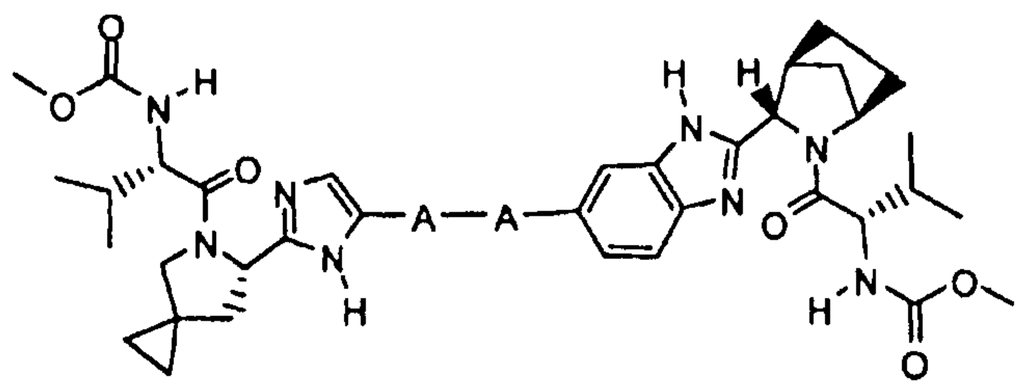
In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic10):



(Ic10)

or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic11):



(Ic11)

or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic9), (Ic10), or (Ic11) wherein –A-A- is $-A^{13}-A^{6}-$.

In another specific embodiment of the invention the compound of formula (Ic) is a compound of formula (Ic9), (Ic10), or (Ic11) wherein –A-A- is $-A^{13}-A^{0}-$.

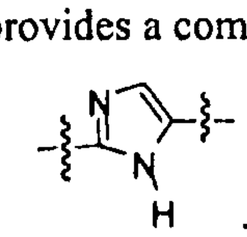
In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ic12):

$$E^{0}\text{-}V^{w}\text{-}Z^{0}\text{-}P^{u}\text{-}M^{t1}\text{-}A^{s1}\text{-}A^{s2}\text{-}M^{t2}\text{-}P^{u}\text{-}Z^{0}\text{-}V^{w}\text{-}E^{0} \quad \text{(Ic12)}$$

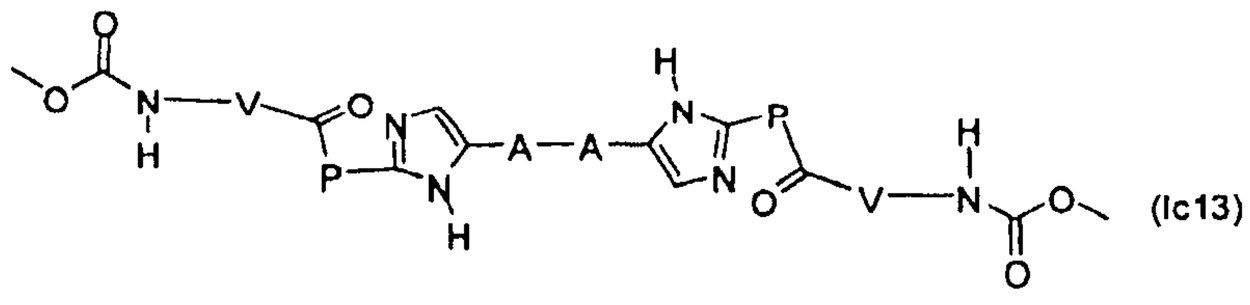
or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

each u is independently 0, 1, 3, 5, 7, 8, 10, or 11; each w is independently 0, 1, 2, 3, 4, or 5; each t1 is 0 or 10; each t2 is 0 or 10; each s1 is 4, 5, 6, 13, 14, 15, or 16; and each s2 is 0, 4, or 13.

In one embodiment the invention provides a compound of formula (Ic12) wherein M^{0} is:



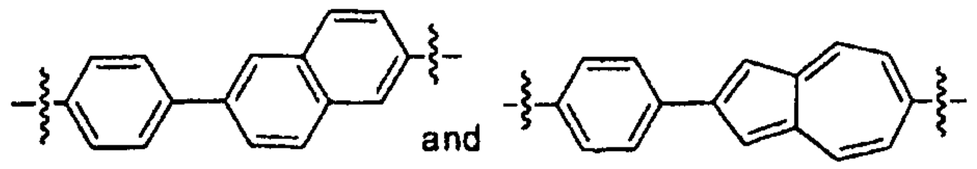
In one embodiment.the invention provides a compound of formula (Ic13)



(Ic13)

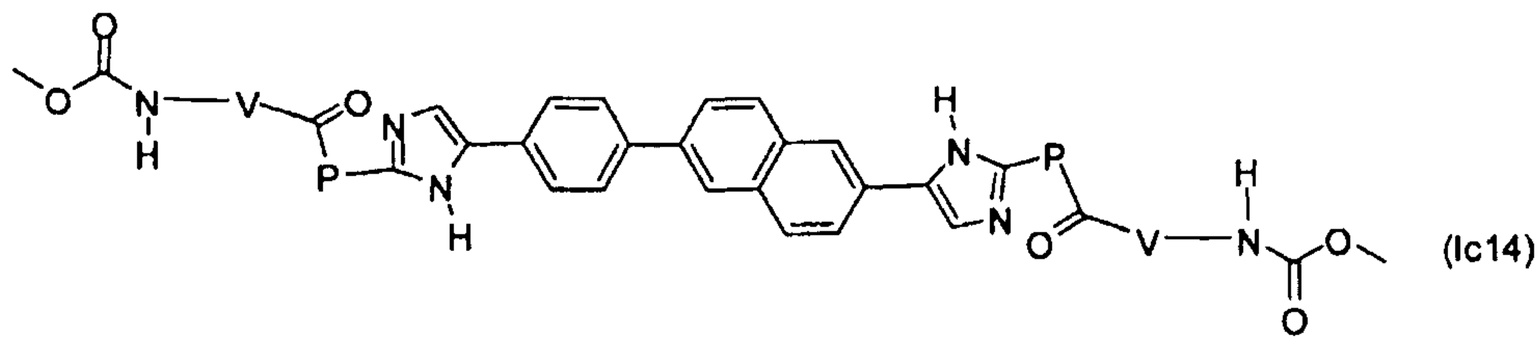
or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{0}-A^{13} and is selected from:



and

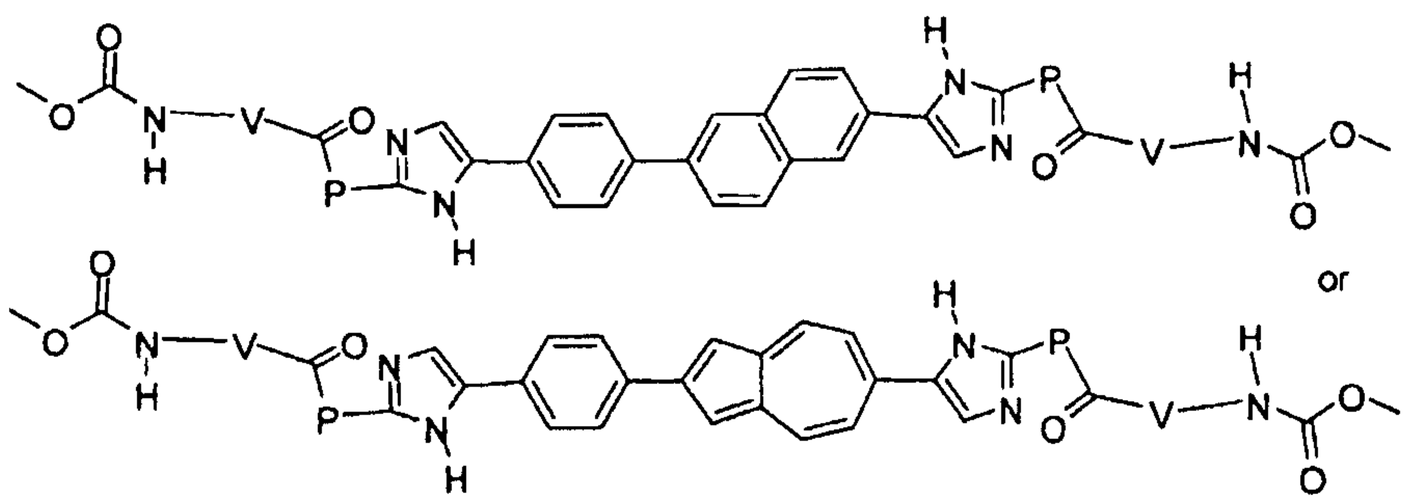
In one embodiment the invention provides a compound of formula (Ic14)



(Ic14)

or a pharmaceutically acceptable salt, or prodrug thereof.

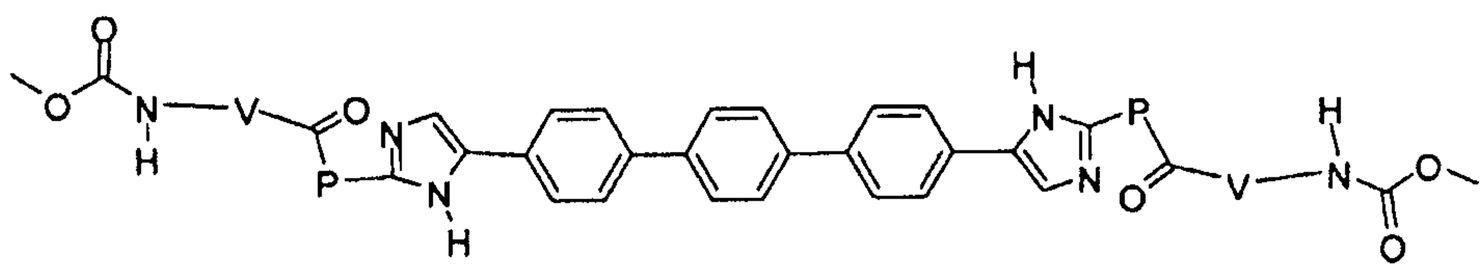
In one embodiment the invention provides a compound of formula (Ic12) which is:



or

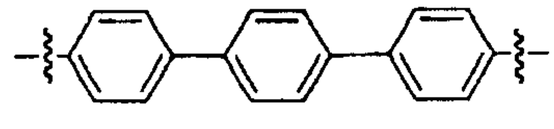
or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic12) which is:

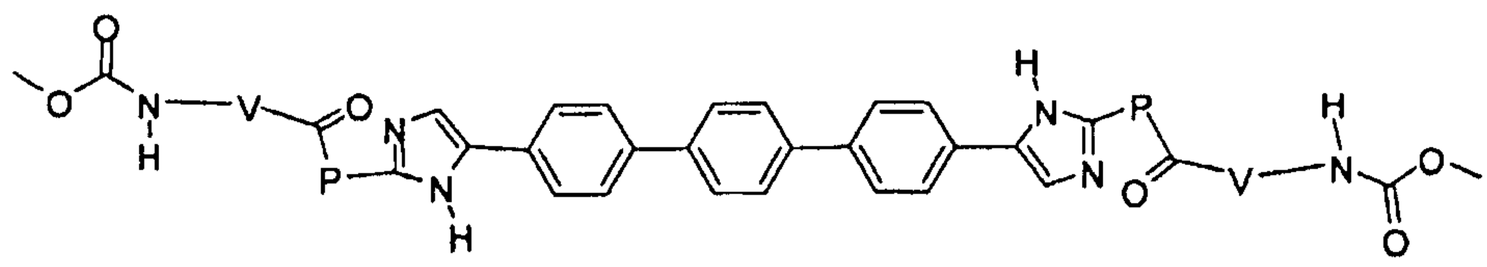


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^0-A^4 and is:

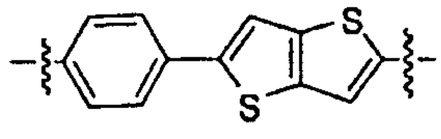


In one embodiment the invention provides a compound of formula (Ic12) which is:

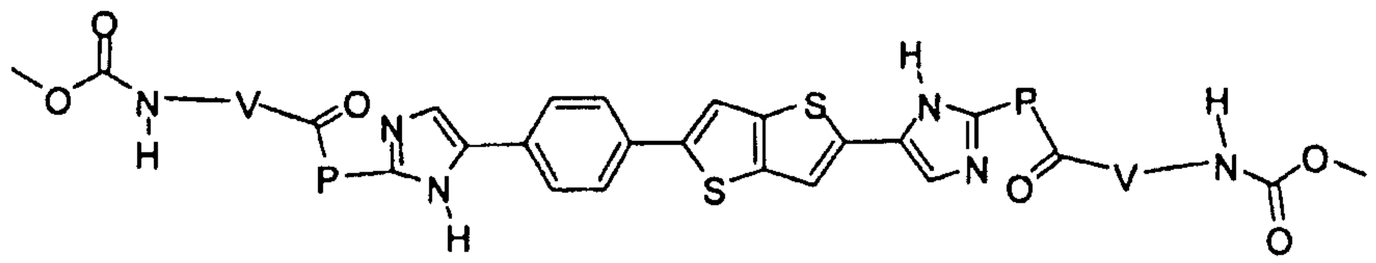


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^0-A^{14} and is:

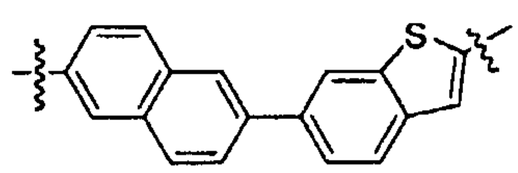


In one embodiment the invention provides a compound of formula (Ic12) which is:

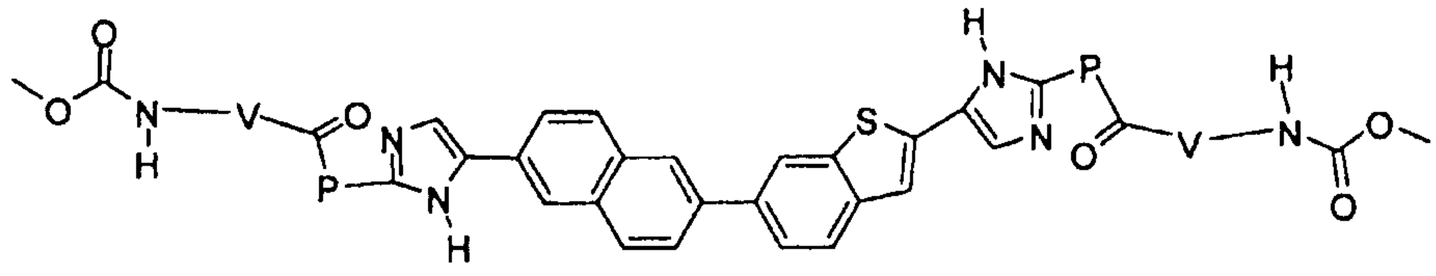


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{13}-A^{14} and is:

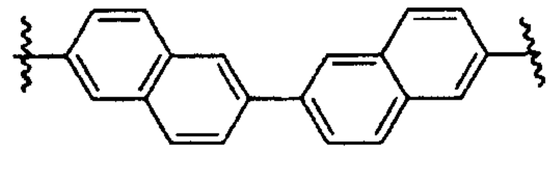


In one embodiment the invention provides a compound of formula (Ic12) which is:

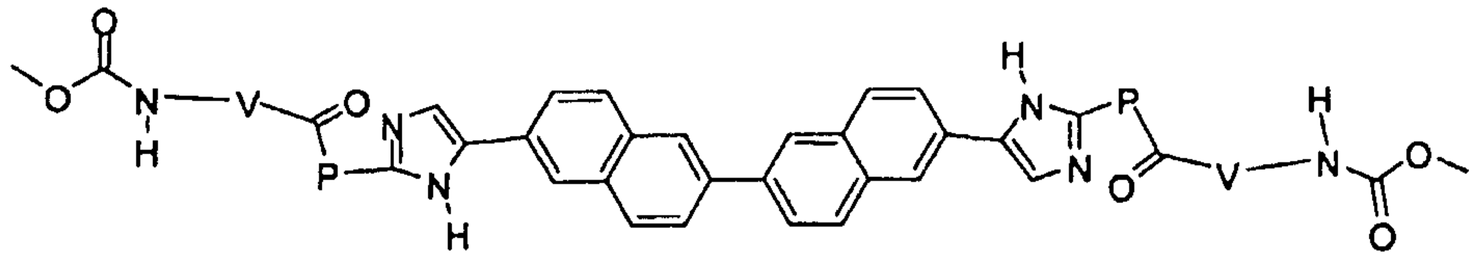


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{13}-A^{13} and is:

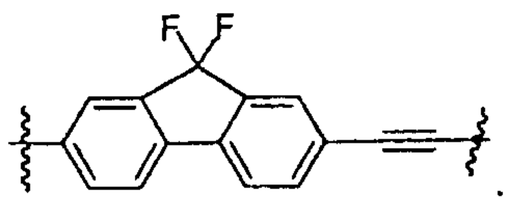


In one embodiment the invention provides a compound of formula (Ic12) which is:

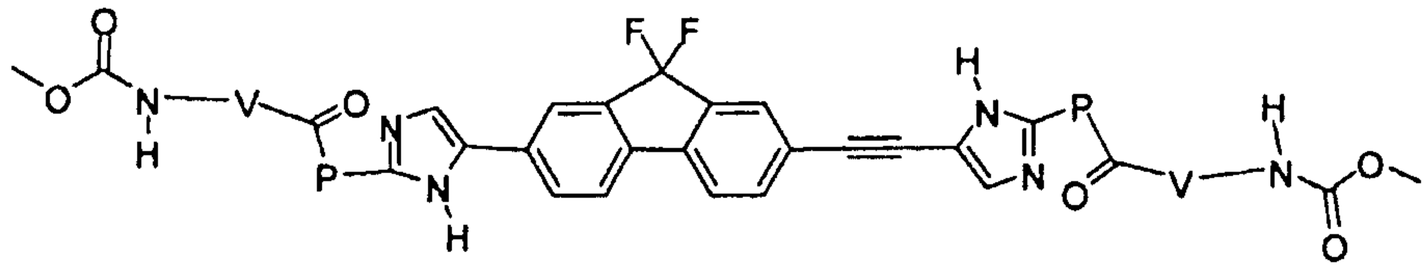


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{15}-A^{6} and is:

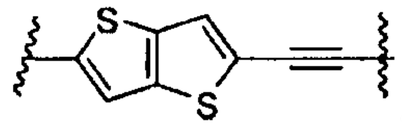


In one embodiment the invention provides a compound of formula (Ic12) which is:

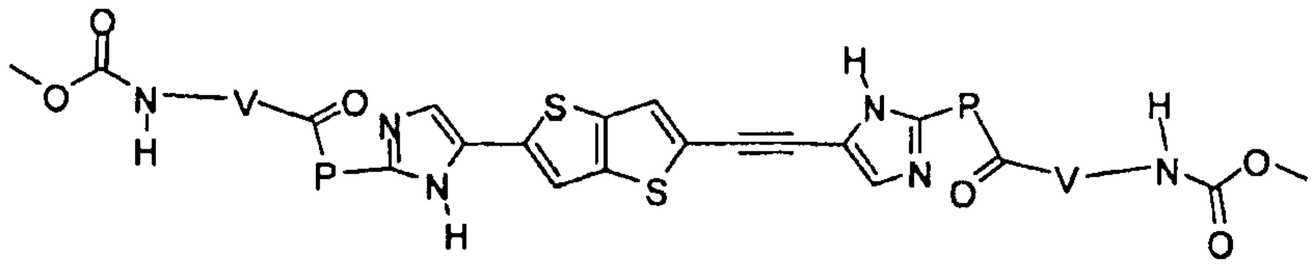


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{14}-A^{6} and is:

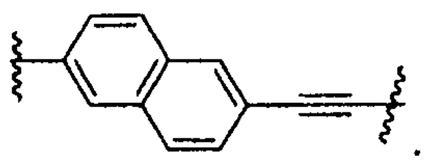


In one embodiment the invention provides a compound of formula (Ic12) which is:

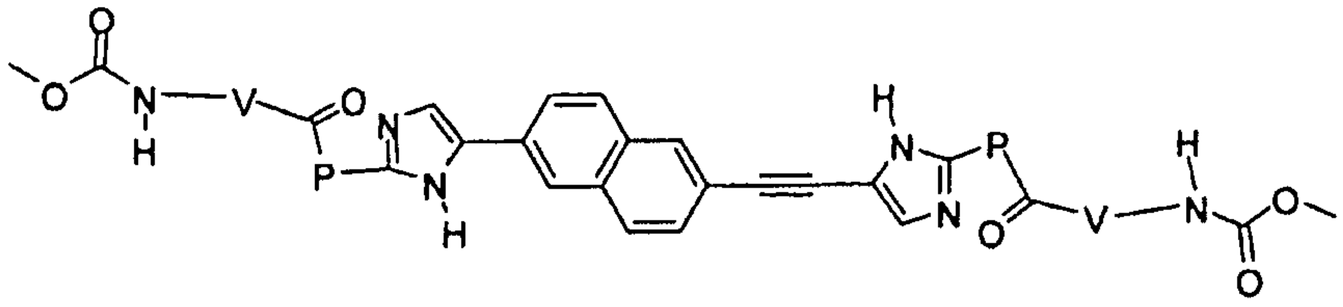


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{13}-A^{6} and is:

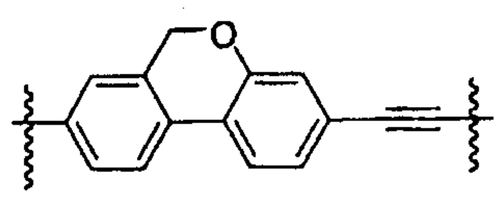


In one embodiment the invention provides a compound of formula (Ic12) which is:

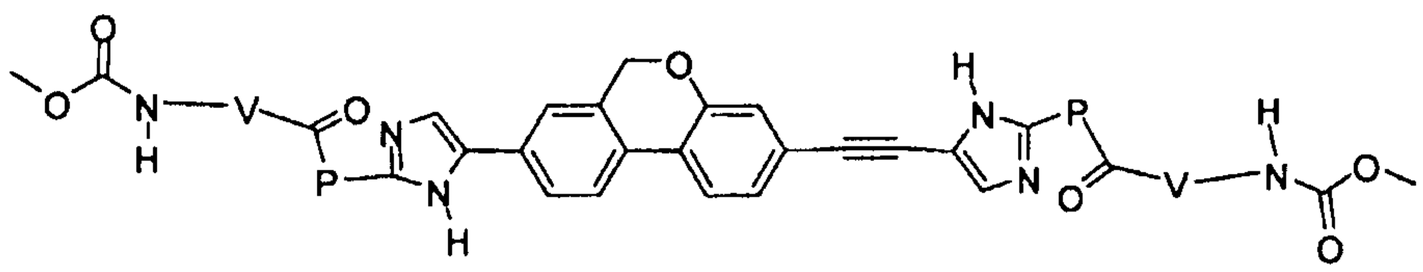


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{16}-A^{6} and is:

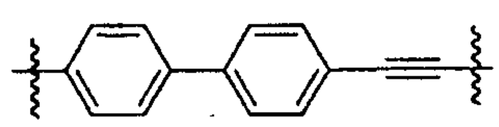


In one embodiment the invention provides a compound of formula (Ic12) which is:

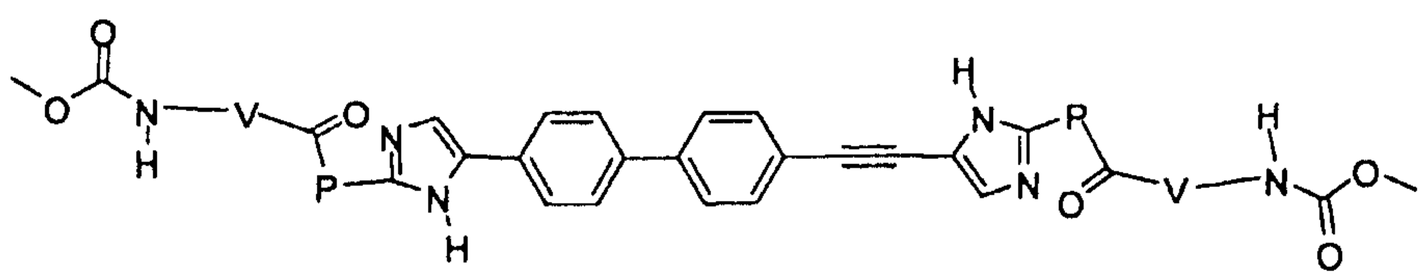


or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{0}-A^{5} and is:



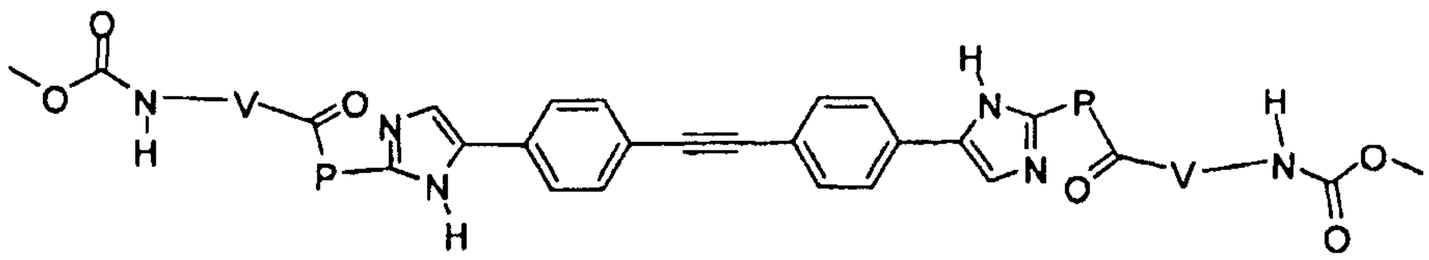
In one embodiment the invention provides a compound of formula (Ic12) which is:



or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic13) wherein A-A is A^{0}-A^{5} and is:

In one embodiment the invention provides a compound of formula (Ic12) which is:



or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ic15):

$$E^0\text{-}V^w\text{-}Z^0\text{-}P^u\text{-}M^{t1}\text{-}A^{s1}\text{-}A^{s2}\text{-}M^{t2}\text{-}P^u\text{-}Z^0\text{-}V^w\text{-}E^0 \quad \text{(Ic15)}$$

or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

each u is independently 0, 1, 3, 5, 7, 8, 10, or 11; each w is independently 0, 1, 2, 3, 4, or 5; each t1 is 0, 10, or 13; t2 is 9; s1 is 4, 5, 6, 13, 14, 15, or 16; and s2 is 0, 4, or 13.

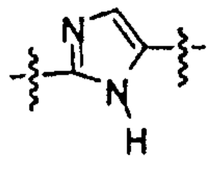
In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ic16):

$$E^0\text{-}V^w\text{-}Z^0\text{-}P^u\text{-}M^{t1}\text{-}A^{s1}\text{-}A^{s2}\text{-}M^{t2}\text{-}P^u\text{-}Z^0\text{-}V^w\text{-}E^0 \quad \text{(Ic16)}$$

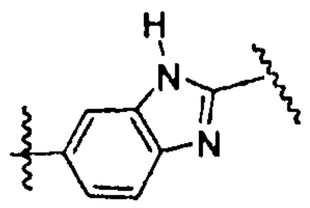
or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

each u is independently 0, 1, 3, 5, 7, 8, 10, or 11; each w is independently 0, 1, 2, 3, 4, or 5; each t1 is 9; t2 is 0, 10, or 13; s1 is 4, 5, 6, 13, 14, 15, or 16; and s2 is 0, 4, or 13.

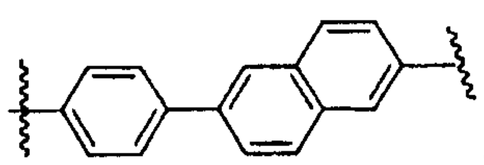
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein M^0 is:



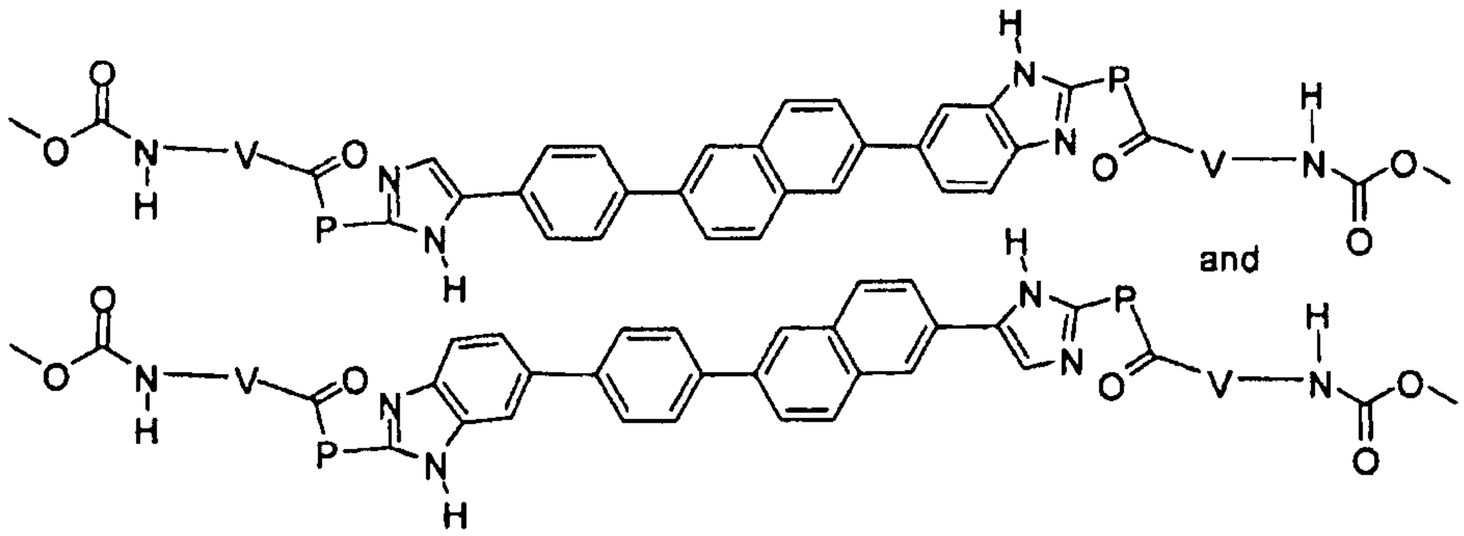
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein M^9 is:



In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^0-A^{13} and is:



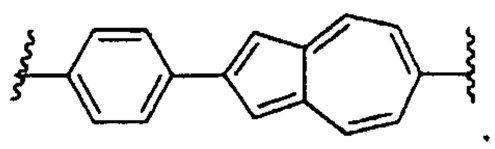
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:



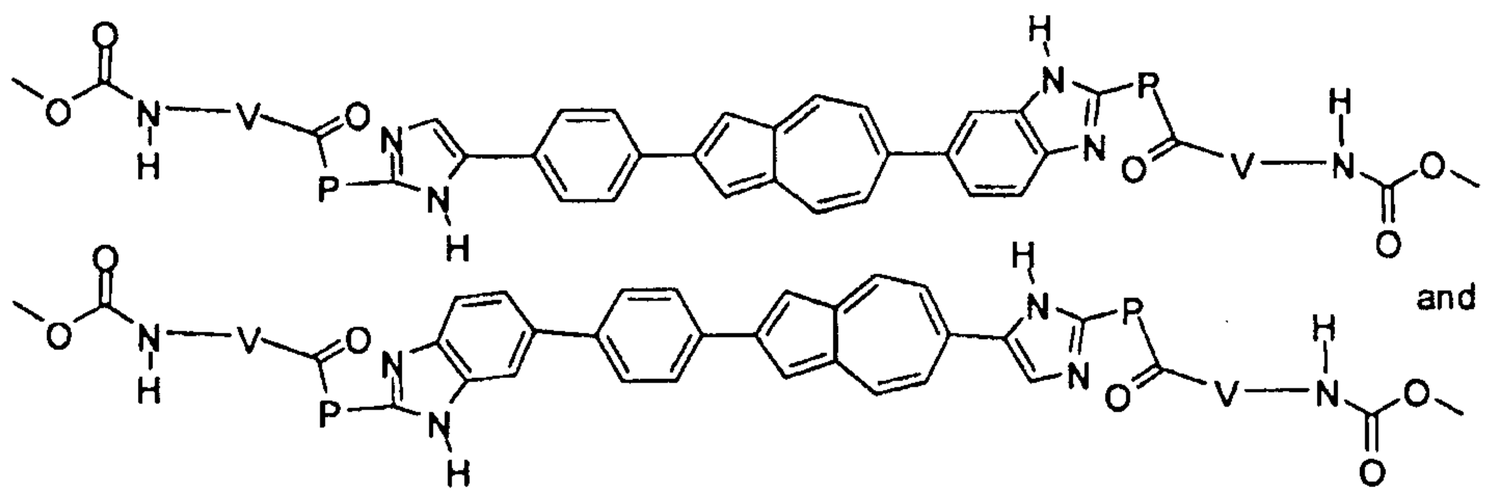
and

and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^0-A^{13} and is:



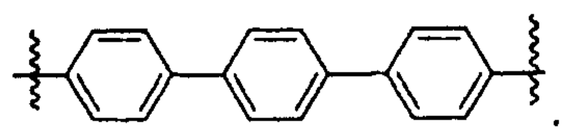
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:



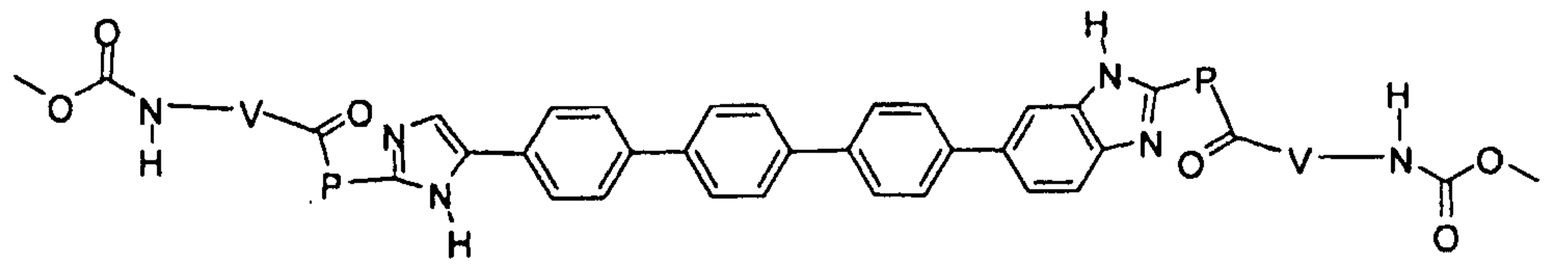
and

and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^0-A^4 and is:

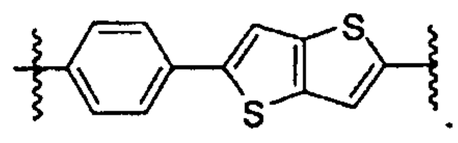


In one embodiment the invention provides a compound of formula (Ic15) or (Ic16):

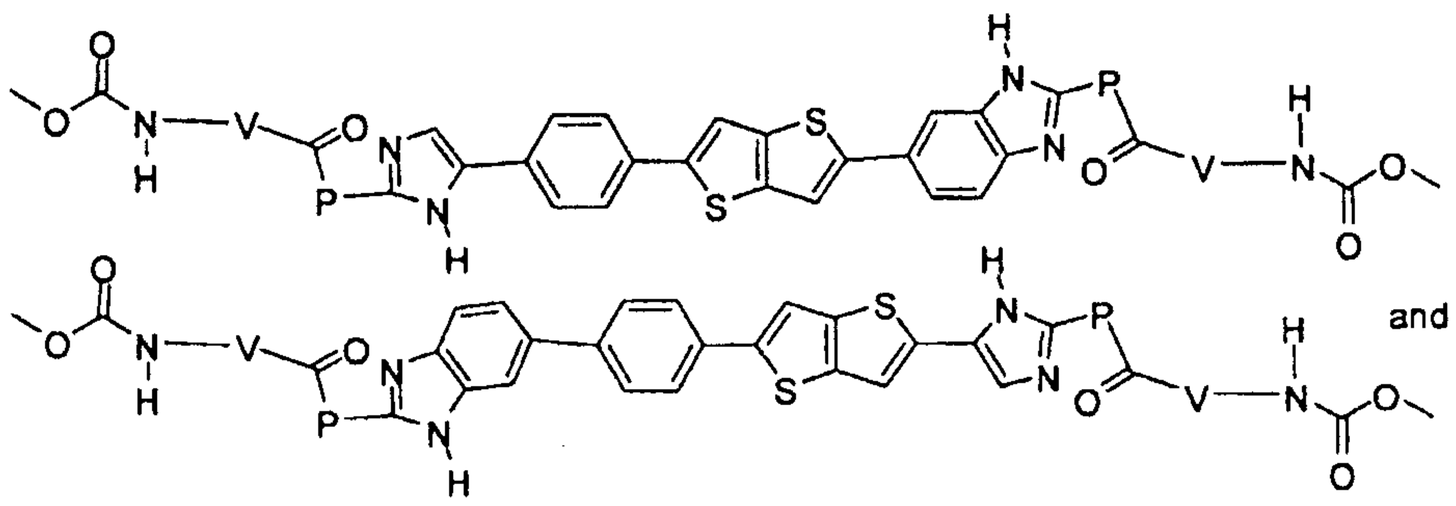


or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^0-A^4 and is:

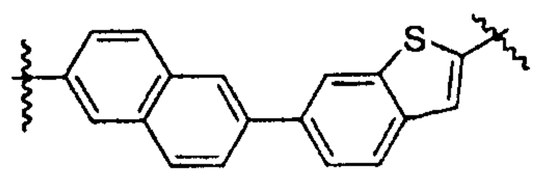


In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:

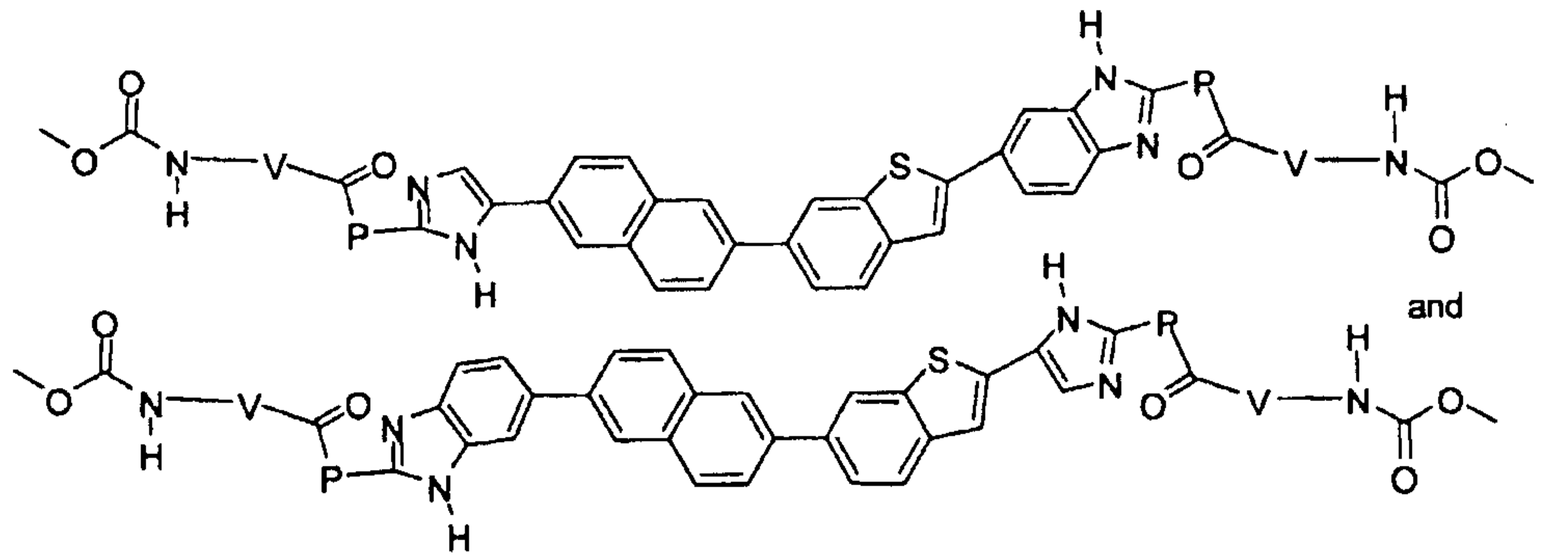


and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{13}-A^{14} and is:

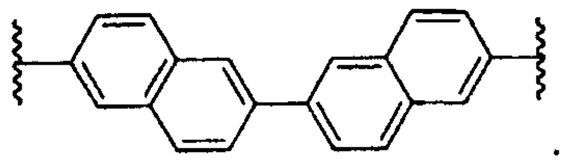


In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:

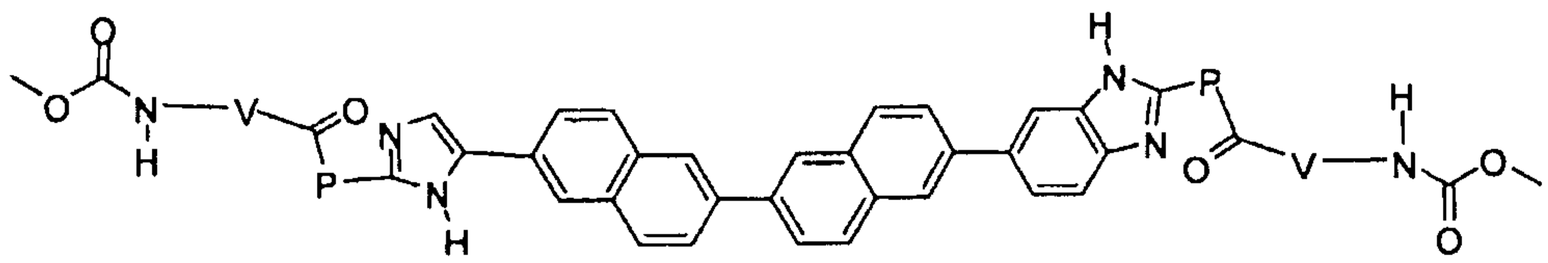


and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{13}-A^{13} and is:

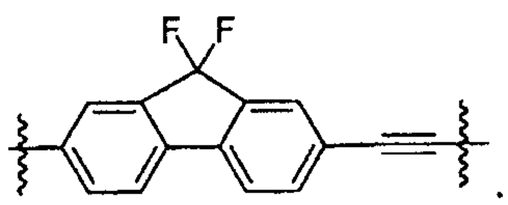


In one embodiment the invention provides a compound of formula (Ic15) or (Ic16):

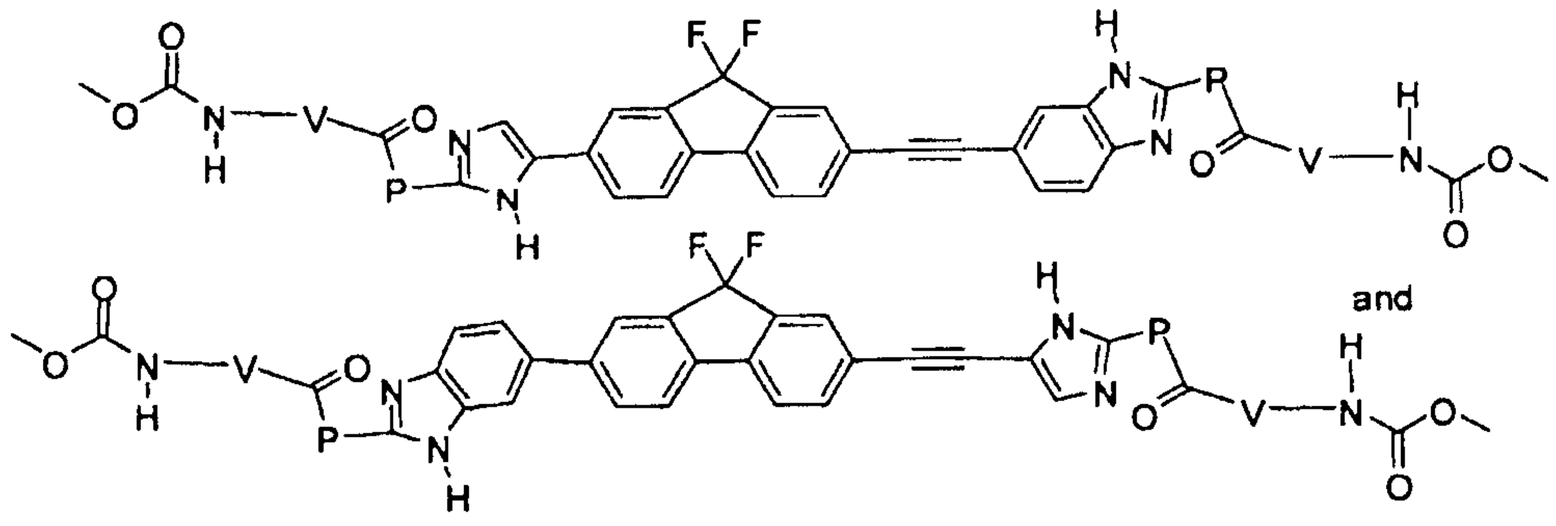


or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{15}-A^{6} and is:



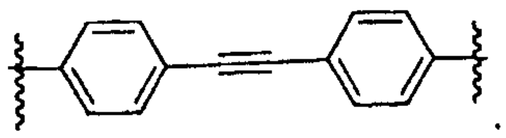
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:



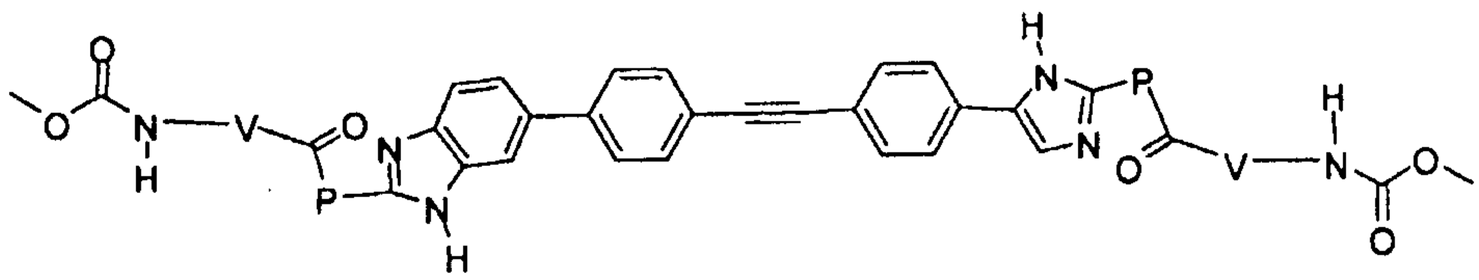
and

and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{0}-A^{5} and is:



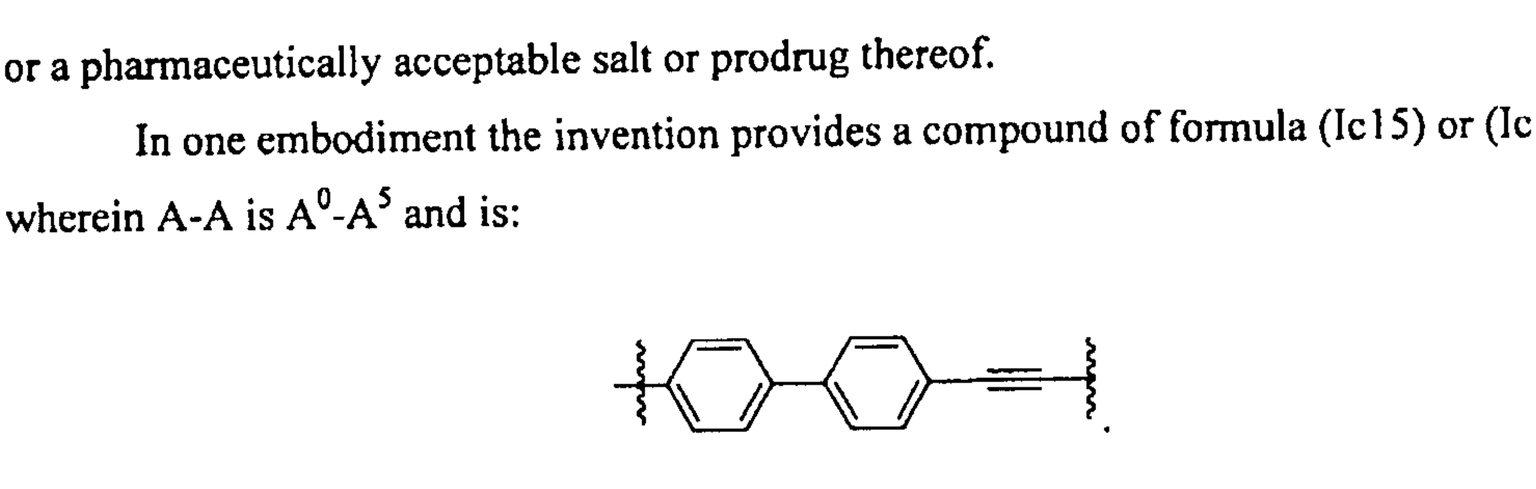
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16):



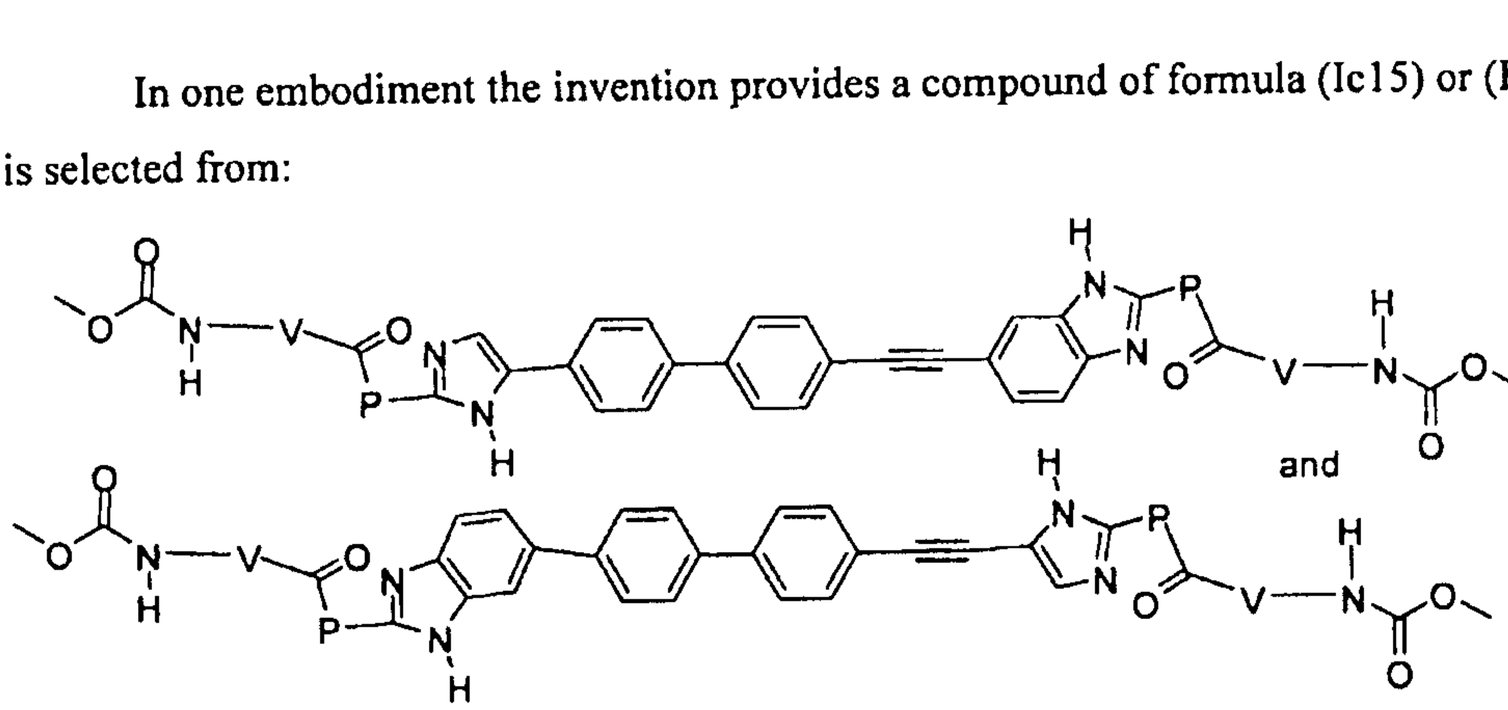
or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^0-A^5 and is:

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:

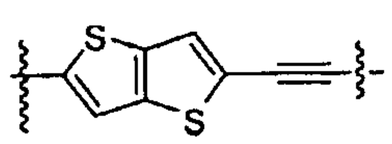


and

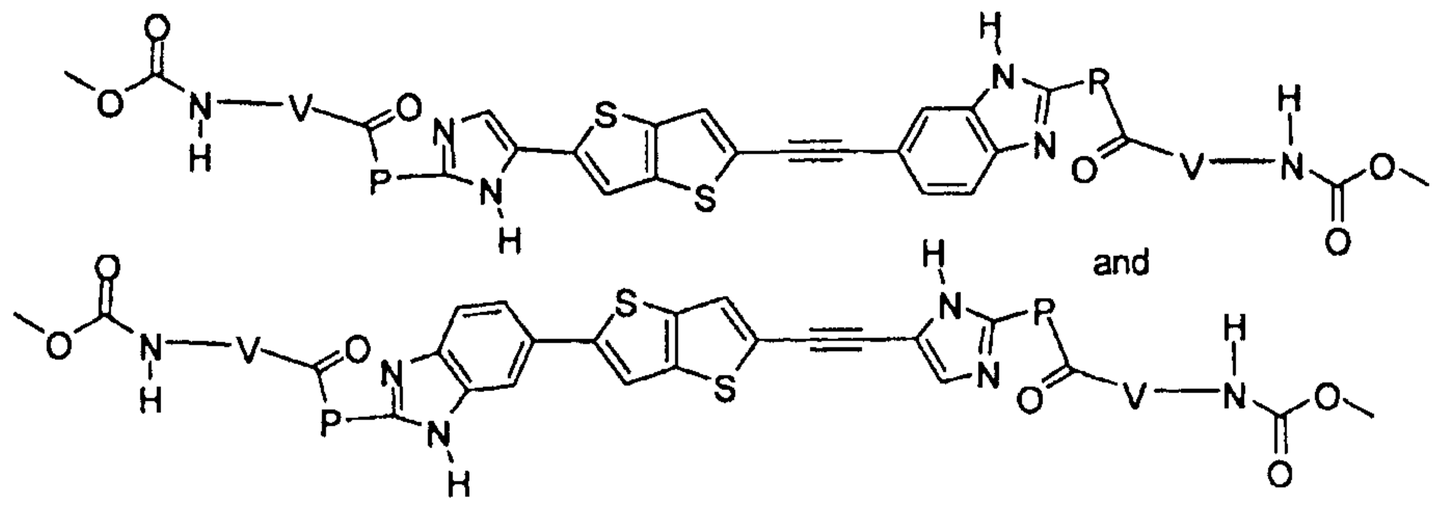


and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{14}-A^6 and is:



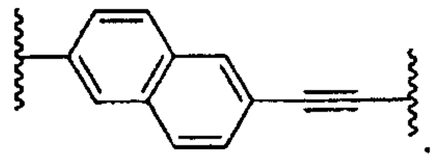
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:



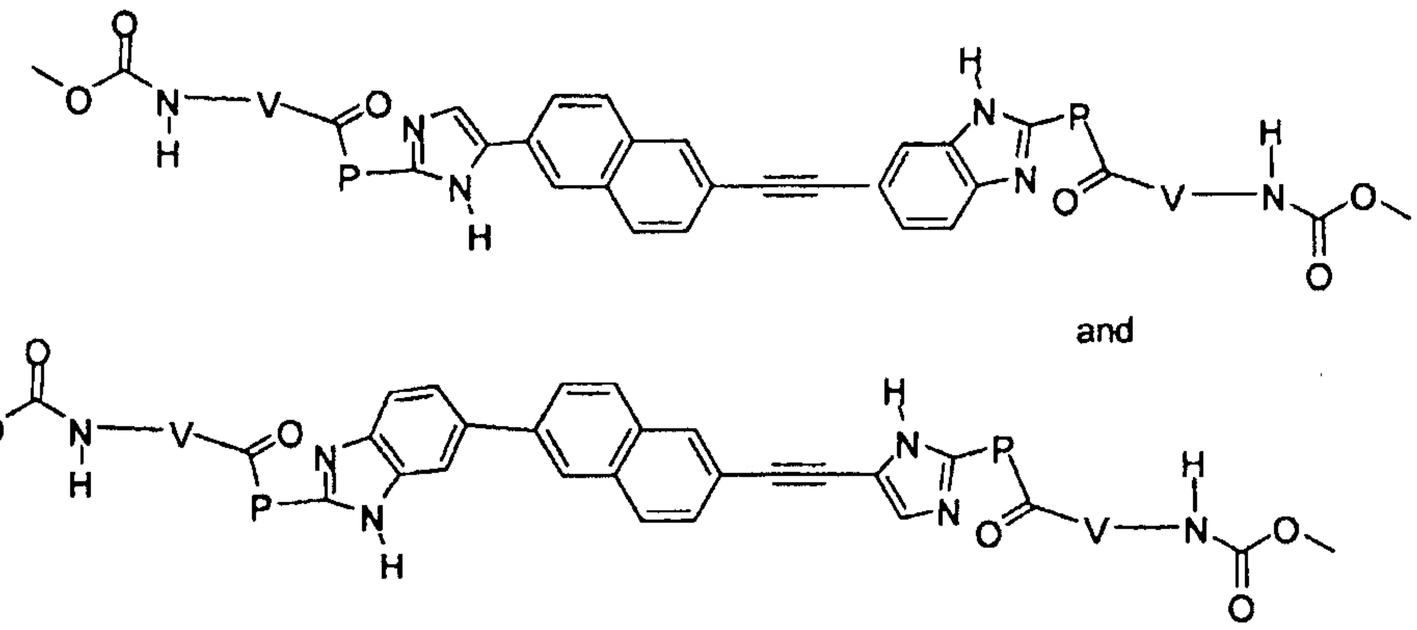
and

and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{13}-A^{6} and is:



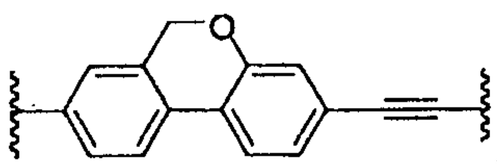
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:



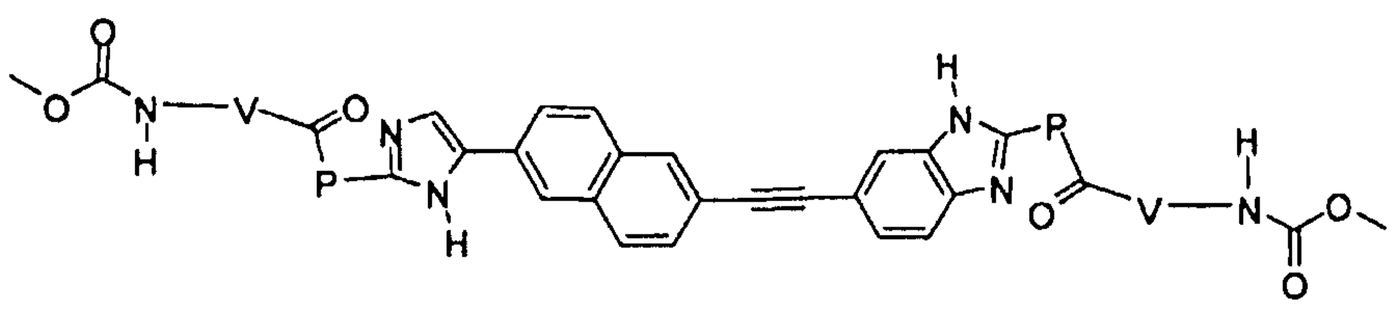
and

and pharmaceutically acceptable salts and prodrugs thereof.

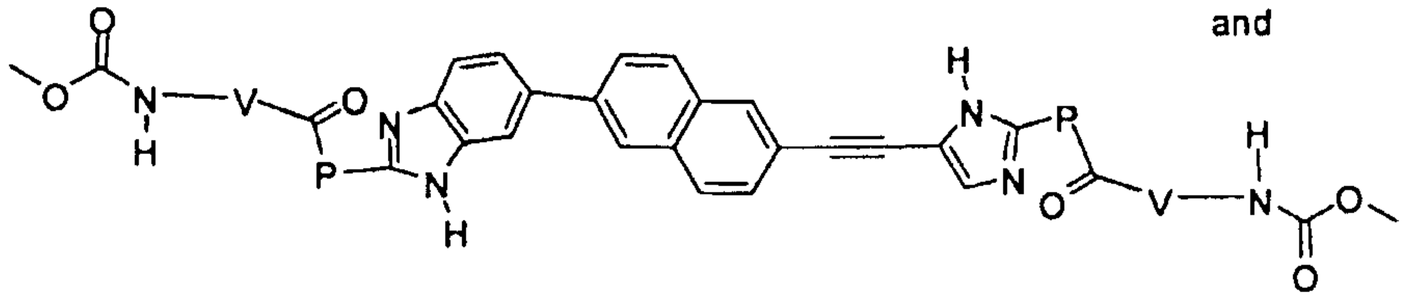
In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) wherein A-A is A^{16}-A^{6} and is:



In one embodiment the invention provides a compound of formula (Ic15) or (Ic16) which is selected from:

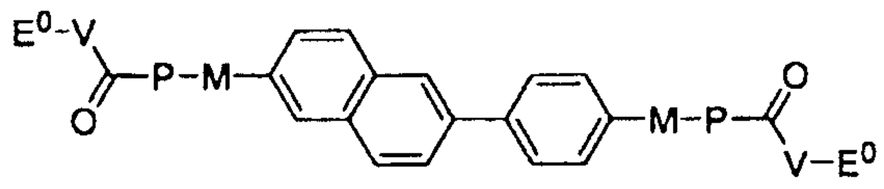


and



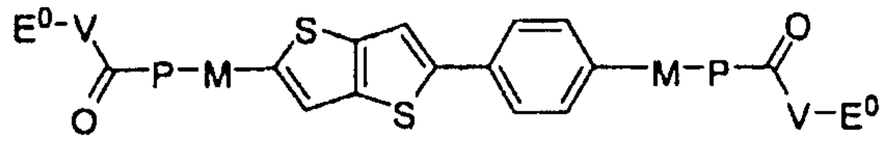
and pharmaceutically acceptable salts and prodrugs thereof.

In one embodiment the invention provides a compound of formula (Ic17) or (Ic18)



(Ic17)

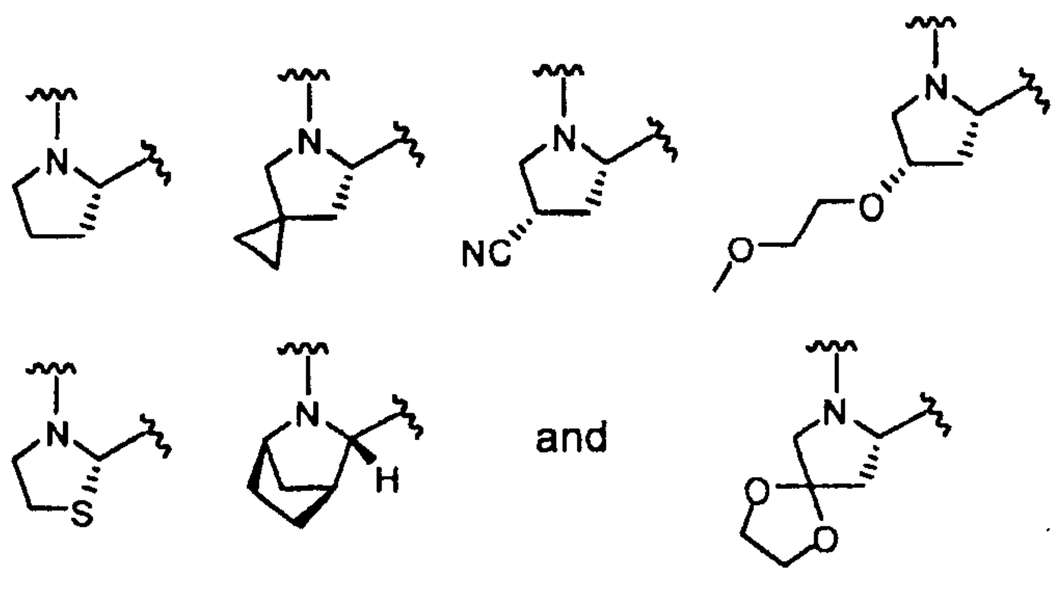
or



(Ic18)

wherein:

each P is independently selected from:



; and

each M is independently M^0, M^9, or M^{10};

or a pharmaceutically acceptable salts or prodrug thereof.

In one embodiment the invention provides a compound of formula (Ic17) or (Ic18) wherein each E^0 is methoxycarbonylamino.

In one embodiment the invention provides a compound of formula (Ic17) or (Ic18) wherein at least one E^0 is $-NR^{Ec}R^{Ed}$ wherein R^{Ec} is H, alkyl or cycloalkyl and R^{Ed} is heterocycle.

In another specific embodiment the invention provides a compound of the following formula (Ic30): E^x-V^w-Z^v-P^u-M^t-A^s-A^s-M^t-P^u-Z^v-V^w-E^x (Ic30) wherein at least two of s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one of u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one t is 0 or 10.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein both t are 9; one s is 0; and one s is 0,1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein both t are 9; one s is 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, 20, or 21; and one s is 0,1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, 20, or 21.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of s, t, u, v, w or x are not zero and at least one t is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least three of s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least three of s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least three of s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least four of s, t, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least four of s, t, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least four of s, t, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least four of s, t, u, v, w or x are not zero and at least four of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein the sum of t, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein the sum of s, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein s, and at least one t, and at least one u are all not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of u, w and t are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of s, u, and w are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of s, u, and w are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least s and both u are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one of u, or w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of u or w are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of u are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein at least two of w are not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein both t are 9; one s is 0; and one s is 0,1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, 20, or 21.

In another specific embodiment the invention provides a compound of formula (Ic30) wherein both t are 9; one s is 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, 20, or 21; and one s is 0,1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, 20, or 21.

In another specific embodiment the invention provides a compound of the following formula (Ic31): E^x-V^w-Z^v-P^u-M^9-A^s-A^s-M^9 -P^u-Z^v-V^w-E^x (Ic31) wherein one s is 0 or 6 and one s is 6.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least two of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least three of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least four of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least two u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least three of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least three of u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least four of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein the sum of u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least one of u or w are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least two of u or w are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein both of u are not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Ic31) wherein both w are not zero.

Compounds of formula (Id)

In one embodiment of the invention, the compound of formula (I) is a compound of formula (Id):

$$E^0\text{-}V^w\text{-}Z^0\text{-}P^u\text{-}L^{n1}\text{-}L^{n2}\text{-}P^u\text{-}Z^0\text{-}V^w\text{-}E^0 \qquad \text{(Id)}$$

wherein:

n1 is 3, 4, or 9;

n2 is 9;

each u is 0, 1, 3, 5, 7, 8, 10, or 11;

each w is 0, 1, 2, 3, 4, or 5;

each L^3 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl,

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

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

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

each L^4 is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

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

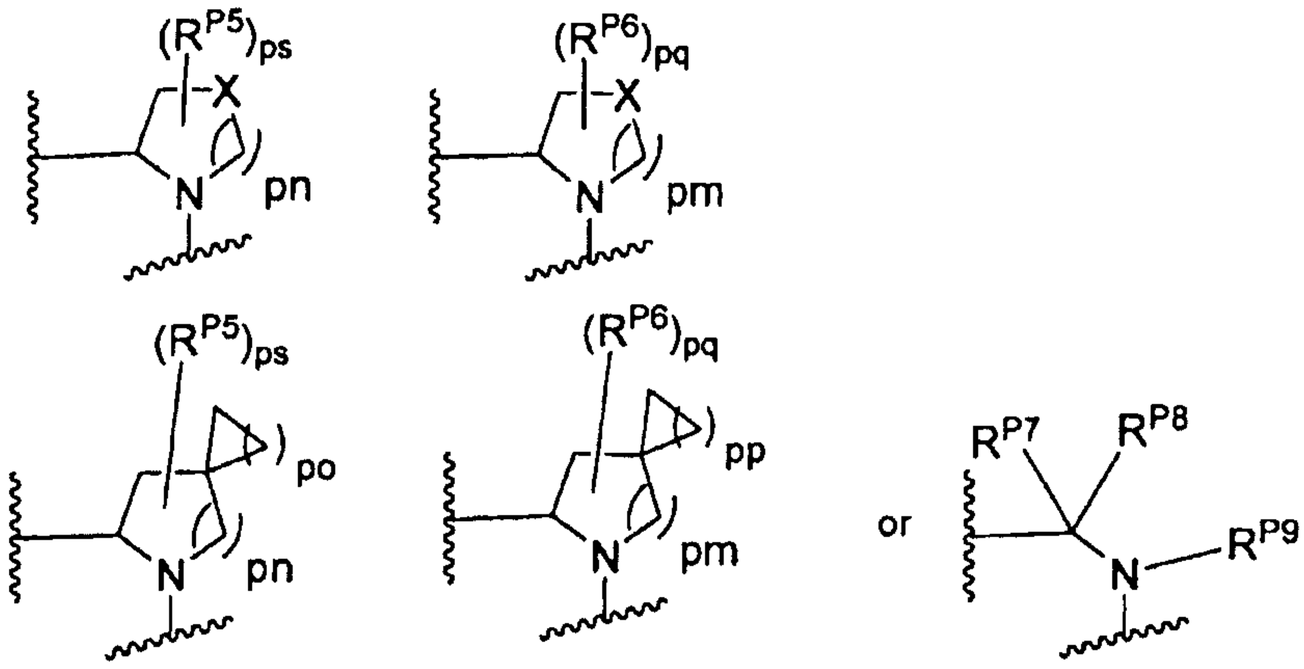
R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each L^9 is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each P^0 is independently:



wherein:

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

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

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

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

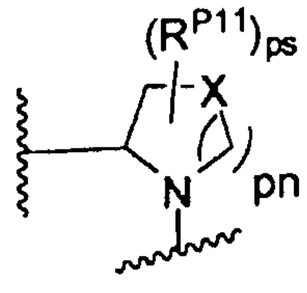
pm and pn are independently 0, 1, or 2;

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

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

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

each P^1 is independently:



wherein:

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

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

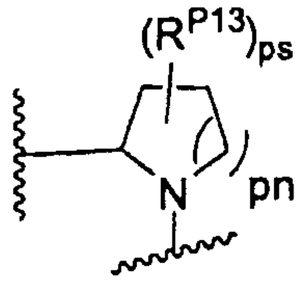
each R^{P10} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl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

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

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

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



wherein:

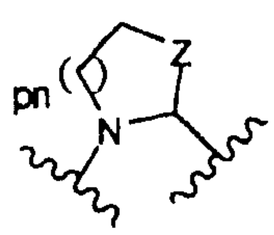
the ring is substituted with one or more oxo groups;

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

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

pn is 0, 1, or 2;

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



wherein:

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

or two alkyl groups; and where two groups R^{P15} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

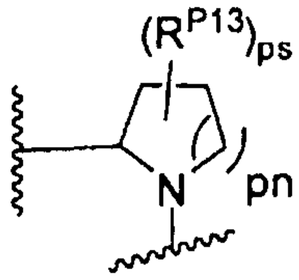
pn is 0, 1, or 2;

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

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

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

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

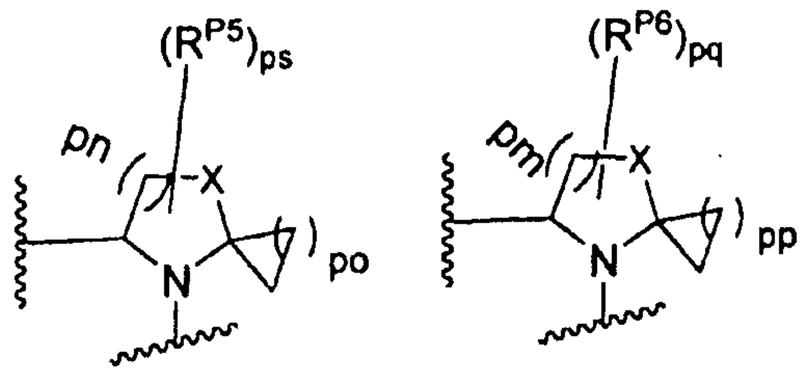


wherein:

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

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

each P^{10} is independently:



wherein:

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

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

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

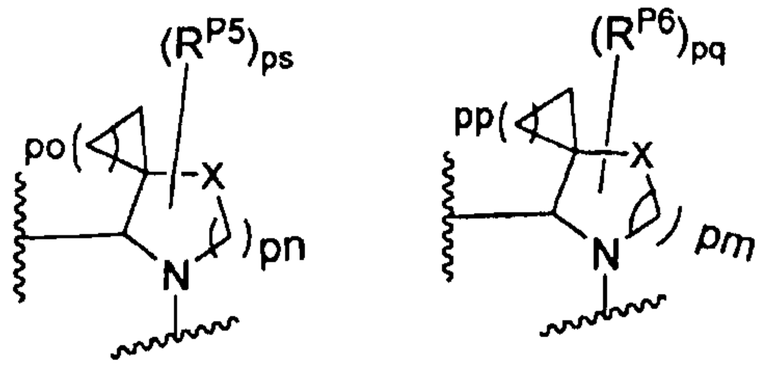
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{11} is independently:



wherein:

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

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

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

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

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

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

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

each $-Z^0-$ is –C(=O)- or –C(=S)-;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

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

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

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

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

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O-$; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle,

heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

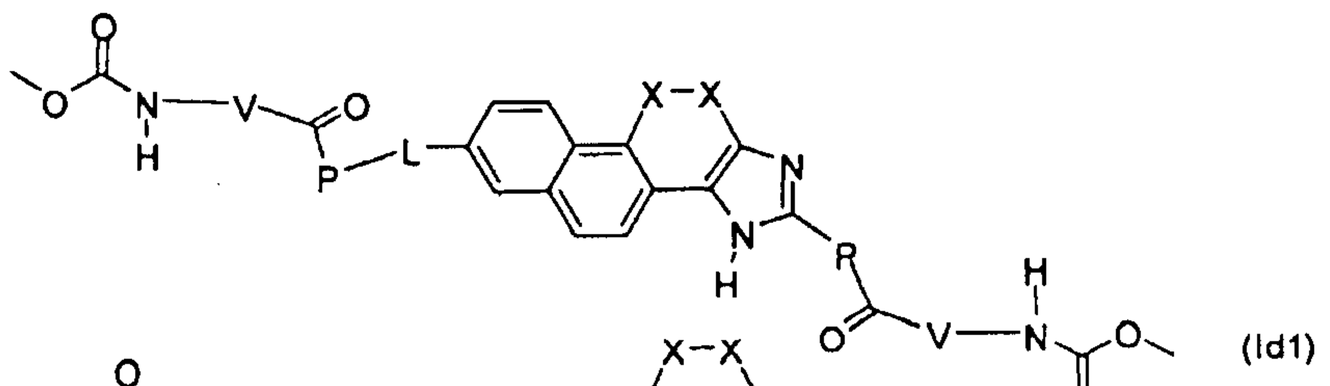
each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano; and

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^aR^bC(=O)O$-; R^a and R^b are each independently selected from hydrogen, alkenyl, and alkyl; and

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl.

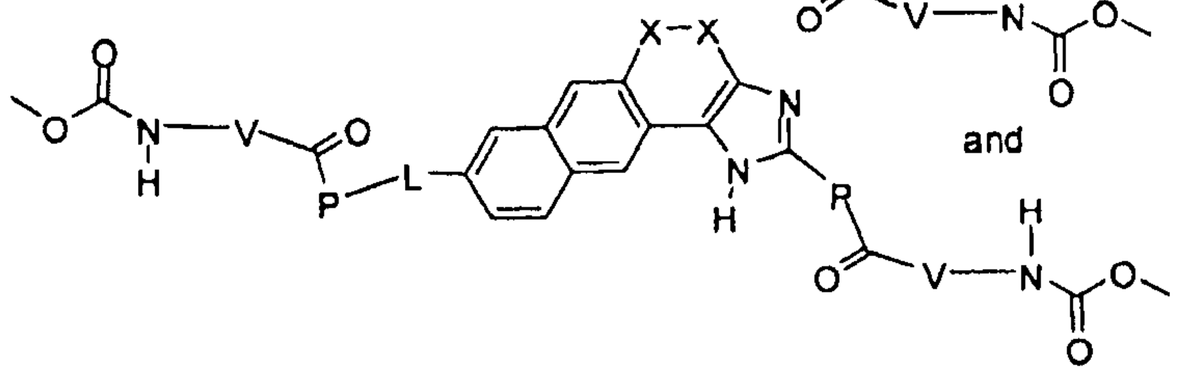
In one embodiment the invention provides a compound of formula (Id) wherein each L is benzimidazolyl.

In one embodiment the invention provides a compound of formula (Id1) or (Id2) which is selected from:



(Id1)

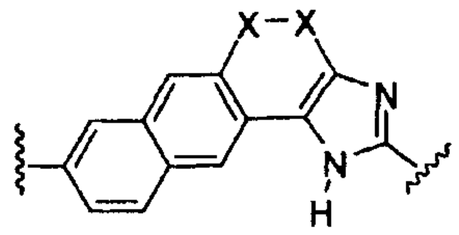
and



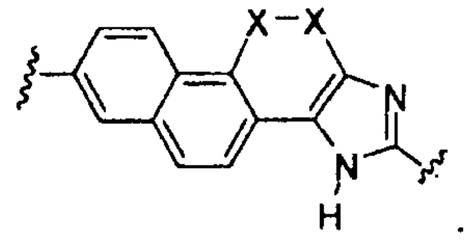
(Id2)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

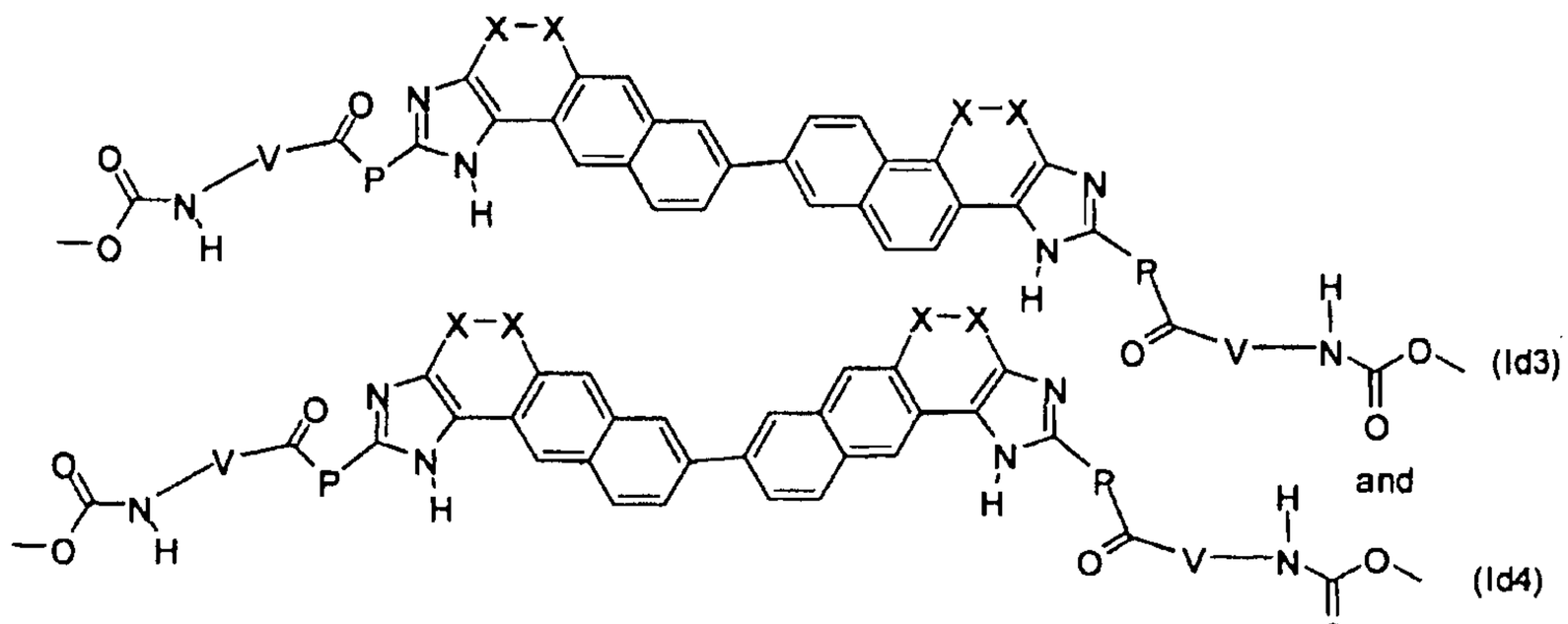
In one embodiment the invention provides a compound of formula (Id) wherein L^9 is:



In one embodiment the invention provides a compound of formula (Id) wherein L^9 is:

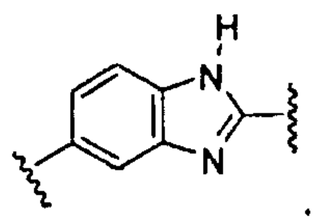


In one embodiment the invention provides a compound of formula (Id3) or (Id4) which is selected from:



wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Id) wherein L^3 is:



In one embodiment the invention provides a compound of formula (Id5) or (Id6) which is selected from:

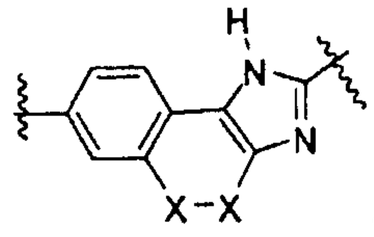
(Id5)

and

(Id6)

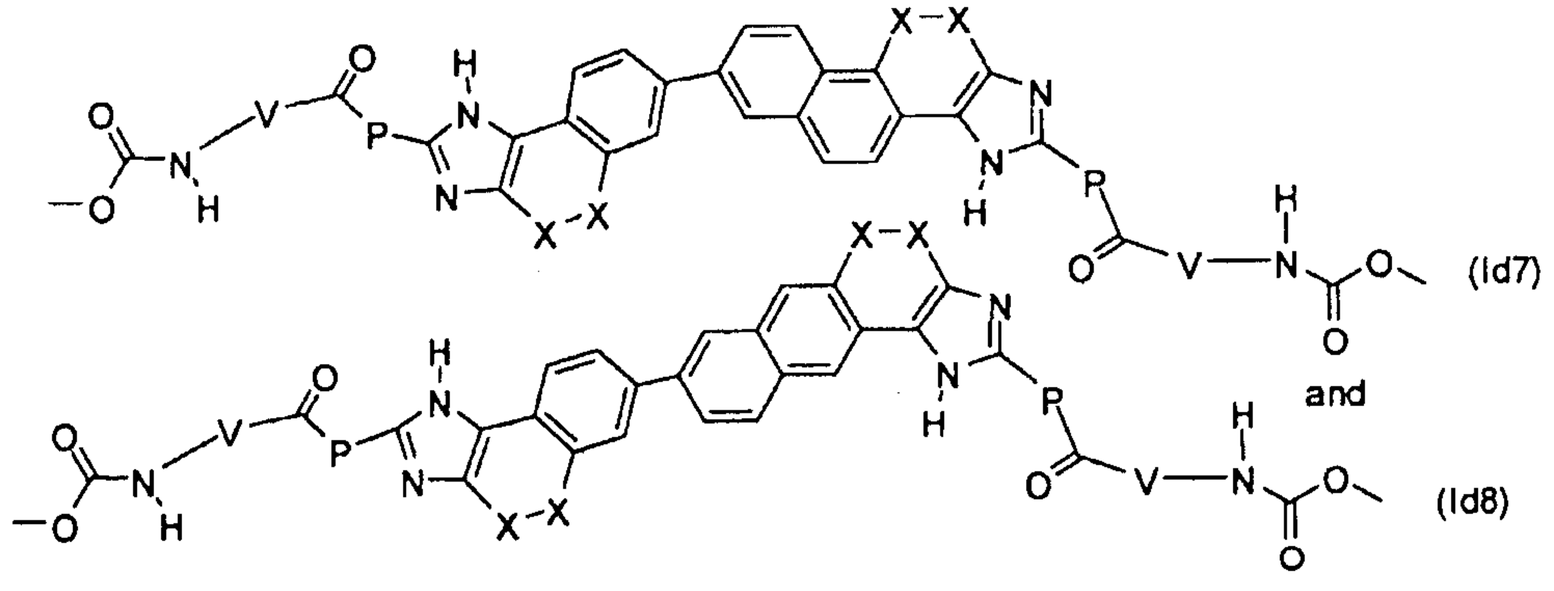
wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In one embodiment the invention provides a compound of formula (Id) wherein L^4 is:



.

In one embodiment the invention provides a compound of formula (Id5) or (Id6) which is selected from:



(Id7)

and

(Id8)

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

In another specific embodiment the invention provides a compound of the following formula (Id30): E^x-V^w-Z^v-P^u-L^n-L^n -P^u-Z^v-V^w-E^x (Id30); wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein one n is 0, 1, 2, 4, 5, 6, 7, 8, 9, or 10; and one n is 1, 2, 3, 5, 6, 7, 8, 9, or 10.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of n, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of n, u, v, w or x are not zero and at least one n is selected from 0, 1, 2, 4, 5, 6, 7, 8, and 10

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of n, u, v, w or x are not zero and at least one n is selected from 0, 1, 2, 3, 5, 6, 7, 8, and 10

Wherein at least three of n, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of n, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least three of n, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least three of n, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least four of n, u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least four of n, u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least four of n, u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least four of n, u, v, w or x are not zero and at least four of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein the sum of n, u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein the sum of u, v, w or x is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least one n, and at least one u are all not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u, w and n are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u, and w are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u, and w are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least w and both u are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least one of u, or w is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of u are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein at least two of w are not zero.

In another specific embodiment the invention provides a compound of formula (Id30) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of the following formula (Id31): E^x-V^w-Z^v-P^u-L^3-L^3 -P^u-Z^v-V^w-E^x (Id31).

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least two of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least three of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least four of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least two u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least three of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least three of u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least four of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id31) wherein the sum of u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least one of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein both of u are not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Id31) wherein both w are not zero.

In another specific embodiment the invention provides a compound of the following formula (Id32): E^x-V^w-Z^v-P^u-L^4-L^4 -P^u-Z^v-V^w-E^x (Id32).

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least one of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least two of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least three of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least four of u, v, w or x are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least two u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least three of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least three of u, v, w or x are not zero and at least three of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least four of u, v, w or x are not zero and at least two of the non-zero groups are not the same letter.

In another specific embodiment the invention provides a compound of formula (Id32) wherein the sum of u, v, w and x is not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least one of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least two of u, or w are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least one u is not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein both u are not zero, and at least one w is not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least one u is not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein both of u are not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein at least one of w is not zero.

In another specific embodiment the invention provides a compound of formula (Id32) wherein both w are not zero.

Compounds of formula (Ie)

In one embodiment of the invention, the compound of formula (I) is a compound of formula (Ie):

$$E^0\text{-}V^w\text{-}Z^0\text{-}P^u\text{-}Y^2\text{-}P^u\text{-}Z^0\text{-}V^w\text{-}E^0 \qquad \text{(Ie)}$$

wherein:

each u is 0, 1, 3, 5, 7, 8, 10, or 11;

each w is 0, 1, 2, 3, 4, or 5;

each Y^2 is independently:

a fused five to eight ring system with up to thirty-two atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, S, SO_2, SO and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl,

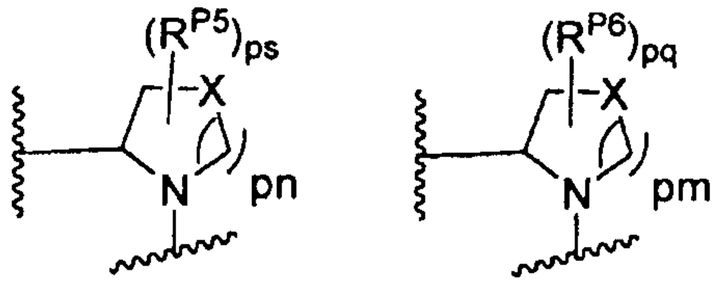
(heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

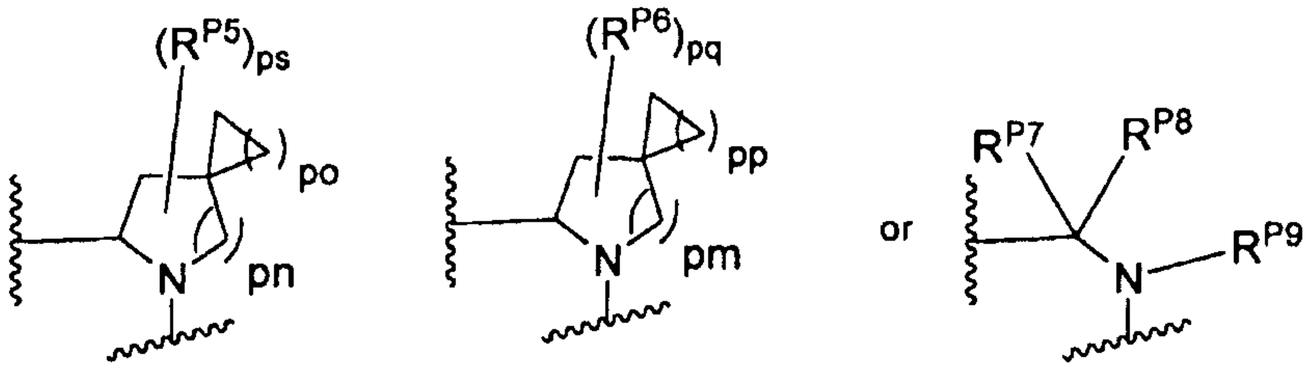
each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl,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

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

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

each P^0 is independently:





wherein:

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

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

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

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

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

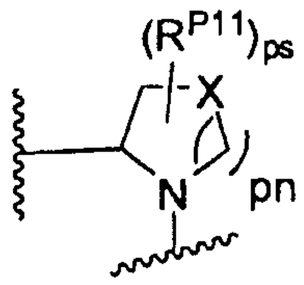
pm and pn are independently 0, 1, or 2;

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

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

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

each P^1 is independently:



wherein:

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

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

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

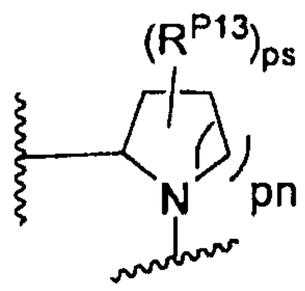
at least one R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy,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

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

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

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



wherein:

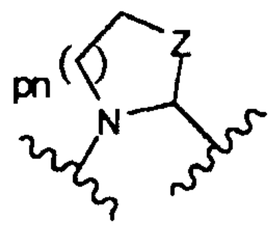
the ring is substituted with one or more oxo group;

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

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

pn is 0, 1, or 2;

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



wherein:

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

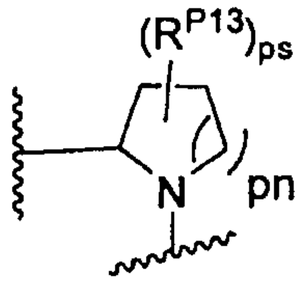
pn is 0, 1, or 2;

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

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

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

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

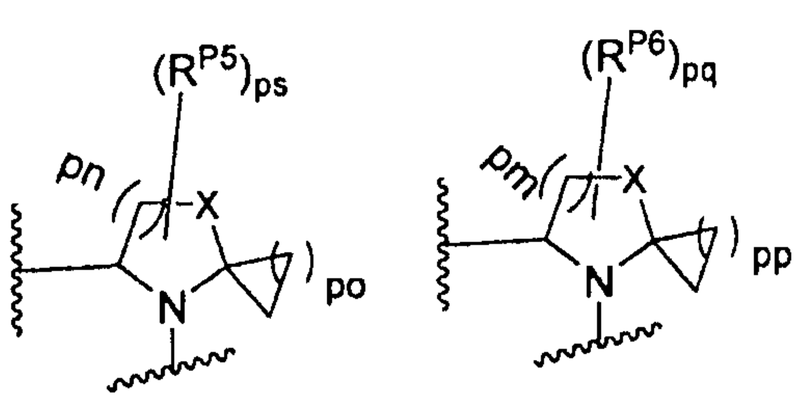


wherein:

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

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

each P^{10} is independently:



wherein:

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

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

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

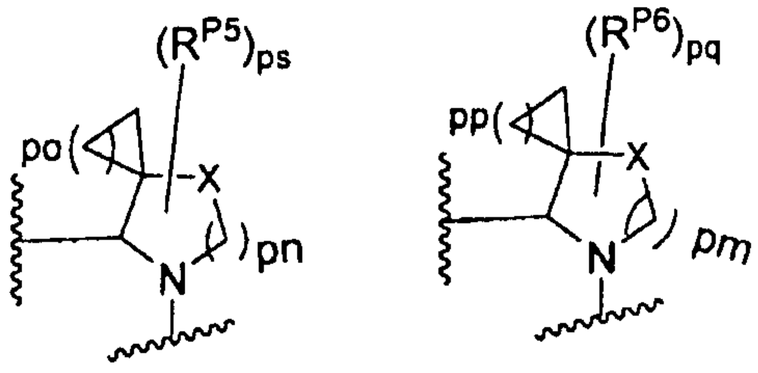
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{11} is independently:



wherein:

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

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

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

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

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

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

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

each $-Z^0-$ is $-C(=O)-$ or $-C(=S)-$;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

R^{Ec} and R^{Ed} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl,

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

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

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are

unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

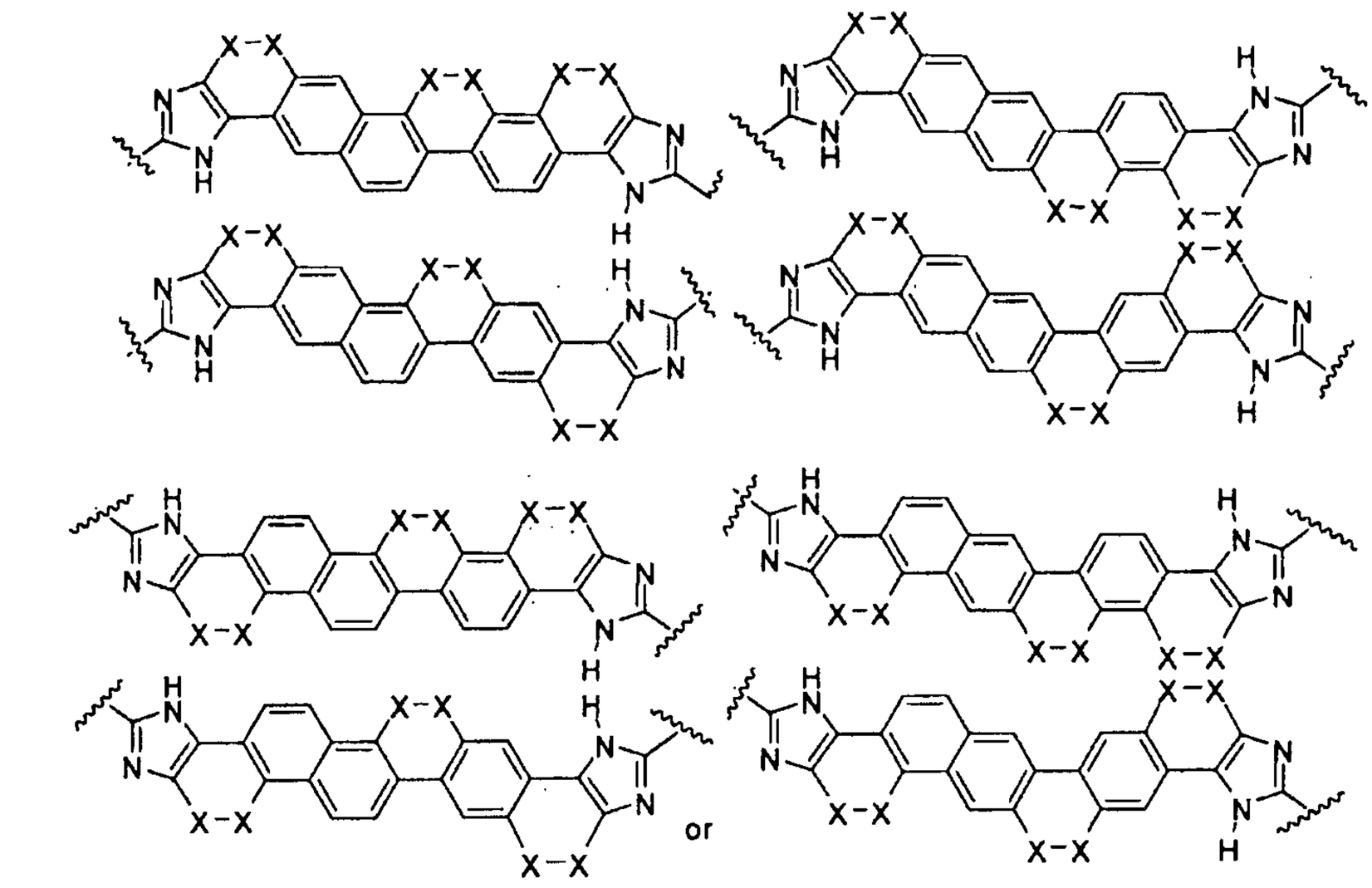
each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^aR^bC(=O)O$-; R^a and R^b are each independently selected from hydrogen, alkenyl, and alkyl; and

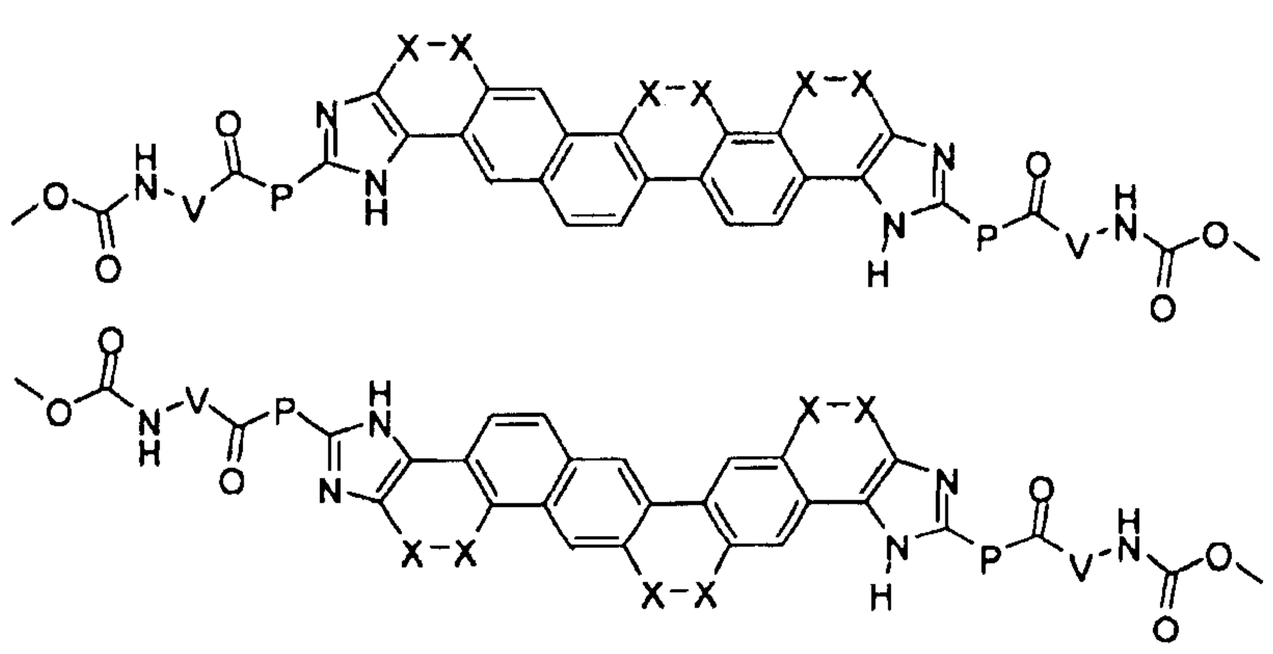
each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

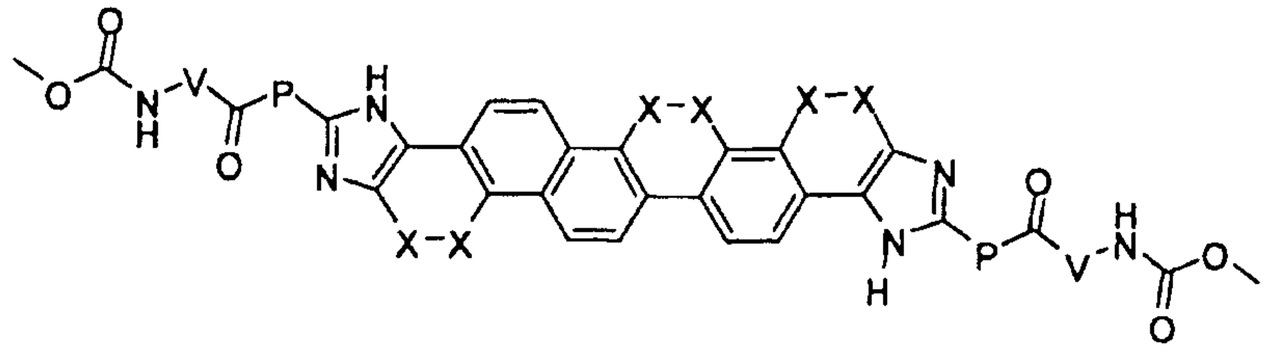
In one embodiment the invention provides a compound of formula (Ie) wherein Y^2 is:

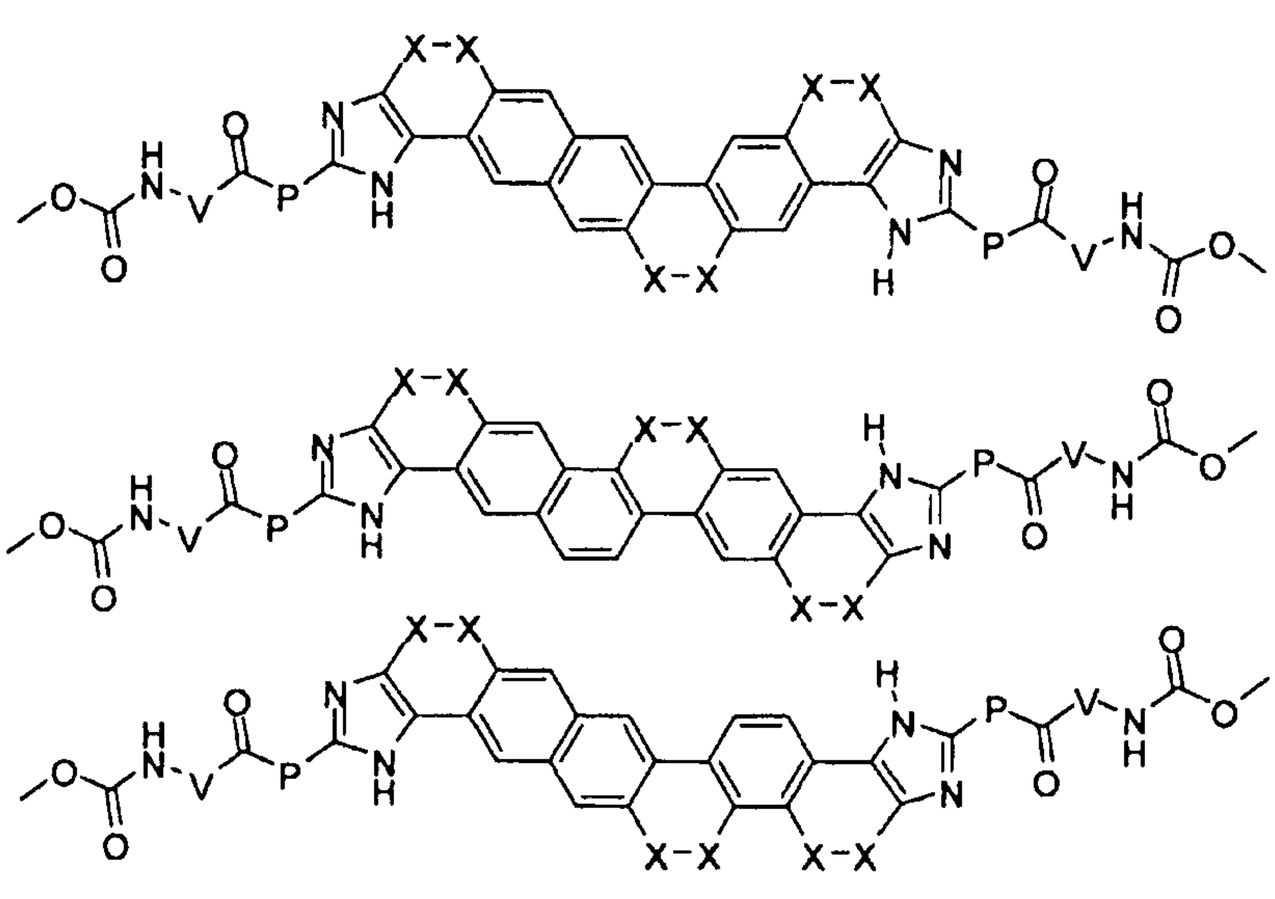


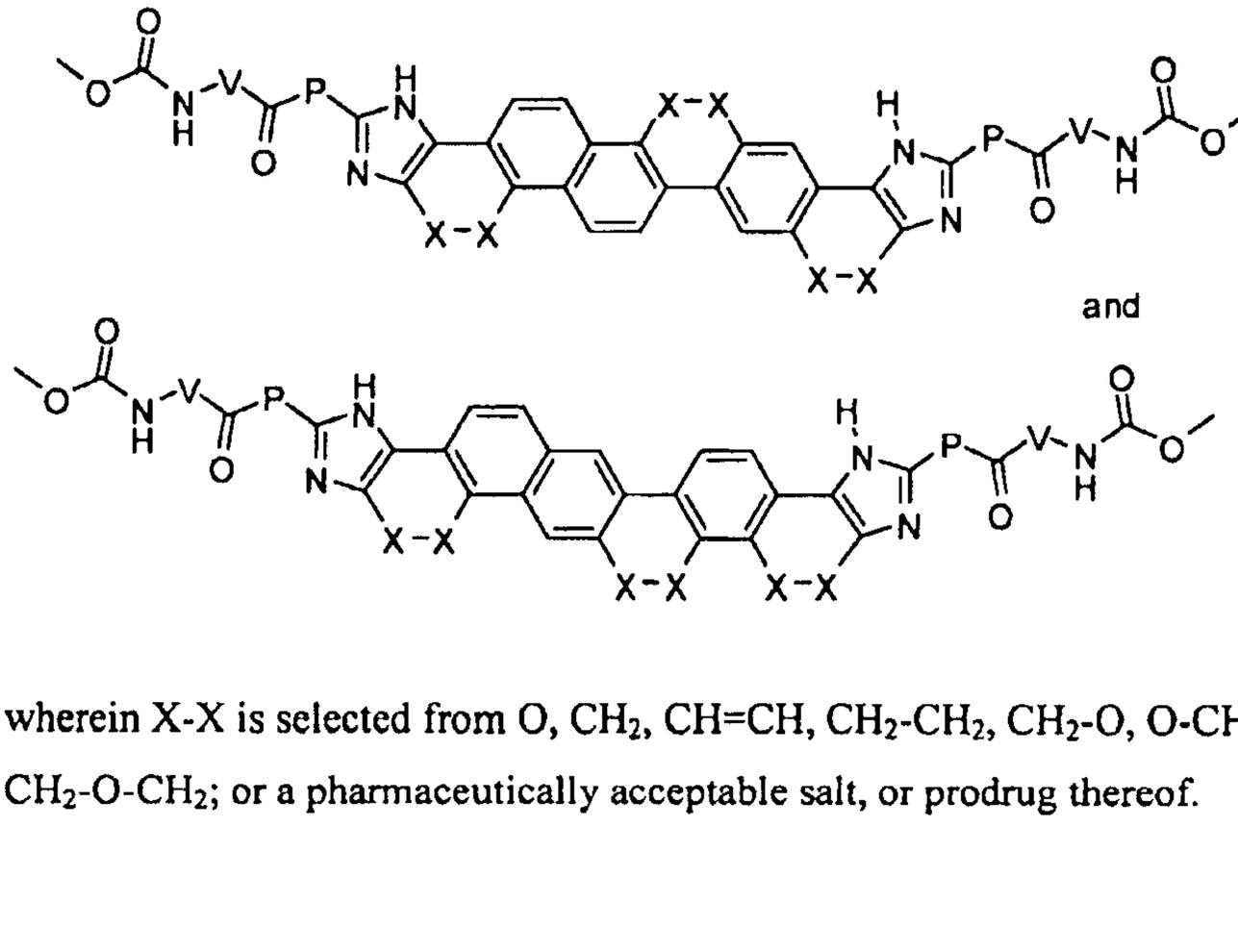
wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2.

In one embodiment the invention provides a compound of formula (Ie) which is selected from:









and

wherein X-X is selected from O, CH_2, CH=CH, CH_2-CH_2, CH_2-O, O-CH_2, CH_2-CH_2-CH_2, and CH_2-O-CH_2; or a pharmaceutically acceptable salt, or prodrug thereof.

Specific values for E, P, V, and Z

In another specific embodiment of the invention each E is E^0.

In another specific embodiment of the invention each E is -NHC(=O)Oalkyl.

In another specific embodiment of the invention E^0 is methoxycarbonylamino.

In one embodiment the invention E^0 is –NH2, alkylamino or dialkylamino.

In one embodiment the invention E^0 is cycloalkylamino or cycloalkyl(alkyl)amino, or dicycloalkylamino.

In one embodiment the invention E^0 is heterocyclyl.

In one embodiment the invention E^0 is heterocyclylamino where the amino is optionally substituted with alkyl.

In one embodiment the invention provides a compound of formula (I) wherein at least one E^0 is $-NR^{Ec}R^{Ed}$ wherein R^{Ec} is H and R^{Ed} is methoxycarbonyl.

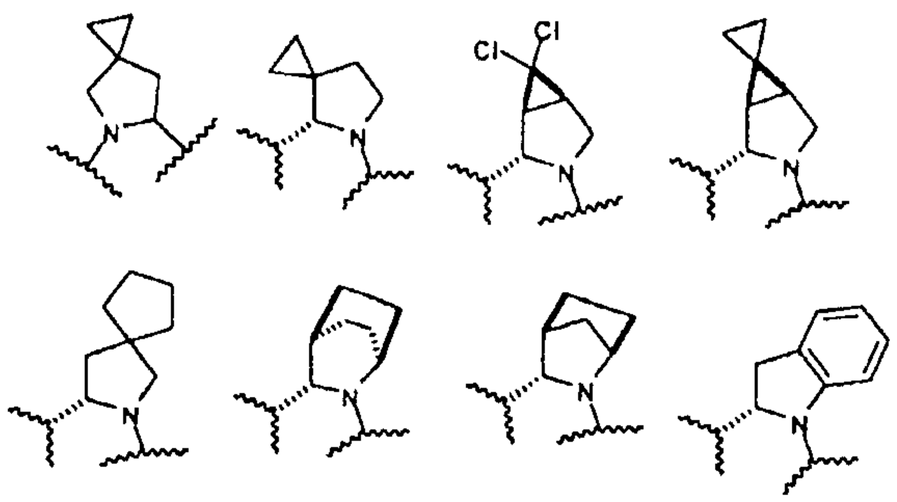
In one embodiment the invention provides a compound of formula (I) wherein at least one E^0 is $-NR^{Ec}R^{Ed}$ wherein R^{Ec} is H or alkyl and R^{Ed} is H or alkyl.

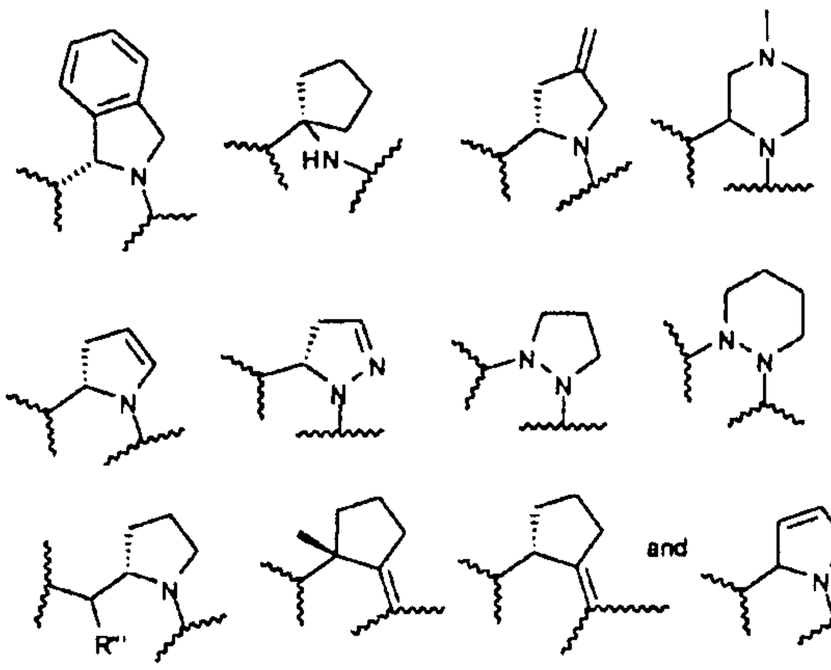
In one embodiment the invention provides a compound of formula (I) wherein at least one E^0 is $-NR^{Ec}R^{Ed}$ wherein R^{Ec} is H, alkyl or cycloalkyl and R^{Ed} is cycloalkyl.

In one embodiment the invention provides a compound of formula (I) wherein at least one E^0 is an N-linked heterocyclyl.

In one embodiment the invention provides a compound of formula (I) wherein at least one E^0 is $-NR^{Ec}R^{Ed}$ wherein R^{Ec} is H, alkyl, or cycloalkyl; and R^{Ed} is heterocycle.

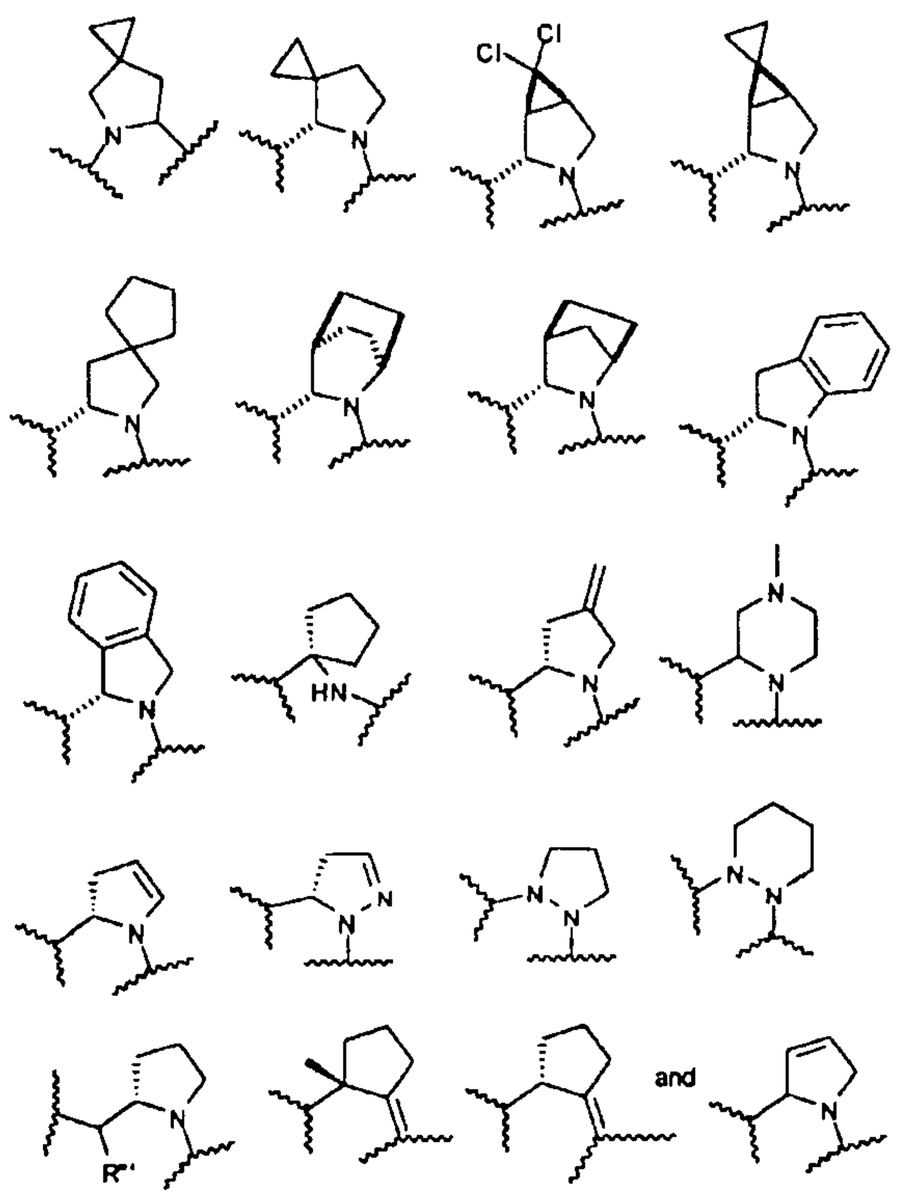
In another specific embodiment of the invention P is selected from:





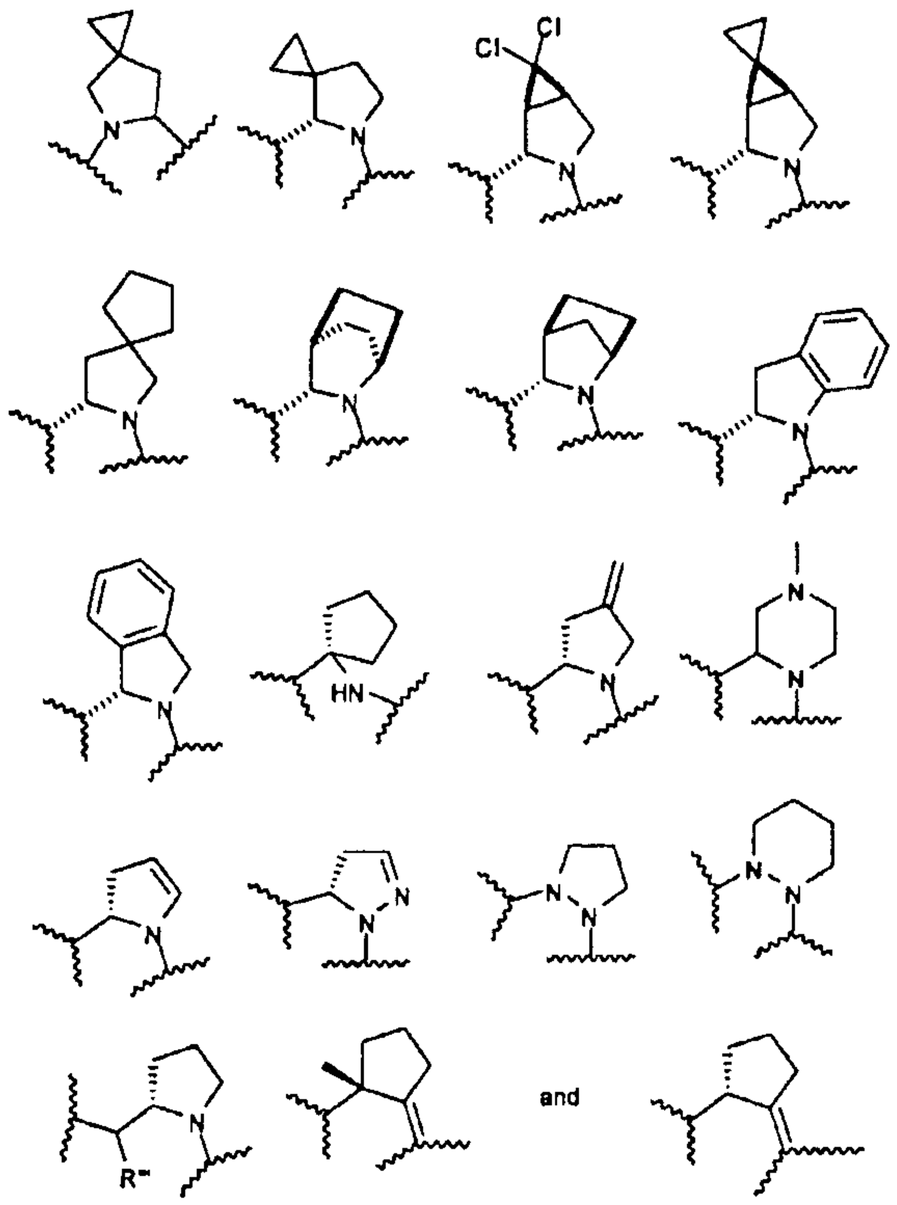
wherein R''' is hydrogen or methyl.

In another specific embodiment of the invention P is selected from



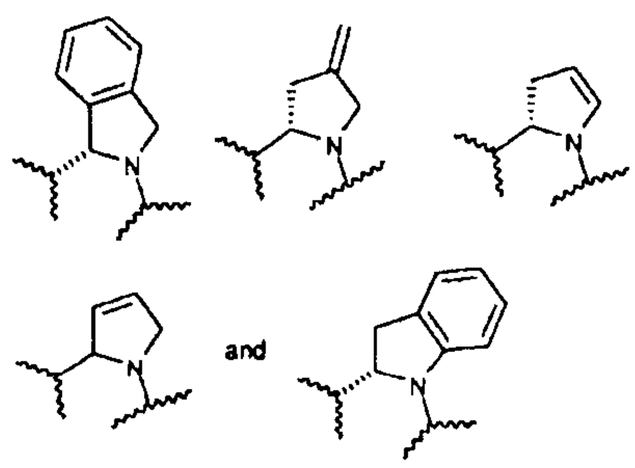
and another P is P^0.

In another specific embodiment of the invention P is selected from

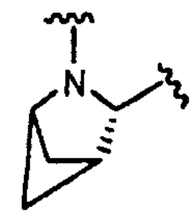


wherein R''' is hydrogen or methyl; and another P is P^0.

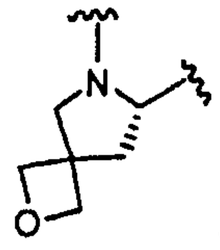
In another specific embodiment of the invention P is selected from:



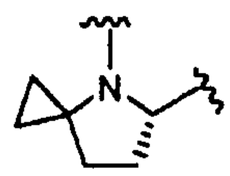
In another specific embodiment of the invention at least one P is P^7 and is:



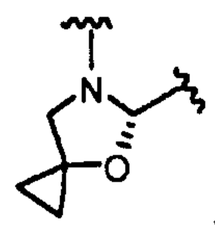
In another specific embodiment of the invention at least one P is P^8 and is:



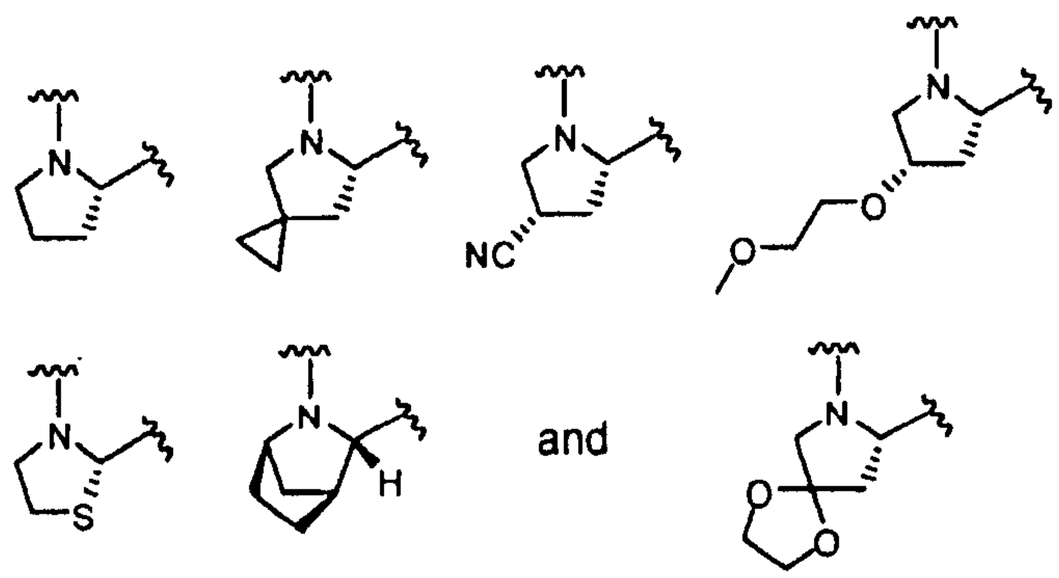
In another specific embodiment of the invention P is P^{10} and is:



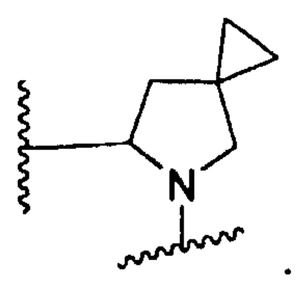
In another specific embodiment of the invention P is P^{11} and is:



In another specific embodiment of the invention each P is independently selected from:

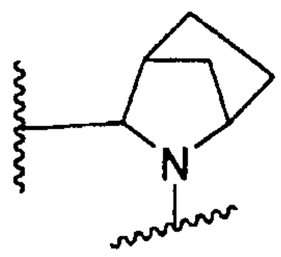


In another specific embodiment of the invention P^0 is



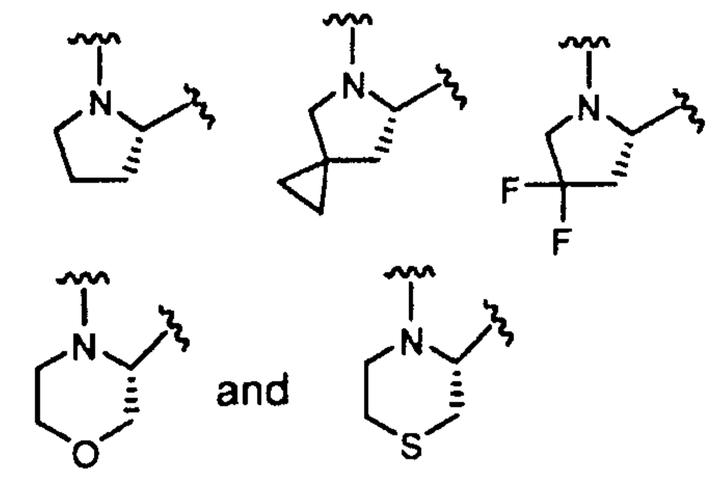
In another specific embodiment of the invention P^7 is a [2.2.1] or a [2.2.2] ring system.

In another specific embodiment of the invention P^7 is

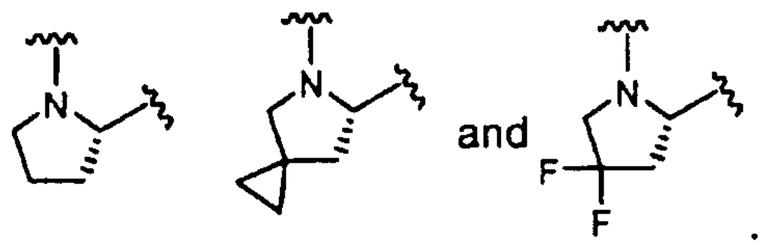


optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

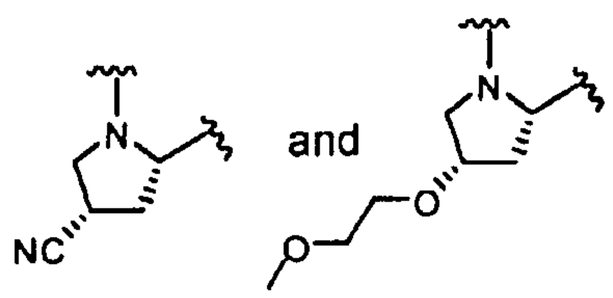
In another specific embodiment of the invention P is selected from:



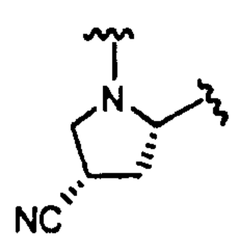
In another specific embodiment of the invention P is selected from:



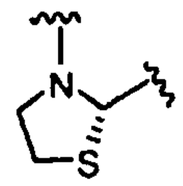
In another specific embodiment of the invention P is selected from:



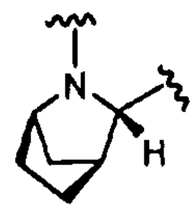
In another specific embodiment of the invention P is:



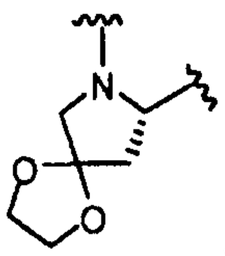
In another specific embodiment of the invention P is:



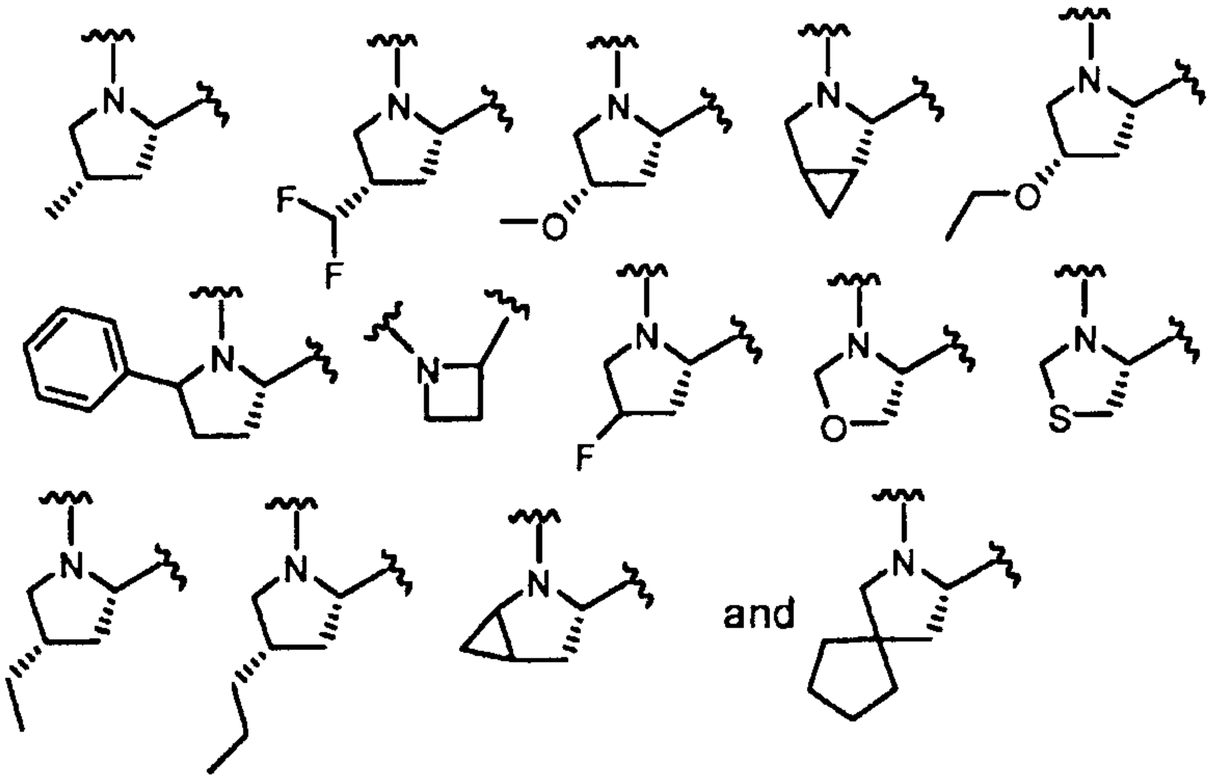
In another specific embodiment of the invention P is:



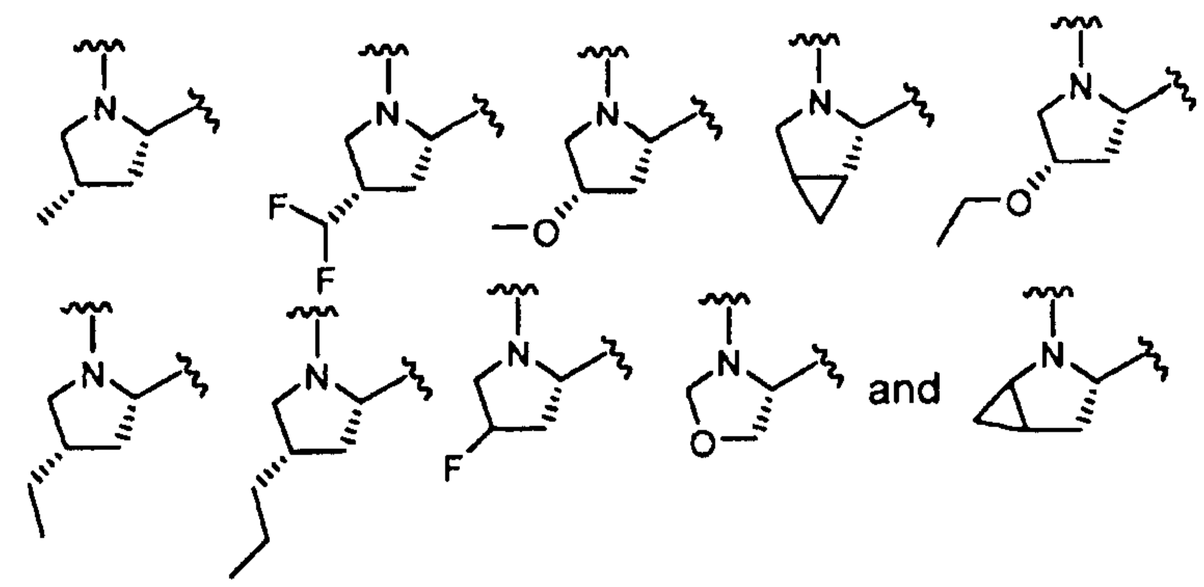
In another specific embodiment of the invention P is:



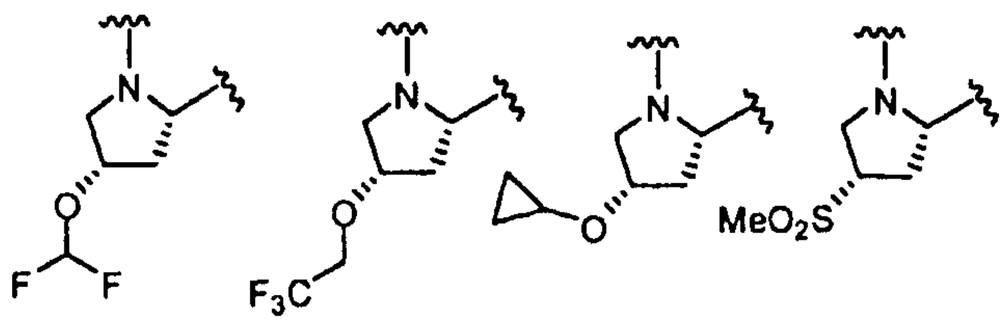
In another specific embodiment of the invention P is selected from:

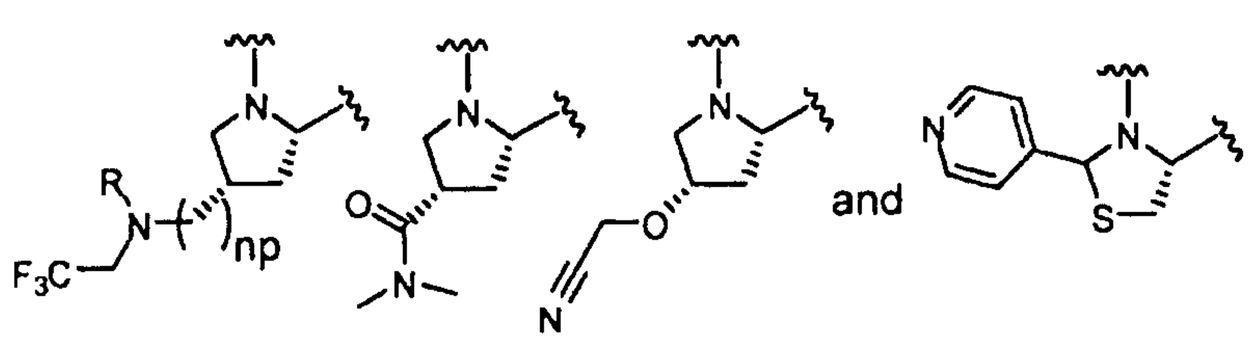


In another specific embodiment of the invention P is selected from:



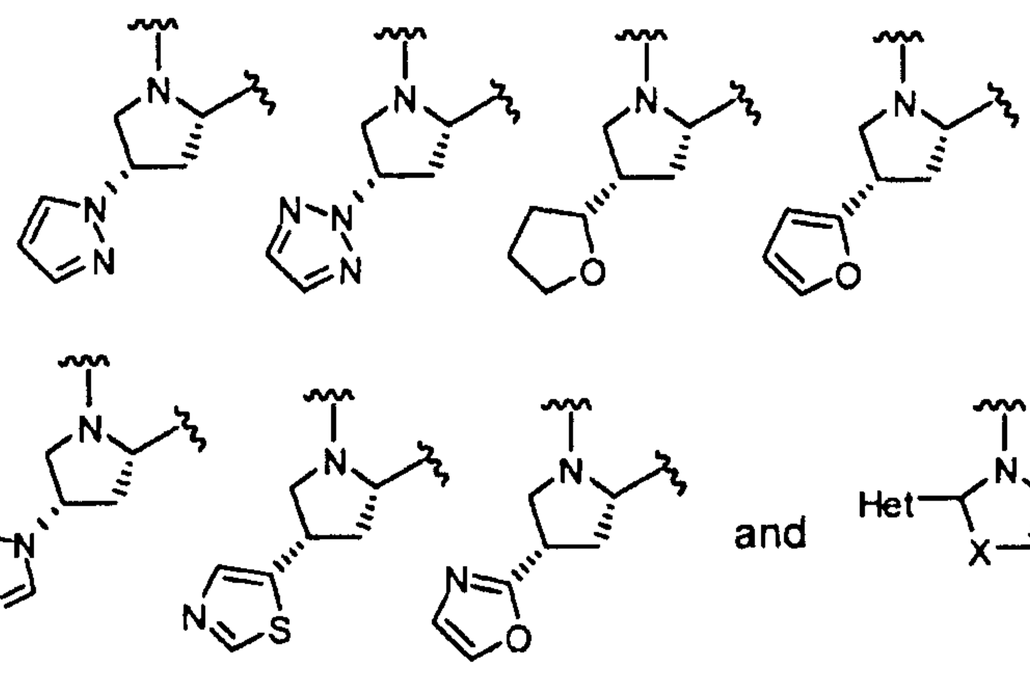
In another specific embodiment of the invention P is selected from:





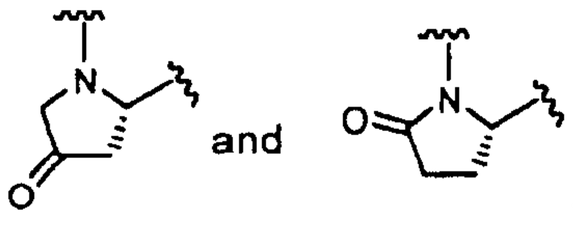
wherein R is hydrogen or methyl and np is 0 or 1.

In another specific embodiment of the invention P is selected from:

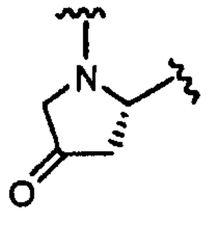


wherein X is O or S; and Het is a heterocycle.

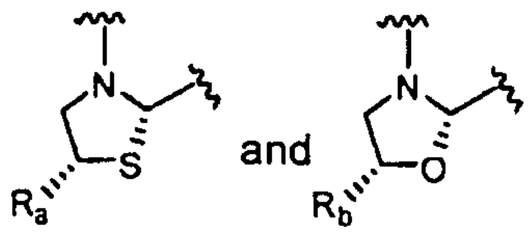
In another specific embodiment of the invention P is selected from:



In another specific embodiment of the invention P is:

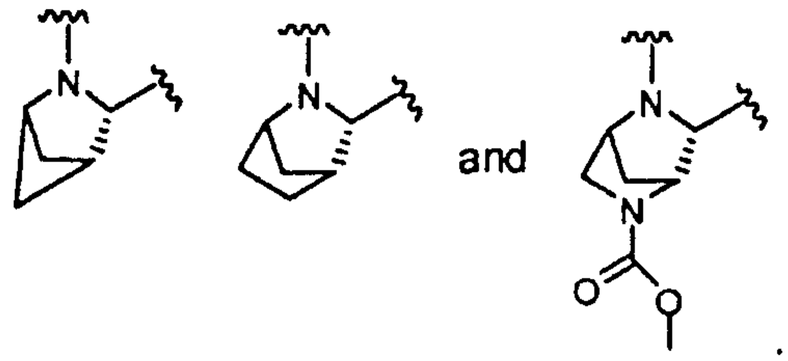


In another specific embodiment of the invention P is selected from:

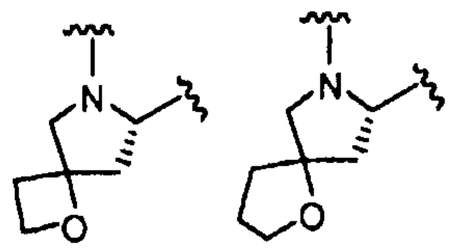


wherein R_a is hydrogen or methyl and R_b is methyl, or ethyl.

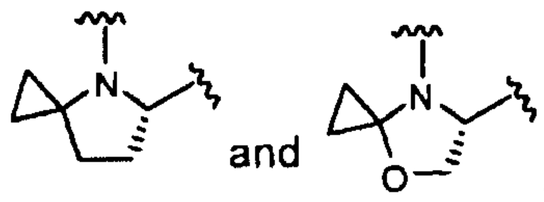
In another specific embodiment of the invention P is selected from:



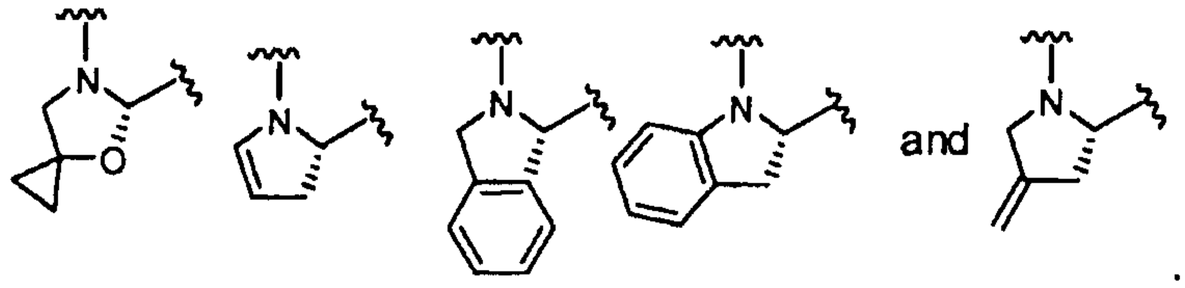
In another specific embodiment of the invention P is selected from:



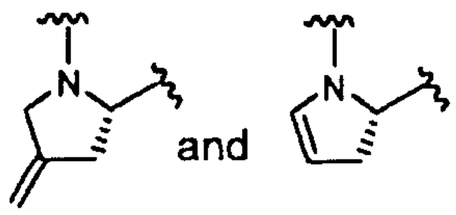
In another specific embodiment of the invention P is selected from:



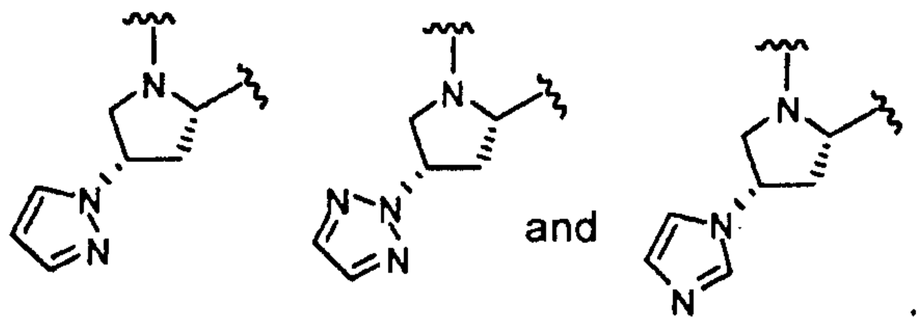
In another specific embodiment of the invention P is selected from:



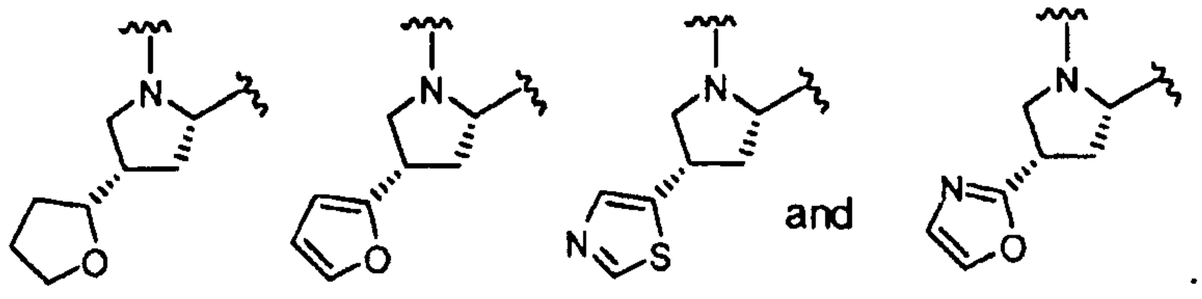
In another specific embodiment of the invention P is selected from:



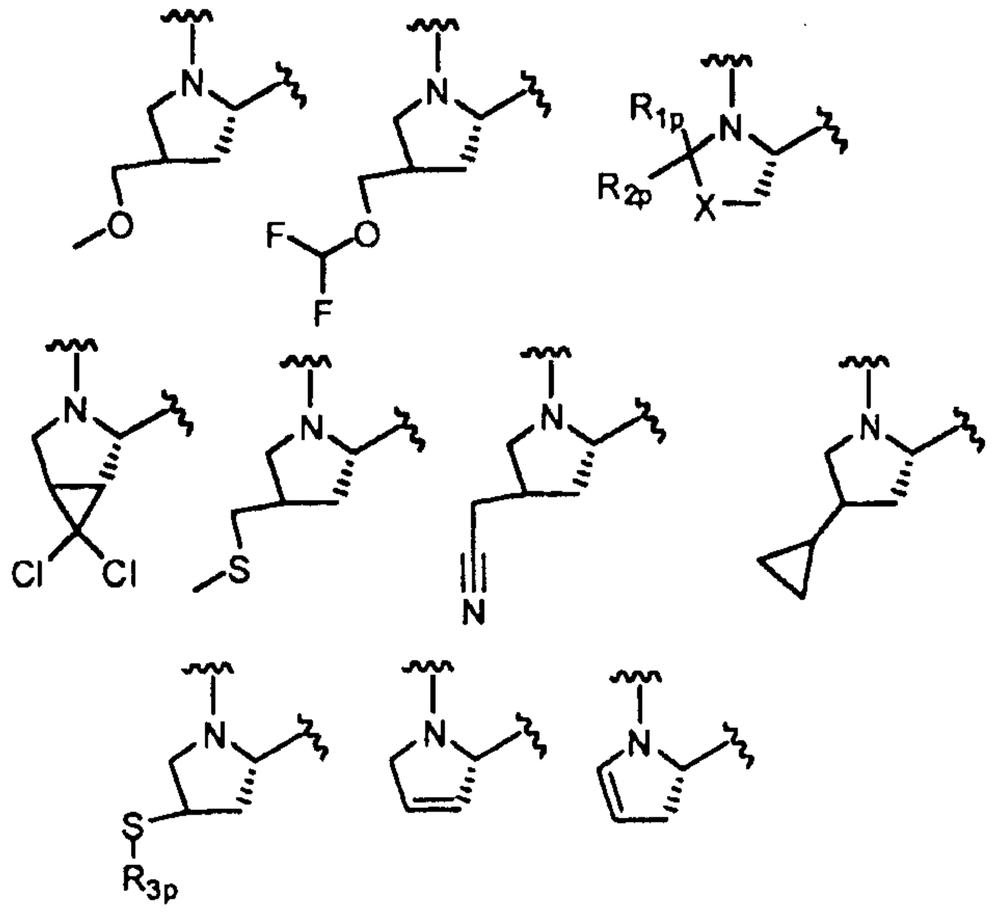
In another specific embodiment of the invention P is selected from:

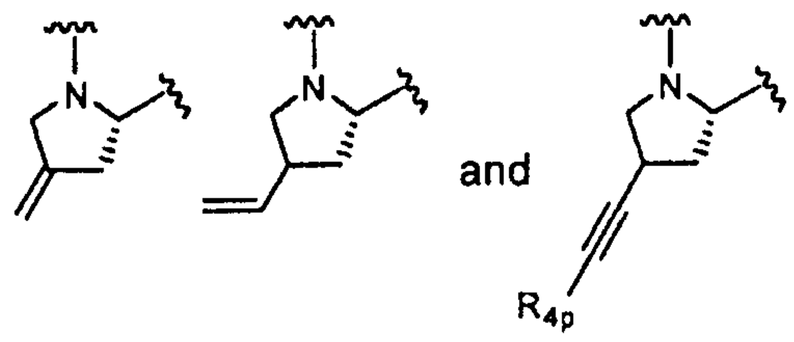


In another specific embodiment of the invention P is selected from:



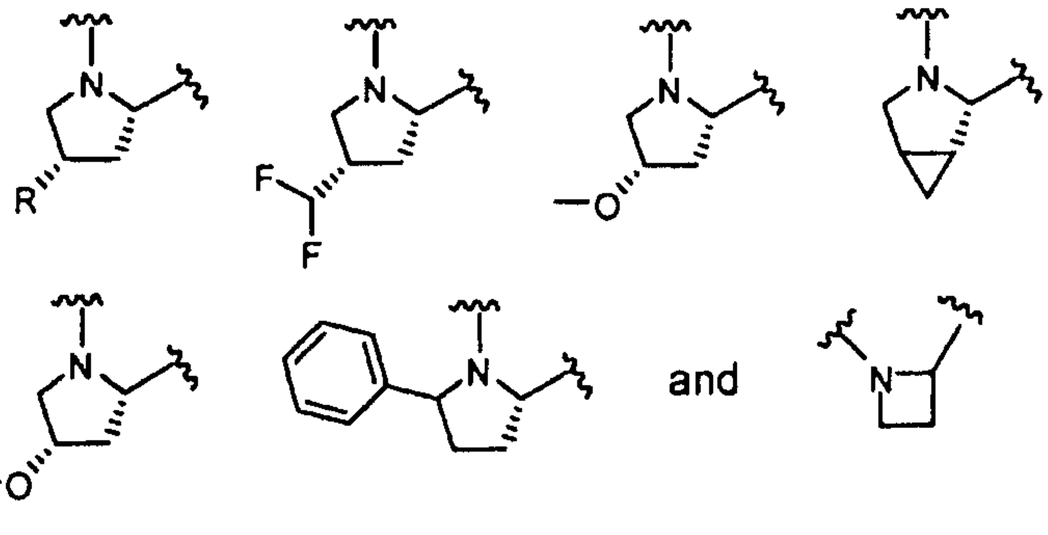
In another specific embodiment of the invention P is selected from:





wherein X is O or S; R_{1p} and R_{2p} are carbon linked and when taken together form a 4-6 membered heterocycle; R_{3p} is alkyl or cycloalkyl; and R_{4p} is hydrogen, methyl, or cyclopropyl.

In another specific embodiment of the invention P is P^0 and is selected from:



wherein R is alkyl.

In another specific embodiment of the invention when P is a divalent group that is linked through a nitrogen of P and through a carbon of P, it is the nitrogen of P that is connected to Z.

In another specific embodiment of the invention each V is V^0.

In another specific embodiment of the invention each V is alkyl.

In another specific embodiment of the invention each V is isopropyl.

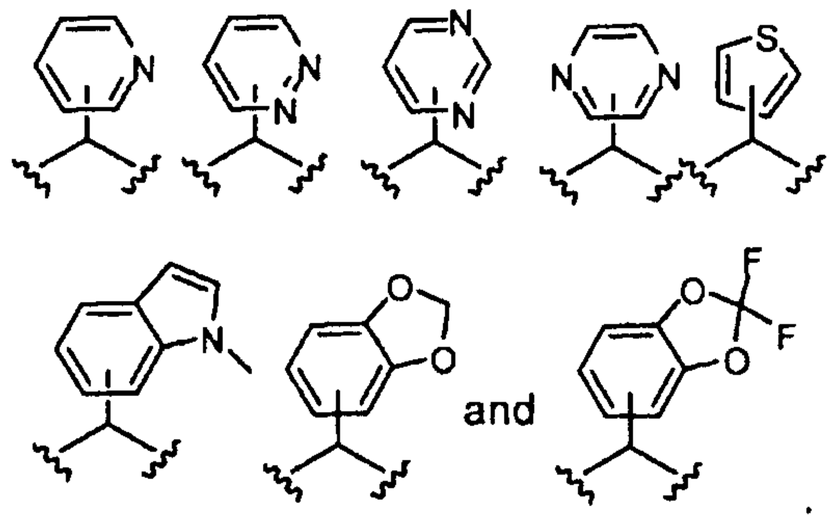
In another specific embodiment of the invention each V is isobutyl.

In another specific embodiment of the invention each V is V^2.

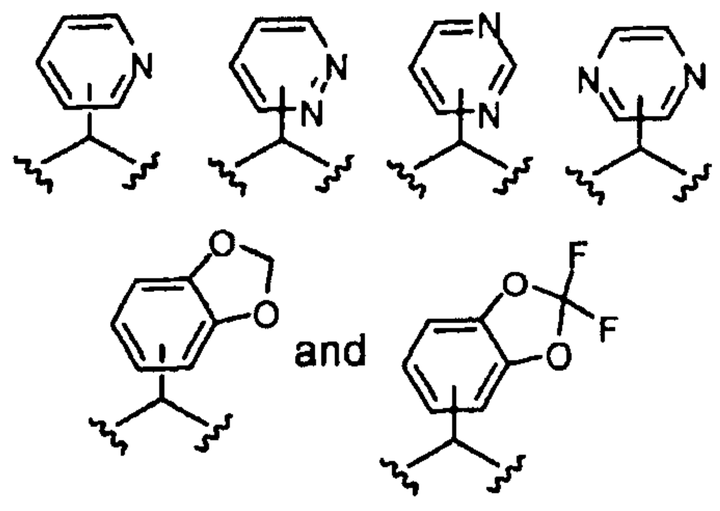
In another specific embodiment of the invention each V is haloalkyl.

In another specific embodiment of the invention each V is independently selected from V^0, V^1, V^2, V^3, V^4, and V^5.

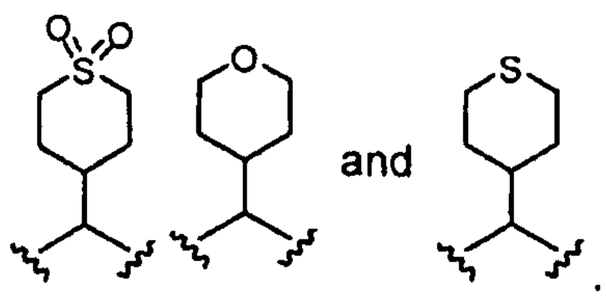
In another specific embodiment of the invention at least one V is selected from:



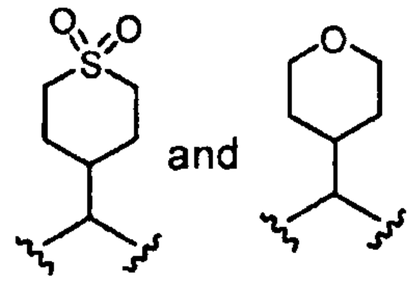
In another specific embodiment of the invention at least one V is selected from:



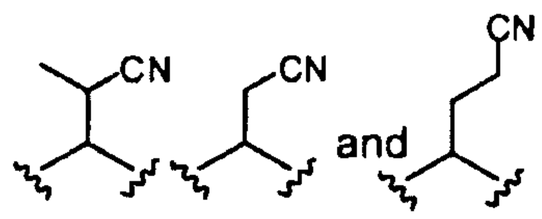
In another specific embodiment of the invention at least one V is selected from:



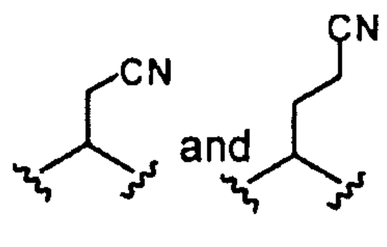
In another specific embodiment of the invention at least one V is selected from:



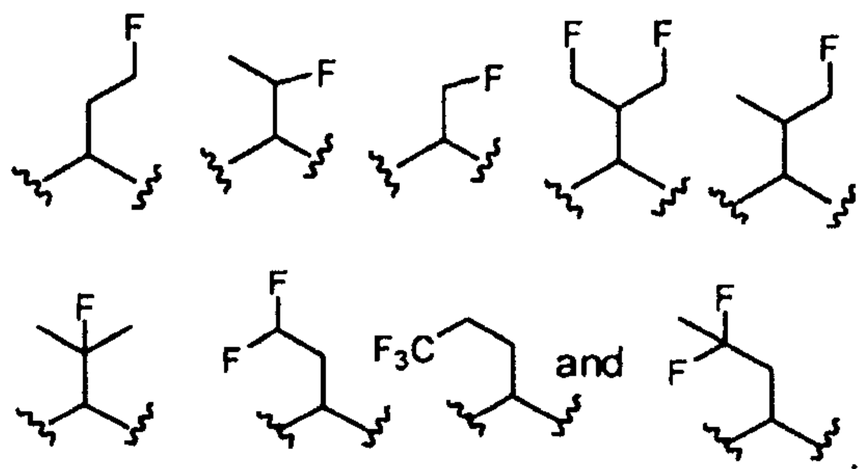
In another specific embodiment of the invention at least one V is selected from:



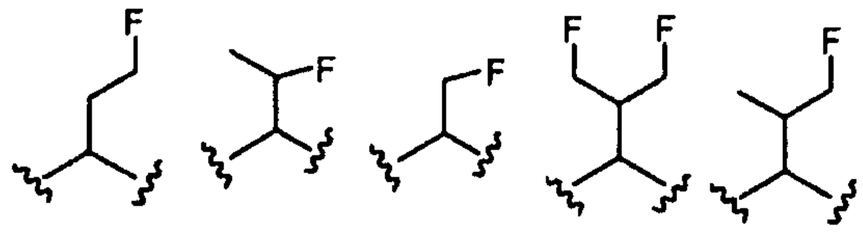
In another specific embodiment of the invention at least one V is selected from:

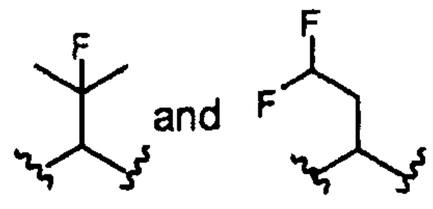


In another specific embodiment of the invention at least one V is selected from:

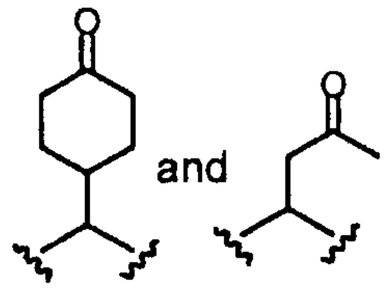


In another specific embodiment of the invention at least one V is selected from:

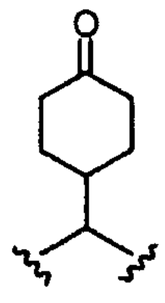




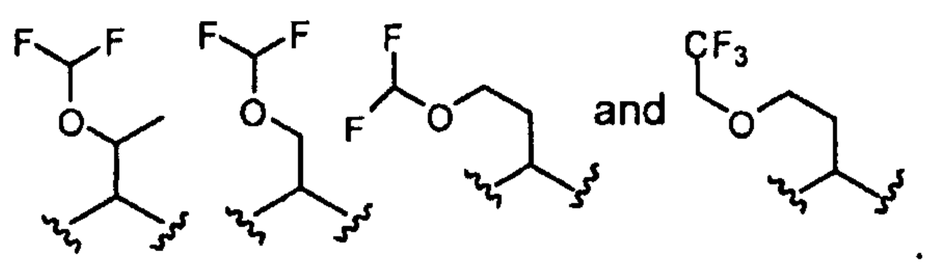
In another specific embodiment of the invention at least one V is selected from:



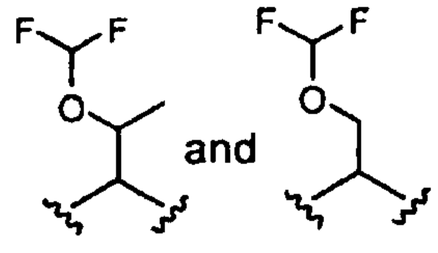
In another specific embodiment of the invention at least one V is:



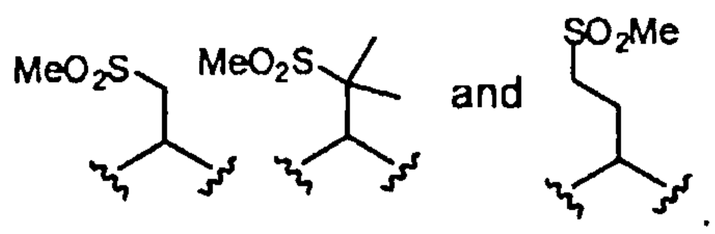
In another specific embodiment of the invention at least one V is selected from:



In another specific embodiment of the invention at least one V is selected from:

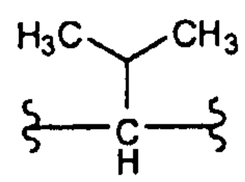


In another specific embodiment of the invention at least one V is selected from:



In another specific embodiment of the invention at least one V is:

In another specific embodiment of the invention each V is:



In another specific embodiment of the invention each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl; and each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, hydroxy, and $NR^{Va}R^{Vb}$ C(=O)O-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl.

In another specific embodiment of the invention each V^0 is independently arylalkyl or heterocyclylalkyl, wherein arylalkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy; and the aryl part can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the heterocyclylalkyl is further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second

heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, -(NR^XR^Y)alkyl, and oxo.

In another specific embodiment the invention each V is isobutyl.

In another specific embodiment the invention at least one V is isobutyl.

In another specific embodiment the invention at least one V is phenylmethyl where the Z and E groups are each connected to the methyl group (i.e. –CH(Ph)-).

In another specific embodiment the invention at least one V is V^0 and at least one V^0 is phenylmethyl where the Z and E groups are each connected to the methyl group and the phenyl can be substitituted as described in the description for the V^0 aryl group.

In another specific embodiment the invention at least one V^0 is arylmethyl where the Z and E groups are each connected to the methyl group and the aryl can be substitituted as described in the description for the V^0 aryl group.

In another specific embodiment the invention at least one V is V^0 and at least one V^0 is heterocyclylmethyl where the Z and E groups are each connected to the methyl group.

In another specific embodiment the invention at least one V is V^0 and at least one V^0 is heterocyclylmethyl where the Z and E groups are each connected to the methyl group and the heterocyclyl group can be substitituted as described in the description for the V^0 heterocyclyl group.

In another specific embodiment the invention each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl.

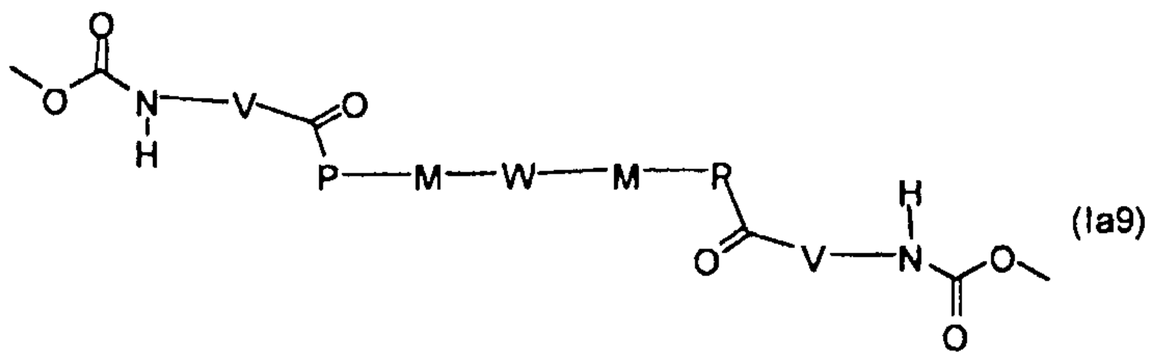
In another specific embodiment the invention each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; wherein R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl.

In another specific embodiment of the invention each Z is Z^0.

In another specific embodiment of the invention each Z is –C(=O)-.

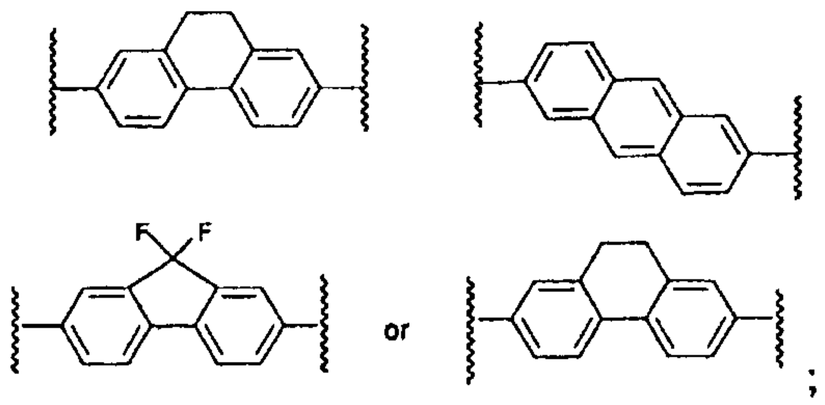
For the compounds of formula (I) described herein, including the compounds of formulae (Ia), (Ib), (Ic), (Id), and (Ie), any of the above specific values or embodiments for the variables E, P, V, and Z, can be applied. Thus, the invention also includes specific embodiments wherein one or more of the specific values or embodiments for J, T, P, W, L, M, A, R9, E, P, V, and Z described herein are combined with one of formulae (Ia), (Ib), (Ic), (Id), and (Ie), to provide a sub-set of compounds that represents a specific embodiment of the invention.

For example, by selecting a compound of formula (Ia9) above, along with specific values for P, M, W, and V identified herein, one can identify a specific embodiment the invention which is a compound of formula (Ia9):


(Ia9)

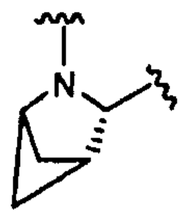
wherein:

W is

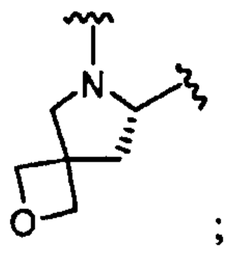

;

one M is imidazolyl and one M is benzimidazolyl;

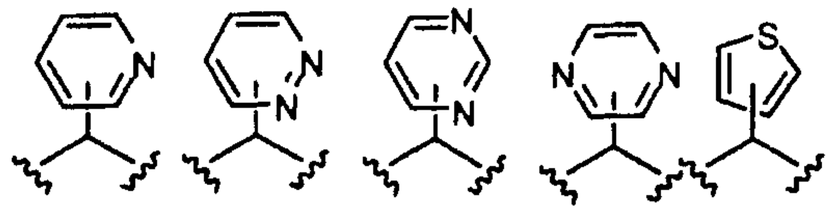
one P is P^7 and is:

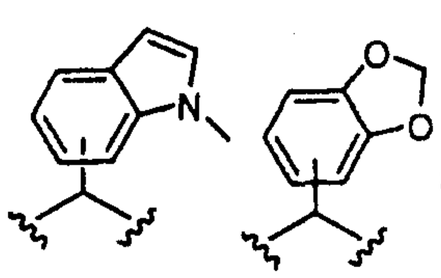
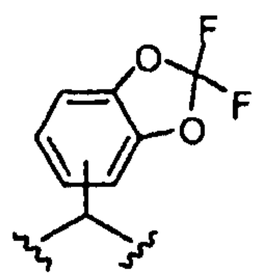


one P is P^8 and is:

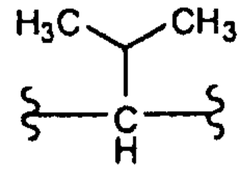

;

one V is selected from:




and

; and

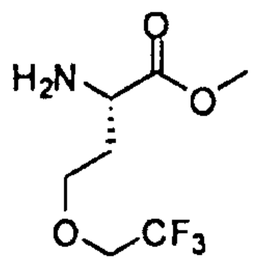
one V is:



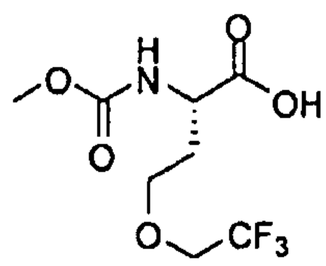
The invention provides all such combinations as specific embodiments of the invention.

Synthetic Intermediates

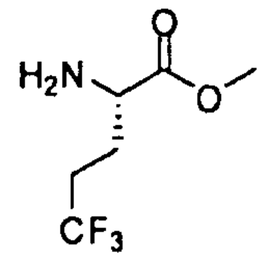
The invention also provides synthetic processes and novel synthetic intermediates disclosed herein. For example, the invention provides the following specific intermediate compounds that are useful for preparing compounds of formula (I):



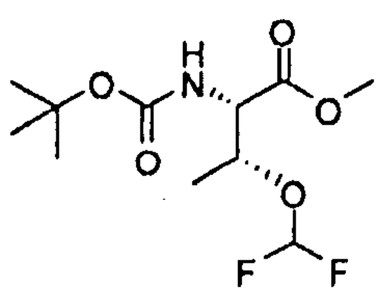
2-Amino-4-(2,2,2-trifluoro-ethoxy)-butyric acid methyl ester



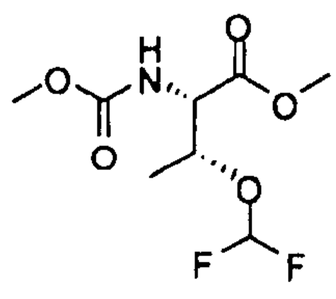
2-Methoxycarbonylamino-4-(2,2,2-trifluoro-ethoxy)-butyric acid



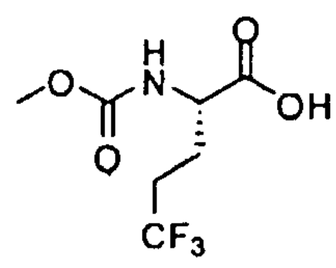
2-Amino-5,5,5-trifluoro-pentanoic acid methyl ester



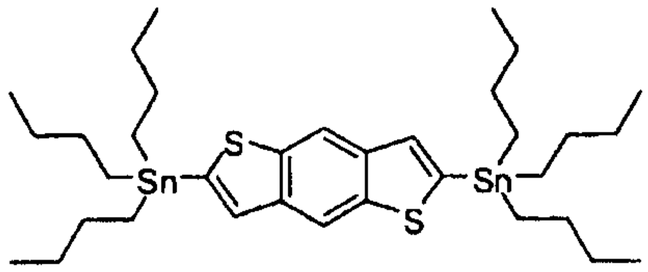
2-*tert*-Butoxycarbonylamino-3-difluoromethoxy-butyric acid methyl ester



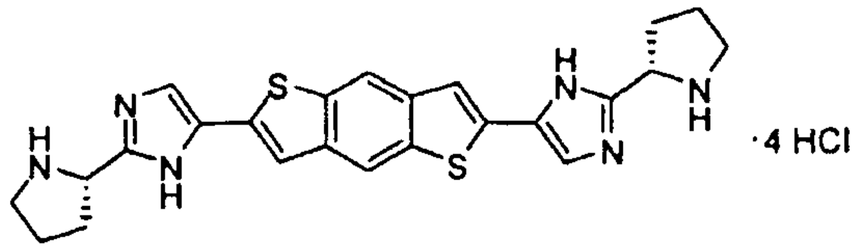
3-Difluoromethoxy-2-methoxycarbonylamino-butyric acid methyl ester



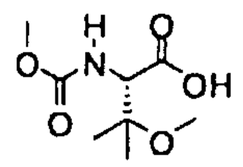
5,5,5-Trifluoro-2-methoxy-carbonylamino-pentanoic acid



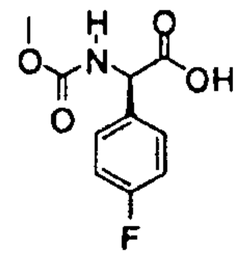
2,6-bis(tri-*n*-butylstannyl)-benzo[1,2-*b*:4,5-*b*']dithiophene



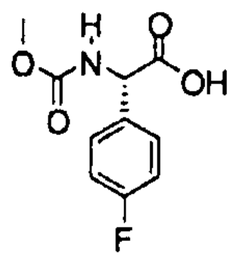
2-{5-(6-{2-[pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-benzo[1,2-*b*:4,5-*b*']dithiophene-2-yl)-1*H*-imidazol-2-yl}-pyrrolidine tetrahydrochloride



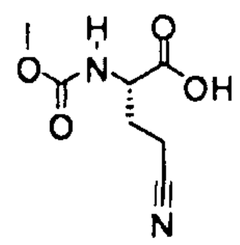
(s)-3-Methoxy-2-methoxycarbonylamino-3-methyl-butyric acid



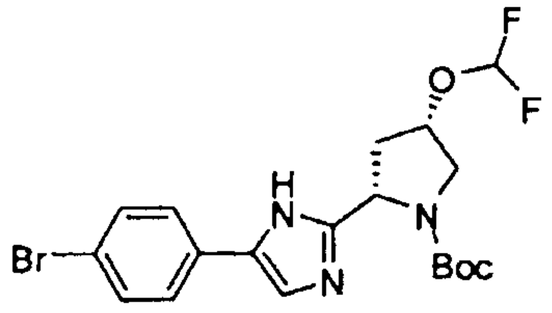
(R)-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid



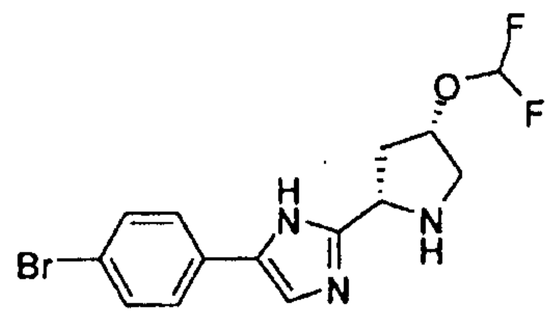
(S)-(4-Fluoro-phenyl)-methoxycarbonylamino-acetic acid



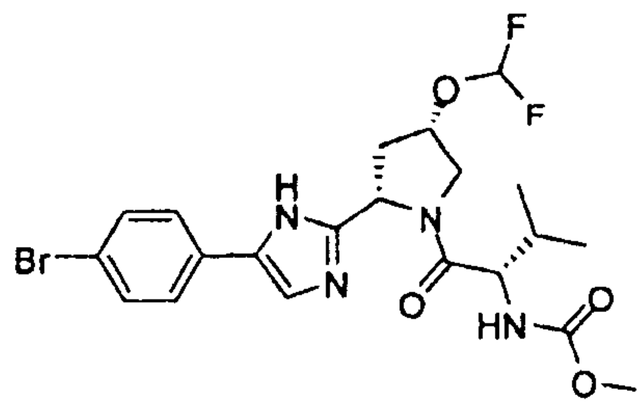
(S)-4-Cyano-2-methoxycarbonyl-aminobutyric acid



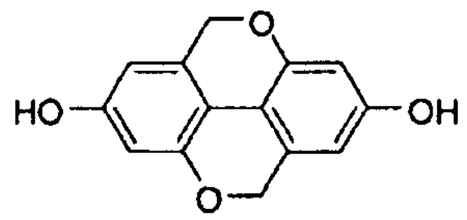
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-difluoromethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester



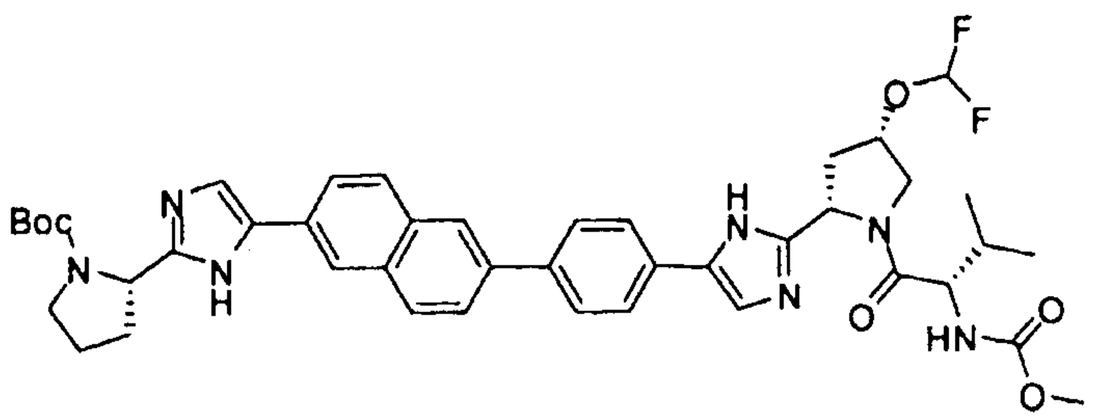
5-(4-Bromo-phenyl)-2-(4-difluoromethoxy-pyrrolidin-2-yl)-1*H*-imidazole



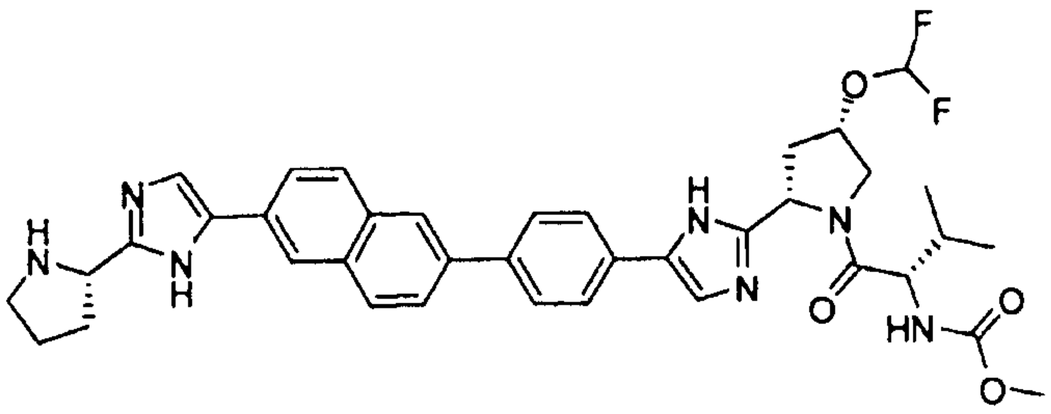
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-difluoromethoxy-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



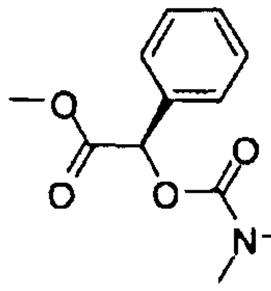
5,10-Dihydro-chromeno[5,4,3-*cde*]chromene-2,7-diol



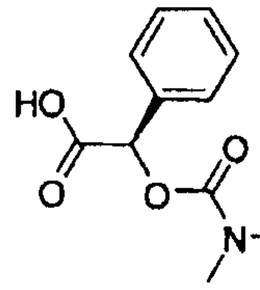
2-{5-[6-(4-{2-[4-Difluoromethoxy-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



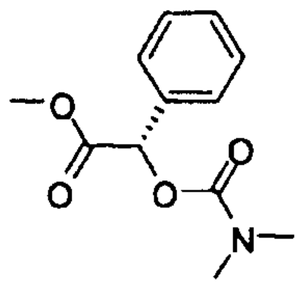
{1-[4-Difluoromethoxy-2-(5-{4-[6-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-naphthalen-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



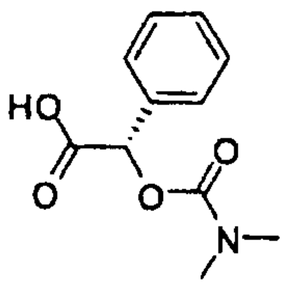
Dimethylcarbamoyloxy-phenyl-acetic acid methyl ester



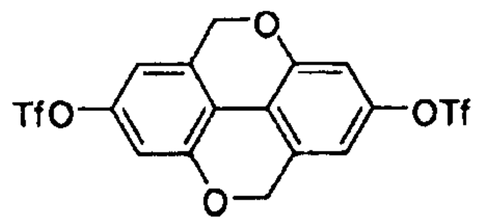
Dimethylcarbamoyloxy-phenyl-acetic acid



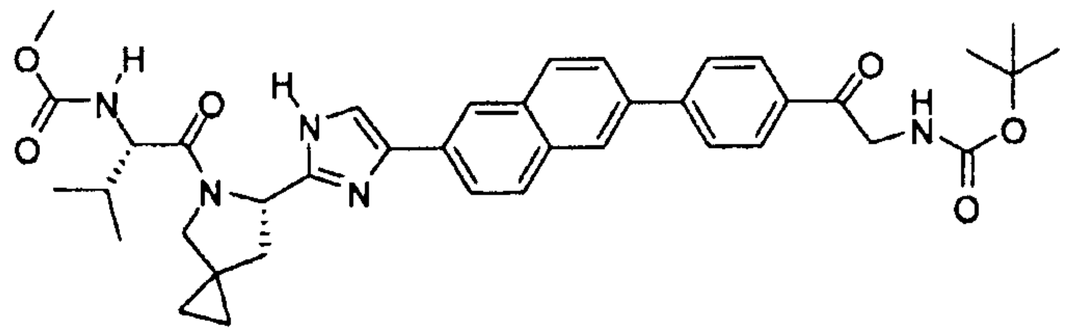
Dimethylcarbamoyloxy-phenyl-acetic acid methyl ester



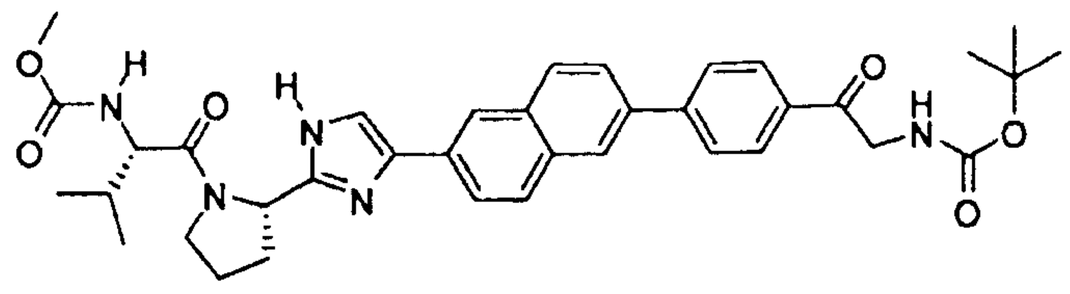
Dimethylcarbamoyloxy-phenyl-acetic acid



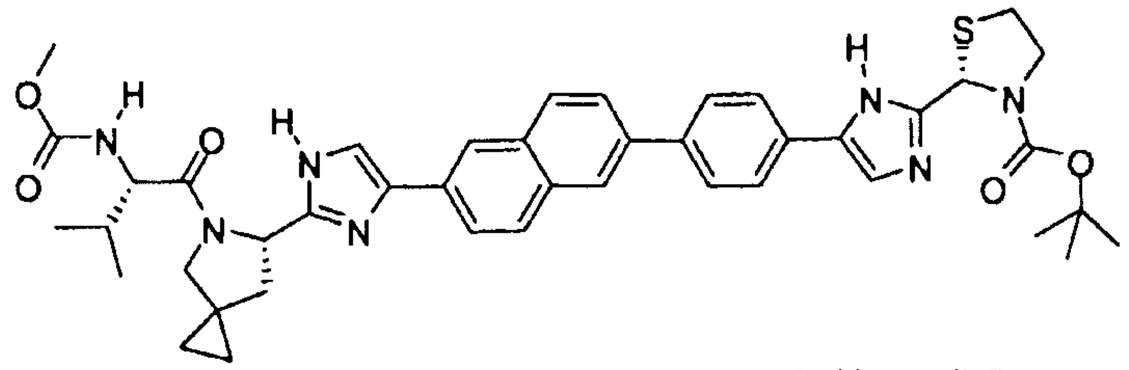
Trifluoro-methanesulfonic acid 7-trifluoro methanesulfonyloxy-5,10-dihydro-chromeno[5,4,3-*cde*]chromen-2-yl ester



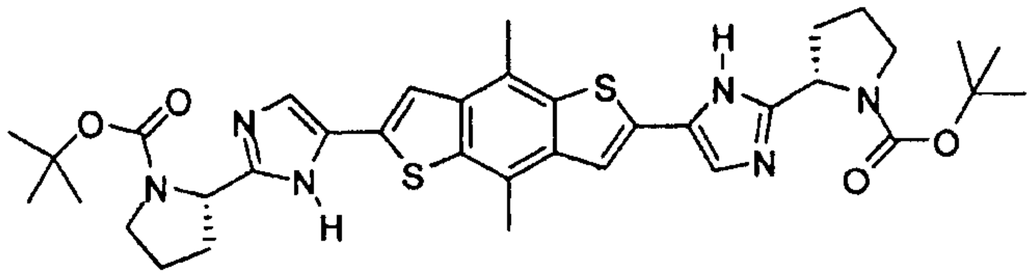
{1-[6-(4-(6-[4-(2-*tert*-Butoxycarbonylamino-acetyl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-5-aza-spiro[2.4]heptane-5-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



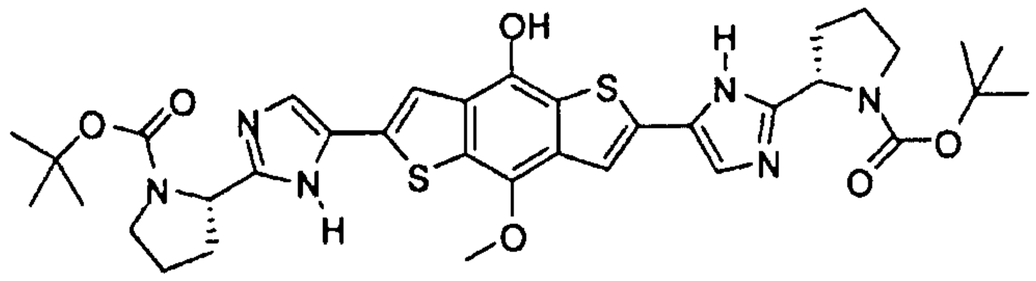
{1-[2-(4-{6-[4-(2-*tert*-Butoxycarbonylamino-acetyl)-phenyl]-naphthalen-2-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



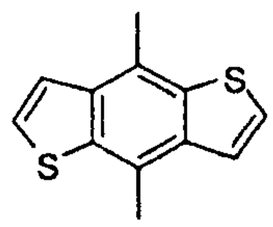
2-{5-[4-(6-{2-[5-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-1*H*-imidazol-4-yl}-naphthalen-2-yl)-phenyl]-1*H*-imidazol-2-yl}-thiazolidine-3-carboxylic acid *tert*-butyl ester



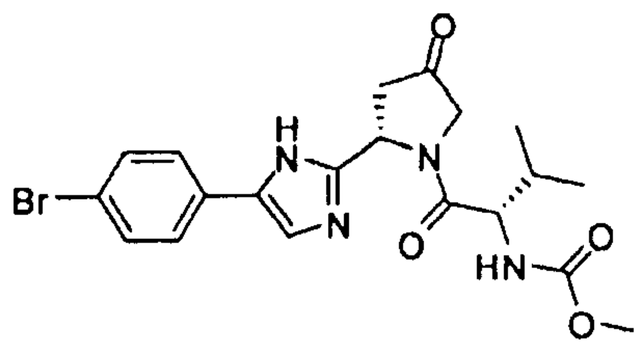
1-{2-[5-(6-{2-[1-carbamic acid tert. buty ester-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethyl-1,5-dithia-*s*-indacen-2-yl)-1*H*-imidazol-2-yl}-pyrrolidine-1-carbamic acid tert.butyl ester



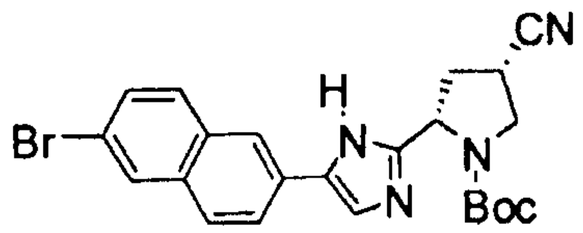
1-{2-[5-(6-{2-[1-carbamic acid tert. buty ester-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-4,8-dimethoxy-1,5-dithia-*s*-indacen-2-yl)-1*H*-imidazol-2-yl}-pyrrolidine-1-carbamic acid tert.butyl ester



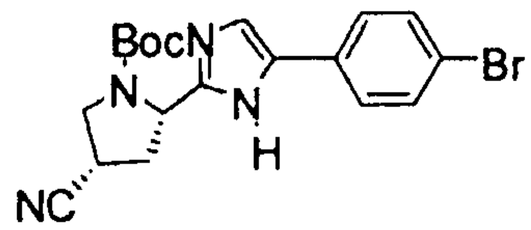
4,8-Dimethyl-1,5-dithia-*s*-indacene



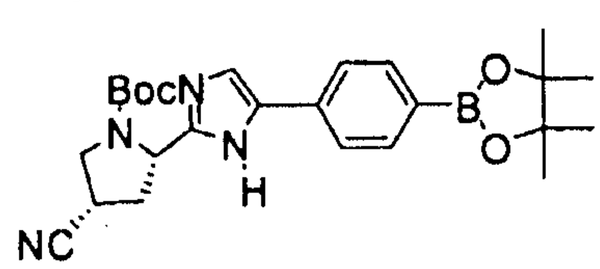
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-oxo-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



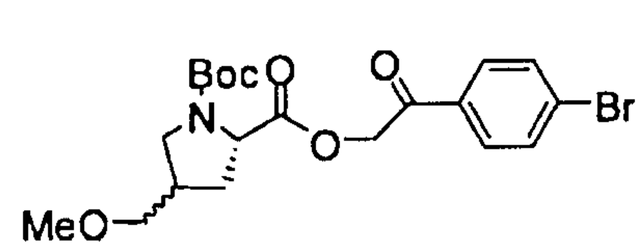
2-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester



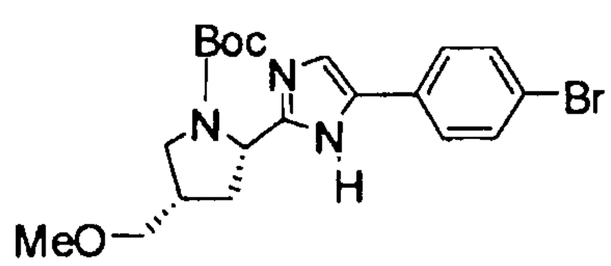
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester



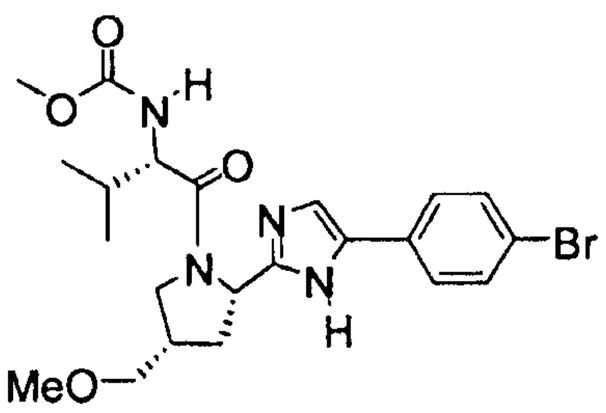
4-Cyano-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



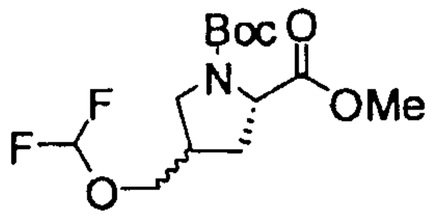
4-Methoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



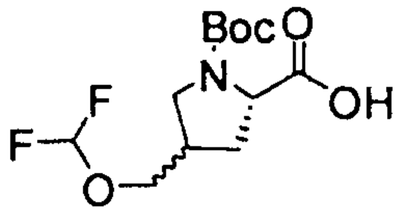
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester



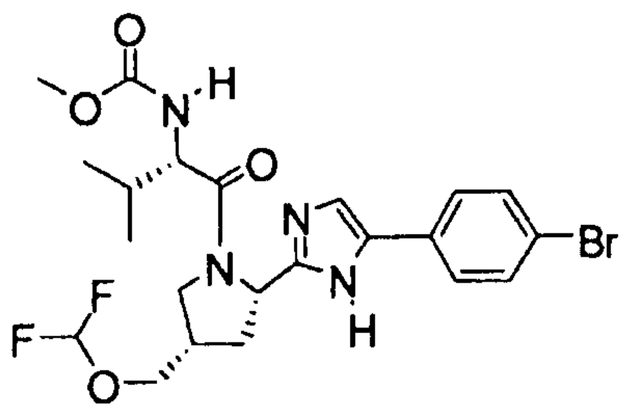
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-methoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



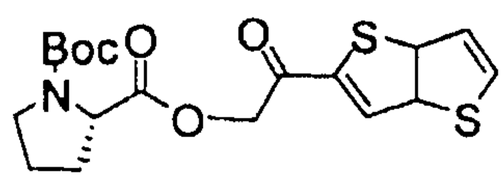
4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester



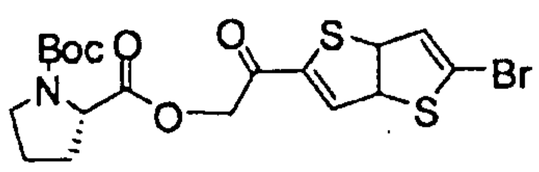
4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester



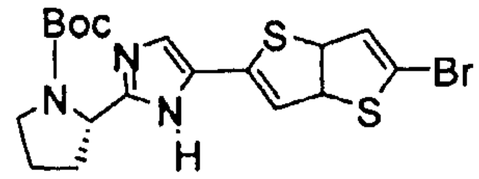
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



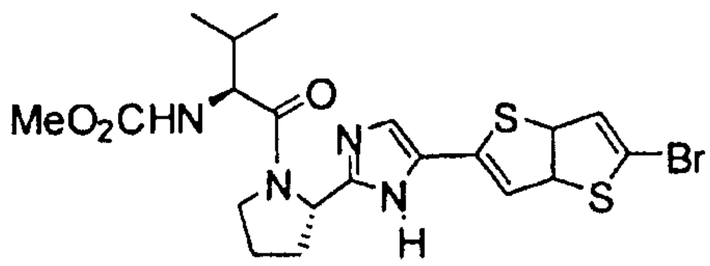
Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-2-oxo-ethyl] ester



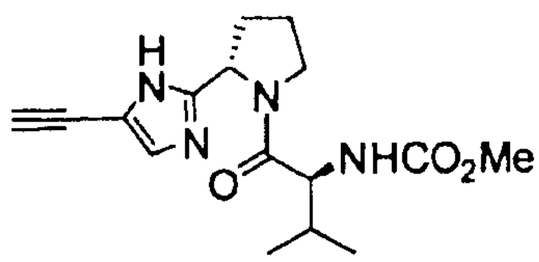
Pyrrolidine-1,2-dicarboxylic acid 2-[2-(5-bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



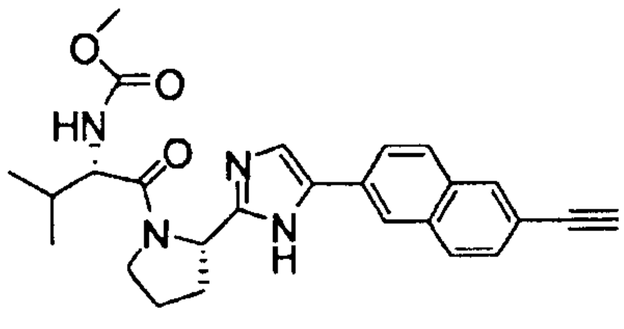
2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



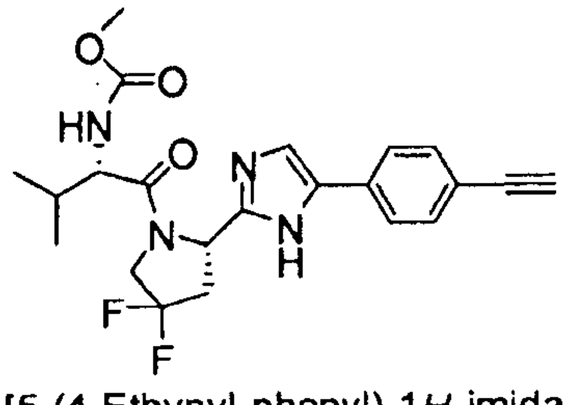
(1-{2-[5-(5-Bromo-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



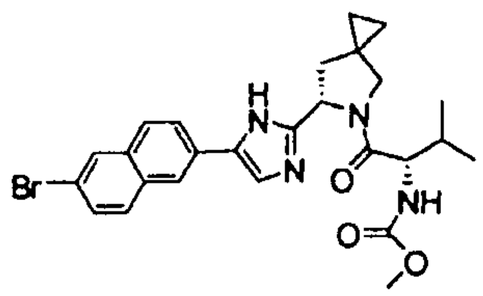
{1-[2-(5-Ethynyl-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



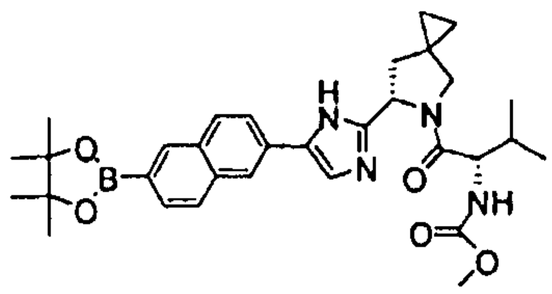
(1-{2-[5-(6-Ethynyl-naphthalen-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



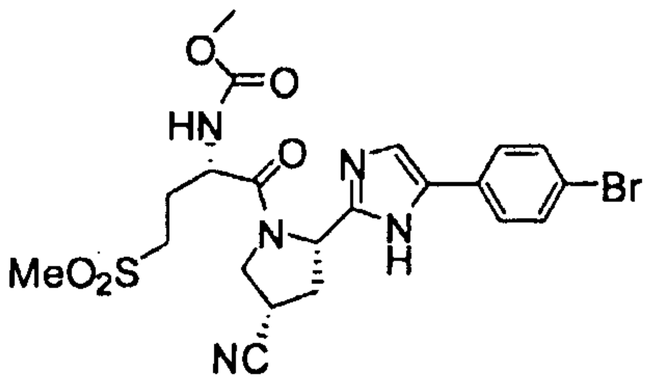
(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



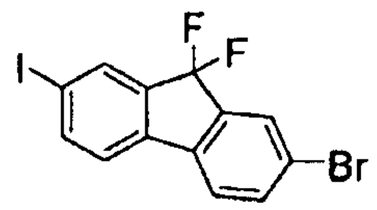
(1-{6-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



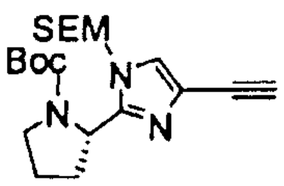
[2-Methyl-1-(6-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-5-aza-spiro[2.4]heptane-5-carbonyl)-propyl]-carbamic acid methyl ester



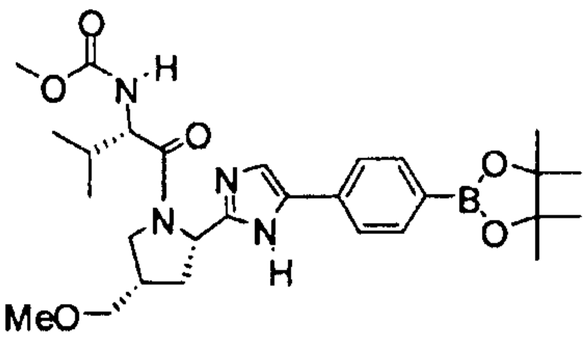
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-cyano-pyrrolidine-1-carbonyl}-3-methanesulfonyl-propyl)-carbamic acid methyl ester



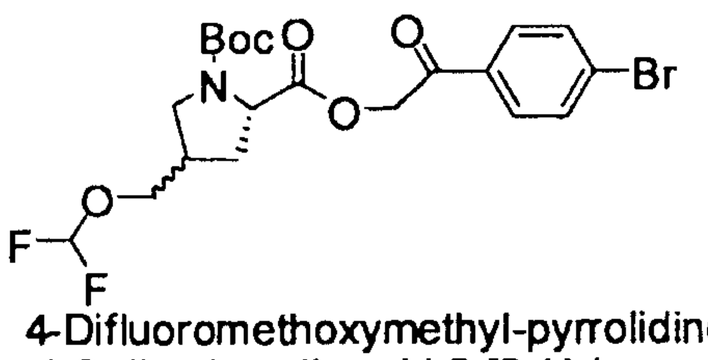
2-Bromo-9,9-difluoro-7-iodo-9*H*-fluorene



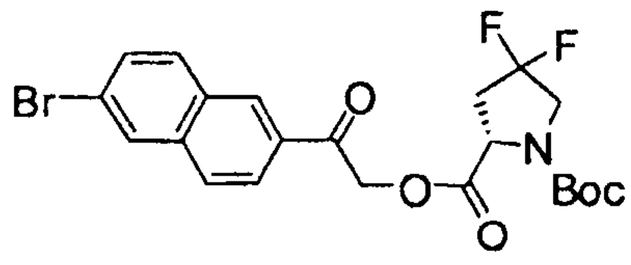
2-[4-Ethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



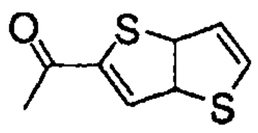
[1-(4-Methoxymethyl-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



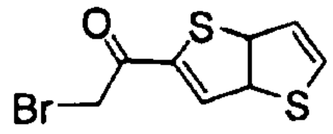
4-Difluoromethoxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



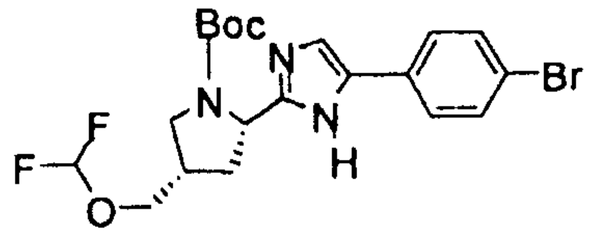
4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester



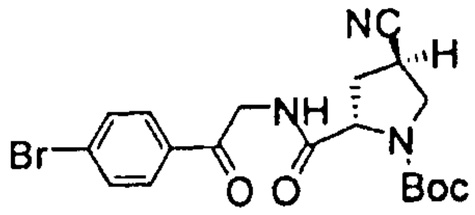
1-(3a,6a-Dihydro-thieno[3,2-*b*]thiophen-2-yl)-ethanone



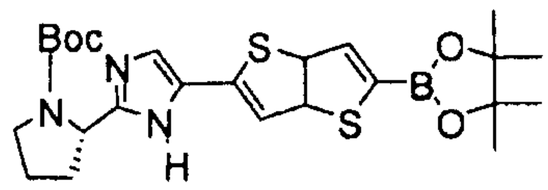
2-Bromo-1-(3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl)-ethanone



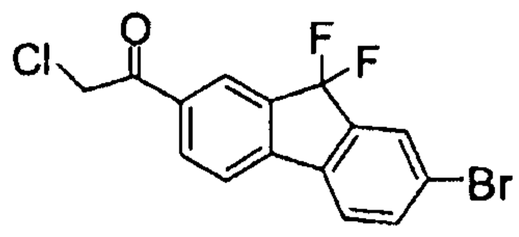
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-difluoromethoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester



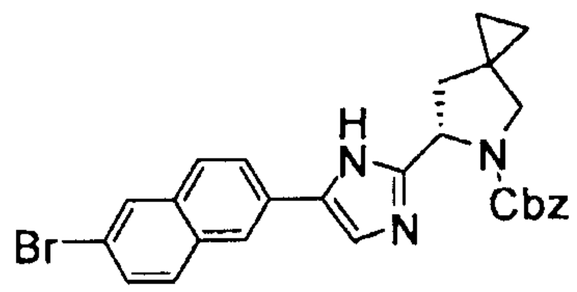
2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester



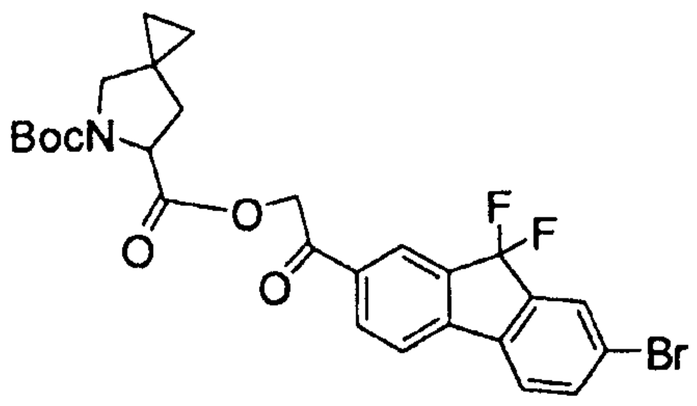
2-{5-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3a,6a-dihydro-thieno[3,2-*b*]thiophen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

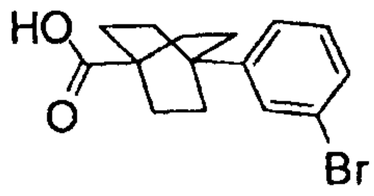


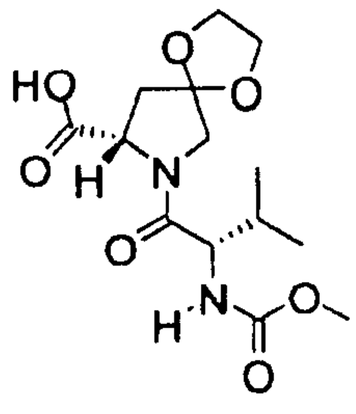
1-(7-Bromo-9,9-difluoro-9*H*-fluoren-2-yl)-2-chloro-ethanone

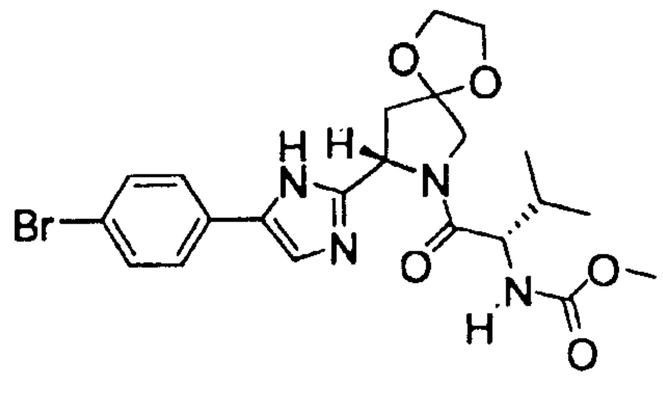


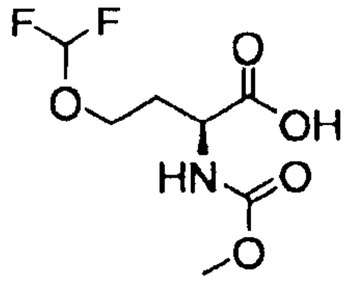
6-[5-(6-Bromo-naphthalen-2-yl)-1*H*-imidazol-2-yl]-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester

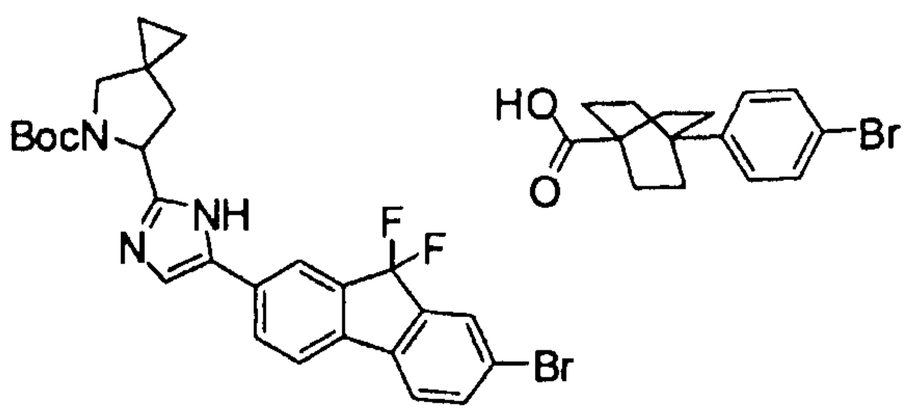


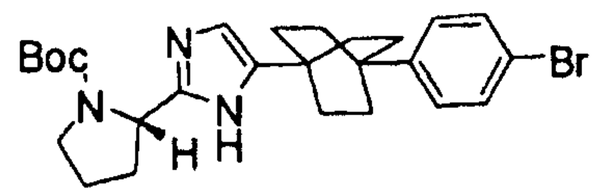


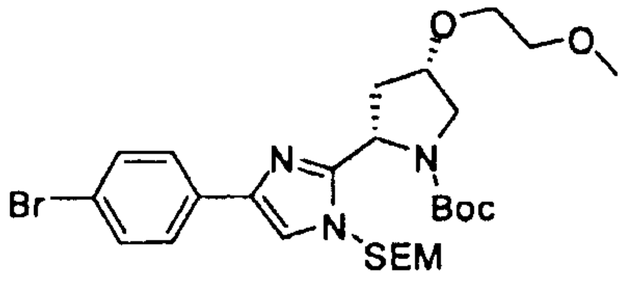




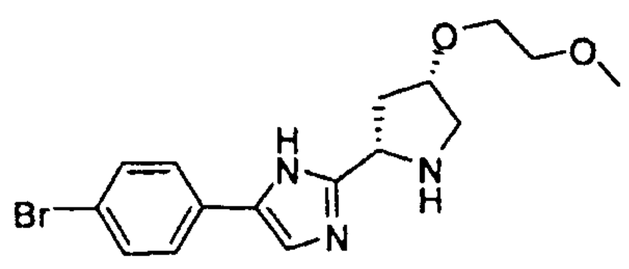




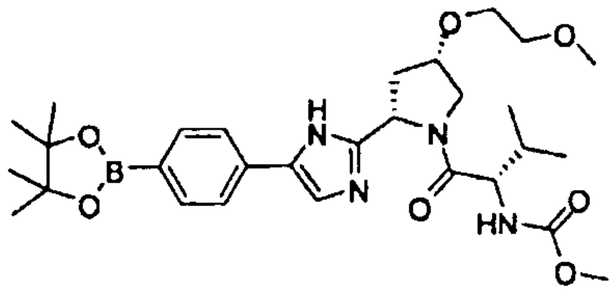




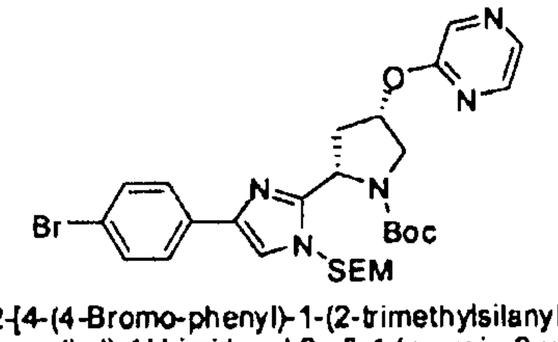
2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-4-(2-methoxy-ethoxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



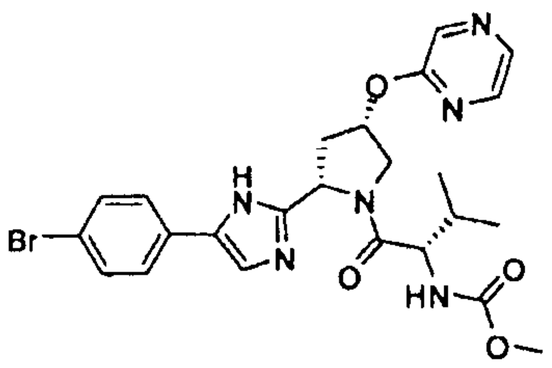
5-(4-Bromo-phenyl)-2-[4-(2-methoxy-ethoxy)-pyrrolidin-2-yl]-1*H*-imidazole



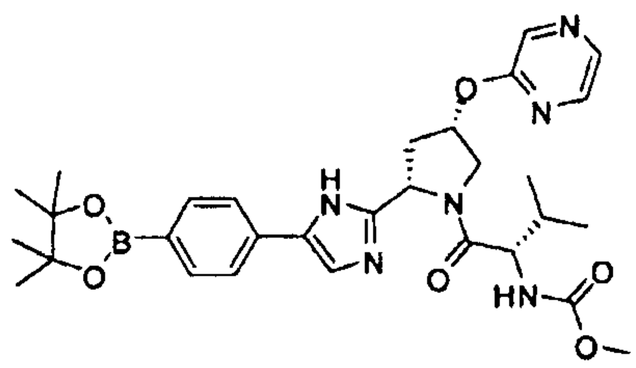
[1-(4-(2-Methoxy-ethoxy)-2-(5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



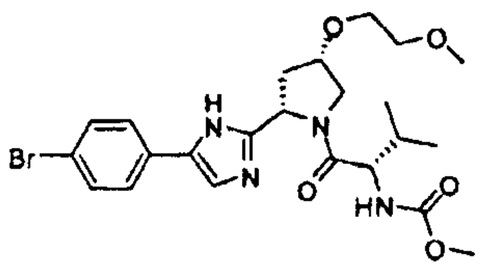
2-[4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



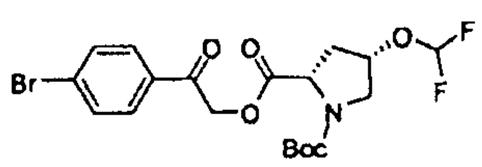
{1-[2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(pyrazin-2-yloxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



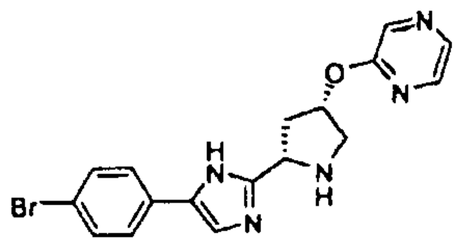
[2-Methyl-1-(4-(pyrazin-2-yloxy)-2-(5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester



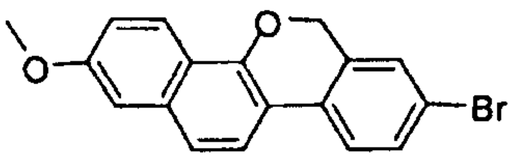
{1-[2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-40-(2-methoxy-ethoxy)-pyrrolidine-1-carbonyl}-2-methyl-propyl}-carbamic acid methyl ester

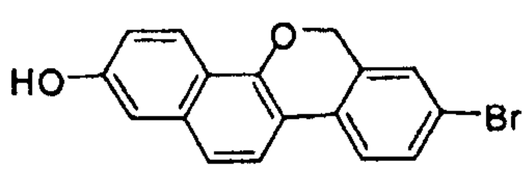


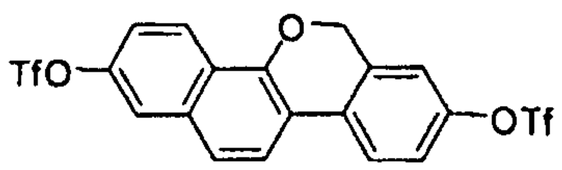
4-Difluoromethoxy-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester

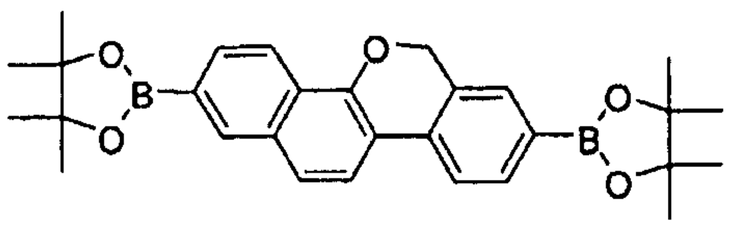


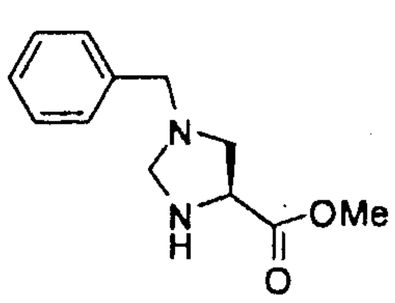
2-{5-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidin-3-yloxy}-pyrazine

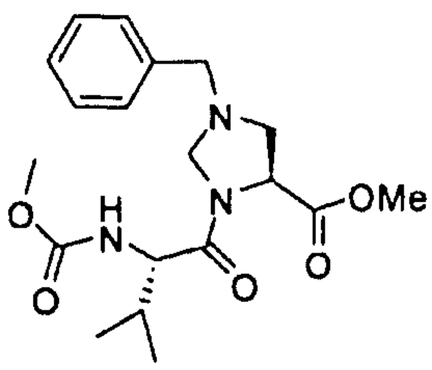


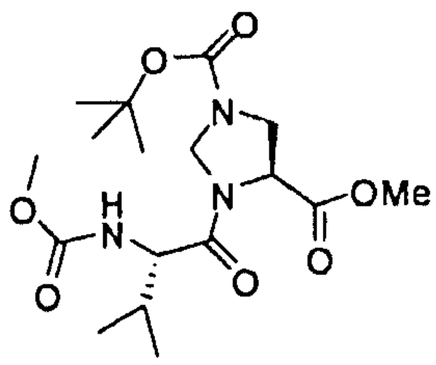


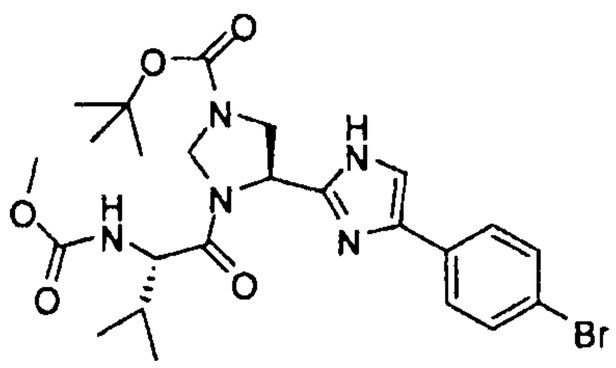


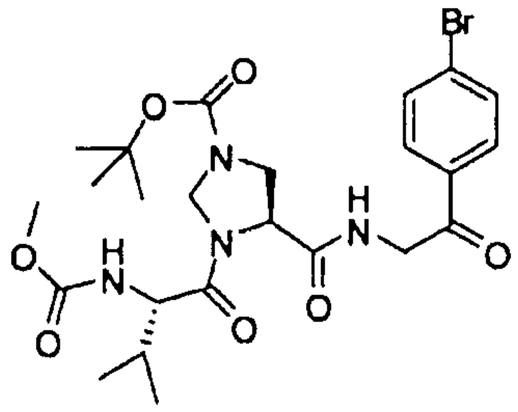


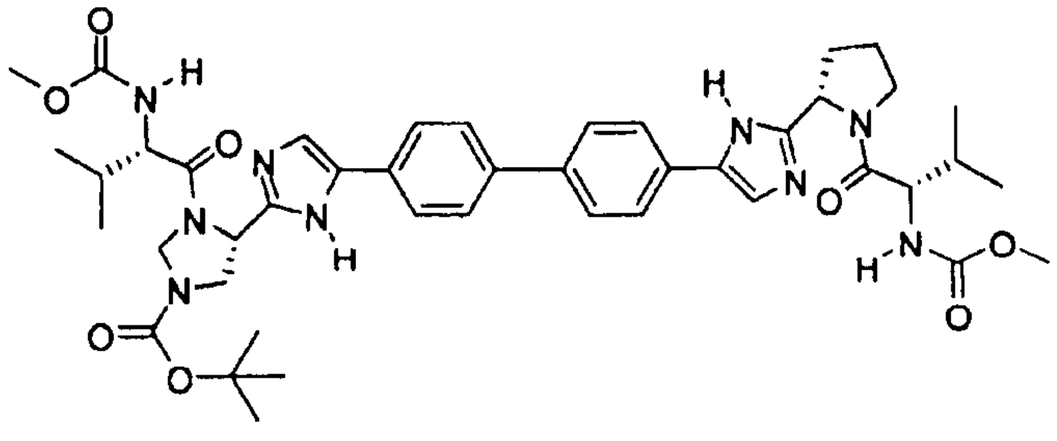


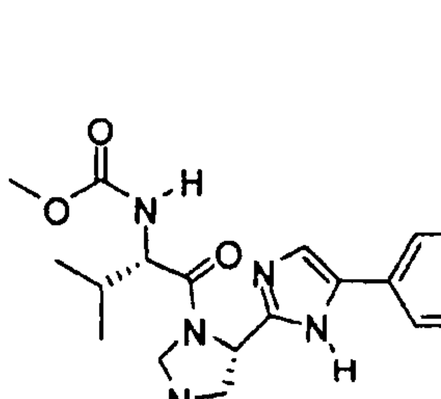


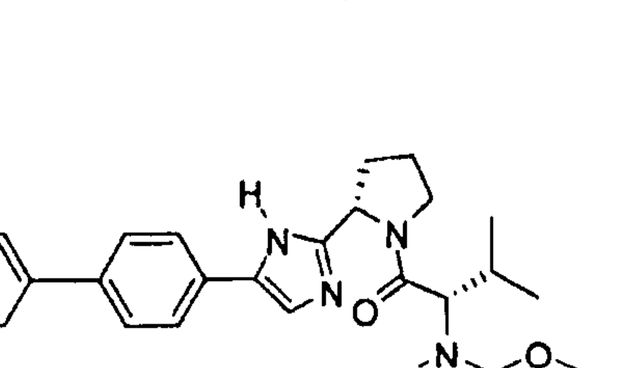


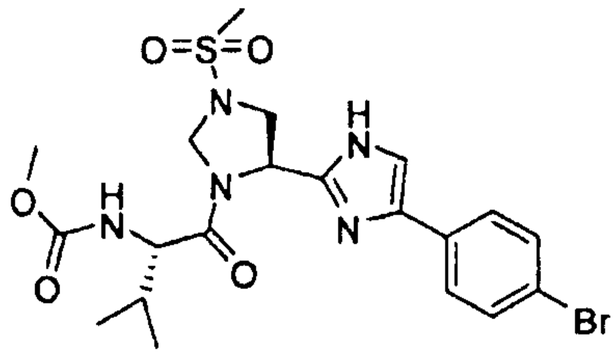












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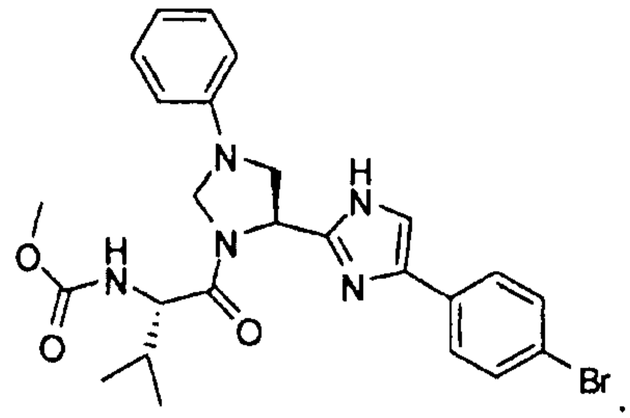


Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing). Other methods suitable for preparing compounds of the invention are described in International Patent Application Publication Number WO 2006/020276.

A number of exemplary methods for the preparation of the compositions of the invention are provided in the schemes and examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the Examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113, 3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

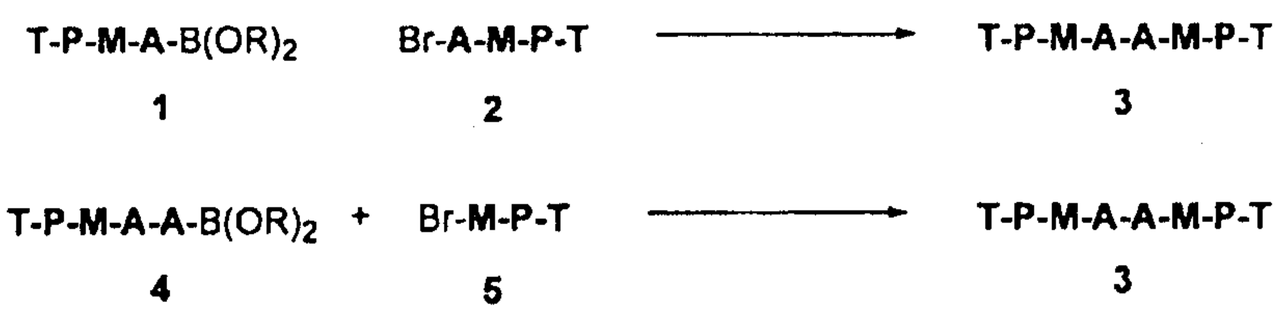
Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched substrate. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

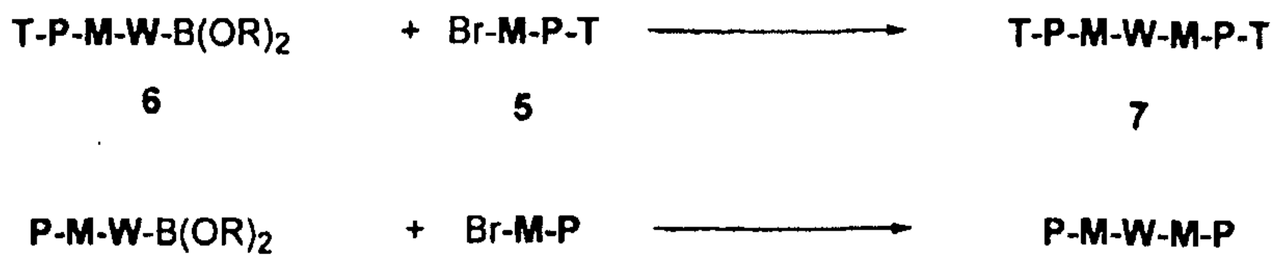
A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention. In the exemplary methods described herein, the fragment **E-V-** can also be written as **R9-**. Subsequently, the fragment **E-V-Z-** or **R9-Z-** can be written as **T-**. The fragments **E-V-Z-P**, **R9-Z-P-**, or **T-P-** can all be written as **J-**.

Scheme 1: Representative synthesis of T-P-M-A-A-M-P-T



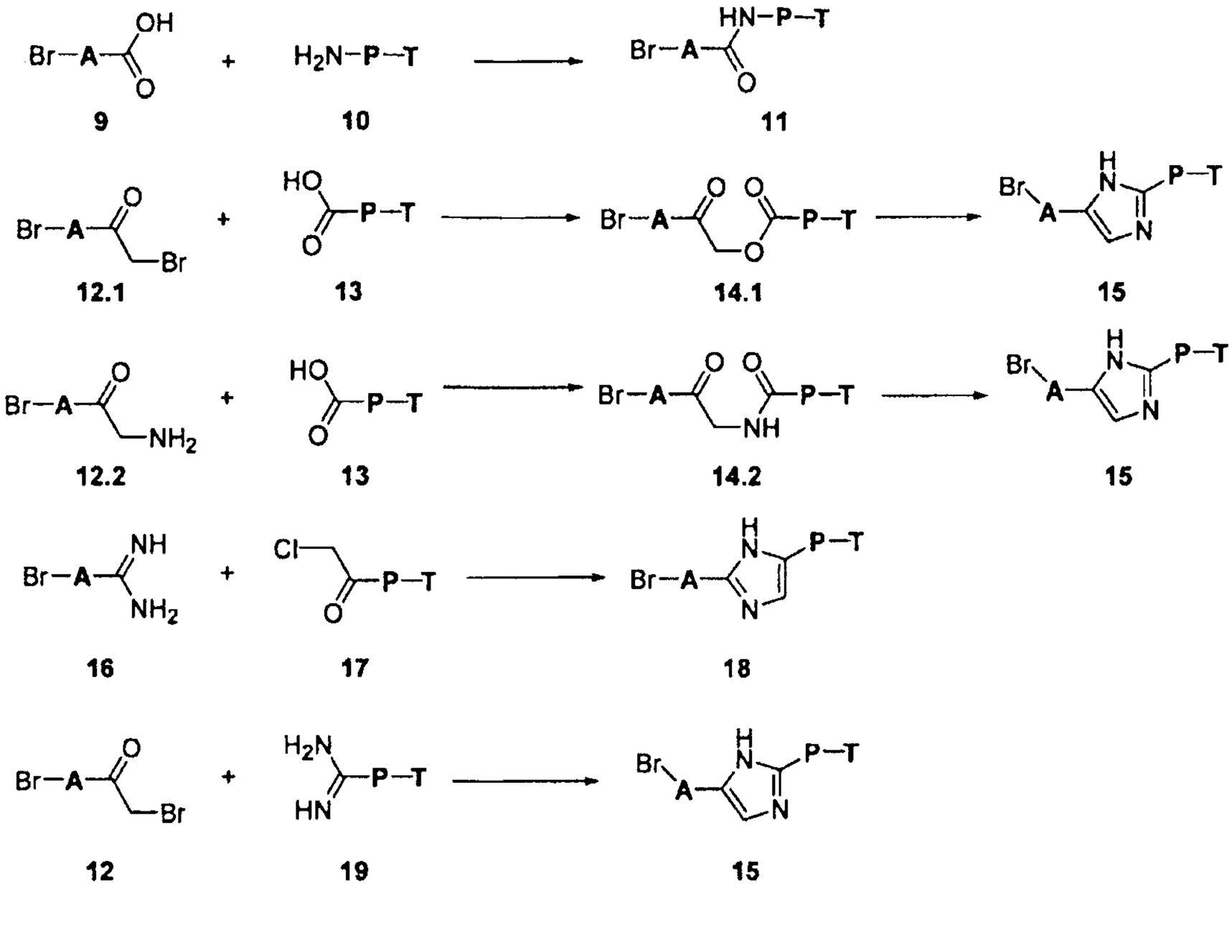
Scheme 1 shows a general synthesis of the **T-P-M-A-A-M-P-T** molecule of the invention, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond and/or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple a **Br-M-P-T** and an $(RO)_2$**B-A-A-M-P-T** intermediate or a **Br-A-M-P-T** and a $(RO)_2$**B-A-M-P-T** intermediate. Boronic ester **1** (or **4**) is coupled with an appropriate coupling partner (e.g. arylbromide **2** or **5**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **3**. Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 1a: Representative synthesis of T-P-M-W-M-P-T



Scheme 1a shows a general synthesis of the **T-P-M-W-M-P-T** molecule and the **P-M-W-M-P** molecule of the invention, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **W-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple a Br-**M-P-T** and a $(RO)_2$B-**W-M-P-T** intermediate or a Br-**M-P**-PG to a $(RO)_2$B-**W-M-P**-PG intermediate. Boronic ester **6** (or **6.1**) is coupled with an appropriate coupling partner (e.g. arylbromide **5** or **5.1**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **7** and **8**. Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

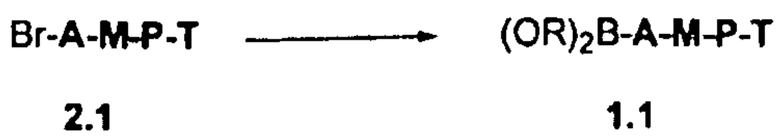
Scheme 2: Representative synthesis of A-M-P-T



Scheme 2 shows a general synthesis of an **A-M-P-T** molecule of the invention wherein, for illustrative purposes, **M** is an amide or an imidazole. Coupling of amine **10** with acid **9** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **11**. The acid **13** is coupled with an α-haloketone, such as α-bromoketone **12.1,** under basic conditions (e.g. Et_3N) to afford **14.1**. Alternatively, the acid **13** is coupled with an α-aminoketone **12.2,** under amide formation conditions (e.g. EDC, Et_3N) to afford **14.2**. Reaction of **14.1** or **14.2** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule Br-**A-M-P-T**.

The benzamidine **16** is coupled with an α-haloketone such as α -chloroketone **17** under basic conditions such as K_2CO_3 to afford the imidazole containing molecule Br-**A-M-P-T 18**. **A-M-P-T 15** can be prepared analogously.

Scheme 3: Representative synthesis of A-M-P-T



2.1 **1.1**

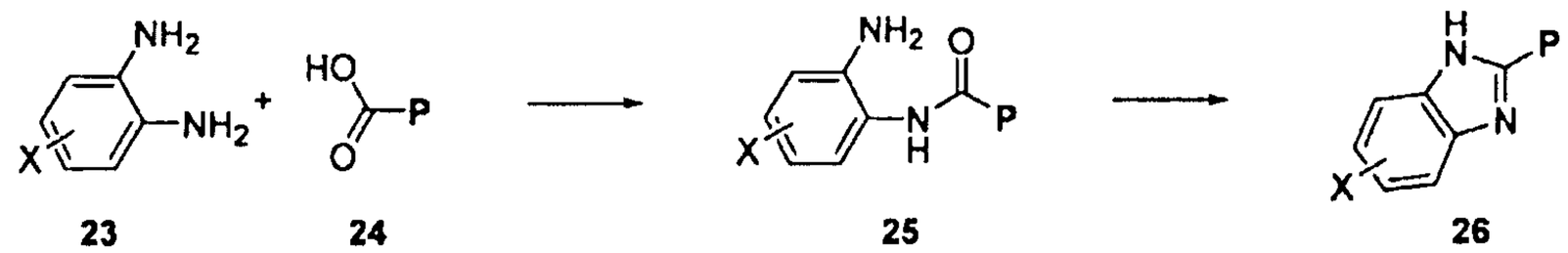
Scheme 3 shows a general synthesis of an **A-M-P-T** molecule of the invention wherein borate or boronic acid **1.1** can be synthesized from bromide **2.1**.

Scheme 4: Representative synthesis of A-M-P-Z-R9

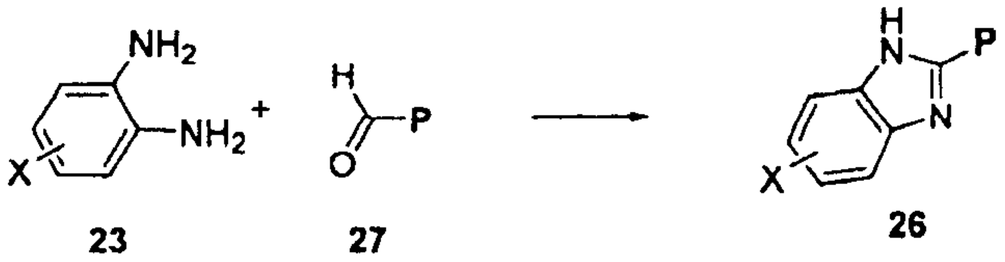
20 **21** **22**

Scheme 4 shows a general synthesis of an **A-M-P-Z-R9** fragment of the invention wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **20** with acid **21** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **22**.

Scheme 5: Representative synthesis of L-P



23 **24** **25** **26**

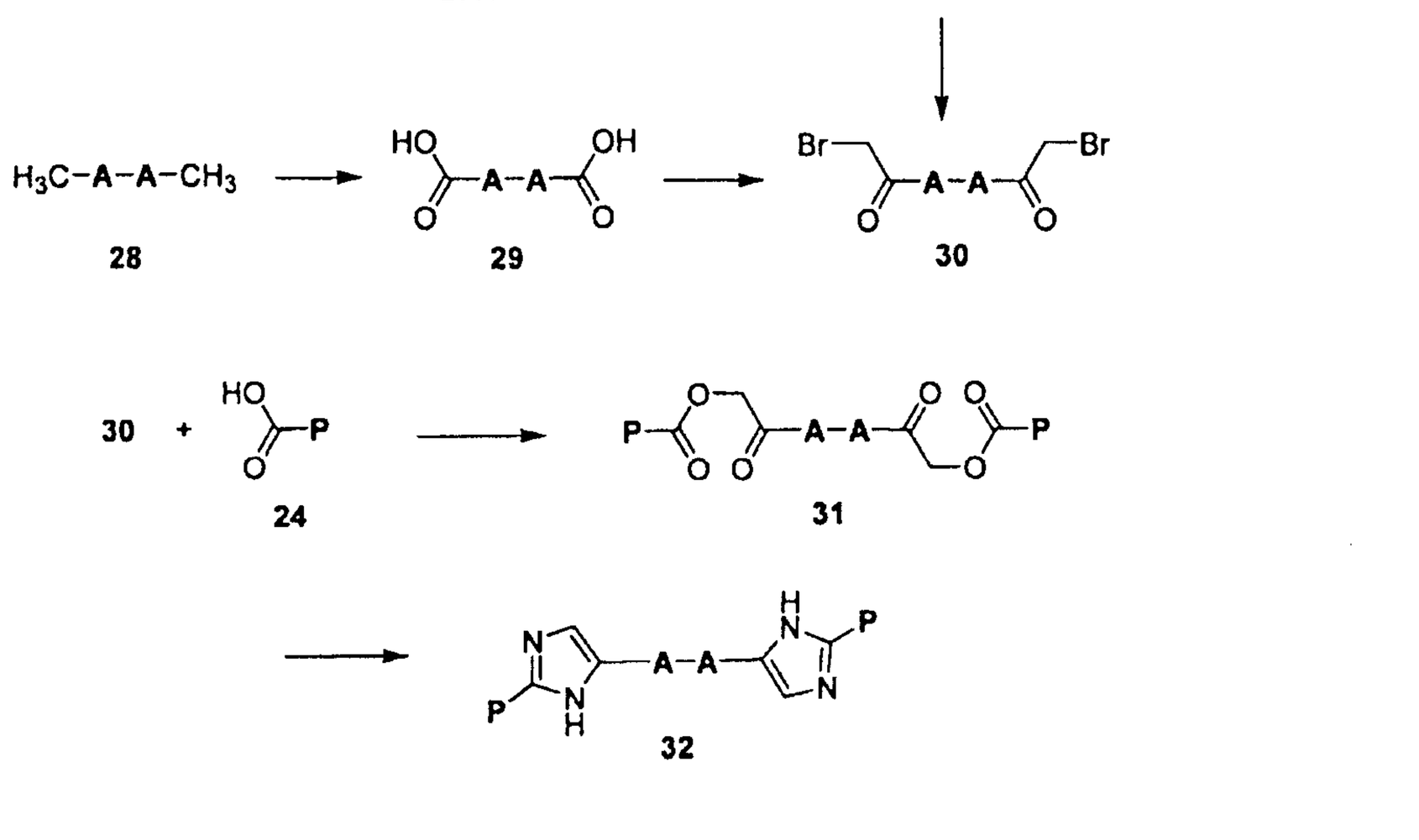


23 **27** **26**

Scheme 5 shows a general synthesis of an **L-P** molecule of the invention wherein, for illustrative purposes, **L** = benzimidazole. The acid **24** is coupled with **23** using a peptide coupling reagent such as HATU to afford **25.** Heating in solvent (such as refluxing ethanol) affords **L-P** fragment **26**.

Alternatively, the **L-P** fragment **26** is obtained by reaction of diamine (such as **23**) and carbonyl compound (such as aldehyde **27**) in a solvent under heating conditions (e.g. ethanol under microwave irradiation).

Scheme 6: Representative synthesis of P-M-A-A-M-P fragment

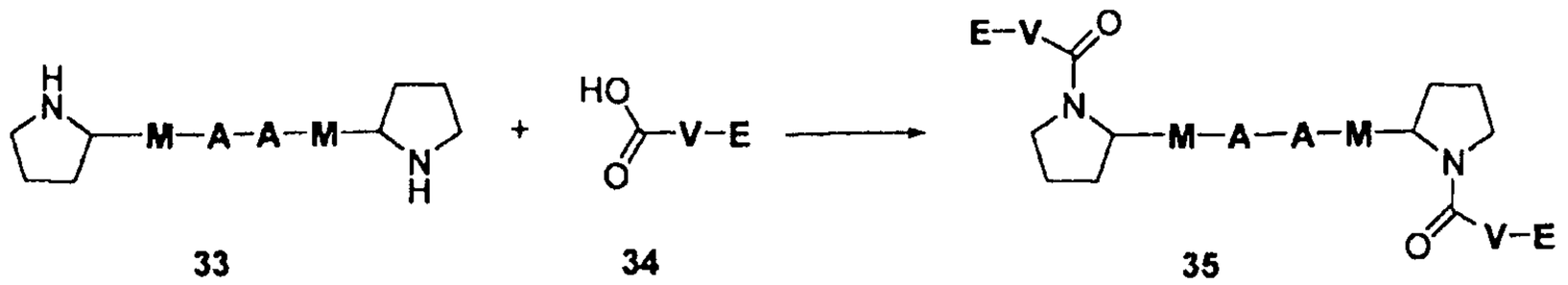


Scheme 6 shows a general synthesis of **P-M-A-A-M-P** molecule of the invention wherein, for illustrative purposes, **M** = imidazole. For example, the diketone **27** is converted to **30** using bromine. Compound **27** can be commercially available or can be prepared from dibromide **27.1** through coupling with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane with palladium. Coupling of **30** with acid **24** under basic conditions such as diisopropylethylamine affords diester **31**. Imidazole formation is accomplished by treatment of **31** with ammonium acetate to provide the imidazole containing molecule **P-M-A-A-M-P**.

Alternatively, bromide **30** can be synthesized from **28**. The methyl compound **28** can be converted to the corresponding diacid **29** using potassium permanganate as oxidant.

Conversion of **29** to **30** can be accomplished by a multi-step reaction, first treatment of **29** with oxalyl chloride, then by trimethylsilyl diazomethane, then with hydrobromic acid to afford compound **30**.

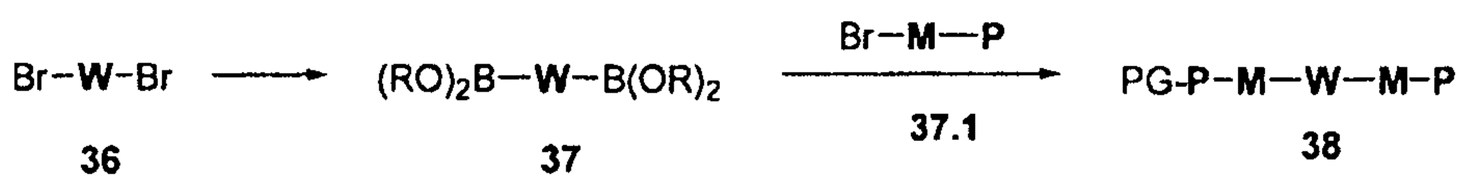
Scheme 7: Representative synthesis of E-V-P-M-A-A-M-P-V-E



33 34 35

Scheme 7 shows a general synthesis of an **E-V-P-M-A-A-M-P-V-E** molecule of the invention wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **33** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **35**.

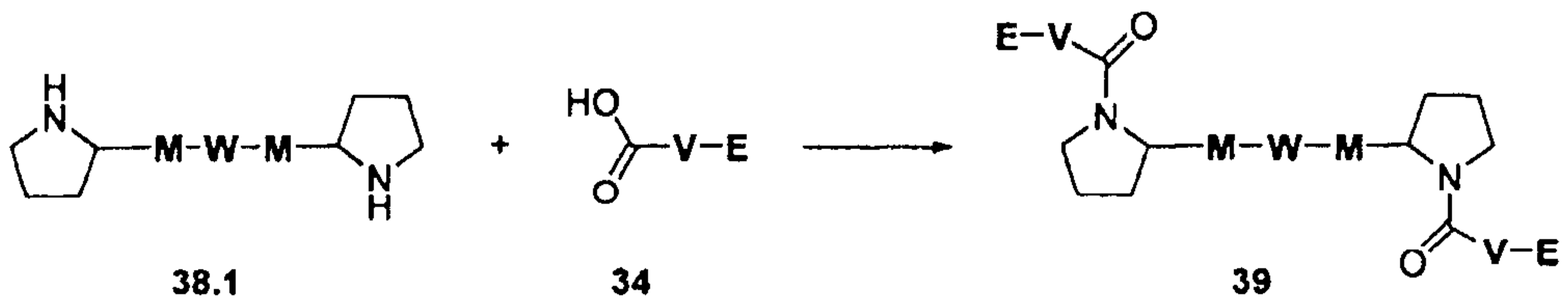
Scheme 8: Representative synthesis of P-M-W-M-P



36 37 38

Scheme 8 shows a general synthesis of **P-M-W-M-P** molecule of the invention wherein, for illustrative purposes, **W** = polycyclic. Conversion of **36** to **37** was accomplished using transition metal-mediated reactions. Diboronic ester or acid **37** is coupled with a suitable reaction partner, such as bromide **37.1** using Suzuki coupling conditions to afford **38**.

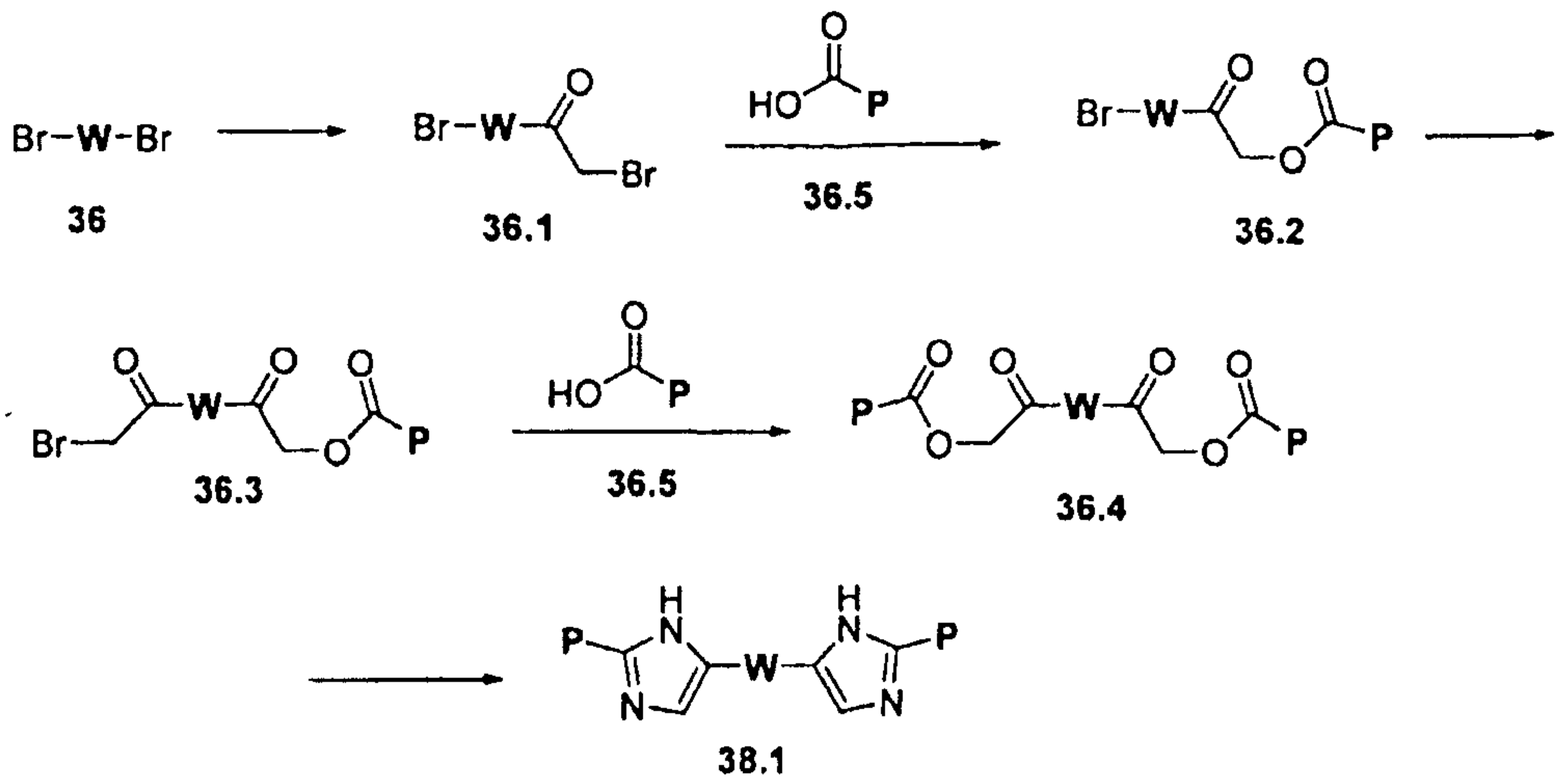
Scheme 9: Representative synthesis of E-V-P-M-W-M-P-V-E



38.1 34 39

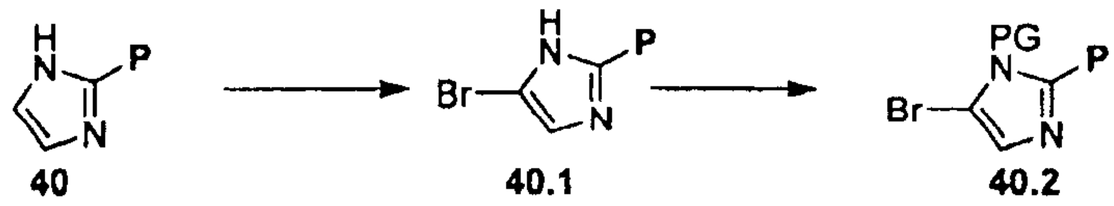
Scheme 9 shows a general synthesis of an **E-V-P-M-W-M-P-V-E** molecule of the invention wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **38.1** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **39**.

Scheme 9a: Representative synthesis of P-M-W-M-P



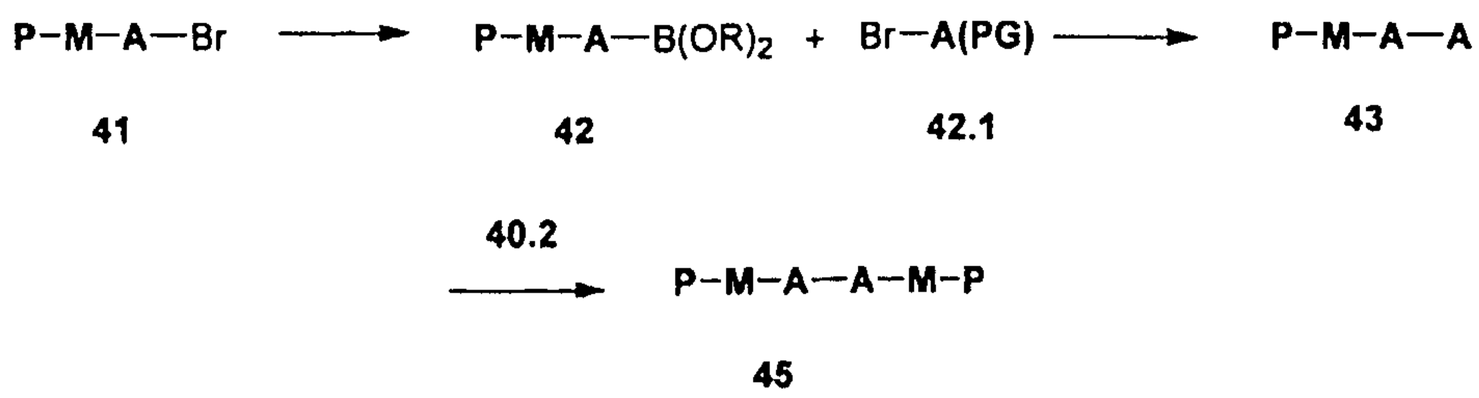
Scheme **9a** shows a general synthesis of a **P-M-W-M-P** molecule of the invention wherein, for illustrative purposes, **M** = imidazole, **W** = polycyclic. The compound **36** was coupled with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane with palladium, followed by bromination and hydrolysis with NBS and water, to give bromoketone **36.1**. The reaction between bromide **36.1** and a carboxylic acid (**36.5**) under basic condition generated ester **36.2**. Following the same reaction sequence, compound **36.2** was converted to diester **36.4**. Conversion of **36.4** to **38.1** was accomplished with ammonia reagents such as ammonium acetate at elevated temperature.

Scheme 10: Representative synthesis of M-P



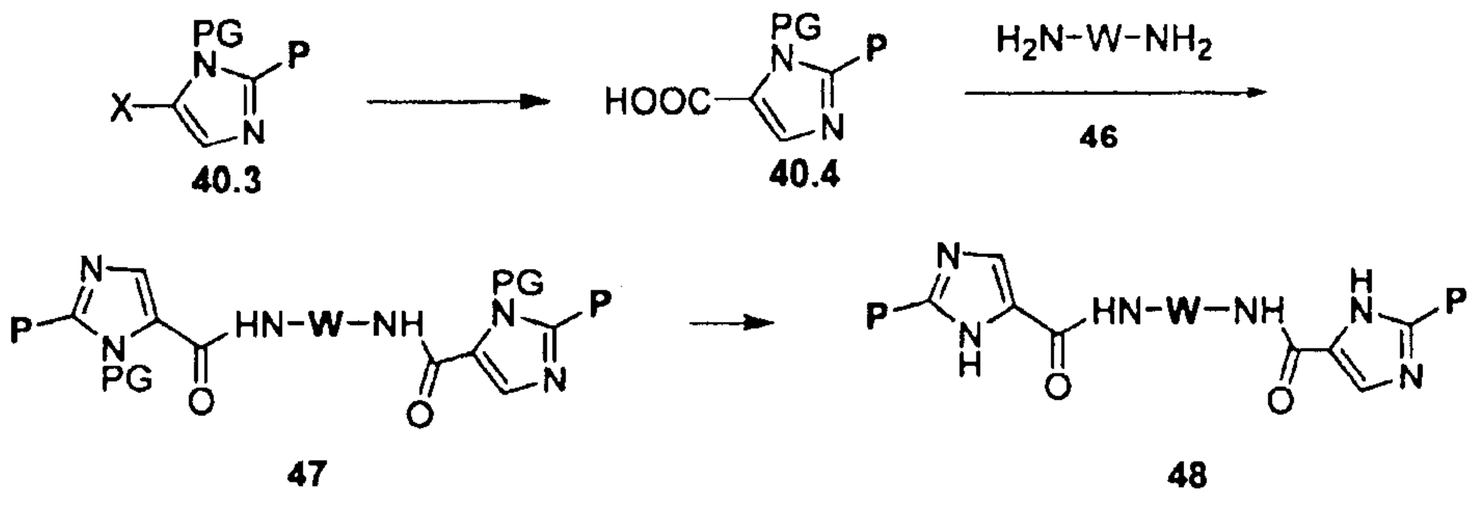
Scheme 10 shows a general synthesis of an **M-P** molecule of the invention wherein, for illustrative purposes, PG is a protecting group. Imidazole **40** can be halogenated, for example, under the action of N-bromosuccinimide to provide bromoimidazole **40.1**. Bromoimidazole **40.1** can be protected using standard conditions to give **40.2**, such as SEM-Cl and sodium hydride when PG = SEM.

Scheme 11: Representative synthesis of P-M-A-A-M-P



Scheme 11 shows a general synthesis of a **P-M-A-A-M-P** molecule of the invention wherein, for illustrative purposes, **M** = imidazole. Boronic ester **42**, which can be prepared from bromide **41**, is coupled with a suitably protected appropriate coupling partner (e.g. arylbromide **42.1**, optionally protected with PG) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **43**. Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada and Stille reactions. If optionally protected, removal of the protecting group (PG) (for example, catalytic hydrogenation of a benzyl ether) provides the deprotected compound **43**. Coupling of **43** with suitably protected imidazole **40.2** (for example, PG = SEM ether) using a metal catalyst (e.g. CuI) gives protected **P-M-A-A-M-P (45)**. Deprotection (for example deprotection of a SEM ether using an acid such as TFA) provides the imidazole containing fragment **P-M-A-A-M-P 45**.

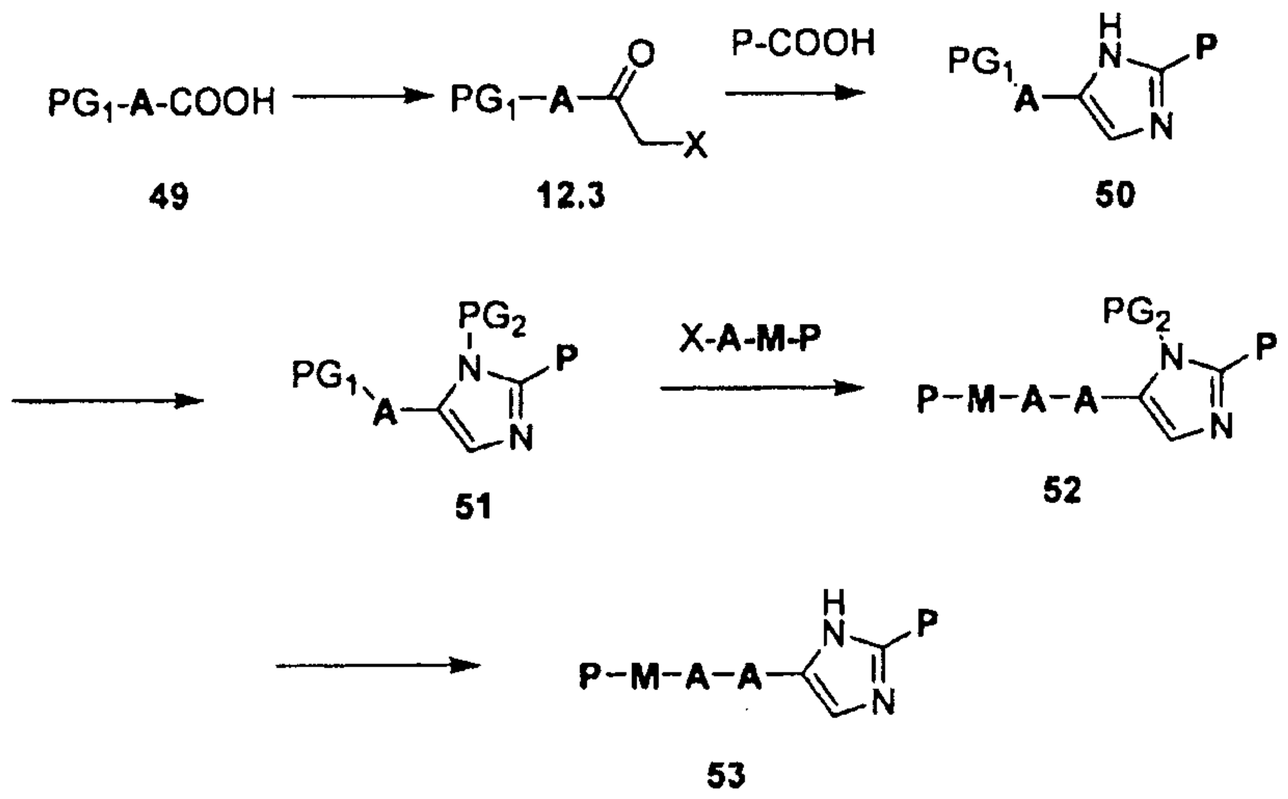
Scheme 12: Representative synthesis of P-M-W-M-P



Scheme 12 shows a general synthesis of a **P-M-W-M-P** molecule of the invention wherein, for illustrative purposes, **X** = halogen or triflate, **M** = imidazole, and **W** is **46**, PG = protecting group. Haloimdiazole **40.3**, such as a bromoimidazole, is subjected to a metal-halogen exchange reaction, such as BuLi in THF, and then treated with a CO_2 source, such as solid CO_2, to give

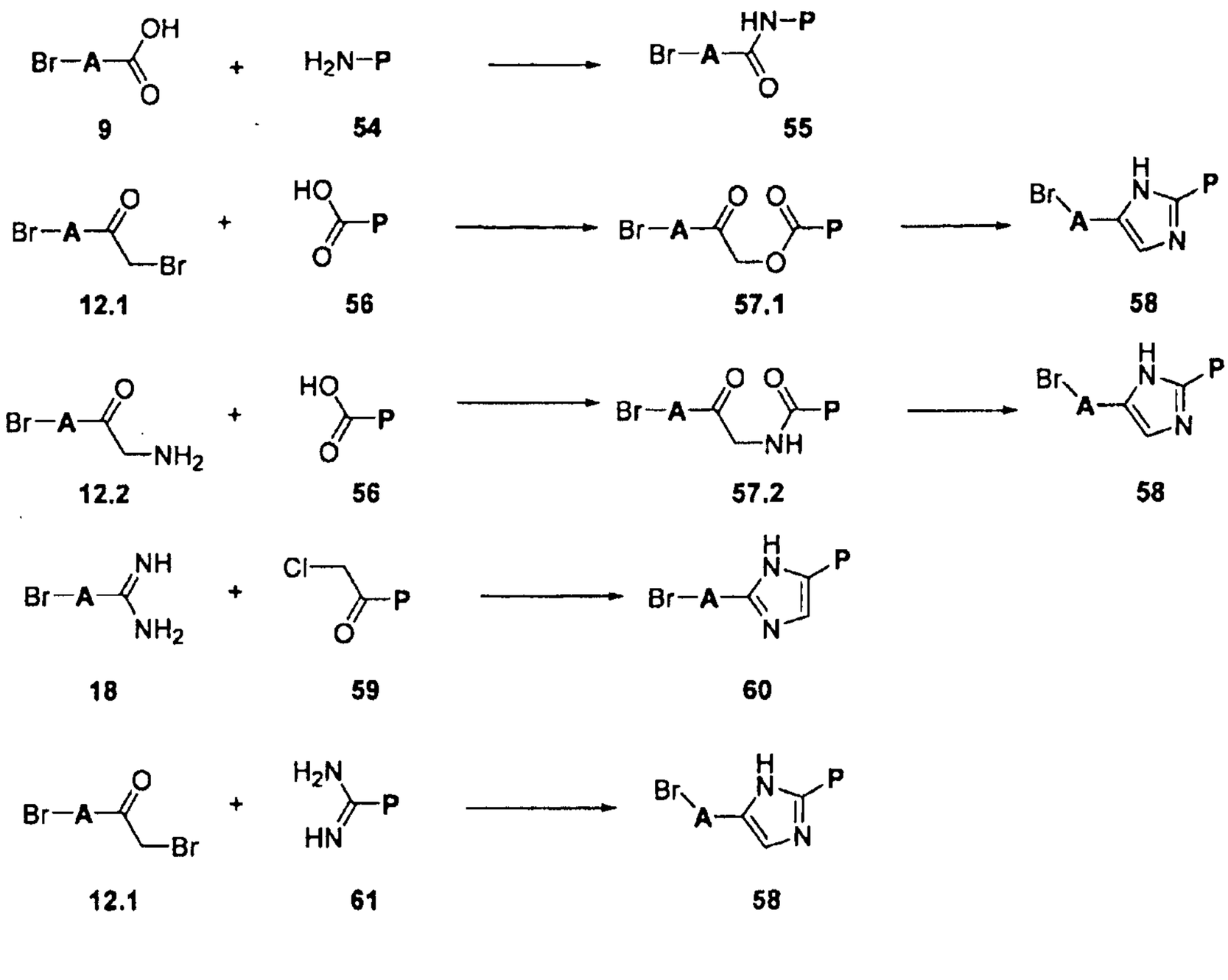
40.4. Coupling of **40.4** and **46** using peptide coupling conditions, such as HATU, gives **47**. PG deprotection, such as TFA deprotection of a SEM group, gives the compound **P-M-W-M-P 48**.

Scheme 13: Representative synthesis of P-M-A-A-M-P



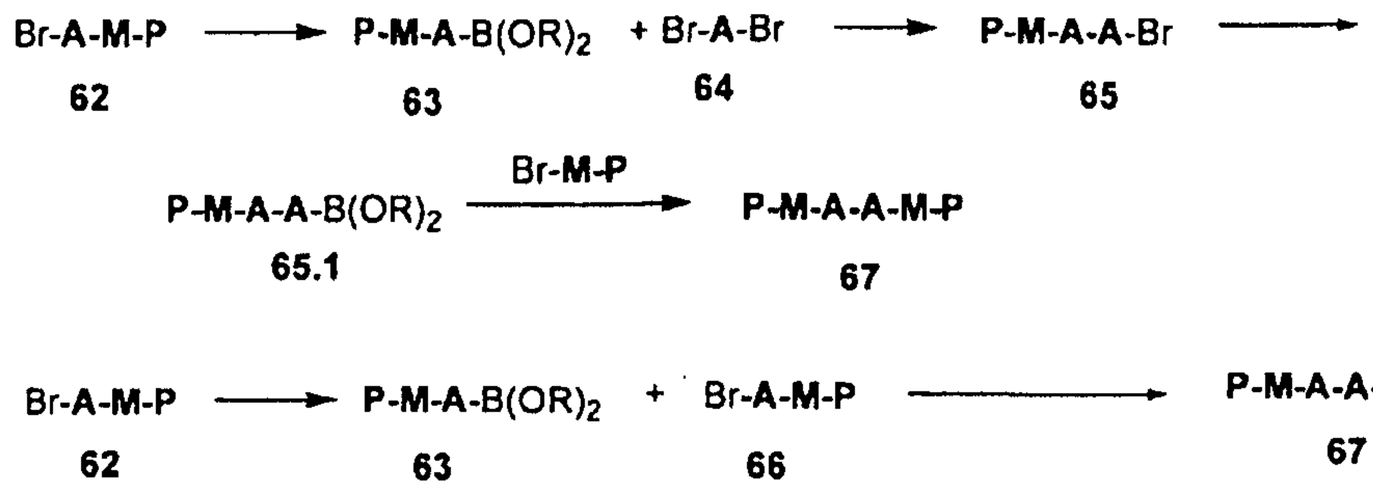
Scheme 13 shows a general synthesis of a **P-M-A-A-M-P** molecule of the invention wherein, for illustrative purposes, **X** = halogen, amine or triflate, **M** = imidazole, PG_1 and PG_2 = protecting groups. The protected acid **49** (PG1 is a suitable protecting group, such as Cbz) is converted to α-halomethyl ketone **12.3**., which is then transformed to PG_1**-A-M-P 50** using the analogous conditions for converting **12.1** and **12.2** to **15**. The imidazole is subjected to protection, with SEM for instance, to afford **51**, which is deprotected, with H_2 and Pd to remove a Cbz for example, followed by coupling with fragment **X-A-M-P**, using standard Pd coupling conditions for example, to afford **52**. PG deprotection, such as TFA deprotection of a SEM group, gives the compound **P-M-A-A-M-P 53**.

Scheme 14: Representative synthesis of A-M-P



Scheme 14 shows a general synthesis of an **A-M-P** molecule of the invention wherein, for illustrative purposes, **M** is an amide bond, or an imidazole. Coupling of amine **54** with acid **9** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **55**.
The acid **56** is coupled with an α-haloketone, such as α-bromoketone **12.1,** under basic conditions (e.g. Et_3N) to afford **57.1**. Alternatively, the acid **56** is coupled with an α-aminoketone **12.2,** under amide formation conditions (e.g. EDC, Et_3N) to afford **57.2**. Reaction of **57.1** and **57.2** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **A-M-P**.
The benzamidine **18** is coupled with an α-haloketone such as α -chloroketone **59** under basic conditions such as K_2CO_3 to afford the imidazole containing molecule **A-M-P 60**. **A-M-P 58** can be prepared analogously.

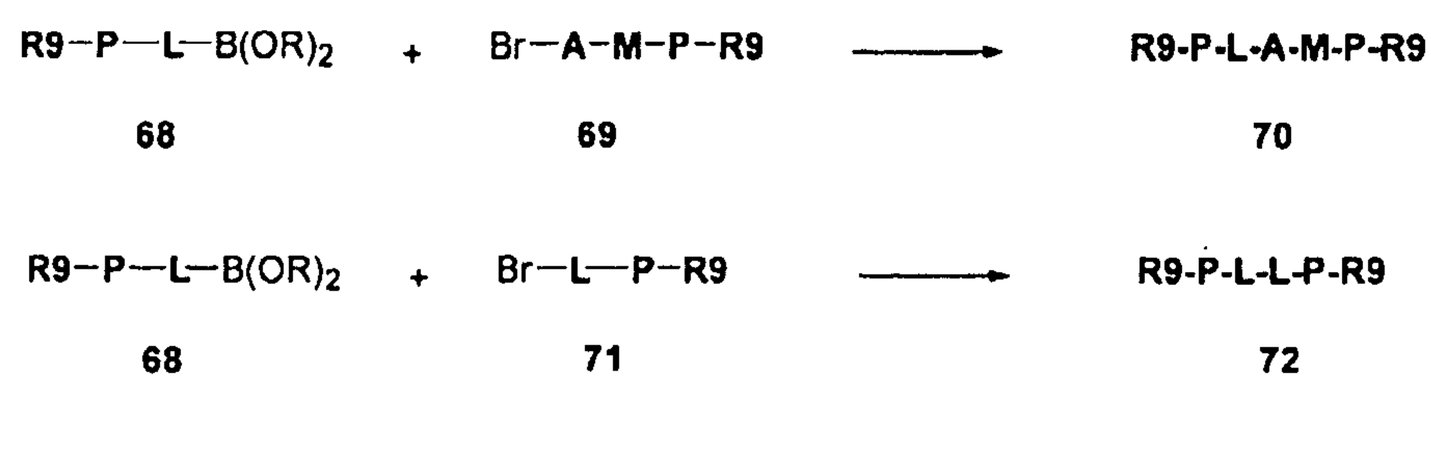
Scheme 15: Representative synthesis of P-M-A-A-M-P



Scheme 15 shows a general synthesis of a **P-M-A-A-M-P** molecule of the invention. Boronic acid or its ester **63**, can be prepared from bromide **62** using a palladium catalyst (e.g. $Pd(PPh_3)_4$) and a boron reagent (bis(pinacolato)diboron, for example), is coupled with an excess of appropriate coupling partner (e.g. a di-halo-aromatic or di-halo-heteroaromatic moiety **64)** using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford bromide **65**, which then is converted to boronic acid or ester **65.1**. Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada and Stille reactions. Suzuki coupling of **65.1** with halo-imidazole such as bromo-imidazole using a palladium catalyst (such as $Pd(PPh_3)_4$) gives **P-M-A-A-M-P** fragment **67**.

Alternatively, Suzuki coupling of **63** with halo-**A-M-P** fragment using a palladium catalyst (such as $Pd(PPh_3)_4$) gives **P-M-A-A-M-P** fragment **67**.

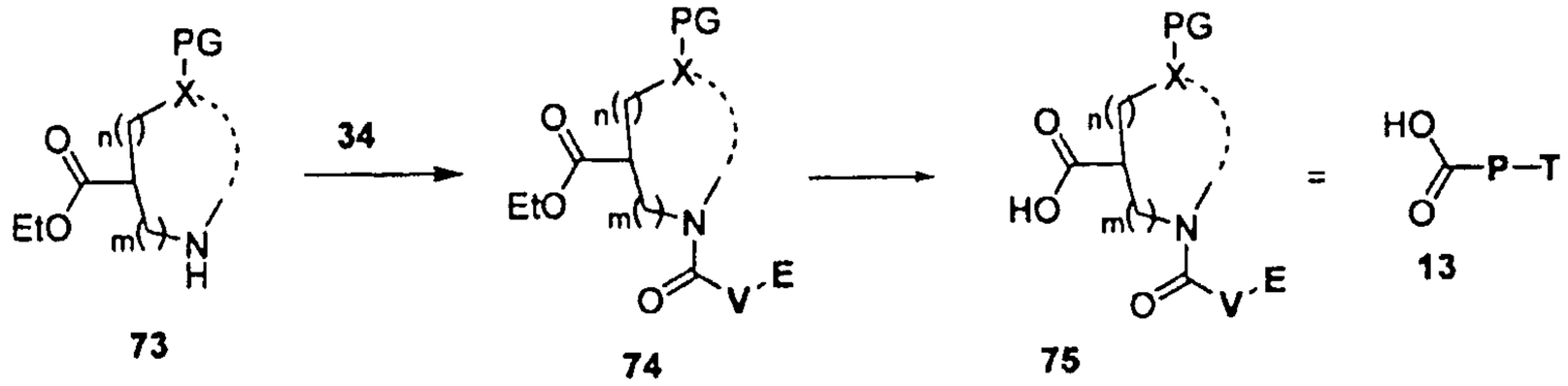
Scheme 16: Representative synthesis of R9-P-L-A-M-P-R9 and R9-P-L-L-P-R9



Scheme 16 shows a general synthesis of an **R9-P-L-A-M-P-R9** molecule and a **R9-P-L-L-P-R9** molecule of the invention wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond. For illustrative purposes, the Suzuki reaction is employed to couple

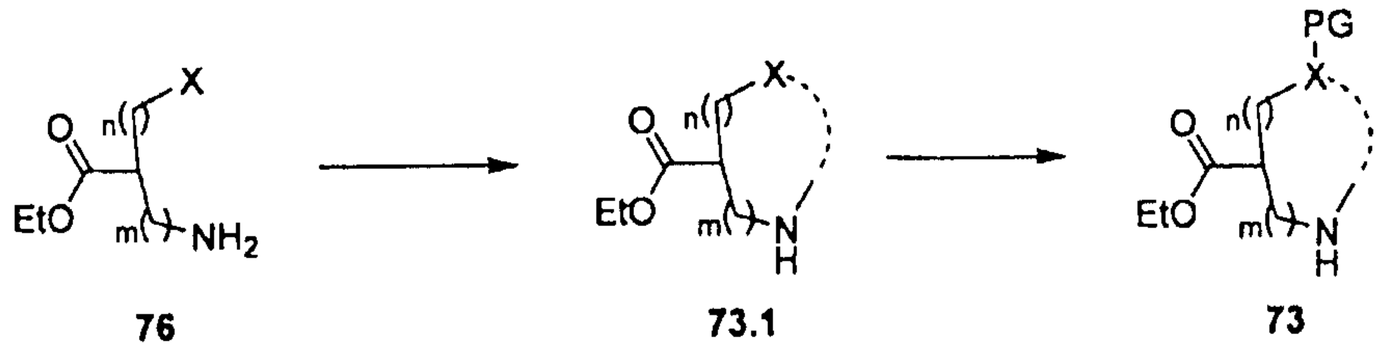
$(RO)_2B$-**L-P-R9** and Br-**A-M-P-R9**. Boronic ester **68** is coupled with an appropriate coupling partner (e.g. arylbromide **69**) using a palladium catalyst (such as $Pd(PPh_3)_4$) to afford **70**. Similarly, **R9-P-L-L-P-R9 72** is prepared by coupling compounds **68** and **71**.

Scheme 17: Representative synthesis of P-T



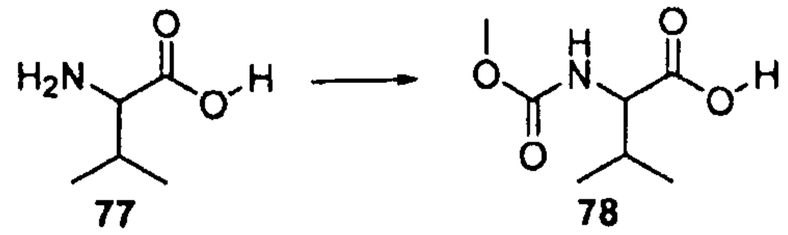
Scheme 17 shows a general synthesis of a **P-T** molecule of the invention wherein, for illustrative purposes, **P** = either an acyclic or cyclic amino ester (such as ethyl ester), optionally protected with PG if necessary, **Z** = carbonyl, **X** = carbon or heteroatom, and m and n = 0 - 5, independently. Coupling of amine **73** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **75**, which after removal of ethyl group provides the **P-T** compound.

Scheme 18: Representative synthesis of P



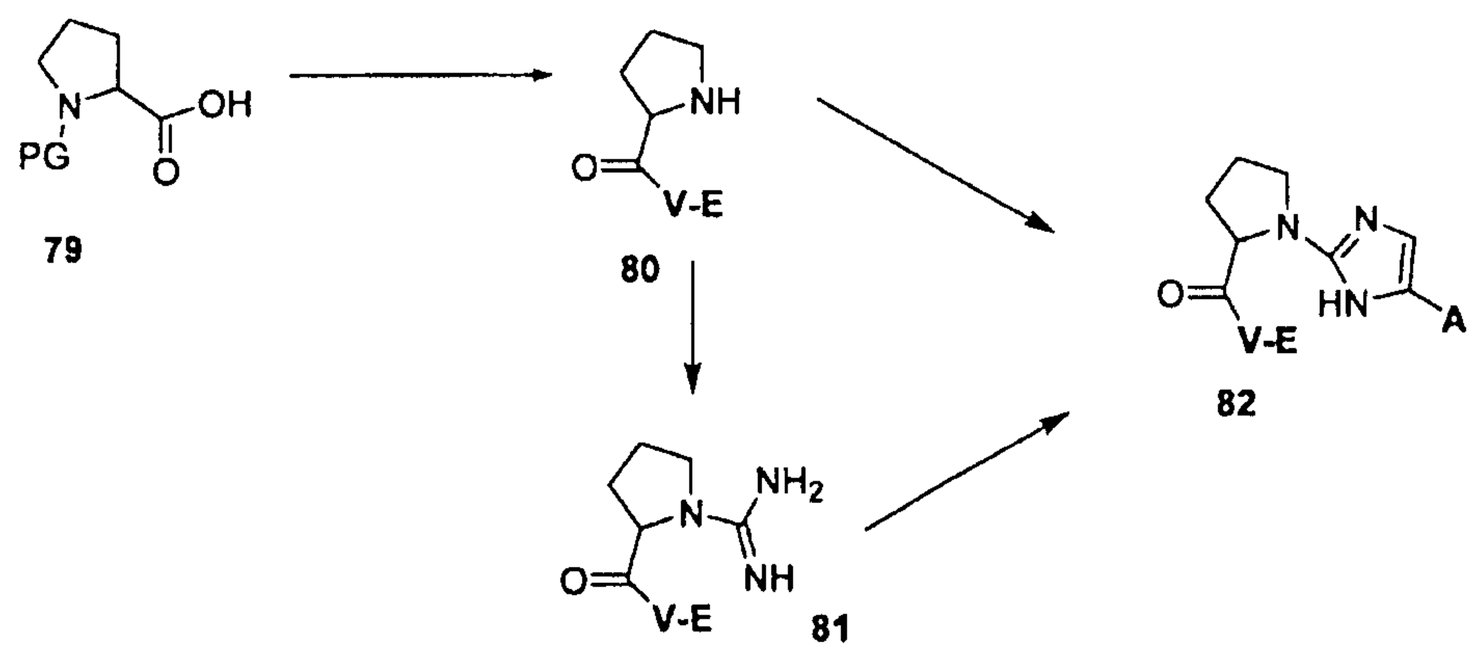
Scheme 18 shows a general synthesis of a **P** molecule of the invention wherein **X** = carbon or heteroatom and m and n = 0 - 5, independently. For illustrative purposes, **P** is substituted with an ethoxylcarbonyl group. Commercially available amino ester such an ethyl ester is converted to substituted or cyclized amino ester **73.1**, through for example, reductive amination or Mitsunobu reaction. Compound **73.1** can be protected to provide compound **73** if necessary.

Scheme 19: Representative Synthesis of E-V



Scheme 19 shows a general synthesis of an **E-V** molecule of the invention wherein, for illustrative purposes, **V** is isobutyl and **E** is methoxycarbonylamino. Amino acid 77 can be converted to the corresponding carbamate **78**, such as a methyl carbamate by reaction with methyl chloroformate under basic conditions (sodium bicarbonate).

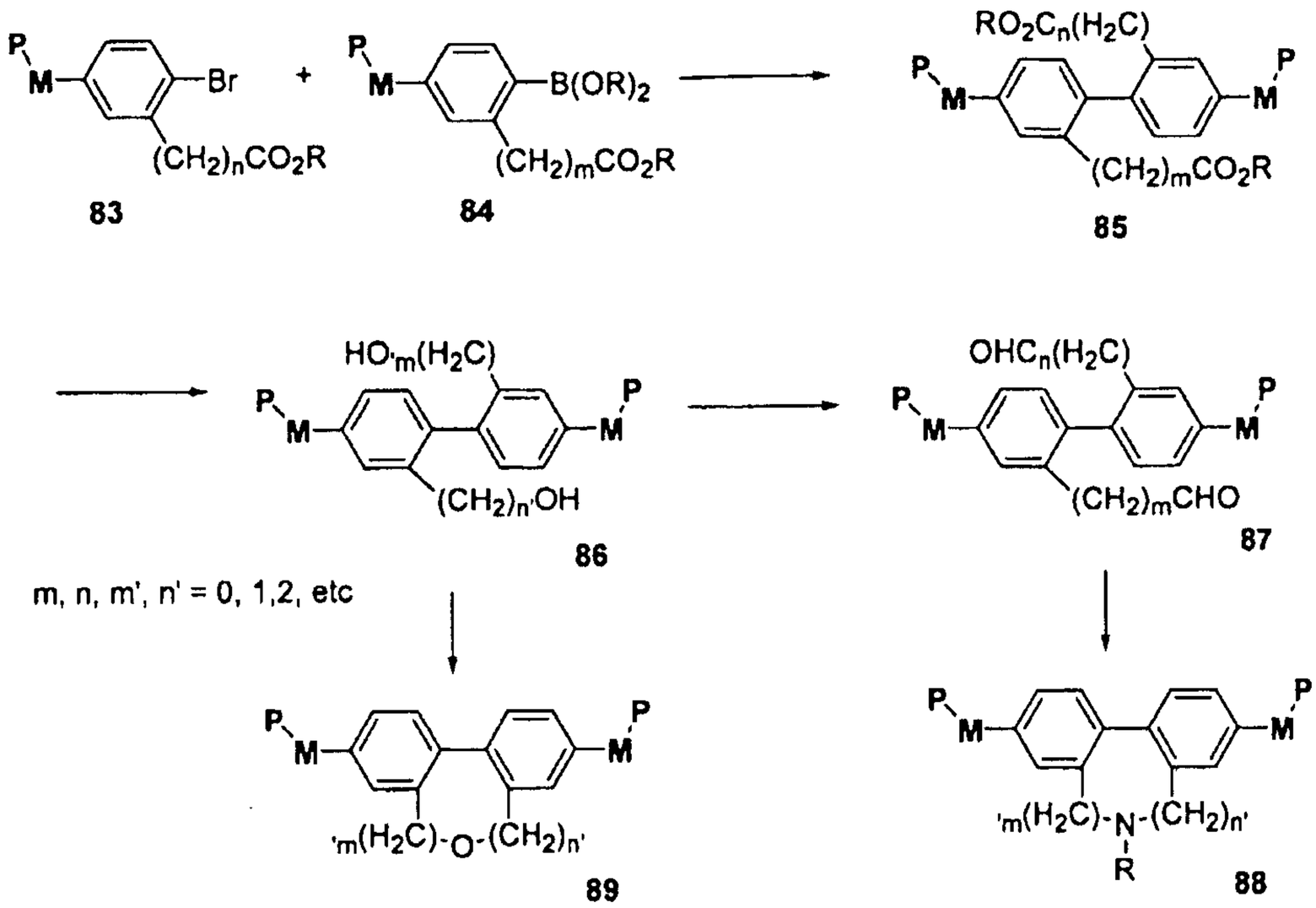
Scheme 20: Synthesis of the E-V-Z-P-M-A



Scheme 20 shows the synthesis of a **E-V-Z-P-M-A** molecule of the invention wherein, for illustrative purposes, **M** is imidazole, **P** is pyrrolidine, and **Z** is carbonyl. An amino acid derivative can be reacted with an N-protected proline derivative via reaction conditions employing a coupling reagent, such as HATU, deprotection of the resulting coupling product, for example in the case of *tert*-butoxy carbonyl, the treatment with a proton source such as HCl yielded compound **80**. The conversion of **80** to **E-V-Z-P-M-A (82)** can be obtained under reaction conditions of nucleophilic aromatic substitution, for example the displacement of methyl sulfonate under basic conditions and elevated temperatures.

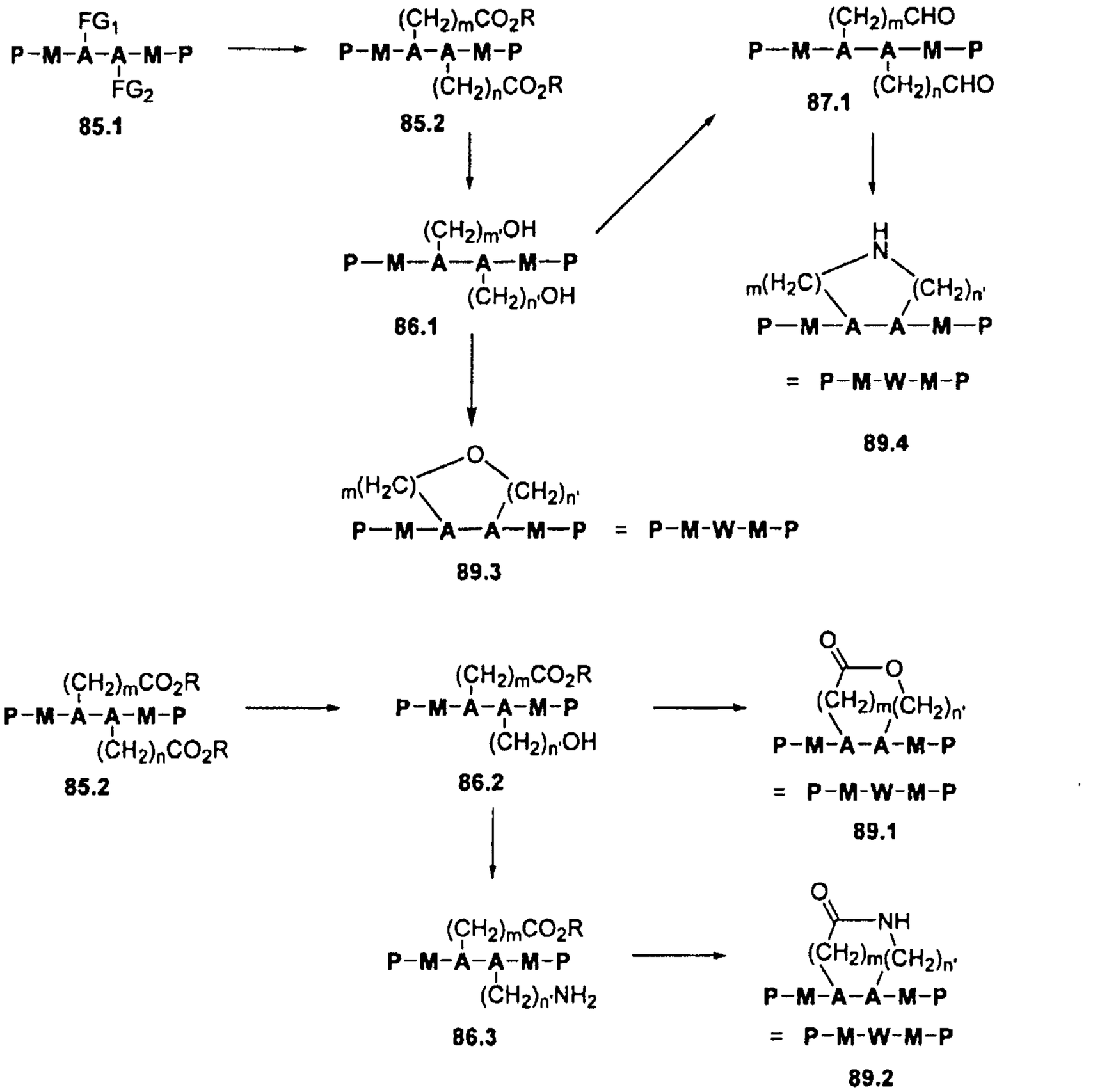
Alternatively, for illustrative purposes, the amino acid derivative **80** can be converted to a guanidinium containing compound **81**, via a reaction with a guanidylation reagent. The **E-V-Z-P-M-A** compound **82** can be obtained via reaction with a 1,2 di-electrophile such as an α-halogenated carbonyl group under basic conditions.

Scheme 21: Representative synthesis of P-M-W-M-P



Scheme **21** shows a general synthesis of a **P-M-W-M-P** molecule of the invention wherein. Boronic ester **84** is coupled with an appropriate coupling partner (e.g. arylbromide **83)** using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **85**. Carboxylate **85** is reduced with reagents such as DIBAL-H to afford diol **86**. The treatment of diol **86** with acids such as H_3PO_4 at elevated temperature generates **P-M-W-M-P** compound **89**. Alternatively, diol **86** can be oxidized with reagents such as pyridine-sulfur trioxide to form dialdehyde **87**, which react with amines in the presence of reducing reagents such as $NaBH(OAc)_3$ to provide **P-M-W-M-P** compound **88**.

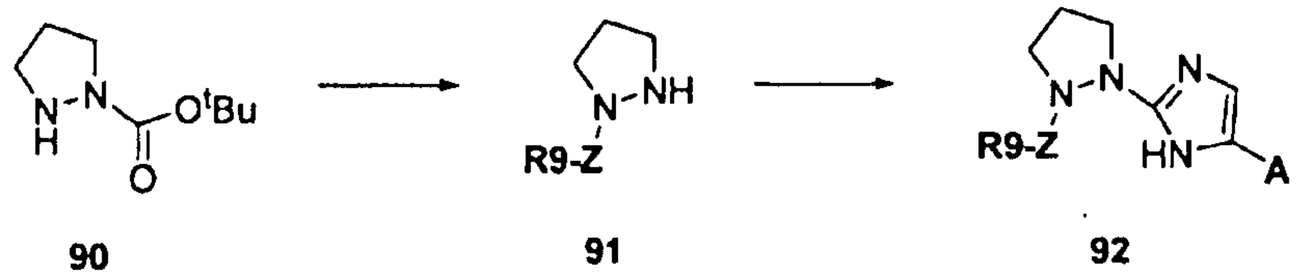
Scheme 21a: Representative synthesis of P-M-W-M-P



Scheme **21a** shows a general synthesis of a **P-M-W-M-P** molecule of the invention. For illustrative purposes, FG_1 and FG_2 can be converted to esters attached to an **A** group. Carboxylate **85.2** is reduced with reagents, such as DIBAL-H, to afford diol **86.1**. The treatment of diol **86.1** with acids, such as H_3PO_4, at elevated temperature generates **P-M-W-M-P** compound **89.3**. Alternatively, diol **86.1** can be oxidized with reagents such as pyridine-sulfur trioxide to form dialdehyde **87.1**, which reacts with amines in the presence of reducing reagents such as $NaBH(OAc)_3$ to provide **P-M-W-M-P** compound **89.4**. The carboxylate **85.2** is selectively reduced to provide hydroxyl ester **86.2**, which can be cyclized to form **P-M-W-M-P** compound **89.1**. Compound **86.1** is converted to amine ester **86.3**, for example through azide

formation and reduction with hydrogenation. Compound **86.3** can be cyclized to form **P-M-W-M-P** compound **89.2**.

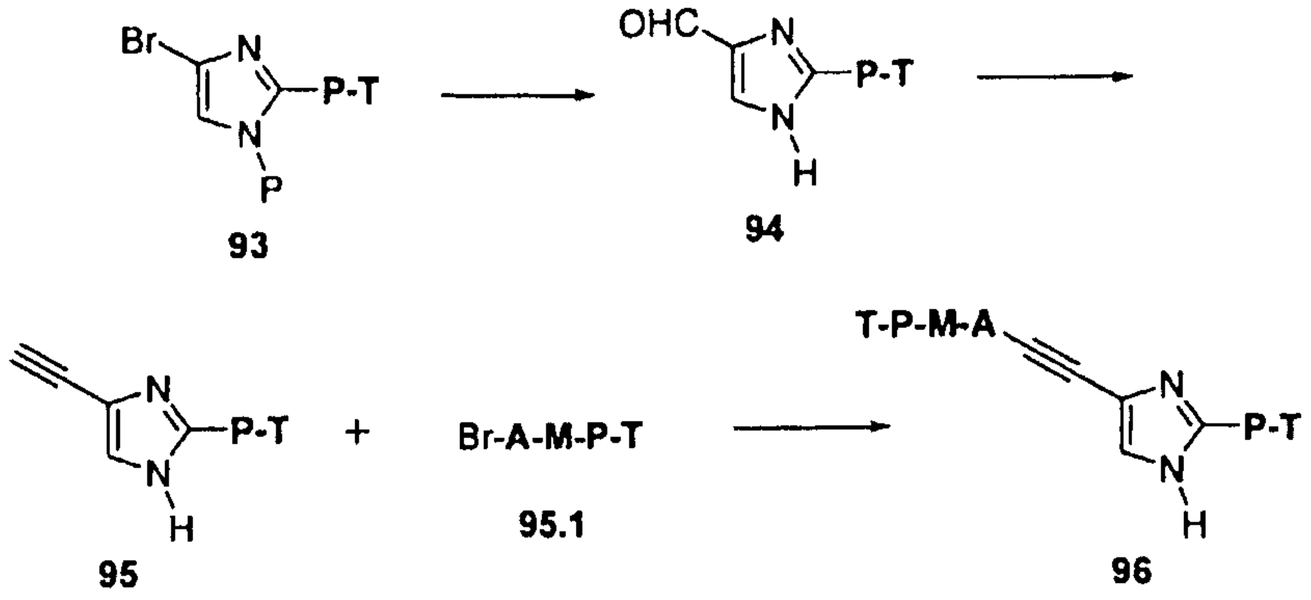
Scheme 22: Construction of a R9-Z-P-M-A



90 **91** **92**

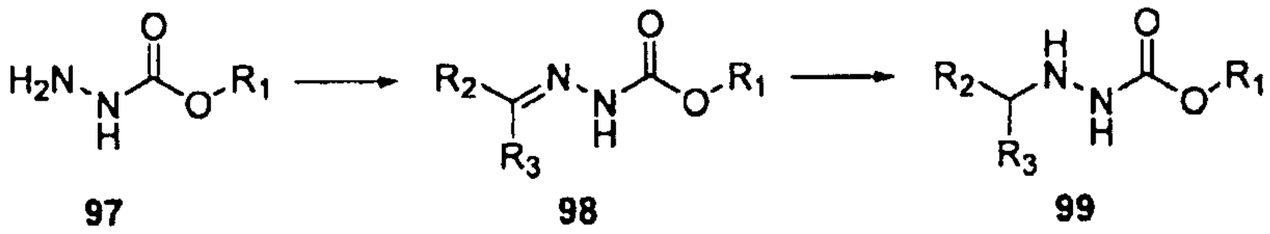
Scheme 22 shows the general synthesis of a **R9-Z-P-M-A** molecule, for illustrative purposes starting with *tert*-butoxy carbonyl derivative **90** (J. Am. Chem. Soc. 2003, 1221). Compound **90** can be acylated with substituent **T** wherein **Z** is carbonyl, via reaction conditions employing a coupling reagent such as HATU. Removal of the protecting group, for example in the case of *tert*-butoxycarbonyl by the treatment with a proton source such as HCl, yields compound **91.** A compound like **91** can be obtained under reaction conditions of nucleophilic aromatic substitution, for example the displacement of methyl sulfonate under basic conditions and elevated temperatures to provide the **R9-Z-P-M-A** compound **92**. Alternatively, **91** can be converted into a guanidinium derivative. When suitably substituted, cyclization provides the **R9-Z-P-M-A** compound **92**.

Scheme 23: Representative synthesis of T-P-M-A-A-M-P-T



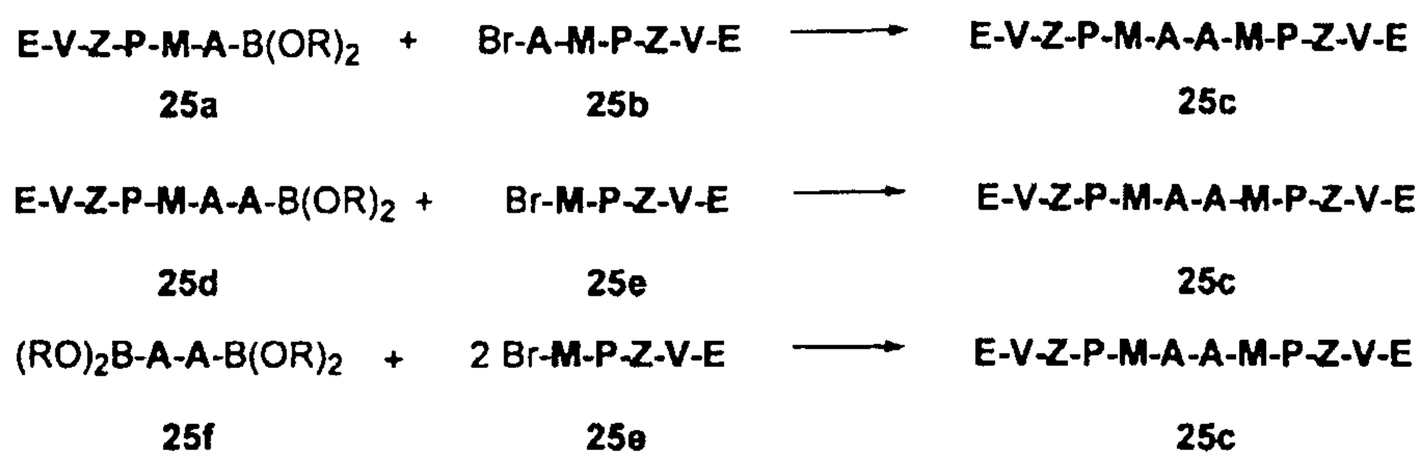
Scheme 23 shows a general synthesis of a **T-P-M-A-A-M-P-T** molecule of the invention wherein, for illustrative purposes, **M** = imidazole and **A** = alkyne. Bromoimidazole **93** is alkynylated by lithiation and trapping with a formate equivalent (e.g. DMF). The aldehyde **94** is converted to alkyne **95** using a phosphorus-based reagent (e.g. Ohira-Bestmann reagent). Compound **95** is coupled with a Br-**A**-**M**-**P**-**T** under Sonagashira conditions to afford the alkyne-containing compound **96**.

Scheme 24: Representative Synthesis of R9 Fragment



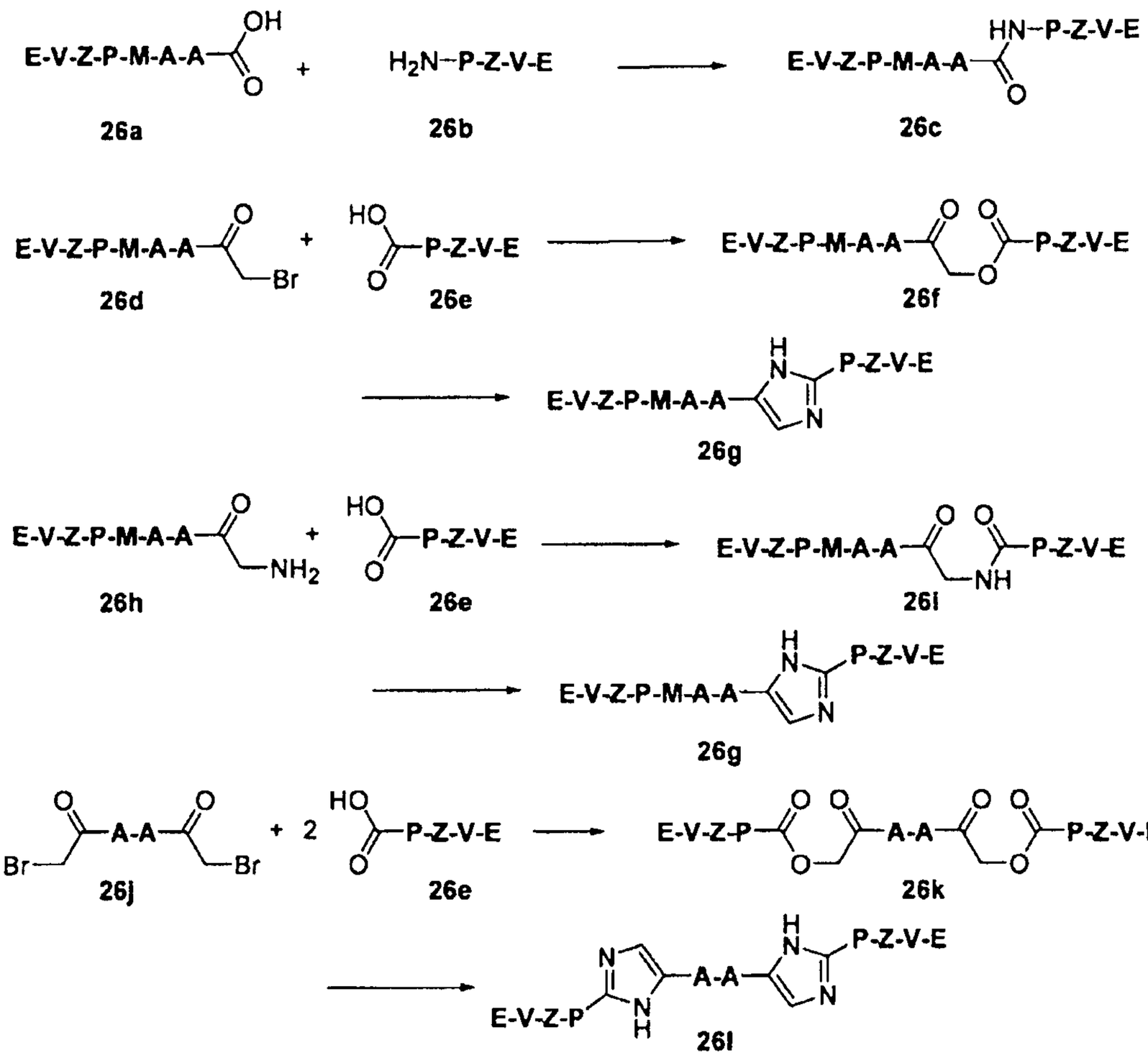
Scheme 24 shows a general synthesis of an **R9** molecule of the invention. Reaction of hydrazine carboxylate **97** with a ketone or aldehyde, such as acetone, under acidic conditions (e.g. AcOH) affords the imine **98**. Reaction of **98** under reducing conditions, such as PtO_2 and hydrogen gas, affords the substituted hydrazinecarboxylate **99**.

Scheme 25: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



Scheme 25 shows a general synthesis of the **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule of the invention, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond and/or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple Br-**M-P-Z-V-E** and $(RO)_2$B-**A-A-M-P-Z-V-E** or $(RO)_2$B-**A-M-P-Z-V-E and** Br-**A-M-P-Z-V-E**. Boronic ester **25a** (or **25d**) is coupled with an appropriate coupling partner (e.g. arylbromide **25b** or **25e**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **25c**. Formation of multiple **A-M** bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple $(RO)_2$B-**A-A-**B$(OR)_2$ (**25f**) and two equivalents of Br-**M-P-Z-V-E**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-A** and/or **A-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

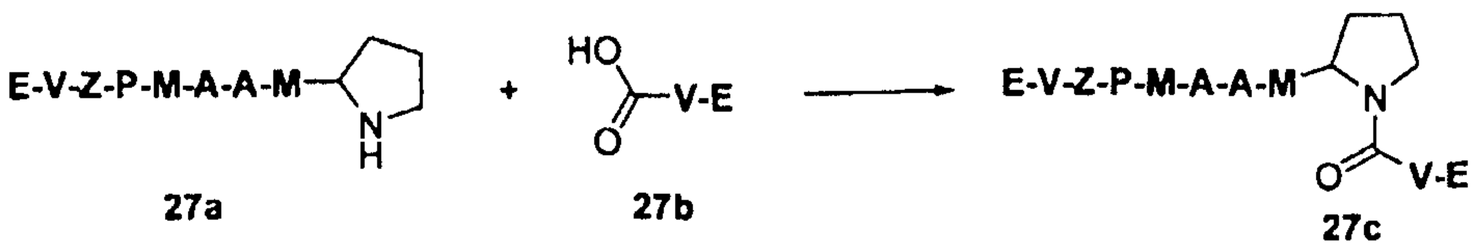
Scheme 26: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E

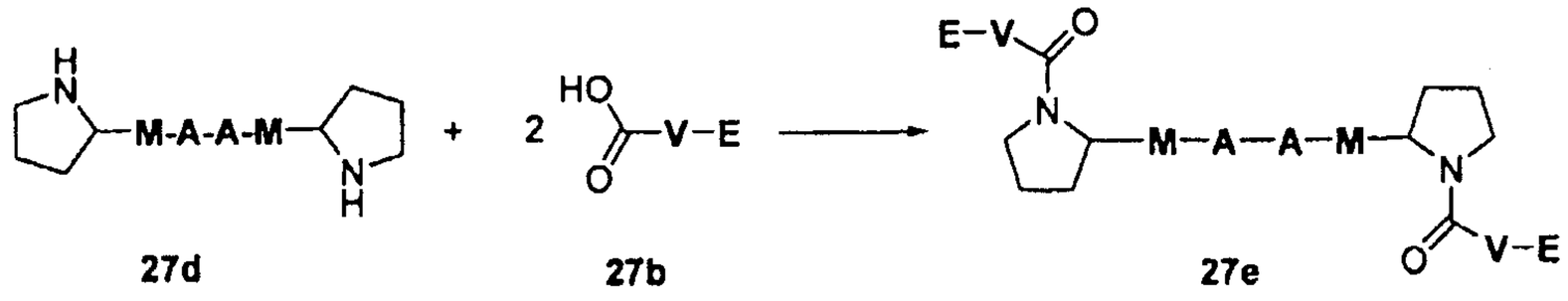


Scheme 26 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **M** is an amide, or an imidazole. Coupling of acid **26a** with amine **26b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford the amide product **26c**.

The formation of an imidazole is accomplished by coupling the acid **26d** with an α-haloketone, such as α-bromoketone **26e,** under basic conditions (e.g. Et_3N) to afford **26f**. Alternatively, the acid **26d** is coupled with an α-aminoketone **26h,** under amide formation conditions (e.g. EDC, Et_3N) to afford **26i**. Reaction of **26f** or **26i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **26g**. The formation of multiple imidazoles is performed in the same manner, starting with a bis- α-haloketone such as α-bromoketone **26j**, to provide molecule **26l**.

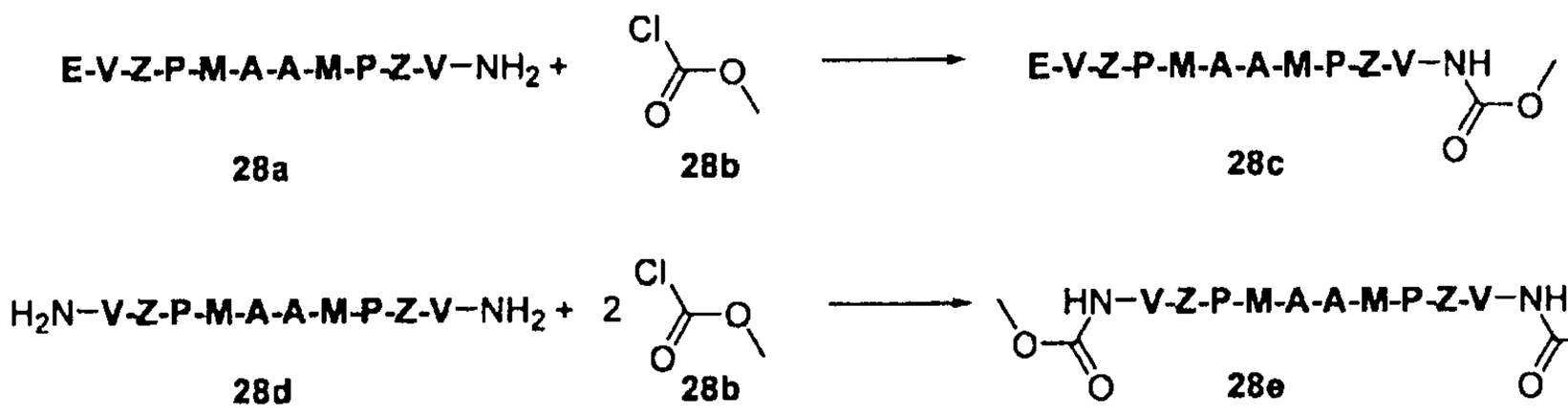
Scheme 27: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E





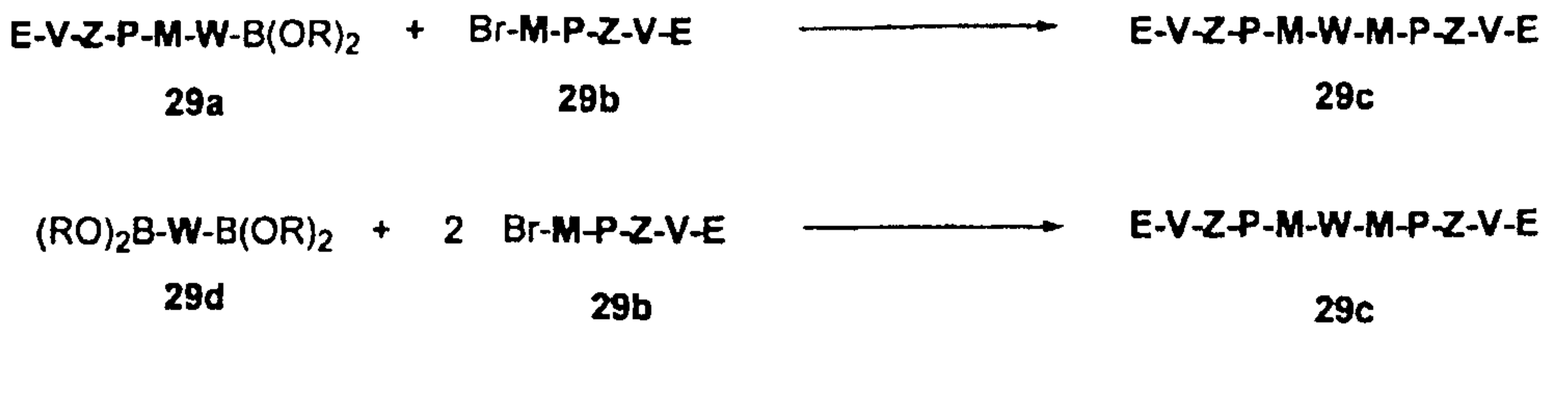
Scheme 27 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **27a** with acid **27b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **27c**. Alternatively, amine **27d** is coupled with two equivalents of **27b** under similar conditions to provide **27e**.

Scheme 28: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



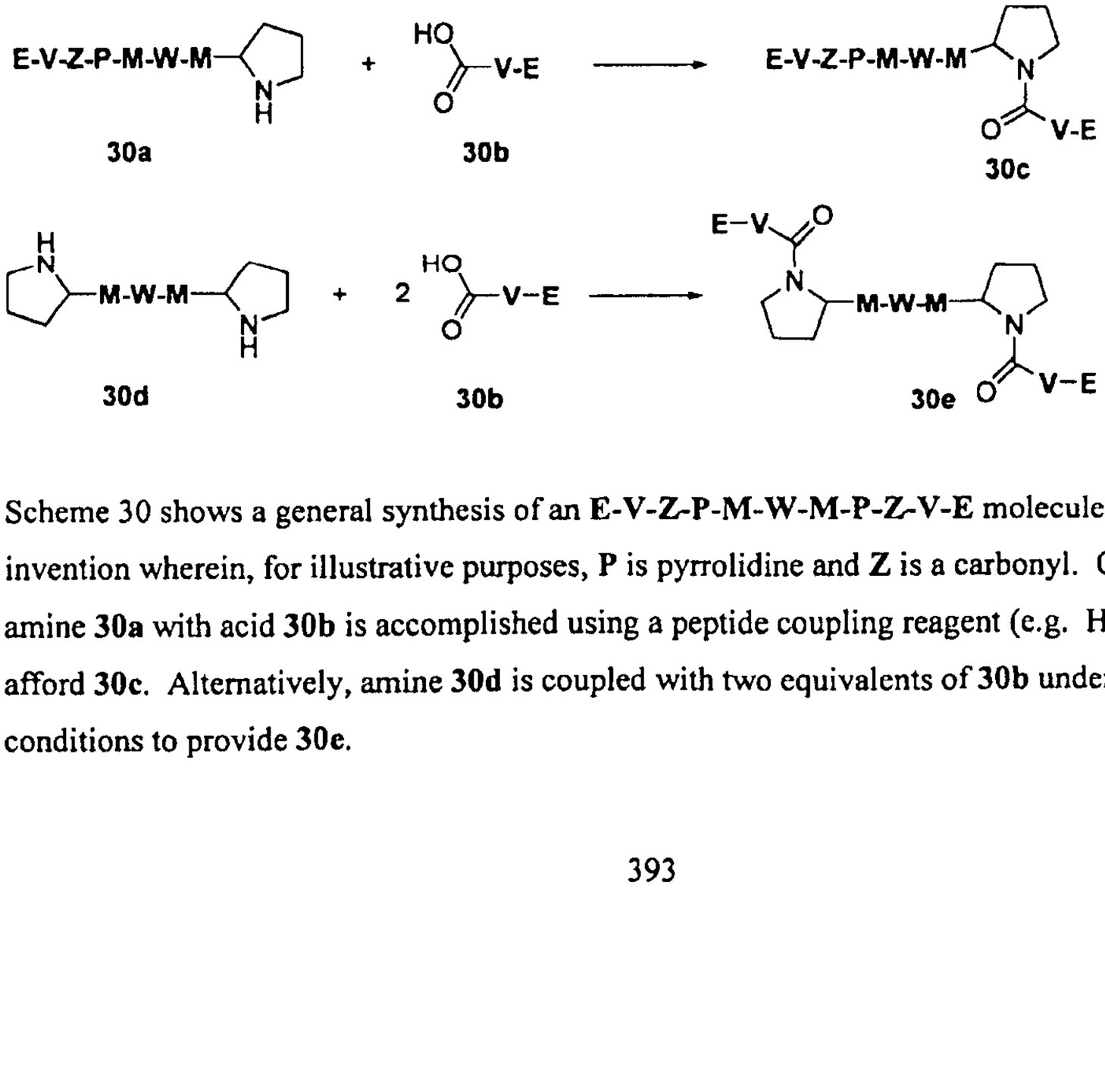
Scheme 28 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **28a** or **28d** with one or two equivalents respectively of **28b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **28c** or **28e**.

Scheme 29: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



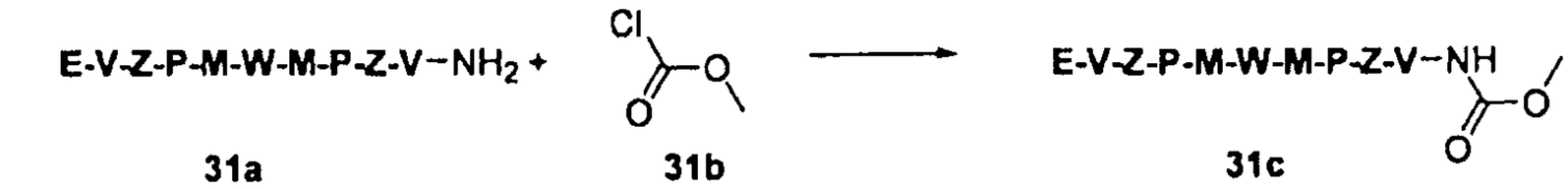
Scheme 29 shows a general synthesis of the **E-V-Z-P-M-W-M-P-Z-V-E** molecule of the invention, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **W-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple Br-**M-P-Z-V-E** to a $(RO)_2$B-**W-M-P-Z-V-E** or $(RO)_2$B-**W**-B$(OR)_2$ molecule. Boronic ester **29a** (or **29d**) is coupled with an appropriate coupling partner (e.g. arylbromide **29b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **29c**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **M-W** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 30: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



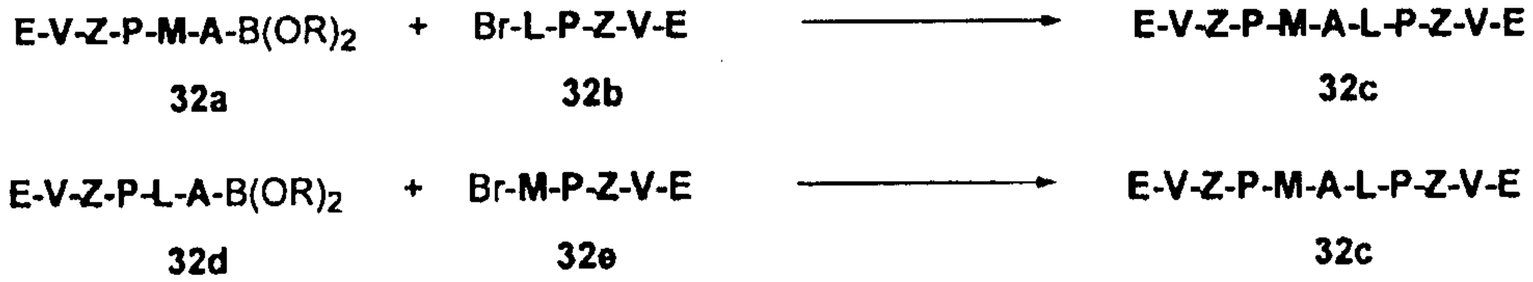
Scheme 30 shows a general synthesis of an **E-V-Z-P-M-W-M-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **30a** with acid **30b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **30c**. Alternatively, amine **30d** is coupled with two equivalents of **30b** under similar conditions to provide **30e**.

Scheme 31: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



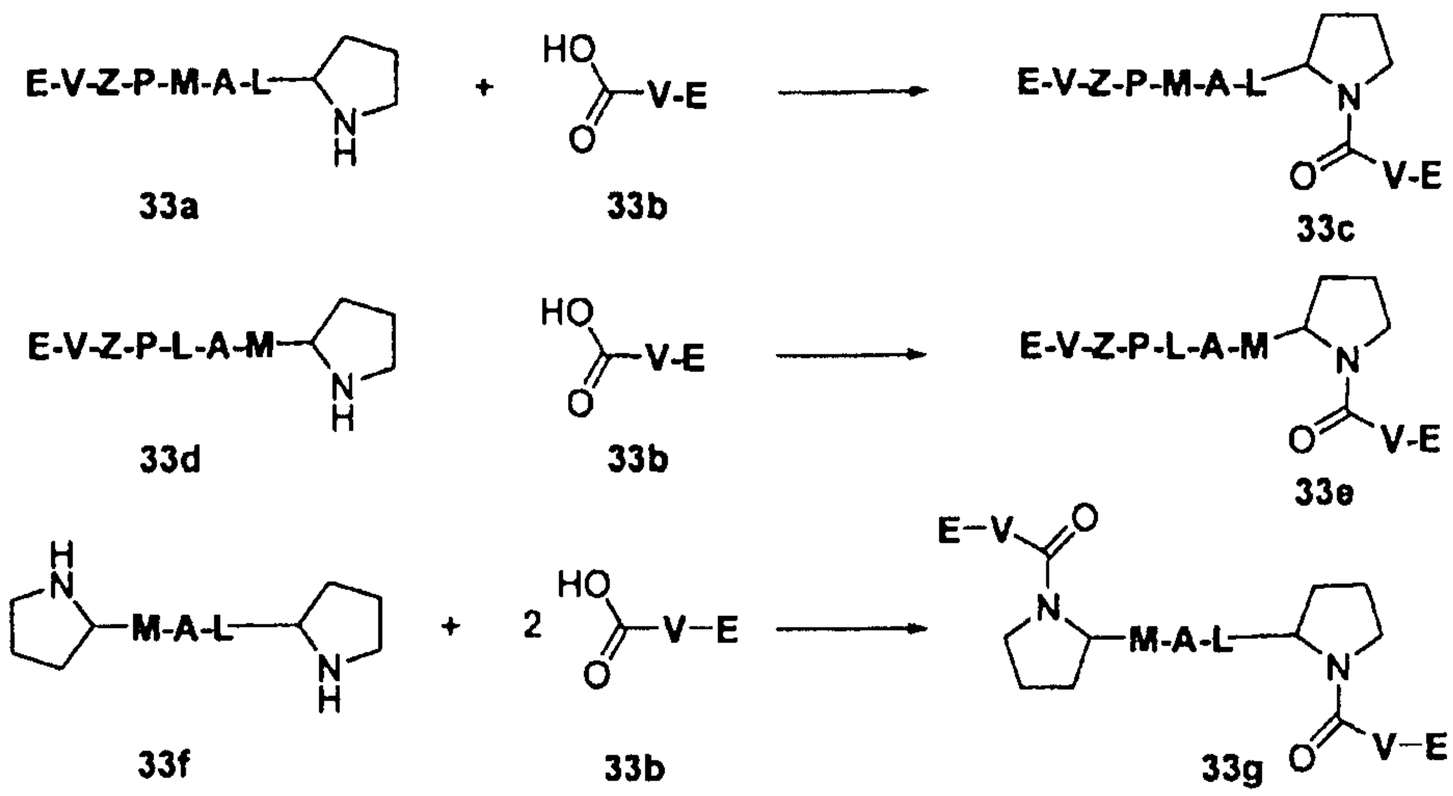
Scheme 31 shows a general synthesis of an **E-V-Z-P-M-W-M-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **31a** or **31d** with one or two equivalents respectively of **31b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **31c** or **31e**.

Scheme 32: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



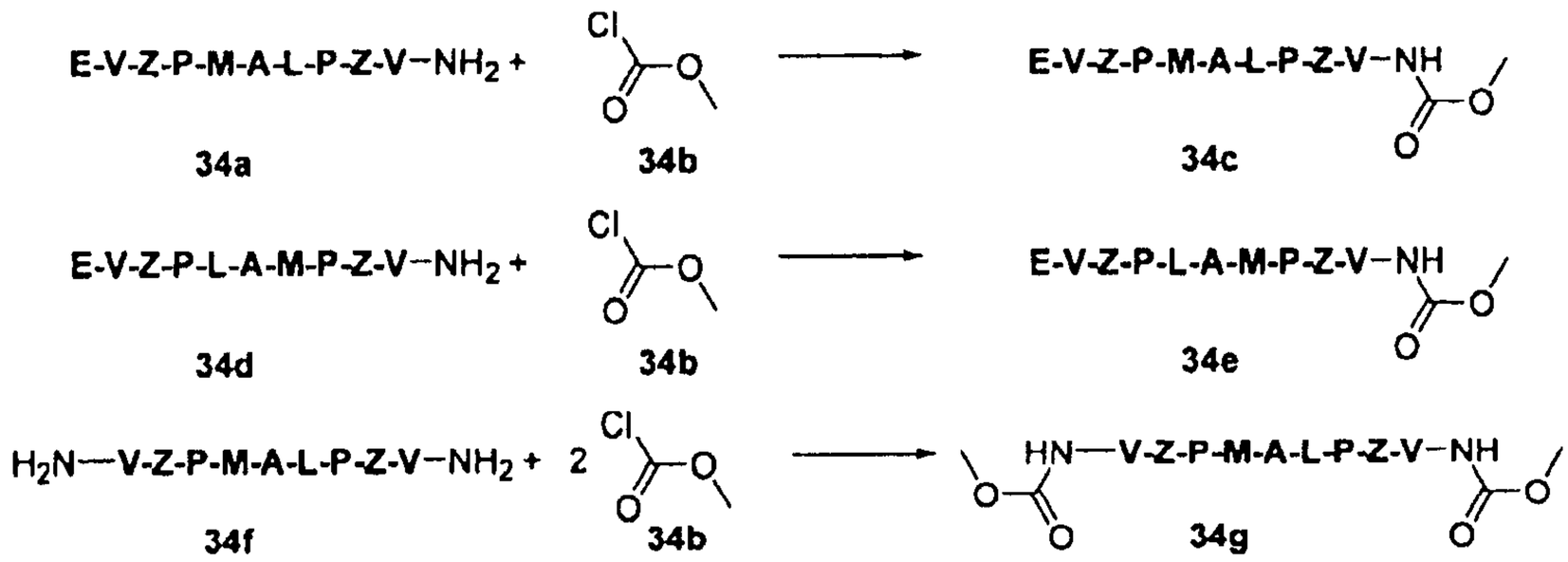
Scheme 32 shows a general synthesis of the **E-V-Z-P-M-A-L-P-Z-V-E** molecule of the invention, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **M-A** or **A-L** bond. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to an arylbromide. Boronic ester **32a** (or **32d**) is coupled with an appropriate coupling partner (e.g. arylbromide **32b** or **32e**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **32c**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable either the **M-A** or **A-L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 33: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



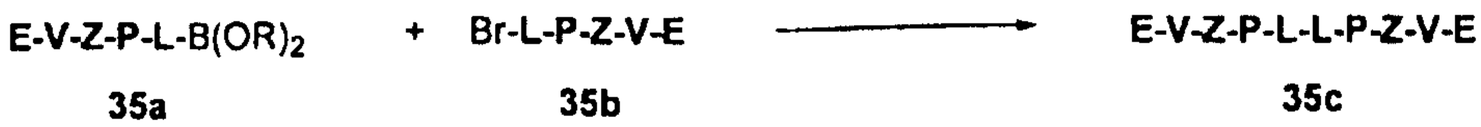
Scheme 33 shows a general synthesis of an **E-V-Z-P-M-A-L-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **33a** or **33d** with acid **33b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **33c** or **33e**, respectively. Alternatively, amine **33f** is coupled with two equivalents of **33b** under similar conditions to provide **33g**.

Scheme 34: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



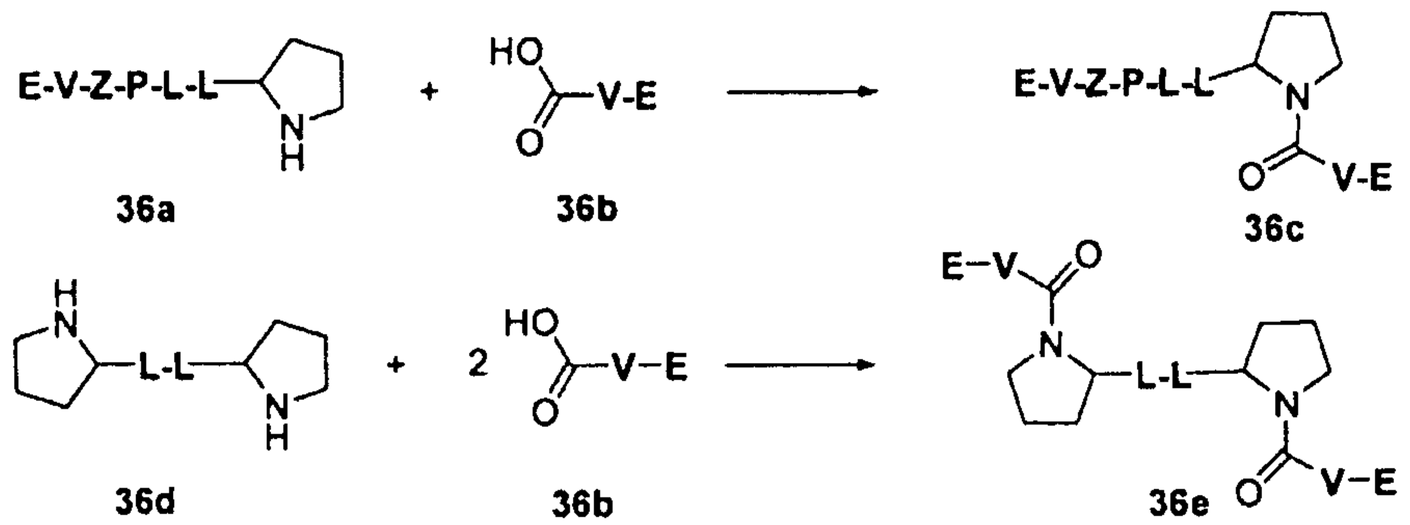
Scheme 34 shows a general synthesis of an **E-V-Z-P-M-A-L-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **34a** or **34d** with **34b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **34c** or **34e**. Correspondingly, the treatment of **34f** with two equivalents of **34b** provides **34g** under similar conditions.

Scheme 35: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



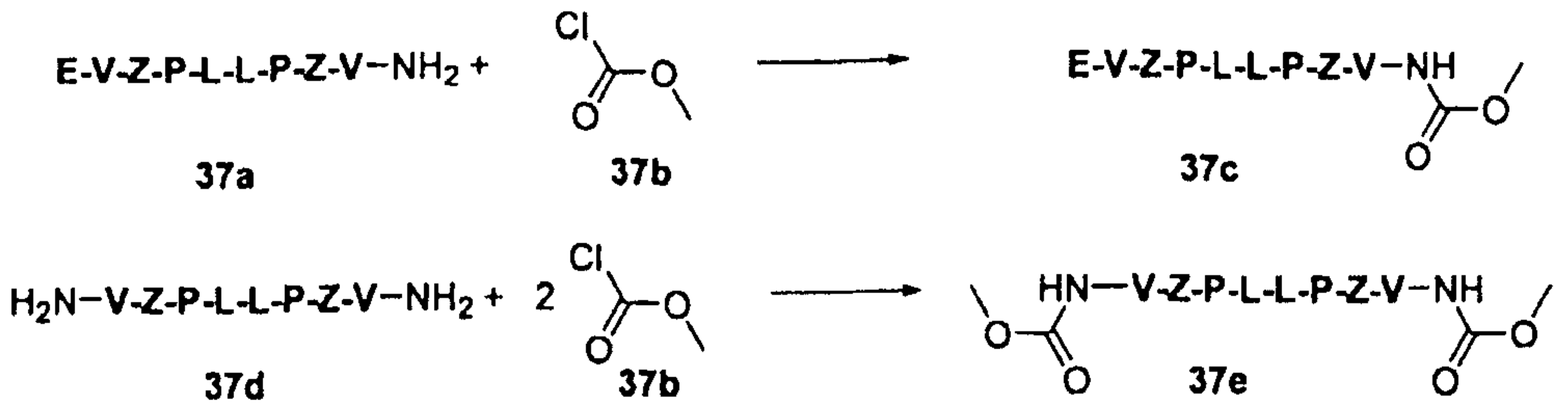
Scheme 35 shows a general synthesis of the **E-V-Z-P-L-L-P-Z-V-E** molecule of the invention, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **L-L** bond. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to an arylbromide. Boronic ester **35a** is coupled with an appropriate coupling partner (e.g. arylbromide **35b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **35c**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable either the **L-L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 36: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



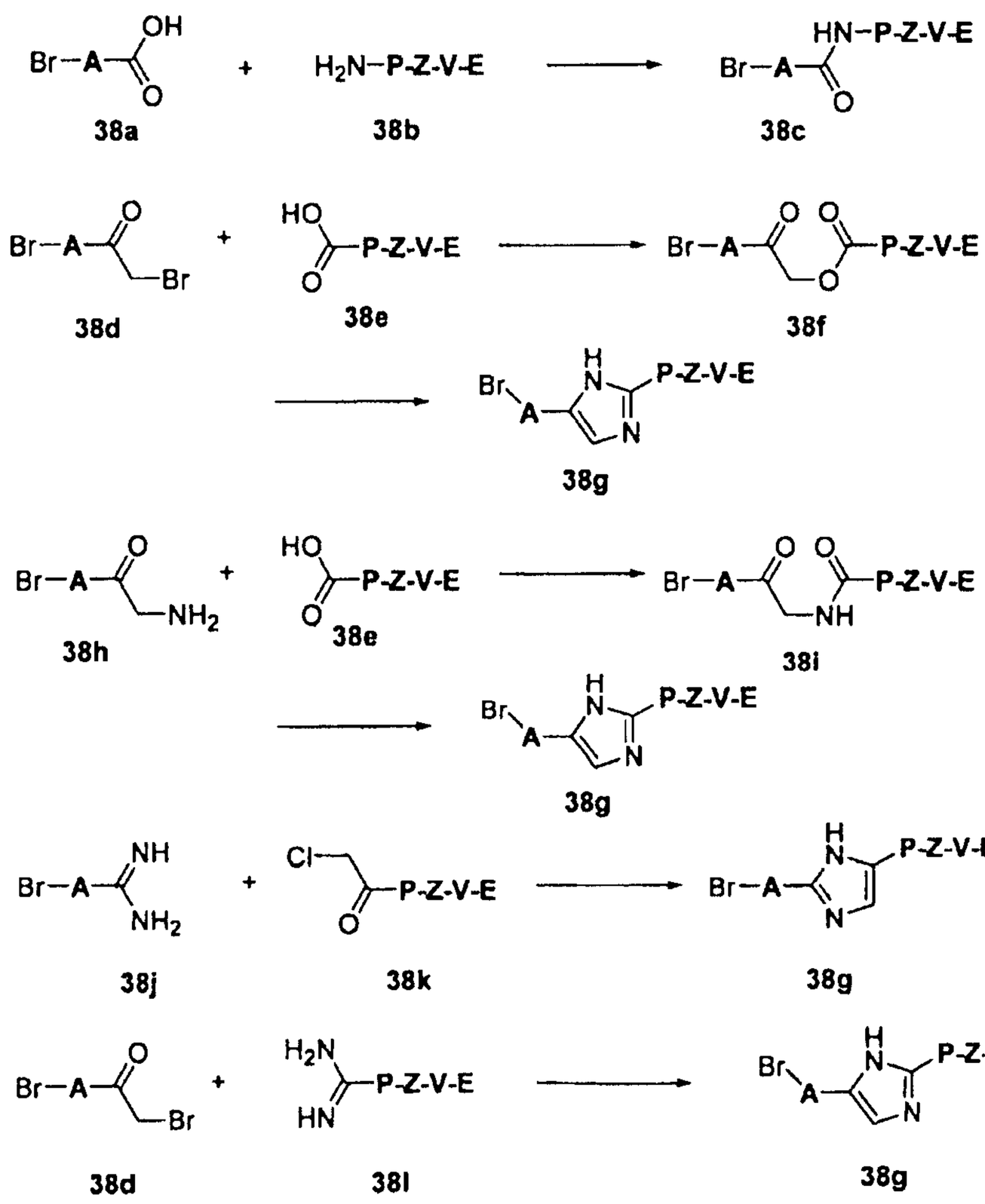
Scheme 36 shows a general synthesis of an **E-V-Z-P-L-L-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **36a** with acid **36b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **36c**. Alternatively, amine **36d** is coupled with two equivalents of **36b** under similar conditions to provide **36e**.

Scheme 37: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



Scheme 37 shows a general synthesis of an **E-V-Z-P-L-L-P-Z-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **37a** or **37d** with **37b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **37c** or **37e**.

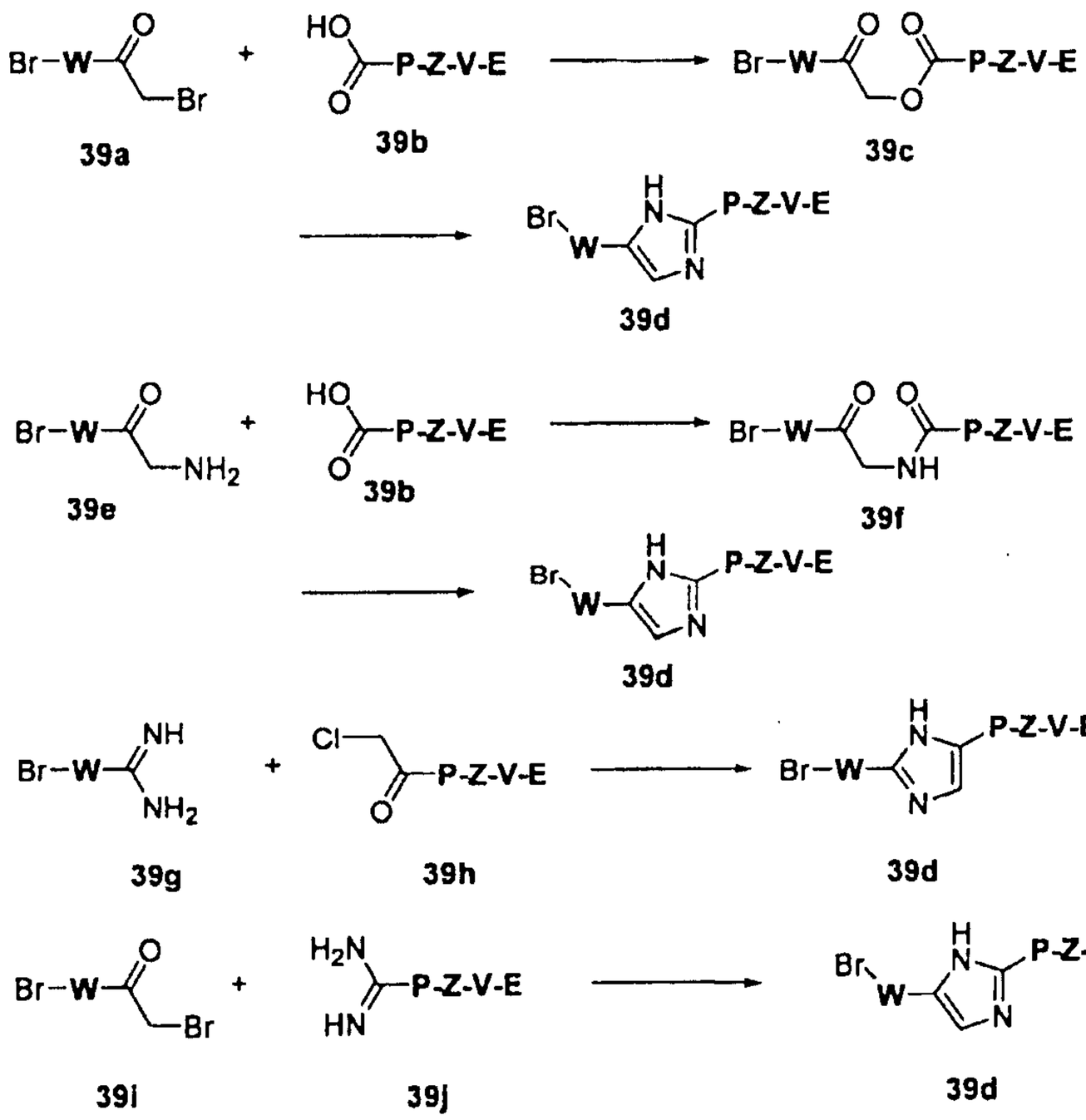
Scheme 38: Representative synthesis of R-A-M-P-R[1]



Scheme 38 shows a general synthesis of an R-**A**-**M**-**P**-R^1 intermediate of the invention wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as -**Z**-**V**-**E**. Coupling of amine **38b** with acid **38a** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **38c**. The acid **38e** is coupled with an α-haloketone, such as α-bromoketone **38d,** under basic conditions (e.g. Et_3N) to afford **38f**. Alternatively, the acid **38e** is coupled with an α-aminoketone **38h,** under amide formation conditions (e.g. EDC, Et_3N) to afford **38i**. Reaction of **38f** or **38i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-**A**-**M**-**P**-**Z**-**V**-**E** (**38g**).

The benzamidine **38j** is coupled with an α-haloketone such as α -chloroketone **38k** under basic conditions such as K_2CO_3 to afford **38g**. The Br-**A**-**M**-**P**-**Z**-**V**-**E** intermediate can be prepared analogously from the coupling of **38d** and **38l**.

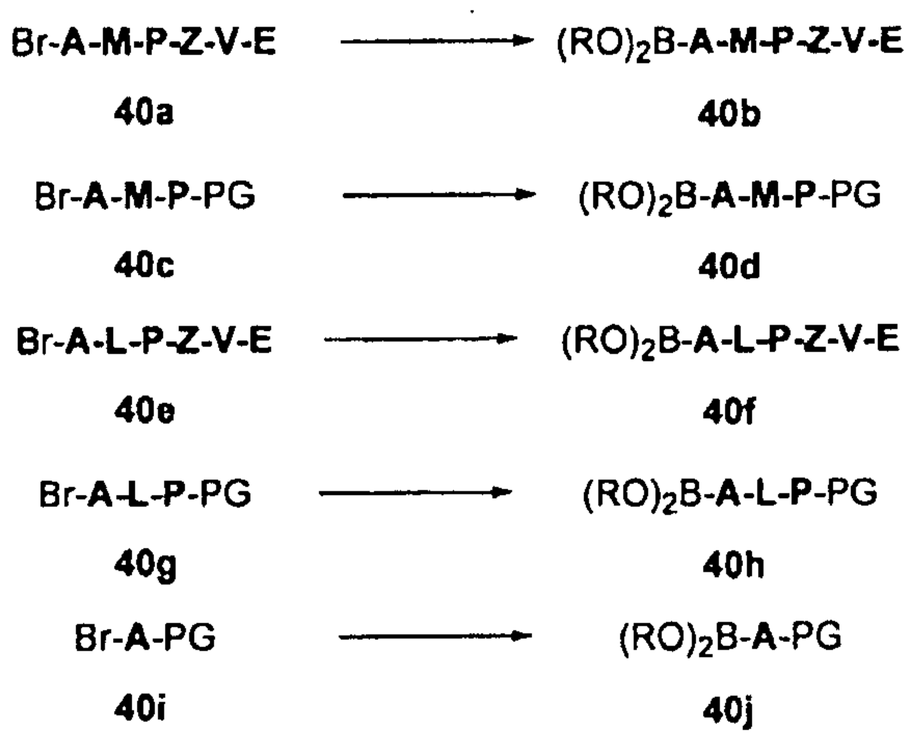
Scheme 39: Representative synthesis of R-W-M-P-R^1



Scheme 39 shows a general synthesis of an R-**W**-**M**-**P**-R^1 intermediate of the invention wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as **-Z-V-E**. The acid **39b** is coupled with an α-haloketone, such as α-bromoketone **39a,** under basic conditions (e.g. Et_3N) to afford **39c**. Alternatively, the acid **39b** is coupled with an α-aminoketone **39e,** under amide formation conditions (e.g. EDC, Et_3N) to afford **39f**. Reaction of **39c** or **39f** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-**A**-**M**-**P**-**Z**-**V**-**E** (**39d**).

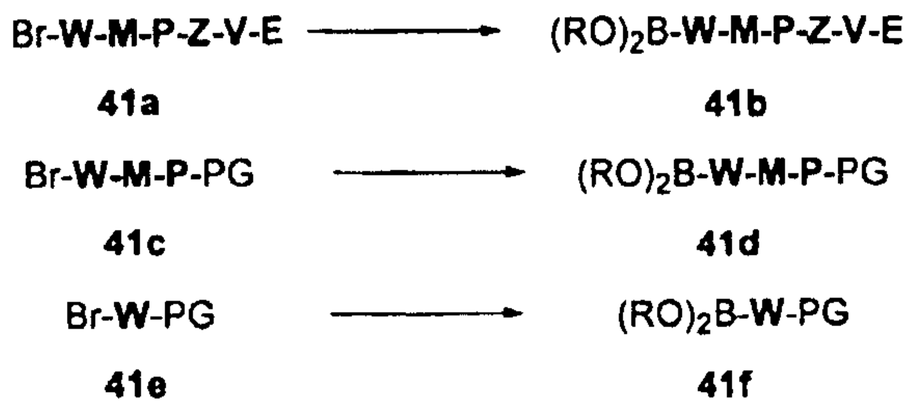
The benzamidine **39g** is coupled with an α-haloketone such as α -chloroketone **39h** under basic conditions such as K_2CO_3 to afford **39d**. The Br-**A**-**M**-**P**-**Z**-**V**-E intermediate can be prepared analogously from the coupling of **39i** and **39j**.

Scheme 40: Representative synthesis of R-A-R^1



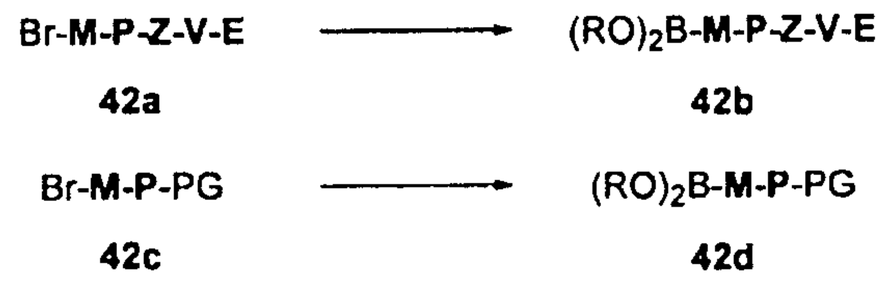
Scheme 40 shows a general synthesis of an R-**A**-R^1 intermediate of the invention wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-M-P-Z-V-E**, **-M-P**-PG, **-L-P-Z-V-E**, **-L-P**-PG, or a protecting group. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an **A** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **40b**, **40d**, **40f**, **40h**, or **40j**.

Scheme 41: Representative synthesis of R-W-R^1



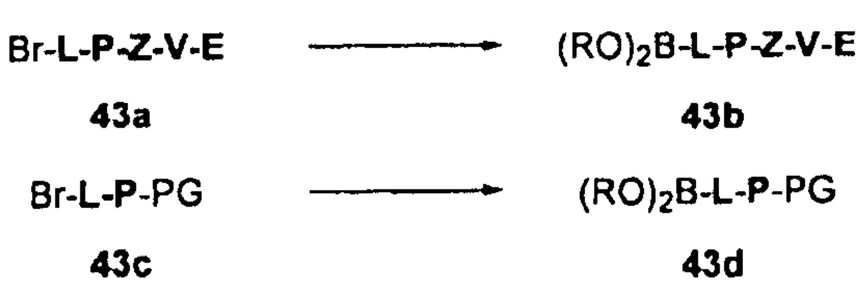
Scheme 41 shows a general synthesis of an R-W-R^1 intermediate of the invention wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as -M-P-Z-V-E, -M-P-PG, or a protecting group. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on a W group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **41b**, **41d**, or **41f**.

Scheme 42: Representative synthesis of R-M-R^1



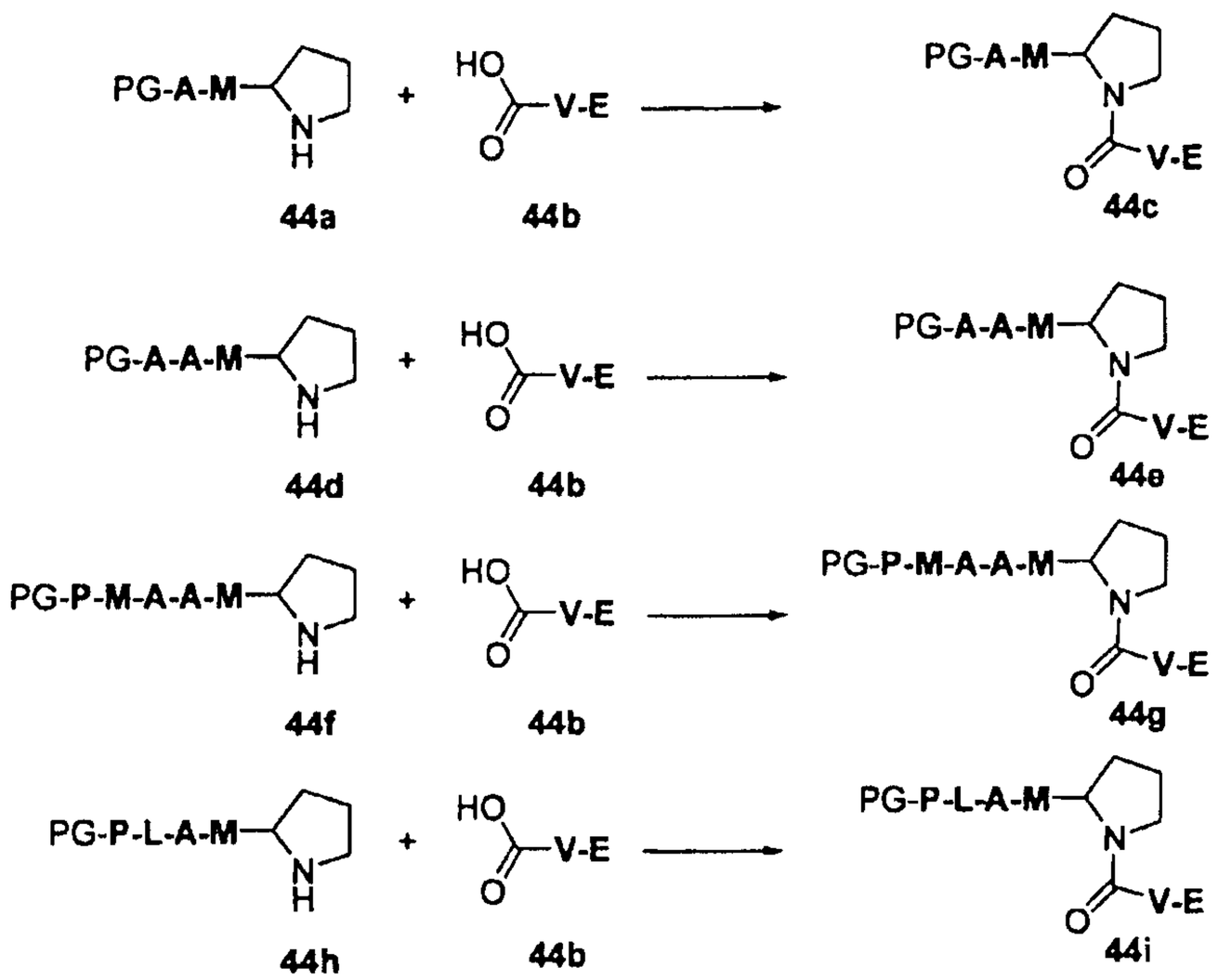
Scheme 42 shows a general synthesis of an R-M-R^1 intermediate of the invention wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as -P-Z-V-E or -P-PG. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an M group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **42b** or **42d**.

Scheme 43: Representative synthesis of R-L-R^1



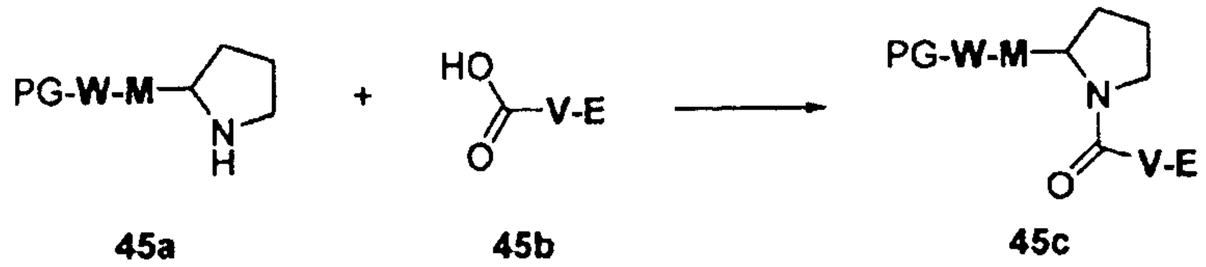
Scheme 43 shows a general synthesis of an R-**L**-R^1 intermediate of the invention wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-P-Z-V-E** or **-P**-PG. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an **L** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **43b** or **43d**.

Scheme 44: Representative synthesis of R-A-M-P-Z-V-E

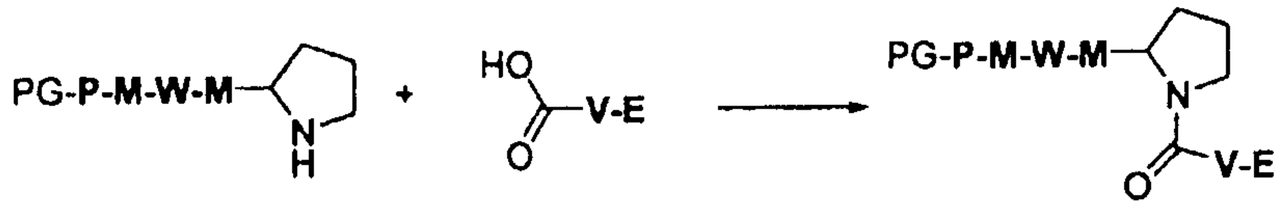


Scheme 44 shows a general synthesis of an R-**A-M-P-Z-V-E** intermediate of the invention wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either **-A**-PG, **-A-M-P**-PG, **-L-P**-PG, or a protecting group. Coupling of amine **44a**, **44d**, **44f**, or **44h** with acid **44b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **44c**, **44e**, **44g**, or **44i**, respectively.

Scheme 45: Representative synthesis of R-W-M-P-Z-V-E



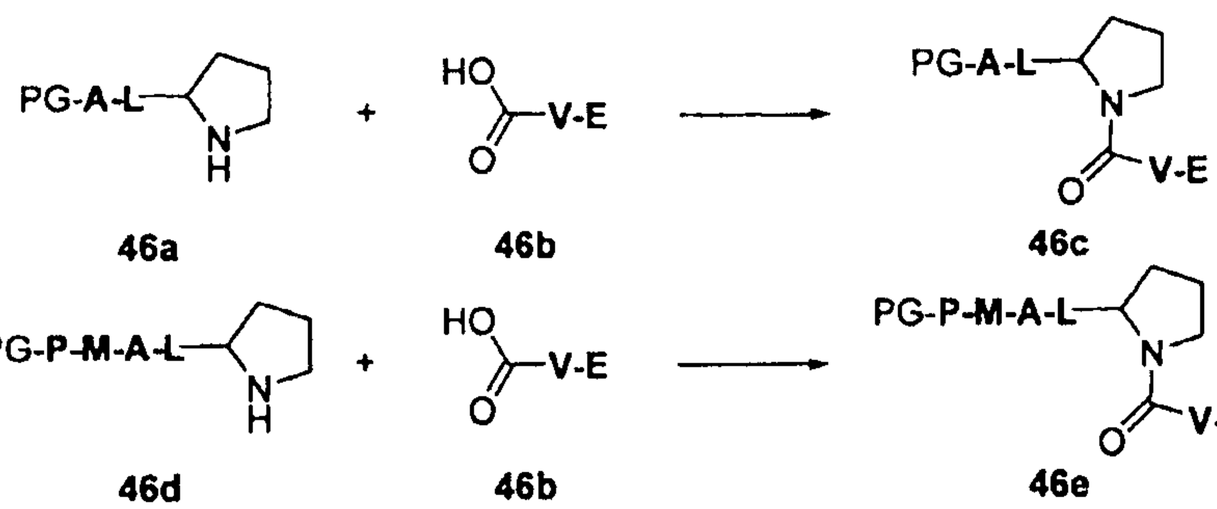
45a **45b** **45c**



45d **45b** **45e**

Scheme 45 shows a general synthesis of an R-**W**-**M**-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either -**M**-**P**-PG or a protecting group. Coupling of amine **45a** or **45d** with acid **45b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **45c** or **45e**, respectively.

Scheme 46: Representative synthesis of R-A-L-P-Z-V-E

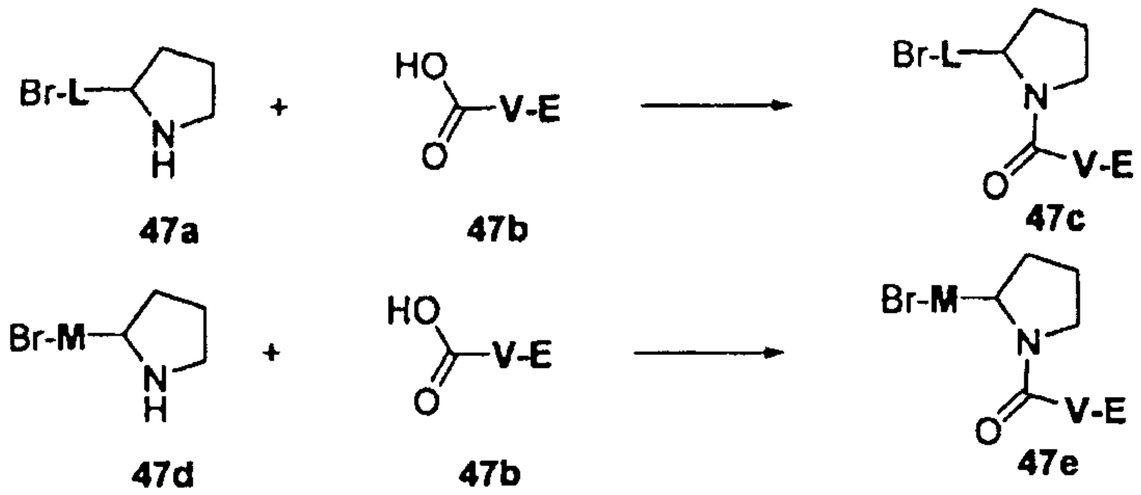


46a **46b** **46c**

46d **46b** **46e**

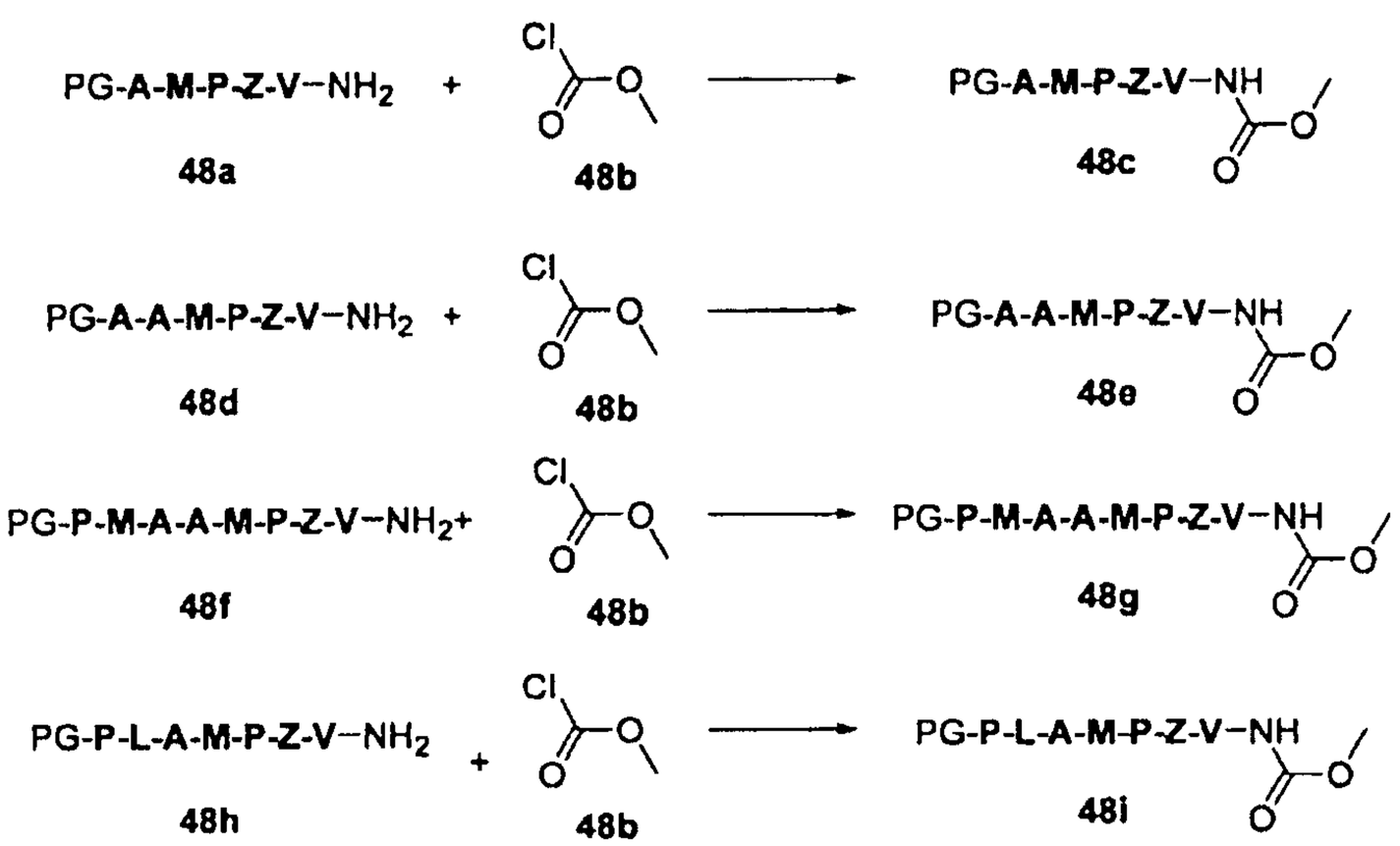
Scheme 46 shows a general synthesis of an R-**A**-**L**-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either -**M**-**P**-PG or a protecting group. Coupling of amine **46a** or **46d** with acid **46b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **46c** or **46e**, respectively.

Scheme 47: Representative synthesis of R-L-P-Z-V-E and R-M-P-Z-V-E



Scheme 47 shows a general synthesis of an R-**L**-**P**-**Z**-**V**-**E** or R-**M**-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as Br. Coupling of amine **47a** or **47d** with acid **47b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **47c** or **47e**, respectively.

Scheme 48: Representative synthesis of R-A-M-P-Z-V-E

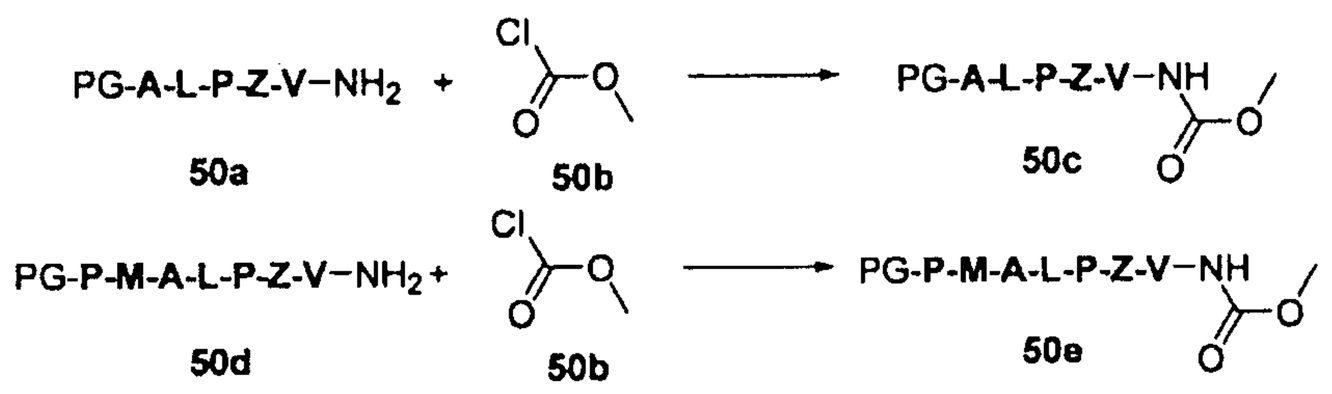


Scheme 48 shows a general synthesis of an R-**A**-**M**-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a either -**A**-PG, -**A**-**M**-**P**-PG, -**L**-**P**-PG, or a protecting group. Treatment of **48a**, **48d**, **48f**, or **48h** with **48b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **48c**, **48e**, **48g**, or **48i**, respectively.

Scheme 49: Representative synthesis of R-W-M-P-Z-V-E

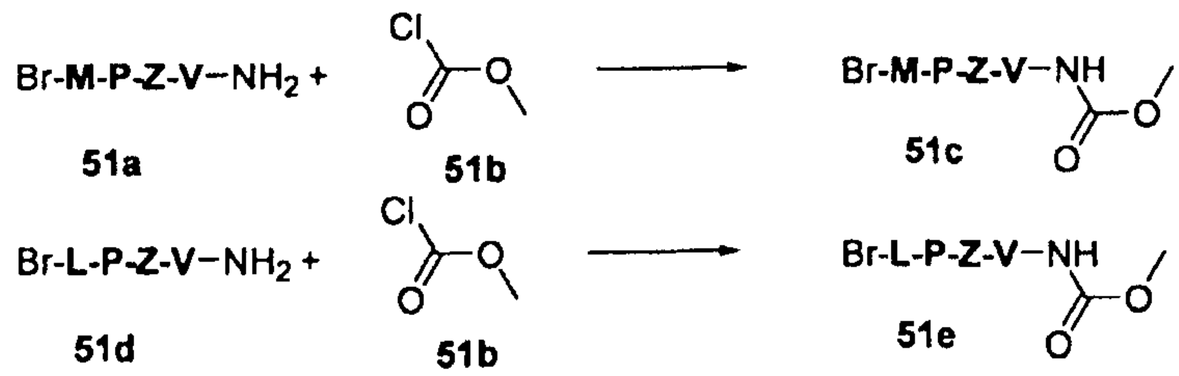
Scheme 49 shows a general synthesis of an R-**W-M-P-Z-V-E** intermediate of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as either -**M-P**-PG or a protecting group. Treatment of **49a** or **49d** with **49b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **49c** or **49e**, respectively.

Scheme 50: Representative synthesis of R-A-L-P-Z-V-E



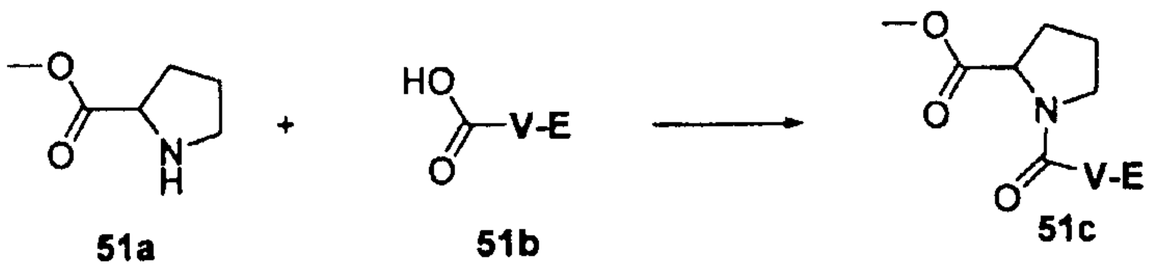
Scheme 50 shows a general synthesis of an R-**A-L-P-Z-V-E** intermediate of the invention wherein, for illustrative purposes, E is methoxycarbonylamino and R is a generic group that is depicted as a either -**M-P**-PG or a protecting group. Treatment of **50a** or **50d** with **50b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **50c** or **50e**, respectively.

Scheme 51: Representative synthesis of R-A-L-P-Z-V-E



Scheme 51 shows a general synthesis of an R-**L**-**P**-**Z**-**V**-**E** or R-**M**-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a Br. Treatment of **51a** or **51d** with **51b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **51c** or **51e**, respectively.

Scheme 51a: Representative synthesis of R-**P**-**Z**-**V**-**E**



51a **51b** **51c**

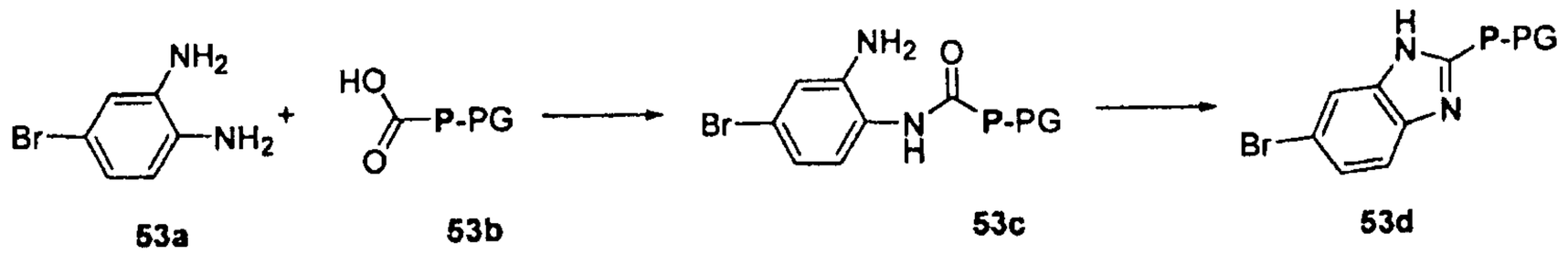
Scheme 51a shows a general synthesis of an R-**P**-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as a methoxycarbonyl. Coupling of amine **51a** with acid **51b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **51c**.

Scheme 52: Representative synthesis of R-**Z**-**V**-**E**

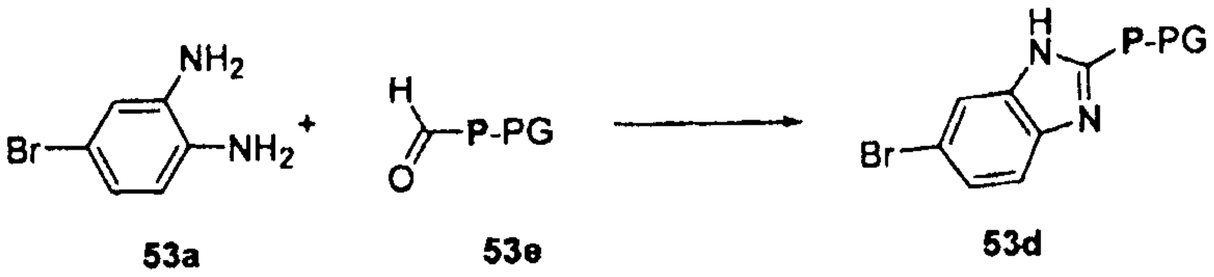
52a **52b** **52c**

Scheme 52 shows a general synthesis of an R-**Z**-**V**-**E** intermediate of the invention wherein, for illustrative purposes, E is methoxycarbonylamino and R is a generic group that is depicted as a hydroxyl. Treatment of **52a** under basic conditions (e.g. sodium bicarbonate) with **52b** provides the intermediate **52c**.

Scheme 53: Representative synthesis of R-L-P-R^1



53a **53b** **53c** **53d**

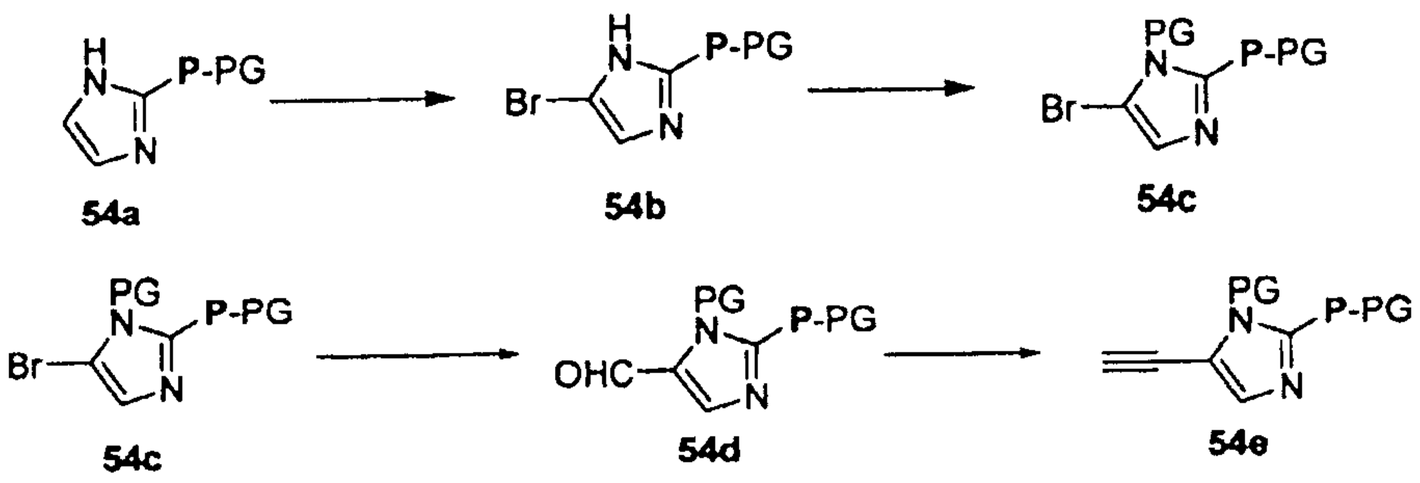


53a **53e** **53d**

Scheme 53 shows a general synthesis of an R-**L**-**P**-R^1 intermediate of the invention wherein, for illustrative purposes, **L** is benzimidazole, R is a generic group that is depicted as a bromide, and R^1 is a protecting group. The acid **53b** is coupled with **53a** using a peptide coupling reagent such as HATU to afford **53c.** Heating in solvent (such as refluxing ethanol) affords the R-**L**-**P**-R^1 intermediate **53d**.

Alternatively, the R-L-P-R^1 intermediate **53d** is obtained by reaction of a diamine (such as **53a**) and carbonyl compound (such as aldehyde **53e**) in a solvent under heating conditions (e.g. ethanol under microwave irradiation).

Scheme 54: Representative synthesis of R-M-P-R^1

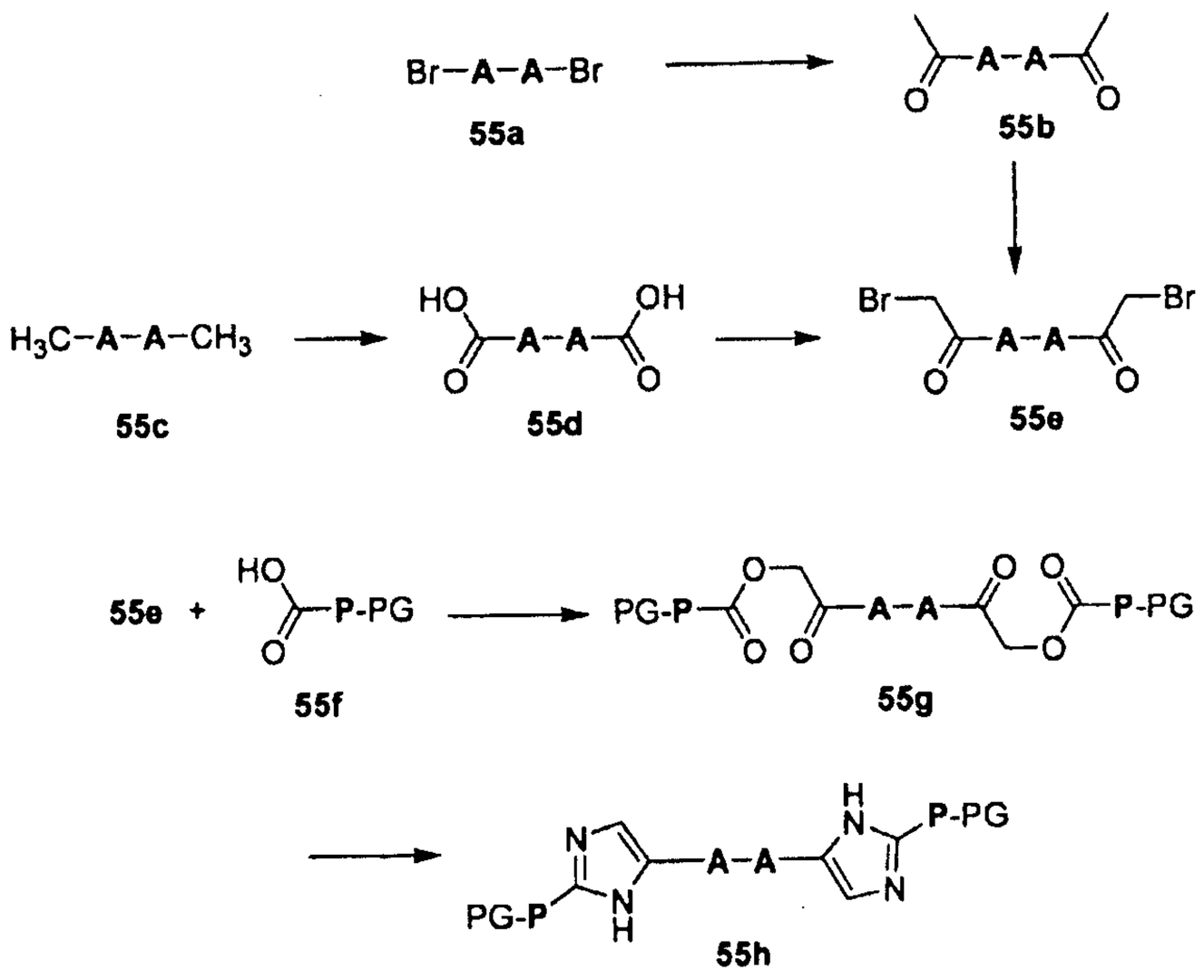


54a **54b** **54c** **54c** **54d** **54e**

Scheme 54 shows a general synthesis of an R-**M**-**P**-R^1 intermediate of the invention wherein, for illustrative purposes, **M** is imidazole, R is a generic group that is depicted as a bromide, aldehyde, or alkyne and R^1 is a protecting group. Imidazole **54a** can be halogenated, for example, under the action of N-bromosuccinimide to provide bromoimidazole **54b**.

Bromoimidazole **54b** can be protected using standard conditions to give **54c**, such as SEM-Cl and sodium hydride when PG = SEM. The bromoimidazole **54b** can be further elaborated, for example, to the corresponding aldehyde or alkyne. Lithiation of **54c** and condensation with a formate equivalent (e.g. DMF) provides the aldehyde **54d**. The aldehyde **54d** is converted to alkyne **54e** using a phosphorus-based reagent (e.g. Ohira-Bestmann reagent).

Scheme 55: Representative synthesis of R-P-M-A-A-M-P-R

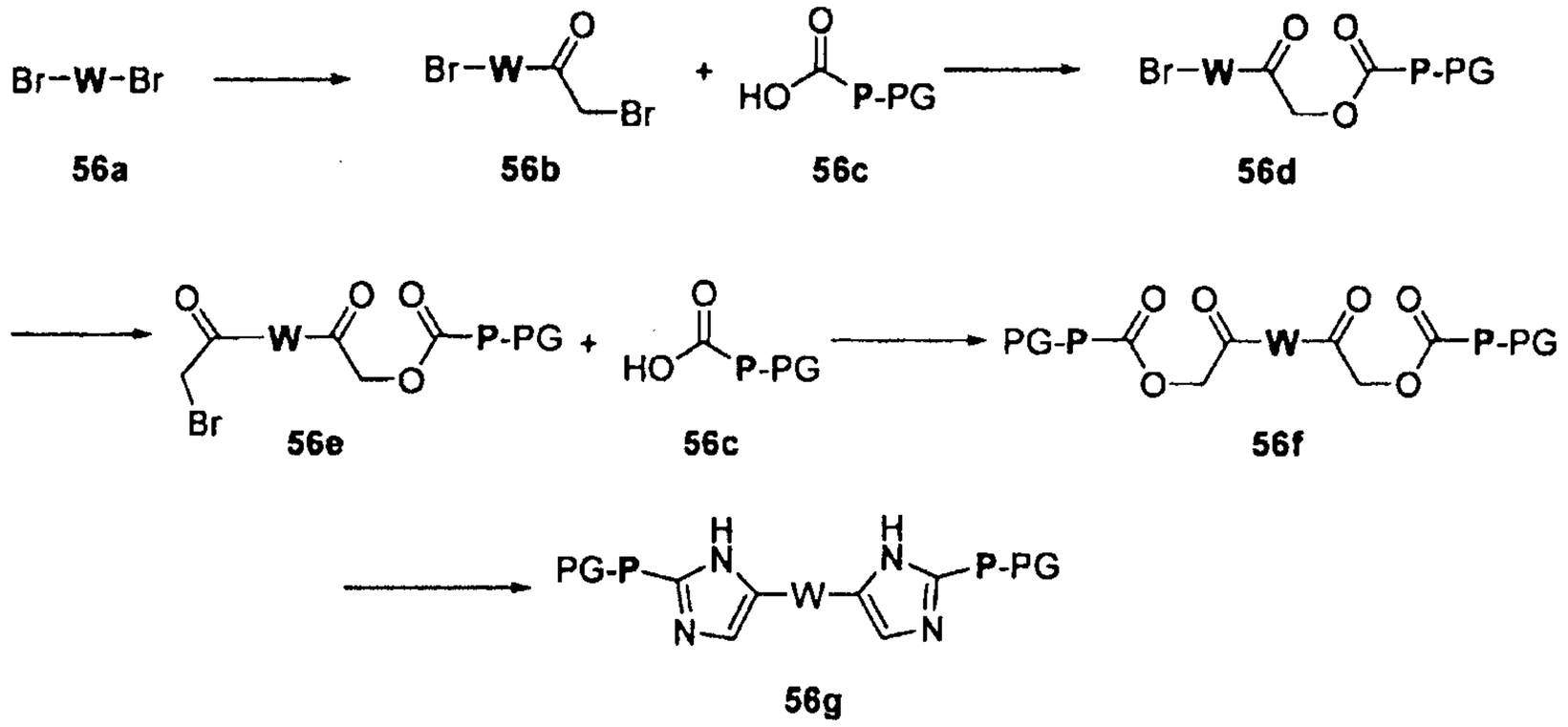


Scheme 55 shows a general synthesis of an R-**P-M-A-A-M-P**-R intermediate of the invention wherein, for illustrative purposes, **M** is imidazole and R is a generic group that is depicted as a protecting group. For example, the diketone **55b** is converted to **55e** using bromine. Compound **55b** can be commercially available or can be prepared from the corresponding dibromide **55a** through coupling with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane in the presence of a palladium catalyst. Coupling of **55e** with acid **55f** under basic conditions such as diisopropylethylamine affords diester **55g**. Imidazole formation is accomplished by treatment of **55g** with ammonium acetate to provide the imidazole containing intermediate R-**P-M-A-A-M-P**-R (**55h**).

Alternatively, bromide **55e** can be synthesized from **55c**. The dimethyl compound **55c** can be converted to the corresponding diacid **55d** using potassium permanganate as oxidant.

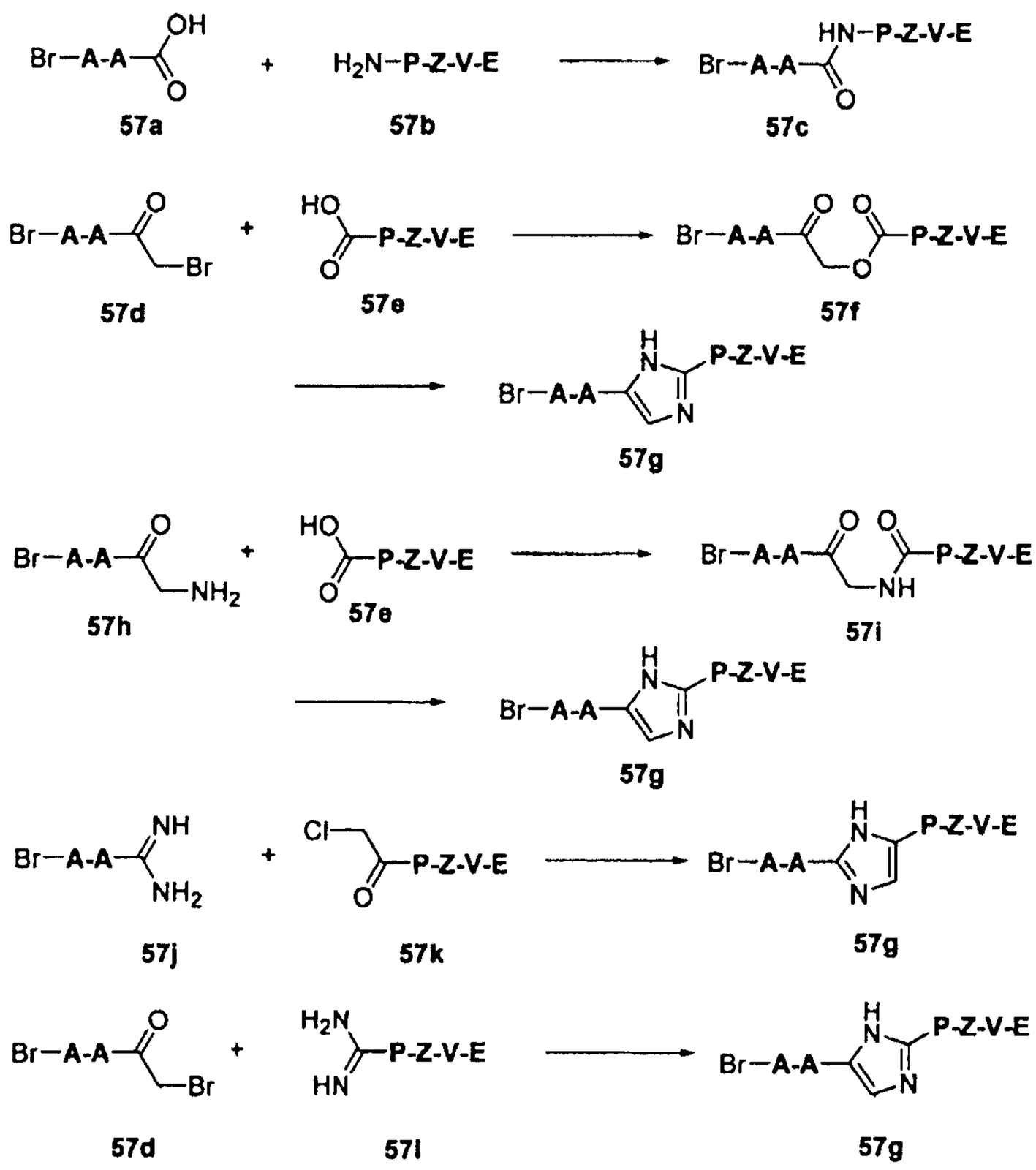
Conversion of **55d** to **55e** can be accomplished by a multi-step homologation. For example, the treatment of **55d** with oxalyl chloride, followed by trimethylsilyl diazomethane and then hydrobromic acid can afford compound **55e**.

Scheme 56: Representative synthesis of R-P-M-W-M-P-R



Scheme **56** shows a general synthesis of an R-**P**-**M**-**W**-**M**-**P**-R intermediate of the invention wherein, for illustrative purposes, **M** is imidazole and R is a generic group that is depicted as a protecting group. The compound **56a** is coupled with vinyltin reagent such as tributyl(ethoxyvinyl)stannane in the presence of a palladium catalyst, followed by bromination and hydrolysis with NBS and water, to give the bromoketone **56b**. The reaction between bromide **56b** and a carboxylic acid under basic condition generates the ester **56d**. Following the same reaction sequence, compound **56d** can be elaborated to the diester **56f**. Conversion of **56f** to **56g** is accomplished with ammonia reagents such as ammonium acetate at elevated temperature.

Scheme 57: Representative synthesis of R-A-A-M-P-R^1

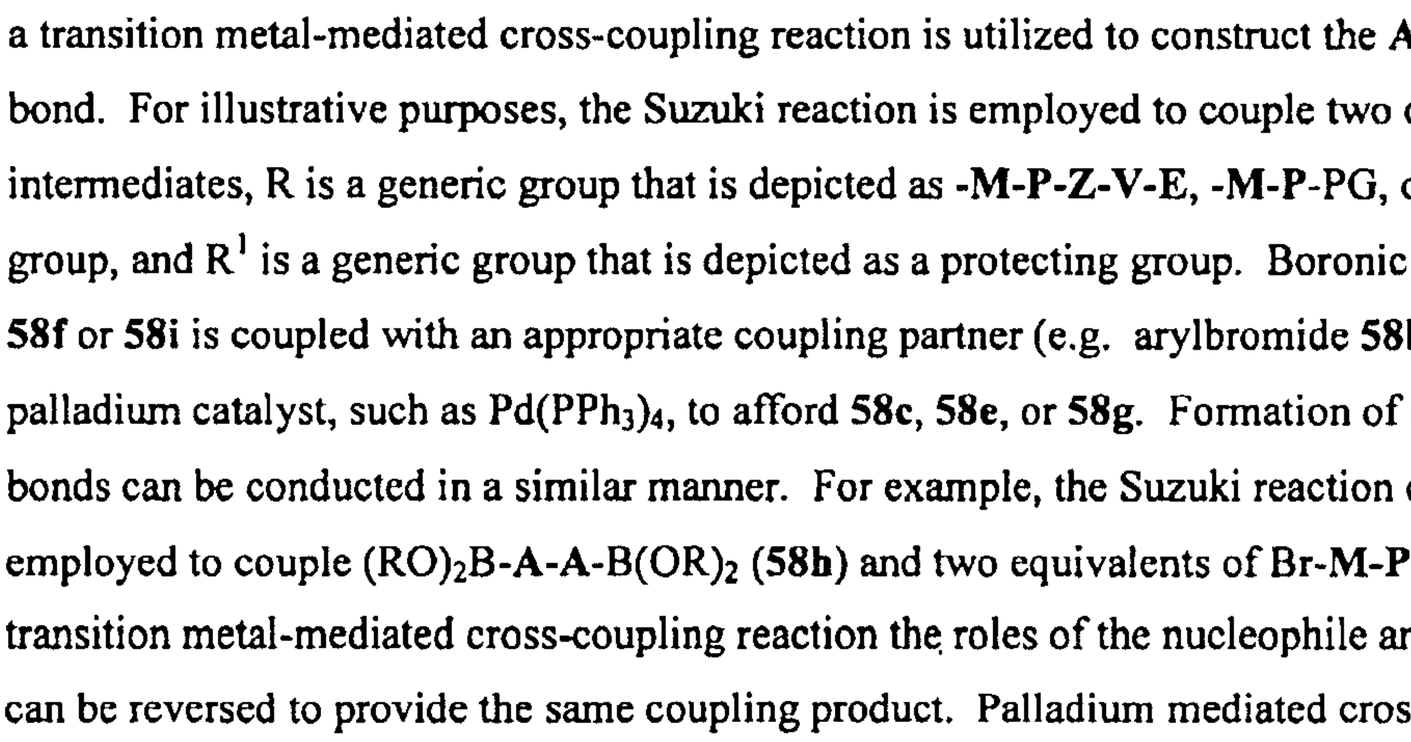


Scheme 57 shows a general synthesis of an R-**A-A-M-P**-R^1 intermediate of the invention wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as -**Z-V-E**. Coupling of amine **57b** with acid **57a** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **57c**.

The acid **57e** is coupled with an α-haloketone, such as α-bromoketone **57d,** under basic conditions (e.g. Et_3N) to afford **57f**. Alternatively, the acid **57e** is coupled with an α-aminoketone **57h,** under amide formation conditions (e.g. EDC, Et_3N) to afford **57i**. Reaction of **57f** or **57i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-**A-M-P-Z-V-E** (**57g**). Coupling of 57j and 57k and, in the

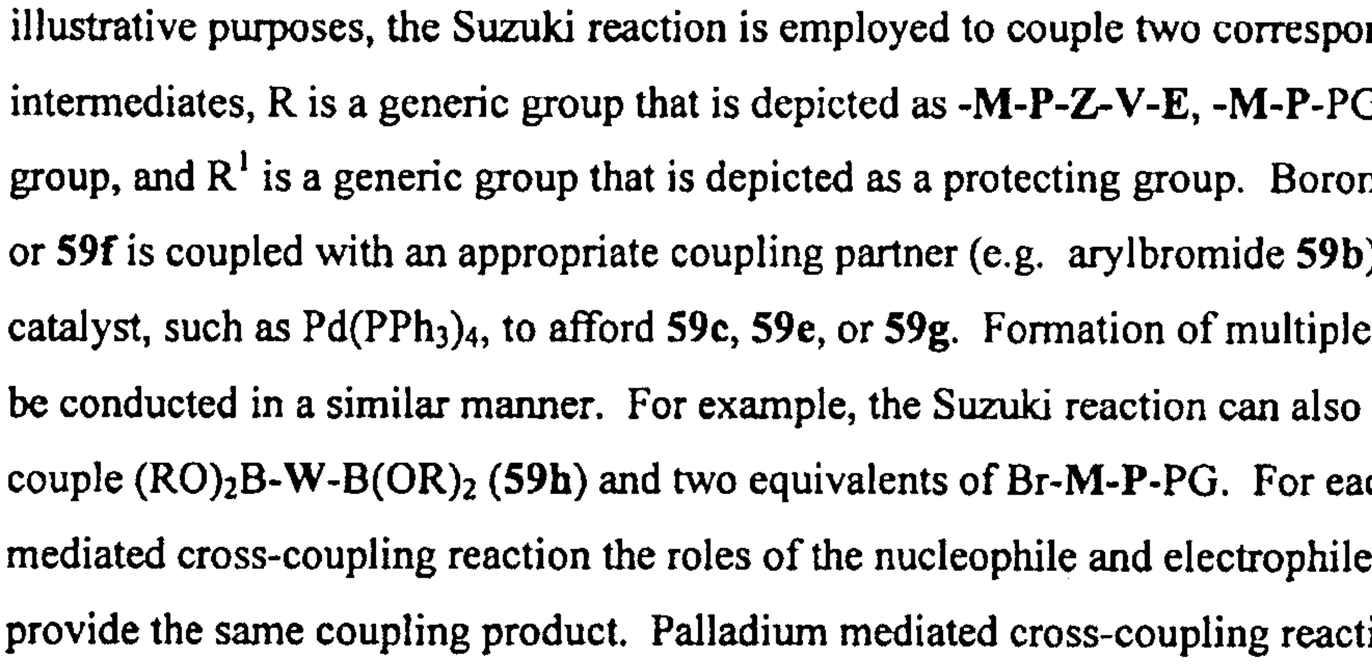
alternative, coupling of 57d and 57l under appropriate conditions can also be used in preparation of intermediate Br-**A-M-P-Z-V-E** (**57g**).

Scheme 58: Representative synthesis of R-A-A-M-P-R[1]



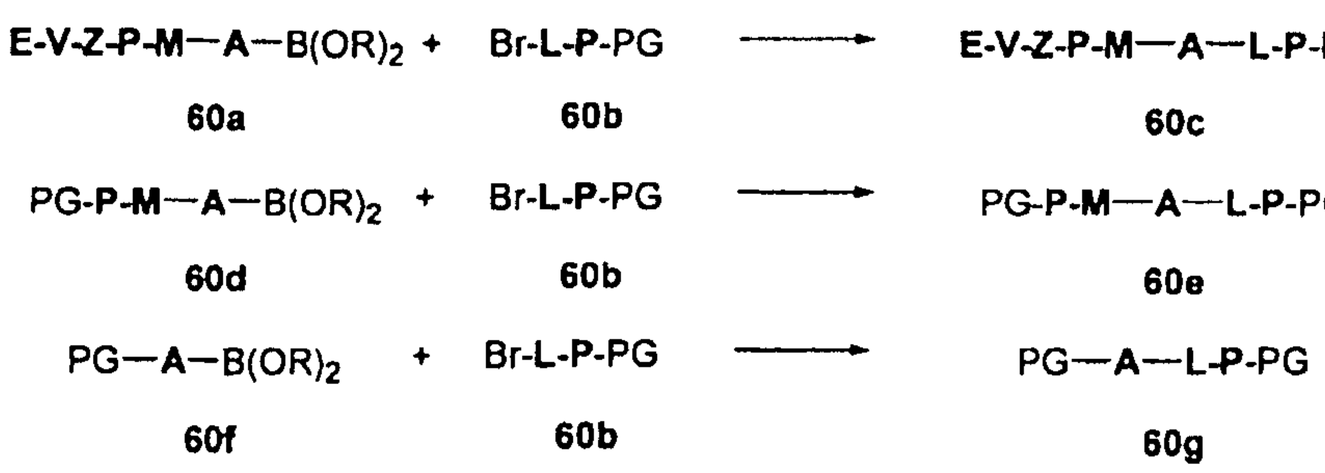
Scheme 58 shows a general synthesis of the R-**A-A-M-P**-R[1] molecule of the invention, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as **-M-P-Z-V-E**, **-M-P**-PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **58a**, **58d**, **58f** or **58i** is coupled with an appropriate coupling partner (e.g. arylbromide **58b** or **58j**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **58c**, **58e**, or **58g**. Formation of multiple **A-M** bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple $(RO)_2B$-**A-A**-$B(OR)_2$ (**58h**) and two equivalents of Br-**M-P**-PG. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-A** and/or **A-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 59: Representative synthesis of R-W-M-P-R^1



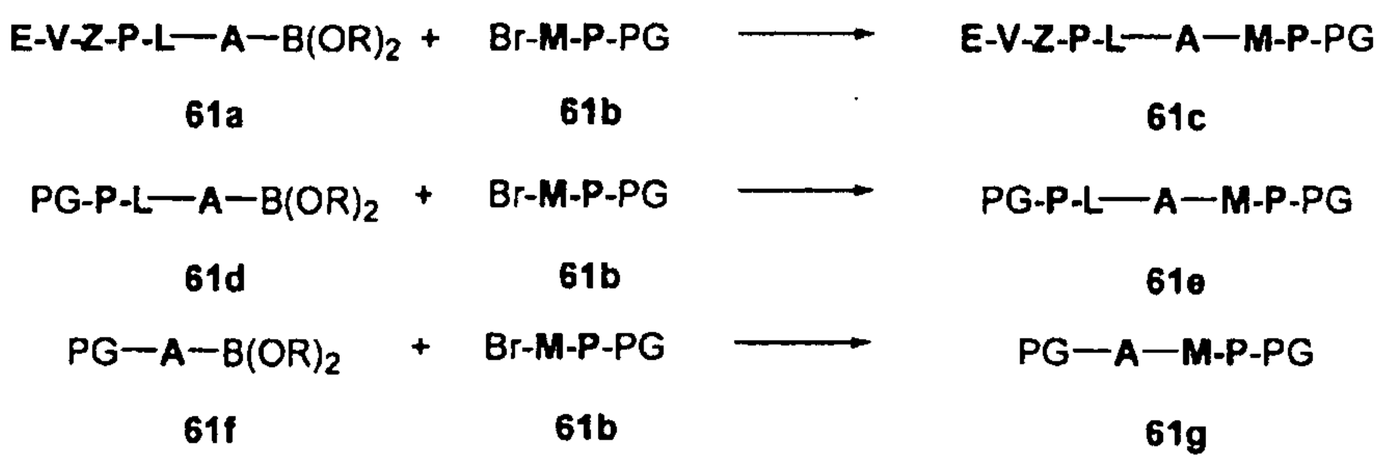
Scheme 59 shows a general synthesis of the R-W-M-P-R^1 molecule of the invention, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the W-M bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as -M-P-Z-V-E, -M-P-PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **59a**, **59d**, or **59f** is coupled with an appropriate coupling partner (e.g. arylbromide **59b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **59c**, **59e**, or **59g**. Formation of multiple W-M bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple $(RO)_2B$-W-$B(OR)_2$ (**59h**) and two equivalents of Br-M-P-PG. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the W-M bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 60: Representative synthesis of R-A-L-P-R^1



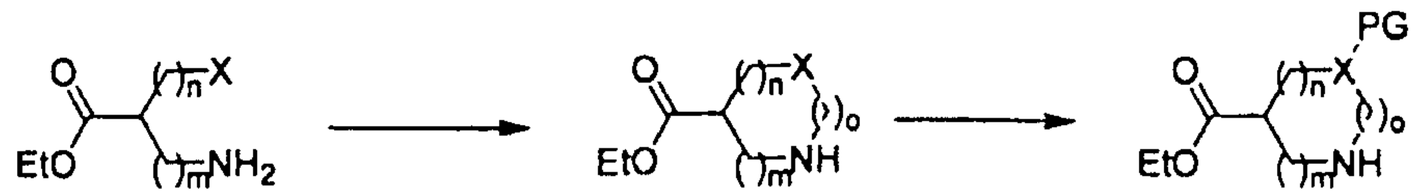
Scheme 60 shows a general synthesis of the R-**A**-**L**-**P**-R^1 molecule of the invention, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A**-**L** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as -**M**-**P**-**Z**-**V**-**E**, -**M**-**P**-PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **60a**, **60d**, or **60f** is coupled with an appropriate coupling partner (e.g. arylbromide **60b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **60c**, **60e**, or **60g**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A**-**L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 61: Representative synthesis of R-A-M-P-R^1



Scheme 61 shows a general synthesis of the R-**A**-**M**-**P**-R^1 molecule of the invention, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A**-**M** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as -**L**-**P**-**Z**-**V**-**E**, -**L**-**P**-PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **61a**, **61d**, or **61f** is coupled with an appropriate coupling partner (e.g. arylbromide **61b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **61c**, **61e**, or **61g**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A**-**M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

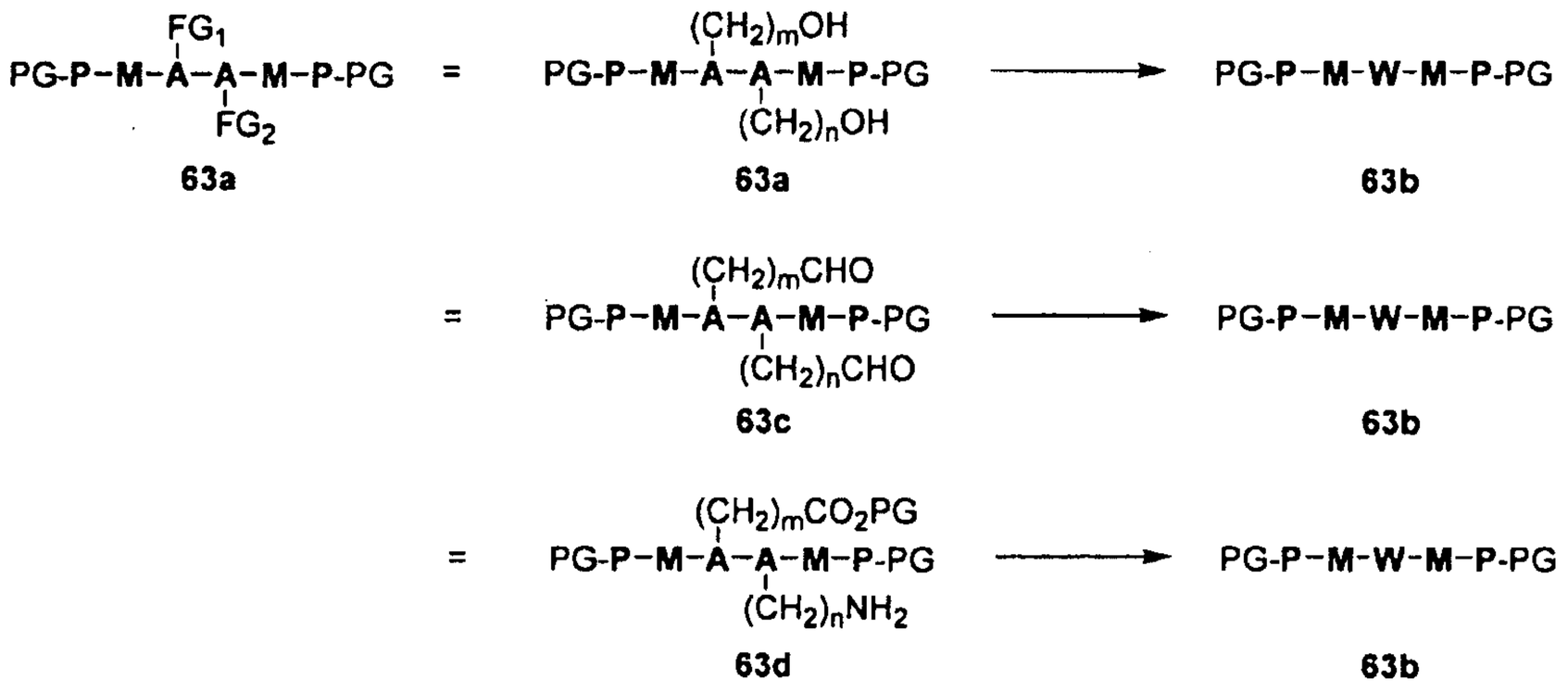
Scheme 62: Representative synthesis of R-P-H



62a **62b** **62c**

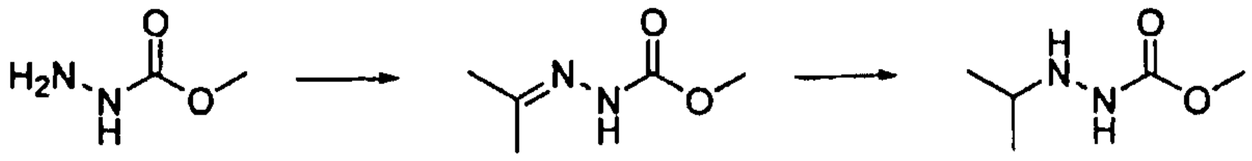
Scheme 62 shows a general synthesis of a R-P-H molecule of the invention wherein, for illustrative purposes, R is a generic group that is depicted as ethoxycarbonyl and P is a carbocyclic or heterocyclic ring (e.g. X is carbon or heteroatom) and m, n, and o are 0 - 3, independently. The amino ester **62a** is converted to the substituted or cyclized amino ester **62b** through for example a reductive amination or Mitsunobu reaction. Compound **62b** can be protected to provide compound **62c** if necessary.

Scheme 63: Representative synthesis of R-P-M-W-M-P-R



Scheme **63** shows a general synthesis of a R-**P**-**M**-**W**-**M**-**P**-R intermediate of the invention wherein, for illustrative purposes, R is a generic group that is depicted as a protecting group and **A** is functionalized with a group depicted as either hydroxyalkyl, aminoalkyl, carbonylalkyl, or alkoxycarbonylalkyl. The cyclization of **63a**, **63c**, and **63d** can be performed through several functional group transformations which include, but are not limited to, Mitsunobu reaction, reductive amination, and lactamization.

Scheme 64: Representative Synthesis of H-V-E



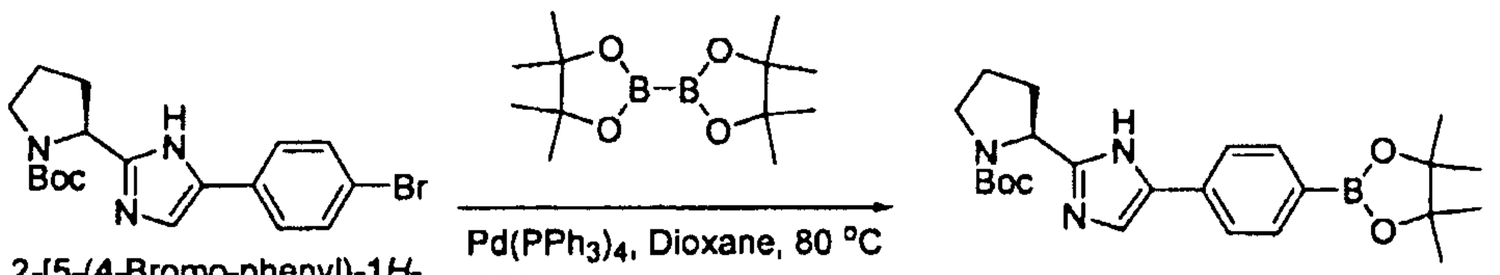
64a **64b** **64c**

Scheme 64 shows a general synthesis of a H-**V**-**E** intermediate of the invention wherein, for illustrative purposes **E** is methoxycarbonylamino and **V** is isopropylamino. The reaction of hydrazine carboxylate **64a** with a ketone or aldehyde, such as acetone, under acidic conditions (e.g. AcOH) affords the imine **64b**. Reaction of **64b** under reducing conditions, such as PtO_2 and hydrogen gas, affords the substituted hydrazinecarboxylate **64c**.

The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

Example AA



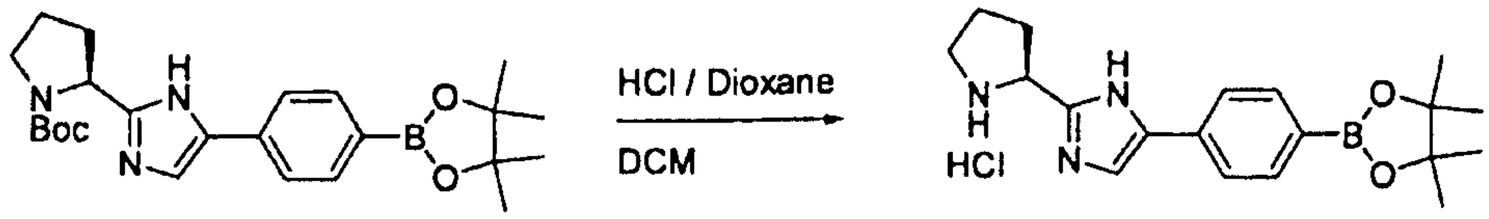
2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(S)-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 1,4-Dioxane (300 mL) was added to a mixture of (S)-2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (21.1 g, 53.7 mmol), bis(pinacolato)diboron (27.3g, 107.5 mmol), tetrakis(triphenylphosphine)palladium (0) (3.10 g, 2.68 mmol), and potassium acetate (15.02 g, 153.0 mmol), and heated at 80°C for 16 hours. The mixture was cooled and the resulting solid was filtered. The majority of the 1,4-dioxane was removed from the filtrate under reduced pressure and resulting residue was taken up in ethyl acetate (300 mL). The organic phase was washed with saturated sodium bicarbonate (2x 150 mL), brine (100 mL) and dried over sodium sulfate. After filtration the solvent was removed from the filtrate under reduced pressure. The resulting oil was subjected to silica gel chromatography using a 330 g ISCO column and effluent of 20-100 % ethyl acetate and hexanes. The fractions containing product were combined and the solvent was removed under reduced pressure to provide (S)-2-{5-[4-(4,4,5,5-tetramethyl-

[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (18 g, 76 %) and light yellow solid.

Example AB

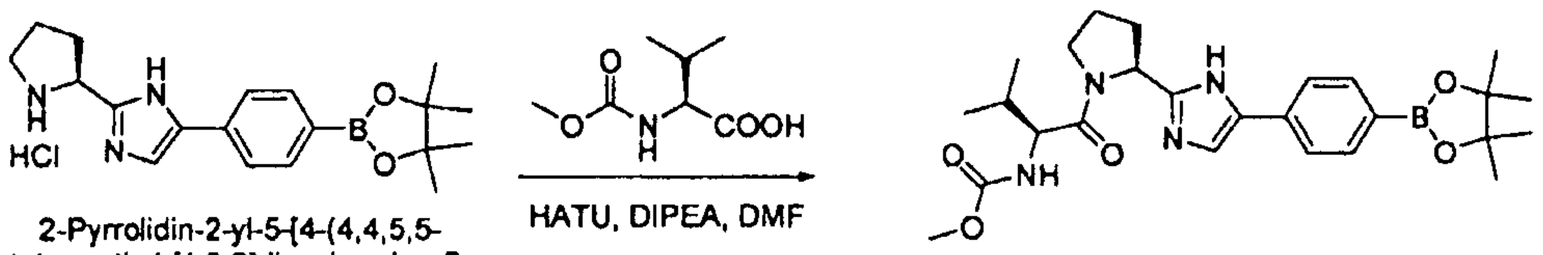


2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Pyrrolidin-2-yl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazole

(S)-2-Pyrrolidin-2-yl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazole hydrochloride: A solution of hydrogen chloride in 1,4-dioxane (4 N, 75 mL) was added to a solution of (S)-2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (7.0 g, 15.9 mmol) in dichloromethane (50 mL). Gas evolution was observed. After 30 minutes, a solid formed. After 1.5 hours, the resulting solid was isolated by filtration with diethyl ether washing. Any residual solvent was removed under reduced pressure to provide (S)-2-pyrrolidin-2-yl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazole hydrochloride (5.6 g, 95 %) as an off-white solid.

Example AC



2-Pyrrolidin-2-yl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazole

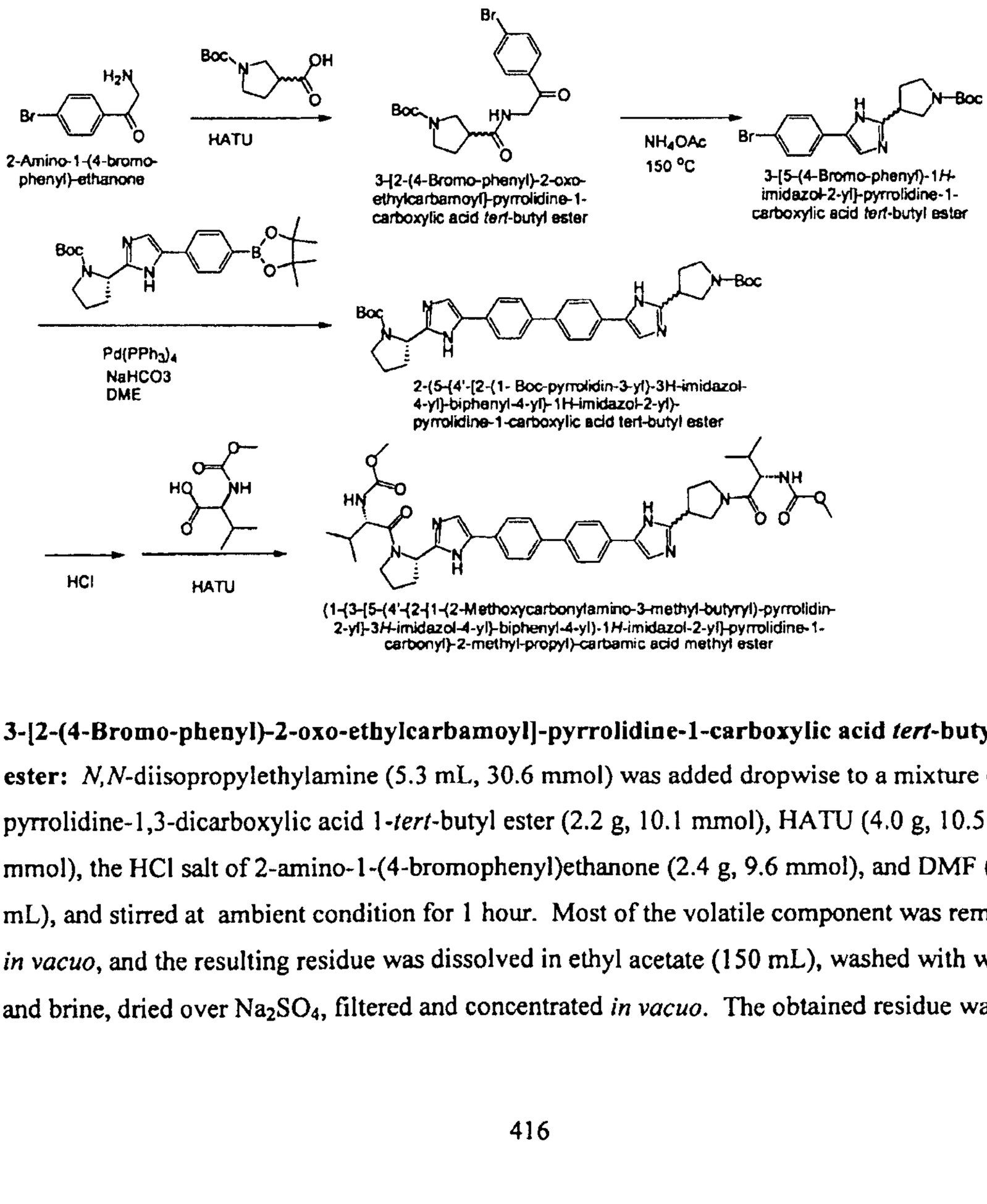
[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

(S,S)-[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester:

Diisopropylethylamine (7.63 mL, 43.8 mmol) was added to a suspension of (S)-2-pyrrolidin-2-yl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazole hydrochloride (7.33 g, 19.5 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (7.6 g, 19.9 mmol) and (*S*) 2-methoxycarbonylamino-3-methyl-butyric acid (3.59 g, 20.5 mmol) in dimethylformamide (75 mL). All solids dissolved. After 30 min the

reaction mixture was diluted with ethyl acetate (300 mL) and was washed with ½ saturated sodium chloride (1 x 300 mL), half saturated sodium bicarbonate (2 x 150 mL) and brine (1 x 100 mL). The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting tan foam was subjected to silica gel chromatography with eluate of 20 -100 % ethyl acetate and hexanes, to provide (S,S)-[2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (6.6 g, 68 %) as a white foam: 1H (DMSO-d6): δ = 11.81 (br s, 1H), 7.72 (m, 2H), 7.61 (m, 2H), 7.51 (br s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 5.05 (m, 1H), 4.04 (m, 2 H), 3.78 (m, 2H), 3.52 (s, 3H), 2.11 (m, 2H), 1.93 (m, 2H), 1.28 (s, 12H), 0.85 (dd, J_1 = 6.6 Hz, J_2 = 11.4 Hz, 6H).

Example AD



3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: *N,N*-diisopropylethylamine (5.3 mL, 30.6 mmol) was added dropwise to a mixture of pyrrolidine-1,3-dicarboxylic acid 1-*tert*-butyl ester (2.2 g, 10.1 mmol), HATU (4.0 g, 10.5 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (2.4 g, 9.6 mmol), and DMF (40 mL), and stirred at ambient condition for 1 hour. Most of the volatile component was removed *in vacuo*, and the resulting residue was dissolved in ethyl acetate (150 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was

purified by flash chromatography to provide the desired product as a white foam-like solid (3.5 g, 90%). m/z 432.9, 434.9 $(M + Na)^+$.

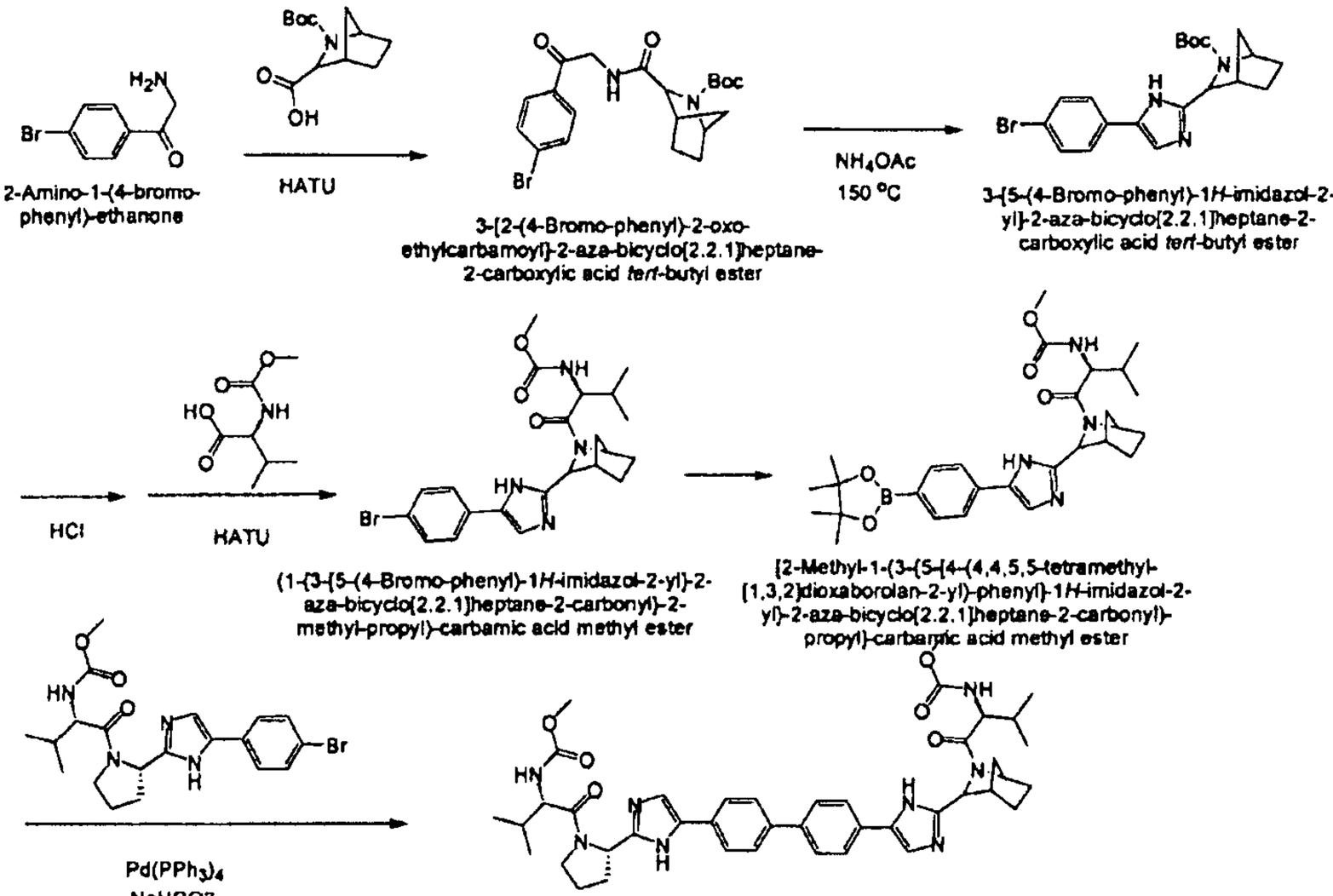
3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.5 g, 3.6 mmol) and ammonium acetate (1.4 g, 18.2 mmol) in xylene (15 mL) was heated in a sealed tube at 140°C for 2 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (150 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (795 mg, 56%). m/z 391.8, 393.8 $(M + H)^+$.

2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: $Pd(Ph_3)_4$ (54 mg, 0.046 mmol) was added to a mixture 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (378 mg, 0.97 mmol), 2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (408 mg, 0.93 mmol), $NaHCO_3$ (273 mg, 3.26 mmol) in 1,2-dimethoxyethane (8 mL) and water (2 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 6 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (370 mg, 64%). m/z 625.1 $(M + H)^+$.

(1-{3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.232 mmol) in methanol (5 mL) was added 4.0 M solution of HCl in dioxane (1 mL, excess). The mixture was stirred for 3 hours at 50°C and concentrated under reduced pressure. The residue was treated with ether to remove excess HCl. The obtained white solid was dissolved in DMF (5 mL). To the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (123 mg, 0.71 mmol), HATU (285 mg, 0.75 mmol) and *N,N*-diisopropylethylamine (0.14 mL, 0.77 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with 1 N

NaOH solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (100 mg, 42%). ^{1}H-NMR (300 MHz, CD_3OD) δ 8.00-7.80 (m, 10H), 5.26 (t, 1H), 4.40-3.42 (m, 15H), 2.65-2.00 (m, 8H), 1.50-0.93 (m, 12H); m/z 739.3 $(M + H)^+$.

Example AE



3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza- bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: Following the procedure used to prepare compound 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester was used instead of pyrrolidine-1,3-dicarboxylic acid 1-*tert*-butyl ester.

3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: Following the procedure used to prepare compound 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester was used instead of 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

(1-{3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To a solution of 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.0 g, 2.4 mmol) in methanol (20 mL) was added 4.0 M solution of HCl in dioxane (4.0 mL, excess). The mixture was stirred for 3 hours at 50°C and concentrated under reduced pressure. The residue was treated with ether to remove excess HCl. The obtained white solid was dissoved in DMF (20 mL). To the solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (0.46 g, 2.6 mmol), HATU (1.0 g, 2.6 mmol) and *N,N*-diisopropylethylamine (2.5 mL, 14.4 mmol). The mixture was stirred at ambient for 2 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with 1 N NaOH solution, water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (1.0 g, 89%). m/z 475.1, 477.1 $(M + H)^+$.

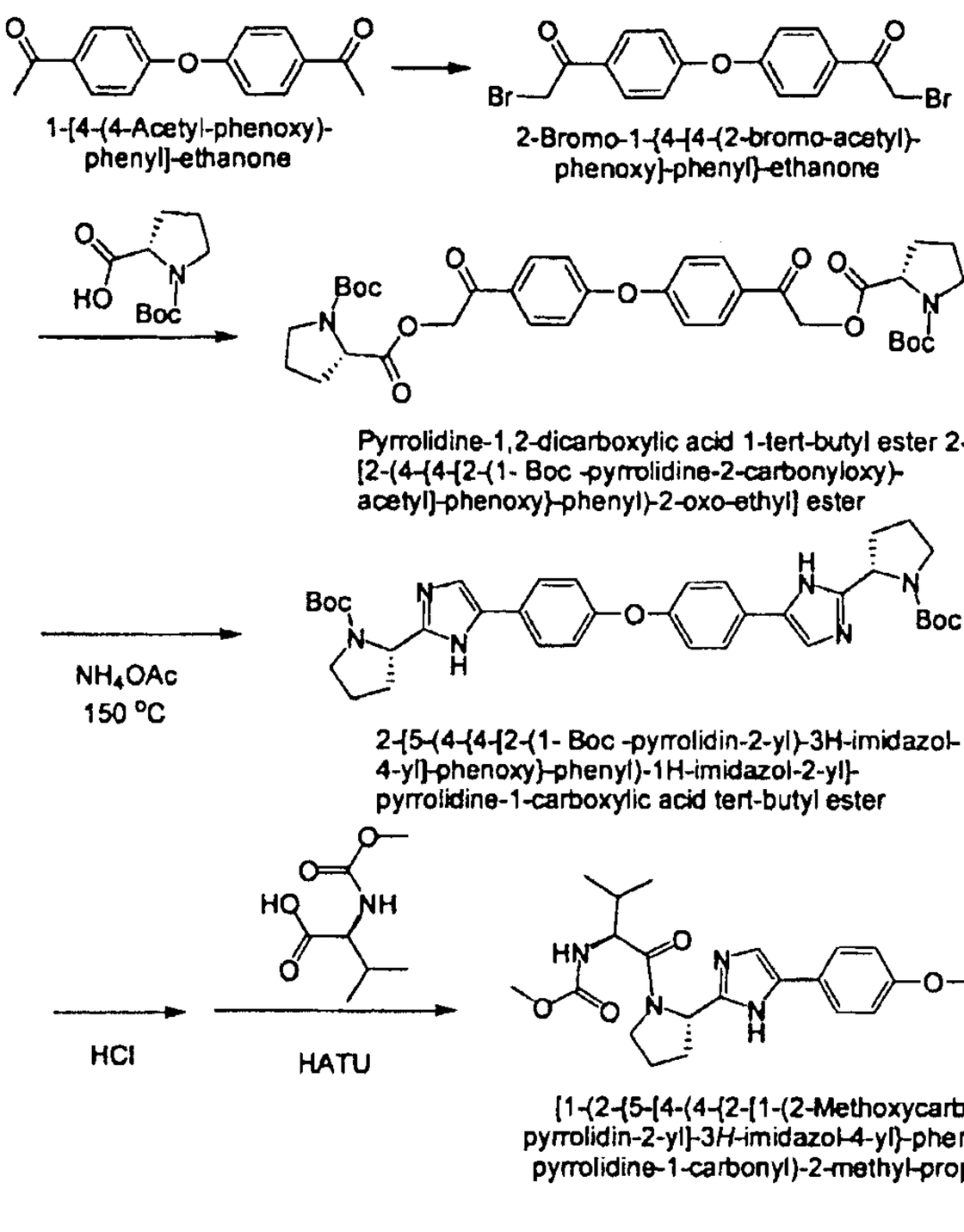
[2-Methyl-1-(3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester: $Pd(PPh_3)_4$ (73 mg, 0.06 mmol) was added to a sealed tube containing a mixture of (1-{3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (600 mg, 1.27 mmol), bis(pinacolato)diboron (675 mg, 2.66 mmol), potassium acetate (324 mg, 3.3 mmol) and 1,4-dioxane (15 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (440 mg, 66%). m/z 523.2 $(M + H)^+$.

(1-{2-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Following the procedure used to prepare compound 2-(5-{4'-[2-(1- Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that [2-methyl-1-(3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester and (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester were used instead of

2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.90-7.70 (m, 10H), 7.20-7.10 (m, 1H), 5.24 (t, 1H), 4.63 (s, 1H), 4.40-3.80 (m, 4H), 3.68 (s, 3H), 3.66 (s, 3H), 2.60-1.60 (m, 13H), 1.05-0.90 (m, 12H); m/z 765.2 $(M + H)^+$.

(1-{3-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Following the procedure used to prepare compound 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that [2-methyl-1-(3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester and (1-{3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester were used instead of 2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.90-7.20 (m, 10H), 4.83-4.25 (m, 5H), 3.90-3.40 (m, 6H), 2.90-2.70 (m, 2H), 2.40-2.10 (m, 3H), 2.10-1.40 (m, 11H), 1.10-0.90 (m, 12H); m/z 791.3 $(M + H)^+$.

Example AF



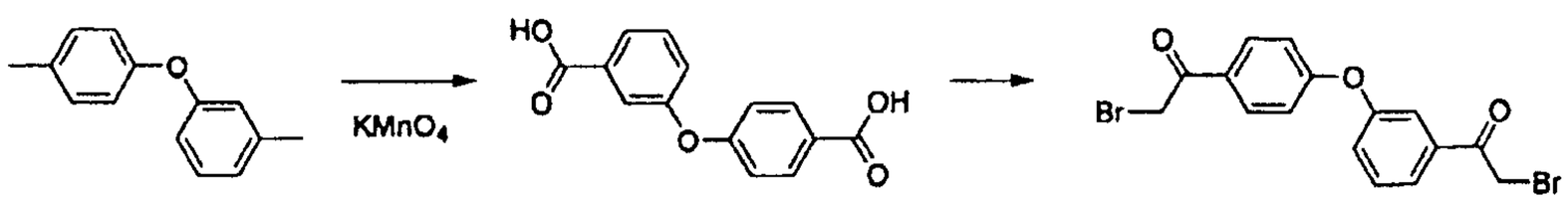
2-Bromo-1-{4-[4-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone: Bromine (2.02 mL, 39.3 mmol) in dichloromethane (25 mL) was added slowly to a stirred solution of 4-acetylphenyl ether (5.0 g, 19.7 mmol) in dichloromethane (65 mL) at 30°C. The mixture was stirred at ambient for 16 hours, and then the volatile component was removed *in vacuo*. The residue was recrystallized from ethanol (40 mL) to get a yellow crystal like product (2.3 g, 29%).

Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(4-{4-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester: To a stirred mixture of 2-bromo-1-{4-[4-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone (2.0 g, 4.9 mmol) and pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (2.2 g, 10.2 mmol) in acetonitrile (20 mL) was added DIPEA (1.76 mL, 10.1 mmol). The slurry was stirred for 3 hours at ambient temperature. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (2.2 g, 65%). m/z 703.1 $(M + Na)^+$.

2-[5-(4-{4-[2-(1-Boc–pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(4-{4-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester (250 mg, 0.37 mmol) and ammonium acetate (570 mg, 7.3 mmol) in xylene (8 mL) was heated in microwave machine at 140°C for 80 minutes. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (62 mg, 26%). m/z 641.1 $(M + H)^+$.

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenoxy)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Following the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-[5-(4-{4-[2-(1- Boc -pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1- Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.80-7.60 (m, 4H), 7.30-7.20 (m, 2H), 7.10-0.95 (m, 4H), 5.16 (t, 1H), 4.30-3.50 (m, 12H), 2.40-1.90 (m, 10H), 1.10-0.90 (m, 12H); m/z 755.2 $(M + H)^+$.

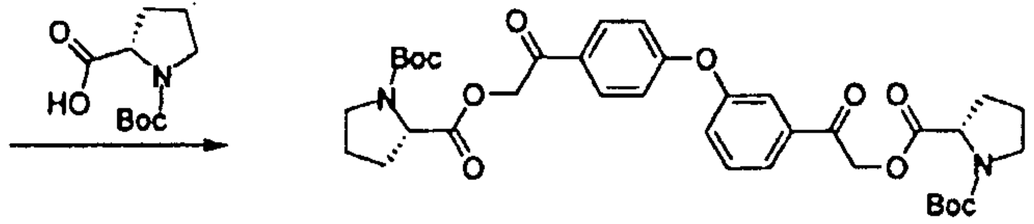
Example AG



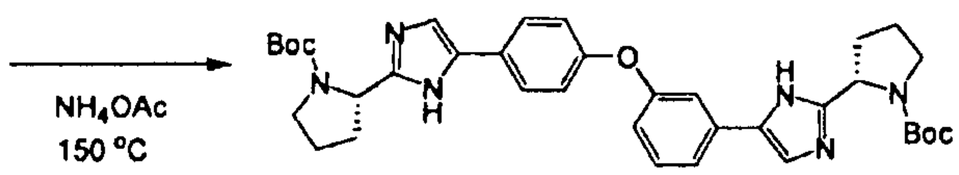
3,4'-dimethylbiphenyl ether

3,4'-Oxybis(benzoic acid)

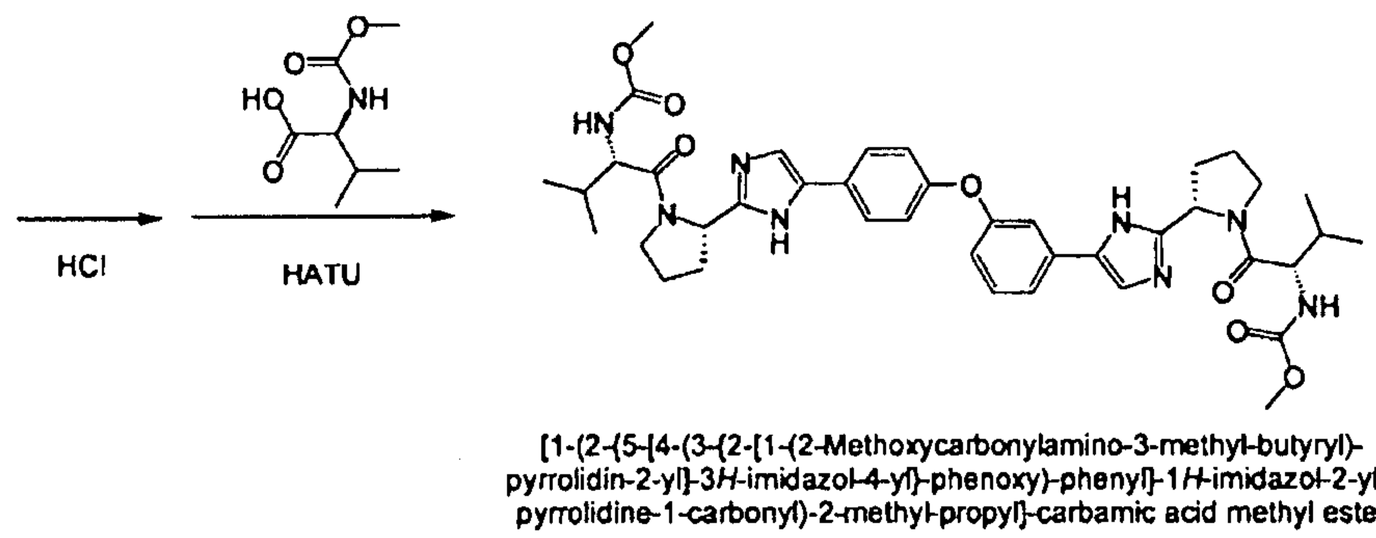
2-Bromo-1-{4-[3-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone



Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-[2-(4-{3-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester



2-[5-(4-{3-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



[1-(2-{5-[4-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenoxy)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

3,4'-Oxybis(benzoic acid): A mixture of 3,4'-dimethylbiphenyl ether (1.7 g, 8.6 mmol) and potassium permanganate (6.0 g, 38 mmol) in water (200 mL) was refluxed for 6 hours. The hot solution was filtered, cooled, and extracted with chloroform. The aqueous layer was acidified by 2 N HCl. The precipitate was filtered off and washed with water to give a white solid (0.55 g, 25%). m/z 257.1 $(M - H)^-$.

2-Bromo-1-{4-[3-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone: A mixture of 3,4'-oxybis(benzoic acid) (0.55 g, 2.1 mmol)) and oxalyl chloride (10.6 mL, 21.3 mmol) in dichloromethane (40 mL) containing DMF (4 drops) was stirred at ambient temperature for 4 hours, then concentrated and co-evaporated with toluene (3x) and dried under high vacuum. The resulting residue was suspended in dichloromethane (15 mL) at 0°C and treated with 2.0 M trimethylsilyldiazomethane in ether (3.2 mL, 6.4 mmol) over 15 minutes to give a brown mixture. Reaction mixture was warmed to ambient temperature overnight and then

concentrated. The resulting brown solid was suspended in ethyl acetate (15 mL) and cooled to 0°C. HBr in acetic acid (1.2 mL, 33%W, 6.4 mmol) was added over 5 minutes and reaction mixture was warmed to ambient temperature over 1 hour. Solid sodium bicarbonate (0.3 g) was added and stirred for 30 minutes. Water was added giving a biphasic mixture with a brown precipitate. The solid was removed by filtration and filtrate was extracted with dichloromethane, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography to give a brown solid (0.47 g).

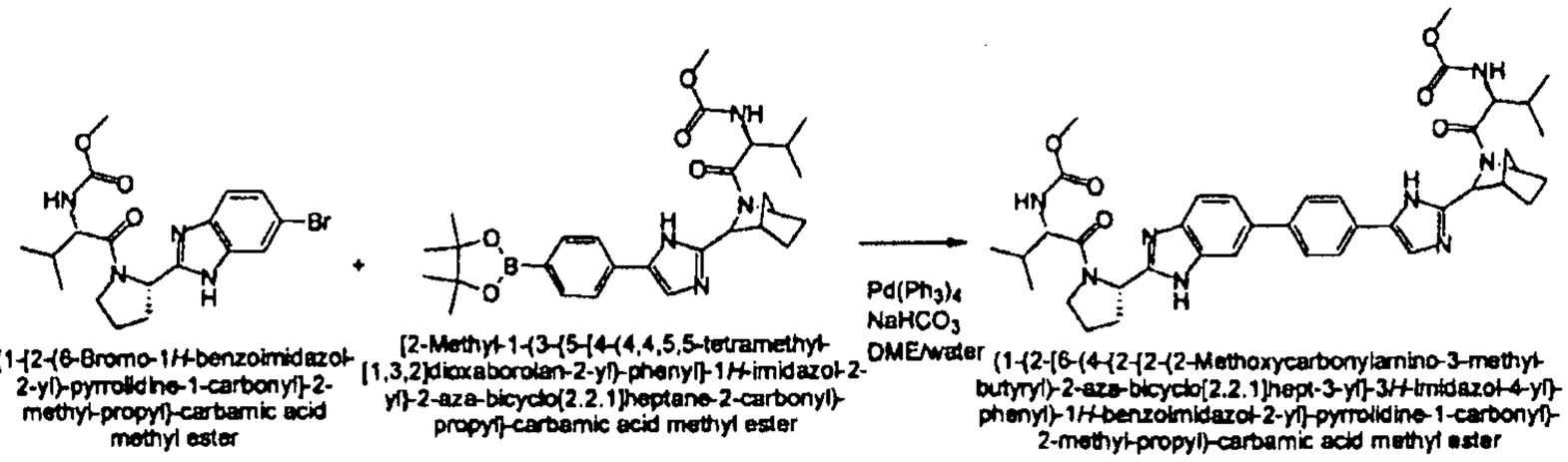
Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(4-{3-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester: Following the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-bromo-1-{4-[3-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone was used instead of 2-bromo-1-{4-[4-(2-bromo-acetyl)-phenoxy]-phenyl}-ethanone. m/z 703.1 $(M + Na)^+$.

2-[5-(4-{3-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Following the procedure used to prepare compound 2-[5-(4-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(4-{3-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester was used instead of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(4-{4-[2-(1-Boc-pyrrolidine-2-carbonyloxy)-acetyl]-phenoxy}-phenyl)-2-oxo-ethyl] ester. m/z 641.0 $(M + H)^+$.

[1-(2-{5-[4-(3-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenoxy)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Following the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-[5-(4-{3-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenoxy}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.80-7.10 (m,

10H), 5.30-5.15 (m, 2H), 4.30-4.20 (m, 2H), 4.18-4.05 (m, 2H), 3.95-3.80 (m, 2H), 3.70-3.60 (m, 6H), 2.65-2.45 (m, 2H), 2.40-2.00 (m, 8H), 1.05-0.85 (m, 12H); m/z 755.3 $(M + H)^+$.

Example AH



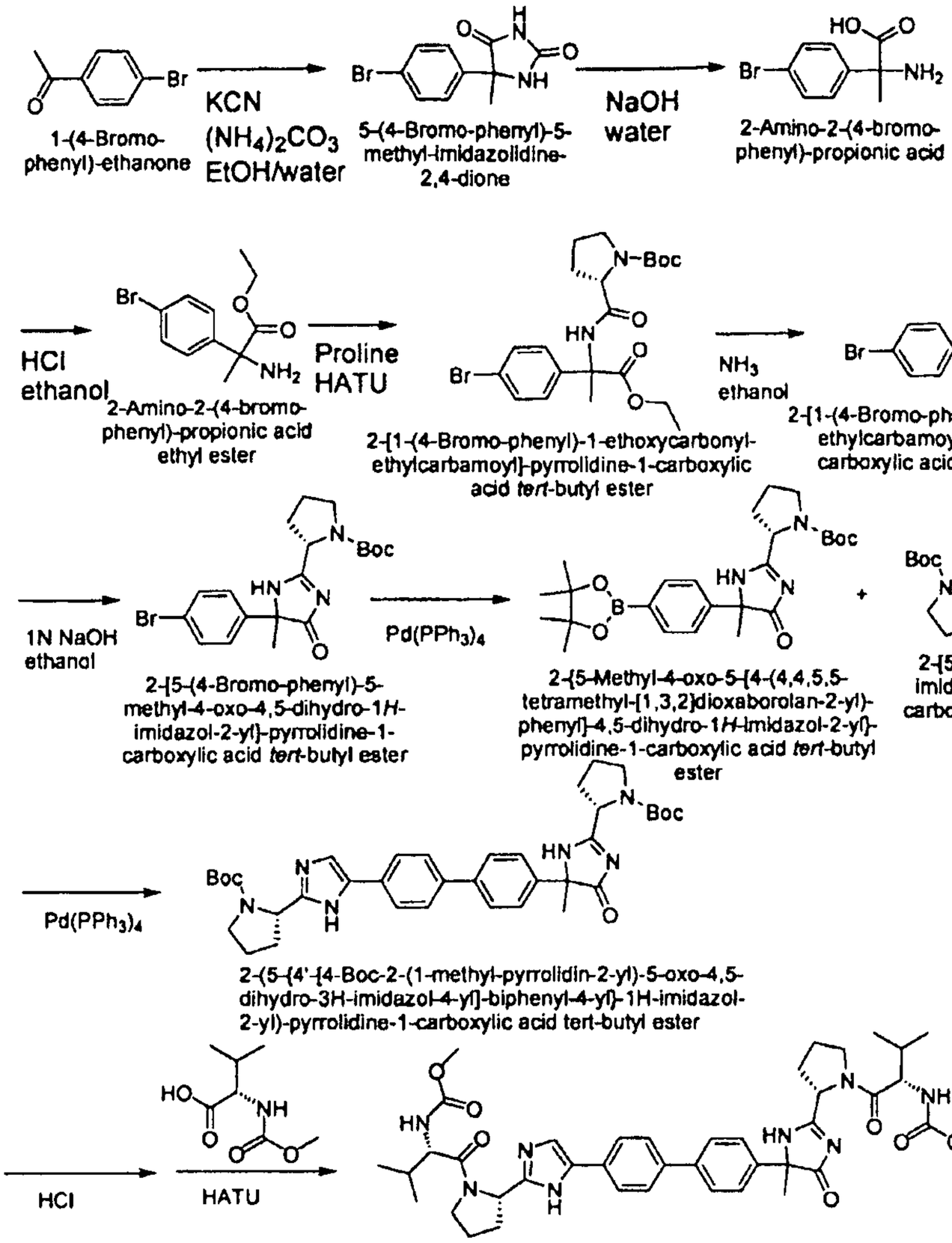
{1-[2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

[2-Methyl-1-(3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester

(1-{2-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-phenyl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[6-(4-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Following the procedure used to prepare compound 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that [2-methyl-1-(3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carbonyl)-propyl]-carbamic acid methyl ester and {1-[2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester were used instead of 2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.10-7.80 (m, 7H), 5.42-5.30 (m, 1H), 4.65 (s, 1H), 4.40-4.25 (m, 2H), 4.20-3.90 (m, 2H, 3.80-3.60 (m, 6H), 3.00-2.80 (m, 1H), 2.70-2.55 (m, 1H), 2.50-1.60 (m, 12H), 1.10-0.80 (m, 12H); m/z 739.3 $(M + H)^+$.

Example AI



5-(4-Bromo-phenyl)-5-methyl-imidazolidine-2,4-dione: A mixture of 4-bromo acetophenone (8.0 g, 40.2 mmol), ammonium carbonate (40 g, 402 mmol) and potassium cyanide (3.4 g, 52.3 mmol) in a mixed solvent of ethanol (90 mL) and water (90 mL) was stirred at 55°C for 5 hours, then 12 hours at ambient. The solution was adjusted to pH = 6 with 6 N HCl carefully and subsequently stirred at room temerature for 2 hours. The precipitate was filtered off, washed with water. The collected white solid was dried under vacuum to give the product (9.2 g, 85%). m/z 267.1, 269.1 $(M - H)^-$.

2-Amino-2-(4-bromo-phenyl)-propionic acid: A mixture of 5-(4-bromo-phenyl)-5-methyl-imidazolidine-2,4-dione (4.0 g, 14.9 mmol) and 3 N NaOH (50 mL) was heated in a sealed tube at 145°C for two days, then diluted with water (100 mL). The solution was adjusted to pH = 4 with 6 N HCl carefully and subsequently stirred at room temerature for 2 hours. The precipitate was filtered off, washed with water. The collected white solid was dried under vacuum to give the product (2.5 g, 65%). m/z 243.7, 245.7 $(M + H)^+$.

2-Amino-2-(4-bromo-phenyl)-propionic acid ethyl ester: To a solution of 2-amino-2-(4-bromo-phenyl)-propionic acid (1.0 g, 4.1 mmol) in ethanol (20 mL) was bubbled through HCl gas for five minutes. The mixture was stirred at ambient for 24 hours, then refluxed for 18 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in ethyl acetate (150 mL), washed with $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product (800 mg, 72%). m/z 271.7, 273.7 $(M + H)^+$.

2-[1-(4-Bromo-phenyl)-1-ethoxycarbonyl-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: *N,N*-diisopropylethylamine (4.1 mL, 23.6 mmol) was added dropwise to a mixture of pyrrolidine-1,3-dicarboxylic acid 1-*tert*-butyl ester (0.7 g, 3.2 mmol), HATU (1.2 g, 3.2 mmol) and 2-amino-2-(4-bromo-phenyl)-propionic acid ethyl ester (0.8 g, 2.9 mmol) in DMF (20 mL), and stirred at ambient condition for 3 hours. Most of the volatile componet was removed *in vacuo*, and the resulting residue was dissolved in ethyl acetate (150 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a colorless oil (0.8 g, 58%). m/z 490.9, 492.9 $(M + Na)^+$.

2-[1-(4-Bromo-phenyl)-1-carbamoyl-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a stirred solution of 2-[1-(4-bromo-phenyl)-1-ethoxycarbonyl-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (280 mg, 0.6 mmol) in ethanol (8 mL) was bubbled through NH_3 gas for 5 minutes at -78°C. The solution was stirred at ambient for 3 days in a sealed tube. Most of the volatile component was removed *in vacuo*, and the resulting residue was dissolved in ethyl acetate (150 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a colorless oil (169 mg, 64%). m/z 439.8, 441.8 $(M + H)^+$.

2-[5-(4-Bromo-phenyl)-5-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a stirred solution of 2-[1-(4-bromo-phenyl)-1-carbamoyl-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (160 mg, 0.36 mmol) in ethanol (10 mL) was added 1 N NaOH (5 mL), and stirred at ambient condition for 3 hours. Most of the volatile componet was removed *in vacuo*, and the resulting residue was dissolved in ethyl acetate (100 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (120 mg, 79%). m/z 421.8, 423.8 $(M + H)^+$.

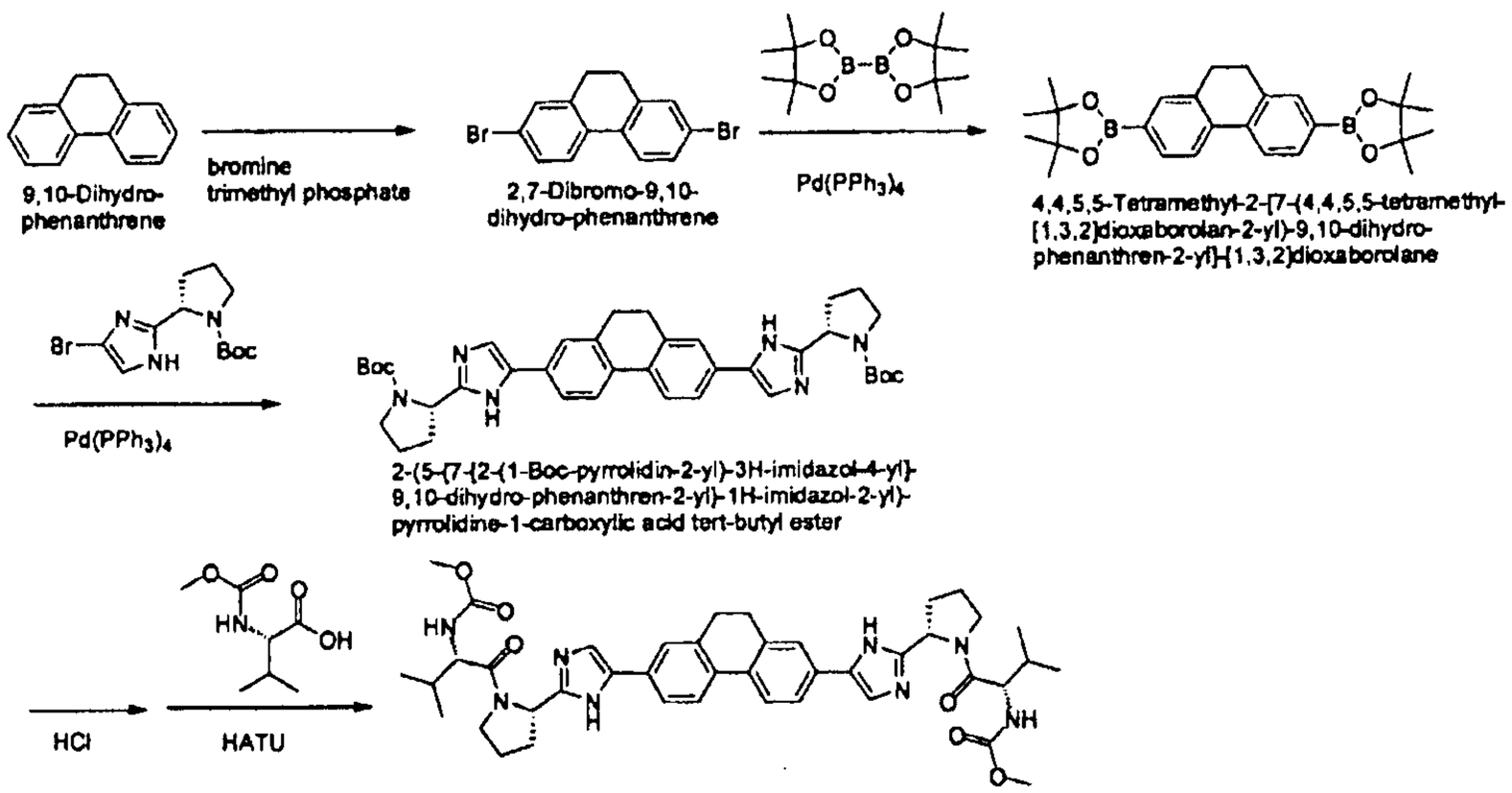
2-{5-Methyl-4-oxo-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4,5-dihydro-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added to a sealed tube containing a mixture of 2-[5-(4-bromo-phenyl)-5-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (113 mg, 0.27 mmol), bis(pinacolato)diboron (144 mg, 0.57 mmol), potassium acetate (66 mg, 0.68 mmol) and 1,4-dioxane (3 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a colorless oil (100 mg, 79%). m/z 470.0 $(M + H)^+$.

2-(5-{4'-[4-Boc-2-(1-methyl-pyrrolidin-2-yl)-5-oxo-4,5-dihydro-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Following the procedure used to prepare compound 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that 2-{5-methyl-4-oxo-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4,5-dihydro-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester. m/z 655.1 $(M + H)^+$.

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-4-methyl-5-oxo-4,5-dihydro-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester.: Following the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-(5-{4'-[4-Boc-2-(1-methyl-pyrrolidin-2-yl)-5-

oxo-4,5-dihydro-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.90-7.50 (m, 9H), 5.25 (t, 1H), 4.23 (d, 2H), 4.18-3.75 (m, 4H), 3.75-3.30 (m, 6H), 2.65-2.40 (m, 2H), 2.40-1.70 (m, 12H), 1.10-0.80 (m, 12H); m/z 769.2 $(M + H)^+$.

Example AJ



2,7-Dibromo-9,10-dihydro-phenanthrene: To a stirred solution of 9,10-dihydrophenanthrend (10 g, 55.5 mmol) in trimethylphosphate (60 mL) was added a solution of bromine (6.13 mL, 119.3 mmol) in trimethylphosphate (40 mL) slowly. After addition, the mixture was stirred at ambient for 18 hours, the volatile component was removed *in vacuo*. The residue was recrystallized from chloroform to give a white crystal (9.45 g, 51%).

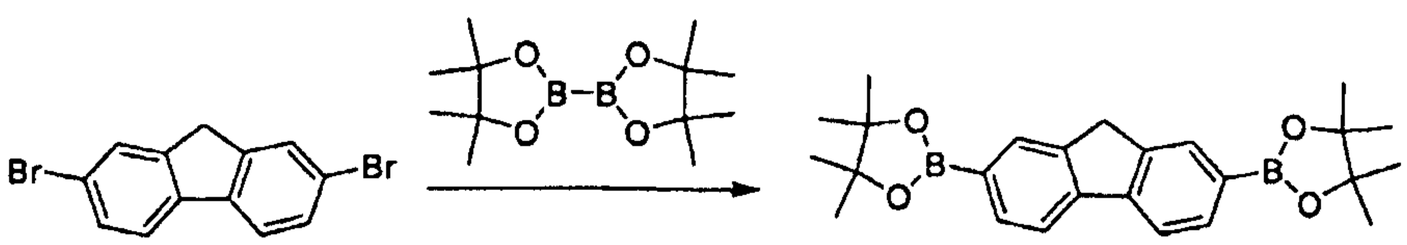
4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane: $Pd(PPh_3)_4$ (24 mg, 0.03 mmol) was added to a sealed tube containing a mixture of 2,7-dibromo-9,10-dihydro-phenanthrene (1.0 g, 3.0 mmol), bis(pinacolato)diboron (3.8 g, 14.9 mmol), potassium acetate (1.5 g, 14.9 mmol) and 1,4-dioxane (30 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 16 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (300 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in*

vacuo. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (1.2 g, 93%). m/z 432.8 $(M + H)^+$.

2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) was added to a mixture 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane (115 mg, 0.27 mmol), 2-(4-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (173 mg, 0.55 mmol), $NaHCO_3$ (159 mg, 1.9 mmol) in 1,2-dimethoxyethane (5 mL) and water (1 mL). The reaction mixture was flushed with nitrogen, heated at 80°C for 6 hours, and then the volatile component was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained residue was purified by flash chromatography to provide the desired product as a white solid (42 mg, 24%). m/z 651.0 $(M + H)^+$.

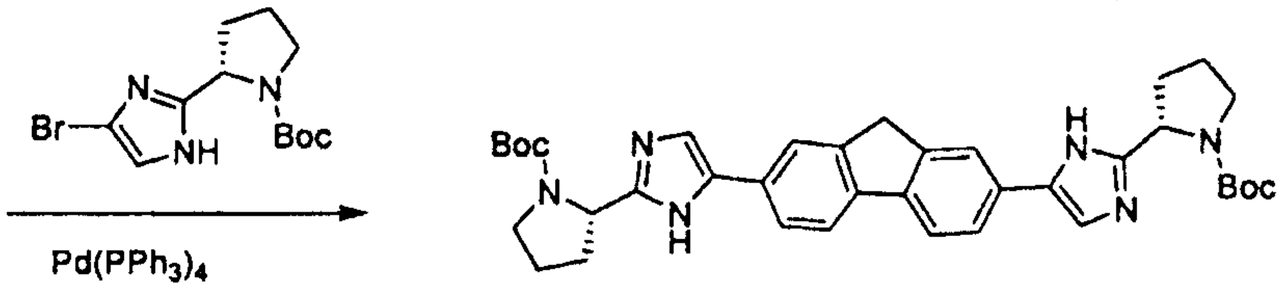
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9,10-dihydro-phenanthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Followed the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.99 (d, 2H), 7.88 (s, 2H), 7.80-7.65 (m, 4H), 5.30-5.20 (m, 2H), 4.24 (d, 2H), 4.20-4.05 (m, 2H), 3.95-3.80 (m, 2H), 3.75-3.60 (m, 6H), 3.00 (s, H), 2.65-2.50 (m, 2H), 2.40-2.00 (m, 8H), 1.05-0.80 (m, 12H); m/z 765.3 $(M + H)^+$.

Example AK

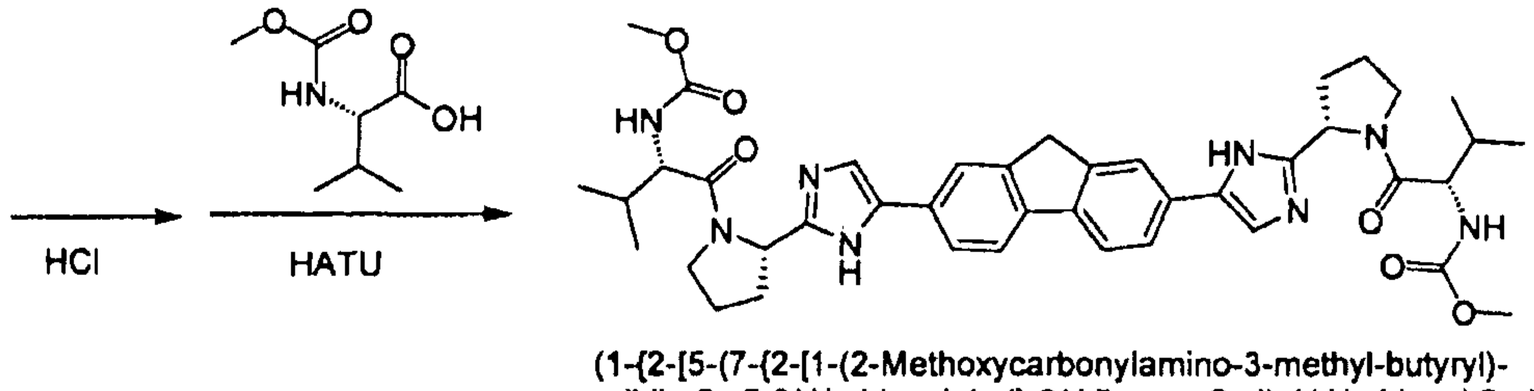


2,7-Dibromo-9*H*-fluorene

4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9H-fluoren-2-yl]-[1,3,2]dioxaborolane



2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester



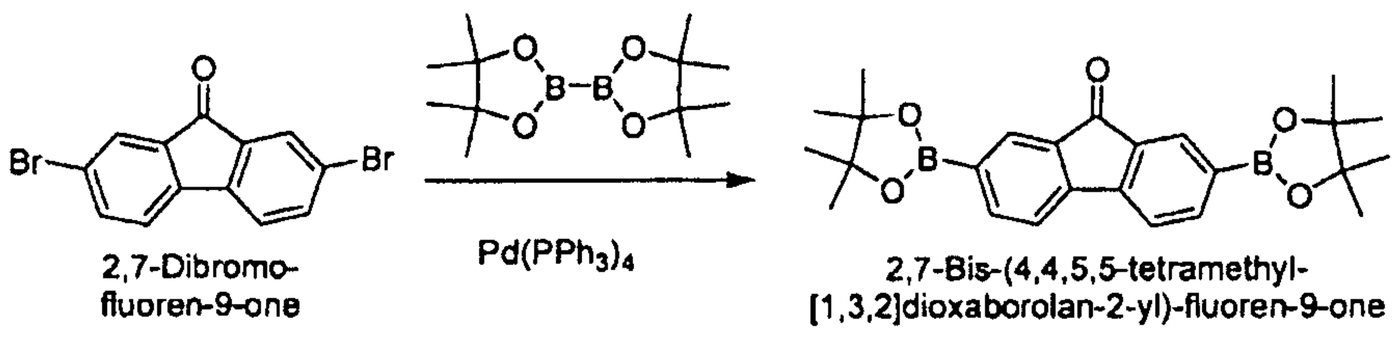
(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

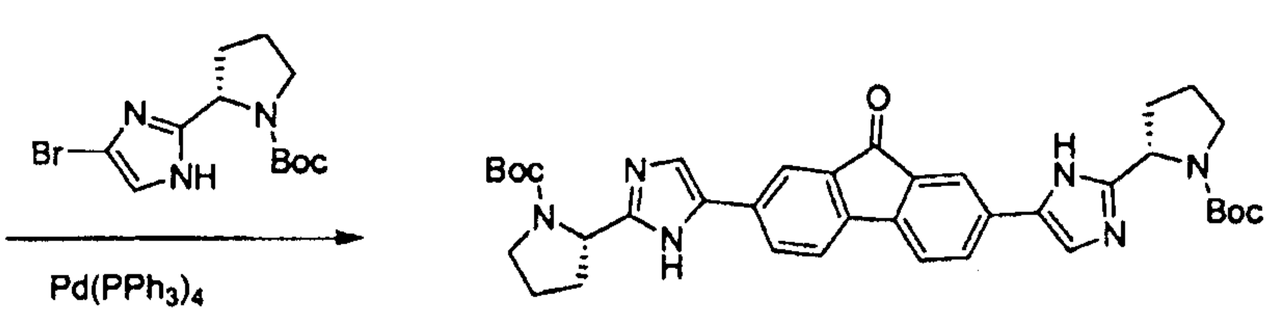
4,4,5,5-Tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9H-fluoren-2-yl]-[1,3,2]dioxaborolane: Followed the procedure used to prepare 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane, except that 2,7-dibromofluorene was used instead of 2,7-dibromo-9,10-dihydro-phenanthrene. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.84 (s, 4H), 3.90 (s, 2H), 1.38 (s, 24H).

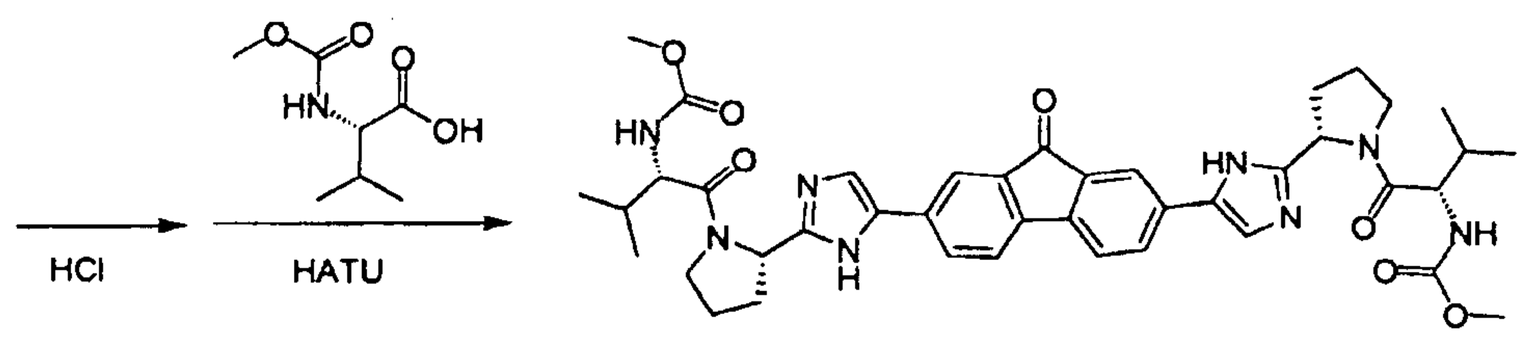
2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Followed the procedure used to prepare compound 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9H-fluoren-2-yl]-[1,3,2]dioxaborolane was used instead of 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane. m/z 637.1 $(M + H)^+$.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Followed the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.03 (d, 2H), 7.96 (s, 2H), 7.88 (s, 2H), 7.77 (d, 2H), 5.26 (t, 2H), 4.24 (d, 2H), 4.20-4.05 (m, 4H), 3.95-3.80 (m, 2H), 3.75-3.60 (m, 6H), 2.65-2.50 (m, 2H), 2.40-2.00 (m, 8H), 1.05-0.90 (m, 12H); m/z 751.3 $(M + H)^+$.

Example AL





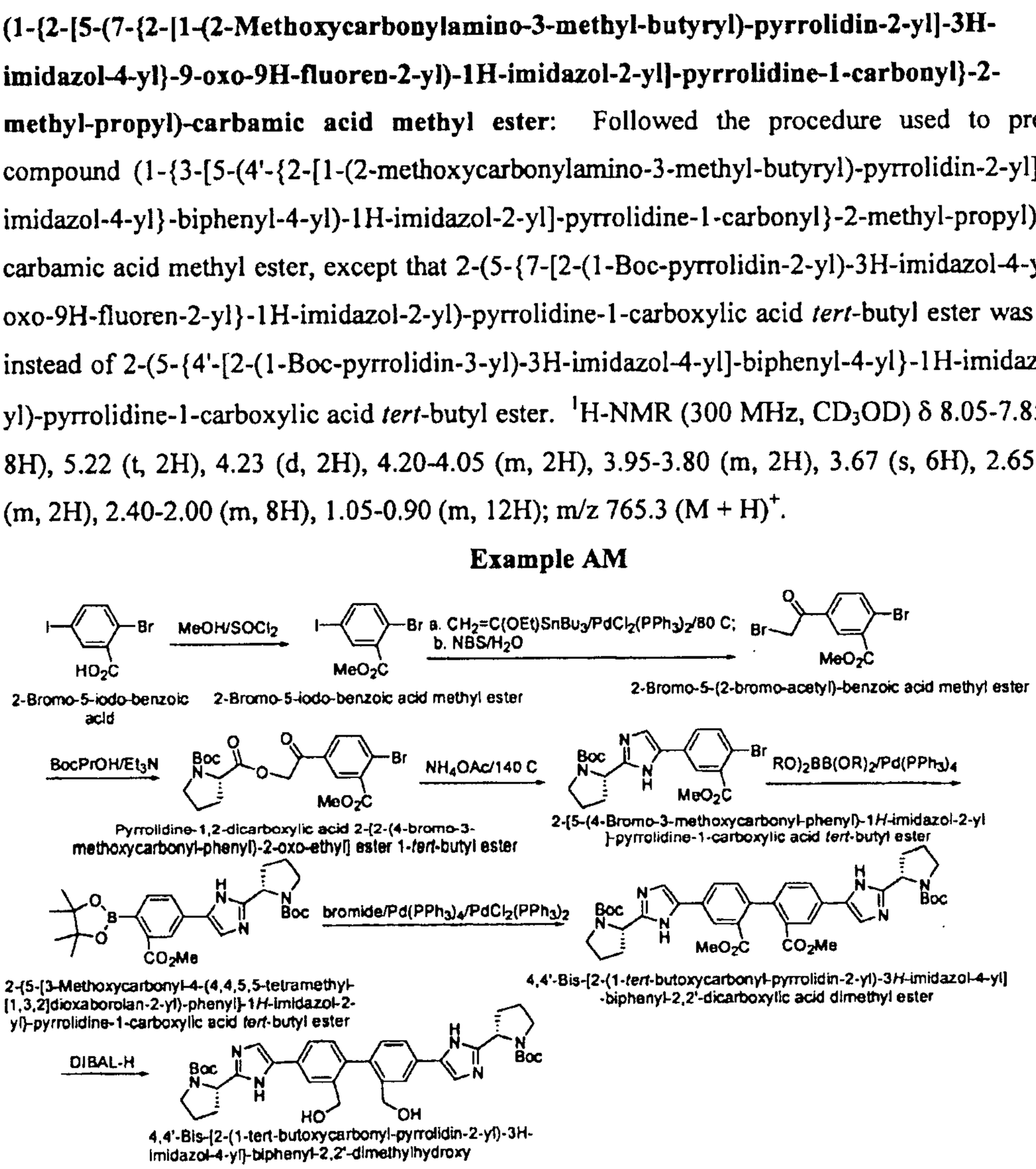


2,7-Bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-fluoren-9-one: Followed the procedure used to prepare 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane, except that 2,7-dibromo-9-fluorenone was used instead of 2,7-dibromo-9,10-dihydro-phenanthrene.

2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9-oxo-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Followed the procedure used to prepare compound 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9,10-dihydro-phenanthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, except that 2,7-bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-fluoren-9-one was used instead of 4,4,5,5-tetramethyl-2-[7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-9,10-dihydro-phenanthren-2-yl]-[1,3,2]dioxaborolane. m/z 650.9 $(M + H)^+$.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Followed the procedure used to prepare compound (1-{3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, except that 2-(5-{7-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-9-oxo-9H-fluoren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was used instead of 2-(5-{4'-[2-(1-Boc-pyrrolidin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.05-7.85 (m, 8H), 5.22 (t, 2H), 4.23 (d, 2H), 4.20-4.05 (m, 2H), 3.95-3.80 (m, 2H), 3.67 (s, 6H), 2.65-2.50 (m, 2H), 2.40-2.00 (m, 8H), 1.05-0.90 (m, 12H); m/z 765.3 $(M + H)^+$.

Example AM



2-Bromo-5-iodo-benzoic acid methyl ester: To the solution of 2-bromo-5-iodo-benzoic acid (10 g, 31 mmol) in methanol (100 ml) was added thionyl chloride (5 ml, 68 mmol). The mixture

was heated at 55°C for 12 hours. The solvent and reagent were removed under reduced pressure and the mixture was diluted with EtOAc. The organic solution was washed with saturated sodium bicarbonate, water, and brine, and was dried with sodium sulfate. Concentration gave 2-bromo-5-iodo-benzoic acid methyl ester (10.5 g).

2-Bromo-5-(2-bromo-acetyl)-benzoic acid methyl ester: To the solution of 2-bromo-5-iodo-benzoic acid methyl ester (4.33 g, 12.7 mmol) and tributyl(ethoxyvinyl)stannane (4.79 g, 13.3 mmol) in dioxane (56 ml) was added $PdCl_2(PPh_3)_2$ (322 mg). The mixture was heated at 80°C for 17 hours and was cooled to 0°C. Water (19 ml) was added, followed by slow addition of NBS (2.33 g, 12.9 mmol) over 10 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc = 2/1) gave 2-bromo-5-(2-bromo-acetyl)-benzoic acid methyl ester (3.48 g).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-3-methoxycarbonyl-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: To the solution of (s)Boc-PrOH (2.5 g, 11.6 mmol) and triethylamine (1.55 ml, 11.1 mmol) in acetonitrile (34 ml) was added a solution of 2-bromo-5-(2-bromo-acetyl)-benzoic acid methyl ester (3.48 g, 10.4 mmol) in acetonitrile (17 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with water and brine, and was dried with sodium sulfate. Purification by flash column chromatography (hexane/EtOAc = 1/1.5) gave pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-3-methoxycarbonyl-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (3.9 g): m/z: 491.9 $(M + Na)^+$.

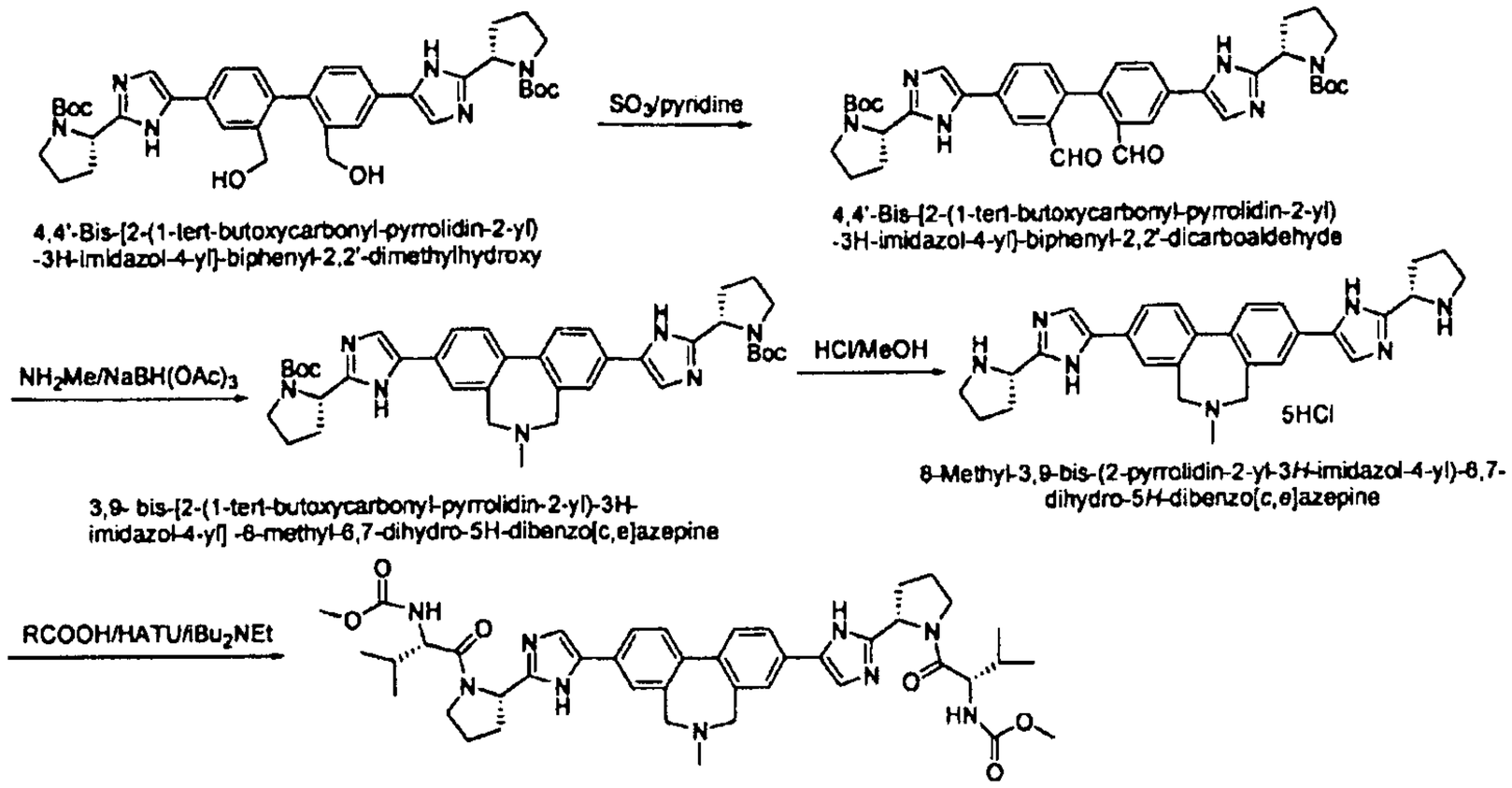
2-[5-(4-Bromo-3-methoxycarbonyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: The mixture of pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-3-methoxycarbonyl-phenyl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (460 mg, 1 mmol) and ammonium acetate (860 mg, 11 mmol) in xylenes (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 2-[5-(4-bromo-3-methoxycarbonyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (320 mg). m/z: 449.8 $(M + H)^+$, 448.1 $(M - H)^-$.

2-{5-[3-Methoxycarbonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(4-bromo-3-methoxycarbonyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.44 mmol) and bis(pinacolato)diboron (225 mg, 0.89 mmol) in 1,4-dioxane (3.4 ml) and DMF (2 ml) was added potassium acetate (110 g, 1.1 mmol), followed by $Pd(PPh_3)_4$ (20 mg) and $PdCl_2(dppf)CH_2Cl_2$ (20 mg). The mixture was heated at 80°C for 12 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 2-{5-[3-Methoxycarbonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (168 mg). m/z: 498.0 $(M + H)^+$.

4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboxylic acid dimethyl ester: To the solution of 2-[5-(4-bromo-3-methoxycarbonyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (158 mg, 0.35 mmol) and 2-{5-[3-Methoxycarbonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (166 mg, 0.33 mmol) in 1,2-dimethoxyether (3 ml) and water (1 ml) was added sodium bicarbonate (91 mg, 1.1 mmol), followed by $Pd(PPh_3)_4$ (15 mg) and $PdCl_2(dppf)CH_2Cl_2$ (15 mg). The mixture was heated at 80°C for 7 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (EtOAc) gave 4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboxylic acid dimethyl ester (85 mg). m/z: 741.0 $(M + H)^+$, 370.9 $(M + 2H)^+/2$.

4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy: To the solution of 4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboxylic acid dimethyl ester (85 mg, 0.11 mmol) in THF (2 ml) at -78°C was added DIBAL-H THF solution (1.4 ml, 1.4 mmol). The mixture was warmed to 25°C and stirred for 5 hours. The mixture was cooled to 0°C and quenched with 2.0 N NaOH solution until PH=11. The mixture was extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/MeOH) gave 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy (54 mg). m/z: 685.1 $(M + H)^+$, 343.0 $(M + 2H)^+/2$.

Example AN



4,4'-Bis-[2-(1-tert-butoxycarbonyl-pyrrolidin-2-yl) -3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy

4,4'-Bis-[2-(1-tert-butoxycarbonyl-pyrrolidin-2-yl) -3H-imidazol-4-yl]-biphenyl-2,2'-dicarboaldehyde

3,9- bis-[2-(1-tert-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl] -6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine

8-Methyl-3,9-bis-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine

(1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-Imidazol-4-yl}-6-methyl -6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

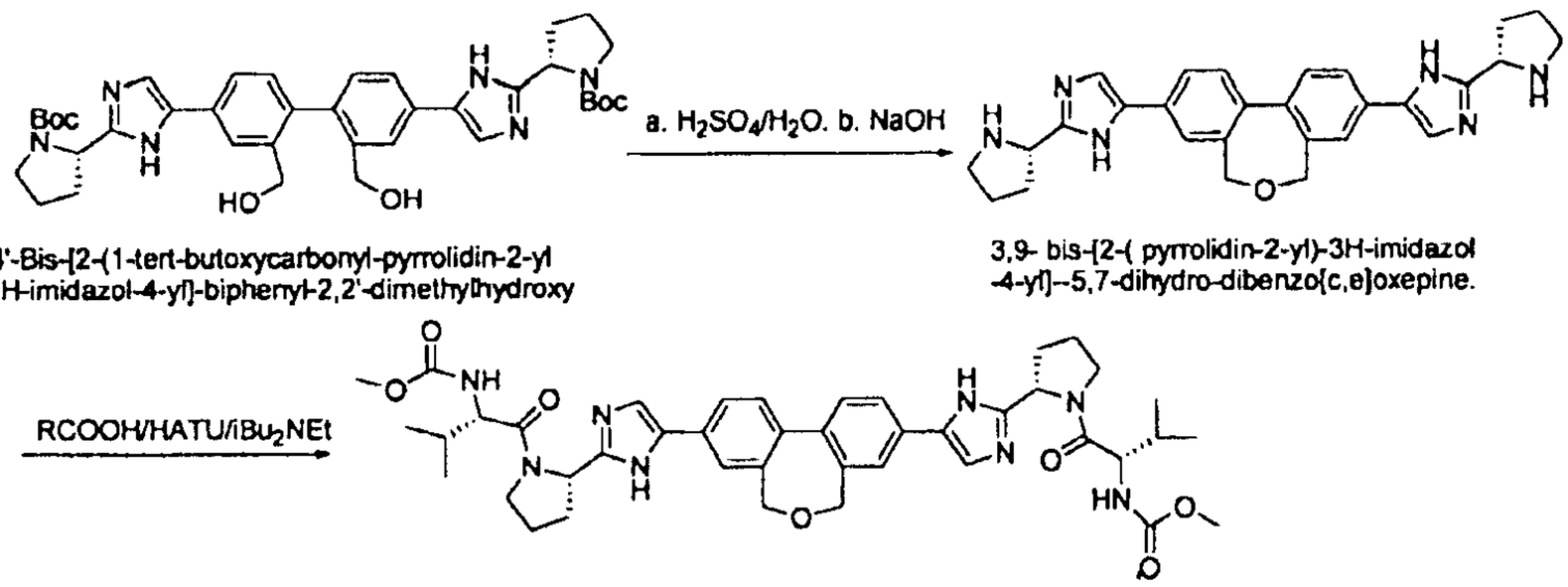
4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboaldehyde: To the solution of 4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy (54 mg, 0.08 mmol) in DMSO (1.2 ml) was added triethylamine (0.14 ml). The mixture was stirred for 5 minutes, and pyridine-sulfur trioxide (170 mg) was added. The mixture was stirred for 90 minutes and was quenched with ice-water. The stirring was continued for additional 30 minutes and the mixture was extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration gave 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboaldehyde (40 mg). m/z: 681.0 $(M + H)^+$.

3,9-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl] -6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine: To the solution of 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dicarboaldehyde (40 mg, 0.06 mmol) in MeOH/THF (2.5 ml/0.5 ml) was added methylamine methanol solution (29 µl, 0.06 mmol), followed by acetic acid (14 µl, 0.23 mmol) and $NaBH(OAc)_3$ (50 mg, 0.23 mmol). The mixture was stirred for 12 hours and was quenched with water. The mixture was extracted with EtOAc. The organic phase was washed with 1.0 N sodium hydroxide solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/MeOH) gave compound 3,9- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl] -6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (24 mg). m/z: 680.3 $(M + H)^+$.

3,9-Bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl]-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine: To the solution of 3,9- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (24 mg) in DCM/MeOH (1.6 ml/0.75 ml) was added hydrochloric acid in dioxane (0.44 ml, 1.7 mmol). The mixture was heated at 50°C for 3 hours and the solvents were evaporated under reduced pressure. The mixture was diluted with water and acetonitrile, and was freezer-dried to give 3,9- bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl] -6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine as brown powder (25 mg). m/z: 480.1 $(M + H)^+$.

1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3,9- bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl] -6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (25 mg, 0.035 mmol) and MeOCO-Val-OH (13 mg, 0.074 mmol) in DMF (1.2 ml) was added HATU (28 mg, 0.074 mmol), followed by diisopropylethylamine (61 µl, 0.35 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(9-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (24 mg). m/z: 794.3 $(M + H)^+$, 397.8 $(M + 2H)^+/2$. ^1H NMR (CD_3OD, 300 MHz) δ 8.0-7.9 (8 H, m), 5.27 (2 H, m), 4.3-4.2 (2 H, m), 4.2-3.8 (8 H, m), 3.66 (6 H, s), 3.08 (3 H, s), 2.7-2.5 (2 H, m), 2.4-1.9 (8 H, m), 0.94-0.90 (12 H, m).

Example AO



4,4'-Bis-[2-(1-tert-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy

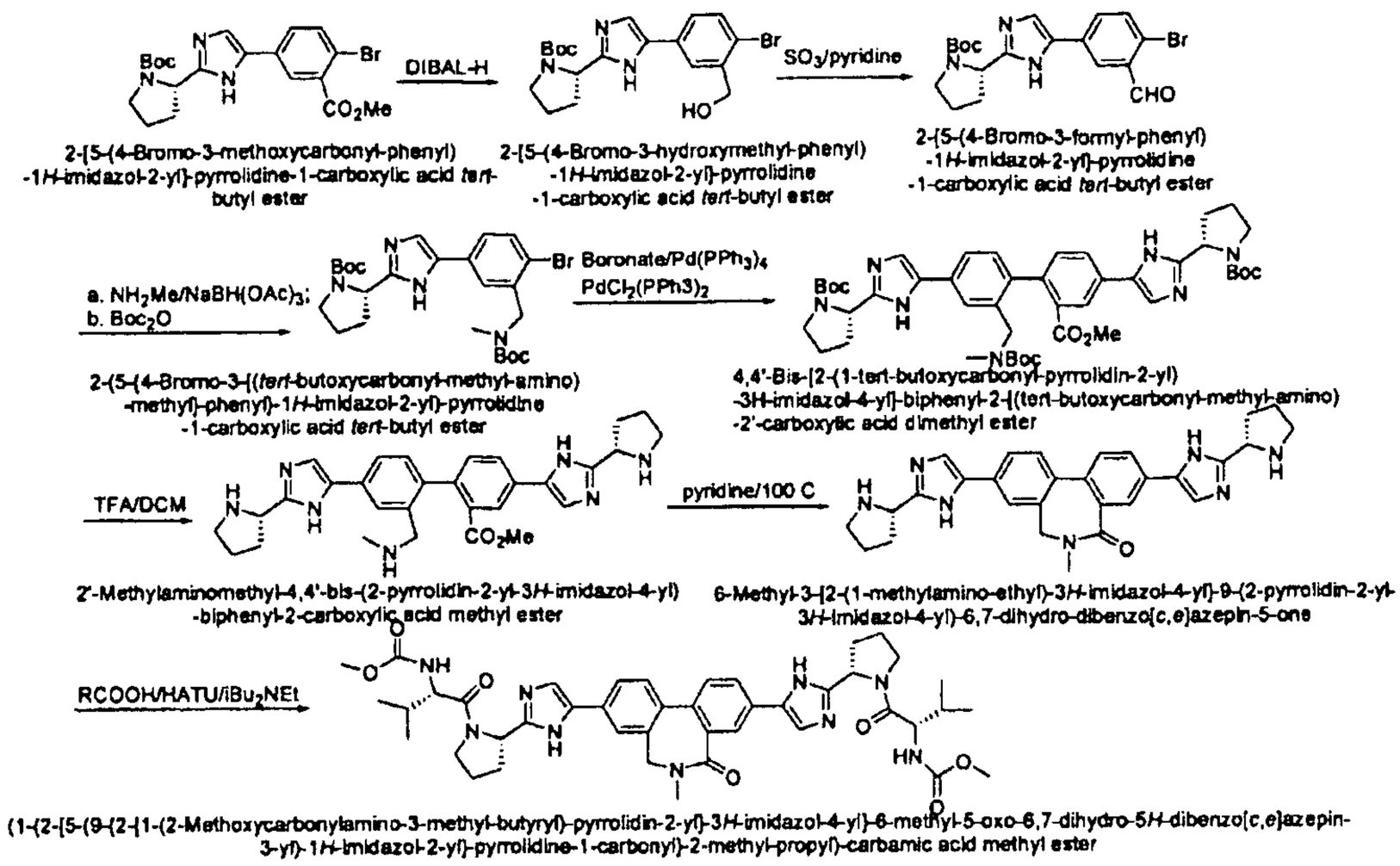
3,9- bis-[2-(pyrrolidin-2-yl)-3H-imidazol -4-yl]--5,7-dihydro-dibenzo[c,e]oxepine.

(1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl) -5,7-dihydro-dibenzo[*c*,*e*]oxepin-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3,9-Bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl]--5,7-dihydrodibenzo[c,e]oxepine: To the suspension of 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2,2'-dimethylhydroxy (8 mg, 0.011 mmol) in water (1.5 ml) was added sulfuric acid (1.5 ml). The mixture was heated at 60°C for 14 hours. The mixture was cooled to 0°C, and 2 N sodium hydroxide solution was added until pH = 7. The mixture was freezer-dried to give 3,9- bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl]--5,7-dihydro-dibenzo[c,e]oxepine. m/z: 467.1 $(M + H)^+$.

(1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3,9- bis-[2-(pyrrolidin-2-yl)-3H-imidazol-4-yl]--5,7-dihydro-dibenzo[c,e]oxepine (0.011 mmol) and MeOCO-Val-OH (4 mg, 0.023 mmol) in DMF (5 ml) was added HATU (9 mg, 0.023 mmol), followed by diisopropylethylamine (38 µl, 0.22 mmol). The mixture was stirred for 60 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(9-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.5 mg). m/z: 781.2 (M+1), 391.2 (M+2)/2; ^1H NMR (CD_3OD, 300 MHz) δ 7.9-7.8 (8 H, m), 5.27 (2 H, m), 4.44 (4 H, s), 4.22 (2 H, m), 4.17-4.05 (2 H, m), 3.95-3.83 (2 H, m), 5.67 (6 H, s), 2.65-2.50 (2 H, m), 2.35-1.95 (8 H, m), 0.99-0.89 (12 H, m).

Example AP



2-[5-(4-Bromo-3-methoxycarbonyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[5-(4-Bromo-3-hydroxymethyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[5-(4-Bromo-3-formyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(5-(4-Bromo-3-[(*tert*-butoxycarbonyl-methyl-amino)-methyl]-phenyl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

4,4'-Bis-[2-(1-tert-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2-[(tert-butoxycarbonyl-methyl-amino)-2'-carboxylic acid dimethyl ester

2'-Methylaminomethyl-4,4'-bis-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-biphenyl-2-carboxylic acid methyl ester

6-Methyl-3-[2-(1-methylamino-ethyl)-3*H*-imidazol-4-yl]-9-(2-pyrrolidin-2-yl-3*H*-imidazol-4-yl)-6,7-dihydro-dibenzo[c,e]azepin-5-one

(1-(2-[5-(9-(2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl)-6-methyl-5-oxo-6,7-dihydro-5*H*-dibenzo[c,e]azepin-3-yl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

2-[5-(4-Bromo-3-hydroxymethyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(4-Bromo-3-methoxycarbonyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.44 mmol) in THF (4 ml) at -78°C was added DIBAL-H THF solution (3.33 ml, 3.33 mmol). The mixture was warmed to 25°C and stirred for 5 hours. The mixture was cooled to 0°C and quenched with 2.0 N NaOH solution until PH=11. The mixture was extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration gave 2-[5-(4-bromo-3-hydroxymethyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (196 mg). m/z: 421.9 $(M + H)^+$, 420.2 $(M - H)^-$.

2-[5-(4-Bromo-3-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(4-bromo-3-hydroxymethyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (196 mg, 0.46 mmol) in DMSO (3.5 ml) was added triethylamine (0.40 ml). The mixture was stirred for 30 minutes, and pyridine-sulfur trioxide (500 mg) was added. The mixture was stirred for 2 hours and was quenched with ice-water. The stirring was continued for additional 30 minutes and the mixture was extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration gave 2-[5-(4-Bromo-3-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (180 mg).

2-(5-{4-Bromo-3-[(*tert*-butoxycarbonyl-methyl-amino)-methyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(4-bromo-3-formyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.46 mmol) in MeOH/THF (2.5 ml/2.5 ml) was added methylamine methanol solution (0.69 ml, 1.38 mmol), followed by acetic acid (110 µl, 1.84 mmol) and $NaBH(OAc)_3$ (975 mg, 4.6 mmol). The mixture was stirred for 12 hours and was quenched with 1 N sodium hydroxide solution. The mixture was extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration gave the intermediate (171mg). To the solution of the above intermediate (171 mg, 0.39 mmol) in DCM (4 ml) was added di-*tert*-butyl dicarbonate (86 mg, 0.39 mmol), followed by diisopropylethylamine (135 6l, 0.78 mmol). The mixture was stirred for 12 hours, and the solvent and reagent was evaporated. Purification by flash column chromatography (hexanes/EtOAc) gave 2-(5-{4-bromo-3-[(*tert*-butoxycarbonyl-methyl-amino)-methyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (142 mg). m/z: 535 $(M + H)^+$.

4,4'-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2-[(*tert*-butoxycarbonyl-methyl-amino)-2'-carboxylic acid dimethyl ester: To the solution of 2-(5-{4-bromo-3-[(*tert*-butoxycarbonyl-methyl-amino)-methyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (142 mg, 0.27 mmol) and 2-{5-[3-Methoxycarbonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (125 mg, 0.25 mmol) in 1,2-dimethoxyether (2.3 ml) and water (0.7 ml) was added sodium bicarbonate (63 mg, 0.75 mmol), followed by $Pd(PPh_3)_4$ (12 mg) and $PdCl_2(dppf)CH_2Cl_2$ (12 mg). The mixture was heated at 80°C for 20 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2-[(*tert*-butoxycarbonyl-methyl-amino)-2'-carboxylic acid dimethyl ester (82 mg). m/z: 826 $(M + H)^+$, 413.6 $(M + 2H)^+/2$.

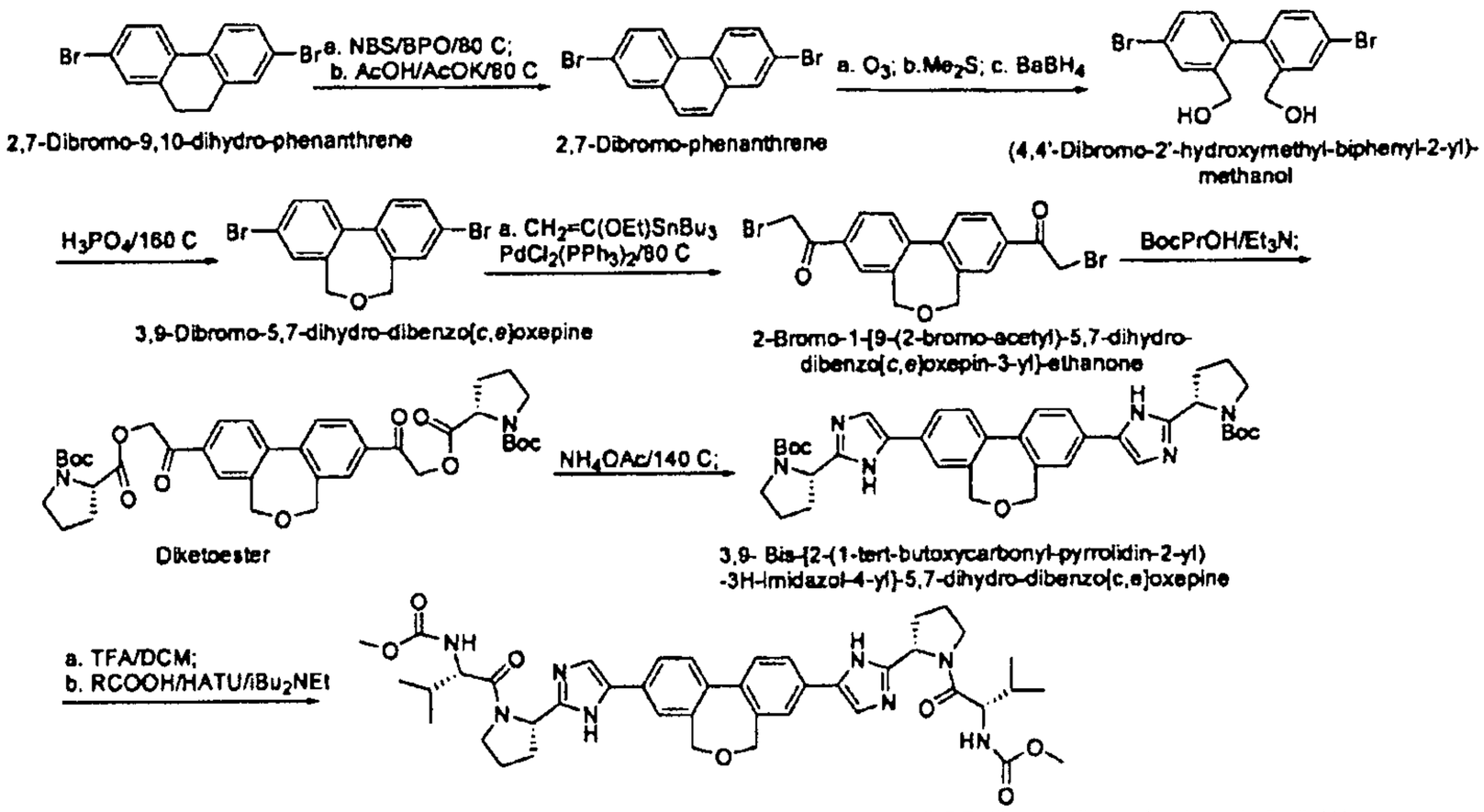
2'-Methylaminomethyl-4,4'-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-2-carboxylic acid methyl ester: To the solution of 4,4'-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-2-[(*tert*-butoxycarbonyl-methyl-amino)-2'-carboxylic acid dimethyl ester (77 mg, 0.09 mmol) in DCM (3 ml) was added trifluoroacetic acid (3 ml). The mixture was stirred for 2 hours, and the solvent and reagent were removed under reduced pressure. The

mixture was diluted with acetonitrile and water, was freezer-dried to give 2'-methylaminomethyl-4,4'-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-2-carboxylic acid methyl ester as white powder (90 mg). m/z: 526.1 $(M + H)^+$.

6-Methyl-3,9-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-6,7-dihydro-dibenzo[c,e]azepin-5-one: To the solution of 2'-methylaminomethyl-4,4'-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-2-carboxylic acid methyl ester (90 mg) in pyridine (5 ml) was added diisopropylethylamine (1 ml). The mixture was heated at 100°C for 2 hours. The solvents were evaporated. The mixture was diluted with acetonitrile and water, was freezer-dried to give 6-Methyl-3,9-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-6,7-dihydro-dibenzo[c,e]azepin-5-one as brown powder. m/z: 494.1 $(M + H)^+$.

(1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-5-oxo-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 6-methyl-3,9-bis-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-6,7-dihydro-dibenzo[c,e]azepin-5-one (0.09 mmol) and MeOCO-Val-OH (33 mg, 0.19 mmol) in DMF (3 ml) was added HATU (71 mg, 0.19 mmol), followed by diisopropylethylamine (323 µl, 1.86 mmol). The mixture was stirred for 60 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-6-methyl-5-oxo-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (16 mg). m/z: 808.2 (M+1), 404.8 (M+2)/2, 806.3 (M-1). ^1H NMR (CD_3OD, 300 MHz) δ 8.1-7.8 (8 H, m), 5.4-5.2 (2 H, m), 4.6-4.2 (4 H, m), 4.2-4.0 (2 H, m), 3.95-3.80 (2 H, m), 3.64 (6 H, m), 3.25 (3 H, s), 2.65-2.45 (2 H, m), 2.35-2.0 (8 H, m), 1.05-0.9 (12 H, m).

Example AQ



2,7-Dibromo-phenanthrene: The mixture of 2,7-dibromo-9,10-dihydro-phenanthrene (2.4 g, 7.1 mmol), NBS (1.4 g, 7.8 mmol), and benzoyl peroxide (0.2 g) in carbon tetrachloride (300 ml) was refluxed for 2 hours. Potassium acetate (3.6 g) and acetic acid (3.2 ml) were added, and the refluxing was continued for additional 2 hours. The mixture was cooled and diluted with EtOAc. The organic phase was washed with water, saturated sodium bicarbonate, and brine, and was dried with sodium sulfate. Concentration gave 2,7-dibromo-phenanthrene (2.3 g).

(4,4'-Dibromo-2'-hydroxymethyl-biphenyl-2-yl)-methanol: The solution of 2,7-dibromo-phenanthrene (3.8 g) in DCM/MeOH (120 ml/1 ml) was cooled to -78°C, and it became a suspension. Ozone was bubbled thorough for 20 minutes, and the mixture became blue. Oxygen was bubbled for 5 minutes and dimethyl sulfide (3 ml) was added. The mixture was warmed to 25°C and stirred for 12 hours. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 4,4'-dibromo-biphenyl-2,2'-dicarbaldehyde (600 mg). To the solution of 4,4'-dibromo-biphenyl-2,2'-dicarbaldehyde (600 mg, 1.7 mmol) in THF/MeOH (10 ml/10 ml) at 0°C was added sodium borohydride (320 mg, 8.2 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration gave (4,4'-dibromo-2'-hydroxymethyl-biphenyl-2-yl)-methanol (550 mg).

3,9-Dibromo-5,7-dihydro-dibenzo[c,e]oxepine: The suspension of (4,4'-dibromo-2'-hydroxymethyl-biphenyl-2-yl)-methanol (460 mg) in phosphoric acid (25 ml) was heated at 160°C for 4 hours. The mixture was cooled and diluted with water (100 ml), and was extracted with EtOAC. The organic phase was washed with water, saturated sodium bicarbonate, and brine, and was dried with sodium sulfate. Concentration yielded 3,9-dibromo-5,7-dihydro-dibenzo[c,e]oxepine (416 mg).

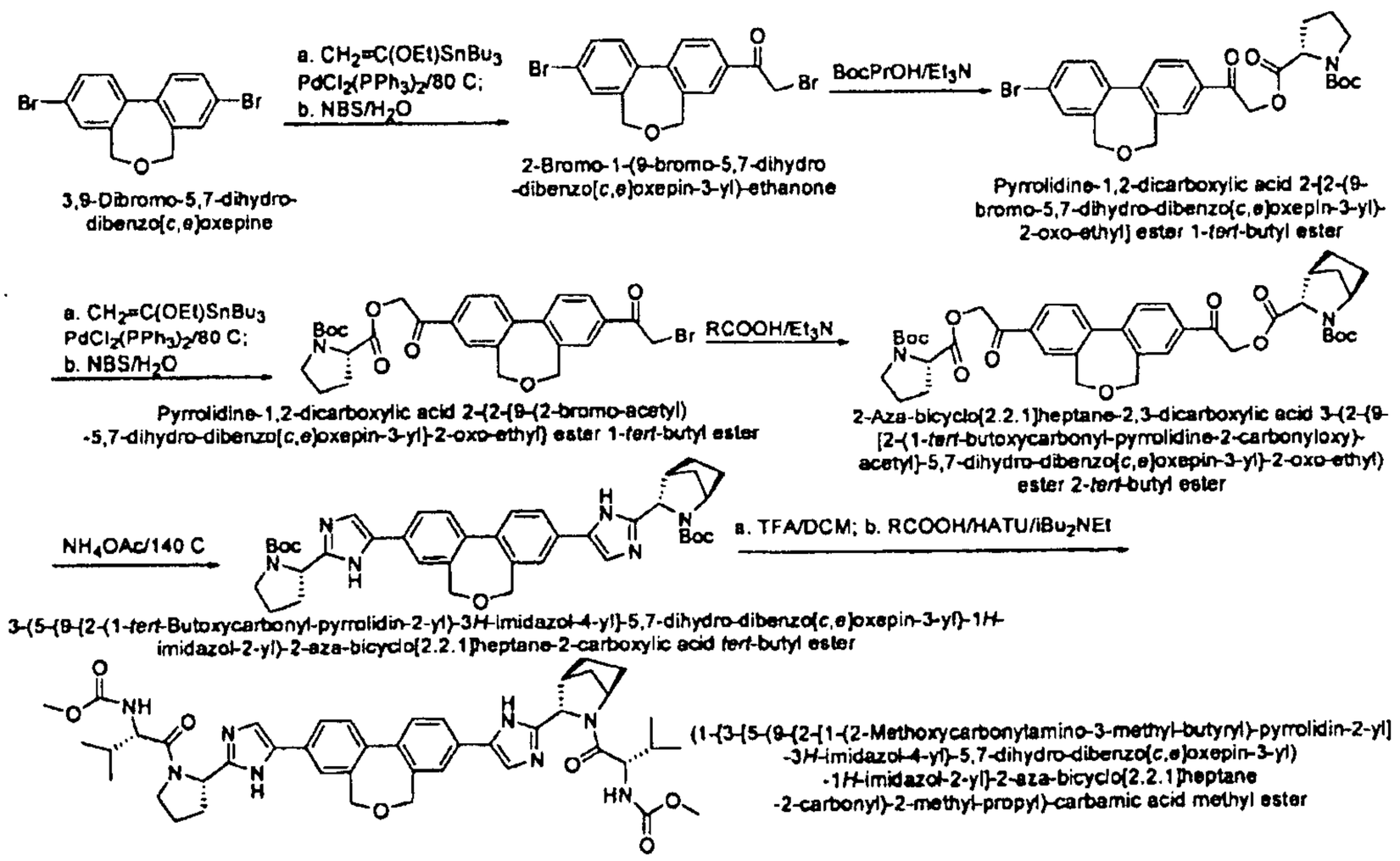
2-Bromo-1-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-ethanone: To the solution of 3,9-dibromo-5,7-dihydro-dibenzo[c,e]oxepine (416 mg, 1.2mmol) and tributyl(ethoxyvinyl)stannane (878 µl, 2.6 mmol) in dioxane (6 ml) was added $PdCl_2(PPh_3)_2$ (30 mg). The mixture was heated at 80°C for 16 hours and was cooled to 0°C. Water (2 ml) was added, followed by slow addition of NBS (464 mg, 2.6 mmol) over 5 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc) gave 2-bromo-1-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-ethanone (160 mg).

Diketoester: To the solution of (*S*)-Boc-Pro-OH (275 mg, 1.28 mmol) and triethylamine (154 µl, 1.11 mmol) in acetonitrile (3.4 ml) was added a solution of 2-bromo-1-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-ethanone (160 mg, 0.37 mmol) in DMF (6 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with water and brine, and was dried with sodium sulfate. Concentration gave the intermediate diketoester. m/z: 729.1 $(M + Na)^+$.

3,9-Bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepine: The mixture of above diketoester (0.37 mmol) and ammonium acetate (860 mg, 11 mmol) in xylene (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3,9- bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepine (195 mg). m/z: 667.1 $(M + H)^+$.

(1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3,9-bis-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepine (190 mg) in DCM (3 ml) was added TFA (1.5 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give dipyrrolidine. To the solution of dipyrrolidine (0.29 mmol) and (S-)-Moc-Val-OH (100 mg, 0.57 mmol) in DMF (8 ml) was added HATU (227 mg, 0.60 mmol), followed by diisopropylethylamine (0.5 ml, 2.9 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{2-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (142 mg). m/z: 781.3 (M+1), 779.3 (M-1), 391.3 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 7.9-7.8 (8 H, m), 5.27 (2 H, m), 4.44 (4 H, s), 4.22 (2 H, m), 4.17-4.05 (2 H, m), 3.95-3.83 (2 H, m), 5.67 (6 H, s), 2.65-2.50 (2 H, m), 2.35-1.95 (8 H, m), 0.99-0.89 (12 H, m).

Example AR



2-Bromo-1-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-ethanone: To the solution of 3,9-dibromo-5,7-dihydro-dibenzo[c,e]oxepine (416 mg, 1.2mmol) and tributyl(ethoxyvinyl)stannane (878 µl, 2.6 mmol) in dioxane (6 ml) was added $PdCl_2(PPh_3)_2$ (30 mg). The mixture was heated at 80°C for 16 hours and was cooled to 0°C. Water (2 ml) was added, followed by slow addition of NBS (464 mg, 2.6 mmol) over 5 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc) gave 2-bromo-1-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-ethanone (120 mg).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: To the solution of (*S*)-Boc-Pro-OH (118 mg, 0.55 mmol) and triethylamine (65 µl, 0.46 mmol) in acetonitrile (2 ml) was added a solution of 2-bromo-1-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-ethanone (120 mg, 0.31 mmol) in DMF (4 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with water and brine, and was dried with sodium sulfate. Concentration gave pyrrolidine-1,2-dicarboxylic acid 2-[2-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (160 mg). m/z: 553.8 $(M + Na)^+$.

Pyrrolidine-1,2-dicarboxylic acid 2-{2-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-2-oxo-ethyl} ester 1-*tert*-butyl ester: To the solution of pyrrolidine-1,2-dicarboxylic acid 2-[2-(9-bromo-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (160 mg, 0.30) and tributyl(ethoxyvinyl)stannane (112 µl, 0.33 mmol) in dioxane (2 ml) was added $PdCl_2(PPh_3)_2$ (8 mg). The mixture was heated at 80°C for 16 hours and was cooled to 0°C. Water (0.7 ml) was added, followed by slow addition of NBS (59, 0.33 mmol) over 5 minutes period. The mixture was stirred at 0°C for additional 40 minutes, and the solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine and dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc) gave pyrrolidine-1,2-dicarboxylic acid 2-{2-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-2-oxo-ethyl} ester 1-*tert*-butyl ester (156 mg). m/z: 593.9 $(M + Na)^+$.

2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{9-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester: To the solution of 2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-

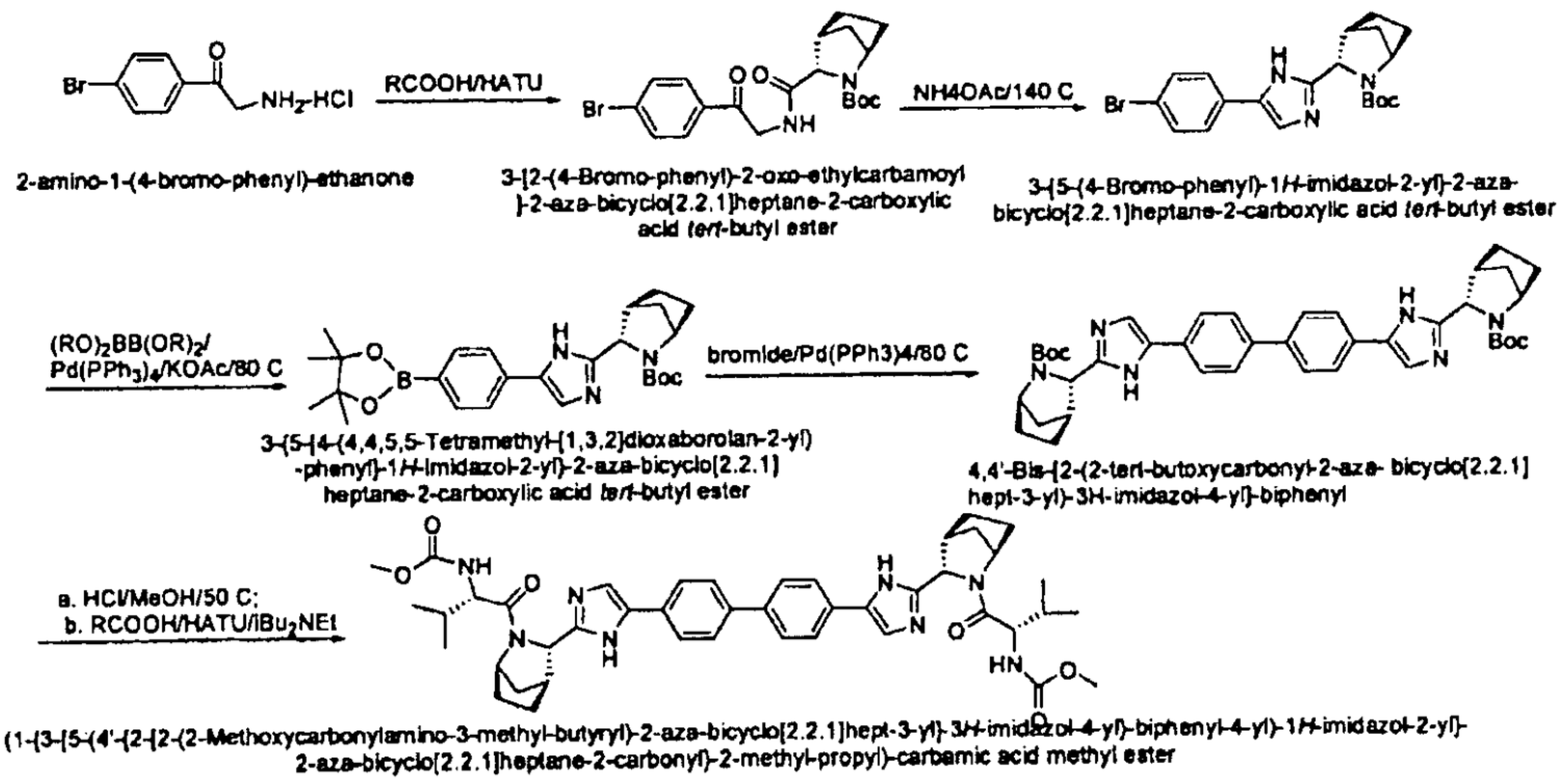
butyl ester (100 mg, 0.42 mmol) and triethylamine (50 µl, 0.36 mmol) in acetonitrile (2 ml) was added a solution of pyrrolidine-1,2-dicarboxylic acid 2-{2-[9-(2-bromo-acetyl)-5,7-dihydro-dibenzo[c,e]oxepin-3-yl]-2-oxo-ethyl} ester 1-*tert*-butyl ester (136 mg, 0.24 mmol) in DMF (4 ml). The mixture was stirred for 10 hours, and the solvent was evaporated. The mixture was diluted with EtOAc, and washed with water and brine, and was dried with sodium sulfate. Concentration gave 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{9-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (142 mg). m/z: 731.3 $(M - H)^-$, 755.2 $(M + Na)^+$.

3-(5-{9-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: The mixture of 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 3-(2-{9-[2-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxy)-acetyl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-2-oxo-ethyl) ester 2-*tert*-butyl ester (142 mg, 0.19 mmol) and ammonium acetate (860 mg, 11 mmol) in xylene (5 ml) was heated at 140°C for 80 minutes under microwave. The mixture was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave 3-(5-{9-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (86 mg). m/z: 693.1 $(M + H)^+$.

(1-{3-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 3-(5-{9-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,7-dihydro-dibenzo[c,e]oxepin-3-yl}-1H-imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (86 mg) in DCM (3 ml) was added TFA (1.5 ml). The mixture was stirred for 60 minutes, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. To the solution of above powder (0.12 mmol) and (*S*)-Moc-Val-OH (44 mg, 0.25 mmol) in DMF (4 ml) was added HATU (99 mg, 0.26 mmol), followed by diisopropylethylamine (0.22 ml, 1.2 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{3-[5-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,7-

dihydro-dibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (84 mg). m/z: 807.4 (M+1), 805.3 (M-1), 404.4 (M+2)/2. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.0-7.8 (8 H, m), 5.26 (2 H, m), 4.66 (1 H, m), 4.44 (4 H, m), 4.35 (1 H, m), 4.25 (1 H, m), 4.15 (1 H, m), 3.89 (1 H, m), 3.67 (6 H, m), 2.85 (2 H, m), 2.60 (2 H, m), 2.3-1.4 (9 H, m), 1.05-0.85 (12 H, m).

Example AS



2-amino-1-(4-bromo-phenyl)-ethanone

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

3-[5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

4,4'-Bis-[2-(2-tert-butoxycarbonyl-2-aza- bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl

(1-{3-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: To the solution of 2-amino-1-(4-bromo-phenyl)-ethanone (HCl salt, 1.0 g, 4 mmol) and 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 2-*tert*-butyl ester (0.98 g, 4 mmol) in DMF (13 ml) was added HATU (1.64 g, 4.3 mmol), followed by slow addition of diisopropylethylamine (2.2 ml, 12.7 mmol). The mixture was stirred for 4 hours and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexane/EtOAc) gave 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.7 g). m/z: 460.9 $(M + Na)^+$.

3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: The mixture of 3-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.7 g, 4 mmol), acetic acid (24 μl), and ammonium acetate (1.54 g, 20 mmol) in xylene (20 ml) was heated at 140°C for 20 hours. The mixture was quenched with saturated sodium carbonate solution, and extracted with EtOAc. The organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 3-[5-(4-

bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (1.21 g). m/z: 417.9 $(M + H)^+$.

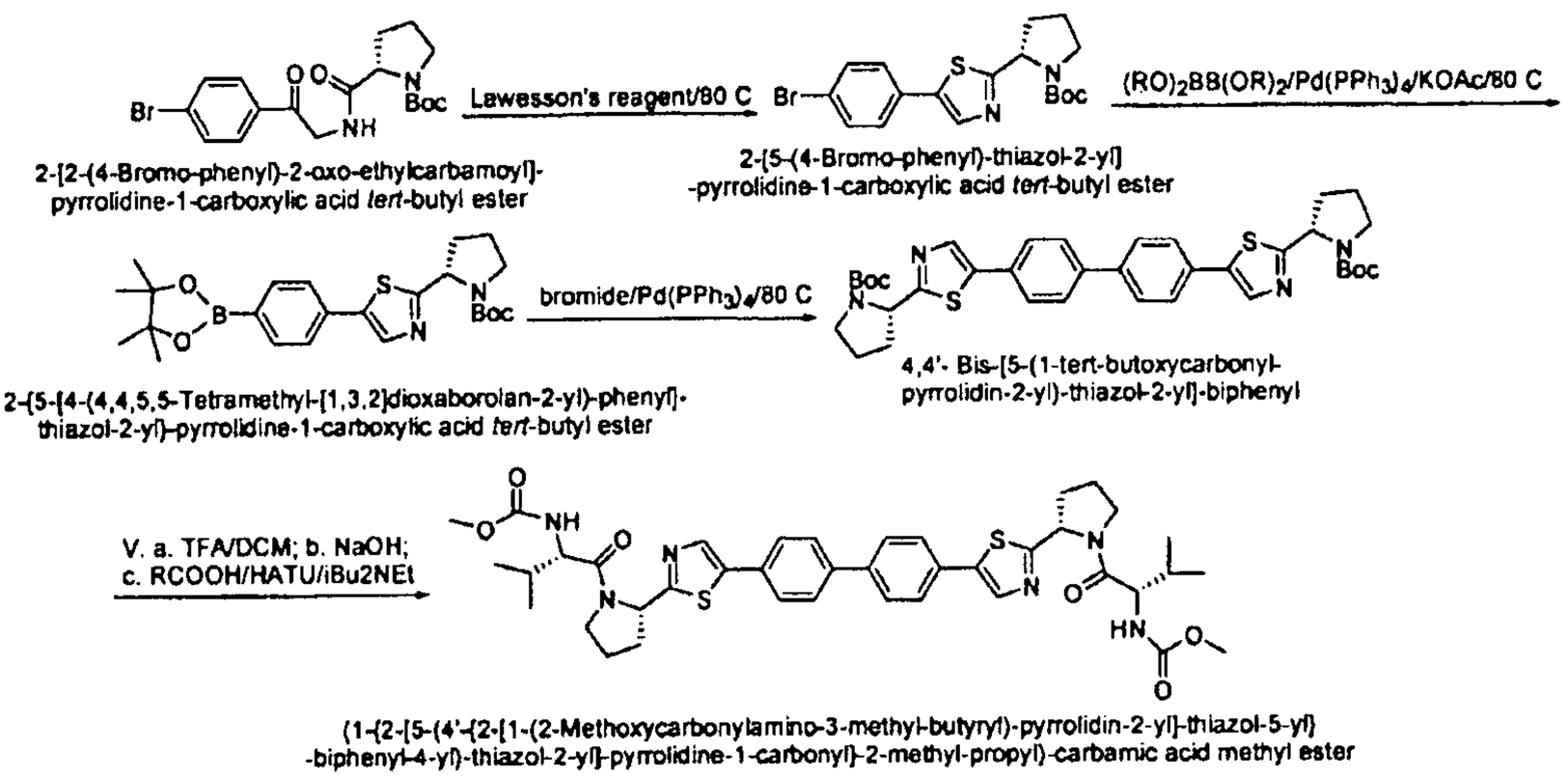
3-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester: To the solution of 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (667 mg, 1.6 mmol) and bis(pinacolato)diboron (813 mg, 3.2 mmol) in 1,4-dioxane (12.5 ml) was added potassium acetate (401 mg, 4.1 mmol), followed by $Pd(PPh_3)_4$ (78 mg). The mixture was heated at 80°C for 12 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 3-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (560 mg). m/z: 466.1 $(M + H)^+$.

4,4'-Bis-[2-(2-*tert*-butoxycarbonyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl: To the solution of 3-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (560 mg, 1.22 mmol) and 3-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (535 mg, 1.28 mmol) in 1,2-dimethoxyether (11 ml) and water (3.5 ml) was added sodium bicarbonate (343 mg, 4 mmol), followed by $Pd(PPh_3)_4$ (55 mg). The mixture was heated at 80°C for 7 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/MeOH) gave 4,4'-bis-[2-(2-*tert*-butoxycarbonyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl (50 mg). m/z: 677.2 $(M + H)^+$.

(1-{3-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 4,4'-Bis-[2-(2-*tert*-butoxycarbonyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl (50 mg, 0.07 mmol) in MeOH (2 ml) was added hydrochloric acid (0.24 ml, 1.48 mmol) The mixture was heated at 50°C for 5 hours, and the solvent and reagent were removed under reduced pressure. The mixture was diluted with acetonitrile and water, and was freezer-dried to give brown powder. m/z: 477.2 (M+1), 239.1 (M+2)/2. To the solution of above powder (29 mg, 0.047 mmol) and MeOCO-Val-OH (20 mg, 0.0.113 mmol) in DMF (1.5 ml) was added HATU (40 mg, 0.10 mmol), followed by diisopropylethylamine (50 ml, 0.28 mmol). The mixture was

stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by HPLC (0.1%TFA/CH_3CN/0.1%TFA/H_2O) gave (1-{3-[5-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (15 mg). m/z: 791.2 (M+1), 396.5 (M+2)/2. ^1H NMR (CD_3OD, 300 MHz) δ 7.92-7.82 (10 H, m), 4.82 (2 H, m), 4.32 (2 H, m), 4.05 (2 H, m), 3.65 (6 H, m), 2.85 (2 H, m), 2.3-1.6 (14 H, m), 1.05-0.85 (12 H, m).

Example AT



2-[5-(4-Bromo-phenyl)-thiazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: The mixture of 2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.0 g, 2.44 mmol) and Lawesson's reagent (1.23 g, 3.0 mmol) in THF (16 ml) was heated at 80°C for 4 hours. The solvent was removed under reduced pressure and the mixture was diluted with EtOAc. The organic phase was washed with saturated sodium bicarbonate, water, and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 2-[5-(4-Bromo-phenyl)-thiazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (655 mg). m/z: 410.7 $(M + H)^+$.

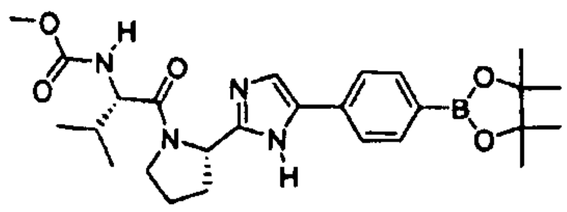
2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To the solution of 2-[5-(4-Bromo-phenyl)-thiazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (380 mg, 0.93 mmol) and bis(pinacolato)diboron (500 mg, 2.0 mmol) in 1,4-dioxane (7 ml) was added potassium acetate (240 mg, 2.1 mmol),

followed by $Pd(PPh_3)_4$ (46 mg). The mixture was heated at 80°C for 20 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (400 mg). m/z: 479.0 $(M + Na)^+$.

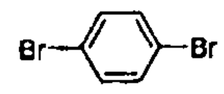
4,4'- Bis-[5-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-thiazol-2-yl]-biphenyl: To the solution of 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (242 mg, 0.53 mmol) and 2-[5-(4-Bromo-phenyl)-thiazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (224 mg, 0.55 mmol) in 1,2-dimethoxyether (4.7 ml) and water (1.5 ml) was added sodium bicarbonate (150 mg, 1.8 mmol), followed by $Pd(PPh_3)_4$ (24 mg). The mixture was heated at 80°C for 7 hours. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/MeOH) gave 4,4'- bis-[5-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-thiazol-2-yl]-biphenyl (270 mg).

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-thiazol-5-yl}-biphenyl-4-yl)-thiazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To the solution of 4,4'- Bis-[5-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-thiazol-2-yl]-biphenyl (270 mg) in DCM (4 ml) was added TFA (2 ml) The mixture was stirred for 4 hours, and the solvent and reagent were removed under reduced pressure. The mixture was diluted DCM, and 1.0 N sodium hydroxide solution was added until pH 11. The organic phase was separated and dried with sodium sulfate. Concentration gave a white solid (182 mg). To the solution of above powder (46 mg, 0.1 mmol) and MeOCO-Val-OH (42 mg, 0.24 mmol) in DMF (3 ml) was added HATU (84 mg, 0.22 mmol), followed by diisopropylethylamine (100 µl, 0.6 mmol). The mixture was stirred for 90 minutes and was diluted with EtOAc. The organic phase was washed with 1 N NaOH solution, water, and brine, and was dried with sodium sulfate. Concentration and purification by flash column chromatography (DCM/EtOAc) gave (1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-thiazol-5-yl}-biphenyl-4-yl)-thiazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (57 mg). m/z: 773.3 (M+1). ^{1}H NMR (DMSO-d6, 300 MHz) δ 8.14 (2 H, s), 7.8-7.6 (8 H, m), 7.37 (2 H, d, J = 8.6 Hz), 5.32 (2 H, m), 4.11 (2 H, m), 3.80 (4 H, m), 3.51 (6 H, s), 2.3-1.9 (10 H, m), 0.90 (12 H, m).

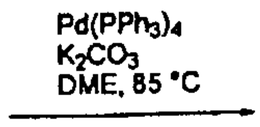
Example AU

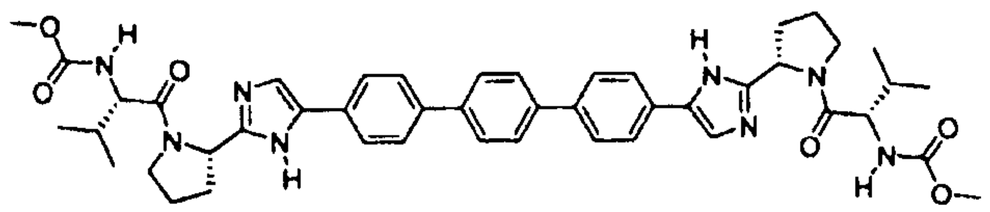


[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester



1,4-dibromo-benzene

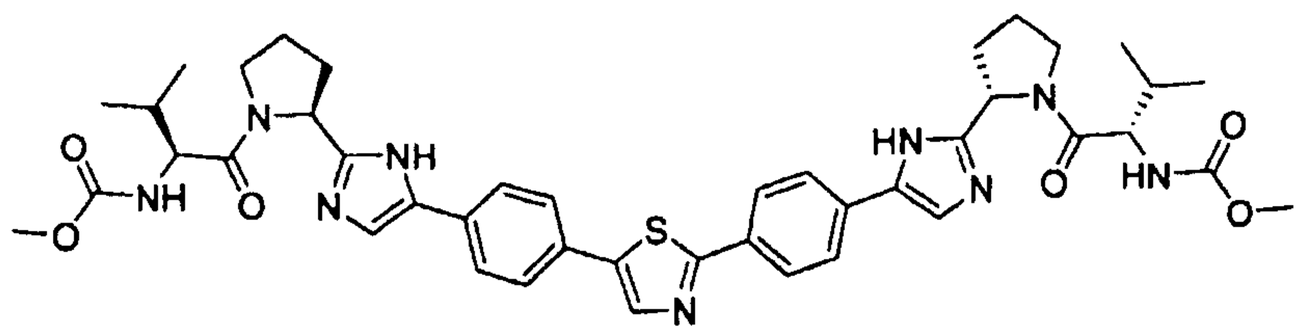




(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-[1,1';4',1"]terphenyl-4"-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-4"-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of [2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (300 mg, 0.60 mmol), 1,4-dibromo-benzene (95 mg, 0.40 mmol) and aqueous K_2CO_3 (800 µl of a 2M solution) in dimethoxyethane (4 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ and the reaction was heated to 85°C overnight. After cooling to room temperature, the reaction was quenched with acetic acid, filtered, and then concentrated. The crude product was purified by reverse phase preparative HPLC (10-85% MeCN-H_2O; 0.1% formic acid modifier) to afford both the monosubstituted product (1-{2-[5-(4'-bromo-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (111 mg, 0.21 mmol, 53% yield) and the desired bis substituted product (1-{2-[5-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-4"-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (24 mg, 0.074 mmol, 19% yield): ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.79 (s, 2H), 7.85-7.62 (m, 12H), 7.53 (s, 2H), 7.29 (d, 2H), 5.02 (m, 2H), 4.07 (t, 2H), 3.82 (m, 4H), 3.54 (s, 6H), 2.15-1.90 (m, 10H), 0.91 (d, 6H), 0.86 (d, 6H). LCMS-ESI$^+$: calc'd for $C_{46}H_{55}N_8O_6$: 815.4 ($M+H^+$); Found: 815.7 $(M + H)^+$.

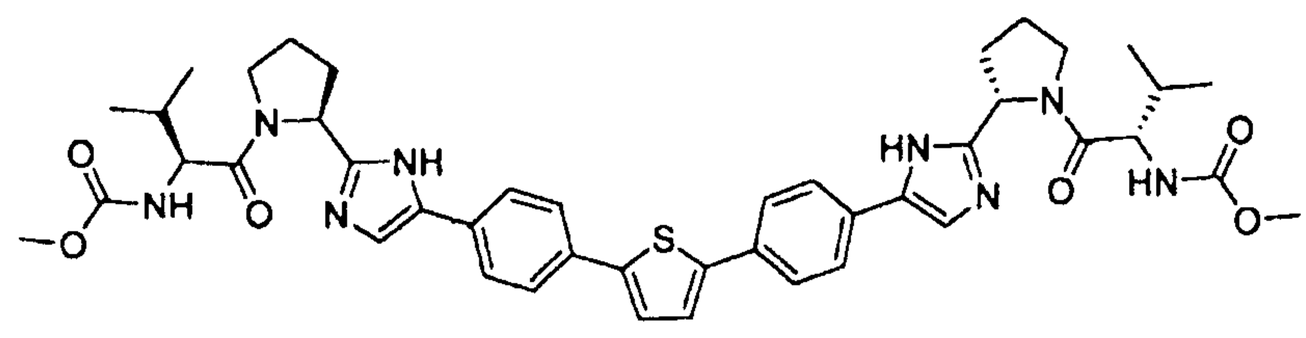
Example AV



{1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-thiazol-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-thiazol-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Title compound was prepared following the method detailed for (1-{2-[5-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-4"-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, substituting 2,5-dibromo-thiazole for 2,6-dibromobenzene: ^{1}H (DMSO-d6): δ = 8.09 (s, 2H), 7.85 (m, 8 H), 7.71 (s, 2H), 7.33 (d, J = 11.2 Hz, 2H), 5.13 (t, J = 8.8 Hz, 2H), 4.11 (t, J = 10.4 Hz, 2H), 3.84 (m, 2H), 3.53 (s, 6H), 2.38 (m, 2H), 2.15 (m, 3H), 2.03 (m, 6H), 0.82 (m 12H). $C_{43}H_{51}N_9O_6S$ calculated 821.4 observed [M + H]$^+$ 822.6; rt = 1.61 min

Example AW

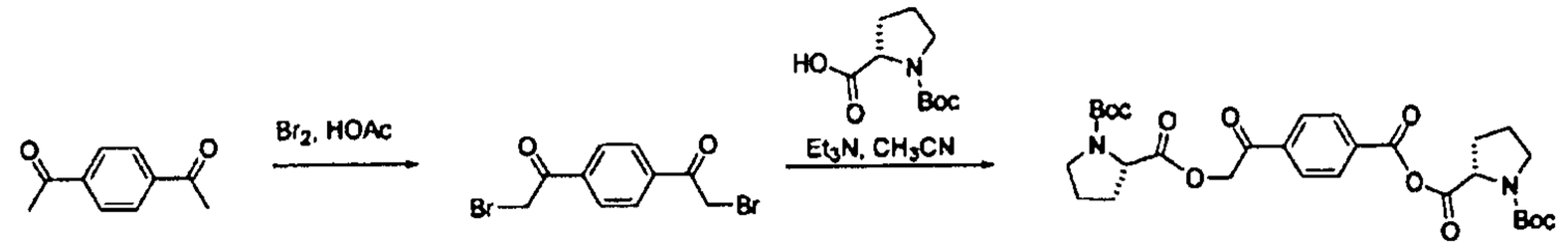


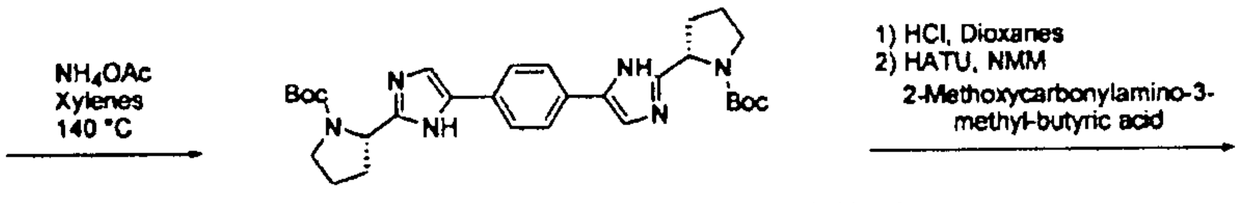
{1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-thiophen-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

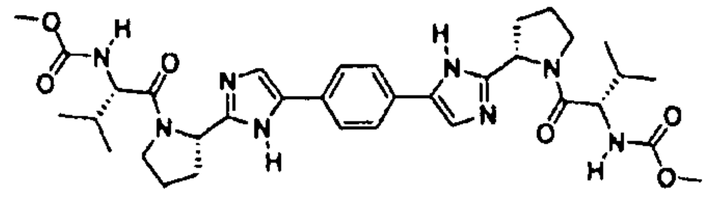
{1-[2-(5-{4-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-thiophen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Title compound was prepared following the method detailed for (1-{2-[5-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[1,1';4',1"]terphenyl-4"-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, substituting 2,5-dibromo-thiophene for 2,6-dibromobenzene: ^{1}H (DMSO-d6): δ = 8.47 (s, 2H), 8.09 (m, 4H), 7.89 (m, 6H), 7.33 (d J =

10.4 Hz, 2H), 5.12 (t, J = 10.0 ZH, 2H), 4.10 (t, J = 11.2 Hz, 2H), 3.82 (m, 2H), 3.61 (m, 4H), 2.37 (m, 2H), 2.10 (m, 9H), 0.822 (m, 12H). $C_{44}H_{52}N_8O_6S$ calculated 820.4 observed $[M + 1]^+$ 821.8; rt = 1.66 min

Example AX







(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-Bromo-1-[4-(2-bromo-acetyl)-phenyl]-ethanone: To a solution of Br_2 (1.27 mL, 24.66 mmol) in HOAc (12 mL) was added 1,4-diacetylbenzene (2.00 g, 12.33 mmol). After stirring for 2 h, the reaction was diluted with water and the precipitate collected by filtration. The crude product was then recrystallized from toluene to afford 2-bromo-1-[4-(2-bromo-acetyl)-phenyl]-ethanone (2.87 g, 8.97 mmol, 73% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 8.13 (s, 4H), 5.01 (s, 4H).

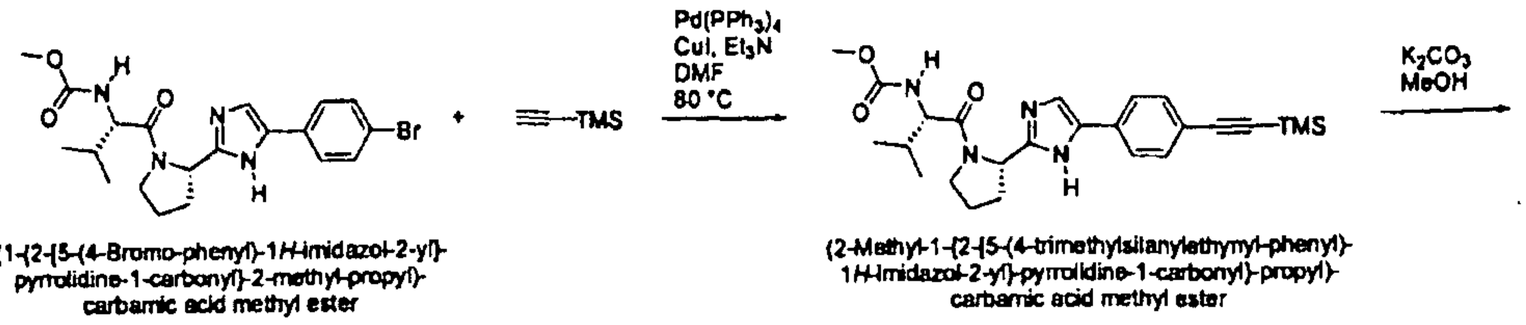
Pyrrolidine-1,2-dicarboxylic acid 2-{2-[4-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxycarbonyl)-phenyl]-2-oxo-ethyl} ester 1-*tert*-butyl ester: A suspension of 2-bromo-1-[4-(2-bromo-acetyl)-phenyl]-ethanone (2.87 g, 8.97 mmol) in CH_3CN (15 mL) was added dropwise to a solution of pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (3.85 g, 17.9 mmol) and triethylamine (2.49 mL, 17.9 mmol) in CH_3CN (30 mL). The reaction was stirred for 4 hours then concentrated and purified by silica gel chromatography (20-60% EtOAc-hexanes gradient) to afford pyrrolidine-1,2-dicarboxylic acid 2-{2-[4-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxycarbonyl)-phenyl]-2-oxo-ethyl} ester 1-*tert*-butyl ester (4.91 g, 8.34

mmol, 93% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 8.11 (s, 4H), 5.69-5.50 (m, 4H), 4.37-4.32 (m, 2H), 3.42-3.29 (m, 6H), 2.34-2.24 (m, 2H), 2.14-2.10 (m, 2H), 1.92-1.82 (m, 4H), 1.40 (s, 9H), 1.37 (s, 9H).

1-[2-(5-{4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone: A solution of pyrrolidine-1,2-dicarboxylic acid 2-{2-[4-(1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyloxycarbonyl)-phenyl]-2-oxo-ethyl} ester 1-*tert*-butyl ester (4.91 g, 8.35 mmol) and ammonium acetate (6.44 g, 8.36 mmol) in xylenes (42 mL) was heated to 140°C overnight in a sealed pressure flask. After cooling to room temperature, the reaction was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 then concentrated. The crude material was purified by silica gel chromatography (3-10% MeOH- CH_2Cl_2 gradient) to afford 1-[2-(5-{4-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone (1.58 g, 2.87 mmol, 34% yield). LCMS-ESI$^+$: calc'd for $C_{30}H_{41}N_6O_4$: 549.3 ($M+H^+$); Found: 549.3 ($M+H^+$).

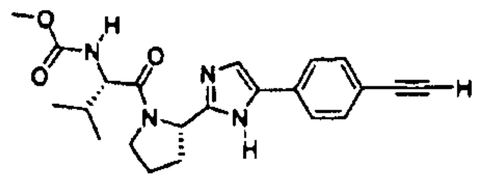
(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To 1-[2-(5-{4-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone (500 mg, 0.91 mmol) in dioxanes (5 mL) was added 4N HCl in dioxanes (3 mL). The suspension was stirred for 2 hours then concentrated to afford the HCl salt of the crude amine (530 mg). To a portion of the crude amine (200 mg, 0.41 mmol) in DMF (2 mL) was added *N*-methylmorpholine (270 µl, 2.44 mmol). After all material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (144 mg, 0.82 mmol) and HATU (312 mg, 0.82 mmol) were added. After stirring for 1 hour the reaction was quenched with AcOH then purified by reverse phase preparative HPLC (10-85% MeCN-H_2O; 0.1% formic acid modifier) to afford (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (56 mg, 0.085 mmol, 21% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.68 (s, 2H), 7.62 (m, 4H), 7.41 (s, 2H), 7.27 (d, 2H), 5.07-5.05 (m, 2H), 4.06 (t, 2H), 3.80 (m, 4H), 3.54 (s, 6H), 2.13 (m, 4H), 1.95 (m, 6H), 0.90 (d, 6H), 0.85 (d, 6H). LCMS-ESI$^+$: calc'd for $C_{34}H_{47}N_8O_6$: 663.4 ($M+H^+$); Found: 663.1 ($M+H^+$).

Example AY



(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

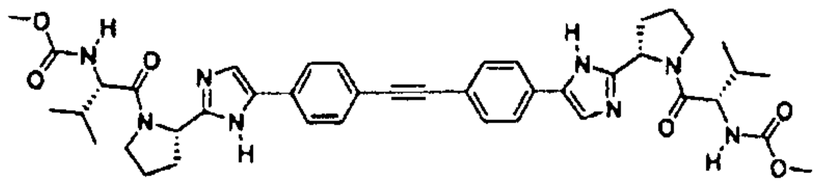
(2-Methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester



(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

$Pd(PPh_3)_4$, CuI, Et_3N,
(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

DMF, 80 °C



[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

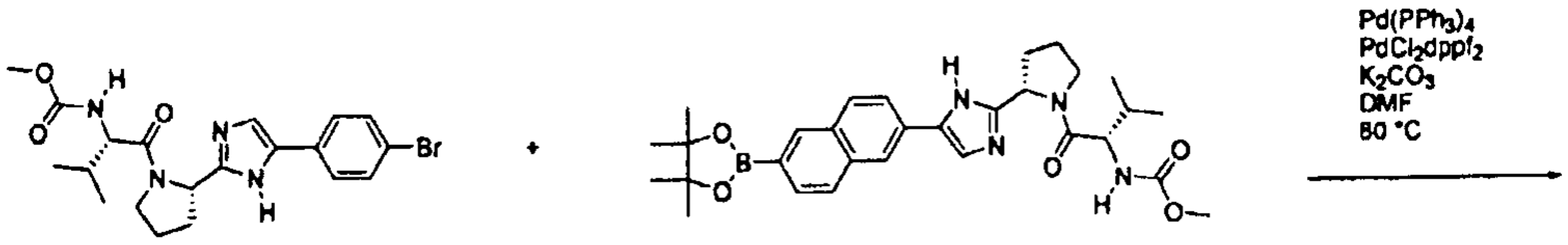
(2-Methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester: A solution of (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (5.00 g, 11.1 mmol), TMS-acetylene (7.90 mL, 55.5 mmol) and triethylamine (4.64 mL, 33.3 mmol) in DMF (56 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (1.28 g, 1.11 mmol) and CuI (106 mg, 0.56 mmol). The pressure flask was sealed then heated at 80°C overnight. After cooling to room temperature, the reaction was concentrated then diluted with EtOAc and washed with water. The aqueous phase was back-extracted two times then the organic phases were combined and dried over Na_2SO_4. After concentration, the crude material was purified by silica gel chromatography (10-80% EtOAc-hexanes gradient) to afford (2-methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (3.08 g, 6.60 mmol, 59% yield). LCMS-ESI$^+$: calc'd for $C_{25}H_{35}N_4O_3Si$: 467.3 ($M+H^+$); Found: 467.1 ($M+H^+$).

(1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To (2-methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (3.08 g, 6.60 mmol) in MeOH was added K_2CO_3 (1.82 g, 13.2 mmol). After stirring for 5 h, the reaction was filtered

then concentrated. The residue was diluted with EtOAc then washed with H_2O. The aqueous phase was back-extracted with EtOAc two times then the organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified by silica gel chromatography (5-10% MeOH- CH_2Cl_2 gradient) to afford (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.62 g, 6.6 mmol, quantitative yield). LCMS-ESI$^+$: calc'd for $C_{22}H_{27}N_4O_3$: 395.2 ($M+H^+$); Found: 395.2 ($M+H^+$).

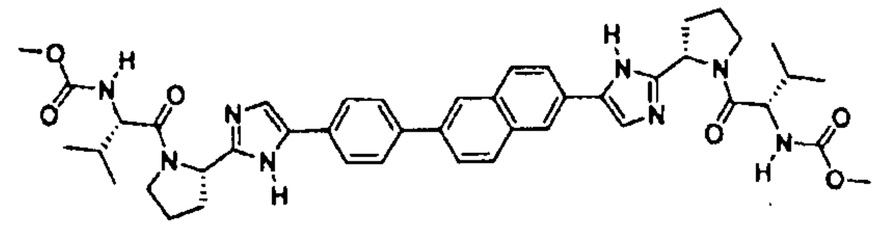
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (947 mg, 2.11 mmol), (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.00 g, 2.53 mmol), and triethylamine (882 µl, 6.33 mmol) in DMF (13 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (244 mg, 0.21 mmol) and CuI (40 mg, 0.21 mmol). The pressure flask was sealed then heated at 80°C overnight. After cooling to room temperature, the reaction was concentrated then diluted with EtOAc and washed with water. The aqueous phase was back-extracted two times then the organic phases were combined and dried over Na_2SO_4. After concentration, the crude material was purified by silica gel chromatography (0-20% MeOH-EtOAc gradient) then reverse phase preparative HPLC (10-85% MeCN-H_2O; 0.1% formic acid modifier) to afford [1-(2-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (600 mg, 1.00 mmol, 47% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.84 (s, 2H), 7.75 (d, 4H), (7.56 (s, 2H), 7.47 (d, 4H), 7.28 (d, 2H), 5.06 (m, 2H), 4.06-4.04 (m, 2H), 3.80 (m, 4H), 3.54 (s, 6H), 2.14 (m, 4H) 2.00-1.90 (m, 6H), 0.89 (d, 6H), 0.84 (d, 6H). LCMS-ESI$^+$: calc'd for $C_{42}H_{51}N_8O_6$: 763.4 ($M+H^+$); Found: 763.4 ($M+H^+$).

Example AZ



(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

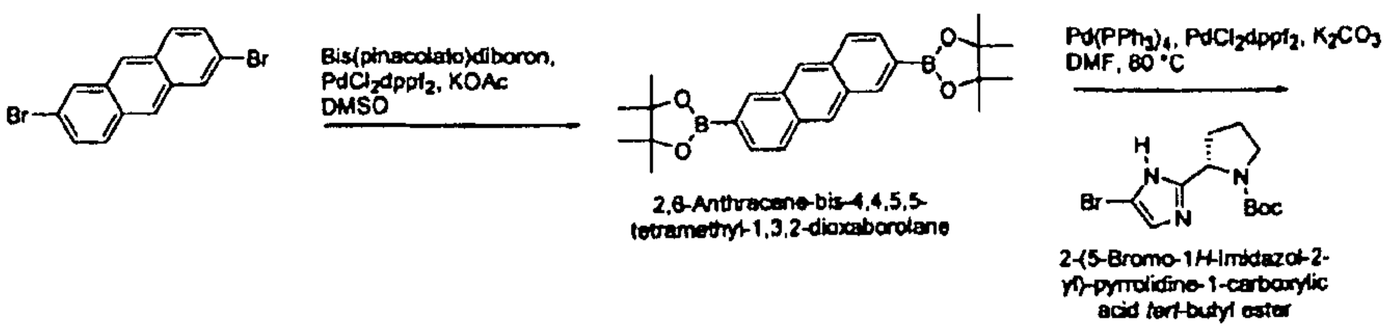
[2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

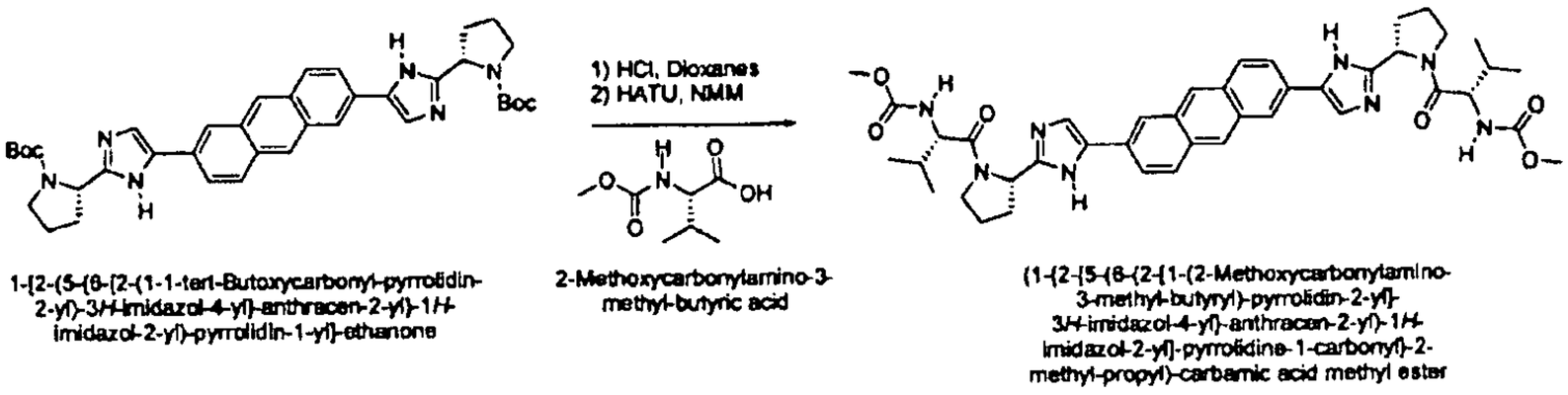


[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (244 mg, 0.54 mmol), [2-methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (270 mg, 0.49 mmol) and aqueous K_2CO_3 (490 µl of a 2M solution, 0.98 mmol) in toluene (3 mL) and DMF (1 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (31 mg, 0.027 mmol) and $PdCl_2(dppf)$ (20 mg, 0.027 mmol) then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was quenched with acetic acid, filtered, and then concentrated. The crude product was purified by reverse phase preparative HPLC (10-85% MeCN-H_2O; 0.1% formic acid modifier) to afford [1-(2-{5-[6-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (149 mg, 0.19 mmol, 35% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.82 (s, 1H), 11.79 (s, 1H), 8.21-8.16 (m, 2H), 7.92-7.79 (m, 8H), 7.62 (s, 1H), 7.54 (s, 1H), 7.31-7.29 (m, 2H), 5.10 (m, 2H), 4.09-4.07 (m, 2H), 3.82 (m, 4H), 3.54 (s, 6H), 2.20-1.85 (m, 10H), 0.95-0.86 (m, 12H). LCMS-ESI$^+$: calc'd for $C_{44}H_{53}N_8O_6$: 789.4 ($M+H^+$); Found: 789.2 ($M+H^+$).

Example AA1





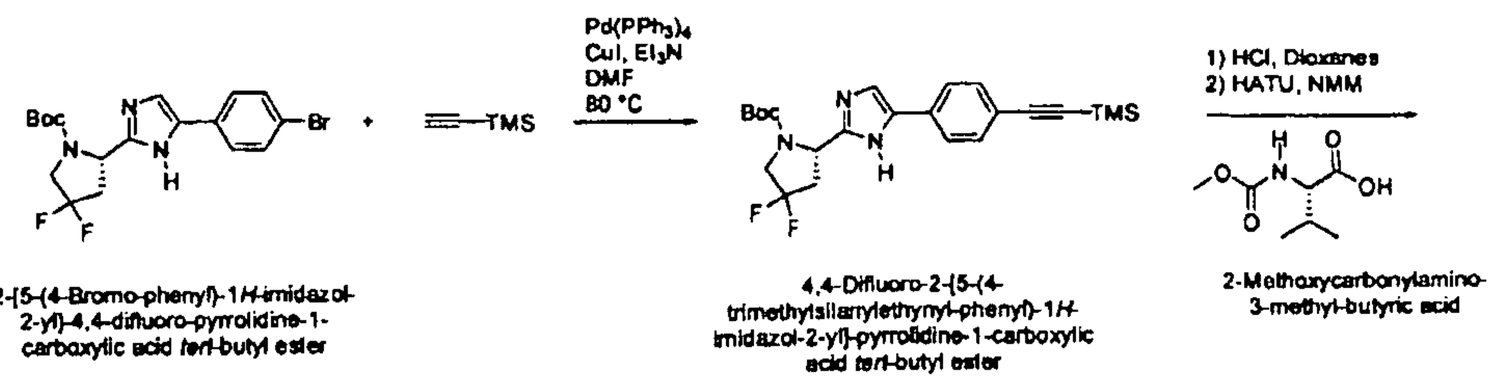
2,6-Anthracene-bis-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: A mixture of 2,6-dibromoanthracene (500 mg, 1.49 mmol), bis(pinacolato)diboron (756 mg, 2.98 mmol)and KOAc (585 mg, 5.96 mmol) in DMSO (10 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $PdCl_2$(dppf) (55 mg, 0.075 mmol) then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was poured into H_2O and extracted with CH_2Cl_2. The organic phase was collected then washed with H_2O and brine. After drying over Na_2SO_4, the organic phase was concentrated then purified by silica gel chromatography (30-100% CH_2Cl_2-hexanes gradient) to afford 2,6-anthracene-bis-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (241 mg, 0.56 mmol, 38% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 8.57 (s, 2H), 8.46 (s, 2H), 8.00 (d, 2H), 7.79 (d, 2H).

1-[2-(5-{6-[2-(1-1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-anthracen-2-yl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone: A solution of 2,6-anthracene-bis-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (241 mg, 0.56 mmol), 2-(5-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (531 mg, 1.68 mmol) and aq K_2CO_3 (1.12 mL of a 2M solution, 2.24 mmol) in toluene (6 mL) and DMF (1 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) and $PdCl_2$(dppf) (21 mg, 0.028 mmol) then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was concentrated. The crude material was diluted with EtOAc then washed with saturated $NaHCO_3$. The aqueous phase was back-extracted two times then the organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by reverse phase preparative HPLC (20-80% MeCN-H_2O; 0.1% formic acid modifier)

to afford 1-[2-(5-{6-[2-(1-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-anthracen-2-yl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone (117 mg, 0.18 mmol, 32% yield). LCMS-ESI$^+$: calc'd for $C_{38}H_{45}N_6O_4$: 649.4 ($M+H^+$); Found: 648.9 ($M+H^+$).

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-anthracen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To 1-[2-(5-{6-[2-(1-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-anthracen-2-yl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethanone (117 mg, 0.18 mmol) in dioxanes (5 mL) was added 4N HCl in dioxanes (180 µl, 0.72 mmol). The suspension overnight then concentrated to afford the HCl salt of the crude amine. To the amine in DMF (3 mL) was added *N*-methylmorpholine (119 µl, 1.08 mmol). After all the material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (76 mg, 0.43 mmol) and HATU (151 mg, 0.40 mmol) were added. After stirring overnight the reaction was quenched with AcOH then purified by reverse phase preparative HPLC (15-70% MeCN-H_2O; 0.1% formic acid modifier) to afford (1-{2-[5-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-anthracen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (46 mg, 0.098 mmol, 54% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.84 (s, 2H), 8.38 (s, 2H), 8.31 (s, 2H), 8.00 (d, 2H), 7.86 (d, 2H), 7.62 (s, 2H), 7.30 (d, 2H), 5.12 (m, 2H), 4.10 (m, 2H), 3.84 (m, 4H), 3.55 (s, 6H), 2.18-1.95 (m, 10 H), 0.96 (d, 6H), 0.88 (d, 6H). LCMS-ESI$^+$: calc'd for $C_{42}H_{51}N_8O_6$: 763.4 ($M+H^+$); Found: 763.1 ($M+H^+$).

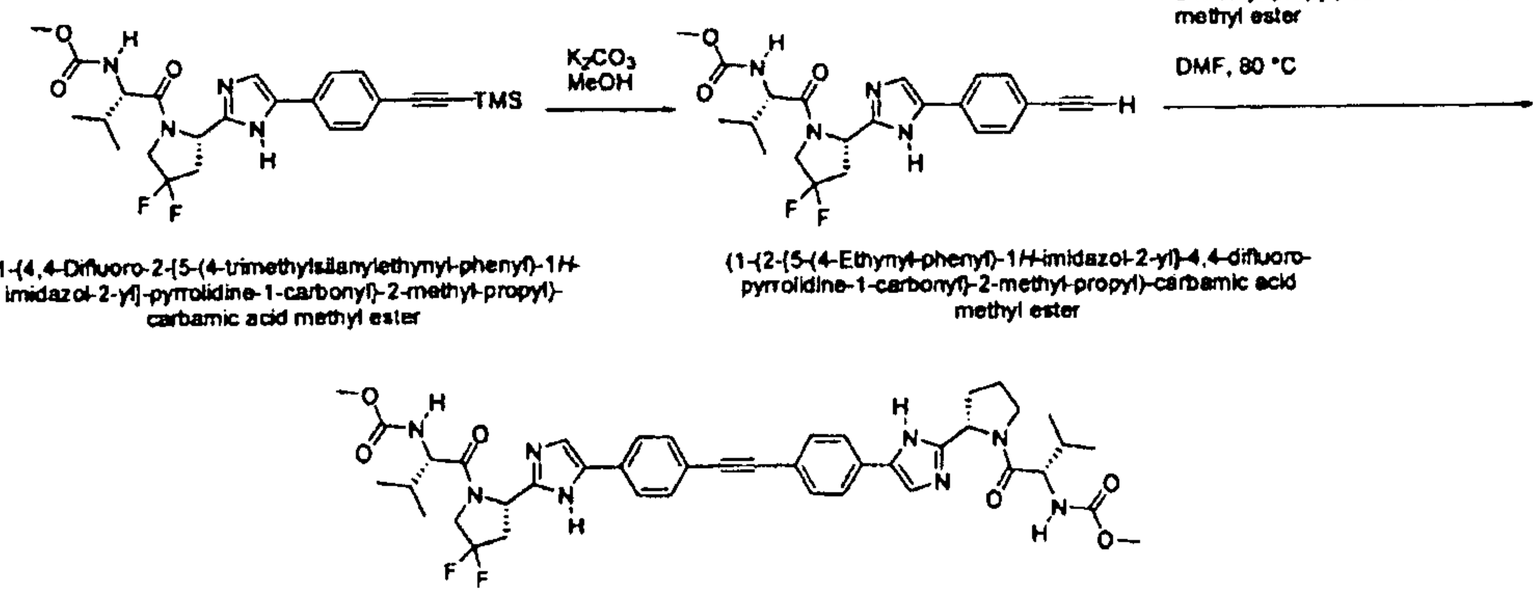
Example AB1



2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester

4,4-Difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



(1-{4,4-Difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[1-(2-{5-[4-(4-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4,4-Difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A solution of 2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester (700 mg, 1.56 mmol), TMS-acetylene (1.11 mL, 7.79 mmol) and triethylamine (1.1 mL, 7.8 mmol) in DMF (8 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (180 mg, 0.16 mmol) and CuI (14.8 mg, 0.078 mmol). The pressure flask was sealed then heated at 80°C overnight. After cooling to room temperature, the reaction was concentrated then diluted with EtOAc and washed with water. The aqueous phase was back-extracted two times then the organic phases were combined and dried over Na_2SO_4. After concentration, the crude material was purified by silica gel chromatography (10-50% EtOAc-hexanes gradient) to afford 4,4-difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (547 g, 1.23 mmol, 79% yield). LCMS-ESI$^+$: calc'd for $C_{23}H_{30}F_2N_3O_2Si$: 446.2 ($M+H^+$); Found: 445.8 ($M+H^+$).

(1-{4,4-Difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To 4,4-difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

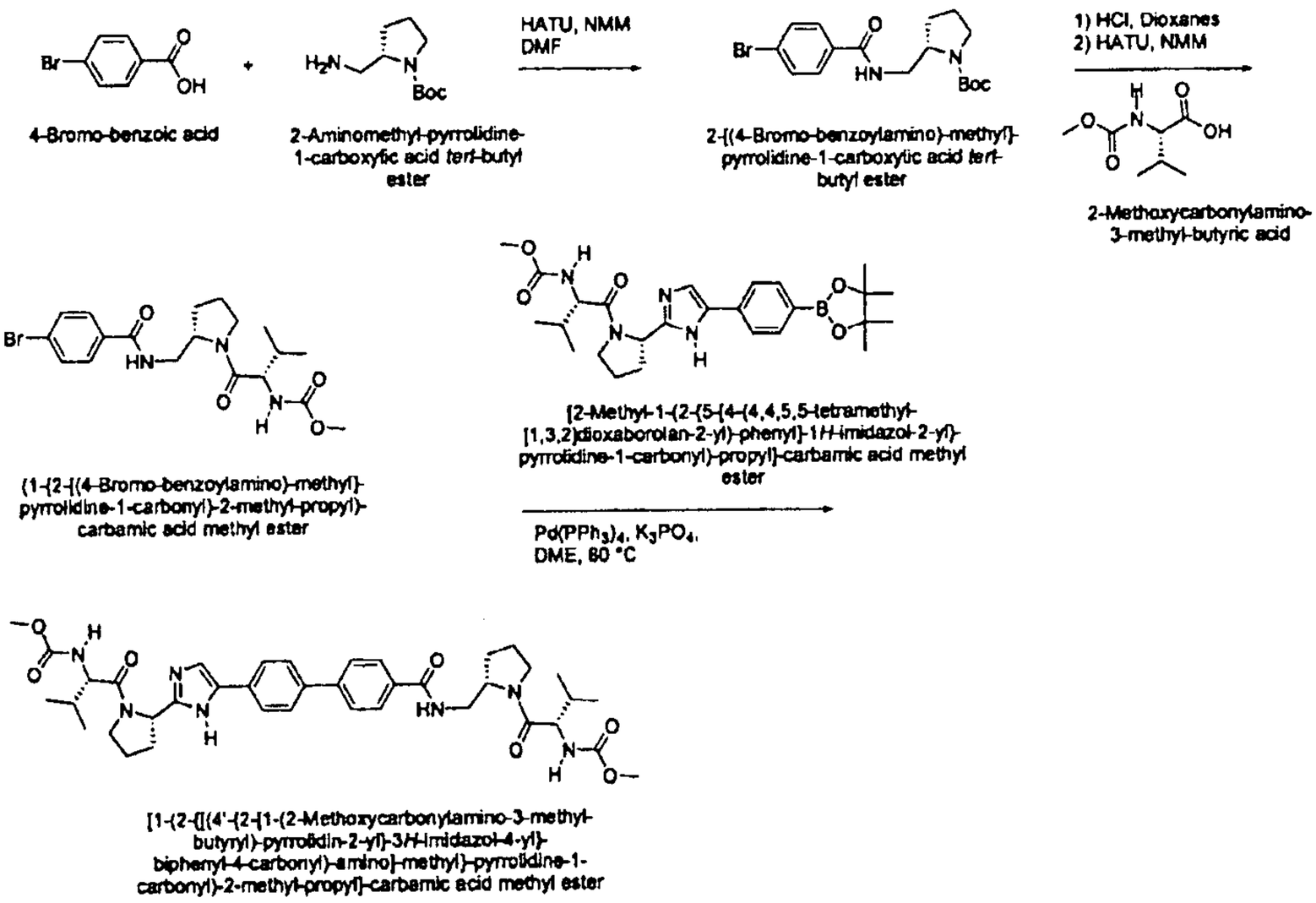
(547 mg, 1.23 mmol) in dioxanes (6 mL) was added 4N HCl in dioxanes (1.65 mL, 6.6 mmol). The suspension was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the amine in DMF (5 mL) was added *N*-methylmorpholine (406 µl, 3.69 mmol). After all the material dissolved, 2-methoxycarbonylamino-3-methyl-butyric acid (236 mg, 1.35 mmol) and HATU (513 mg, 1.35 mmol) were added. After stirring for 2 hours the reaction was concentrated then diluted with EtOAc and washed with H_2O. The aqueous phase was back-extracted two times then the organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (20-60% EtOAc-hexanes gradient) to afford (1-{4,4-difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (412 mg, 0.82 mmol, 67% yield). LCMS-ESI$^+$: calc'd for $C_{25}H_{33}F_2N_4O_3Si$: 503.2 ($M+H^+$); Found: 503.2 ($M+H^+$).

(1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-4,4-difluoro-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To (1-{4,4-difluoro-2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (412 mg, 0.82 mmol) in MeOH (8 mL) was added K_2CO_3 (227 mg, 1.64 mmol). After stirring for 5 h, the reaction was filtered then concentrated. The residue was diluted with EtOAc then washed with H_2O. The aqueous phase was back-extracted with EtOAc two times then the organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified by silica gel chromatography (20-80% EtOAc-hexanes gradient) to afford (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (371 mg, 0.82 mmol, quantitative yield). LCMS-ESI$^+$: calc'd for $C_{22}H_{25}F_2N_4O_3$: 431.2 ($M+H^+$); Found: 431.1 ($M+H^+$).

[1-(2-{5-[4-(4-{2-[4,4-Difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (400 mg, 0.89 mmol), (1-{2-[5-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (371 mg, 0.89 mmol), and triethylamine (372 µl, 2.67 mmol) in DMF (8 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (103 mg, 0.089 mmol) and CuI (17 mg, 0.089 mmol). The pressure flask was sealed then heated at 80°C overnight. After cooling to room temperature, the reaction was quenched with AcOH then purified by reverse phase preparative

HPLC (10-70% MeCN-H_2O; 0.1% formic acid modifier) then silica gel chromatography (0-10% MeOH-EtOAc gradient) to afford [1-(2-{5-[4-(4-{2-[4,4-difluoro-1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (231 mg, 0.29 mmol, 33% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 12.04 (s, 1H), 11.84 (s, 1H), 7.78-7.76 (m, 4H), 7.61 (s, 1H), 7.56 (s, 1H), 7.50-7.48 (m, 6H), 7.28 (d, 2H), 5.29 (t, 1H), 5.07 (m, 1H), 4.52 (m, 1H), 4.24-4.14 (m, 1H), 4.06 (t, 1H), 3.93 (t, 1H), 3.80 (m, 2H), 3.55 (s, 3H), 3.54 (s, 3H), 2.93 (m, 1H), 2.77 (m, 1H), 2.14-1.88 (m, 6H), 0.90-0.84 (m, 12H). LCMS-ESI$^+$: calc'd for $C_{42}H_{49}N_8O_6$: 799.4 ($M+H^+$); Found: 799.0 ($M+H^+$).

Example AC1



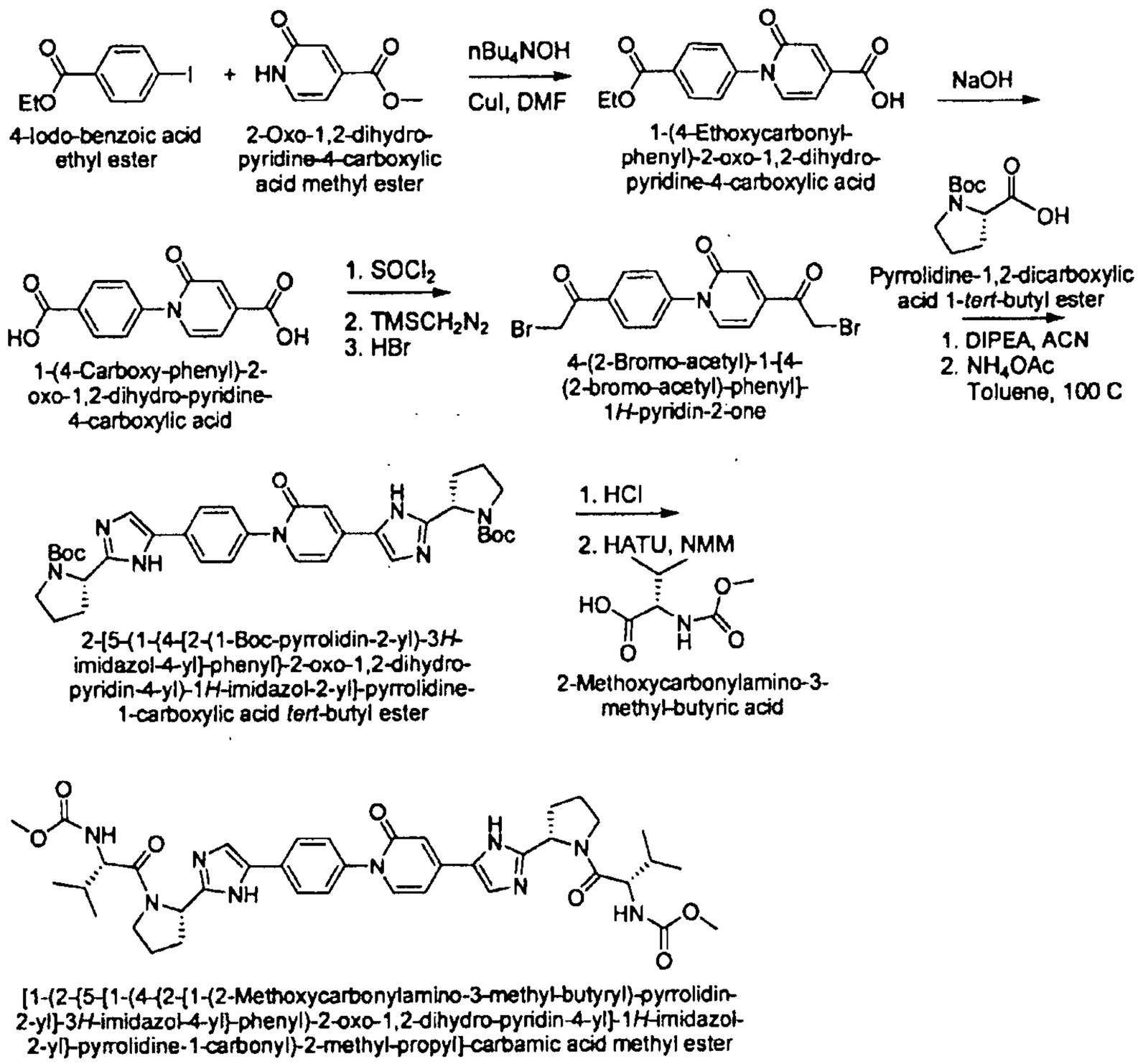
2-[(4-Bromo-benzoylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To 2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.00 g, 4.97 mmol) and 4-bromo-benzoic acid (996 mg, 4.97 mmol) in DMF (25 mL) was added *N*-methylmorpholine (655 µl, 5.96 mmol) and HATU (1.89 g, 4.97 mmol). After stirring for 3 hours the reaction was concentrated then diluted with EtOAc and washed with 1N HCl, saturated $NaHCO_3$, and brine. The organic phase was then dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (20-50% EtOAc-hexanes gradient) to afford 2-[(4-bromo-benzoylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.91g, 4.97 mmol,

quantitative yield). LCMS-ESI$^+$: calc'd for $C_{17}H_{24}BrN_2O_3$: 383.1 ($M+H^+$); Found: 383.6 ($M+H^+$).

(1-{2-[(4-Bromo-benzoylamino)-methyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: To 2-[(4-bromo-benzoylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.00 g, 2.61 mmol) in dioxanes (15 mL) was added 4N HCl in dioxanes (5 mL, 20 mmol). The solution was stirred overnight then concentrated to afford the HCl salt of the crude amine. To the amine in DMF (13 mL) was added *N*-methylmorpholine (574 µl, 5.22 mmol), 2-methoxycarbonylamino-3-methyl-butyric acid (457 mg, 2.61) and HATU (992 mg, 2.61 mmol). After stirring for 2 hours the reaction was concentrated then diluted with EtOAc and washed with 1N HCl, saturated $NaHCO_3$, and brine. The crude product was purified by silica gel chromatography (100% EtOAc) to afford (1-{2-[(4-bromo-benzoylamino)-methyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (950 mg, 2.18 mmol, 84% yield). LCMS-ESI$^+$: calc'd for $C_{19}H_{27}BrN_3O_4$: 440.1 ($M+H^+$); Found: 440.2 ($M+H^+$).

[1-(2-{[(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of (1-{2-[(4-bromo-benzoylamino)-methyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (104 mg, 0.24 mmol), [2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (117 mg, 0.24 mmol) and aq K_3PO_4 (480 µl of a 2M solution, 0.96 mmol) in DME (3 mL) was degassed with N_2 gas for 20 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (13.9 mg, 0.012 mmol) then the reaction was heated to 80°C overnight. After cooling to room temperature, the reaction was concentrated and purified by reverse phase preparative HPLC (15-60% MeCN-H_2O; 0.1% formic acid modifier) to afford [1-(2-{[(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (26 mg, 0.036 mmol, 15% yield). ^{1}H-NMR: 400 MHz, (DMSO-d_6) δ: 11.8 (s, 1H), 8.61 (m, 1H), 7.94-7.73 (m, 9H), 7.34 (d, 1H), 7.29 (d, 1H), 5.08 (m, 1H), 4.23 (t, 1H), 4.30 (m, 1H), 4.07 (t, 1H), 4.01 (t, 1H), 4.07-4.01 (m, 1H), 3.18 (m, 2H), 3.73-3.70 (m, 1H), 3.61 (m, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 2.16-1.81 (m, 10H), 0.90-0.84 (m, 12H). LCMS-ESI$^+$: calc'd for $C_{39}H_{52}N_7O_7$: 730.4 ($M+H^+$); Found: 730.1 ($M+H^+$).

Example AD1



1-(4-Ethoxycarbonyl-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid: A mixture of 2-oxo-1,2-dihydro-pyridine-4-carboxylic acid methyl ester (2.00 g), 1.0M tetrabutylammonium hydroxide in H_2O (13 ml) and toluene (50 mL) was stirred for 2 hours at ambient temperature. Mixture was concentrated and co-evaporated with toluene (3 x 100 mL) and dried under high vacuum. To the residue was added 4-Iodo-benzoic acid ethyl ester (2.40 g) and co-evaporated with toluene (2 x 20 mL). Copper iodide (0.829 g) and DMF (10 mL) were added and reaction mixture heated at 95°C for 18 hours, protected from light. To the cooled reaction mixture was added 3N ammonium hydroxide and extracted with dichloromethane (4x). Organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 5% methanol/dichloromethane + 1% triethylamine) to give 1-(4-Ethoxycarbonyl-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (1.155 g) as the triethylammonium salt: LCMS-ESI$^-$: calc'd for $C_{15}H_{12}NO_5$: 286.27 ($M-H^+$); Found: 286.1 ($M-H^+$).

1-(4-Carboxy-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid: To a solution of 1-(4-Ethoxycarbonyl-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (1.155 g) in THF (20 mL) at 0°C was added 5 M sodium hydroxide (1.19 mL) and mixture stirred overnight at ambient temperature. Reaction mixture was acidified to pH 1 with concentrated HCl, producing a precipitate. The solid was collected by filtration, washed with H_2O and dried under high vacuum to give 1-(4-Carboxy-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (0.7196 g). LCMS-ESI$^-$: calc'd for $C_{13}H_8NO_5$: 258.2 ($M-H^+$); Found: 258.1 ($M-H^+$).

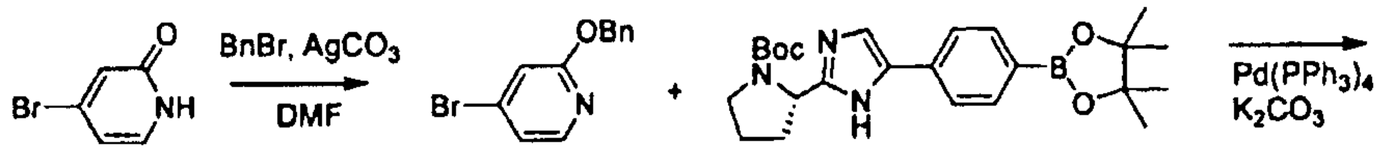
4-(2-Bromo-acetyl)-1-[4-(2-bromo-acetyl)-phenyl]-1H-pyridin-2-one: A mixture of 1-(4-Carboxy-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (0.696 g) and oxalyl chloride (2.34 mL) in dichloromethane (20 mL) containing DMF (4 drops) was stirred at ambient temperature for 4 hours, then concentrated and co-evaporated with toluene (3x) and dried under high vacuum. The resulting residue was suspended in dichloromethane (10 mL) at 0°C and treated with 2.0 M trimethylsilyldiazomethane in ether (4.0 mL) over 15 minutes to give a brown mixture. Reaction mixture was warmed to ambient temperature overnight and then concentrated. The resulting brown solid was suspended in ethyl acetate (10 mL) and cooled to 0°C. 5.7 M HBr in acetic acid was added over 5 minutes and reaction mixture was warmed to ambient temperature over 1 hour. Solid sodium bicarbonate (0.3 g) was added and stirred for 30 minutes. H_2O was added giving a biphasic mixture with a brown precipitate. The solid was removed by filtration and filtrate was extracted with dichloromethane (2x), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 30 to 80% ethyl acetate/hexanes) to give 4-(2-Bromo-acetyl)-1-[4-(2-bromo-acetyl)-phenyl]-1H-pyridin-2-one (0.555 g). LCMS-ESI$^+$: calc'd for $C_{15}H_{12}Br_2NO_3$: 414.06 ($M+H^+$); Found: 411.9, 413.9, 415.8 ($M+H^+$).

2-[5-(1-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-2-oxo-1,2-dihydro-pyridin-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 4-(2-Bromo-acetyl)-1-[4-(2-bromo-acetyl)-phenyl]-1H-pyridin-2-one (0.555 g) Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.6 g) and diisopropylethylamine (0.48 mL) in acetonitrile (10.8 mL) was stirred for 2 hours at ambient temperature. Reaction mixture was diluted with ethyl acetate, washed with brine and back-extracted with ethyl acetate. The combined organic layer was washed with diluted brine (2x), dried ($MgSO_4$) and concentrated to give a brown oil (1.034 g). LCMS-ESI$^-$: calc'd for $C_{35}H_{42}N_3O_{11}$: 680.73 ($M-H^+$); Found: 680.3 ($M-H^+$). Residue was dissolved in toluene (5.5 mL) and ammonium acetate (2.066 g) was added. The reaction mixture was stirred at 100°C for 2 hours and then concentrated. The residue was

partitioned between dichloromethane and dilute sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane containing methanol (3x) and the combined organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 15% methanol/dichloromethane) to give 2-[5-(1-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-2-oxo-1,2-dihydro-pyridin-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.098 g). LCMS-ESI$^+$: calc'd for $C_{35}H_{44}N_7O_5$: 642.76 ($M+H^+$); Found: 642.1 ($M+H^+$).

[1-(2-{5-[1-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-[5-(1-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-2-oxo-1,2-dihydro-pyridin-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.098 g) in dichloromethane (6.0 mL) was treated with 4N HCl in dioxane (2.0 mL) for 90 minutes at ambient temperature. Reaction mixture was concentrated and dried overnight under vacuum. Residue was dissolved in DMF (2.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.055 g), 4-methylmorpholine (0.099 mL), followed by HATU (0.116 g). Reaction mixture was stirred for 90 minutes at ambient temperature and then concentrated. Residue was dissolved in dichloromethane and washed with dilute sodium bicarbonate solution. Aqueous layer back-extracted with dichloromethane and combined organic layer dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H2O + 0.1% TFA). Product was lyophilized to give [1-(2-{5-[1-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.037 g): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.14 (s, 2H), 7.88 (d, J=8.4, 2H), 7.79 (d, J=7.2, 1H), 7.63 (d, J=8.4, 2H), 7.35-7.30 (m, 2H), 6.88 (s, H), 6.74 (d, J=8.4, 1H), 5.13-5.10 (m, 2H), 3.90-3.80 (m, 8H), 3.53 (s, 6H), 2.40-2.01 (m, 10H), 0.83-0.75 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{39}H_{50}N_9O_7$: 756.86 ($M+H^+$); Found: 756.3 ($M+H^+$).

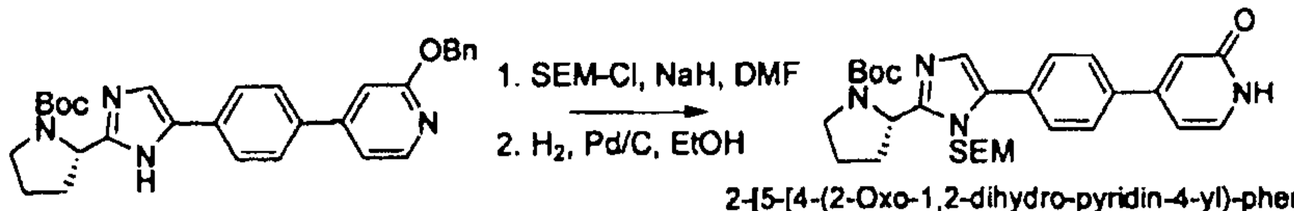
Example AE1



4-Bromo-1*H*-pyridin-2-one

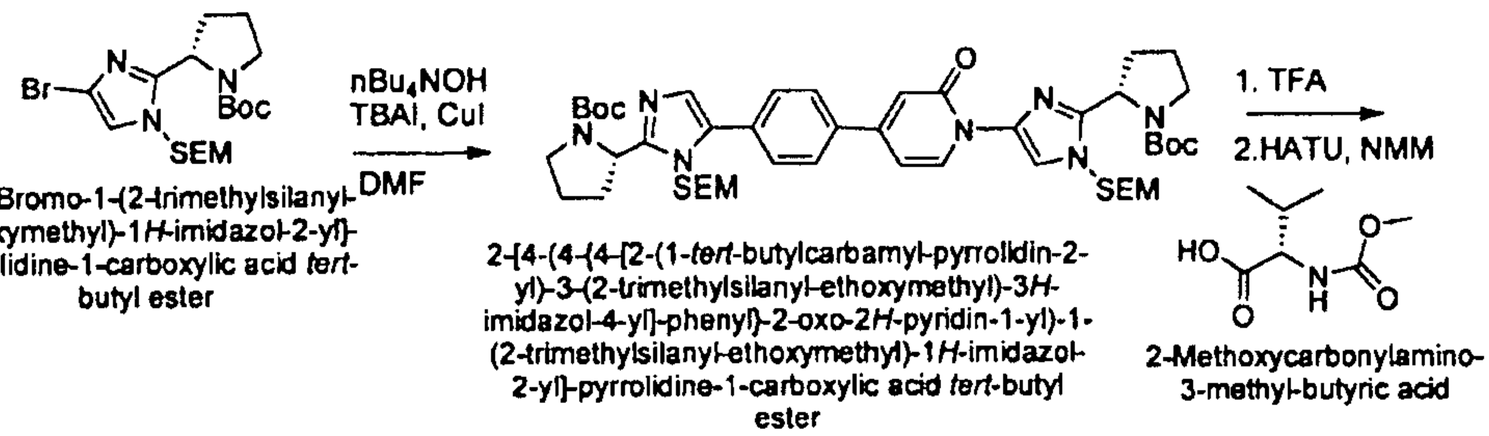
2-Benzyloxy-4-bromo-pyridine

2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



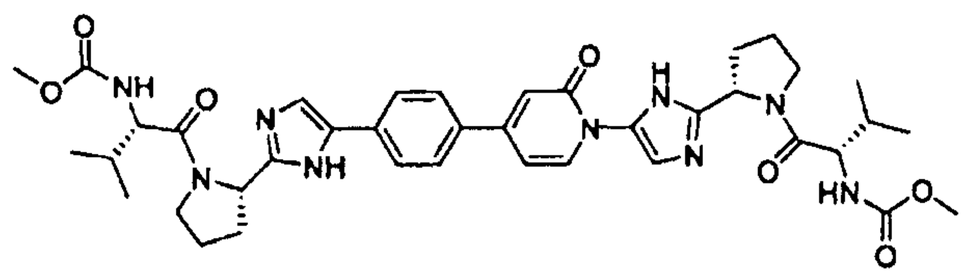
2-{5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-{5-[4-(2-Oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-{5-[4-(4-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-phenyl}-2-oxo-2*H*-pyridin-1-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-2-oxo-2*H*-pyridin-1-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-Benzyloxy-4-bromo-pyridine: A mixture of 4-Bromo-1H-pyridin-2-one (0.613 g), silver carbonate (0.63 g) and benzyl bromide (0.50 mL) in benzene (10 mL) was heated at 50°C for 24 hours, protected from light. Reaction mixture stirred ambient temperature for 16 hours. Reaction mixture was filtered through a pad of CELITE, which was washed ethyl acetate. The filtrate was concentrated and purified by flash column chromatography (silica gel, 0 to 10% ethyl acetate/hexanes) to give 2-Benzyloxy-4-bromo-pyridine (0.6043 g): LCMS-ESI$^+$: calc'd for $C_{12}H_{11}BrNO$: 265.12 ($M+H^+$); Found: 263.8, 265.8 ($M+H^+$).

2-{5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-Benzyloxy-4-bromo-pyridine (0.292 g), 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.533 g, prepared according to WO2008021927 A2) and $Pd(PPh_3)_4$ (0.064 g) in aq. K_2CO_3 solution/dimethoxyethane (1.82 mL/5.0 mL) was heated at 80-90°C for 8 hours.

Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried (MgSO4) and concentrated. The residue was purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexanes) to give 2-{5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.530 g): LCMS-ESI$^+$: calc'd for $C_{30}H_{33}N_4O_3$: 497.6 ($M+H^+$); Found: 497.0 ($M+H^+$).

2-[5-[4-(2-Oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a solution of 2-{5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.530 g) in DMF (5.0 mL) at 0°C was added 60% sodium hydride (0.047 g). After stirring for 5 minutes, 2-(trimethylsilyl)ethoxylmethyl chloride was added and reaction mixture stirred for 2 hours. Saturated ammonium chloride was added and mixture was extracted with ethyl acetate (2x). Organic layer was washed with 5% lithium chloride solution (2x), brine and dried ($MgSO_4$). Concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexanes) to give 2-[5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.495 g). LCMS-ESI$^+$: calc'd for $C_{36}H_{47}N_4O_4Si$: 627.87 ($M+H^+$); Found: 627.1 ($M+H^+$). A mixture of 2-[5-[4-(2-Benzyloxy-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.495 g) and 10% Pd/C (0.023 g) in ethanol (5.5 mL) was stirred under hydrogen atmosphere for 1 hour. Reaction mixture was filtered through a pad of Celite, which was washed with methanol. The filtrate was concentrated and purifed by flash column chromatography (silica gel, 0 to 10% methanol/ethyl acetate) to give 2-[5-[4-(2-Oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3027 g): LCMS-ESI$^+$: calc'd for $C_{29}H_{41}N_4O_4Si$: 537.47 ($M+H^+$); Found: 537.0 ($M+H^+$).

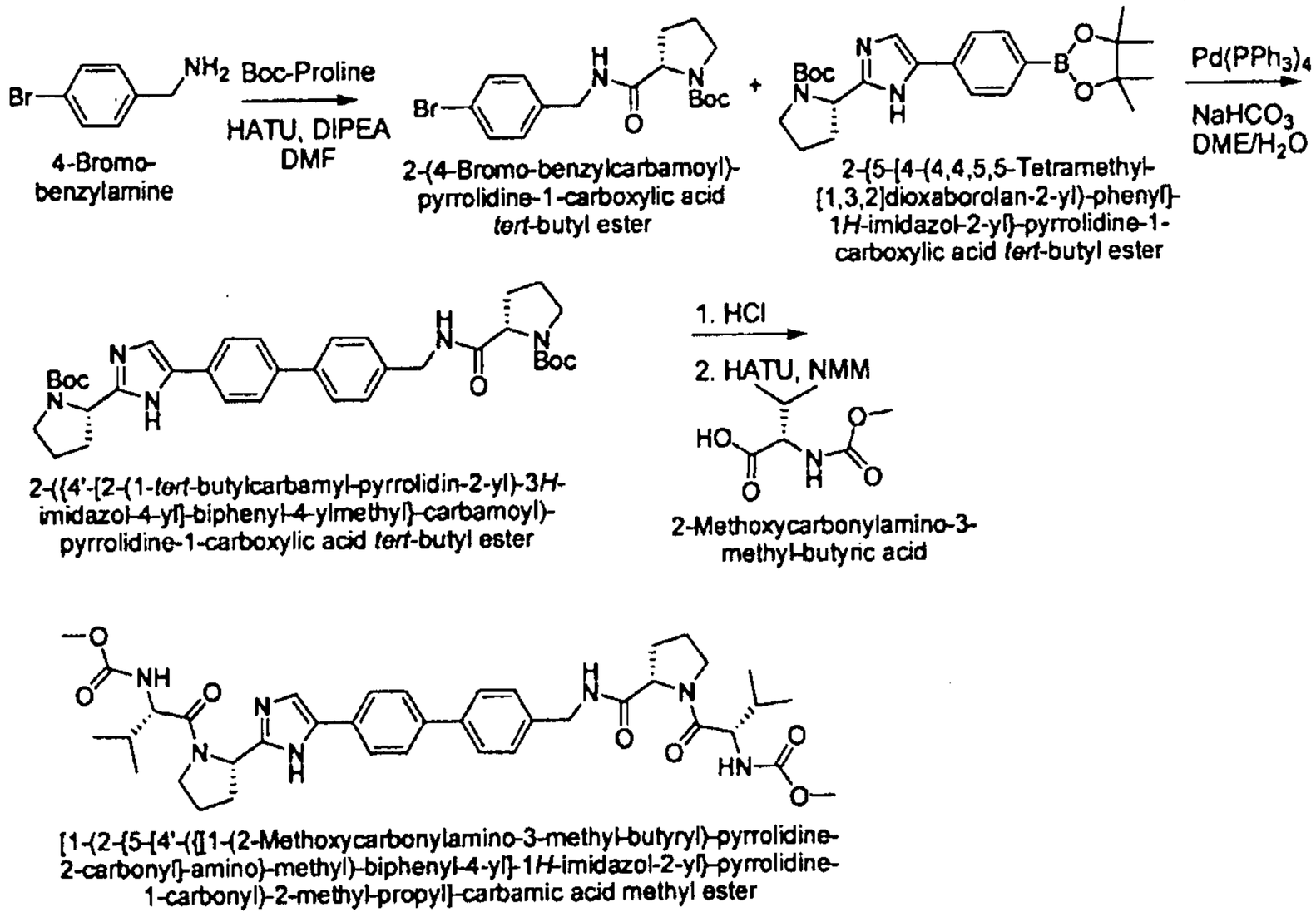
2-[4-(4-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-2-oxo-2H-pyridin-1-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a solution of 2-[5-[4-(2-Oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3027 g) in ethanol (5.0 mL) was added tetrabutylammonium hydroxide (0.375 mL of 1.5 M solution) and reaction mixture stirred for 1 hour., then concentrated to give a colorless oil. Residue was lyophilized from acetonitrile to give a yellow residue. To this residue was added 2-[4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.301 g,

prepared by reacting 2-(4-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (prepared according to WO2008021927 A2) with 2-(trimethylsilyl)ethoxylmethyl chloride using sodium hydride in DMF) and mixture co-evaporated with toluene (15 mL). DMF (1.0 mL) and copper(I) iodide (0.035 g) were added and the reaction mixture was stirred at 95°C for 24 hour, protected from light. To the reaction mixture was added tetrabutylammonium iodide (50 mg) and reaction continued for 2 days. Added more 2-[4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.35 g) and copper(I) iodide (0.050 g) and reaction continued for 24 hours. Reaction mixture was cooled and diluted with ethyl acetate and washed with 3N ammonium hydroxide. The aqueous layer was back-extracted with ethyl acetate (2x). The combined organic layer was washed with 3N ammonium hydroxide, H_2O, brine and dried ($MgSO_4$) then concentrated and purified by flash column chromatography (silica gel, 0 to 10% isopropanol/hexane) to give impure product that was repurified by preparative reverse phase HPLC (Gemini, 25 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give 2-[4-(4-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-2-oxo-2H-pyridin-1-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.042g): LCMS-ESI$^+$: calc'd for $C_{47}H_{72}N_7O_7Si_2$: 903.28 ($M+H^+$); Found: 902.2, 903.2 ($M+H^+$).

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-2-oxo-2H-pyridin-1-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-[4-(4-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-2-oxo-2H-pyridin-1-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.042g) in dichloromethane (1.0 mL) was treated with trifluoroacetic acid (0.3 mL) for 7 hours at ambient temperature. Reaction mixture was concentrated and dried for 1 hour under vacuum. Residue was dissolved in DMF (0.7 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.013 g), 4-methylmorpholine (0.024 mL), followed by HATU (0.028 g). Reaction mixture was stirred for 45 minutes at ambient temperature and then more 4-methylmorpholine (0.024 mL) was added. Reaction continued for 30 minutes, diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, brine and dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-2-oxo-2H-pyridin-1-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid

methyl ester as the bis-TFA salt (0.077 mg): ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.48 (d, J=7.2, 1H), 7.96-7.80 (m, 6H), 7.64 (s, 1H), 6.92-6.85 (m, 2H), 5.29-5.17 (m, 2H), 4.26-3.88 (m, 8H), 3.66 (s, 6H), 2.60-2.01 (m, 12H), 0.83-0.75 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{39}H_{50}N_9O_7$: 756.86 ($M+H^+$); Found: 756.3 ($M+H^+$).

Example AF1



2-(4-Bromo-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a mixture of 4-Bromo-benzylamine (2.00 g), Boc-L-proline (2.01 g), and 4-methylmorpholine (3.26 mL) in DMF (40 mL) was added HATU (3.48 g). Reaction mixture was stirred for 45 minutes, then concentrated, diluted with dichloromethane and washed with 10:1 H_2O/saturated sodium bicarbonate solution. The aqueous layer was back-extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give 2-(4-Bromo-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.38 g): LCMS-ESI$^+$: calc'd for $C_{17}H_{24}BrN_2NaO_3$: 405.29 ($M+Na^+$); Found: 405.0 ($M+Na^+$).

2-({4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl methyl}-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(4-Bromo-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.257 g), 2-{5-[4-(4,4,5,5-

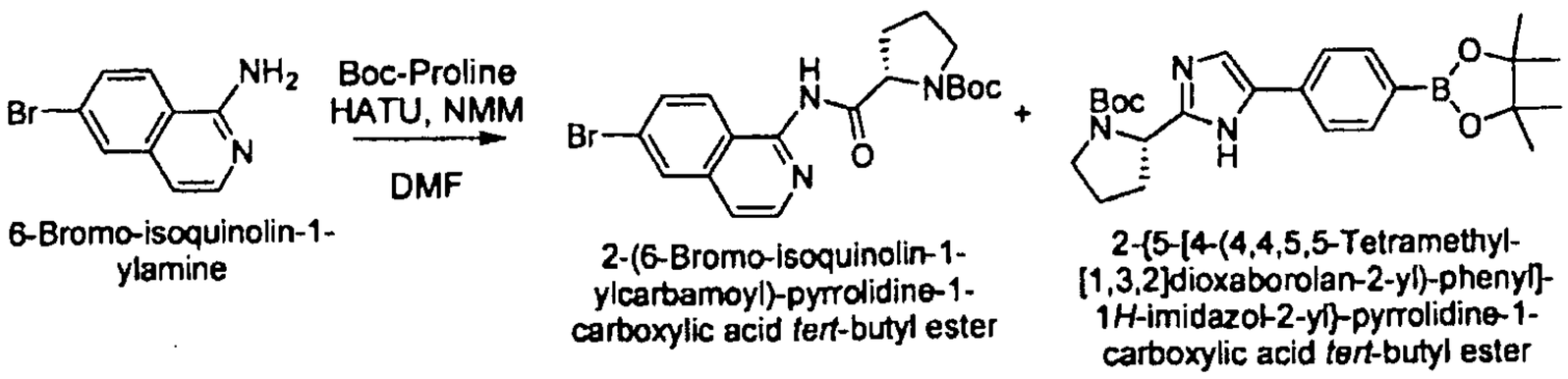
Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.309 g, prepared according to WO2008021927 A2), $NaHCO_3$ (0.186 g) and $Pd(PPh_3)_4$ (0.064 g) in H_2O (2.0 mL)/dimethoxyethane (6.0 mL) was heated at 80°C for 16 hours. Reaction mixture was cooled and concentrated. Residue was dissolved in dichloromethane, washed with H_2O. Aqueous layer was back-extracted with dichloromethane and combined organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give 2-({4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl methyl}-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.280 g): LCMS-ESI$^+$: calc'd for $C_{35}H_{46}N_5O_5$: 616.76 ($M+H^+$); Found: 616.1 ($M+H^+$).

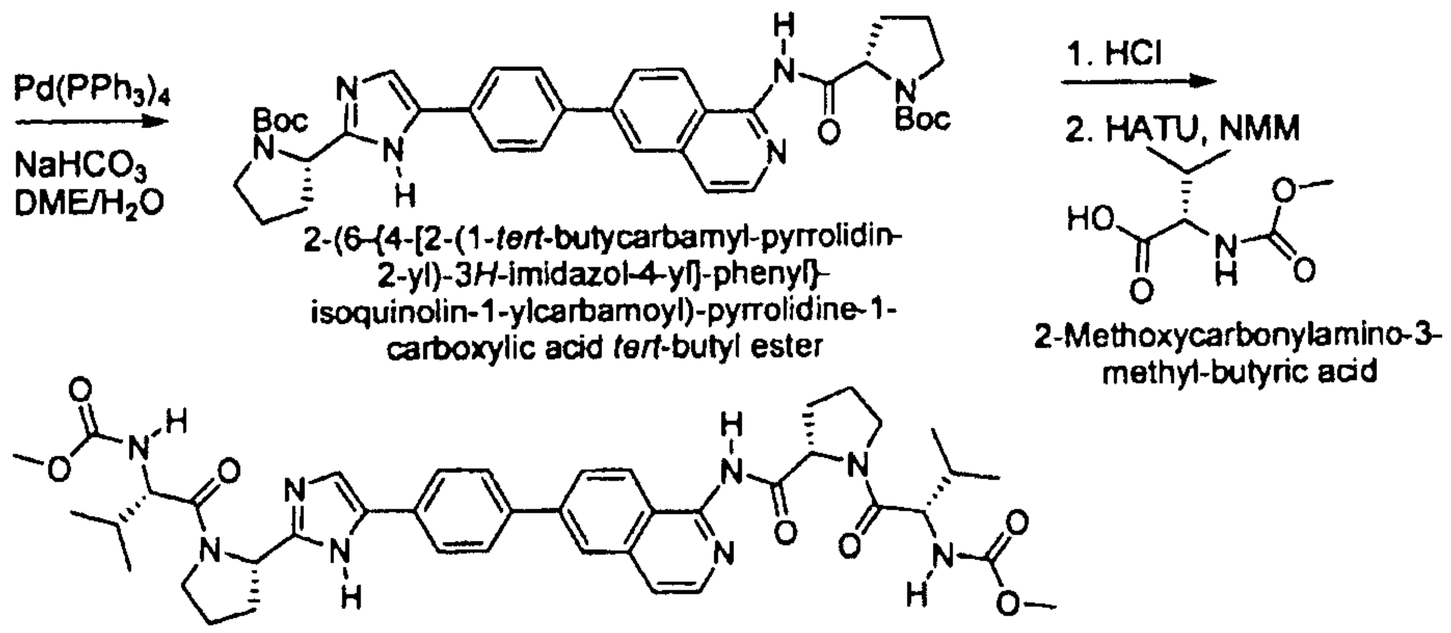
[1-(2-{5-[4'-({[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-methyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-({4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-ylmethyl}-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.280 g) in dichloromethane (5.0 mL) was treated with 4N HCl in dioxane (3.0 mL) for 2 hours at ambient temperature. Reaction mixture was concentrated and dried overnight under vacuum to give a yellow powder (0.2548 g). Yellow powder (0.129 g) was dissolved in DMF (2.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.090 g), 4-methylmorpholine (0.136 mL), followed by HATU (0.192 g). Reaction mixture was stirred for 90 minutes at ambient temperature and then concentrated. Residue was dissolved in dichloromethane and washed with dilute sodium bicarbonate solution. The aqueous layer was back-extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{5-[4'-({[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-methyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.089 mg).

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.40-8.37 (m, 1H), 8.02 (s, 1H), 7.83 (d, J=8.4, 2H), 7.72 (d, J=8.1, 2H), 7.63 (d, J=8.4, 2H), 7.37-7.29 (m, 3H), 4.90-4.87 (m, 1H), 4.35-4.28 (m, 3H), 4.03-3.95 (m, 4H), 3.90-3.80 (m, 3H), 3.53 (s, 6H), 2.30-1.80 (m, 10H), 0.90 (d, J=6.9, 3H), 0.86 (d, J=6.3, 3H), 0.78 (d, J=6.6, 3H), 0.68 (d, J=6.9, 3H).

LCMS-ESI$^-$: calc'd for $C_{39}H_{50}N_7O_7$: 728.86 ($M-H^+$); Found: 728.2 ($M-H^+$).

Example AG1





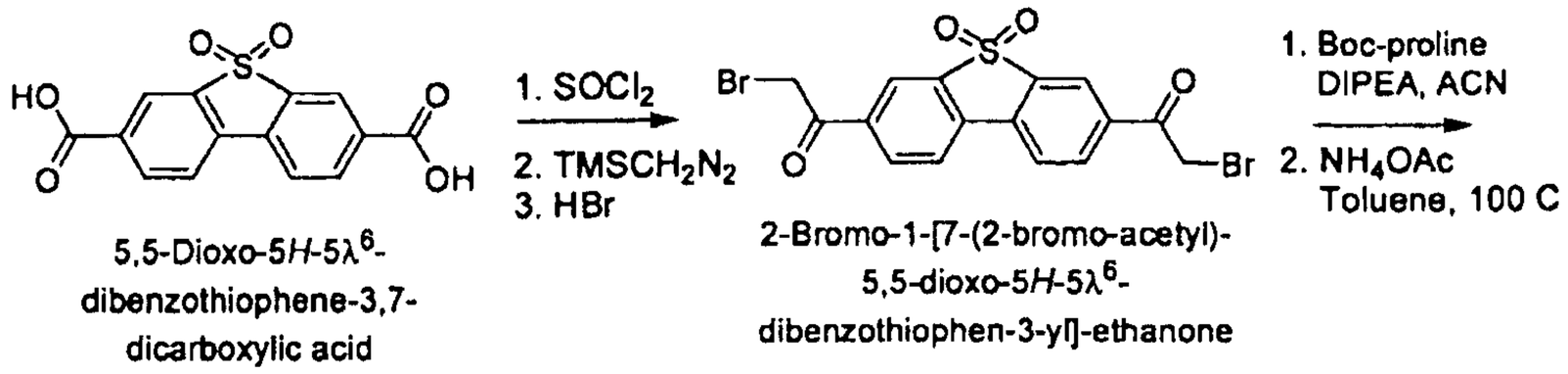
2-(6-Bromo-isoquinolin-1-yl carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a mixture of 6-Bromo-isoquinolin-1-ylamine (0.80 g), Boc-L-proline (0.803 g), and 4-methylmorpholine (0.83 mL) in DMF (10 mL) was added HATU (1.39 g). Reaction mixture was stirred for 6 hours. Additional Boc-L-proline (0.803 g), 4-methylmorpholine (0.83 mL) and HATU (1.39 g) were added and reaction stirred overnight at ambient temperature and then concentrated. The residue was dissolved in ethyl acetate and washed with 10:1 H_2O/saturated sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 70% ethyl acetate/hexanes) to give 2-(6-Bromo-isoquinolin-1-yl carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.74 g): LCMS-ESI$^+$: calc'd for $C_{19}H_{23}BrN_3O_3$: 421.31 ($M+H^+$); Found: 419.8, 421.8 ($M+H^+$).

2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-isoquinolin-1-yl carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture 2-(6-Bromo-isoquinolin-1-yl carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.426 g), 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-

carboxylic acid *tert*-butyl ester (0.405 g, prepared according to WO2008021927 A2), and $Pd(PPh_3)_4$ (0.053 g) in 2M aq. K_2CO_3 (1.4 mL)/dimethoxyethane (3.0 mL) was heated at 90°C for 16 hours. Reaction mixture was cooled and diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-isoquinolin-1-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.272 g): LCMS-ESI$^+$: calc'd for $C_{37}H_{45}N_6O_5$: 653.78 ($M+H^+$); Found: 653.1 ($M+H^+$).

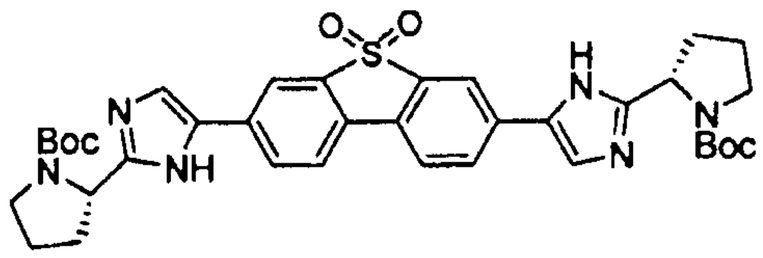
[1-(2-{5-[4-(1-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-isoquinolin-6-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-isoquinolin-1-yl carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.272 g) in dichloromethane (5.0 mL) was treated with 4N HCl in dioxane (5.0 mL) for 2 hours at ambient temperature. Reaction mixture was concentrated and suspended in ethyl ether. The solid was collected by filtration, washed with ethyl ether and dried overnight under vacuum to give a yellow powder (0.2279 g). Yellow powder (0.1005 g) was dissolved in DMF (1.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.061 g), 4-methylmorpholine (0.092 mL), followed by HATU (0.130 g). Reaction mixture was stirred for 1 hour at ambient temperature and then diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{5-[4-(1-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-isoquinolin-6-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.093 mg).
^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.36 (s, 1H), 8.30-8.15 (m, 2H), 8.13 (s, 1H), 8.05-7.95 (m, 3H), 7.88 (d, J=8.7, 2H), 7.70 (d, J=8.4, 1H), 7.32 (d, J=8.7, 1H), 7.29 (d, J=8.7, 1H), 5.10-5.05 (m, 1H), 4.70-4.65 (m, 1H), 4.10-3.908 (m, 3H), 4.03-3.95 (m, 4H), 3.90-3.80 (m, 3H), 3.49 (s, 6H), 2.39-1.80 (m, 10H), 0.90-0.70 (m, 12H): LCMS-ESI$^+$: calc'd for $C_{41}H_{51}N_8O_7$: 767.89 ($M+H^+$); Found: 767.2 ($M+H^+$).

Example AH1

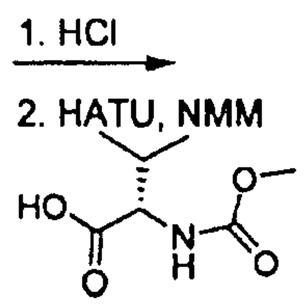


5,5-Dioxo-5*H*-5λ^6-dibenzothiophene-3,7-dicarboxylic acid

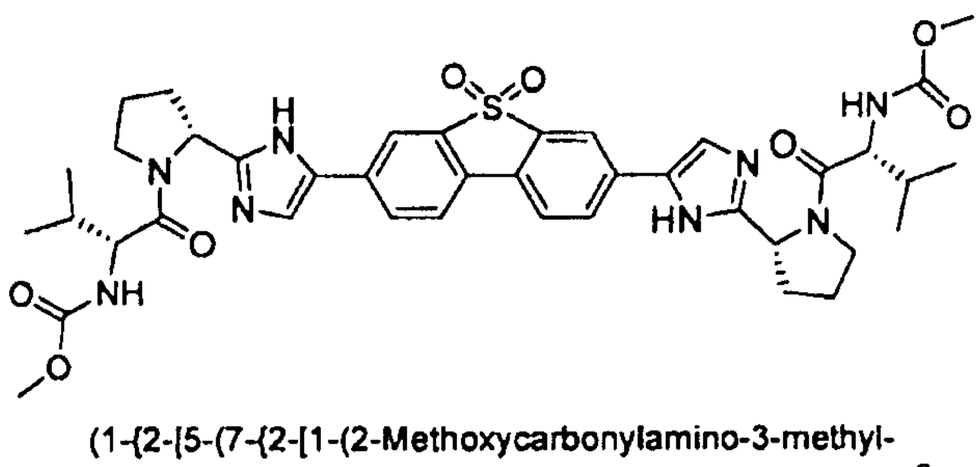
2-Bromo-1-[7-(2-bromo-acetyl)-5,5-dioxo-5*H*-5λ^6-dibenzothiophen-3-yl]-ethanone



2-(5-{7-[2-(1-*tert*butyl-carbamyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-5,5-dioxo-5*H*-5λ^6-dibenzothiophen-3-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-5,5-dioxo-5*H*-5λ^6-dibenzothiophen-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-Bromo-1-[7-(2-bromo-acetyl)-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl]-ethanone: A mixture of 5,5-Dioxo-5H-5λ^6-dibenzothiophene-3,7-dicarboxylic acid (10.85 g, prepared according to OL' Khouk et. Al. Russian J. Org. Chem. 2006, 42(8) 1164-1168) and oxalyl chloride (31.11 mL) in dichloromethane (250 mL) containing DMF (0.2 mL) was stirred at ambient temperature for 6 hours. A small amount of solid material was removed by filtration and the filtrate was concentrated to give a brown solid.

This brown solid was suspended in dichloromethane and cooled to 0°C. To this mixture was added 2.0M (trimethylsilyl)diazomethane in hexane (52.5 mL) and warmed to ambient temperature over 16 hours. Reaction mixture was concentrated providing a brown residue. The resulting brown residue was suspended in ethyl acetate (200 mL) and cooled to 0°C. 5.7M Hydrobromic acid in acetic acid (15.3 mL) was added slowly and stirred for 1 hour at 0°C, then 1 hour at ambient temperature. The reaction mixture was quenched with solid sodium

bicarbonate and stirred for 30 minutes Saturated sodium bicarbonate solution was added, giving a brown precipitate. The solid was collected, washed with H_2O, ethyl acetate and dried under vacuum to give 2-Bromo-1-[7-(2-bromo-acetyl)-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl]-ethanone as a brown solid (25 g): LCMS-ESI$^-$: calc'd for $C_{16}H_{11}Br_2O_4S$: 459.12 ($M+H^+$); Found: no product mass observed.

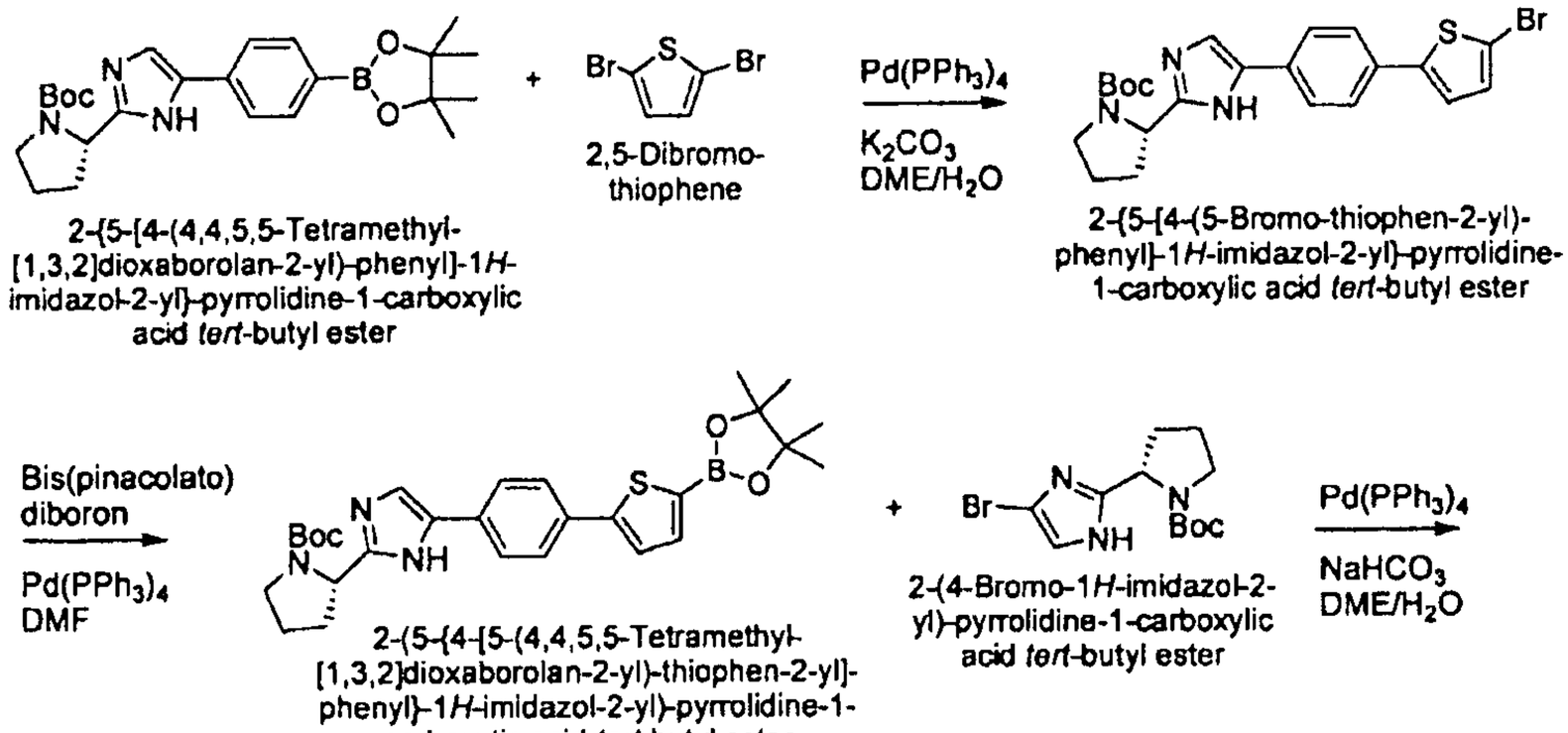
2-(5-{7-[2-(1-*tert*butyl-carbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-Bromo-1-[7-(2-bromo-acetyl)-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl]-ethanone (25 g), Boc-L-proline (15.82 g) and diisopropylethylamine (12.6 mL) in acetonitrile (300 mL) was stirred for 3 hours at ambient temperature. Reaction mixture was concentrated and residue dissolved in ethyl acetate, washed with brine and back-extracted with ethyl acetate (3x). The combined organic layer was washed with brine, dried ($MgSO_4$) and purified by flash column chromatography (silica gel, 20 to 800% ethyl acetate/hexanes) to give yellow foam (10 g). LCMS-ESI$^-$: calc'd for $C_{36}H_{41}N_2O_{12}S$: 725.79 ($M-H^+$); Found: 725.1 ($M-H^+$). A mixture of the yellow foam (7 g) and ammonium acetate (3.72 g) in xylenes (20 mL) was stirred at 120°C for 3.5 hours and then cooled. Diluted with ethyl acetate and washed with dilute sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3x), then dichloromethane containing methanol (3x). The combined organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 5% methanol/ethyl acetate) to give 2-(5-{7-[2-(1-*tert*-butyl-carbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.56 g): LCMS-ESI$^+$: calc'd for $C_{36}H_{43}N_6O_6S$: 687.82 ($M+H^+$); Found: 687.0 ($M+H^+$).

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-(5-{7-[2-(1-*tert*butyl-carbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.56 g) in dichloromethane (50 mL) was treated with 4N HCl in dioxane (50 mL) for 3 hours at ambient temperature. Reaction mixture was concentrated, triturated with ethyl ether and the orange solid dried overnight under vacuum. A portion of this orange solid (0.15g) was dissolved in DMF (2.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.187 g), 4-methylmorpholine (0.13 mL), followed by HATU (0.184 g). Reaction mixture was stirred for 1 hour at ambient temperature and then diluted with ethyl acetate, washed with dilute sodium bicarbonate solution,

5% lithium chloride solution, brine dried ($MgSO_4$). Concentration and purification by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilization gave (1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-5,5-dioxo-5H-5λ^6-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.150 mg): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.40-8.14 (m, 8H), 7.33 (d, J=8.1, 2H), 5.13-5.10 (m, 2H), 4.13-4.07 (m, 2H), 3.90-3.80 (m, 4H), 3.53 (s, 6H), 2.34-1.98 (m, 10H), 0.85 (d, J=6.6, 6H), 0.81 (d, J=6.6, 6H).

LCMS-ESI$^+$: calc'd for $C_{40}H_{49}N_8O_8S$: 801.92 ($M+H^+$); Found: 801.2 ($M+H^+$).

Example AI1



2-{5-[4-(5-Bromo-thiophen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2,5-Dibromo-thiophene (4.93 g), 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.896 g, prepared according to WO2008021927 A2), and $Pd(PPh_3)_4$ (0.118 g) in 2M K_2CO_3 (3.06 mL)/dimethoxyethane (6.12 mL) was heated at 90°C for 8 hours. Reaction mixture was cooled, diluted with ethyl acetate and washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give 2-{5-[4-(5-Bromo-thiophen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.955 g): LCMS-ESI$^+$: calc'd for $C_{22}H_{25}BrN_3O_2S$: 475.42 ($M+H^+$); Found: 473.8, 475.9 ($M+H^+$).

2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{5-[4-(5-Bromo-thiophen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.4807 g), bis(pinacolato)diboron (0.54 g), $Pd(PPh_3)_4$ (0.058) and potassium acetate (0.257 g) in 1,4-dioxane was heated at 90°C for 16 hours. Reaction mixture was cooled to ambient temperatures and diluted with ethyl acetate. Organic layer was washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexanes) to give 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3752 g) as a brown foam: LCMS-ESI$^+$: calc'd for $C_{28}H_{37}BN_3O_4S$: 522.48 ($M+H^+$); Found: 521.9 ($M+H^+$).

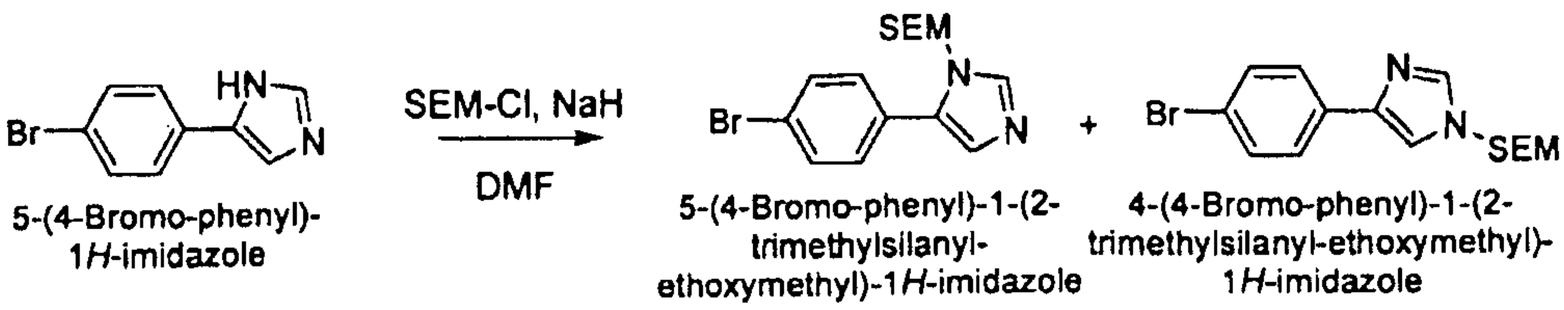
2-[5-(5-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.1050 g), 2-(4-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.070 g, prepared according to WO2008021927 A2) and $Pd(PPh_3)_4$ (0.012 g) in 2.0M sodium bicarbonate solution (0.33 mL) and dimethoxyethane (0.66 mL) was stirred under microwave irradiation at 120°C for 20 minutes. Reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give 2-[5-(5-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.069

g) as a brown foam: LCMS-ESI$^+$: calc'd for $C_{34}H_{43}N_6O_4S$: 631.80 ($M+H^+$); Found: 631.0 ($M+H^+$).

[1-(2-{5-[4-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thiophen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-[5-(5-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.069 g) in dichloromethane (3.0 mL) was treated with 4N HCl in dioxane (3.0 mL) for 30 minutes at ambient temperature. Reaction mixture was concentrated and dried overnight under vacuum to give a reddish-brown solid (0.084 g). Residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.053 g), 4-methylmorpholine (0.083 mL), followed by HATU (0.113 g). Reaction mixture was stirred for 1 hour at ambient temperature then diluted with ethyl acetate, washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine, then dried ($MgSO_4$). Concentration and purification by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilization gave [1-(2-{5-[4-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thiophen-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.040 mg).

^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.09 (s, 1H), 7.81 (br s, 4H), 7.65-7.60 (m, 1H), 7.45-7.40 (m, 1H), 7.402-7.30 (m, 21H), 5.20-5.00 (m, 2H), 4.10 (q, J=6.9, 3H), 3.90-3.80 (m, 3H), 3.53 (s, 6H), 2.40-1.90 (m, 10H), 0.90-0.76 (m, 12H): LCMS-ESI$^-$: calc'd for $C_{38}H_{49}N_8O_6S$: 745.90 ($M+H^+$); Found: 745.2 ($M+H^+$).

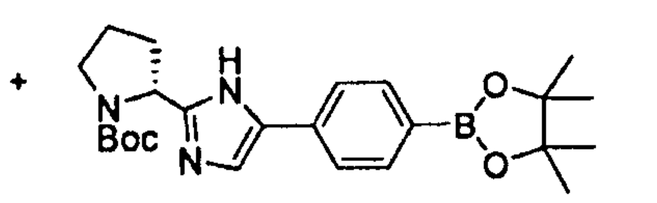
Example AJ1



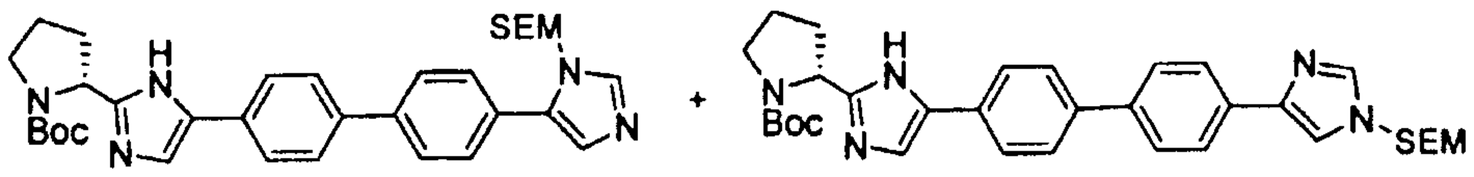
5-(4-Bromo-phenyl)-1*H*-imidazole

5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole

4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole

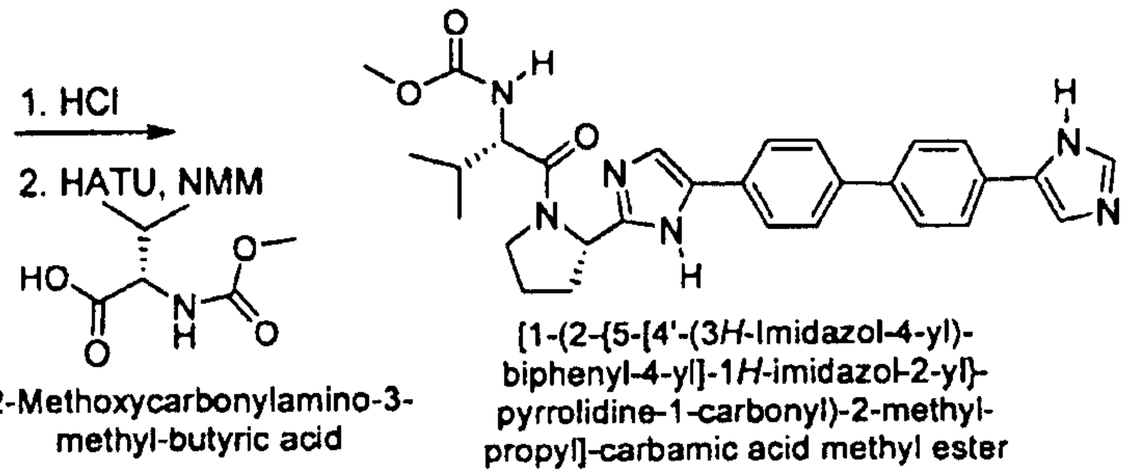


2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-(5-{4'-[3-(2-Trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(5-{4'-[1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid

[1-(2-{5-[4'-(3*H*-Imidazol-4-yl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

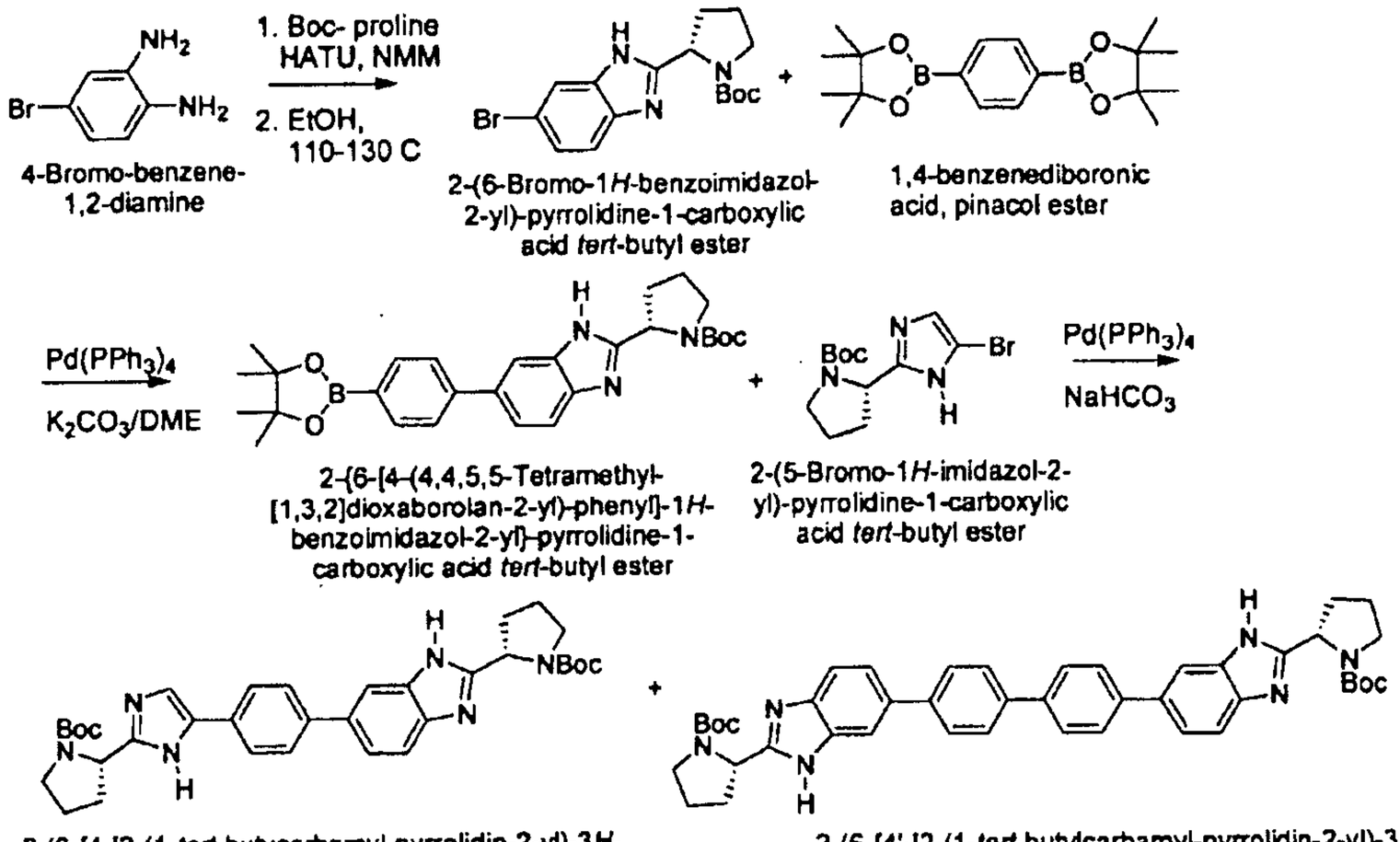
5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole and 4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole: To a solution of 5-(4-Bromo-phenyl)-1H-imidazole (0.997 g) in DMF (15.0 mL) at 0°C was added 60% sodium hydride (0.197 g). After stirring for 5 minutes, 2-(trimethylsilyl)ethoxylmethyl chloride (1.18 mL) was added and reaction mixture stirred for 2 hours. Reaction mixture was concentrated, dissolved in ethyl acetate. Organic layer was washed with 5% lithium chloride solution (2x), brine and dried ($MgSO_4$). Concentrated and purified by flash column chromatography (silica gel, ethyl acetate/hexanes) to give a 1:1 mixture of 5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole and 4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole (0.89 g): LCMS-ESI$^+$: calc'd for $C_{15}H_{22}BrN_2OSi$: 354.33 ($M+H^+$); Found: no product mass observed.

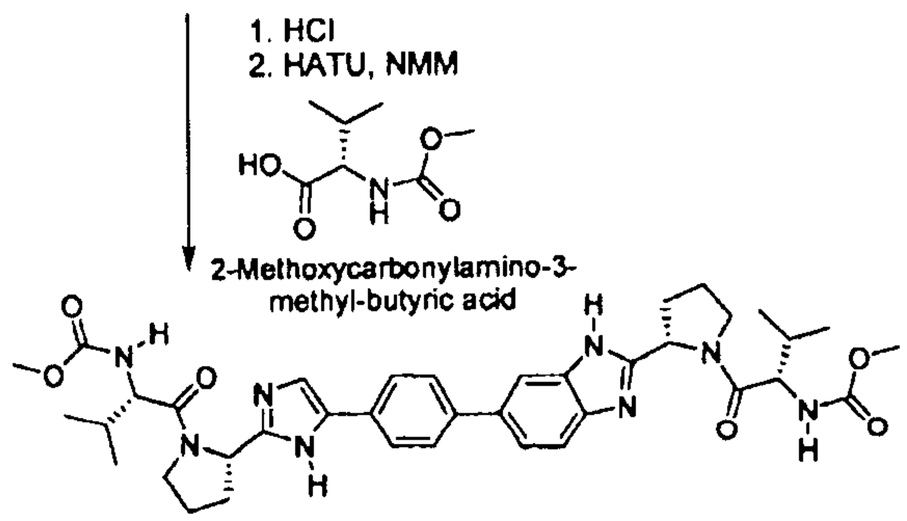
2-(5-{4'-[3-(2-Trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 2-(5-{4'-[1-(2-Trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 1:1 mixture of 5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole and 4-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole (0.145 g), 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.150 g, prepared according to WO2008021927 A2) and $Pd(PPh_3)_4$ (0.020 g) in aq. K_2CO_3 solution (0.51 mL)/ dimethoxyethane (1.5 mL) was heated at 80°C for 18 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give a 1:1 mixture 2-(5-{4'-[3-(2-Trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 2-(5-{4'-[1-(2-Trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0998 g): LCMS-ESI$^+$: calc'd for $C_{33}H_{44}N_5O_3Si$: 586.82 ($M+H^+$); Found: 586.0 ($M+H^+$).

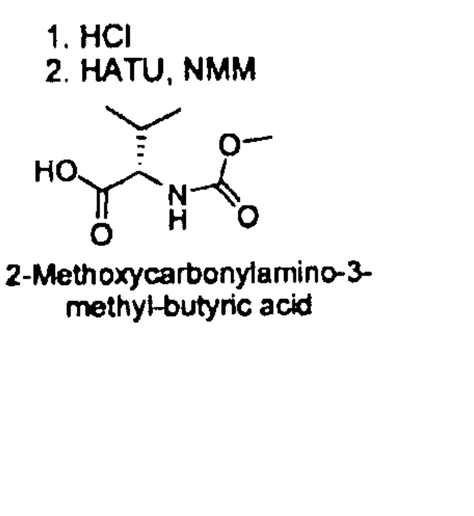
[1-(2-{5-[4'-(3H-Imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A 1:1 mixture 2-(5-{4'-[3-(2-Trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 2-(5-{4'-[1-(2-Trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0998 g) in dichloromethane (3.0 mL) was treated with trifluoroacetic acid (3.0mL) for 18 hours at ambient temperature. Reaction mixture was concentrated, co-evaporated with acetonitrile and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and concentrated to give a yellow film (0.087 g). Residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.023 g), 4-methylmorpholine (0.055 mL), followed by HATU (0.049 g). Reaction mixture was stirred for 1 hour at ambient temperature, diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, brine and dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{5-[4'-(3H-Imidazol-4-yl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.016 mg): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 9.10 (s, 1H), 8.20 (s, 1H), 8.05 (br s, 1H), 7.93-7.80 (m, 8H), 7.32 (d, J=7.8, 1H), 5.20-5.12 (m, 1H), 4.15-4.05 (m, 1H), 3.85-3.80 (m, 3H), 3.54 (s, 3H), 2.40-1.85 (m,

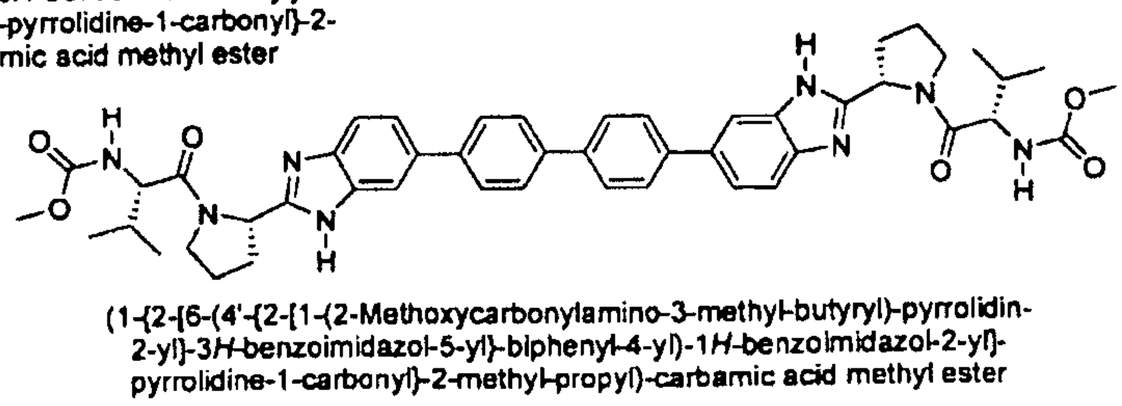
6H), 0.83 (d, J=7.2, 3H), 0.80 (d, J=6.9, 3H): LCMS-ESI$^+$: calc'd for $C_{29}H_{33}N_6O_3$: 513.61 ($M+H^+$); Found: 513.1 ($M+H^+$).

Examples AK1 and AL1









2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: To a mixture of 4-Bromo-benzene-1,2-diamine (5.0 g), Boc-L-proline (6.0 g), and 4-methylmorpholine (5.88 mL) in DMF (100 mL) was added HATU (10.7 g). Reaction mixture was stirred for 16 hours and then concentrated. Residue was dissolved in ethyl acetate and washed with 5% lithium chloride solution (2x), brine and dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 30 to 60% ethyl acetate/hexanes) to a dark brown foam. Brown foam was dissolved in ethanol (100 mL) and heated in a sealed tube at 110-130°C for 2 days. Reaction mixture was cooled and concentrated. Residue was dissolved in ethyl acetate and extracted with 1N HCl (3x). Aqueous layer was basified with 50% NaOH solution to pH 10 and extracted with ethyl acetate (2x). The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0 to 10% isopropanol/hexanes) to give 2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (6.5 g) as an off-white foam: LCMS-ESI$^+$: calc'd for $C_{16}H_{21}BrN_3O_2$: 367.26 ($M+H^+$); Found: 365.8, 367.8 ($M+H^+$).

2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture 2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.257 g), 1,4-benzenediboronic acid, pinacol ester (1.158 g), $Pd(PPh_3)_4$ (0.041 g) and potassium carbonate (0.485 g) in H_2O (2.0 mL)/dimethoxyethane (5.0 mL) was heated in microvave at 120°C for 30 minutes. Reaction mixture was cooled and diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 70% ethyl acetate/hexanes) to give 2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.187 g): LCMS-ESI$^+$: calc'd for $C_{28}H_{37}BN_3O_4$: 490.42 ($M+H^+$); Found: 490.0 ($M+H^+$).

2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.116 g), 2-(5-Bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.112 g, prepared according to WO2008021927 A2) and $Pd(PPh_3)_4$ (0.014 g) in 2.0M potassium carbonate solution (0.35 mL) and dimethoxyethane (1.0 mL) was heated at 90°C for 6 hours. Additional $Pd(PPh_3)_4$ (0.014 g) was added and reaction continued for 12 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with H_2O, brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica

gel, 1 to 30% isopropanol/hexanes) and preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.035 g) as a bis-TFA salt: LCMS-ESI$^+$: calc'd for $C_{34}H_{43}N_6O_4$: 599.74 ($M+H^+$); Found: 599.1 ($M+H^+$). A reaction side-product was also isolated and determined to be 2-(6-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.013 g) as the bis-TFA salt: LCMS-ESI$^+$: calc'd for $C_{44}H_{49}N_6O_4$: 725.89. ($M+H^+$); Found: 725.1 ($M+H^+$).

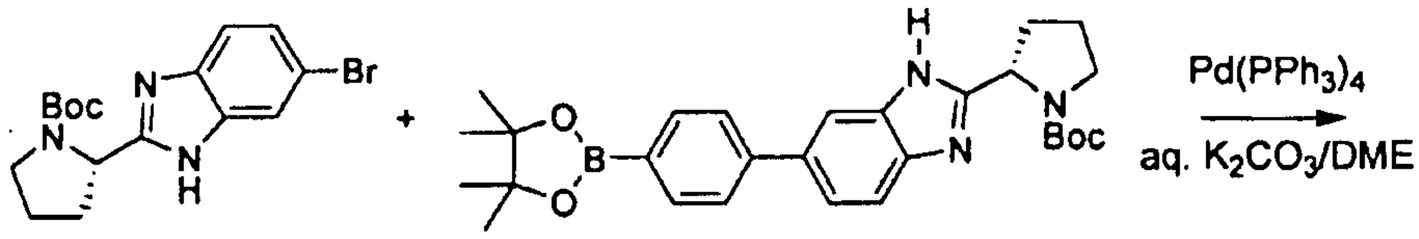
(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.035 g) in dichloromethane (1.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0155 g), 4-methylmorpholine (0.023 mL), followed by HATU (0.033 g). Reaction mixture was stirred for 1 hour at ambient temperature and then diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.0226 g).
^{1}H-NMR: 300 MHz, (CD_3OD) δ: 7.98 (s, 1H), 7.90-7.70 (m, 8H), 5.32 (t, J=6.9, 1H), 5.21 (t, J=6.9, 1H), 4.22 (dd, J=10.8, 6.9, 2H), 4.10-3.80 (m, 4H), 3.61 (s, 6H), 2.65-1.80 (m, 10H), 0.950-0.80 (m, 12H): LCMS-ESI$^+$: calc'd for $C_{38}H_{49}N_8O_6$: 713.84 ($M+H^+$); Found: 713.3 ($M+H^+$).

Example AL1

(1-{2-[6-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-(6-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.013 g) in dichloromethane (1.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under

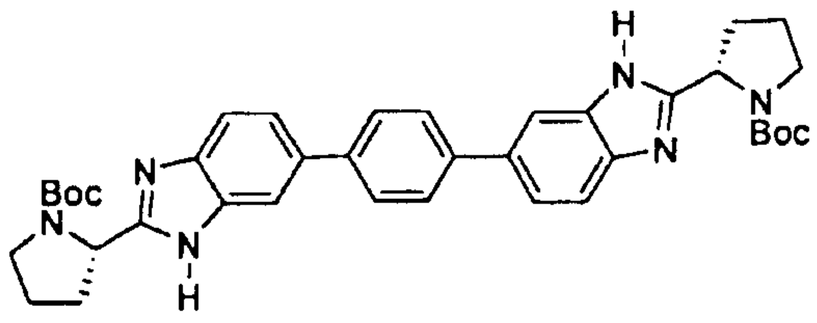
vacuum. The residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0155 g), 4-methylmorpholine (0.023 mL), followed by HATU (0.033 g). After stirring for 1 hour at ambient temperature, additional 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0155 g), HATU (0.033 g) were added followed by 4-methylmorpholine (0.023 mL). After stirring for 30 minutes, reaction mixture was diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[6-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.0106 g). ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.00 (s, 2H), 7.90-7.70 (m, 14H), 5.40-5.35 (m, 2H), 4.28 (d, J=7.2, 2H), 4.15-3.85 (m, 5H), 3.67 (s, 6H), 2.65-2.06 (m, 10H), 0.95 (d, J=6.6, 6H), 0.88 (d, J=6.6, 6H): LCMS-ESI$^+$: calc'd for $C_{48}H_{55}N_8O_6$: 839.99 ($M+H^+$); Found: 839.4 ($M+H^+$).

Example AM1

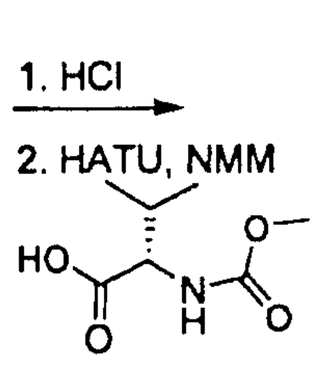


2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

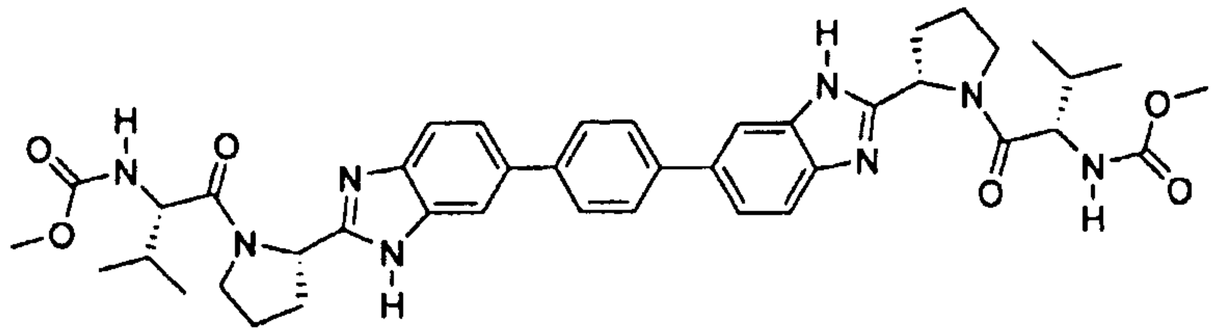
2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3*H*-benzoimidazol-5-yl]-phenyl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



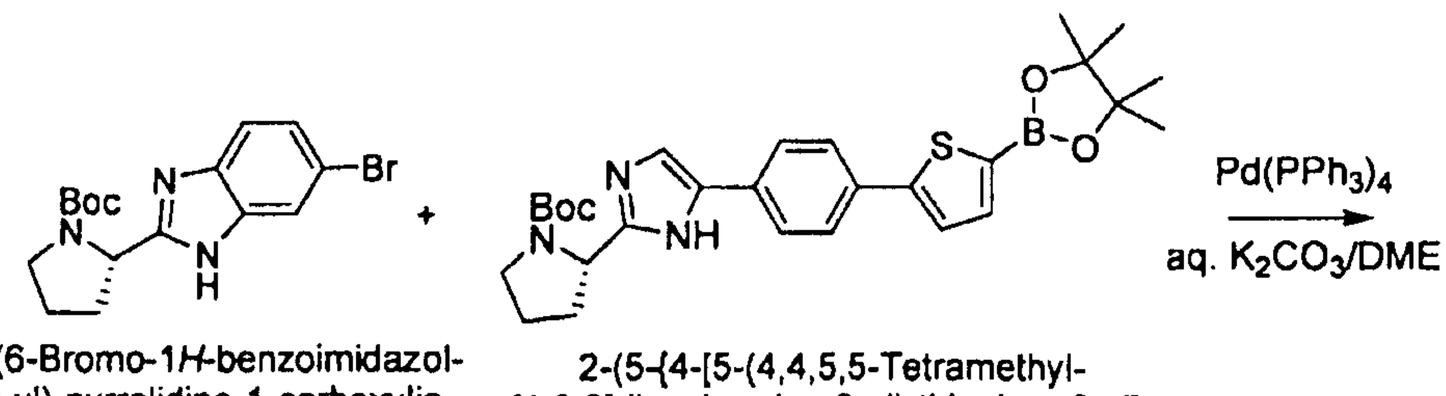
(1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-phenyl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.058 g), 2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.052 g) and Pd(PPh3)4 (0.0069 g) in 2.0M potassium carbonate solution (0.18 mL) and dimethoxyethane (0.36 mL) was heated in microwave at 110°C for 30 minutes, then at 120°C for 60 minutes. Additional $Pd(PPh_3)_4$ (0.069 g) was added and reaction was heated conventially at 90°C for 12 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 1 to 20% isopropanol/hexanes) and preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-

carboxylic acid *tert*-butyl ester (0.0315 g) as a bis-TFA salt: LCMS-ESI$^+$: calc'd for $C_{38}H_{45}N_6O_4$: 649.79 ($M+H^+$); Found: 649.1 ($M+H^+$).

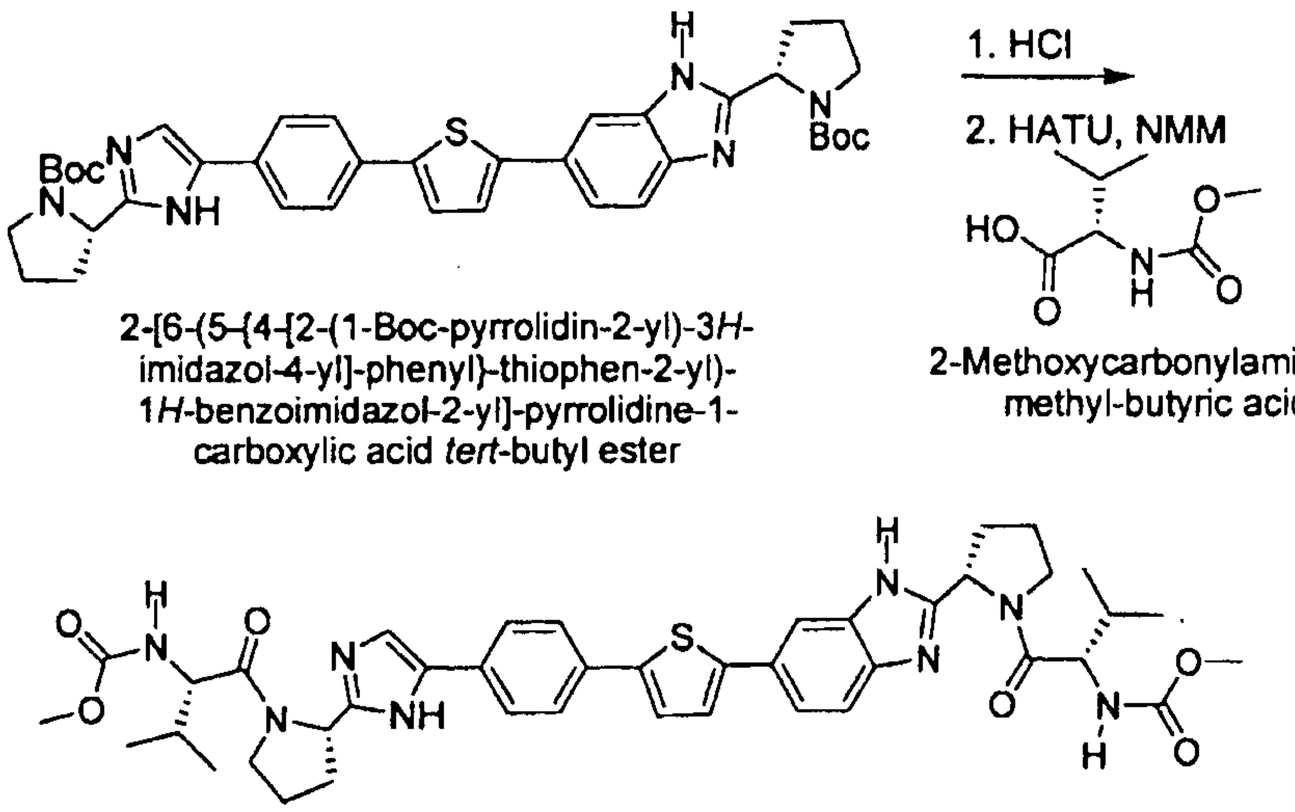
(1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(6-{4-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-phenyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0315 g) in dichloromethane (2.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0128 g), 4-methylmorpholine (0.023 mL), followed by HATU (0.027 g). Reaction mixture was stirred for 1 hour at ambient temperature and additional 4-methylmorpholine (0.023 mL) was added. After stirring for 30 minutes, reaction mixture was diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-phenyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.0263 g). ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.00 (s, 2H), 7.90-7.70 (m, 8H), 5.40-5.35 (m, 2H), 4.28 (d, J=7.2, 2H), 4.15-3.85 (m, 4H), 3.67 (s, 6H), 2.65-2.06 (m, 10H), 0.95 (d, J=6.6, 6H), 0.88 (d, J=6.6, 6H): LCMS-ESI$^-$: calc'd for $C_{42}H_{51}N_8O_6$: 763.90 ($M+H^+$); Found: 763.3 ($M+H^+$).

Example AN1



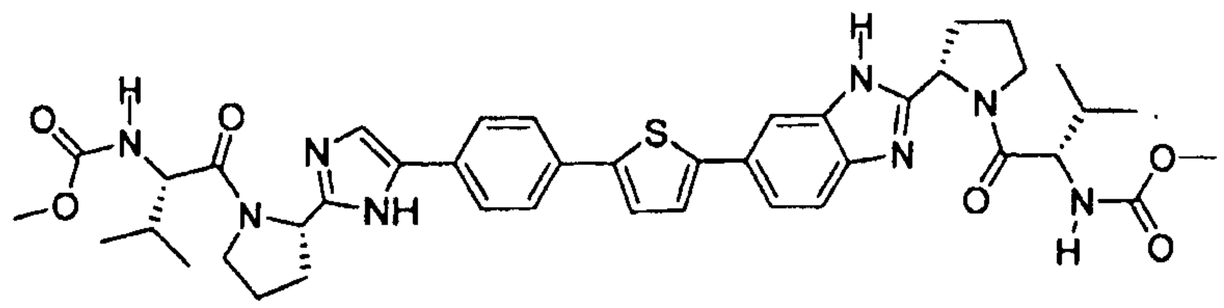
2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-[6-(5-{4-[2-(1-Boc-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



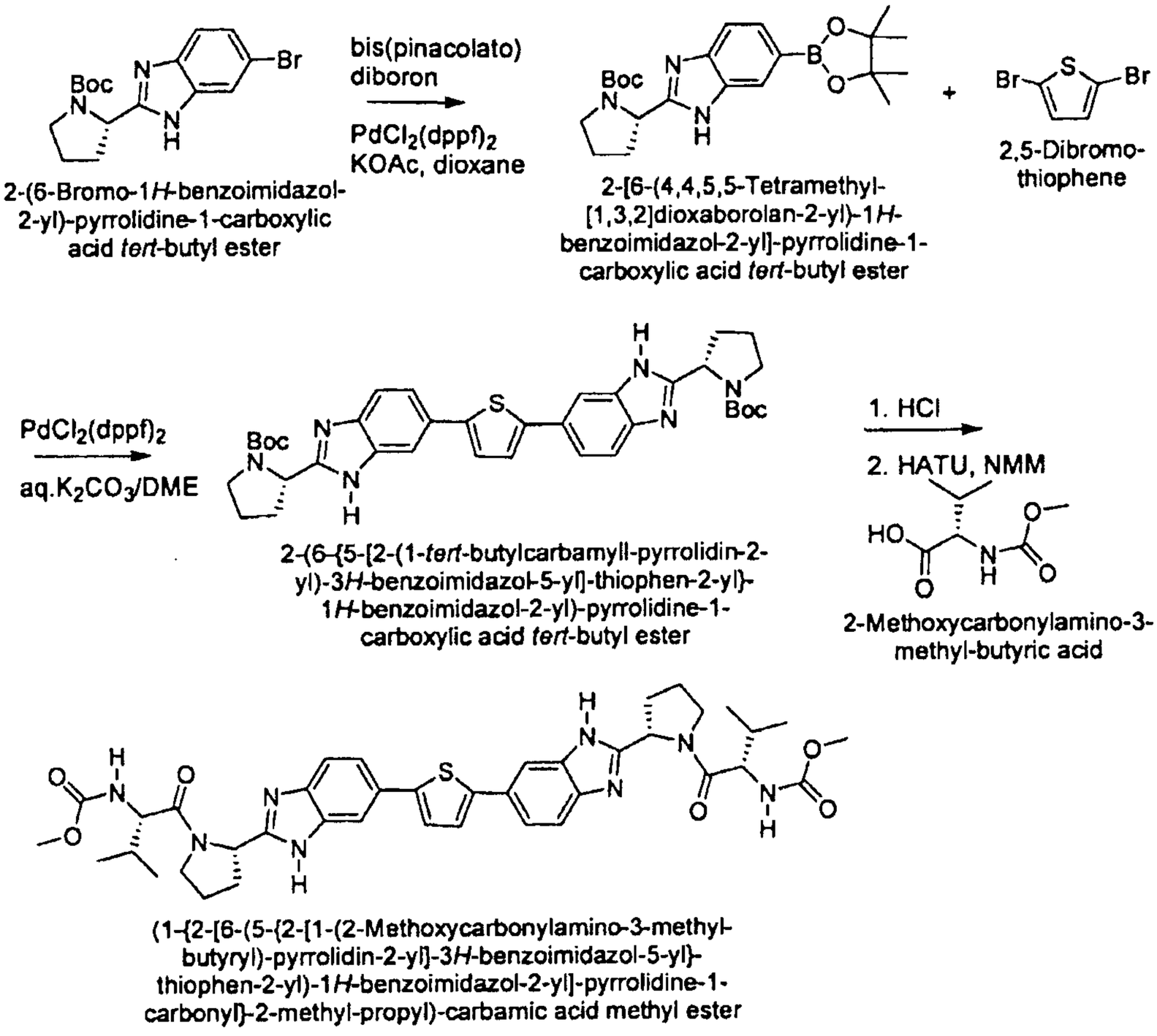
[1-(2-{6-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-thiophen-2-yl]-1*H*-benzoimidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-[6-(5-{4-[2-(1-Boc-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(5-{4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiophen-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.110 g), 2-(6-Bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.115 g) and $Pd(PPh_3)_4$ (0.012 g) in 2.0M potassium carbonate solution (0.32 mL) and dimethoxyethane (0.64 mL) was heated in microwave at 110°C for 30 minutes. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) and preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-[6-(5-{4-[2-(1-Formyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl

ester (0.085 g) as a bis-TFA salt: LCMS-ESI$^+$: calc'd for $C_{38}H_{45}N_6O_4S$: 681.86 ($M+H^+$); Found: 681.0 ($M+H^+$).

[1-(2-{6-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-thiophen-2-yl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A solution of 2-[6-(5-{4-[2-(1-Formyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-thiophen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.085 g) in dichloromethane (2.0 mL) was treated with 4N HCl in dioxane (2.0 mL) for 1.5 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.033 g), 4-methylmorpholine (0.060 mL), followed by HATU (0.070 g). Reaction mixture was stirred for 45 minutes at ambient temperature and reaction mixture was diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{6-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-thiophen-2-yl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (0.048 mg): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.09 (br s, 1H), 7.90-7.75 (m, 8H), 7.70-7.55 (m, 4H), 7.34 (d, J=8.1, 2H), 5.25-5.10 (m, 2H), 4.20-4.15 (m, 4H), 4.15-3.85 (m, 4H), 3.54 (s, 6H), 2.50-1.85 (m, 10H), 0.87-0.75 (m, 12H): LCMS-ESI$^+$: calc'd for $C_{42}H_{51}N_8O_6S$: 795.96 ($M+H^+$); Found: 795.2 ($M+H^+$).

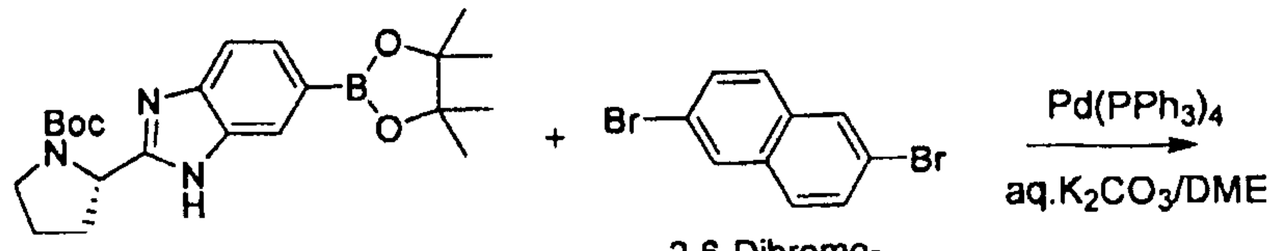
Example AO1


Boc
N
N
H
Br
bis(pinacolato) diboron
$PdCl_2(dppf)_2$
KOAc, dioxane
B
O
O
+
S
Br
Br
$PdCl_2(dppf)_2$
aq.K_2CO_3/DME
1. HCl
2. HATU, NMM
HO
O
O
O

carboxylic acid *tert*-butyl ester (0.149 g), 2,5-Dibromo-thiophene (0.035 g) and $PdCl_2(dppf)_2$ (0.006 g) in 2.0M potassium carbonate solution (0.36 mL) and dimethoxyethane (1.0 mL) was heated at 90°C for 18 hours. Additional 2M potassium carbonate solution (0.36 mL) and $PdCl_2(dppf)$ (0.006 g) was added and reaction was continued for 48 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified using preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-(6-{5-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-thiophen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0475 g) as a bis-TFA salt: LCMS-ESI$^+$: calc'd for $C_{36}H_{43}N_6O_4S$: 655.82 ($M+H^+$); Found: 655.0 ($M+H^+$).

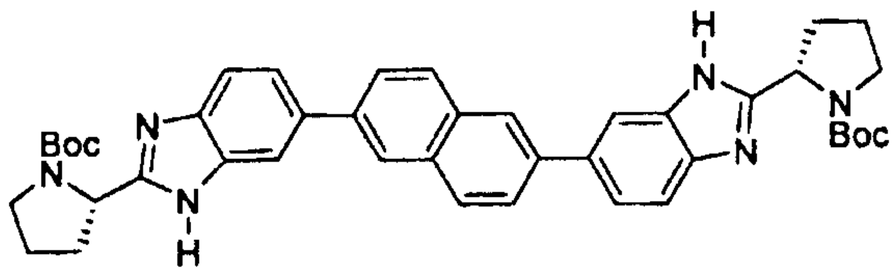
(1-{2-[6-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-thiophen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(6-{5-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-thiophen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0475 g)in dichloromethane (1.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1.5 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (1.0 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0196 g), 4-methylmorpholine (0.035 mL), followed by HATU (0.042 g). Reaction mixture was stirred for 1 hour at ambient temperature and additional 4-methylmorpholine (0.023 mL) was added. After stirring for 30 minutes, reaction mixture was diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[6-(5-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-thiophen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.0296 g): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 7.91(s, 2H), 7.71 (s, 4H), 7.61 (s, 2H), 7.35 (d, J=9.0, 2H), 5.25-5.15 (m, 2H), 4.15-4.00 (m, 4H), 3.95-3.75 (m, 4H), 3.54 (s, 6H), 2.25-1.85 (m, 10H), 0.83 (d, J=6.6, 6H), 0.79 (d, J=6.9, 6H); LCMS-ESI$^-$: calc'd for $C_{40}H_{49}N_8O_6S$: 769.92 ($M+H^+$); Found: 769.2 ($M+H^+$).

Example AP1

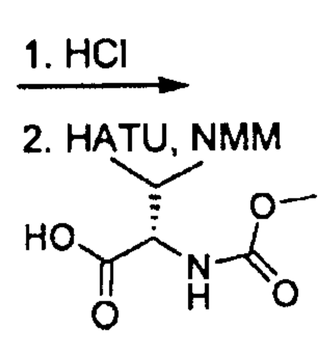


2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

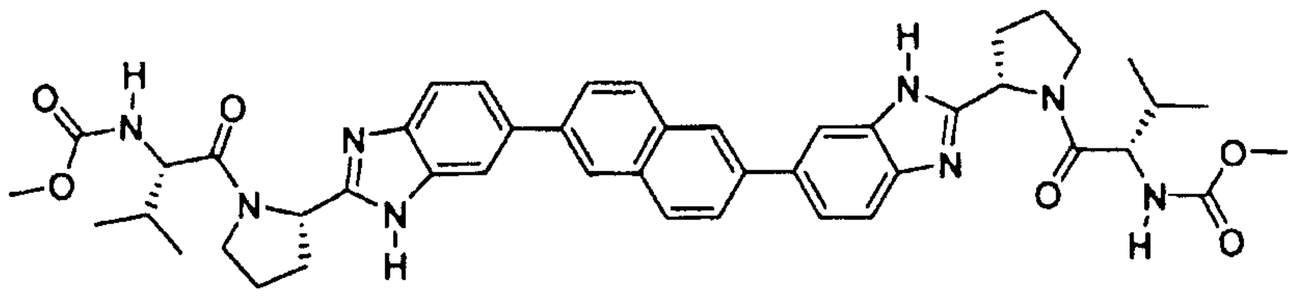
2,6-Dibromo-naphthalene



2-(6-{6-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3*H*-benzoimidazol-5-yl]-naphthalen-2-yl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid

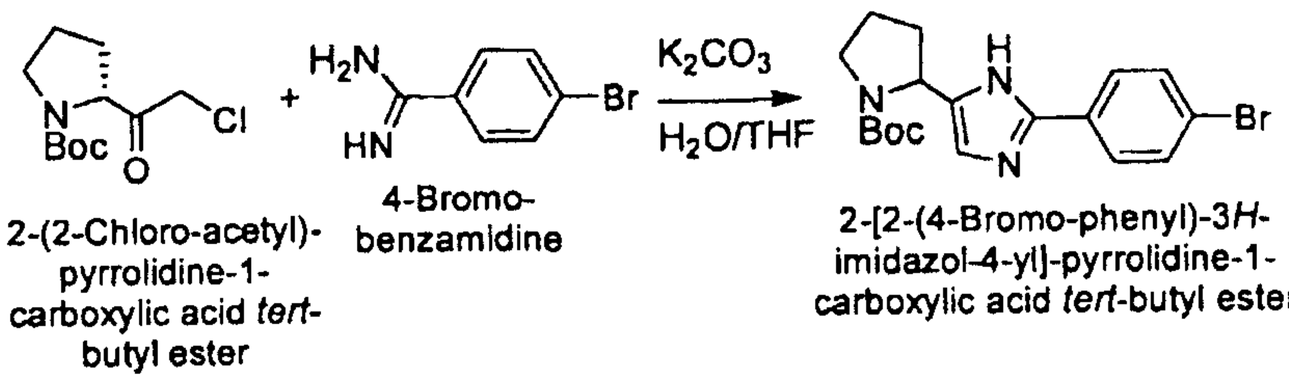


(1-{2-[6-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-naphthalen-2-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(6-{6-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-naphthalen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.170 g), 2,6-Dibromo-naphthalene (0.047 g) and $Pd(PPh_3)_4$ (0.0095 g) in 2.0M potassium carbonate solution (0.41 mL) and dimethoxyethane (0.8 mL) was heated in microwave at 110°C for 40 minutes. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50 to 100% ethyl acetate/hexanes) to give 2-(6-{6-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-naphthalen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0961 g) as a yellow film: LCMS-ESI$^+$: calc'd for $C_{42}H_{47}N_6O_4$: 699.85 ($M+H^+$); Found: 699.1 ($M+H^+$).

(1-{2-[6-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(6-{6-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-benzoimidazol-5-yl]-naphthalen-2-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0961 g) in dichloromethane (2.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (1.1 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0501 g), 4-methylmorpholine (0.091 mL), followed by HATU (0.107 g). Reaction mixture was stirred for 1 hour at ambient temperature, diluted with ethyl acetate and washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$). Organic layer was concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[6-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-naphthalen-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.035 mg): ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.33 (s, 2H), 8.18-8.01 (m, 4H), 7.95-7.80 (m, 5H), 7.35 (d, J=8.70, 2H), 5.25-5.15 (m, 2H), 4.20-4.00 (m, 4H), 3.95-3.75 (m, 4H), 3.55 (s, 6H), 2.55-1.90 (m, 10H), 0.84 (d, J=6.6, 6H), 0.79 (d, J=6.9, 6H); LCMS-ESI$^-$: calc'd for $C_{46}H_{53}N_8O_6$: 813.96 ($M+H^+$); Found: 813.3 ($M+H^+$).

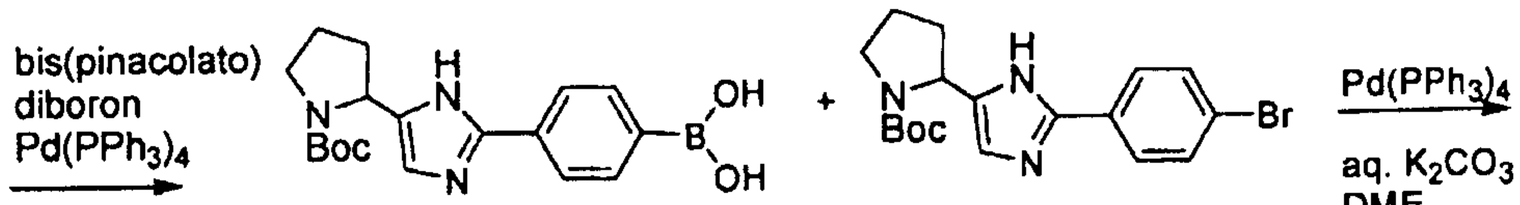
Example AQ1



2-(2-Chloro-acetyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

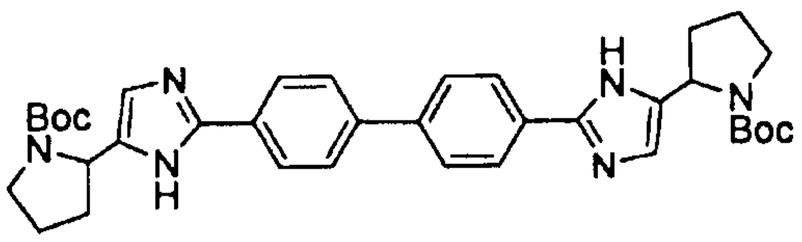
4-Bromo-benzamidine

2-[2-(4-Bromo-phenyl)-3*H*-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

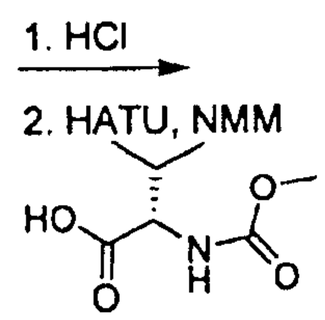


4-[2-(3*H*-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid

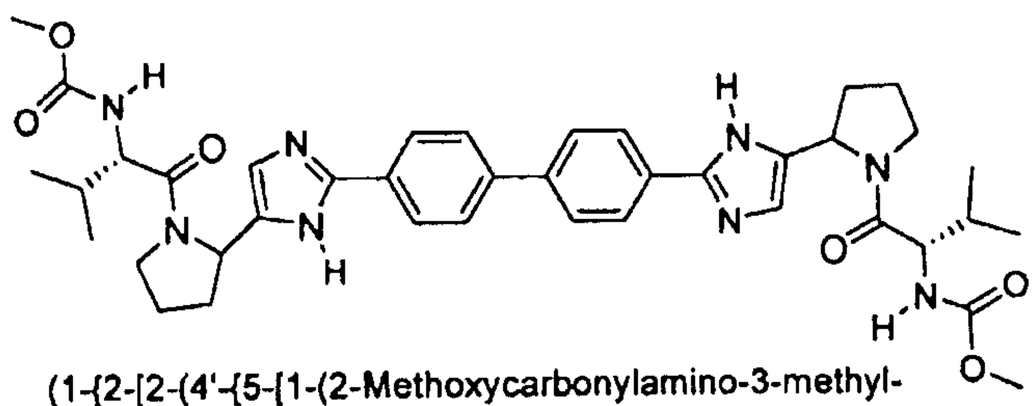
2-[2-(4-Bromo-phenyl)-3*H*-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-(2-{4'-[5-(1-*tert*-butyl-carbamyl-pyrrolidin-2-yl)-1*H*-imidazol-2-yl]-biphenyl-4-yl}-3*H*-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



(1-{2-[2-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-2-yl}-biphenyl-4-yl)-3*H*-imidazol-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-[2-(4-Bromo-phenyl)-3H-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 4-Bromo-benzamidine (0.202 g) and potassium carbonate (0.237 g) in H_2O (0.286 mL) and THF (1.1 mL) was heated to 65°C. 2-(2-Chloro-acetyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.106 g) in THF (0.7 mL) was added over 1 hour and reaction mixture heated at 65°C for 18 hours. Reaction mixture was concentrated to ~ 0.5 mL and extracted with ethyl acetate. Organic layer was washed with H_2O, brine and dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexanes) to give 2-[2-(4-Bromo-phenyl)-3H-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.075 g) as an orange film: LCMS-ESI$^-$: calc'd for $C_{18}H_{23}BrN_3O_2$: 393.30 ($M+H^+$); Found: 391.8, 393.83 ($M+H^+$).

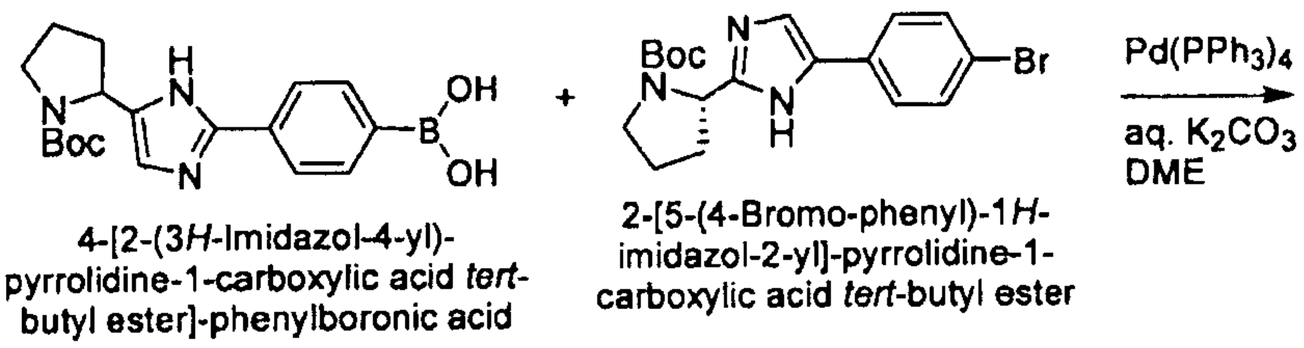
4-[2-(3H-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid: A mixture of 2-[2-(4-Bromo-phenyl)-3H-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.075 g), bis(pinacolato)diboron (0.102 g), $Pd(PPh_3)_4$ (0.011 g) and potassium acetate (0.049 g) in 1,4-dioxane (1.5 mL) was heated at 100°C for 16 hours. More $Pd(PPh_3)_4$ (0.011 g) was added and the reaction was continued for 24 hours. Reaction mixture was cooled to ambient temperatures and diluted with ethyl acetate. Organic layer was washed with brine, dried ($MgSO_4$), concentrated and purified by purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give 4-[2-(3H-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid (0.027 g) as a white powder: LCMS-ESI$^+$: calc'd for $C_{18}H_{25}BN_3O_4$: 357.21 ($M+H^+$); Found: 357.9 ($M+H^+$).

2-(2-{4'-[5-(1-*tert*-butyl-carbamyl-pyrrolidin-2-yl)-1H-imidazol-2-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 4-[2-(3H-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid (0.0098 g), 2-[2-(4-Bromo-phenyl)-3H-imidazol-4-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0118 g) and $Pd(PPh_3)_4$ (0.0012 g) in 2.0M potassium carbonate solution (0.031 mL) and dimethoxyethane (0.8 mL) was heated at 90°C for 18 hours. $PdCl_2(dppf)$ (0.003 g) was added and reaction mixture was heated at 100°C for 18 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified using preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give 2-(2-{4'-[5-(1-*tert*-butyl-carbamyl-pyrrolidin-2-yl)-1H-imidazol-2-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0018 g) as a white powder: LCMS-ESI$^+$: calc'd for $C_{36}H_{45}N_6O_4$: 624.77 ($M+H^+$); Found: 625.0 ($M+H^+$).

(1-{2-[2-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-2-yl}-biphenyl-4-yl)-3H-imidazol-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(2-{4'-[5-(1-*tert*-butyl-carbamyl-pyrrolidin-2-yl)-1H-imidazol-2-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0018 g) in dichloromethane (0.5 mL) was treated with 4N HCl in dioxane (0.5 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (0.4 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (0.0008 g), 4-methylmorpholine (0.0024 mL), followed by HATU (0.0016 g). Reaction mixture was stirred for 1.5 hour at ambient temperature, then purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O +

0.1% TFA). Product was lyophilized to give (1-{2-[2-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-2-yl}-biphenyl-4-yl)-3H-imidazol-4-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a mixture of diastereomers of the bis-TFA salt (0.0017 g): ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.10-7.95 (m, 8H), 7.55-7.40 (m, 2H), 5.25-5.15 (m, 2H), 4.20-3.65 (m, 6H), 3.62 (s, 6H), 2.40-1.90 (m, 10H), 1.05-0.85 (m, 12H); LCMS-ESI$^+$: calc'd for $C_{40}H_{51}N_8O_6$: 739.88 ($M+H^+$); Found: 739.3 ($M+H^+$).

Example AR1

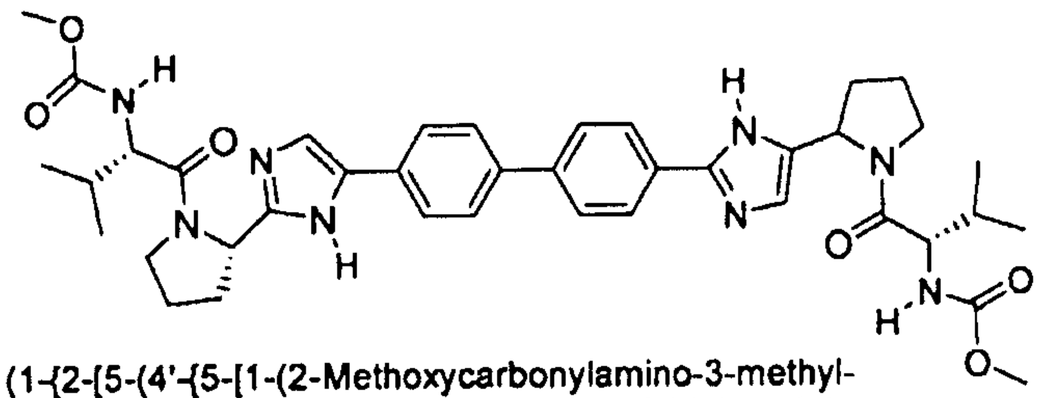


4-[2-(3*H*-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid

2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(2-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-3*H*-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid



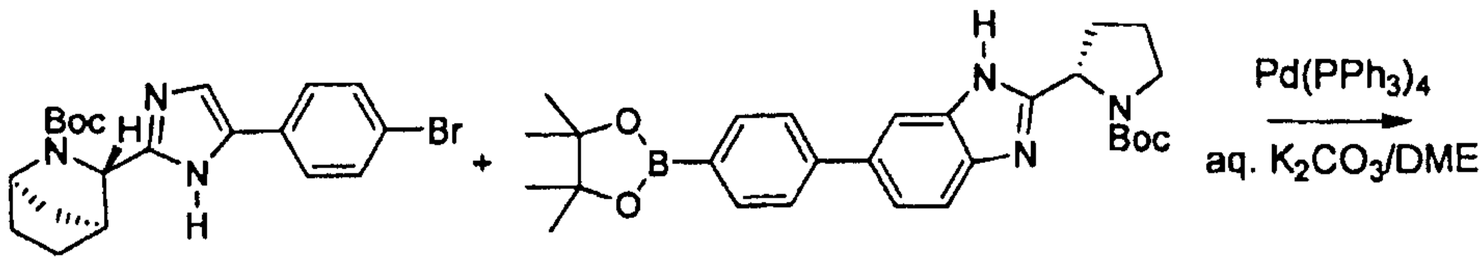
(1-{2-[5-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-2-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(2-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 4-[2-(3H-Imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester]-phenylboronic acid (0.0177 g), 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0148 g) and $Pd(PPh_3)_4$ (0.0022 g), $PdCl_2$(dppf) (0.0016 g) in 2.0M potassium carbonate solution (0.056 mL) and dimethoxyethane (0.8 mL) was heated at 90°C for 18 hours. Reaction mixture was cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified

using preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H2O + 0.1% TFA). Product was lyophilized to give 2-(2-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0066 g) as a white powder: LCMS-ESI$^+$: calc'd for $C_{36}H_{45}N_6O_4$: 624.77 ($M+H^+$); Found: 625.0 ($M+H^+$).

(1-{2-[5-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-2-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(2-{4'-[2-(1-*tert*-butylcarbamyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-3H-imidazol-4-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.0066 g) in dichloromethane (0.5 mL) was treated with 4N HCl in dioxane (0.5 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (0.4 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.0028 g), 4-methylmorpholine (0.012 mL), followed by HATU (0.006 g). Reaction mixture was stirred for 2 hours at ambient temperature, then purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(4'-{5-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-2-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as a mixture of diastereomers of the bis-TFA salt (0.0081 g): ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.05-7.80 (m, 9H), 7.55-7.40 (m, 1H), 5.25-5.15 (m, 2H), 4.20-3.65 (m, 6H), 3.62 (s, 6H), 2.55-1.95 (m, 10H), 1.05-0.85 (m, 12H); LCMS-ESI$^+$: calc'd for $C_{40}H_{51}N_8O_6$: 739.88 ($M+H^+$); Found: 739.3 ($M+H^+$).

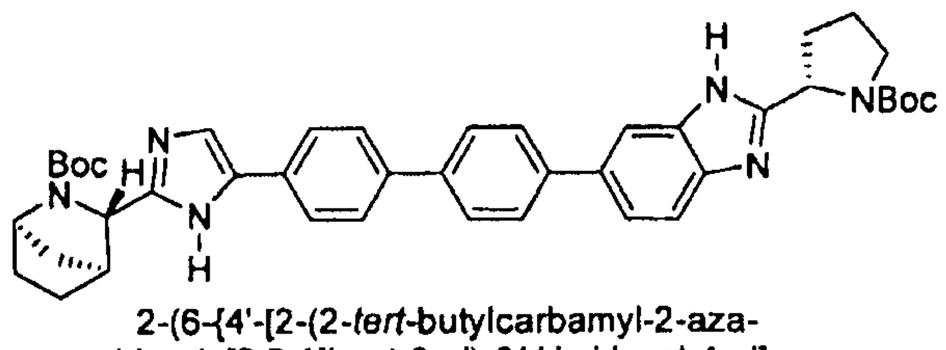
Example AS1



3-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

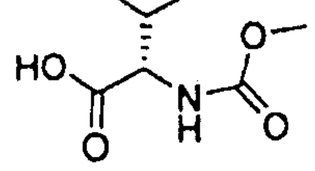
2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

$Pd(PPh_3)_4$, aq. K_2CO_3/DME

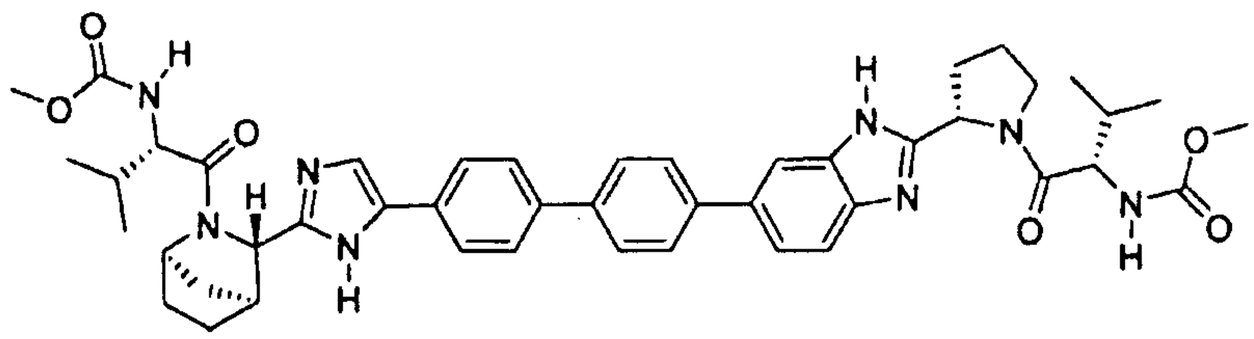


2-(6-{4'-[2-(2-*tert*-butylcarbamyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

1. HCl
2. HATU, NMM



2-Methoxycarbonylamino-3-methyl-butyric acid

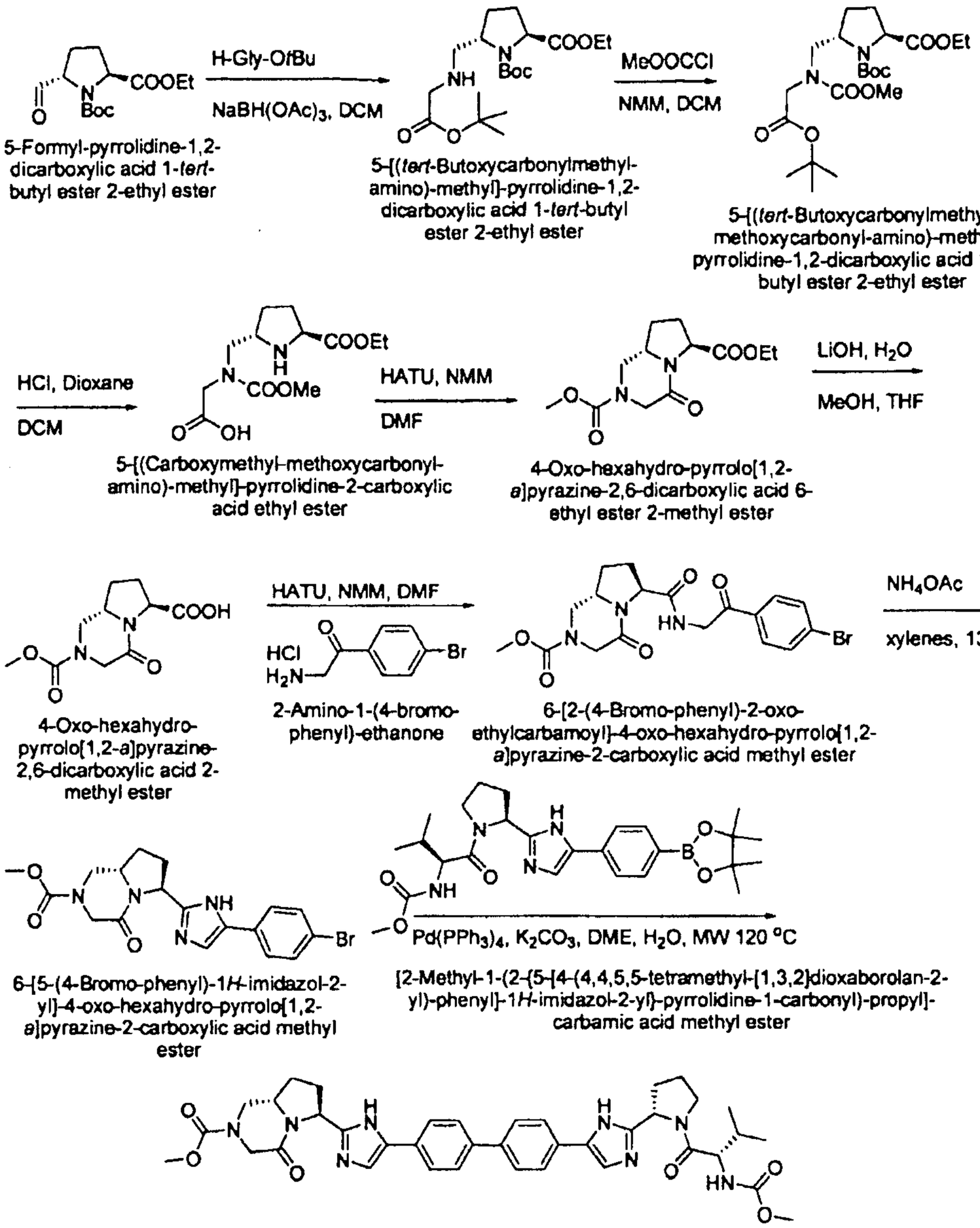


(1-{2-[6-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-(6-{4'-[2-(2-*tert*-butylcarbamyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.142 g), 3-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester (0.1013 g) and $Pd(PPh_3)_4$ (0.014 g) in 2.0M potassium carbonate solution (0.036 mL) and dimethoxyethane (0.8 mL) was heated in microwave at 110°C for 30 minutes. Reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), concentrated and purified using preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give 2-(6-{4'-[2-(2-*tert*-butylcarbamyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.128 g) as a white powder: LCMS-ESI$^+$: calc'd for $C_{42}H_{49}N_6O_4$: 701.87 ($M+H^+$); Found: 701.1 ($M+H^+$).

(1-{2-[6-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A solution of 2-(6-{4'-[2-(2-*tert*-butylcarbamyl-2-aza-bicyclo[2.2.1]hept-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.128 g) in dichloromethane (2.0 mL) was treated with 4N HCl in dioxane (1.0 mL) for 1 hour at ambient temperature. Reaction mixture was concentrated and dried under vacuum. The residue was dissolved in DMF (2.0mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (0.050 g), 4-methylmorpholine (0.090 mL), followed by HATU (0.106 g). Reaction mixture was stirred for 1 hour at ambient temperature. Additional 4-methylmorpholine (0.090 mL) was added and reaction mixture stirred for 1 hour. Reaction mixture was diluted with ethyl acetate, washed with dilute sodium bicarbonate solution, 5% lithium chloride solution, brine and dried ($MgSO_4$), then concentrated and purified by preparative reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to (1-{2-[6-(4'-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (0.080 g): ^{1}H-NMR: 300 MHz, (CD_3OD) δ: 8.05-7.70 (m, 13H), 7.35-7.25 (m, 2H), 5.25-5.15 (m, 1H), 4.67 (s, 1H), 4.43 (s, 1H), 4.20-4.00 (m, 2H), 3.85-3.75 (m, 4H), 3.51 (s, 3H), 3.49 (s, 3H), 2.50-1.45 (m, 14H), 0.95-0.75 (m, 12H); LCMS-ESI$^+$: calc'd for $C_{46}H_{55}N_8O_6$: 815.97 ($M+H^+$); Found: 815.3 ($M+H^+$).

Example AT1



5-Formyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester

5-[(*tert*-Butoxycarbonylmethyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester

5-[(*tert*-Butoxycarbonylmethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester

5-[(Carboxymethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-2-carboxylic acid ethyl ester

4-Oxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester

4-Oxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2,6-dicarboxylic acid 2-methyl ester

2-Amino-1-(4-bromo-phenyl)-ethanone

6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2-carboxylic acid methyl ester

6-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2-carboxylic acid methyl ester

[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

6-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-*a*]pyrazine-2-carboxylic acid methyl ester

5-Formyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester: 5-Formyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester was prepared according to: *J. Org. Chem.* **1995**, *60*, 5011 – 5015.

5-[(*tert*-Butoxycarbonylmethyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester: Sodium triacetoxyborohydride (2.08 g, 9.86 mmol) was added to a

solution of 5-formyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (891 mg, 3.29 mmol) and glycine *t*-butyl ester (1.65 g, 9.86 mmol) in dichloromethane (20 mL) over 2 minutes – a small amount of gas evolution was observed. After 1 hour the reaction was quenched with saturated ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography with methanol and dichloromethane as the eluant at a gradient of 0 – 10%. The fractions containing product were combined and the solvent was removed under reduced pressure to provide 5-[(*tert*-butoxycarbonylmethyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (601 mg, 1.55 mmol, 47 %). $C_{19}H_{34}N_2O_6$ calculated 386.2, observed $[M + 1]^+$ 387.2; rt = 1.61 min.

5-[(*tert*-Butoxycarbonylmethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester: Methyl chloroformate (0.065 mL, 0.85 mmol) was added to a solution of 5-[(*tert*-butoxycarbonylmethyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (300 mg, 0.77 mmol) and 4-methylmorpholine (0.12 mL, 1.2 mmol) in dichloromethane (10 mL) at 0°C. After 15 minutes the mixture was diluted with dichloromethane (30 mL) and washed with water (15 mL), saturated ammonium chloride (15 mL) and saturated sodium chloride (15 mL). The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to provide 5-[(*tert*-butoxycarbonylmethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (304 mg, 0.68 mmol, 88 %). $C_{21}H_{36}N_2O_8$ calculated 444.3, observed $[M + 1]^+$ 445.3; rt = 2.58 min.

5-[(Carboxymethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-2-carboxylic acid ethyl ester: 5-[(*tert*-Butoxycarbonylmethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (304 mg, 0.68 mmol) was added to a solution of hydrogen chloride in dioxane (4N, 15 mL). After 16 hours the solvent was removed under reduced pressure and the resulting residue was azeotroped with toluene to provide 5-[(carboxymethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-2-carboxylic acid ethyl ester (224 mg) – assumed 100 % yield.

4-Oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester: HATU (390 mg, 1.03 mmol) was added to solution of 5-[(carboxymethyl-methoxycarbonyl-amino)-methyl]-pyrrolidine-2-carboxylic acid ethyl ester (187 mg, 0.68

mmol) and 4-methylmorpholine (375 μL, 3.4 mmol) in dimethylformamide (30 mL). After 50 minutes the solvent was removed under reduced pressure and the resulting residue was taken up in ethyl acetate (20 mL) which was washed with half saturated sodium chloride (2 x 10 mL), saturated sodium bicarbonate (2 x 10 mL) and dried over sodium sulfate. The aqueous phase also contained product. The water was removed under reduced pressure and the residue was azeotroped with toluene and then stirred with ethyl acetate (50 mL). The mixture was filtered and combined with the organic extracts. The solvent was removed under reduced pressure and the resulting residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester (141 mg, 0.52 mmol, 76 %). $C_{12}H_{18}N_2O_5$ calculated 270.1, observed $[M + 1]^+$ 271.1; rt = 1.54 min.

The following (ester hydrolysis) constitutes an example of Method 801

4-Oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 2-methyl ester: A solution of lithium hydroxide monohydrate (16.8 mg, 0.38 mmol) in water (0.5 mL) was added to a solution of 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester (86 mg, 0.32 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL). After 2 hours, an aqueous solution of hydrogen chloride (1N, 0.41 mL, 0.41 mmol) was added and the organic solvents were removed under reduced pressure. The resulting aqueous solution was lyophilized for 16 hours to give 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 2-methyl ester. A yield of 100 % was assumed for the subsequent step. $C_{10}H_{14}N_2O_5$ calculated 242.1, observed $[M + 1]^+$ 242.9, $[M + 1]^-$ 241.1; rt = 1.54 min.

The following three steps (amide formation, imidazole cyclization and Suzuki coupling) constitute an example of Method 802

6-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester: A solution of 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 2-methyl ester (81 mg, 0.33 mmol), HATU (152 mg, 0.40 mmol), and 4-methyl morpholine (146 μL, 1.33 mmol) in dimethylformamide (4 mL) was stirred at ambient temperature for 5 minutes. 2-Amino-1-(4-bromo-phenyl)-ethanone hydrochloride (91 mg, 0.37 mmol) was added to the reaction mixture. After 1 hour the solvent was removed under reduced pressure and the resulting residue was taken up in ethyl acetate (10 mL). The resulting mixture

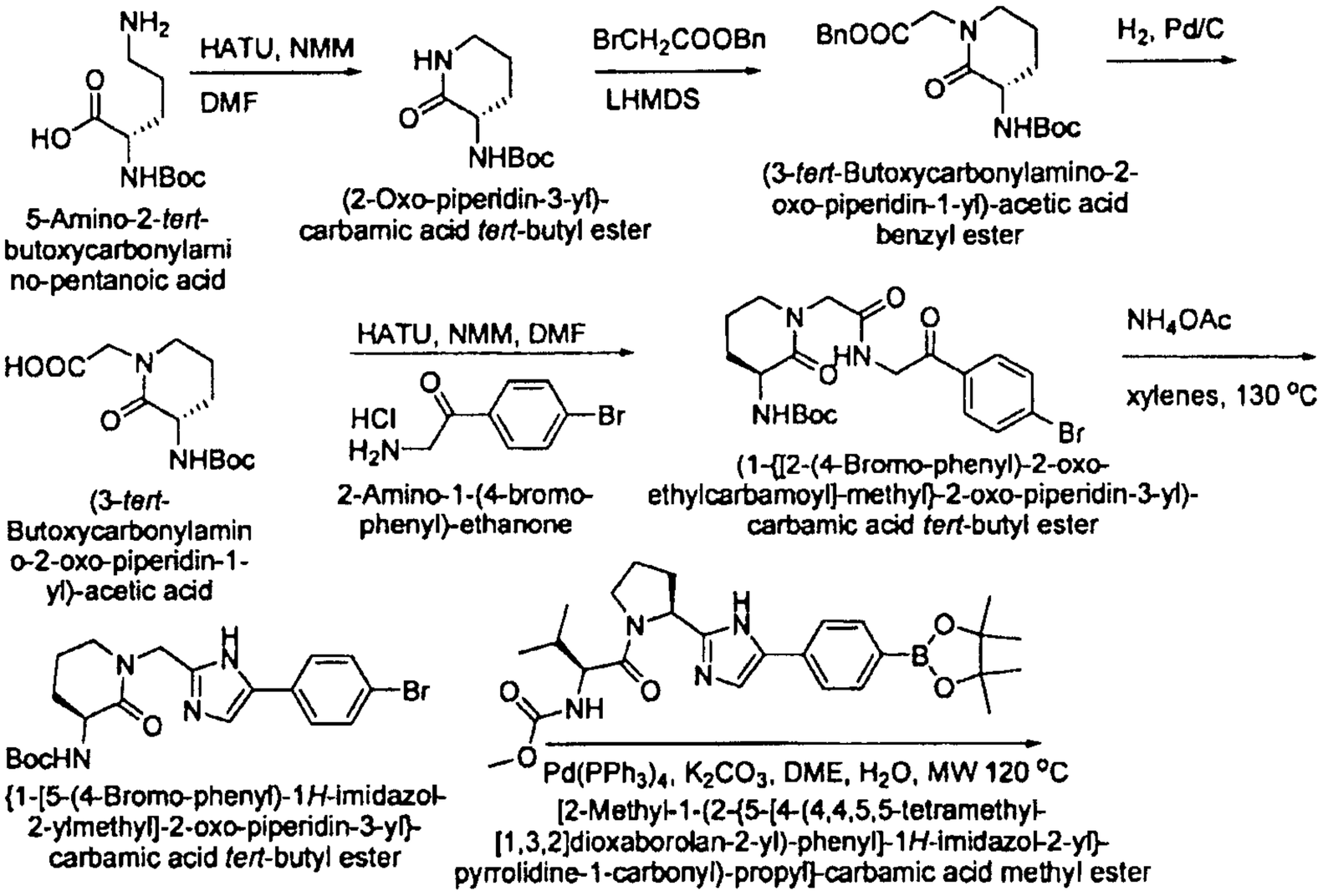
contained a solid and was filtered. The solvent was removed under reduced pressure from the filtrate. The resulting residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide 6-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester (110 mg, 0.25 mmol, 75 %). $C_{18}H_{20}BrN_3O_5$ calculated 437.1observed $[M + 1]^+$ 438.1; rt = 1.82 min.

6-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester: A mixture of 6-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester (110 mg, 0.25 mmol), ammonium acetate (193 mg, 2.5 mmol) and xylenes (8 mL) was heated to 130°C. After 1 hour the mixture was cooled and the xylenes were removed under reduced pressure. Dichloromethane was added to the resulting residue and the mixture was filtered. The solvent was removed under reduced pressure from the filtrate and the resulting residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide 6-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester (65 mg, 0.15 mmol, 60 %). $C_{18}H_{19}BrN_4O_3$ calculated 418.1observed $[M + 1]^+$ 419.1; rt = 1.50 min.

6-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester: A mixture of 6-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester (65 mg, 0.15 mmol), [2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (77 mg, 0.15 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.015 mmol), potassium carbonate (42.8 mg, 0.31 mmol), 1,2-dimethoxyethane (4 mL) and water (1mL) was heated in a microwave reactor at 120°C for 20 minutes. The mixture was cooled and all volatiles were removed under reduced pressure. The resulting residue was taken up in dimethylformamide (2 mL) and subjected to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization to provide 6-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester (16.8 mg, 0.024 mmol, 15 %). $C_{38}H_{44}BrN_8O_6$

calculated 708.3 observed $[M + 1]^+$ 709.4; rt = 1.39 min. ^1H (DMSO-d6): δ = 8.10 (s, 2H), 7.89 (m, 7H), 7.33 (d, *J* = 9 Hz, 1H), 5.03 (t, *J* = 7.8 Hz, 1H), 5.12 (m, 1H), 4.30 (m, 1H), 4.23 (m, 1H), 4.11 (t, *J* = 8.1 Hz, 1H), 3.99 (m, 2H), 3.83 (m, 1H), 3.67 (s, 3H), 3.54 (m,3 H), 2.90 (m, 1H), 2.41 (m, 1H), 2.18 (m, 2H), 2.01 (m,4H), 1.67 (m, 1H), 0.82 (m, 6H).

Example AU1



5-Amino-2-*tert*-butoxycarbonylamino-pentanoic acid

(2-Oxo-piperidin-3-yl)-carbamic acid *tert*-butyl ester

(3-*tert*-Butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid benzyl ester

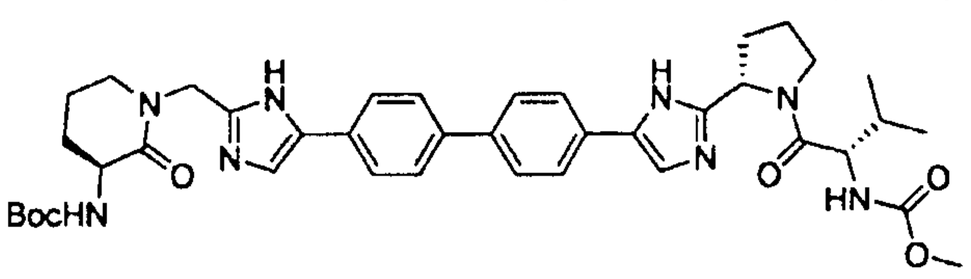
(3-*tert*-Butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid

2-Amino-1-(4-bromo-phenyl)-ethanone

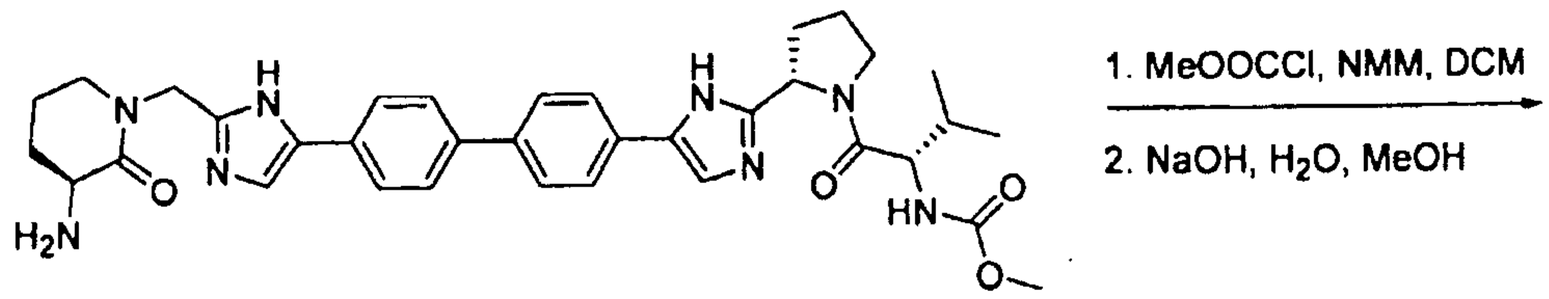
(1-{[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-2-oxo-piperidin-3-yl)-carbamic acid *tert*-butyl ester

{1-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester

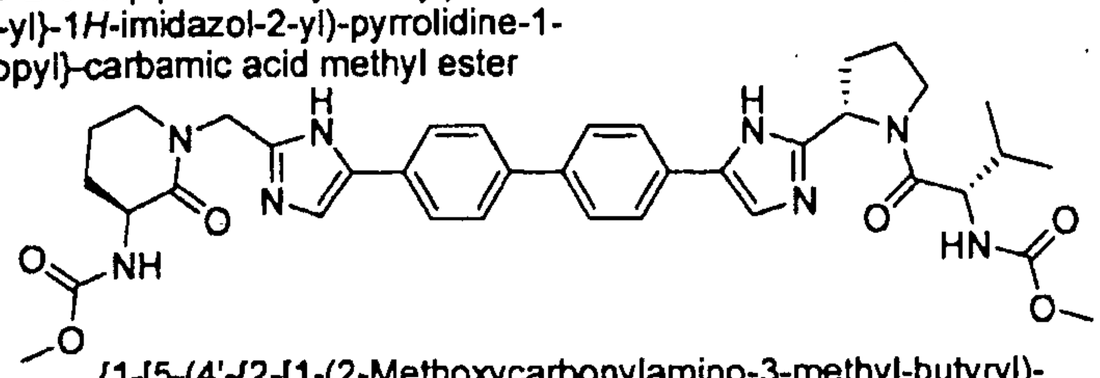
[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester



{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester



{1-[2-(5-{4'-[2-(3-Amino-2-oxo-piperidin-1-ylmethyl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester

(2-Oxo-piperidin-3-yl)-carbamic acid *tert*-butyl ester: 4-Methylmorpholine (4.73 mL, 43.0 mmol) was added to a suspension of R-5-amino-2-*tert*-butoxycarbonylamino-pentanoic acid (5 g, 21.5 mmol) and HATU (9 g, 23.6 mmol) in dimethylformamide (100 mL). After 2 hours the solvent was removed under reduced pressure. Saturated sodium bicarbonate (100 mL) was added to the residue and the resulting mixture was extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL), dried over sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide (*R*)-(2-oxo-piperidin-3-yl)-carbamic acid *tert*-butyl ester (3 g, 14.0 mmol, 66 %). $C_{10}H_{18}N_2O_3$ calculated 214.1 observed $[M + 1]^+$ 215.2; rt = 1.73 min.

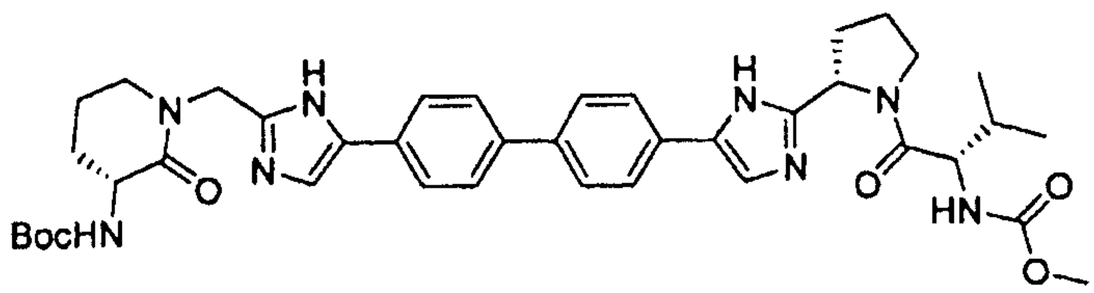
***R*-(3-*tert*-Butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid benzyl ester:** A solution of lithium bis(trimethylsilyl)amide (1.0 M, 16.8 mL, 16.8 mmol) in tetrahydrofuran was added dropwise to a solution of R-2-oxo-piperidin-3-yl)-carbamic acid *tert*-butyl ester (3 g, 14.0 mmol) in tetrahydrofuran in a dry flask under an atmosphere of nitrogen. After 30 minutes bromo-acetic acid benzyl ester (2.41 mL, 15.4 mmol) was added dropwise. After an additional 30 minutes the mixture was quenched with saturated ammonium chloride (30 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with saturated sodium chloride (50 mL) and dried over sodium sulfate. The mixture was filtered and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of ethyl acetate and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide (*R*)-(3-*tert*-

butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid benzyl ester (2.31 g, 6.37 mmol, 45 %). $C_{19}H_{26}N_2O_5$ calculated 362.2 observed $[M + 1]^+$ 363.1; rt = 2.40 min.

The following (benzyl ester cleavage) constitutes and example of Method 803

***(R)*-(3-*tert*-Butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid:** Palladium on carbon (10 %, 500 mg) was added to a solution of (*R*)-(3-*tert*-butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid benzyl ester (2.31 g, 6.37 mmol) in ethanol (50 mL). The atmosphere was replaced with hydrogen and maintained with a balloon filled with hydrogen and the above mixture was vigorously stirred. After 16 hours the hydrogen was removed and CELITE was added to the mixture with stirring and then the mixture was filtered though a pad of CELITE. The solvent was removed under reduced pressure and the resulting residue was azeotroped with toluene to provide (*R*)-(3-*tert*-butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid (1.65 g, 6.06 mmol, 95 %). $C_{12}H_{20}N_2O_5$ calculated 272.3 observed $[M + 1]^+$ 271.2; rt = 1.80 min.

***(R)*-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester:** (*R*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester was prepared by Method **802** substituting (3-*tert*-butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid for 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 2-methyl ester. $C_{40}H_{50}N_8O_6$ calculated 738.4 observed $[M + 1]^+$ 739.5; rt = 1.83 min; ^1H (DMSO-d6): δ =11.82 (s, 1H), 7.79 (m, 4H), 7.64 (m, 4H), 7.47 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 5.05 (m, 1H), 4.62 (d, J = 15.6 Hz, 1H), 4.43 (d, J = 15.2 Hz, 1H), 4.03 (m, 2H), 3.77 (m, 1H), 3.50 (s, 2H), 3.1 (m, 1H), 3.28 (s, 3H), 2.11 (m, 2 H), 1.93 (m, 4H), 1.74 (m, 3H), 1.37 (s, 9H), 0.850 (m, 6H).

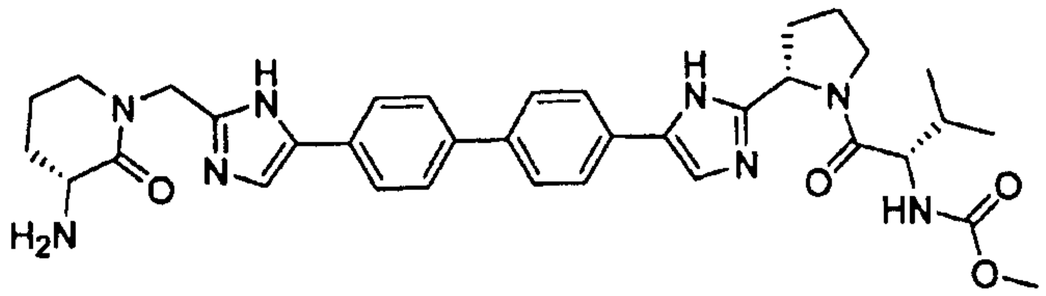


{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester

(*S*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester: (*S*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester was prepared following the method described above. $C_{40}H_{50}N_8O_6$ calculated 738.4 observed $[M + 1]^+$ 739.5; rt = 1.80 min. ^1H (DMSO-d6): δ = 8.09 (s, 1H), 7.90 (m, 8H), 7.30 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 5.10 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 16.4 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.09 (t, J = 8.0 Hz, 1H), 3.99 (m, 2H), 3.82 (m, 2H), 3.51 (s, 2H), 3.43 (t, J = 5.6 Hz, 1H), 2.20 (m, 1H), 2.14 – 1.86 (series m, 9H), 1.34 (s, 9H), 0.810 (m, 6H).

The following (Boc deportation) constitutes an example of Method 804

***(R)*-{1-[2-(5-{4'-[2-(3-Amino-2-oxo-piperidin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:** A solution of hydrogen chloride (4N, 8 mL) in dioxane was added to a solution of (*R*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester (175 mg, 0.24 mmol) in dichloromethane (2 mL). After 1 hour the solvent was removed under reduced pressure. The resulting residue was placed on a high vacuum for 1 hour to provide (*R*)-{1-[2-(5-{4'-[2-(3-amino-2-oxo-piperidin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester. The yield was assumed to be 100 % percent. A sample suitable for analysis was obtained by subjection to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization. $C_{35}H_{42}N_8O_4$ calculated 638.3 observed $[M + 1]^+$ 639.4; rt = 1.41 min. ^1H (DMSO-d6): δ = 8.33 (m, 1H), 8.12 (m, 1H), 7.99 (m, 1 H), 7.92 (m, 6H), 7.26 (d, J = 8.4 Hz, 1H), 5.13 (t, J = 8.0 Hz, 1H), 4.83 (m, 2H), 4.09 (t J = 8.0 Hz,1H), 4.09 – 3.82 (series m, 6H), 2.36 (m, 2H), 2.14 (m, 2H), 1.96 (m, 4H), 0.76 (m, 6H).



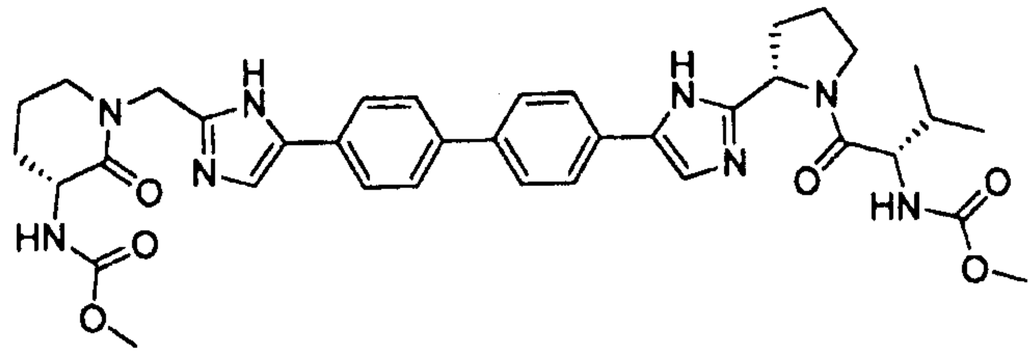
{1-[2-(5-{4'-[2-(3-Amino-2-oxo-piperidin-1-ylmethyl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

(*S*)-{1-[2-(5-{4'-[2-(3-Amino-2-oxo-piperidin-1-yl methyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (*S*)-{1-[2-(5-{4'-[2-(3-Amino-2-oxo-piperidin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester was prepared following the method used for the (R)-isomer with the appropriate substitution described above. $C_{35}H_{42}N_8O_4$ calculated 638.3 observed $[M + 1]^+$ 639.5; rt = 1.39 min. ^1H (DMSO-d6): δ = 8.32 (m, 2H), 7.91 (m, 8H), 7.27 (d, *J* = 8.8 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 4.79 (m, 3H), 4.09 (t, *J* = 7.2 Hz, 1H), 3.89 (m, 4H), 3.51 (s, 3H), 3.45 (m, 1H), 3.40 (m, 1H), 2.35 (m, 2H), 2.32 (m, 3H), 1.95 (m, 6H), 0.78 (m, 6H).

The following two steps (Carbamate formation and imidazole deprotection) constitute an example of Method 805

(*R*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl methyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester: 4-Methylmorpholine (71 μL, 0.64 mmol) was added to a suspension of (*R*)-{1-[2-(5-{4'-[2-(3-amino-2-oxo-piperidin-1-yl methyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (137 mg, 0.21 mmol) in dichloromethane (5 mL). Methyl chloroformate (16.5 μL, 0.21 mmol) was added to the resulting solution. After 20 minutes the solvent was removed under reduced pressure. The residue was taken up in tetrahydrofuran (4 mL) and methanol (2 mL) and an aqueous solution of sodium hydroxide (2 N, 1 mL) was added. After 2 hours the organic solvents were removed under reduced pressure and the aqueous phase was decanted. The residue was taken up in dimethylformamide (2 mL) and subjected to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization to provide (*R*)-{1-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester (46.7 mg, 0.67

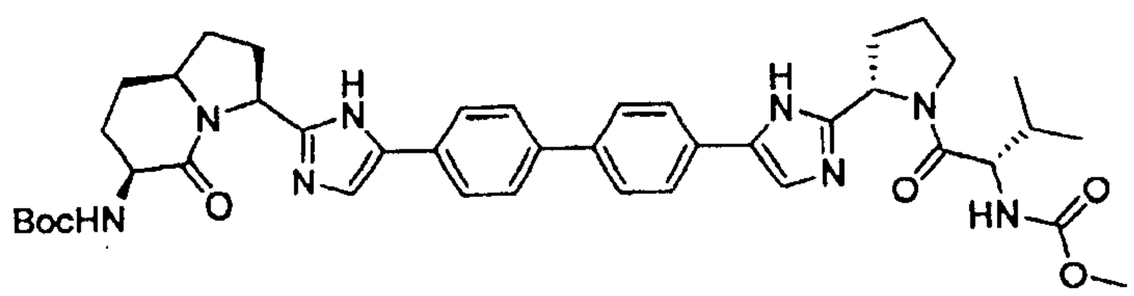
mmol, 32 %). $C_{37}H_{44}N_8O_6$ calculated 696.3 observed $[M + 1]^+$ 697.4; rt = 1.58 min. ^1H (DMSO-d6,): δ = 8.05 (s, 1H), 7.87 (m, 8H) 7.30 (m, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.08 (m, 2H), 3.81 (m, 2H), 3.51 (s, 3H), 3.50 (s, 3H), 2.14 (m, 1H), 2.05 – 1.78 (series m, 8H), 0.78 (m, 6H).



{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester

(*S*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester: (*S*)-{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid methyl ester was prepared following the method described above for the (R) isomer with the appropriate substitution. $C_{37}H_{44}N_8O_6$ calculated 696.3 observed $[M + 1]^+$ 697.4; rt = 1.54 min. ^1H (DMSO-d6): δ = 8.03 (m, 1H), 7.86 (m, 8H), 7.03 (m, 1H), 5.10 (t, *J*= 6.4 Hz, 1H), 4.84 (d, *J* = 16.8 Hz, 1H), 4.52 (d, *J* = 16.4 Hz, 1H), 4.08 (m, 2H), 3.80 (m, 3H), 3.51 (s, 3H), 3005 (s, 3H), 2.29 (m, 1H), 2.14 – 1.78 (series m, 9H), 0.78 (m, 6H).

Example AV1

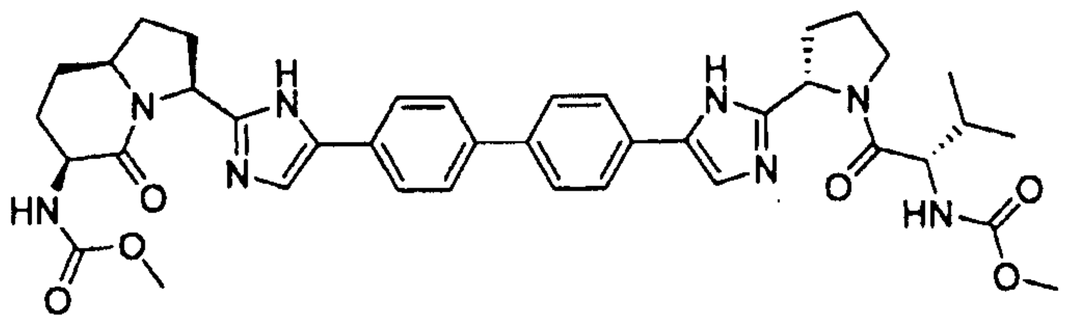


{3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid *tert*-butyl ester

{3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid *tert*-butyl ester: {3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic

acid *tert*-butyl ester was prepared following method **802** substituting 6-*tert*-butoxycarbonylamino-5-oxo-octahydro-indolizine-3-carboxylic acid for 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 2-methyl ester. $C_{42}H_{52}N_8O_6$ calculated 764.4 observed $[M + 1]^+$ 765.5; rt = 1.86 min. ^1H (DMSO-d6): δ = 7.89 (m, 8H), 7.33 (d, J = 11.2 Hz, 1H), 6.88 (m, 1H), 5.12 (m, 2H), 4.09 (m, 2H), 3.84 (m, 2H), 3.60 – 3.45 (series m, 4H), 3.53 (s, 3H), 2.34 (m, 2H), 2.10 (m 8H), 1.79 (m, 3H), 1.37 (s, 9H), 0.81 (dd, J = 8.8 Hz, J = 17.2 Hz, 6H).

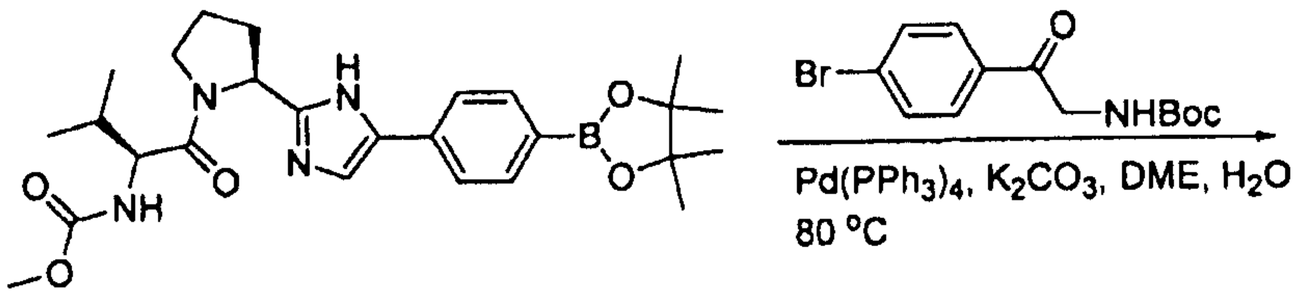
Example AW1



{3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid methyl ester

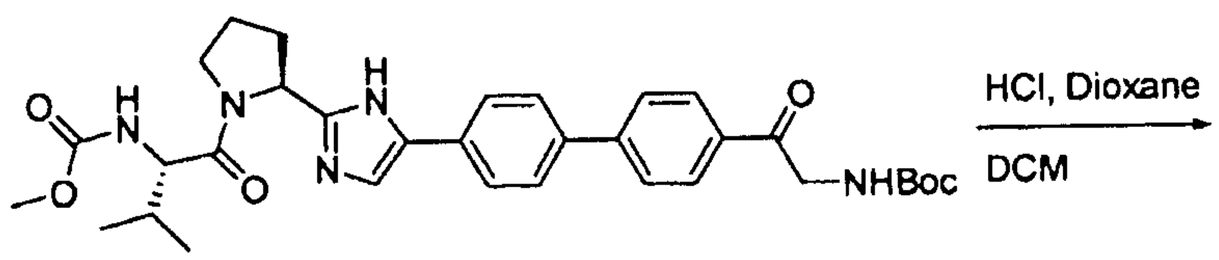
{3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid methyl ester: {3-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid methyl ester was prepared following method **804** followed by method **805**, substituting {3-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-5-oxo-octahydro-indolizin-6-yl}-carbamic acid *tert*-butyl ester for {1-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester in method **804**, and substituting {1-[2-(5-{4'-[2-(6-Amino-5-oxo-octahydro-indolizin-3-yl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester for {1-[2-(5-{4'-[2-(3-amino-2-oxo-piperidin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester in method **805**. $C_{39}H_{46}N_8O_6$ calculated 722.4 observed $[M + 1]^+$ 723.4; rt = 1.62 min. ^1H (DMSO-d6): δ = 8.10 (m, 1H), 7.90 (m, 8H), 7.31 (m, 2H), 5.12 (m, 2H), 4.11 (m, 2H), 3.84 (m 2H), 3.74 (m, 1H), 3.53 (s, 6H), 2.38 (m, 2H), 2.14 (m, 3H), 2.05 (m, 5H), 1.82 (m 3H), 0.81 (dd, J = 8.8 Hz, J = 17.6 Hz, 6H).

Example AX1

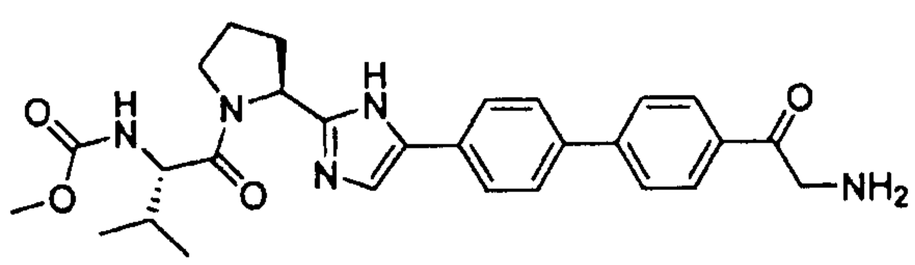


[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

[2-(4-Bromo-phenyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester



[1-(2-{5-[4'-(2-*tert*-Butoxycarbonylamino-acetyl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



[1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

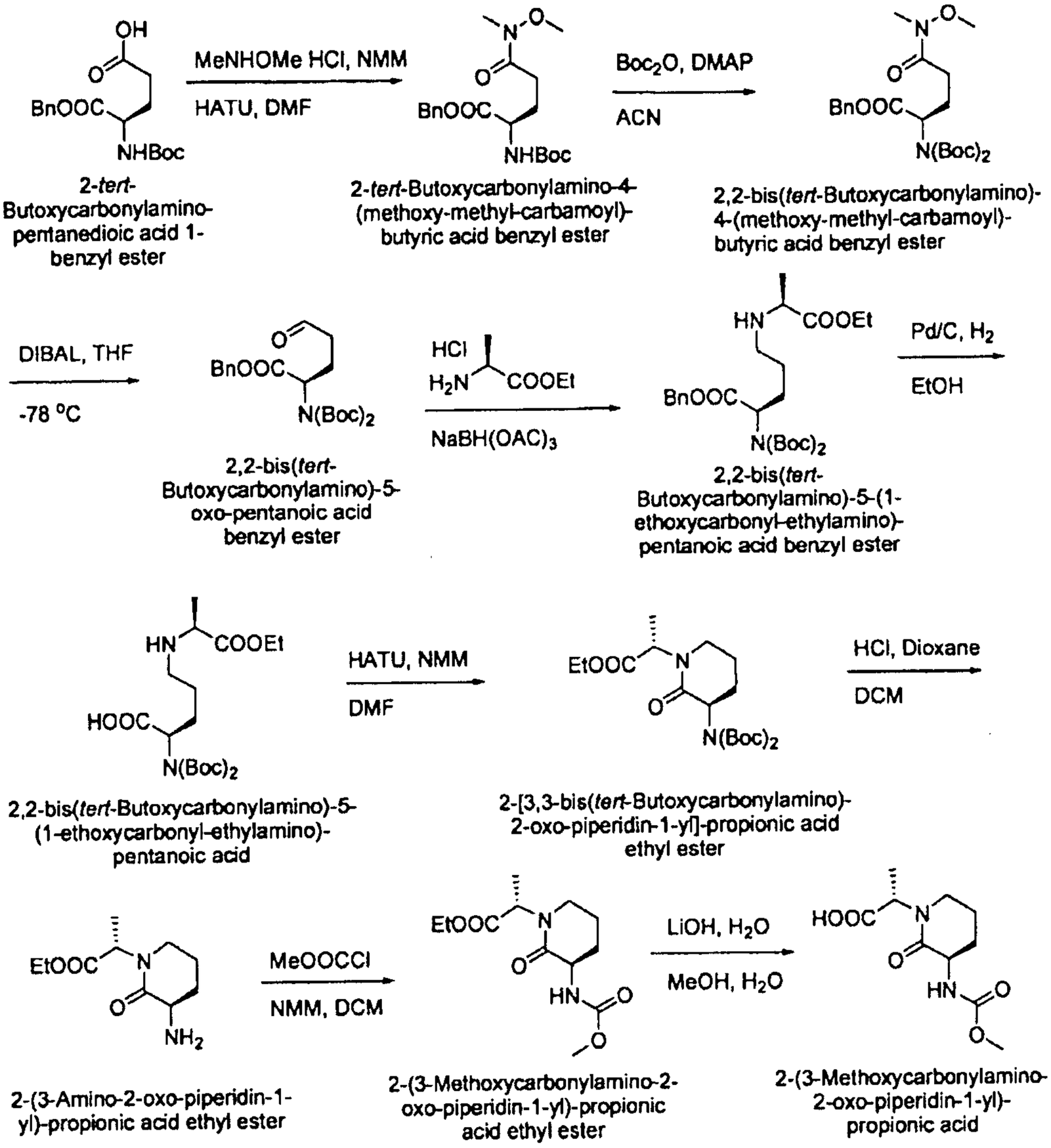
[1-(2-{5-[4'-(2-*tert*-Butoxycarbonylamino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: A mixture of [2-(4-Bromo-phenyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (1 g, 3.2 mmol), [2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (1.57 g, 3.2 mmol), tetrakis(triphenylphosphine)palladium(0) (183 mg, 0.15 mmol), potassium carbonate (878 mg, 6.5 mmol), 1,2-dimethoxyethane (25 mL) and water (2.5 mL) was stirred at 80°C for 16 hours. The mixture was cooled and all volatiles were removed under reduced pressure. The resulting residue was taken up in dichloromethane (100 mL) and washed with water (25 mL) and saturated sodium chloride (25mL). The organic phase was dried over sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to

provide [1-(2-{5-[4'-(2-*tert*-butoxycarbonylamino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (869 mg, 1.4 mmol, 44 %).

$C_{33}H_{41}N_5O_6$ calculated 603.3 observed $[M + 1]^+$ 604.3; rt = 2.01 min. ^1H (DMSO-d6): δ = 11.82 (s, 1H), 8.03 (m, 2H), 7.84 (m 4H), 7.72 (m, 2H), 7.56 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.08 (m, 1H), 5.08 (m, 1H), 4.46 (d, J = 5.7 Hz, 2H), 4.03 (m, 1H), 3.80 (m, 2H), 3.53 (s, 3H), 2.14 (m, 2H), 1.95 (m, 2H), 0.86 (dd, J = 6.9 Hz, J = 15.9 Hz, 6H).

[1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: [1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester was prepared using method **804** substituting [1-(2-{5-[4'-(2-*tert*-butoxycarbonylamino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester for {1-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester. $C_{28}H_{33}N_5O_4$ calculated 503.3 observed $[M + 1]^+$ 504.2; rt = 1.42 min.

Example AY1



2-*tert*-Butoxycarbonylamino-pentanedioic acid 1-benzyl ester

2-*tert*-Butoxycarbonylamino-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester

2,2-bis(*tert*-Butoxycarbonylamino)-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester

2,2-bis(*tert*-Butoxycarbonylamino)-5-oxo-pentanoic acid benzyl ester

2,2-bis(*tert*-Butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid benzyl ester

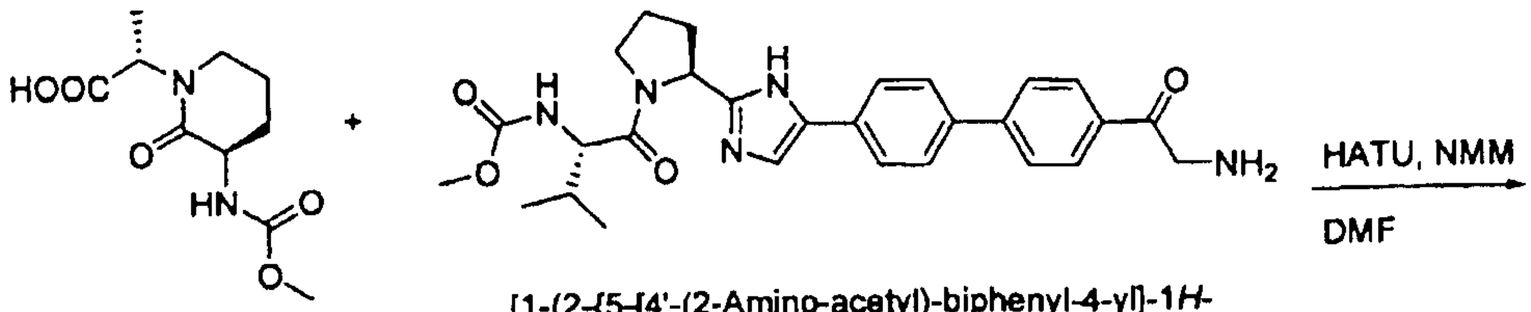
2,2-bis(*tert*-Butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid

2-[3,3-bis(*tert*-Butoxycarbonylamino)-2-oxo-piperidin-1-yl]-propionic acid ethyl ester

2-(3-Amino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester

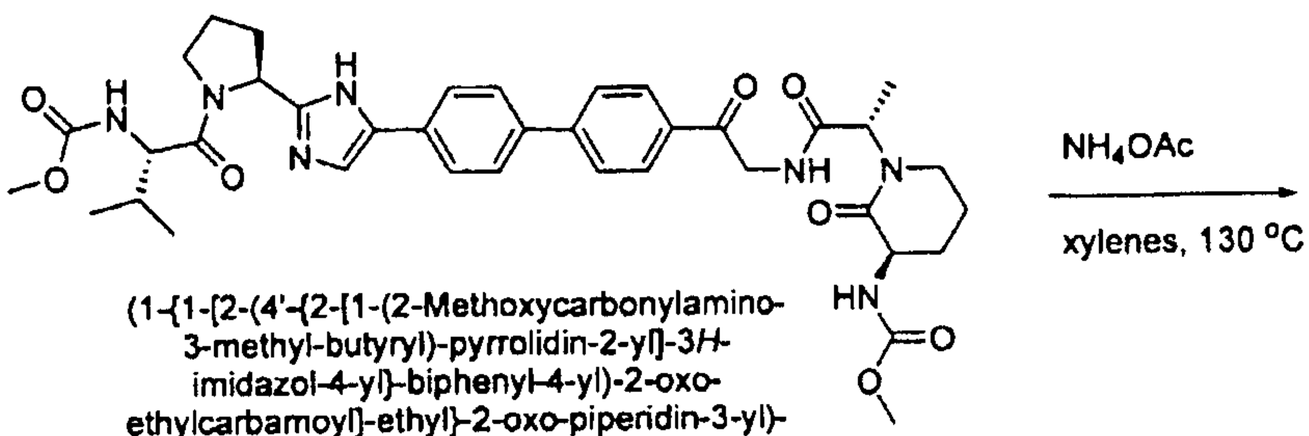
2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester

2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid

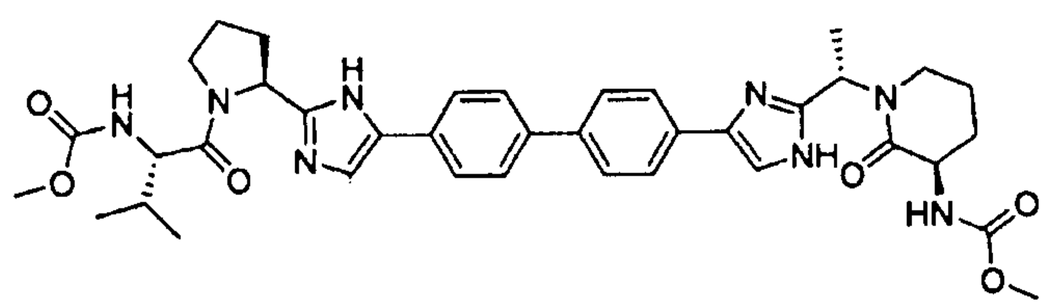


2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid

[1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



(1-{1-[2-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester



(1-{1-[4-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester

2-*tert*-Butoxycarbonylamino-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester: 4-Methylmorpholine (9.77 mL, 88.9 mmol) was added to a suspension of 2-*tert*-butoxycarbonylamino-pentanedioic acid 1-benzyl ester (6 g, 17.7 mmol), and HATU (8.11 g, 21.3 mmol) in dimethylformamide (20 mL). After 5 minutes *N,O*- dimethylhydroxylamine hydrochloride (2.60 g, 26.7 mmol), was added to the solution. After 1 hour the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (150 mL), and washed with water (100 mL), aqueous hydrogen chloride (0.5 N, 2 x 100 mL), saturated sodium bicarbonate (100 mL), and saturated sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of ethyl acetate and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield 2-*tert*-butoxycarbonylamino-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester (6.8 g, 17.8 mmol, 99 %). $C_{19}H_{28}N_2O_6$ calculated 380.2 observed $[M + 1]^+$ 381.2; rt = 2.48 min.

2,2-bis(*tert*-Butoxycarbonylamino)-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester: Di-*tert*-butyl dicarbonate (4.20 g, 19.6 mmol) was added to a solution of 2-*tert*-butoxycarbonylamino-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester (6.8 g, 17.8 mmol) and dimethylamino pyridine (436 mg, 3.5 mmol) in acetonitrile (40 mL). After 16 hours starting material remained and di-*tert*-Butyl dicarbonate (4.20 g, 19.6 mmol) was added again. After 6 days the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (250 mL), washed with water (2 x 100 mL) and saturated ammonium chloride (100 mL), dried over sodium sulfate and filtered. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of ethyl acetate and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield 2,2-bis(*tert*-butoxycarbonylamino)-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester (8.2 g, 17.0 mmol, 95 %). $C_{24}H_{36}N_2O_6$ calculated 480.3 observed $[M + 1]^+$ 481.1; rt = 2.83 min.

2,2-bis(*tert*-Butoxycarbonylamino)-5-oxo-pentanoic acid benzyl ester: A solution of DIBAL (1.0 M, 14.7 mL, 14.7 mmol) in hexane was added dropwise to a solution of 2,2-bis(*tert*-butoxycarbonylamino)-4-(methoxy-methyl-carbamoyl)-butyric acid benzyl ester (4 g, 10.5 mmol) under an atmosphere of nitrogen at –78°C. After 2 hours the mixture was quenched with saturated ammonium chloride (30 mL) and allowed to warm to room temperature. Water (20 mL) was added, and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organic phases were left to stand at room temperature for 15 minutes. The resulting thick gel was filtered through a pad of CELITE. The filtrate was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to provide 2,2-bis(*tert*-butoxycarbonylamino)-5-oxo-pentanoic acid benzyl ester (3.34 g, 7.9 mmol, 75 %). This was used immediately in the next step.

2,2-bis(*tert*-Butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid benzyl ester: Sodium triacetoxyborohydride (5 g, 23.5 mmol) was added to a solution of 2,2-bis(*tert*-butoxycarbonylamino)-5-oxo-pentanoic acid benzyl ester (3.34 g, 7.9 mmol) and alanine ethyl ester hydrochloride (3.62 g, 23.5 mmol) in dichloromethane (30 mL). After 1 hour saturated ammonium chloride (10 mL) was added and the mixture was stirred for 5 minutes. The aqueous phase was extracted with dichloromethane (2 x 15 mL), and the combined organic phases were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl

acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide 2,2-bis(*tert*-butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid benzyl ester (1.7 g, 3.3 mmol, 41 %). $C_{27}H_{42}N_2O_8$ calculated 522.3 observed $[M + 1]^+$ 523.3; rt = 2.08 min.

2,2-bis(*tert*-Butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid: 2,2-bis(*tert*-Butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid was prepared using method **803**, substituting 2,2-bis(*tert*-butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid benzyl ester for (3-*tert*-butoxycarbonylamino-2-oxo-piperidin-1-yl)-acetic acid benzyl ester. $C_{20}H_{36}N_2O_8$ calculated 432.3 observed $[M + 1]^+$ 433.1; rt = 1.73 min.

2-[3,3-bis(*tert*-Butoxycarbonylamino)-2-oxo-piperidin-1-yl]-propionic acid ethyl ester: HATU (1.72 g, 4.5 mmol) was added to a solution of 2,2-bis(*tert*-butoxycarbonylamino)-5-(1-ethoxycarbonyl-ethylamino)-pentanoic acid (1.31 g, 3.0 mmol) and 4-methylmorpholine in dimethylformamide (50 mL). After 30 minutes the solvent was removed under reduced pressure and the residue was subjected to flash chromatography with eluent of ethyl acetate and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide 2-[3,3-bis(*tert*-butoxycarbonylamino)-2-oxo-piperidin-1-yl]-propionic acid ethyl ester (1.11 g, 2.6 mmol, 86 %). $C_{20}H_{34}N_2O_7$ calculated 414.2 observed $[M + 1]^+$ 415.2; rt = 2.77 min.

2-(3-Amino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester: 2-(3-Amino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester was prepared using method **804** substituting 2-[3,3-bis(*tert*-butoxycarbonylamino)-2-oxo-piperidin-1-yl]-propionic acid ethyl ester for {1-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester. $C_{10}H_{18}N_2O_3$ calculated 214.2 observed $[M + 1]^+$ 215.2; rt = 1.21 min.

The following (carbamate formation) constitutes an example of Method 806

2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester: Methyl chloroformate (192 μL, 2.5 mmol) was added to a solution of 2-(3-amino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester (353mg, 1.6 mmol) and 4-methylmorpholine (907 μL, 8.24 mmol) in dichloromethane (10 mL). After 15 minutes the mixture was diluted with dichloromethane (20 mL) and washed with water (10 mL), and aqueous hydrogen chloride (0.5 N, 10 mL). The

organic phase was dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to provide 2-(3-methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester (332 mg, 1.2 mmol, 75 %). $C_{12}H_{20}N_2O_5$ calculated 272.1 observed $[M + 1]^+$ 273.0; rt = 1.82 min.

2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid: 2-(3-Methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid was prepared by method **801** substituting 2-(3-methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid ethyl ester for 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester. $C_{10}H_{16}N_2O_5$ calculated 244.1 observed $[M + 1]^+$ 245.1; rt = 1.53 min.

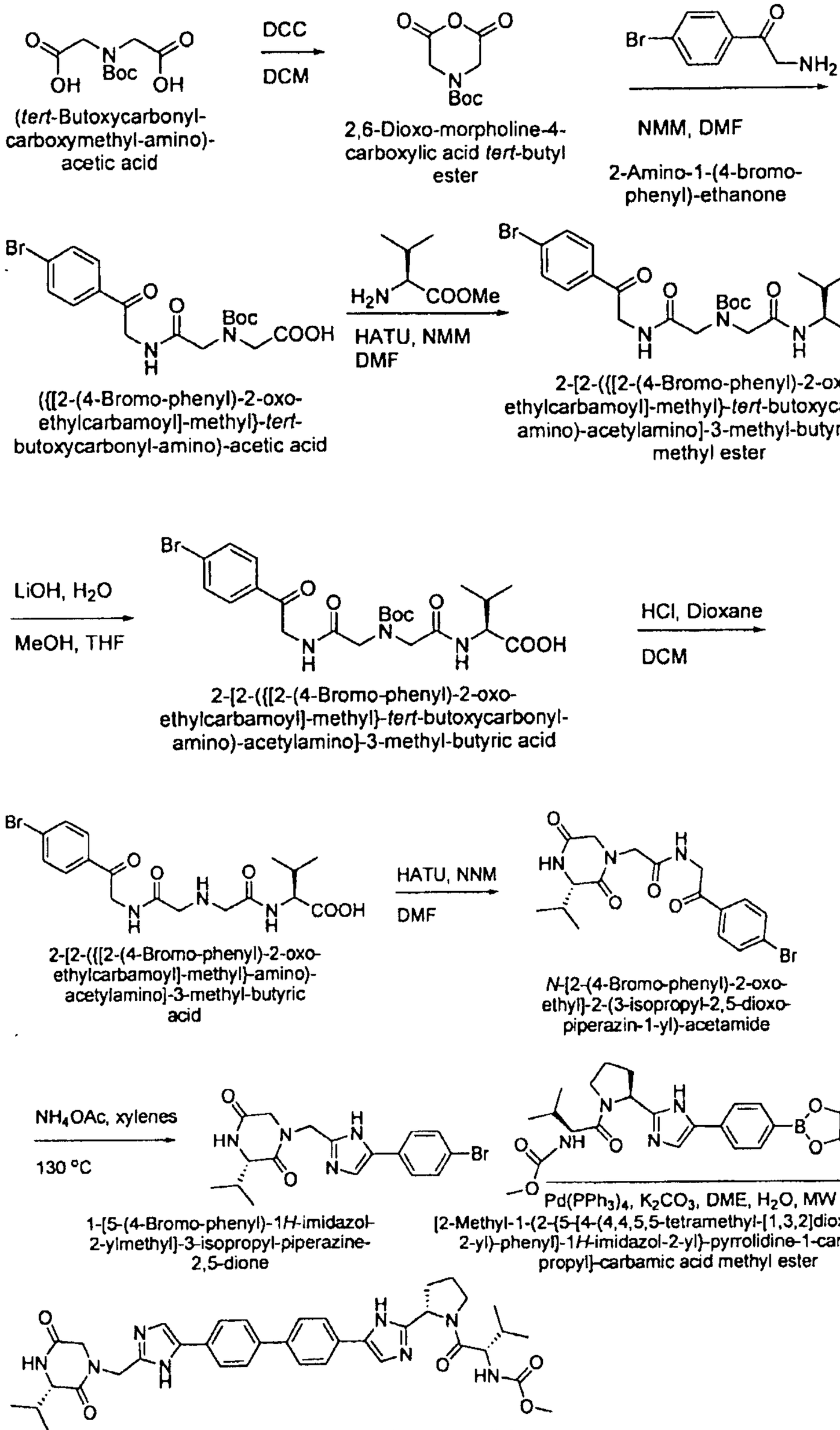
(1-{1-[2-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester: A solution of 2-(3-methoxycarbonylamino-2-oxo-piperidin-1-yl)-propionic acid (48.5 mg, 0.20 mmol), HATU (91 mg, 0.24 mmol), and 4-methylmorpholine (109 µL, 0.99 mmol) in dimethylformamide (5 mL) was stirred at ambient temperature for 5 minutes. [1-(2-{5-[4'-(2-Amino-acetyl)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (100 mg, 0.20 mmol) was added to the reaction mixture. After 40 minutes the solvent was removed under reduced pressure and the resulting residue was taken up in ethyl acetate (10 mL). The resulting mixture contained a solid and was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane followed by 30 % methanol in DCM. The product-containing fractions were combined and the solvent was removed under reduced pressure to provide (1-{1-[2-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester (149 mg, 0.20 mmol, 99%). $C_{38}H_{47}N_7O_8$ calculated 729.4 observed $[M + 1]^+$ 730.6; rt = 1.78 min.

(1-{1-[4-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester: A mixture of ammonium acetate (157 mg, 2.0 mmol), (1-{1-[2-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2-oxo-ethylcarbamoyl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester (149 mg, 0.20 mmol) and xylenes (20 mL) was heated at 130°C for 1 hour. The solvent was removed under reduced pressure. The residue was taken up in dichloromethane (15 mL) and filtered. The solvent was removed under reduced pressure. The residue was taken up in dimethylformamide

(2 mL) and subjected to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization to provide (1-{1-[4-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-ethyl}-2-oxo-piperidin-3-yl)-carbamic acid methyl ester (20.5 mg, 0.029 mmol, 15 %). $C_{38}H_{46}N_8O_6$ calculated 710.4 observed $[M + 1]^+$ 711.4; rt = 1.59 min.

^1H (DMSO-d6): δ = 8.10 (m, 1H), 7.88 (m, 8H), 7.33 (d, J = 8.7 Hz, 2H), 5.33 (m, 1H), 5.12 (t, J = 6.9 Hz, 1H), 4.11 (t, J = 9.0 Hz, 1H), 3.97 (m, 1H), 3.54 (s, 3H), 3.26 (m, 2H), 2.37 (m, 1H), 2.26 – 1.74 (series m, 8H), 1.63 (d, J = 6.3 Hz, 3H), 0.81 (dd, J = 6.9 Hz, J = 13.2 Hz, 6H).

Example AZ1



(*tert*-Butoxycarbonyl-carboxymethyl-amino)-acetic acid

2,6-Dioxo-morpholine-4-carboxylic acid *tert*-butyl ester

2-Amino-1-(4-bromo-phenyl)-ethanone

({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetic acid

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid methyl ester

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-amino)-acetylamino]-3-methyl-butyric acid

N-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-2-(3-isopropyl-2,5-dioxo-piperazin-1-yl)-acetamide

1-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-ylmethyl]-3-isopropyl-piperazine-2,5-dione

[2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

{1-[2-(5-{4'-[2-(3-Isopropyl-2,5-dioxo-piperazin-1-ylmethyl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

2,6-Dioxo-morpholine-4-carboxylic acid *tert*-butyl ester: A suspension of (*tert*-butoxycarbonyl-carboxymethyl-amino)-acetic acid (5 g, 21.4 mmol) and DCC (4.85 g, 23.6 mmol) in dichloromethane was stirred for 16 hours. The mixture was filtered and the solvent was removed from the filtrate to provide 2,6-dioxo-morpholine-4-carboxylic acid *tert*-butyl ester (4.86 g, 21.0 mmol, 99 %).

({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetic acid: 2,6-Dioxo-morpholine-4-carboxylic acid *tert*-butyl ester (2.5 g, 11.6 mmol) was added to a solution of 2-amino-1-(4-bromo-phenyl)-ethanone hydrochloride (3.05 g, 12.2 mmol) and 4-methylmorpholine (1.92 mL, 17.4 mmol) in dimethylformamide (15 mL). After 30 min the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (100 mL) and washed with water (50 mL), aqueous hydrogen chloride (0.5 N, 2 x 50 mL), and saturated sodium bicarbonate (2 x 50 mL). The basic extracts were neutralized and extracted with ethyl acetate (2 x 75 mL). The combined organic phases from the second extraction were dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to provide ({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetic acid (4 g, 9.3 mmol, 80 %). $C_{17}H_{21}BrN_2O_6$ calculated 428.0 observed $[M + 1]^+$ 431.1; rt = 2.36 min.

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid methyl ester: 4-Methylmorpholine (4.1 mL, 37.3 mmol) was added to a suspension of ({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetic acid (4 g, 9.3 mmol), and HATU (4.61 g, 12.1 mmol) in dimethylformamide (25 mL). After 5 minutes *d*-valine methyl ester hydrochloride (1.56 g, 9.3 mmol), was added to the solution. After 1 hour the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (150 mL), and washed with water (100 mL), aqueous hydrogen chloride (0.5 N, 2 x 100 mL), saturated sodium bicarbonate (100 mL), and saturated sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield 2-[2-({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid methyl ester (4.37 g, 8.1 mmol, 87 %). $C_{23}H_{32}BrN_3O_7$ calculated 541.1 observed $[M + 1]^+$ 431.1; rt = 2.65 min.

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid: 2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid was prepared using method **801** substituting 2-[2-({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid methyl ester for 4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2,6-dicarboxylic acid 6-ethyl ester 2-methyl ester. $C_{22}H_{30}BrN_3O_7$ calculated 527.1 observed $[M + 1]^+$ 528.1; rt = 2.39 min.

2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-amino)-acetylamino]-3-methyl-butyric acid: 2-[2-({[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-amino)-acetylamino]-3-methyl-butyric acid was prepared using method **804** substituting 2-[2-({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-*tert*-butoxycarbonyl-amino)-acetylamino]-3-methyl-butyric acid for 1-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester. $C_{17}H_{22}BrN_3O_5$ calculated 427.1 observed $[M + 1]^+$ 428.0; rt = 2.39 min.

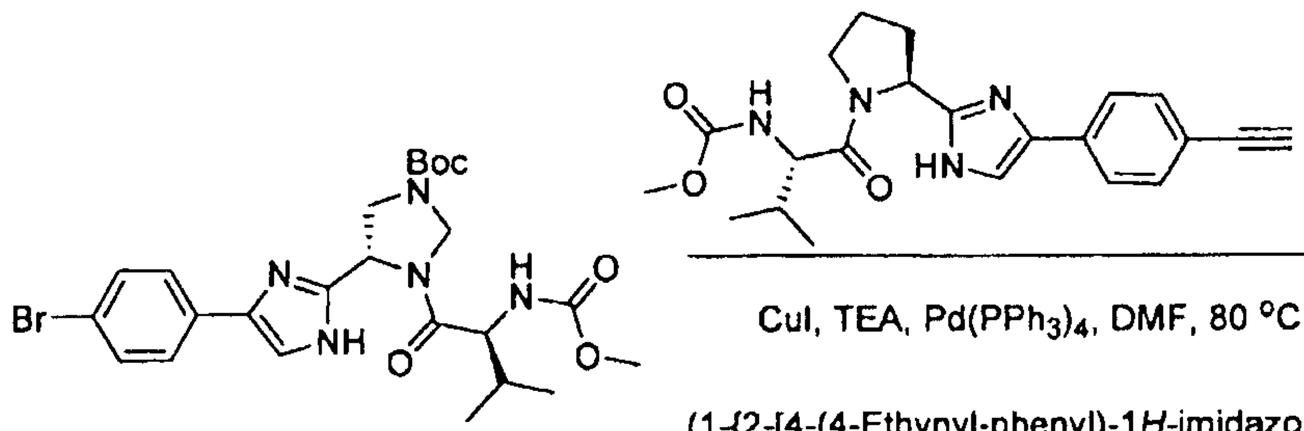
N-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-2-(3-isopropyl-2,5-dioxo-piperazin-1-yl)-acetamide: HATU (3.70 g, 9.7 mmol) was added to a solution of 2-[2-({[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-amino)-acetylamino]-3-methyl-butyric acid (2.78 g, 6.5 mmol), and 4-methylmorpholine (3.57 mL, 32.5 mmol) in DMF (100mL). After 30 min the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (150 mL) and washed with water (50 mL), aqueous hydrogen chloride (0.5 N, 2 x 50 mL), saturated sodium bicarbonate (50 mL) and dried over sodium sulfate. The mixture was filtered and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield N-[2-(4-bromo-phenyl)-2-oxo-ethyl]-2-(3-isopropyl-2,5-dioxo-piperazin-1-yl)-acetamide (1.56 g, 3.8 mmol, 60 %). $C_{17}H_{20}BrN_3O_4$ calculated 409.1 observed $[M + 1]^+$ 410.1; rt = 2.00 min.

{1-[2-(5-{4'-[2-(3-Isopropyl-2,5-dioxo-piperazin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[2-(5-{4'-[2-(3-Isopropyl-2,5-dioxo-piperazin-1-ylmethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid

methyl ester was prepared using the imidazole cyclization from method **802**, substituting N-[2-(4-bromo-phenyl)-2-oxo-ethyl]-2-(3-isopropyl-2,5-dioxo-piperazin-1-yl)-acetamide for 6-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazine-2-carboxylic acid methyl ester and using [2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester in the coupling reaction. $C_{37}H_{44}N_8O_5$ calculated 680.3 observed $[M + 1]^+$ 681.4; rt = 1.57 min. ^1H (DMSO-d6): δ = 8.39 (d, J = 3.0 Hz, 1H), 8.11 (m, 1H), 8.04 (m, 1H), 7.88 (m, 5H), 7.33 (d, J = 8.7 Hz, 1H), 8.13 (m, 1H), 4.79 (m, 1H), 4.65 (d, J = 15.9 Hz, 1H), 4.26 – 4.02 (m, 2H), 3.83 (m, 2H), 3.73 (m, 1H), 3.54 (s, 3H), 2.38 (m, 1H), 2.14 (m, 2H), 2.05 (m, 2H), 8.40 (m, 8H).:

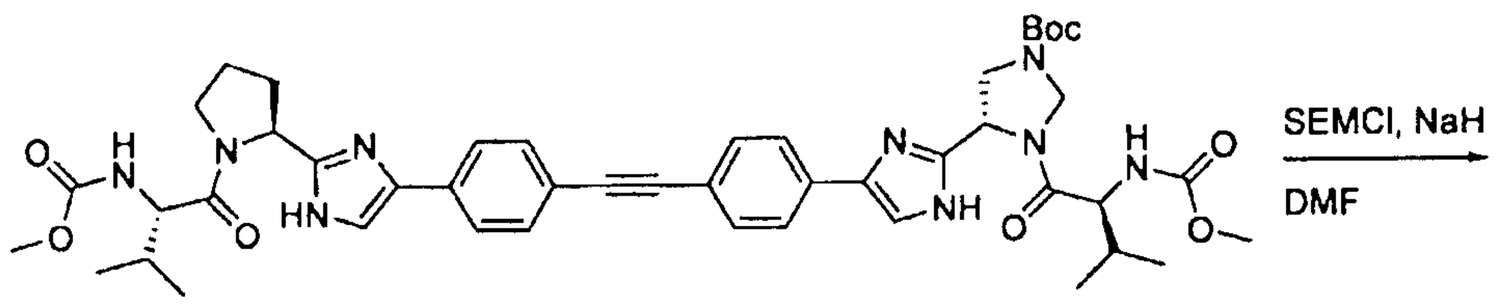
The following 3 steps (Sonogashira coupling, SEM protection, Boc deprotection) constitute an example of method 807

Example BA

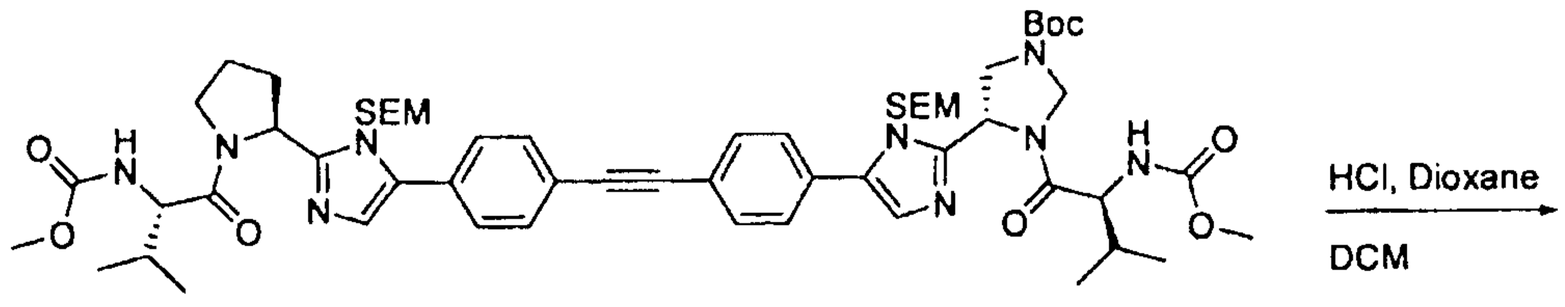


4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester

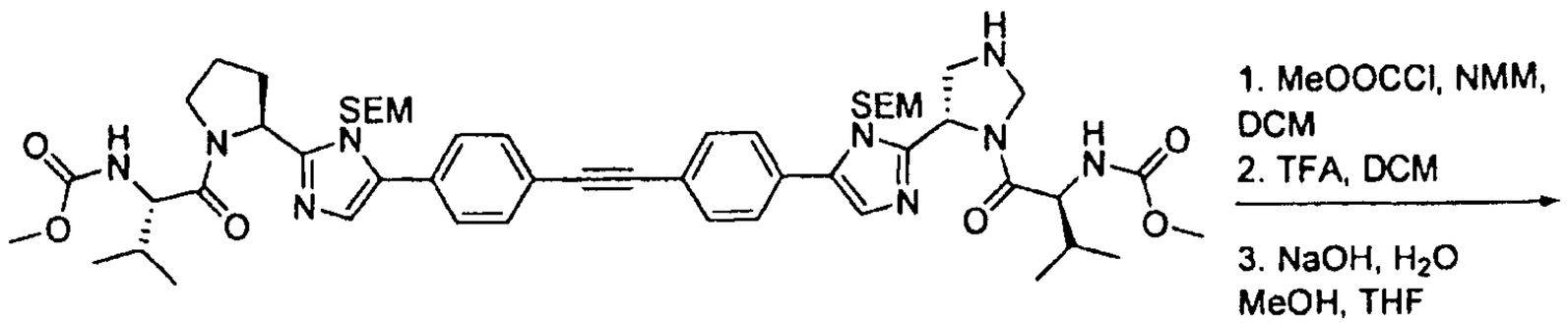
(1-{2-[4-(4-Ethynyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



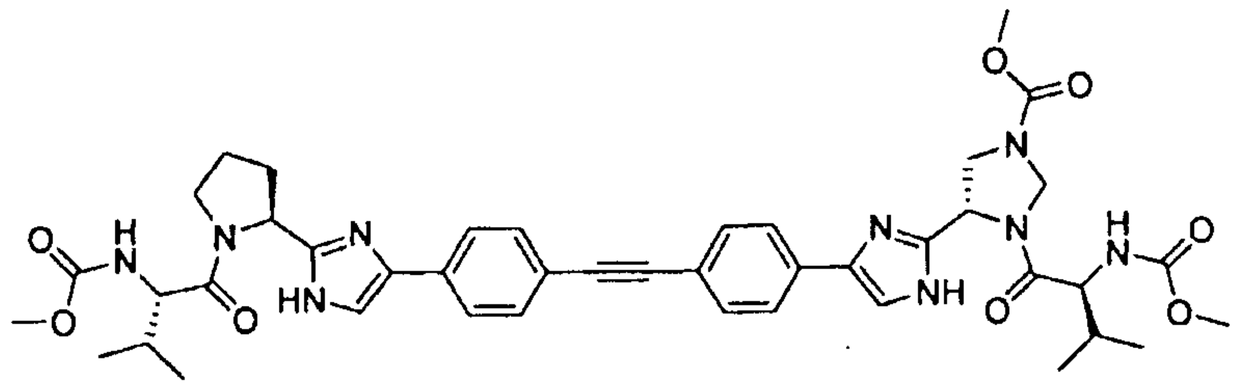
3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester



3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester



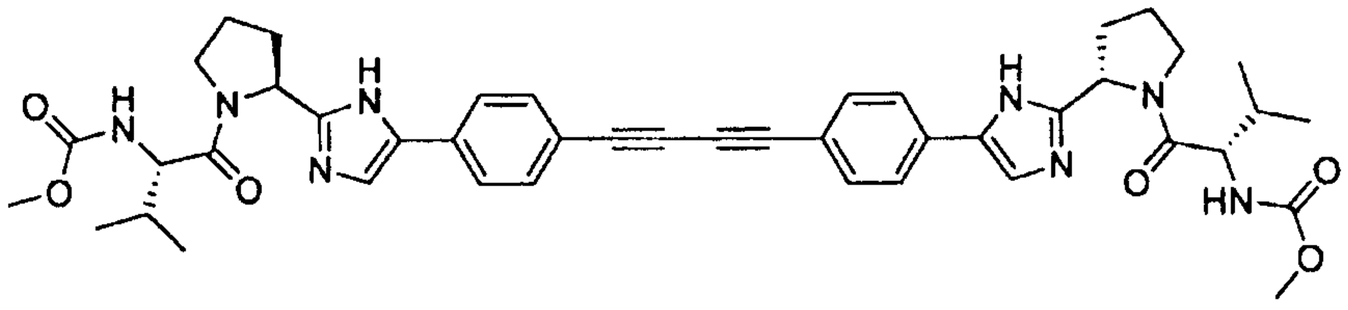
3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazole



3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid methyl ester

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester: A mixture of 4-(4-bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (686 mg, 1.74 mmol), (1-{2-[4-(4-ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (800 mg, 1.45 mmol), copper(I) iodide (28 mg, 0.14 mmol), tetrakis(triphenylphosphine)palladium(0) (167 mg, 0.14 mmol), triethylamine (2.0 mL, 14.5 mmol) and degassed dimethylformamide (10 mL) was stirred at 80°C for 1 hour. (1-{2-[4-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (200 mg, 0.57 mmol) was added. After 1 hour the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (50 mL) and washed with water (10 mL), saturated ammonium chloride (2 x 10 mL), dried over sodium sulfate and filtered. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (439 mg, 0.50 mmol, 35%).

$C_{46}H_{57}N_9O_8$ calculated 863.4 observed $[M + 1]^+$ 864.5; rt = 1.91 min. ^1H (DMSO-d6): δ = 8.07 (m, 1H), 7.76 (m, 4H), 7.68 (m, H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 5.37 (m, 1H), 5.21 (m, 1H), 5.08 (m, 2H), 4.80 (m, 1H), 4.07 (t, *J* = 7.2 Hz, 2H), 3.81 (m, 2H), 3.52 (s, 3H), 3.51 (s, 3H), 2.33 (m, 2H), 2.08 (m, 1H), 1.97 (m, 4H), 1.39 (s, 9H), 1.34 (m, 2H), 0.81 (m, 12H).



{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-buta-1,3-diynyl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-buta-1,3-diynyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-buta-1,3-diynyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester was also isolated in the flash chromatography. The fractions containing this product were combined and the solvent was removed under reduced pressure. The resulting residue was taken up in dimethylformamide (2 mL) and subjected to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization to provide
{1-[2-(5-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-buta-1,3-diynyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (83.2 mg, 0.10 mmol). $C_{44}H_{50}N_8O_6$ calculated 786.4 observed $[M + 1]^+$ 787.6; rt = 2.59 min
^1H (DMSO-d6): δ = 8.06 (s, 2H), 7.79 (m, 4H), 7.72 (m, 4H), 7.28 (d, *J* = 8.8 Hz, 2H), 5.08 (t, *J* = 7.2 Hz, 2H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.80 (m, 4H), 3.51 (s, 6H), 2.32 (m, 2H), 2.11 (m, 2H), 1.99 (m 6H), 0.84 (m, 1H), 0.78 (dd, *J* = 6.8 Hz, *J* = 17.6 Hz, 12H).

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-

[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester: Sodium hydride (60 % in mineral oil, 27 mg, 0.55 mmol) was added to a solution of 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (248 mg, 0.23 mmol) in dimethylformamide (8 mL) under an atmosphere of nitrogen at 0°C. After 15 minutes 2-(trimethylsilyl)ethoxymethyl chloride (107.5 μL, 0.48 mmol) was added and the reaction was allowed to warm to ambient temperature. After 2 hours the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (50 mL) washed with water (20 mL), and dried over sodium sulfate and filtered. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography with eluent of (10 % methanol in ethyl acetate) and hexane. The product-containing fractions were combined and the solvent was removed under reduced pressure to yield 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (410 mg, 0.36 mmol). $C_{58}H_{85}N_9O_{10}Si_2$ calculated 1123.6 observed $[M + 1]^+$ 1124.7; rt = 3.10 min.

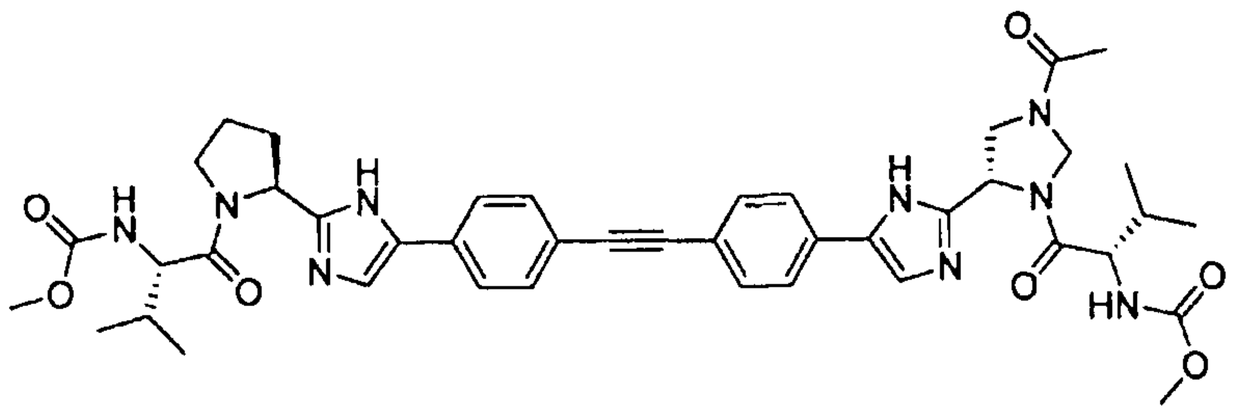
3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazole: 3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazole was prepared using method **804** substituting 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester for {1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-ylmethyl]-2-oxo-piperidin-3-yl}-carbamic acid *tert*-butyl ester. $C_{53}H_{77}N_9O_8Si_2$ calculated 1023.5 observed $[M + 1]^+$ 1024.7; rt = 2.81 min.

The following step constitutes an example of method 808.

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid methyl ester: Methyl chloroformate (15 μL, 0.19 mmol) was added to a solution of 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazole (97 mg, 0.09 mmol), and 4-methylmorpholine (40 μL, 0.36 mmol) in dichloromethane (3 mL). After 30 minutes the solvent was removed under reduced pressure and azeotroped with toluene. The residue was taken up in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added. After 16 hours the volatiles were removed under reduced pressure and the residue was taken up in tetrahydrofuran (4 mL) and methanol (2 mL). An aqueous solution of sodium hydroxide (2 N, 1 mL) was added. After 30 min the organic solvents were removed under reduced pressure and the resulting precipitate was isolated by filtration. The solid was taken up in dimethylformamide (2 mL) and subjected to reverse phase chromatography with an eluent of 0.1 % TFA in water and 0.1 % TFA in acetonitrile. The product-containing fractions were combined and the solvent was removed by lyophilization to provide 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid methyl ester (14.1 mg, 0.017 mmol, 10 %).

$C_{43}H_{51}N_9O_8$ calculated 821.4 observed $[M + 1]^+$ 822.8; rt = 1.72 min. ^1H (DMSO-d6): δ = 8.07 (m, 1H), 7.77 (m, 7H), 7.67 (m, 2H), 7.57 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 5.41 (m, 1H), 5.27 (d, *J* = 5.6 Hz, 1H), 5.15 (d, *J*= 5.6 Hz, 1H), 5.08 (t, *J* = 7.6 Hz, 2H), 4.07 (t, *J* = 13.2 Hz, 2H), 3.83 (m, 2H), 3.76 (m, 2H), 3.64 (s, 3H), 3.58 (m, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 2.33 (m, 2H), 2.13 (m, 1H), 2.03 (m, 5H), 1.90 (m, 2H), 0.805 (m, 18H).

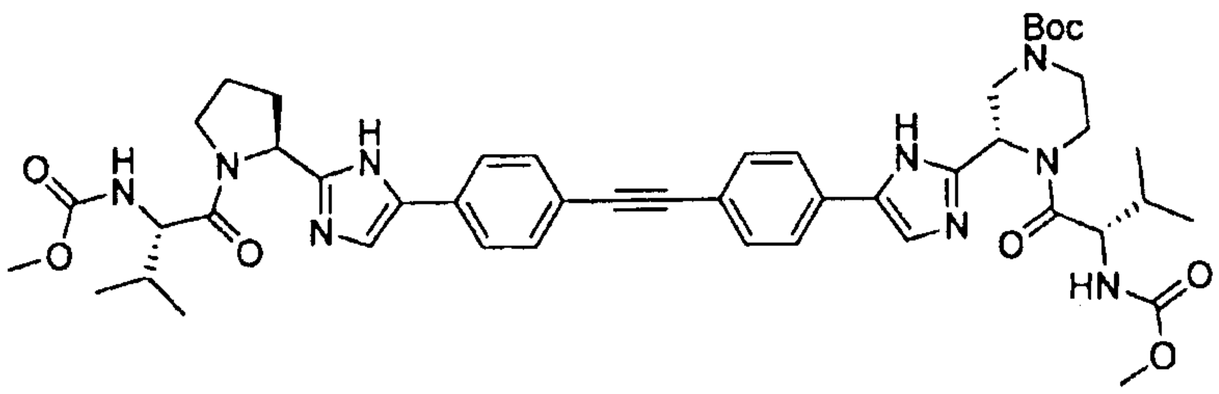
Example BB



(1-{2-[5-(4-{4-[1'-Acetyl-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-3*H*,1'*H*-[2,4']biimidazolyl-4-yl]-phenylethynyl}-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-{4-[1'-Acetyl-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-3H,1'H-[2,4']biimidazolyl-4-yl]-phenylethynyl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester was prepared following method **808** in Example BA substituting acetic anhydride for methyl chloroformate in the first step of the synthesis. $C_{43}H_{51}N_9O_7$ calculated 805.4 observed $[M + 1]^+$ 806.5; rt = 1.65 min; ^1H (DMSO-d6): δ = 8.06 (m,1 H), 776 (m, 6H), 7.68 (m, 3H), 7.56 (d, *J* = 7.6 Hz, 3H), 7.29 (d, *J* = 9.2 Hz, 1H), 5.47 (m, 1H), 5.38 (m, 1H), 5.27 (m,1 H), 5.18 (m,1 H), 5.08 (t, *J* = 6.8 Hz, 2H), 4.17 (m,1 H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.93 (m, 2H), 3.84 (m, 4H), 3.52 (s, 3H), 3.51 (s, 6H), 3.37 (m, 1H), 2.34 (m, 2H), 2.13 (m, 1H), 1.99 (m, 12H), 0.81 (m, 18H).

Example BC



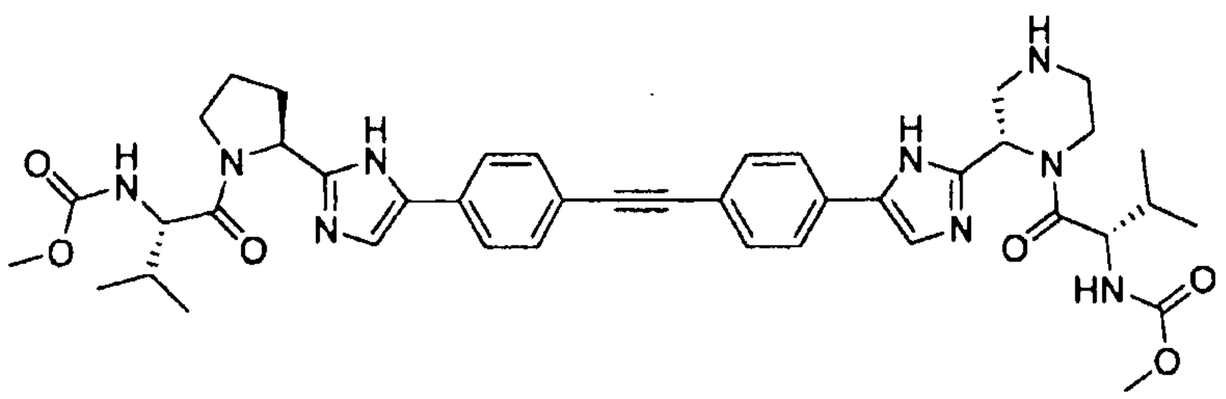
4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester

4-(2-Methoxycarbonylamino-3-methyl-butyryl)-3-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-piperazine-1-carboxylic acid *tert*-butyl ester was prepared following step one of method **807**, substituting (1-{2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-piperazine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for 4-(4-bromo-phenyl)-3'-(2-methoxycarbonylamino-3-

methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester in the first step of Example BA. $C_{47}H_{59}N_9O_8$ calculated 877.5 observed $[M + 1]^+$ 878.5; rt = 1.65 min

^1H (DMSO-d6): δ = 8.08 (m, 1H), 7.78 (m, 4H), 7.68 (m, 2H), 7.54 (m, 2H), 7.29 (d, *J* = 9.2 Hz, 2H), 5.54 (m, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.32 (m, 2H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.81 (m, 4H), 3.52 (s, 3H), 3.51 (s, 3H), 3.41 (m, 1H), 2.34 (m, 1H), 2.14 (m, 1H), 2.00 (m, 4H), 1.28 (3, 3H), 1.17 (br s, 3H), 0.80 (m, 12 H).

Example BD



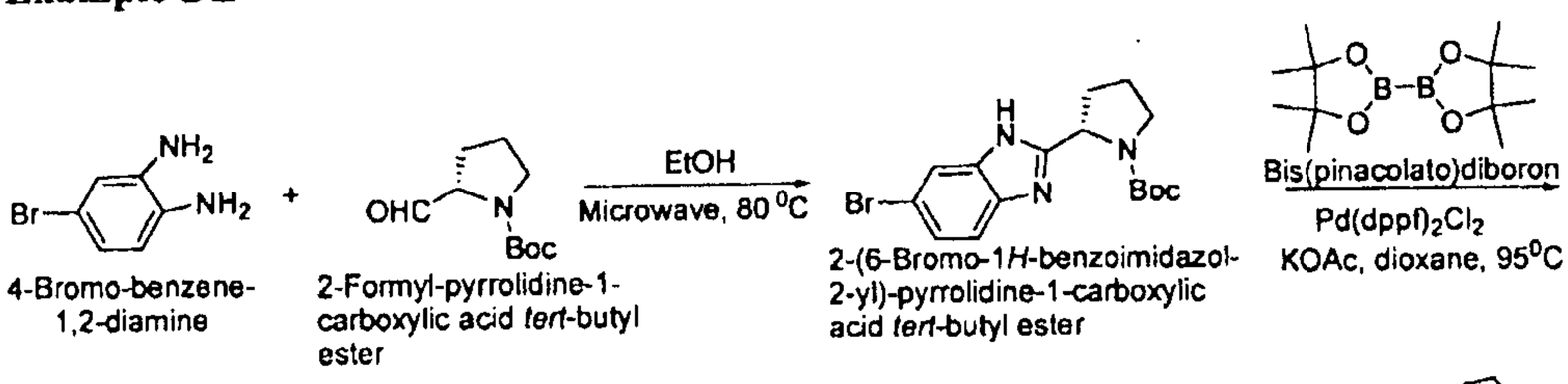
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-3*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

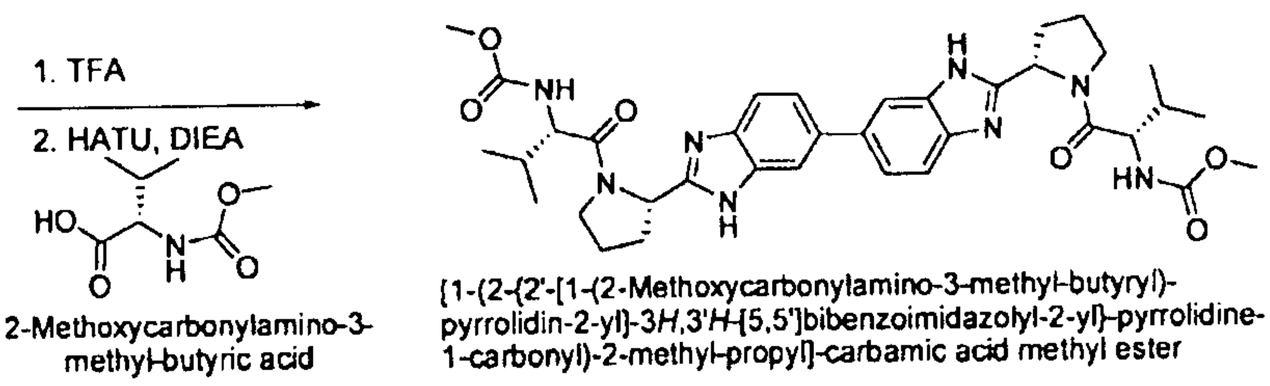
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester was prepared following method 807 substituting (1-{2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-piperazine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester for 4-(4-bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester. Followed by method 808, substituting [1-(2-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester for 3'-(2-methoxycarbonylamino-3-methyl-butyryl)-4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazole and leaving

out methyl chloroformate. $C_{42}H_{51}N_9O_6$ calculated 777.4 observed $[M + 1]^+$ 778.4; rt = 1.58 min.

^1H (DMSO-d6): δ = 9.30 (m, 1H), 7.9 (m, 2H), 7.75 (m, 3H), 7.63 (m, 2H), 7.52 (m 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 5.96 (1H), 5.07 (m, 1H), 4.49 (m, 1H), 4.28 (m, 2H), 4.06 (m, 2H), 3.80 (m, 4H), 3.56 (m, 1H), 3.53 (s, 3H), 3.51 (s, 3H), 3.27 (m, 2.12 (m, 1H), 1.96 (m, 4H), 0.95 (m, 1H), 0.81 (m, 12H).

Example BE





2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 4-bromo-benzene-1,2-diamine (2.4 g) and 2-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.55 g) in ethanol (5 mL) was heated in microwave at 80°C for 1 hour. Mixture was concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.6 g, yield 55%). LCMS-ESI$^-$: calc'd for $C_{16}H_{20}BrN_3O_2$: 366.25; Found: 365.8 ($M+H^+$).

2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (890 mg, 2.43 mmol), bis(pinacolato)diboron(1.36g, 5.35 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(99 mg, 0.12 mmol) and potassium acetate (620 mg, 6.32 mmol) in 15 mL dioxane was heated to 95°C for 4 hour. The reaction mixture was cooled and dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (588 mg, yield 59%). LCMS-ESI$^-$: calc'd for $C_{32}H_{20}BN_3O_4$: 413.32; Found: 414.0 ($M+H^+$).

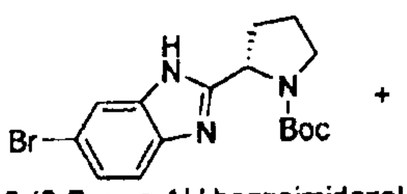
2-[2'-(1-Boc-pyrrolidin-2-yl)-3H,3'H-[5,5']bibenzoimidazolyl-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (64 mg, 0.174 mmol), 2-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (72 mg, 0.174 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (48 mg, 0.35 mmol) in 2 ml 1,2-dimethoxyethane and 1 mL water was heated to 110°C in microwave for 15 minutes. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 10% methanol/ethyl acetate) to give 2-[2'-(1-Boc-pyrrolidin-2-yl)-3H,3'H-[5,5']bibenzoimidazolyl-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15 mg, yield 15%). LCMS-ESI$^-$: calc'd for $C_{32}H_{40}N_6O_4$: 572.70; Found: 573.1 ($M+H^+$).

[1-(2-{2'-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H,3'H-[5,5']bibenzoimidazolyl-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Trifluoroacetic acid (0.5 mL) was added to (2-[2'-(1-Boc-pyrrolidin-2-yl)-3H,3'H-[5,5']bibenzoimidazolyl-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15 mg, 0.0262 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1.5 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (10 mg, 0.058 mmol), diisopropylethylamine (27 μL), followed by HATU (20 mg). Reaction mixture was stirred at 0°C for 60 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried

(MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give [1-(2-{2'-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H,3'H-[5,5']bibenzoimidazolyl-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester as the bis-TFA salt (8.1 mg).

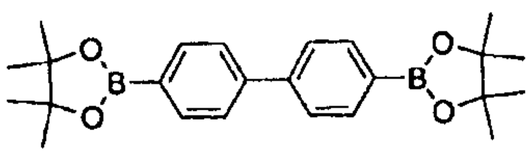
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.02 (s, 2H), 7.88 (m, 4H), 5.38 (m, 2H), 4.27(d, 2H), 4.12(m, 2H), 3.96 (m, 2H), 3.62 (s, 6H), 2.62 (m, 2H), 2.40-2.20 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{36}H_{46}N_8O_6$: 686.80; Found: 687.3 ($M+H^+$).

Example BF

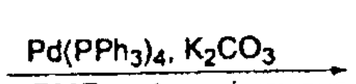


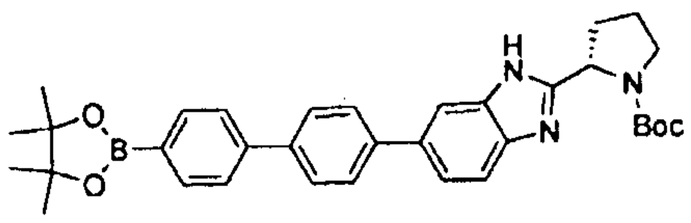
2-(6-Bromo-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

+

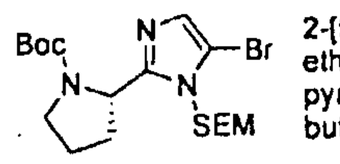


4,4'-bipheynldiboronic acid dipinacol ester

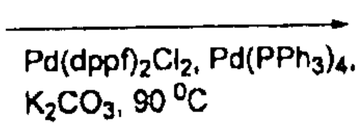


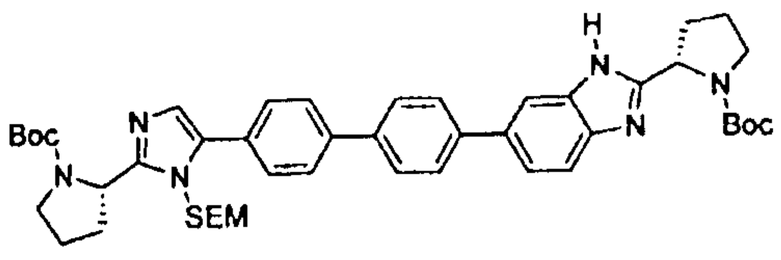


2-{6-[4'-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1*H*-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

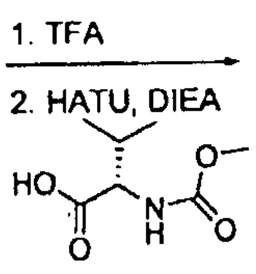


2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

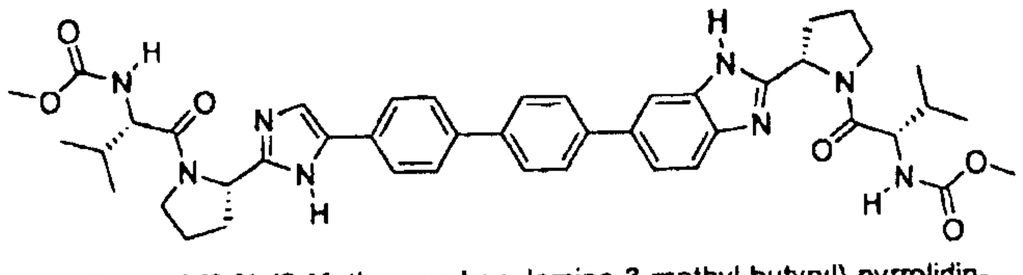




2-(6-{4'-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-biphenyl-4-yl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid



(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-{6-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (230 mg, 0.628 mmol), 4,4'-bipheynldiboronic acid dipinacol ester (1.28 g, 3.14 mmol),

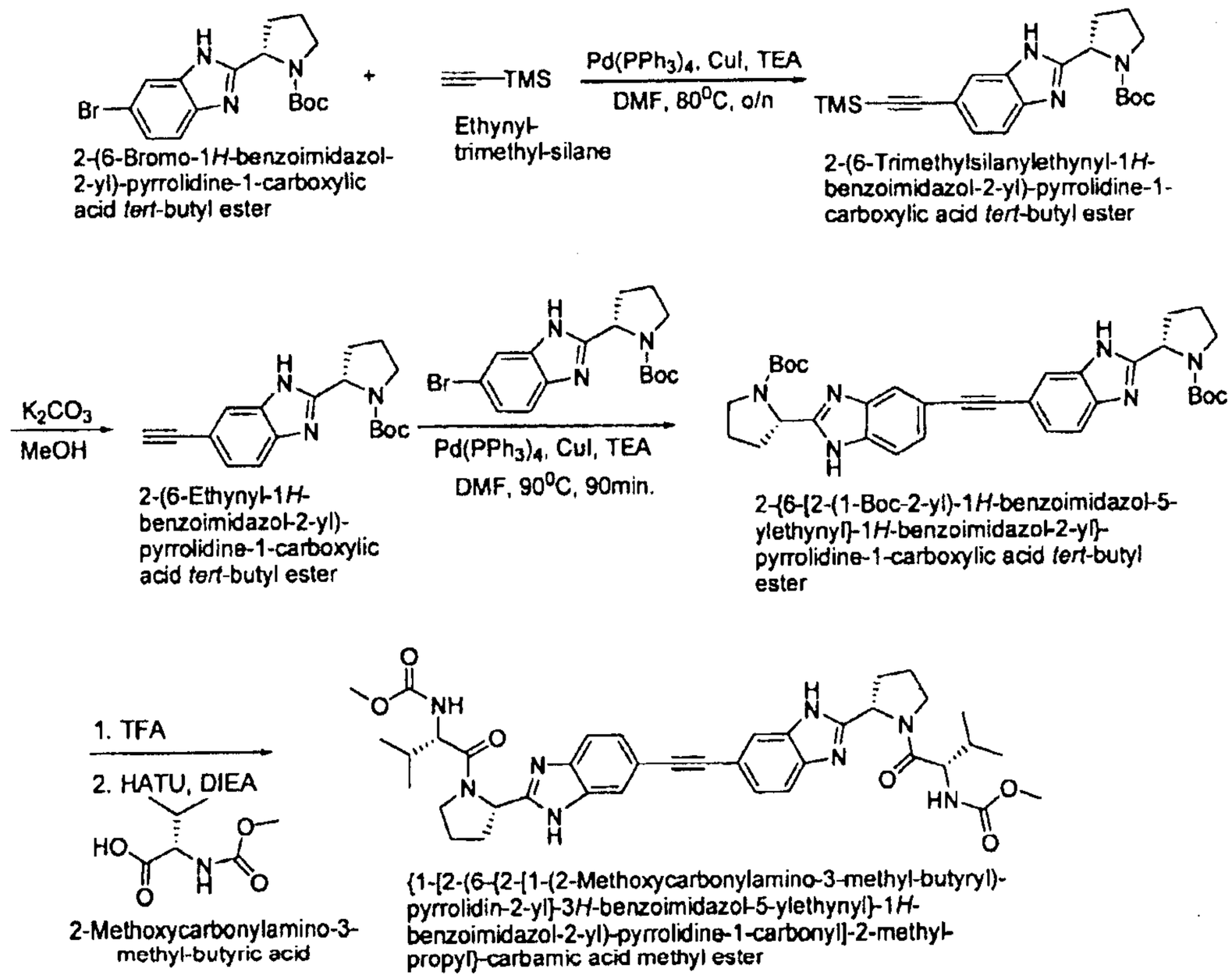
tetrakis(triphenylphosphine)palladium (73 mg, 0.063 mmol) and potassium carbonate (521 mg, 3.77 mmol) in 10 ml 1,2-dimethoxyethane and 5 mL water was heated to 120°C in microwave for 40 minutes. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-{6-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15 mg, yield 15%). LCMS-ESI⁺: calc'd for $C_{34}H_{40}BN_3O_4$: 65.51; Found: 566.1 ($M+H^+$).

2-(6-{4'-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{6-[4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-yl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (147 mg, 0.26 mmol), 2-[5-bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (116 mg, 0.26 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol), $Pd(dppf)Cl_2$ (21 mg, 0.026 mmol) and potassium carbonate (72 mg, 0.52mmol) in 3 ml 1,2-dimethoxyethane and 1 mL water was heated to 90°C for 2.5 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give 2-(6-{4'-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (52 mg, yield 25%); LCMS-ESI⁺: calc'd for $C_{46}H_{60}N_6O_5Si$: 805.09; Found: 805.1 ($M+H^+$).

(1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Trifluoroacetic acid (2 mL)was added to 2-(6-{4'-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (52 mg, 0.056 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1.5 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (20 mg), diisopropylethylamine (59 µL), followed by HATU (43 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), concentrated and purified

by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (4.8 mg).
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 8.0 (s, 1H), 7.92-7.82 (m, 11H), 5.38 (t, 1H), 5.24 (t, 1H), 4.27(dd, 2H), 4.16(m, 2H), 3.96 (m, 2H), 3.63 (s, 6H), 2.62 (m, 2H), 2.40-2.18 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{44}H_{52}N_8O_6$: 788.93; Found: 789.3 ($M+H^+$).

Example BG



2-(6-trimethylsilanylethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (309 mg, 0.84 mmol), ethynyl-trimethyl-silane (1.2 mL, 8.4 mmol), tetrakis(triphenylphosphine)palladium (97 mg, 0.08 mmol), copper(I) iodide (32 mg, 0.16 mmol) and triethylamine (0.7 mL, 5,04 mmol) in 5 ml DMF was heated to 80°C for 8 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(6-

trimethylsilanylethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, yield 62%). LCMS-ESI$^+$: calc'd for $C_{21}H_{29}N_3O_2Si$: 383.56; Found: 384.1 ($M+H^+$).

2-(6-ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Potassium carbonate (144 mg) was added to 2-(6-trimethylsilanylethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.52 mmol) in 6 ml methanol. The reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-(6-ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (121 mg, yield 75%). LCMS-ESI$^+$: calc'd for $C_{18}H_{21}N_3O_2$: 311.38; Found: 311.8 ($M+H^+$).

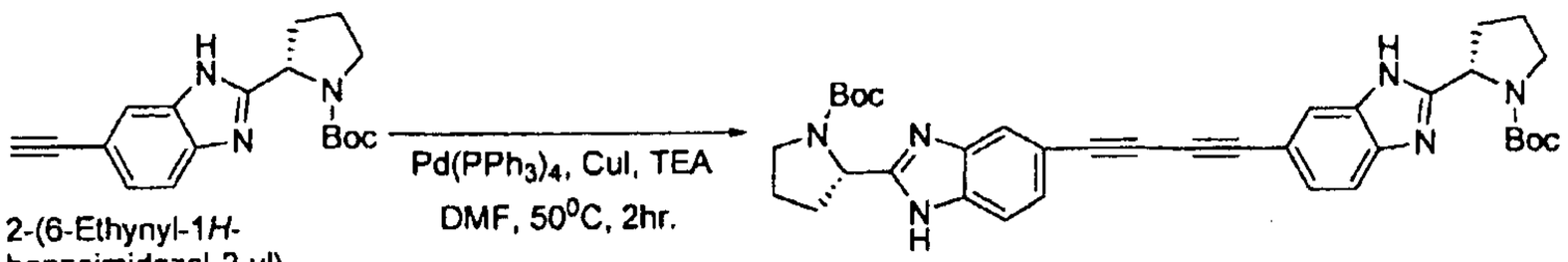
2-{6-[2-(1-Boc-2-yl)-1H-benzoimidazol-5-ylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-bromo-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (91 mg, 0.24 mmol), 2-(6-ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (77 mg, 0.24 mmol), tetrakis(triphenylphosphine)palladium (14 mg), copper(I) iodide (5 mg) and triethylamine (138 μL) in 2 ml DMF was heated to 90°C for 2 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 0-10% IPA/ DCM: acetone(3:2) mixture) to give 2-{6-[2-(1-Boc-2-yl)-1H-benzoimidazol-5-ylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5.4 mg). LCMS-ESI$^+$: calc'd for $C_{34}H_{40}N_6O_4$: 596.72; Found: 597.0 ($M+H^+$).

{1-[2-(6-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-ylethynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Trifluoroacetic acid (1 mL)was added to 2-{6-[2-(1-Boc-2-yl)-1H-benzoimidazol-5-ylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5.4 mg, 0.0065 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (2.6 mg), diisopropylethylamine (9 μL), followed by HATU (5.5 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give {1-[2-(6-{2-[1-(2-

methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-ylethynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester as the bis-TFA salt (0.9 mg).

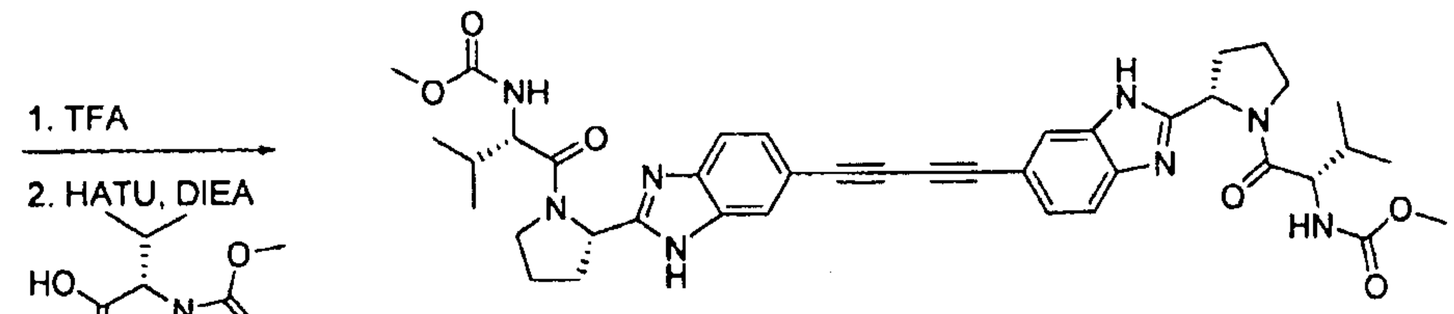
^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 7.82 (s, 2H), 7.68-7.60 (m, 4H), 5.32 (m, 2H), 4.27(dd, 2H), 4.11(m, 2H), 3.96 (m, 2H), 3.63 (s, 6H), 2.58 (m, 2H), 2.40-2.12 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{38}H_{46}N_8O_6$: 710.82; Found: 711.2 ($M+H^+$).

Example BH



2-(6-Ethynyl-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-1*H*-benzoimidazol-5-yl]-buta-1,3-diynyl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-yl}-buta-1,3-diynyl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

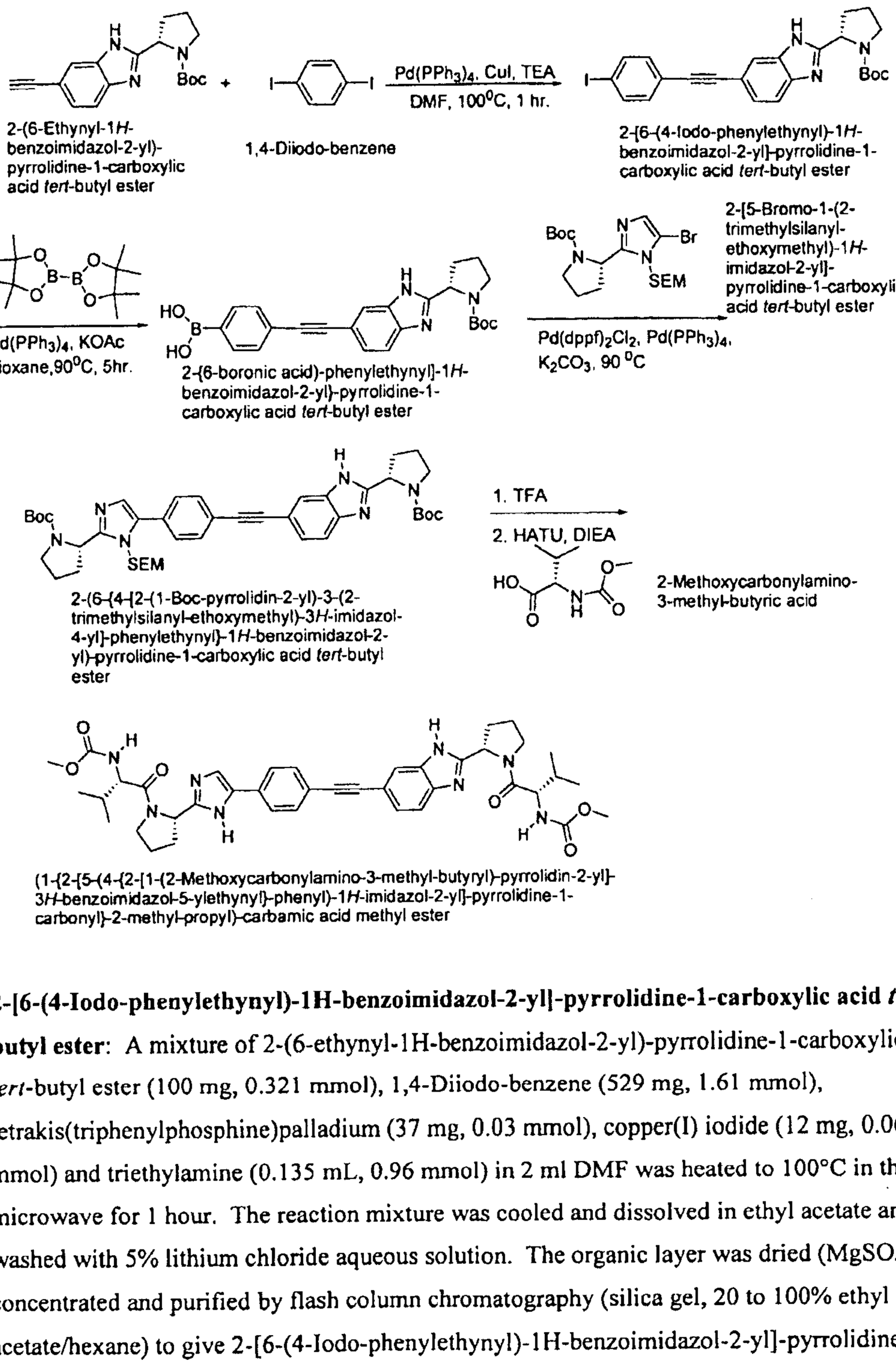
2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-buta-1,3-diynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (88 mg), tetrakis(triphenylphosphine)palladium (16 mg), copper(I) iodide (3 mg) and triethylamine (120 μL) in 1.5 ml DMF was heated to 50°C for 2 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-buta-1,3-diynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12 mg). LCMS-ESI$^+$: calc'd for $C_{36}H_{40}N_6O_4$: 620.74; Found: 621.0 ($M+H^+$).

(1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-buta-1,3-diynyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Trifluoroacetic acid (1 mL)was added to 2-(6-

{4-[2-(1-Boc-pyrrolidin-2-yl)-1H-benzoimidazol-5-yl]-buta-1,3-diynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12 mg) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (5.5 mg), diisopropylethylamine (13 µL), followed by HATU (12 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[6-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-yl}-buta-1,3-diynyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (4 mg).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 7.82 (s, 2H), 7.72-7.62 (m, 4H), 5.32 (m, 2H), 4.27(d, 2H), 4.11(m, 2H), 3.90 (m, 2H), 3.63 (s, 6H), 2.54 (m, 2H), 2.38-2.12 (m, 6H), 2.06 (m, 2H), 0.95-0.85 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{40}H_{46}N_8O_6$: 734.84; Found: 735.2 ($M+H^+$).

Example BI



2-(6-Ethynyl-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

1,4-Diiodo-benzene

2-[6-(4-Iodo-phenylethynyl)-1*H*-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-{6-boronic acid)-phenylethynyl]-1*H*-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-phenylethynyl}-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-benzoimidazol-5-ylethynyl}-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

2-[6-(4-Iodo-phenylethynyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-(6-ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.321 mmol), 1,4-Diiodo-benzene (529 mg, 1.61 mmol), tetrakis(triphenylphosphine)palladium (37 mg, 0.03 mmol), copper(I) iodide (12 mg, 0.06 mmol) and triethylamine (0.135 mL, 0.96 mmol) in 2 ml DMF was heated to 100°C in the microwave for 1 hour. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give 2-[6-(4-Iodo-phenylethynyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (123 mg, yield 75%). LCMS-ESI$^+$: calc'd for $C_{24}H_{24}IN_3O_2$: 513.37; Found: 531.8 ($M+H^+$).

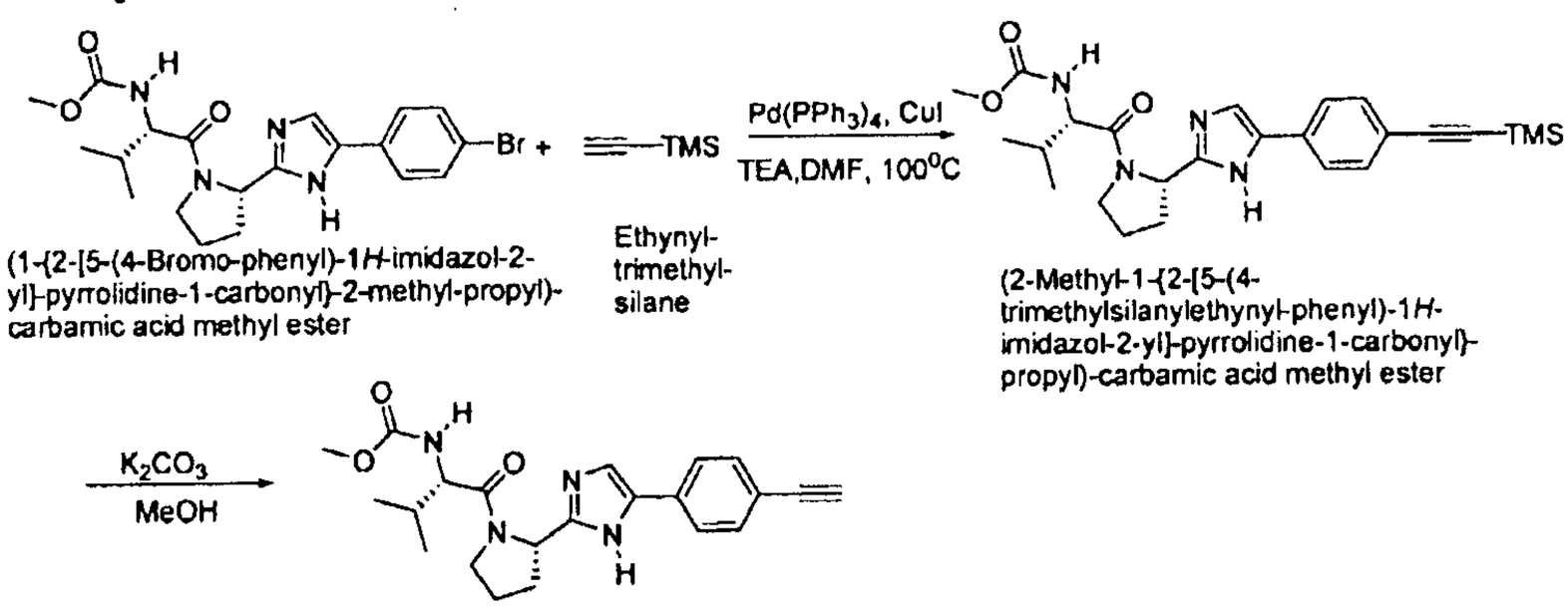
2-{6-[4-boronic acid-phenylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-[6-(4-Iodo-phenylethynyl)-1H-benzoimidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (123 mg, 0.24 mmol), bis(pinacolato)diboron (122 mg, 0.48 mmol), tetrakis(triphenylphosphine)palladium (52 mg, 0.02 mmol) and potassium acetate (52 mg, 0.53 mmol) in 3 ml 1,4-dioxane was heated to 90°C for 5 hours. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) and followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA) to give the corresponding boronic acid of 2-{6-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15 mg). LCMS-ESI$^-$: calc'd for $C_{24}H_{26}BN_3O_4$: 431.29; Found: 431.9 ($M+H^+$).

2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenylethynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: A mixture of 2-{6-[4-boronic acid-phenylethynyl]-1H-benzoimidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11 mg, 0.025), 2-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (34 mg, 0.076 mmol), tetrakis(triphenylphosphine)palladium (1.5 mg), $Pd(dppf)Cl_2$ (1 mg) and potassium carbonate (3.5 mg) in 1 ml DME and 0.3 mL water was heated to 90°C for 30 minutes. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA) to give 2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenylethynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4 mg, yield 21%). LCMS-ESI$^-$: calc'd for $C_{43}H_{60}N_6O_5Si$; 753.02; Found: 751.4 ($M-H^+$).

(1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-ylethynyl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Trifluoroacetic acid (1 mL)was added to 2-(6-{4-[2-(1-Boc-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenylethynyl}-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4 mg) and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (2 mg), diisopropylethylamine (6

μL), followed by HATU (4 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-benzoimidazol-5-ylethynyl}-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester as the bis-TFA salt (2.8 mg): ^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 7.86 (s, 1H), 7.82(s, 1H), 7.78-7.60 (m, 5H), 5.32 (m, 2H), 4.27(dd, 2H), 4.11(m, 2H), 3.96 (m, 2H), 3.63 (s, 6H), 2.58 (m, 2H), 2.40-2.12 (m, 6H), 2.08(m, 2H), 0.95-0.85 (m, 12 H); LCMS-ESI$^+$: calc'd for $C_{40}H_{46}N_8O_6$: 736.86; Found: 737.3 ($M+H^+$).

Example BJ

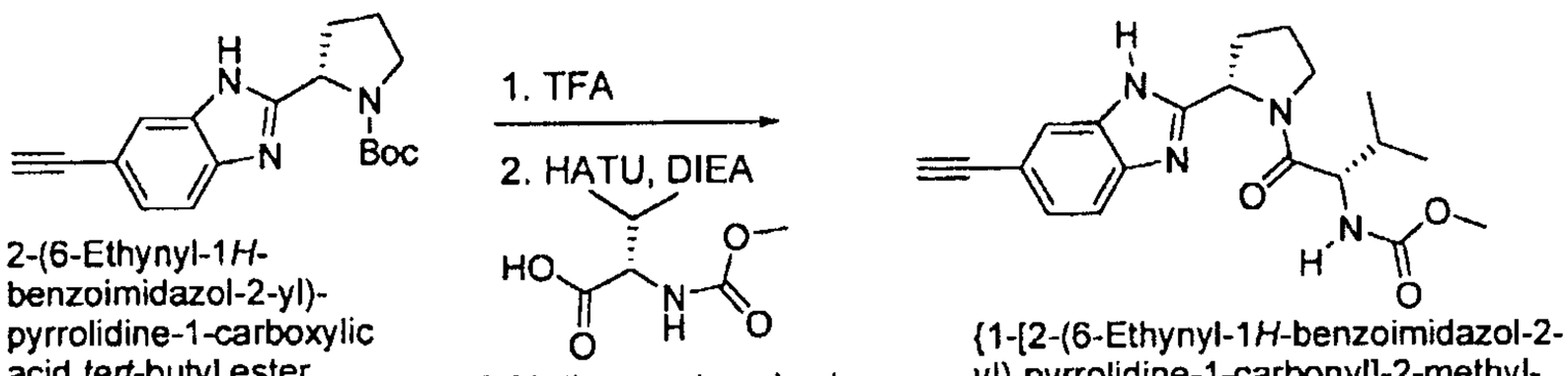


(2-Methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester: A mixture of (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (364 mg, 0.81 mmol), Ethynyl-trimethyl-silane (0.68mL, 4.9 mmol), Copper(I) iodide (154 mg, 0.81 mmol), tetrakis(triphenylphosphine)palladium (94 mg, 0.08 mmol) and triethylamine (0.67 mL, 4.9 mmol) in 5 ml DMF was heated to 70°C overnight. The reaction mixture was cooled and dissolved in ethyl acetate and washed with 5% lithium chloride aqueous solution. The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) and followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA) to give (2-Methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (324 mg). LCMS-ESI$^-$: calc'd for $C_{25}H_{34}BN_4O_3Si$: 466.65; Found: 467.1 ($M+H^+$).

(1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Potassium carbonate (192 mg) was added to (2-Methyl-1-{2-[5-(4-trimethylsilanylethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (324 mg) in 7 mL MeOH solution. The reaction was stirred at room temperature overnight. The reaction mixture was concentrated down and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (234 mg).

^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 7.84 (s, 1H), 7.84(d, 2H), 6.98 (d, 2H), 5.22 (t, 1H), 4.21(d, 1H), 4.11(m, 1H), 3.86 (m, 1H), 3.63 (s, 3H), 2.55 (m, 1H), 2.31-2.02 (m, 4H), 0.95-0.85 (m, 6 H); LCMS-ESI$^+$: calc'd for $C_{22}H_{26}N_4O_3$: 394.47; Found: 395.1 ($M+H^+$).

Example BK



2-(6-Ethynyl-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

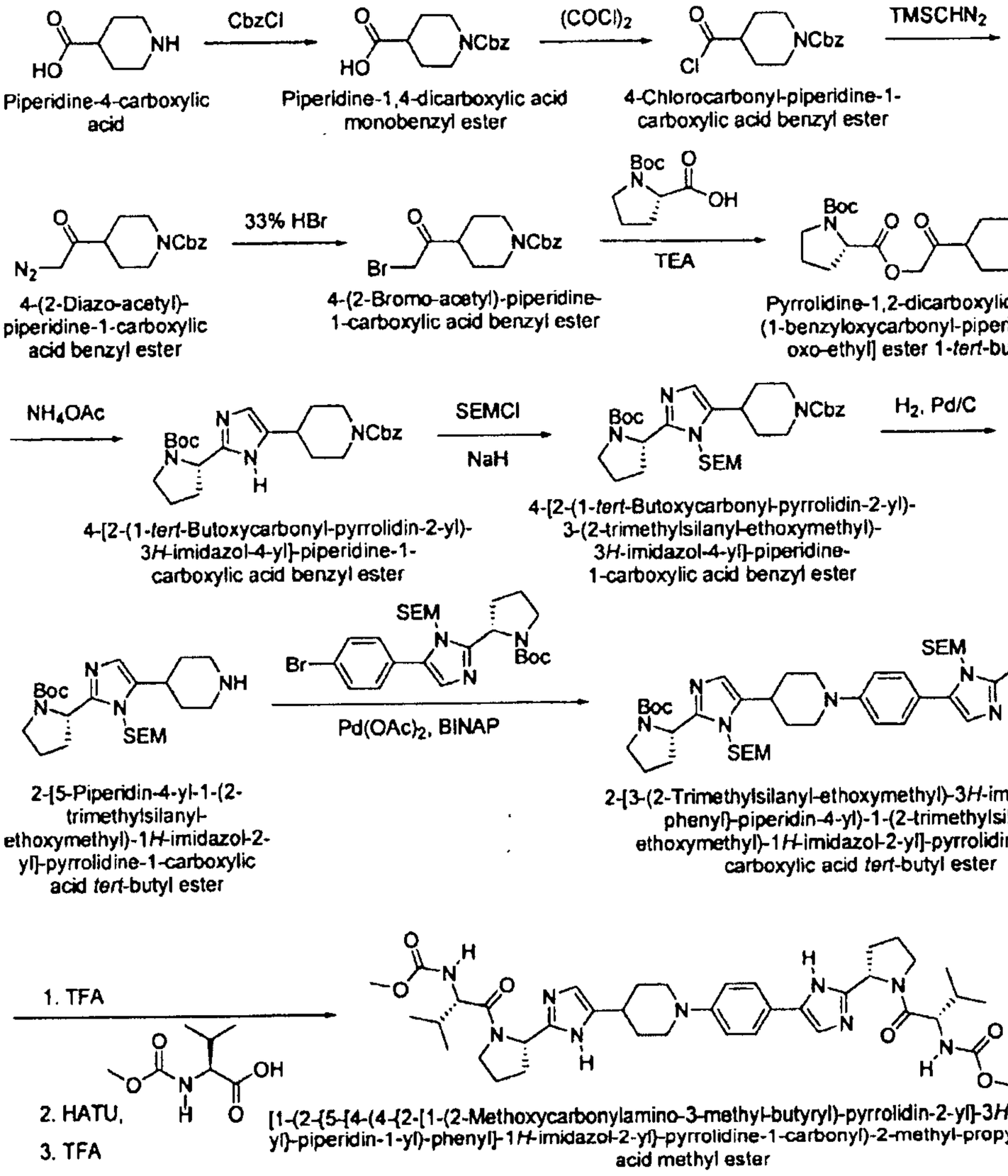
2-Methoxycarbonylamino-3-methyl-butyric acid

{1-[2-(6-Ethynyl-1*H*-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-(6-Ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: Trifluoroacetic acid (1 mL) was added to 2-(6-Ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (20 mg) and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (1 mL) and to this solution was added 2-methoxycarbonylamino-3-methyl-butyric acid (12 mg), diisopropylethylamine (67 μL), followed by HATU (24 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), concentrated and purified by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give {1-[2-(6-Ethynyl-1H-benzoimidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester as the mono TFA salt (23 mg): ^{1}H-NMR: 300 MHz, (CD_3OD-d_4) δ: 7.82 (s, 1H), 7.72(d, 1H), 7.62 (d, 1H), 5.32 (t, 1H), 4.24(d, 1H), 4.11(m, 1H), 3.90 (m, 1H),

3.63 (s, 4H), 2.58 (m, 1H), 2.38-2.12 (m, 3H), 2.04(m, 1H), 0.95-0.85 (m, 6 H); LCMS-ESI$^+$: calc'd for $C_{22}H_{26}N_4O_3$: 368.43; Found: 369.0 ($M+H^+$).

Example BL



Piperidine-1,4-dicarboxylic acid monobenzyl ester: Piperidine-4-carboxylic acid (64.8 g, 0.5 mol) in H_2O (50 mL) was treated with NaOH (44.0 g, 1.1 mol). The reaction mixture was cooled to 0°C and treated with CbzCl (93.8 g, 0.55 mol). The reaction mixture was stirred at ambient temperature for 4 hours and the mixture was extracted with Et_2O (3 150 mL). The aqueous phase was acidified with 6 N HCl (140 mL) and extracted with EtOAc (3 200 mL). The solution was dried over MgSO4, filtered, and concentrated to afford crude piperidine-1,4-dicarboxylic acid monobenzyl ester (120 g), which was used without further purification: MS (ESI) *m/z* 262 $[M - H]^+$.

4-Chlorocarbonyl-piperidine-1-carboxylic acid benzyl ester: Piperidine-1,4-dicarboxylic acid monobenzyl ester (40.2 g, 0.15 mol) in dichloromethane (300 mL) was treated with oxalyl chloride (100 g, 0.79 mol). The reaction mixture was stirred at ambient temperature for 4 hours and the mixture was concentrated to afford crude 4-chlorocarbonyl-piperidine-1-carboxylic acid benzyl ester (43 g), which was used without further purification.

4-(2-Diazo-acetyl)-piperidine-1-carboxylic acid benzyl ester: 4-Chlorocarbonyl-piperidine-1-carboxylic acid benzyl ester (43 g, 0.15 mol) in dichloromethane (300 mL) was treated with (trimethylsilyl)diazomethane (2.0 M in hexanes, 150 mL, 0.31 mol) over 15 min. The reaction mixture was stirred at ambient temperature for 18 hours and the mixture was concentrated to afford crude 4-(2-diazo-acetyl)-piperidine-1-carboxylic acid benzyl ester (44 g), which was used without further purification.

4-(2-Bromo-acetyl)-piperidine-1-carboxylic acid benzyl ester: 4-(2-Diazo-acetyl)-piperidine-1-carboxylic acid benzyl ester (44 g, 0.15 mol) in EtOAc (300 mL) was cooled to 0°C. The solution was treated with 33% HBr/HOAc (75 mL, 0.42 mol) over 15 min and stirred at ambient temperature for 2 hours. The mixture was slowly treated with saturated $NaHCO_3$ solution (300 mL) until pH was neutral or slightly basic and filtered. The solution was dried over $MgSO_4$ and subjected to a 330 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford 4-(2-bromo-acetyl)-piperidine-1-carboxylic acid benzyl ester (38.1 g, 81%): MS (ESI) *m/z* 341 $[M + H]^+$.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(1-benzyloxycarbonyl-piperidin-4-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: (*S*)-Proline (13 g, 61 mmol) in MeCN (250 mL) was treated with triethylamine (8.5 mL, 61 mmol). 4-(2-Bromo-acetyl)-piperidine-1-carboxylic acid benzyl ester (19 g, 56 mmol) in MeCN (50 mL) was added dropwise over 15 min and the reaction was stirred for 2 hours. The mixture was concentrated and suspended in dicholormethane (100 mL) and washed with H_2O (50 mL). The solution was dried over $MgSO_4$ and subjected to a 330 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford pyrrolidine-1,2-dicarboxylic acid 2-[2-(1-benzyloxycarbonyl-piperidin-4-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (20 g, 75%): MS (ESI) *m/z* 497 $[M + Na]^+$.

4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester: Pyrrolidine-1,2-dicarboxylic acid 2-[2-(1-benzyloxycarbonyl-piperidin-4-

yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (20 g, 42 mmol) in xylenes (100 mL) was treated with ammonium acetate (16 g, 210 mmol). The reaction was stirred at 130°C in a sealed tube for 3 hours. The mixture was concentrated and suspended in dicholormethane (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The solution was dried over $MgSO_4$ and subjected to a 330 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient) to afford 4-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester (6.8 g, 36%): MS (ESI) *m/z* 455 $[M + H]^+$.

4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester: 4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester (6.8 g, 14.9 mmol) in DMF (115 mL) was treated with NaH (60% dispersion in mineral oil, 655 mg, 16.4 mmol) in one portion. After 5 min, the mixture was treated with SEMCl (2.75 mL, 15.7 mmol) in 0.1 mL portions over 10 min. The reaction was stirred for 3 hours and diluted with saturated NH_4Cl solution (50 mL) and EtOAc (100 mL). The organic layer was washed with H_2O (3 50 mL) and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient) to afford 4-[2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester (2.8 g, 32%): MS (ESI) *m/z* 585 $[M + H]^+$.

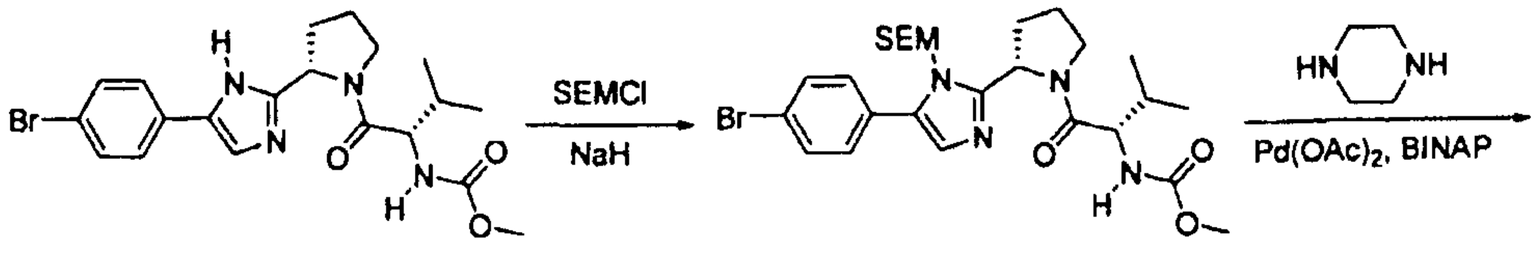
2-[5-Piperidin-4-yl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-piperidine-1-carboxylic acid benzyl ester (2.8 g, 6.1 mmol) in EtOH (60 mL) was treated with 20% PdOH/C (600 mg) and placed under an atmosphere of H_2. The reaction was stirred for 18 hours and filtered through a CELITE plug to afford crude 2-[5-piperidin-4-yl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.0 g), which was used without further purification: MS (ESI) *m/z* 451 $[M + H]^+$.

2-[3-(2-Trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperidin-4-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester: 2-[5-Piperidin-4-yl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (170 mg, 0.37 mmol) and 4-Bromophenyl-1-SEM-imidazol-2-yl-pyrrolidine-1-Boc (164 mg, 0.31 mmol, prepared according to WO 2008/021927)

in toluene (3.5 mL) were treated with $Pd(OAc)_2$ (1.4 mg, 0.0064 mmol, via 10% solution in toluene), BINAP (19 mg, 0.031 mmol), and NaOtBu (42 mg, 0.44 mmol). The mixture was stirred in a sealed tube at 110°C for 36 hours. The solution was concentrated, diluted with EtOAc (50 mL), and washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$ and subjected to a 40 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient) to afford 2-[3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperidin-4-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester (35 mg, 13%): MS (ESI) *m/z* 892 $[M + H]^+$.

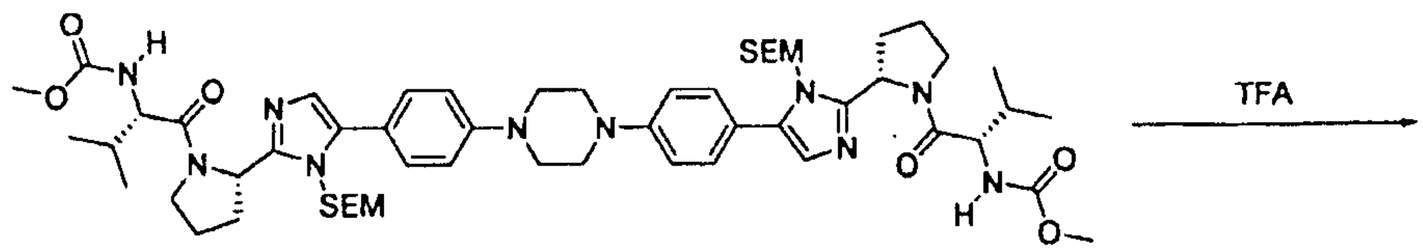
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-piperidin-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-[3-(2-Trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperidin-4-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester (35 mg, 0.04 mmol) in dichloromethane (1.0 mL) was treated with trifluoroacetic acid (0.2 mL) and the mixture was stirred for 1 hours. The solution was concentrated and the residue was suspended in DMF (1.0 mL) and treated with (*S*)-Moc-Val-OH (15 mg, 0.086 mmol), HATU (32 mg, 0.085 mmol), and *N*-methyl morpholine (0.034 mL, 0.31 mmol). The mixture was stirred for 2 hours then diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ and suspended in trifluoroacetic acid (1.0 mL) and stirred in a screw-cap vial at 40°C for 1 hour. The solution was concentrated and subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford [1-(2-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-piperidin-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (9.5 mg, 33%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.64 (s, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.29 (s, 1H), 7.11 (d, J = 9.0 Hz, 2H), 5.18 (m, 2H), 4.21 (m, 2H), 4.08 (m, 2H), 3.96 (m, 2H), 3.84 (m, 2H), 3.65, (s, 3H), 3.64 (s, 3H), 2.96 (m, 3H), 2.51 (m, 2H), 2.20 (m, 2H), 2.13 (m, 7H), 1.82 (m, 2H), 0.91 (m, 12H); MS (ESI) *m/z* 746 $[M + H]^+$.

Example BM

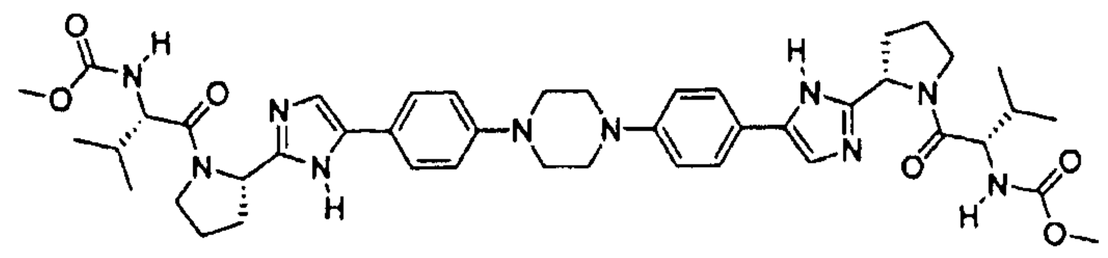


(1-{2-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



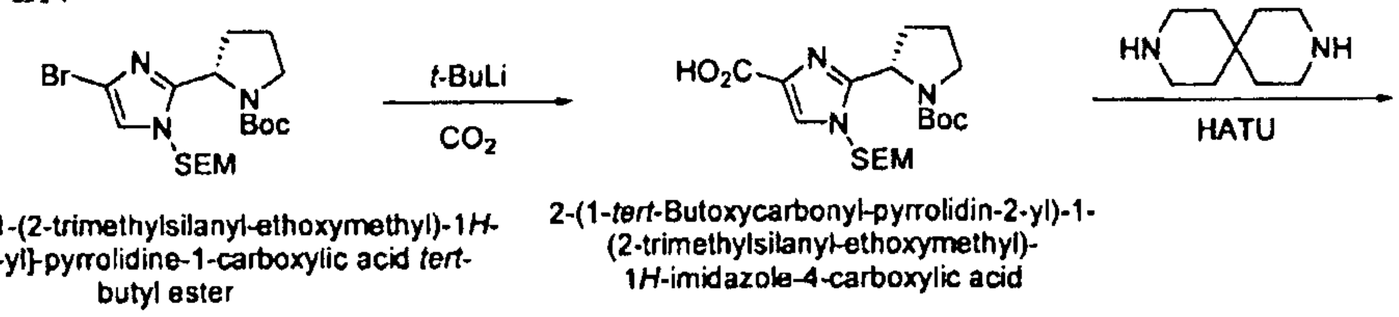
{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

(1-{2-[5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.6 g, 5.8 mmol) in DMF (60 mL) was treated with NaH (60% dispersion in mineral oil, 256 mg, 6.4 mmol) in one portion. After 5 min, the mixture was treated with SEMCl (1.08 mL, 6.1 mmol) in 0.1 mL portions over 10 min. The reaction was stirred for 2 hours and diluted with saturated NH_4Cl solution (50 mL) and EtOAc (100 mL). The organic layer was washed with H_2O (3 50 mL) and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford (1-{2-[5-(4-bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.4 g, 71%).

{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (222 mg, 0.38 mmol) and piperazine (17 mg, 0.19 mmol) in toluene (3.5 mL) were treated with $Pd(OAc)_2$ (2.1 mg, 0.0096 mmol, via 10% solution in toluene), BINAP (12 mg, 0.019 mmol), and NaOtBu (64 mg, 0.67 mmol). The mixture was stirred in a sealed tube at 120°C for 4 hours. The solution was concentrated, diluted with EtOAc (50 mL), and washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$ and subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford {1-[2-(5-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (8 mg, 4%): MS (ESI) *m/z* 1105 $[M + Na]^+$.

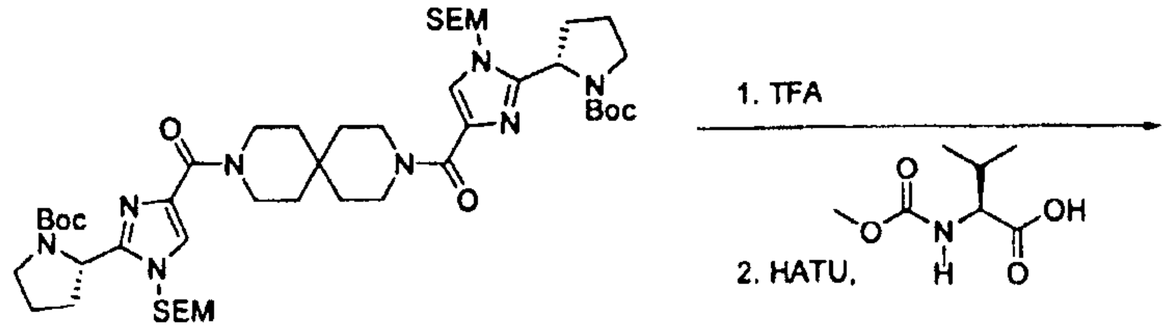
{1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[2-(5-{4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (8 mg, 0.007 mmol) in trifluoroacetic acid (1.0 mL) was stirred in a screw-cap vial at 40°C for 1 hours. The solution was concentrated and subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford {1-[2-(5-{4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-piperazin-1-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (1.9 mg, 32%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.66 (s, 2H), 7.60 (d, J = 8.7 Hz, 4H), 7.13 (d, J = 8.7 Hz, 4H), 5.21 (app t, J = 8.1 Hz, 2H), 4.22 (d, J = 7.2 Hz, 2H), 4.09 (m, 2H), 3.85 (m, 2H), 3.66 (s, 6H), 3.31 (m, 5H), 2.52 (m, 2H), 2.16 (m, 8H), 0.91 (m, 12H); MS (ESI) *m/z* 824 $[M + H]^+$.

Example BN

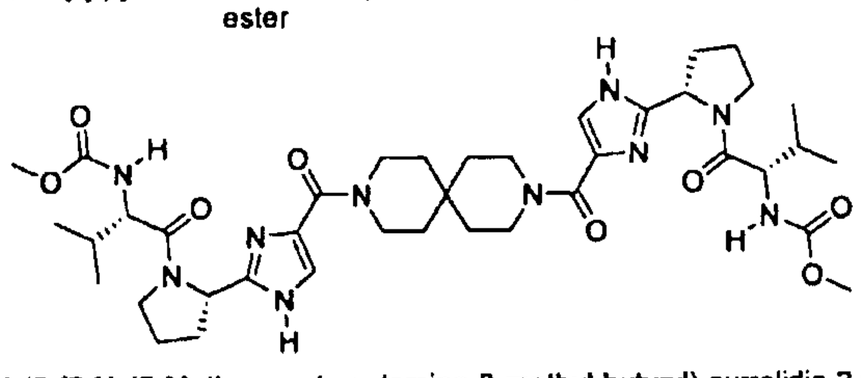


2-[4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole-4-carboxylic acid



2-[4-{9-[1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-imidazole-4-carbonyl]-3,9-diaza-spiro[5.5]undecane-3-carbonyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester



(1-{2-[4-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazole-4-carbonyl}-3,9-diaza-spiro[5.5]undecane-3-carbonyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

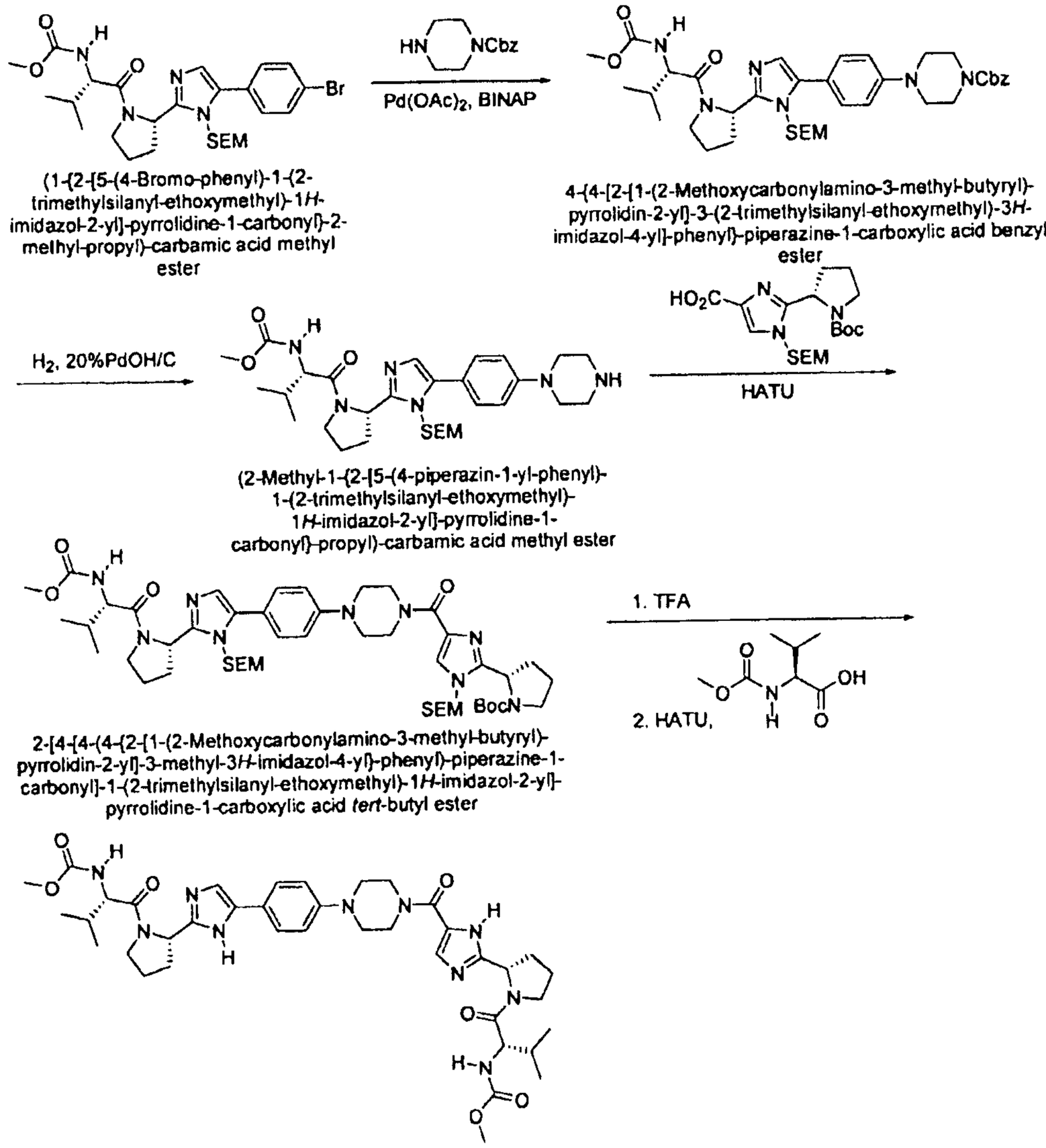
2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid: 2-[4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.0 g, 2.2 mmol) in THF (10 mL) was cooled to –78°C and treated with *t*-BuLi (1.7 M in pentane, 2.7 mL, 4.6 mmol). The reaction mixture was stirred for 1 hour and treated with solid CO_2 (500 mg). The mixture was warmed to ambient temperature and mixture was concentrated. The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient) to afford 2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid (200 mg, 22%): MS (ESI) *m/z* 412 $[M + H]^+$.

2-[4-{9-[1-(2-Trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbonyl]-3,9-diaza-spiro[5.5]undecane-3-carbonyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid (141 mg, 0.34 mmol) in DMF (1.0 mL) was treated with spiro-diamine (38 mg, 0.16 mmol), HATU (136 mg, 0.36

mmol), and *N*-methyl morpholine (0.90 mL, 0.82 mmol). The mixture was stirred for 2 hours then diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ to afford crude 2-[4-{9-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbonyl]-3,9-diaza-spiro[5.5]undecane-3-carbonyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester which was used without further purification: MS (ESI) *m/z* 941 $[M + H]^+$.

(1-{2-[4-(9-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazole-4-carbonyl}-3,9-diaza-spiro[5.5]undecane-3-carbonyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[4-{9-[1-(2-Trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbonyl]-3,9-diaza-spiro[5.5]undecane-3-carbonyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (153 mg, 0.17 mmol) in trifluoroacetic acid (3.0 mL) was stirred for 18 hours. The mixture was concentrated, suspended in DMF (1.7 mL), and treated with (*S*)-Moc-Val-OH (64 mg, 0.37 mmol), HATU (140 mg, 0.38 mmol), and *N*-methyl morpholine (185 mL, 1.66 mmol). The mixture was stirred for 2 hours then diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ and subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford 1-{2-[4-(9-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazole-4-carbonyl}-3,9-diaza-spiro[5.5]undecane-3-carbonyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (3.0 mg, 2%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.77 (s, 2H), 5.18 (app t, J = 6.9 Hz, 2H), 4.22 (d, J = 7.2 Hz, 2H), 4.09 (m, 2H), 3.85 (m, 2H), 3.66 (s, 6H), 3.31 (m, 5H), 2.52 (m, 2H), 2.16 (m, 8H), 0.91 (m, 12H); MS (ESI) *m/z* 796 $[M + H]^+$.

Example BO



(1-{2-[5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

4-{4-[2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-phenyl}-piperazine-1-carboxylic acid benzyl ester

(2-Methyl-1-{2-[5-(4-piperazin-1-yl-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester

2-[4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-methyl-3*H*-imidazol-4-yl}-phenyl)-piperazine-1-carbonyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazole-4-carbonyl}-piperazin-1-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

4-{4-[2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperazine-1-carboxylic acid benzyl ester: (1-{2-[5-(4-Bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1033 mg, 1.8 mmol) and 4-Cbz-piperazine (588 mg, 2.7 mmol) in toluene (9 mL) were treated with $Pd(OAc)_2$ (20 mg, 0.09 mmol), BINAP (110 mg, 0.1 mmol), and NaOtBu (428 mg, 4.45 mmol). The mixture

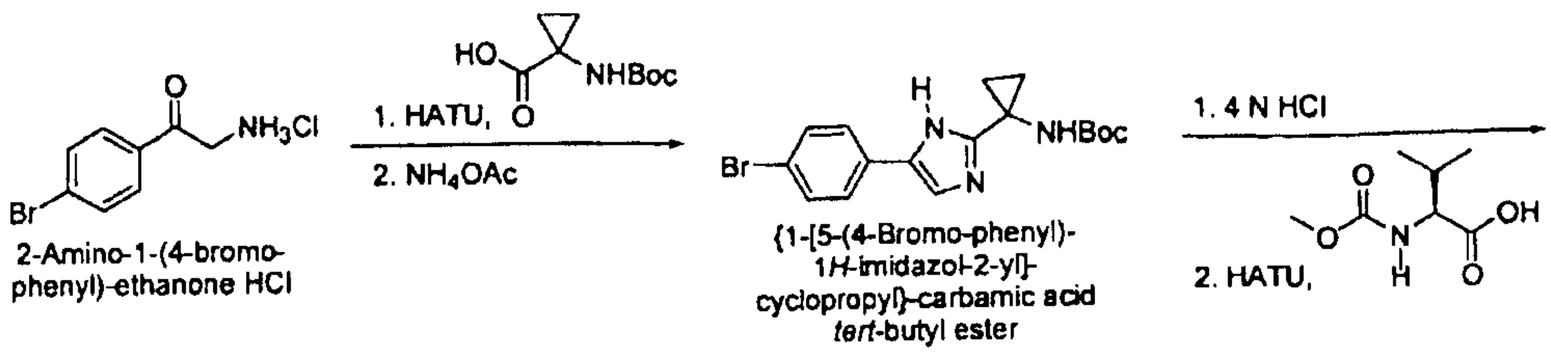
was stirred in a sealed tube at 110°C for 18 hours. The solution was concentrated, diluted with EtOAc (50 mL), and washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford 4-{4-[2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperazine-1-carboxylic acid benzyl ester (166 mg, 13%): MS (ESI) *m/z* 719 $[M + H]^+$.

(2-Methyl-1-{2-[5-(4-piperazin-1-yl-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester: 4-{4-[2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-phenyl}-piperazine-1-carboxylic acid benzyl ester (166 mg, 0.23 mmol) in EtOH (2.5 mL) was treated with 20% PdOH/C (60 mg) and placed under an atmosphere of H_2. The reaction was stirred for 18 hours and filtered through a CELITE plug to afford crude (2-methyl-1-{2-[5-(4-piperazin-1-yl-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (120 mg), which was used without further purification: MS (ESI) *m/z* 585 $[M + H]^+$.

2-[4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-methyl-3H-imidazol-4-yl}-phenyl)-piperazine-1-carbonyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: (2-Methyl-1-{2-[5-(4-piperazin-1-yl-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (28 mg, 0.047 mmol) and 2-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid (20 mg, 0.047 mmol) in DMF (1 mL) were treated with HATU (20 mg, 0.052 mmol) and *N*-methyl morpholine (0.26 mL, 0.23 mmol). The mixture was stirred for 18 hours then diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ to afford crude 2-[4-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-methyl-3H-imidazol-4-yl}-phenyl)-piperazine-1-carbonyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, which was used without further purification: MS (ESI) *m/z* 978 $[M + H]^+$.

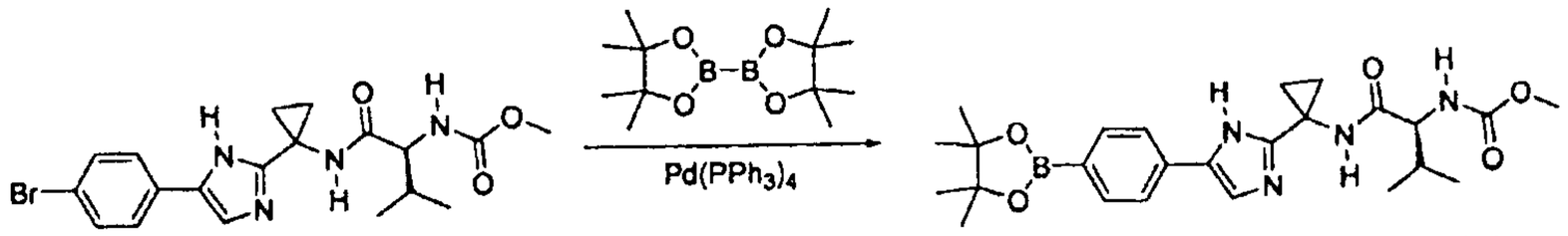
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazole-4-carbonyl}-piperazin-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: 2-[4-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3-methyl-3H-imidazol-4-yl}-phenyl)-piperazine-1-carbonyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (47 mg, 0.05 mmol) in trifluoroacetic acid (3.0 mL) was stirred for 18 hours. The mixture was concentrated, suspended in DMF (1.5 mL), and treated with (*S*)-Moc-Val-OH (9 mg, 0.0.053 mmol), HATU (20 mg, 0.0.053 mmol), and *N*-methyl morpholine (0.26 mL, 0.24 mmol). The mixture was stirred for 18 hours then diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ and subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford [1-(2-{5-[4-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazole-4-carbonyl}-piperazin-1-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (6.6 mg, 18%) as a white solid (TFA salt): ^{1}H NMR (CD_3OD, 300 MHz) 7.67 (s, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 9.3 Hz, 2H), 5.20 (app t, J = 7.2 Hz, 2H), 4.22 (d, J = 7.2 Hz, 2H), 4.01 (m, 5H), 3.85 (m, 2H), 3.66 (s, 6H), 3.38 (m, 2H), 2.52 (m, 2H), 2.16 (m, 8H), 0.91 (m, 12H); MS (ESI) *m/z* 775 [M + H]$^+$.

Example BP



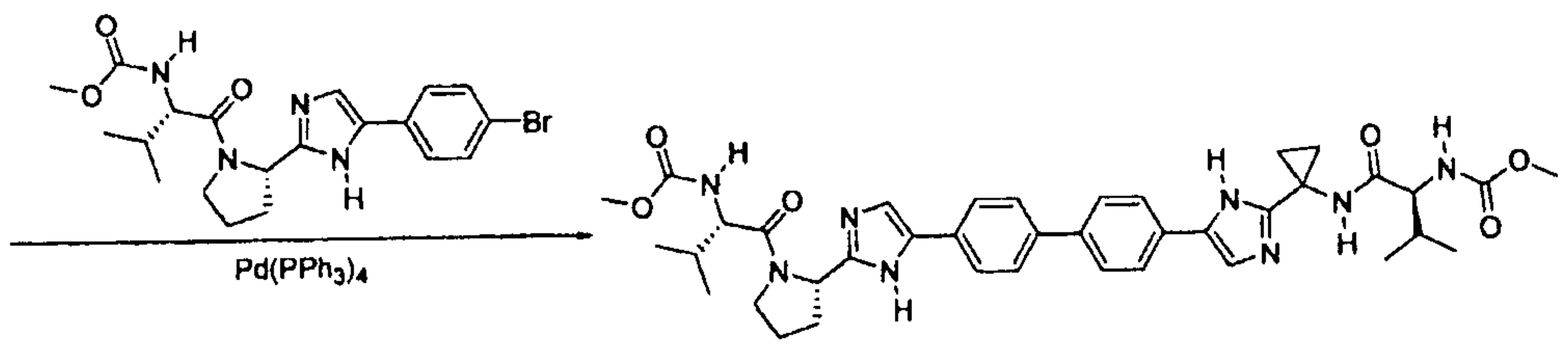
2-Amino-1-(4-bromo-phenyl)-ethanone HCl

{1-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-cyclopropyl}-carbamic acid *tert*-butyl ester



(1-{1-[5-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-cyclopropylcarbamoyl}-2-methyl-propyl)-carbamic acid methyl ester

[2-Methyl-1-(1-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-cyclopropylcarbamoyl)-propyl]-carbamic acid methyl ester



(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyrylamino)-cyclopropyl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

{1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclopropyl}-carbamic acid *tert*-butyl ester: 2-Amino-1-(4-bromo-phenyl)-ethanone HCl (2.5 g, 10 mmol) in DMF (30 mL) was treated with 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid (1.97 g, 9.8 mmol), HATU (4.02 g, 10.5 mmol), and DIPEA (5.6 mL, 31.1 mmol). The mixture was stirred for 18 hours and concentrated. The mixture was diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ and subjected to a 80 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford {1-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-cyclopropyl}-carbamic acid *tert*-butyl ester (3.49 g, 90%). This material (3.49 g, 8.8 mmol) in xylenes (20 mL) was treated with ammonium acetate (3.4 g, 44 mmol). The reaction was stirred at 130°C in a sealed tube for 18 hours. The mixture was concentrated and suspended in dicholormethane (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The solution was dried over $MgSO_4$ to afford crude {1-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-cyclopropyl}-carbamic acid *tert*-butyl ester, which was used without further purification: MS (ESI) *m/z* 379 $[M + H]^+$.

(1-{1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclopropylcarbamoyl}-2-methyl-propyl)-carbamic acid methyl ester: {1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclopropyl}-carbamic acid *tert*-butyl ester (3.3 g, 8.77 mmol) was treated with 4 N HCl/dioxane (40 mL) and

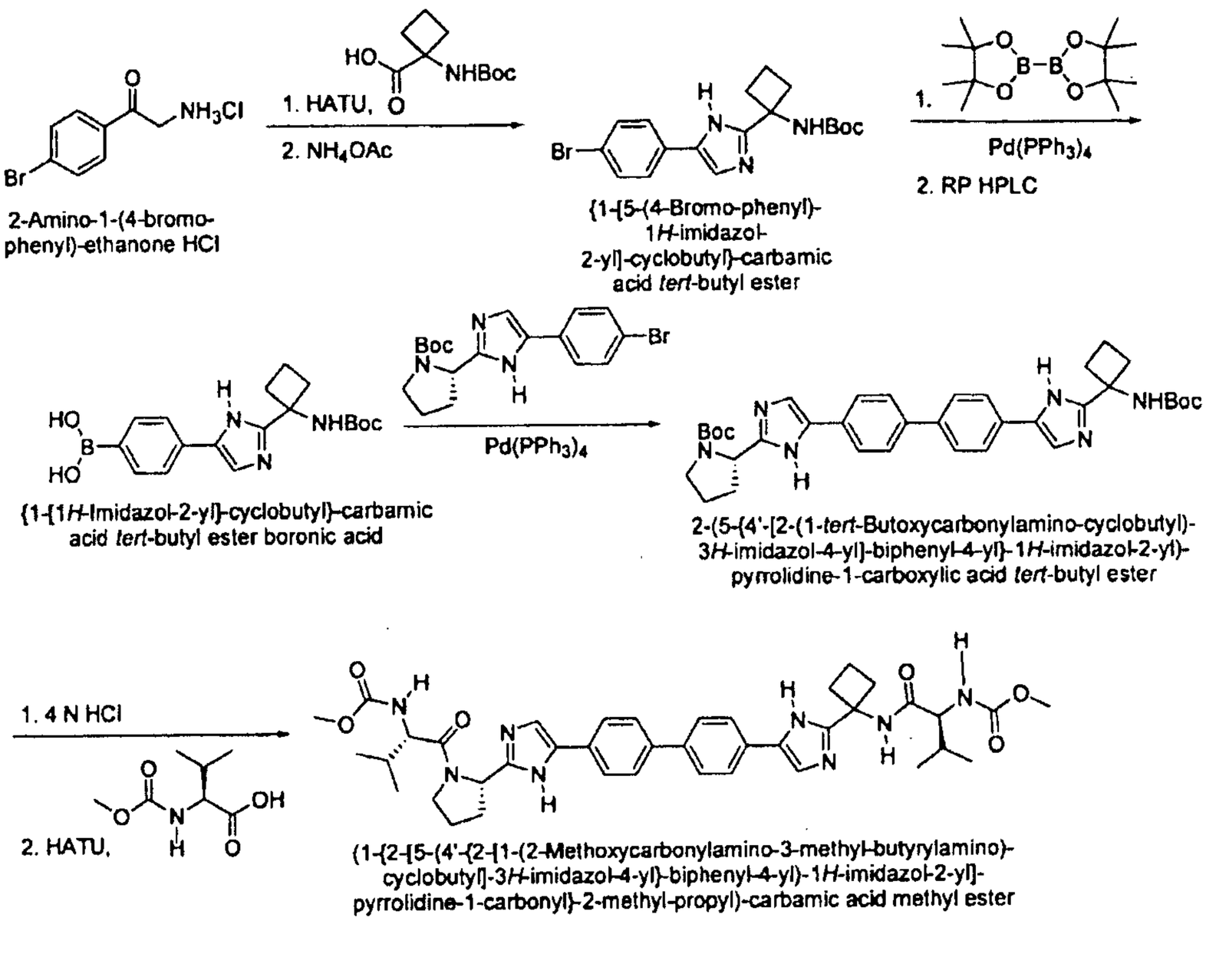
stirred for 2 hours. The mixture was concentrated and suspended in DMF (50 mL). The mixture was treated with (*S*)-Moc-Val-OH (1.69 g, 9.7 mmol), HATU (3.67 g, 9.7 mmol), and *N*-methyl morpholone (4.8 mL, 43.9 mmol). The mixture was stirred for 18 hours and concentrated. The mixture was diluted with EtOAc (100 mL), and washed with saturated $NaHCO_3$ (3 50 mL), H_2O (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford (1-{1-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-cyclopropylcarbamoyl}-2-methyl-propyl)-carbamic acid methyl ester (3.37 g, 88%): MS (ESI) *m/z* 436 $[M + H]^+$.

[2-Methyl-1-(1-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-cyclopropylcarbamoyl)-propyl]-carbamic acid methyl ester: (1-{1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclopropylcarbamoyl}-2-methyl-propyl)-carbamic acid methyl ester (1.38 g, 3.2 mmol) in 1,4-dioxane (25 mL) was treated with bis(pinacolato)diboron (1.69 g, 6.7 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol), and KOAc (810 mg, 8.2 mmol). The mixture was stirred in a sealed tube at 80°C for 18 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was then suspended in dichloromethane (10 mL) and filtered and subjected to a 120 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes gradient) to afford [2-methyl-1-(1-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-cyclopropylcarbamoyl)-propyl]-carbamic acid methyl ester (1.24 g, 81%): MS (ESI) *m/z* 483 $[M + H]^+$.

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyrylamino)-cyclopropyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: [2-Methyl-1-(1-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-cyclopropylcarbamoyl)-propyl]-carbamic acid methyl ester (85 mg, 0.21 mmol) and (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (97 mg, 0.21 mmol) in 3:1 DME/H_2O (2.5 mL) were treated with $Pd(PPh_3)_4$ (10 mg, 0.0084 mmol) and K_2CO_3 (2 M solution, 0.42 mL, 0.84 mmol). The mixture was stirred in a sealed tube at 80°C for 3 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford (1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyrylamino)-cyclopropyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.3 mg, 2%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.93 (s, 2H), 7.84 (m, 4H), 5.20 (m, 1H), 4.23 (d, J = 7.2 Hz, 2H), 4.01 (m, 2H), 3.83 (m, 4H), 3.70 (s, 3H), 3.66 (s,

3H), 3.38 (m, 2H), 2.57 (m, 2H), 2.18 (m, 4H), 2.04 (m, 4H), 1.75 (m, 4H), 1.58 (m, 4H), 0.95 (m, 12H); MS (ESI) *m/z* 725 $[M + H]^+$.

Example BQ



{1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester: 2-Amino-1-(4-bromo-phenyl)-ethanone HCl (5.8 g, 23 mmol) in DMF (75 mL) was treated with 1-*tert*-butoxycarbonylamino-cyclobutanecarboxylic acid (5.0 g, 23 mmol), HATU (9.7 g, 25 mmol), and DIPEA (12.9 mL, 34 mmol). The mixture was stirred for 18 hours and concentrated. The mixture was diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (3 10 mL), H_2O (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$ to afford crude {1-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-cyclobutyl}-carbamic acid *tert*-butyl ester, which was used without further purification. This material (6.54 g, 16 mmol) in xylenes (40 mL) was treated with ammonium acetate (6.1 g, 80 mmol). The reaction was stirred at 130°C in a sealed tube for 18 hours. The mixture was concentrated and suspended in dicholormethane (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The solution was dried over $MgSO_4$ to afford crude {1-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester, which was used without further purification: MS (ESI) *m/z* 393 $[M + H]^+$.

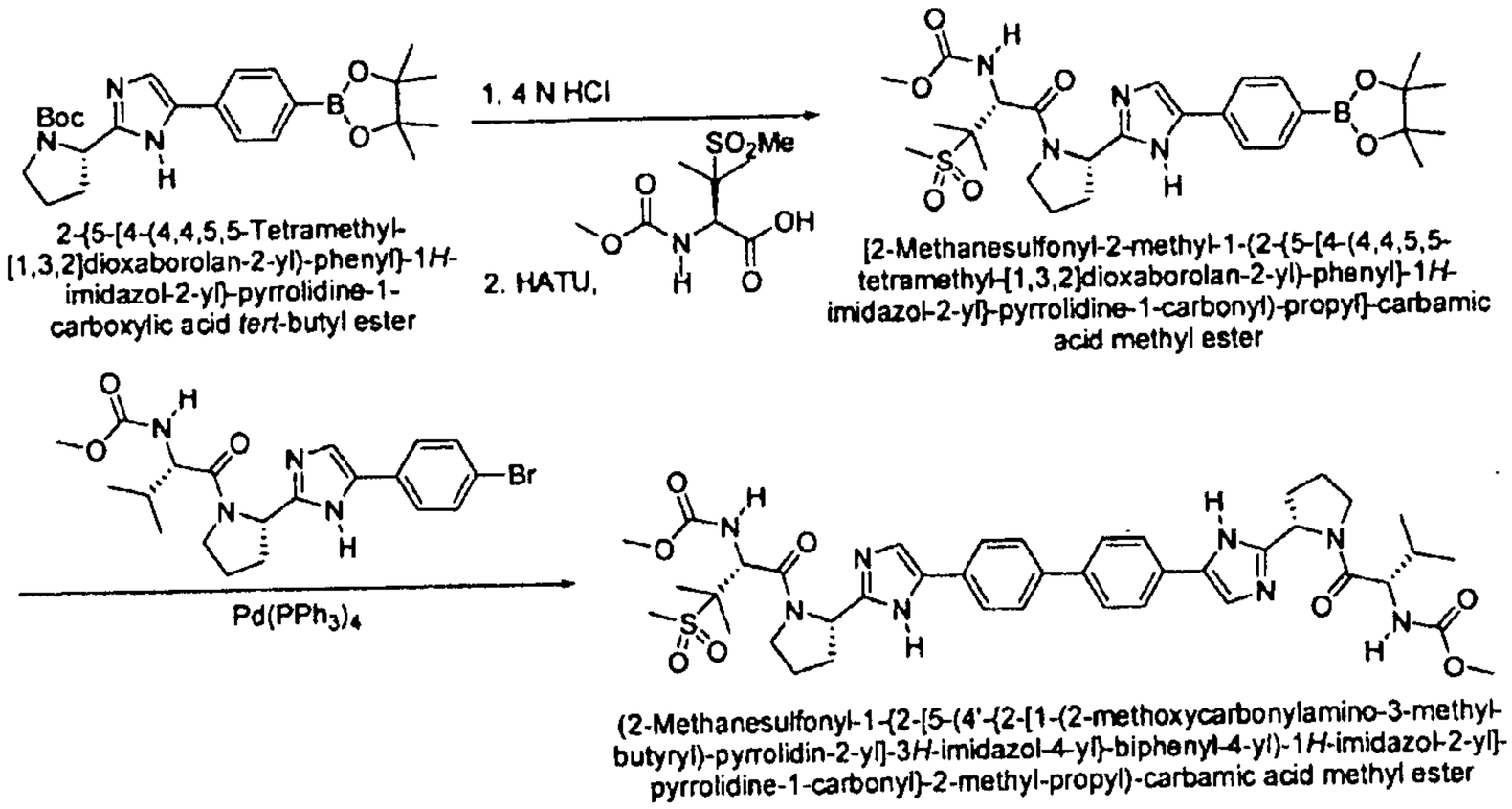
{1-[1H-Imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester boronic acid: {1-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester (110 mg, 0.28) in 1,4-dioxane (2.5 mL) was treated with bis(pinacolato)diboron (150 mg, 0.59 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol), and KOAc (71 mg, 0.73 mmol). The mixture was stirred in a sealed tube at 80°C for 18 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford {1-[1H-imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester boronic acid.

2-(5-{4'-[2-(1-*tert*-Butoxycarbonylamino-cyclobutyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 1-[1H-Imidazol-2-yl]-cyclobutyl}-carbamic acid *tert*-butyl ester boronic acid (60 mg, 0.17 mmol) and 2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (65 mg, 17 mmol) in 3:1 DME/H_2O (1.5 mL) were treated with $Pd(PPh_3)_4$ (10 mg, 0.0084 mmol) and K_2CO_3 (2 M solution, 0.25 mL, 0.50 mmol). The mixture was stirred in a sealed tube at 80°C for 18 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford 2-(5-{4'-[2-(1-*tert*-butoxycarbonylamino-cyclobutyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10 mg, 9%): MS (ESI) *m/z* 625 $[M + H]^+$.

(1-{2-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyrylamino)-cyclobutyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-(5-{4'-[2-(1-*tert*-Butoxycarbonylamino-cyclobutyl)-3H-imidazol-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9.8 mg, 0.016 mmol) was treated with 4 N HCl/dioxane (1.5 mL) and stirred for 4 hours. The mixture was concentrated and suspended in DMF (1.5 mL). The mixture was treated with (*S*)-Moc-Val-OH (6.0 mg, 0.032 mmol), HATU (13 mg, 0.034 mmol), and *N*-methyl morpholone (0.009 mL, 0.080 mmol). The mixture was stirred for 18 hours and concentrated. The mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford (1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyrylamino)-cyclobutyl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (2.8 mg, 24%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.88 (m, 10H), 5.20 (m, 1H), 4.23 (d, J = 7.2 Hz, 1H), 4.12 (m, 1H), 3.88 (app d, J = 7.2

Hz, 2H), 3.66 (s, 3H), 3.63 (s, 3H), 2.85 (br m, 2H), 2.65 (m, 4H), 2.09 (m, 10H), 0.95 (m, 12H); MS (ESI) *m/z* 739 $[M + H]^+$.

Example BR



2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester

[2-Methanesulfonyl-2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

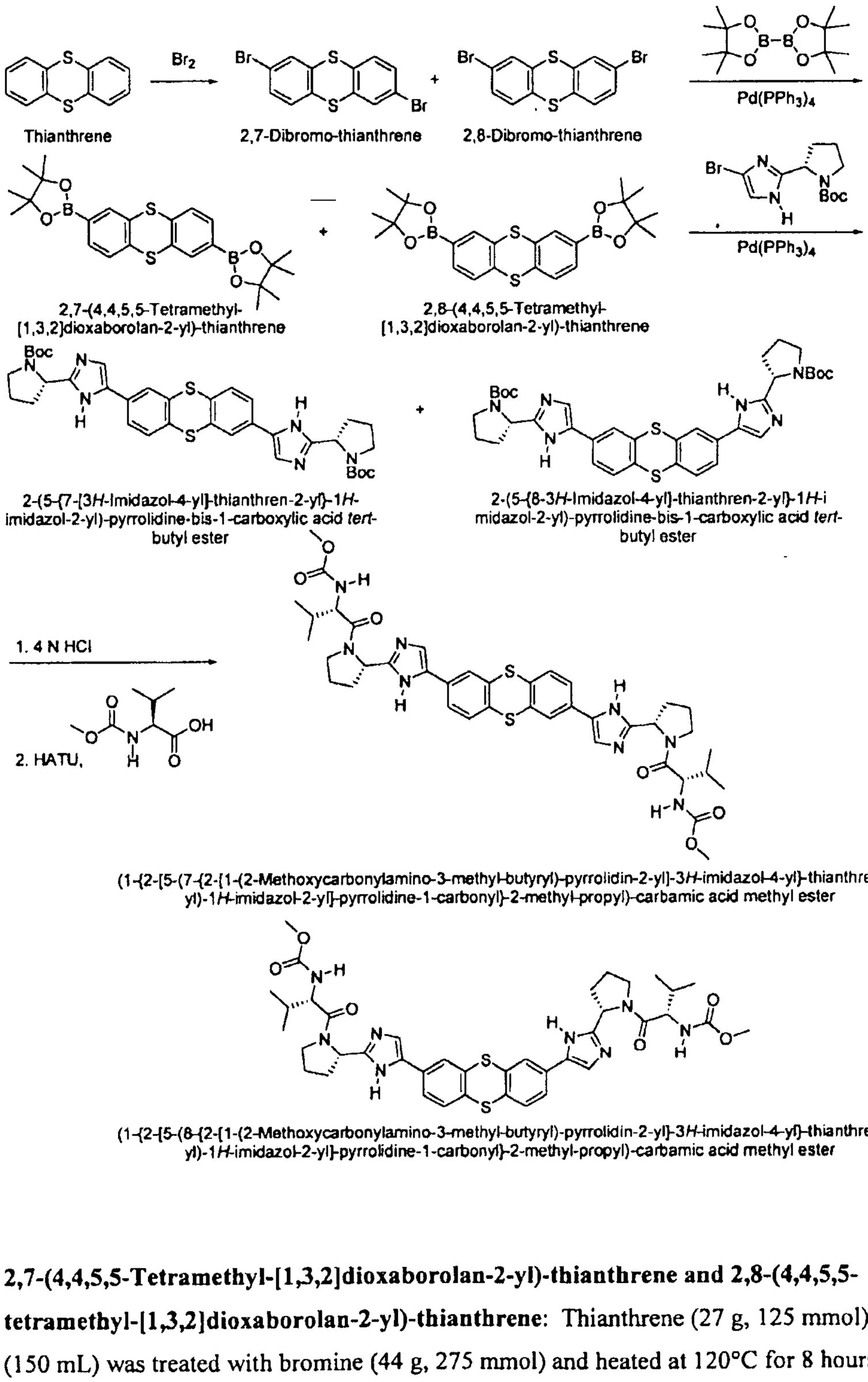
(2-Methanesulfonyl-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

[2-Methanesulfonyl-2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester: 2-{5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.02 g, 1.73 mmol) was treated with 4 N HCl/dioxane (5 mL) and stirred for 4 hours. The mixture was concentrated and suspended in DMF (1.5 mL). The mixture was treated with (*S*)-Moc-3-methanesulfonyl-2-methoxycarbonylamino-3-methyl-butyric acid (460 mg, 1.82 mmol), HATU (772 mg, 2.03 mmol), and *N*-methyl morpholone (0.950 mL, 8.65 mmol). The mixture was stirred for 18 hours and concentrated. The mixture was diluted with EtOAc (100 mL), and washed with saturated $NaHCO_3$ (3 50 mL), H_2O (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 40g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient) to afford [2-methanesulfonyl-2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (728 mg, 73%): MS (ESI) *m/z* 575 $[M + H]^+$.

(2-Methanesulfonyl-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: [2-Methanesulfonyl-2-methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-

carbonyl)-propyl]-carbamic acid methyl ester (700 mg, 1.22 mmol) and (1-{2-[5-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (565 mg, 1.26 mmol) in 3:1 DME/H_2O (15 mL) were treated with $Pd(PPh_3)_4$ (56 mg, 0.0050 mmol) and $NaHCO_3$ (350 mg, 4.15 mmol). The mixture was stirred in a sealed tube at 80°C for 24 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford (2-methanesulfonyl-1-{2-[5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (150 mg, 15%) as a white solid (TFA salt): ^1H NMR (CD_3OD, 300 MHz) 7.85 (m, 10H), 5.25 (m, 2H), 4.24 (d, J = 7.5 Hz, 1H), 4.13 (m, 2H), 3.88 (app d, J = 7.5 Hz, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 2.99 (s, 3H), 2.57 (m, 2H), 2.16 (m, 10H), 1.81 (s, 3 H), 1.79 (s, 1H), 0.93 (m, 6H); MS (ESI) *m/z* 818 $[M + H]^+$.

Example BS



2,7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene and 2,8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene: Thianthrene (27 g, 125 mmol) in AcOH (150 mL) was treated with bromine (44 g, 275 mmol) and heated at 120°C for 8 hours. The mixture was allowed to stand overnight at ambient temperature, at which time a white solid appeared. The solid was filtered, washed with H_2O (3 50 mL) and air dried to afford a mixture

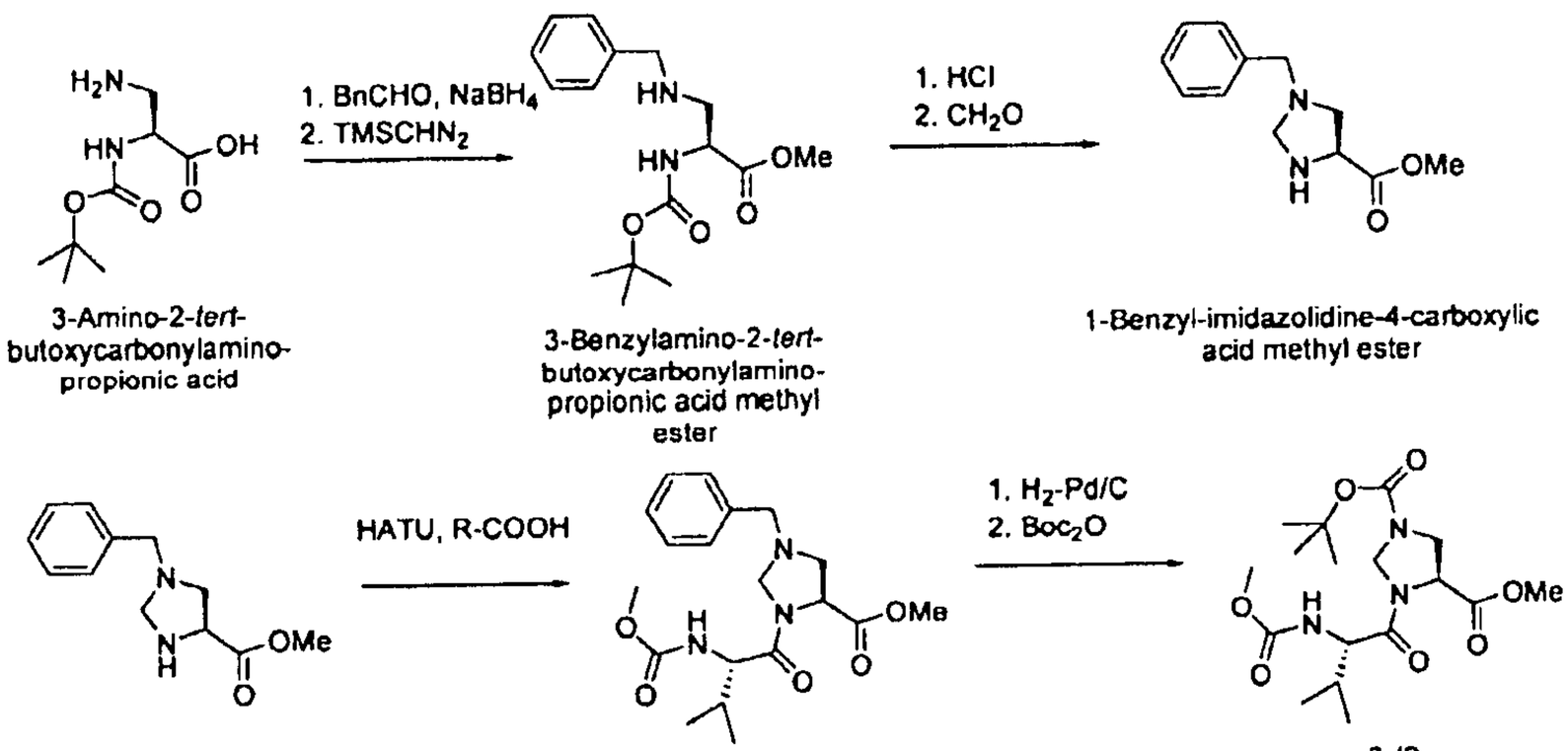
of 2,7-dibromo-thianthrene and 2,8-dibromo-thianthrene which was carried forward without further purification (42 g). The 2,7-bibromo-thianthrene/2,8-dibromo-thianthrene mixture (1 g, 2.7 mmol) in DMSO (25 mL) was treated with bis(pinacolato)diboron (2.7 g, 10.7 mmol), $PdCl_2dppf$ (218 mg, 0.27 mmol), and KOAc (2.1 g, 21.4 mmol). The mixture was stirred in a sealed tube at 80°C for 18 hours. The mixture was diluted with EtOAc (100 mL), and washed with saturated $NaHCO_3$ (3 50 mL), H_2O (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 40 g SiO_2 COMBIFLASH column (0–50% EtOAc–hexanes gradient) to afford a mixture of 2,7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene and 2,8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene (1.25 g, 99%): MS (ESI) *m/z* 796 $[M + H]^+$.

2-(5-{7-[3H-Imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester and 2-(5-{8-3H-imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester: A mixture of 2,7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene and 2,8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thianthrene (1.25 g, 2.67 mmol) and 2-(4-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.77 g, 5.6 mmol) in 3:1 DME/H_2O (25 mL) were treated with $Pd(PPh_3)_4$ (185 mg, 0.160 mmol) and $NaHCO_3$ (1.12 g, 13.35 mmol). The mixture was stirred in a sealed tube at 90°C for 24 hours. The mixture was filtered through a fritted glass funnel and concentrated. The mixture was diluted with EtOAc (100 mL), and washed with saturated $NaHCO_3$ (3 50 mL), H_2O (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 120 g SiO_2 COMBIFLASH column (0–50% EtOAc–hexanes gradient) to afford a mixture of 2-(5-{7-[3H-imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester and 2-(5-{8-3H-imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester.

(1-{2-[5-(7-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester and (1-{2-[5-(8-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: A mixture of 2-(5-{7-[3H-Imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester and 2-(5-{8-3H-imidazol-4-yl]-thianthren-2-yl}-1H-imidazol-2-yl)-pyrrolidine-bis-1-carboxylic acid *tert*-butyl ester (150 mg, 0.22 mmol) was treated with 4 N HCl/dioxane (2.5 mL) and stirred for 4 hours. The mixture was concentrated and suspended in DMF (2.5

mL). The mixture was treated with (*S*)-Moc-Val-OH (84 mg, 0.48 mmol), HATU (191 mg, 0.50 mmol), and *N*-methyl morpholone (120 mL, 1.09 mmol). The mixture was stirred for 2 hours and concentrated. The mixture was diluted with EtOAc (100 mL), and washed with saturated $NaHCO_3$ (3 50 mL), H_2O (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$ and subjected to a 40 g SiO_2 COMBIFLASH column (0–100% EtOAc–hexanes followed by 0–20% MeOH–EtOAc gradient), which gave a pure mixture of 2,7/2,8 products. The 2,7/2,8 mixture was subjected to a reverse phase HPLC column (5–95% MeCN–H_2O; 0.1% TFA modifier) to afford (1-{2-[5-(7-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (26 mg, 15%) as a white solid (TFA salt): ^{1}H NMR (CD_3OD, 400 MHz) 7.88 (s, 2H), 7.80 (s, 2H), 7.63 (s, 4H), 5.20 (m, 2H), 4.23 (d, J = 7.5 Hz, 2H), 4.13 (m, 2H), 3.88 (m, 2H), 3.72 (s, 6H), 2.99 (s, 3H), 2.52 (m, 2H), 2.16 (m, 10H), 0.95 (m, 12H); MS (ESI) *m/z* 818 $[M + H]^+$; and (1-{2-[5-(8-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-thianthren-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (10 mg, 5%) as a white solid (TFA salt): ^{1}H NMR (CD_3OD, 400 MHz) 7.86 (s, 2H), 7.80 (s, 2H), 7.63 (s, 4H), 5.20 (m, 2H), 4.23 (d, J = 7.5 Hz, 2H), 4.13 (m, 2H), 3.88 (m, 2H), 3.72 (s, 6H), 2.99 (s, 3H), 2.52 (m, 2H), 2.16 (m, 10H), 0.95 (m, 12H); MS (ESI) *m/z* 801 $[M + H]^+$.

Example BT



3-Benzylamino-2-*tert*-butoxycarbonylamino-propionic acid methyl ester: 3-Amino-2-*tert*-butoxycarbonylamino-propionic acid (5.0 g, 24.5 mmol) was suspended in methanol (100 mL) and benzaldehyde (5.2 g, 49 mmol) was added, followed by triethylamine (TEA, 10.2 mL, 73.5 mmol). The reaction mixture was stirred at ambient temperature for 90 minutes and cooled to 0 °C. Solid sodium borohydride (2.78 g, 73.5 mmol) was added in small portions and the reaction was stirred for additional 60 minutes after addition was complete. All volatiles were removed *in vacuo* and the crude was dissolved in NaOHaq (0.1 M, 100 mL). The solution was washed with diethyl ether and acidified with HCl aq. The mixture was extracted with chloroform. The organic extracts were washed with brine and dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded crude semi-solid (9.0 g). The crude material was dissolved in methanol (40 mL) and toluene (20 mL) and the solution was cooled to 0°C. Trimethysilyl diazomethane solution (2M, in hexanes) was added until the yellow color persisted (~25 mL). The reaction mixture was stirred for additional 60 minutes at room temperature. The volatiles were removed *in vacuo* and the crude product was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the pure product 3-Benzylamino-2-tert-butoxycarbonylamino-propionic acid methyl ester (4.09 g): LCMS-ESI$^+$: calc'd for $C_{16}H_{24}N_2O_4$: 308.3 (M^+); Found: 309.2 ($M+H^+$).

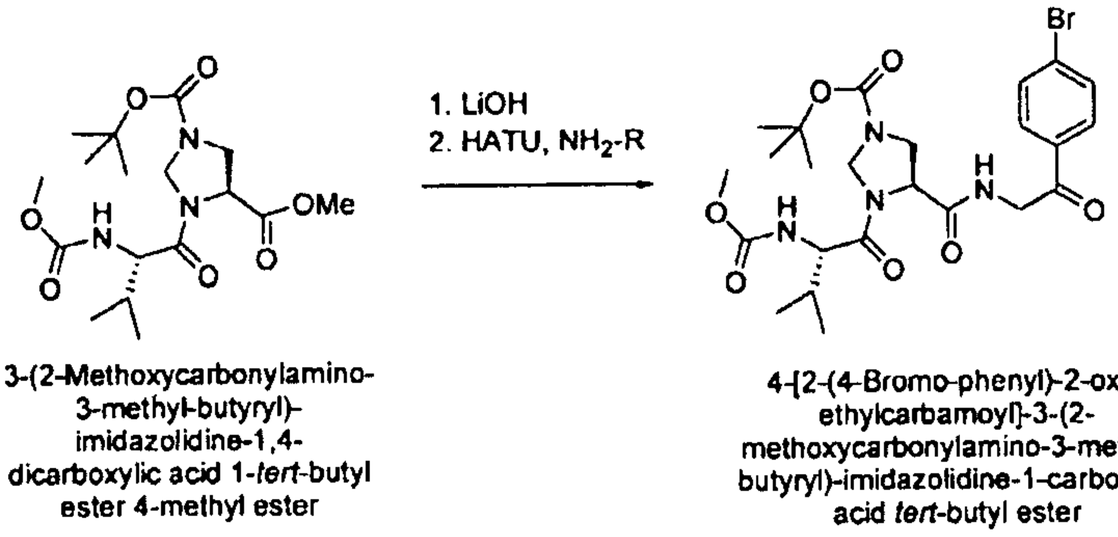
1-Benzyl-imidazolidine-4-carboxylic acid methyl ester: 3-Benzylamino-2-*tert*-butoxycarbonylamino-propionic acid methyl ester (4.01 g, 13.02 mmol) was dissolved in dichloromethane (20 mL) and HCl (4M Dioxane, 40 mL) was added. The resultant suspension was stirred at room temperature for 30 minutes, after which all volatiles were removed *in vacuo*. The crude material was mixed with para-formaldehyde (390 mg, 13.02 mmol), magnesium sulfate (2.6 g), potassium carbonate (2.6 g) and suspended in chloroform (40 mL). Triethylamine (5.07 mL) was added and the reaction was stirred at room temperature for 48 hours. The suspension was filtered and the volatiles were removed *in vacuo*. The crude material 1-Benzyl-imidazolidine-4-carboxylic acid methyl ester (3.5 g) was used in the next step without further analysis.

1-Benzyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester: Crude 1-Benzyl-imidazolidine-4-carboxylic acid methyl ester (3.0 g, 13.6 mmol) was added as a DMF suspension to a premixed solution of *N*-(methylcarbamoyl)(*L*)-valine (2.39 g, 13.6 mmol), HATU (5.16g, 13.6 mmol) and di*iso*propyl ethylamine (DIEA, 3.58 g, 27.2 mmol) at room temperature. After 60 minutes, all volatiles were removed *in vacuo* and the crude material was taken into dichloromethane. The organic layer was washed with aqueous

hydrochloric acid (0.1M), aqueous lithium chloride solution (5%), saturated aqueous sodium bicarbonate solution, brine and was dried over sodium sulfate. Filtration and evaporation of solvents yielded crude material. Purification via silica gel chromatography (eluent: EtOAc w MeOH 10% / hexanes) yielded the product 1-Benzyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester (1.95 g, 5.15 mmol): LCMS-ESI$^+$: calc'd for $C_{19}H_{27}N_3O_5$: 377.4 (M^+); Found: 378.4 ($M+H^+$).

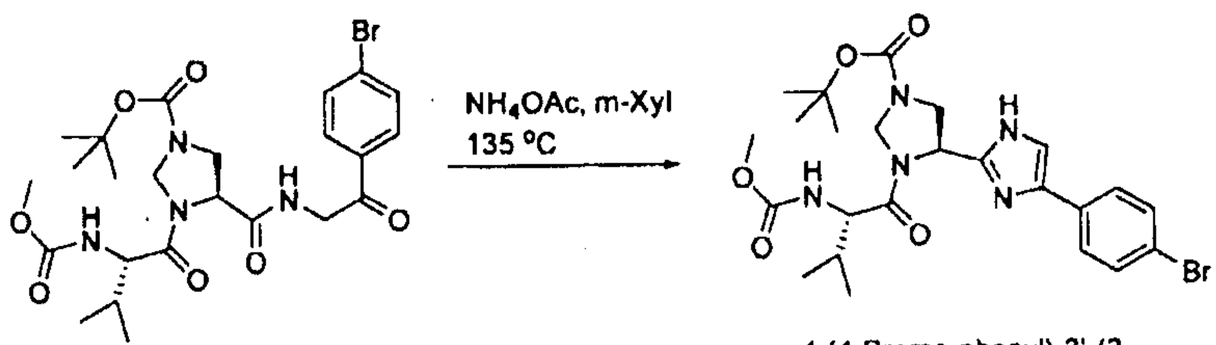
3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester: 1-Benzyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester (1.0 g, 2.64 mmol) was dissolved in MeOH (30 mL) at room temperature. Pd on carbon (10%, 350 mg) was added and the reaction was stirred under an atmosphere of hydrogen. After three hours the reaction mixture was filtered through CELITE and the volatiles were removed *in vacuo*. The crude material was dissolved in tetrahydrofuran (10 mL) and Boc_2O (576 mg) and di*iso*-propyl ethylamine (340 mg) were added and the reaction was stirred at room temperature. After 60 minutes all volatiles were removed *in vacuo* and the crude material was purified via silica gel chromatography (eluent: EtOAc w10% MeOH / hexanes) and yielded the product (0.812 g): LCMS-ESI$^+$: calc'd for $C_{17}H_{29}N_3O_7$: 387.4 (M^+); Found: 388.4 ($M+H^+$).

Example BU



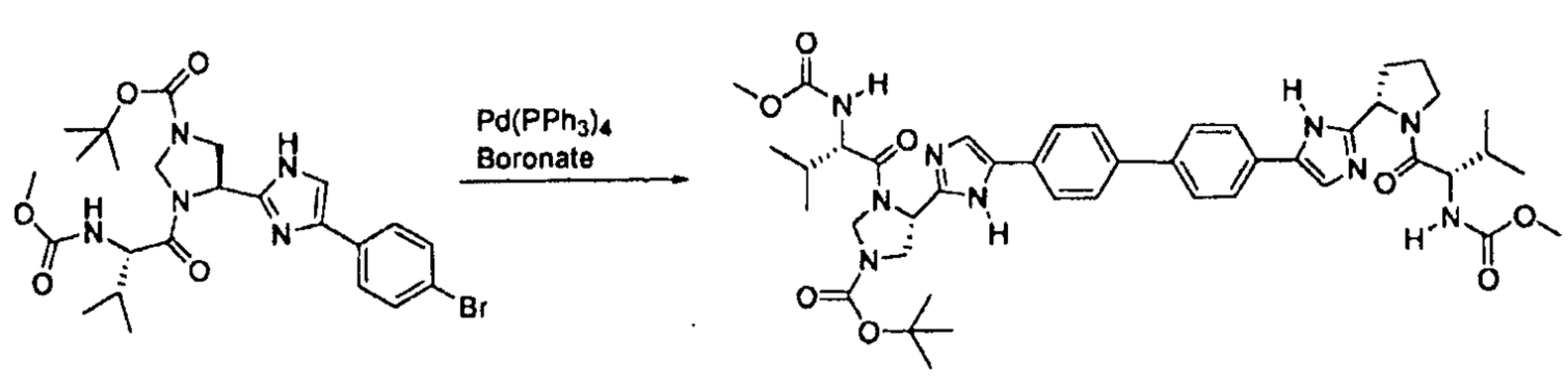
3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester

4-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1-carboxylic acid *tert*-butyl ester



4-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1-carboxylic acid *tert*-butyl ester

4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-letrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester



4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester

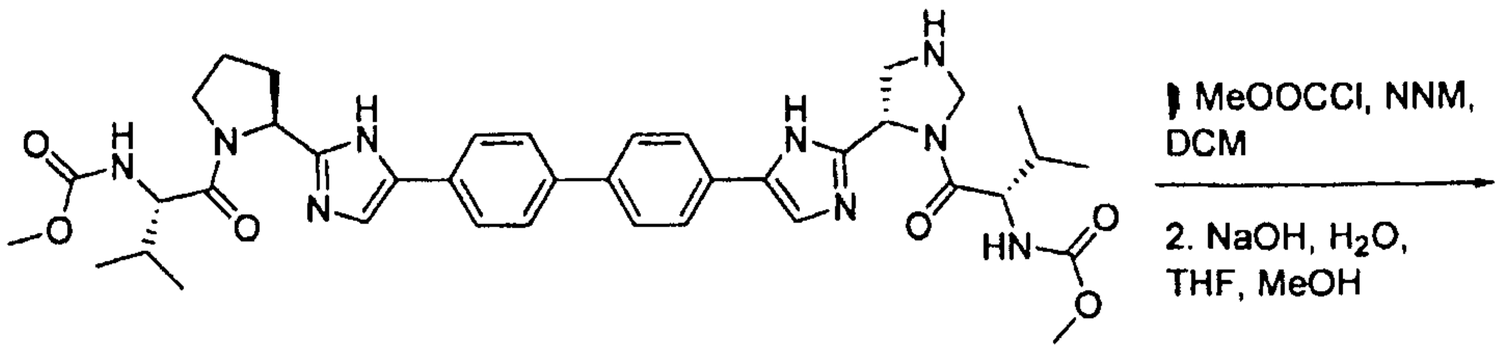
4-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1-carboxylic acid *tert*-butyl ester: 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (460 mg, 1.18 mmol) was dissolved in THF (3 mL) and MeOH (2 mL). An aqueous solution of LiOH (49.8 mg, 1.18 mmol) was added and stirring at room temperature was continued. After the hydrolysis was complete, the reaction was neutralized with aqueous HCl (1.18 mL, 1M). The organic solvents were removed *in vacuo* and the aqueous suspension was frozen and lyophilized. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (4.0 mL) and HATU (448 mg, 1.18 mmol) and DIEA (152 mg, 1.18

mmol) were added. The reaction was stirred at room temperature for five minutes, after which the amino-(4'bromo) acetophenone hydrochloride salt (295 mg, 1.18 mmol) was added. Stirring at room temperature was continued. After 90 minutes, all volatiles were removed *in vacuo* and the crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the slightly impure product 4-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1-carboxylic acid *tert*-butyl ester (723 mg): LCMS-ESI$^+$: calc'd for $C_{24}H_{33}BrN_4O_7$: 569.4 (M^+); Found: 570.4 / 572.4 ($M+H^+$).

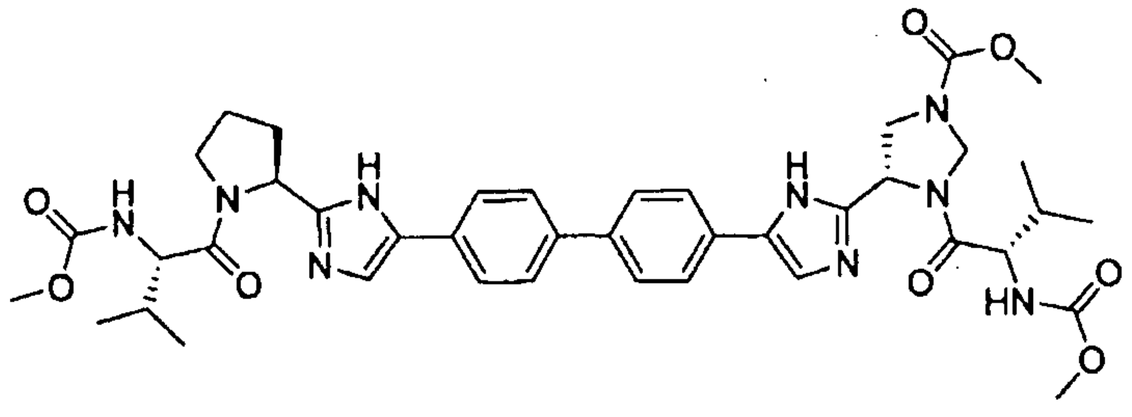
4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester: 4-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1-carboxylic acid *tert*-butyl ester (723 mg) was dissolved in m-xylenes (6.0 mL) and heated at 135 °C. Solid ammonium acetate (500 mg, 6.48 mmol) was added and the reaction was stirred at 135 °C. After 45 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc w 10% MeOH / hexanes) to yield the product 4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (436 mg): LCMS-ESI$^+$: calc'd for $C_{24}H_{32}BrN_5O_5$: 550.4 (M^+); Found: 551.2 / 553.2 ($M+H^+$).

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester: 4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester (75 mg, 0.136 mmol) was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (67.6 mg, 0.136 mmol) under an argon atmosphere. Potassium carbonate (37.5 mg, 0.272 mmol) and $Pd(PPh_3)_4$ (15.7 mg, 0.014 mmol) were added, followed by DME (3 mL) and water (0.6 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product (55 mg): LCMS-ESI$^+$: calc'd for $C_{44}H_{57}N_9O_8$: 839.9 (M^+); Found: 840.5 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.90-7.81 (m, 10H), 5.58 (m,1H), 5.43 (m, 1H), 5.25-5.20 (m, 2H), 4.24 (d,J= 7.5Hz, 1H), 4.11 (m, 1H), 3.99 (m, 1H), 3.86 (m,2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.46 (d, J= 7.2Hz, 1H), 2.59 (m, 1H), 2.22-2.10 (m, 5H), 1.53 & 1.44 (s, 9H) 1.04-0.89 (m, 12H).

Example BV



{1-[2-(5-{4'-[3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-3*H*,1'*H*-[2,4']biimidazolyl-4-yl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



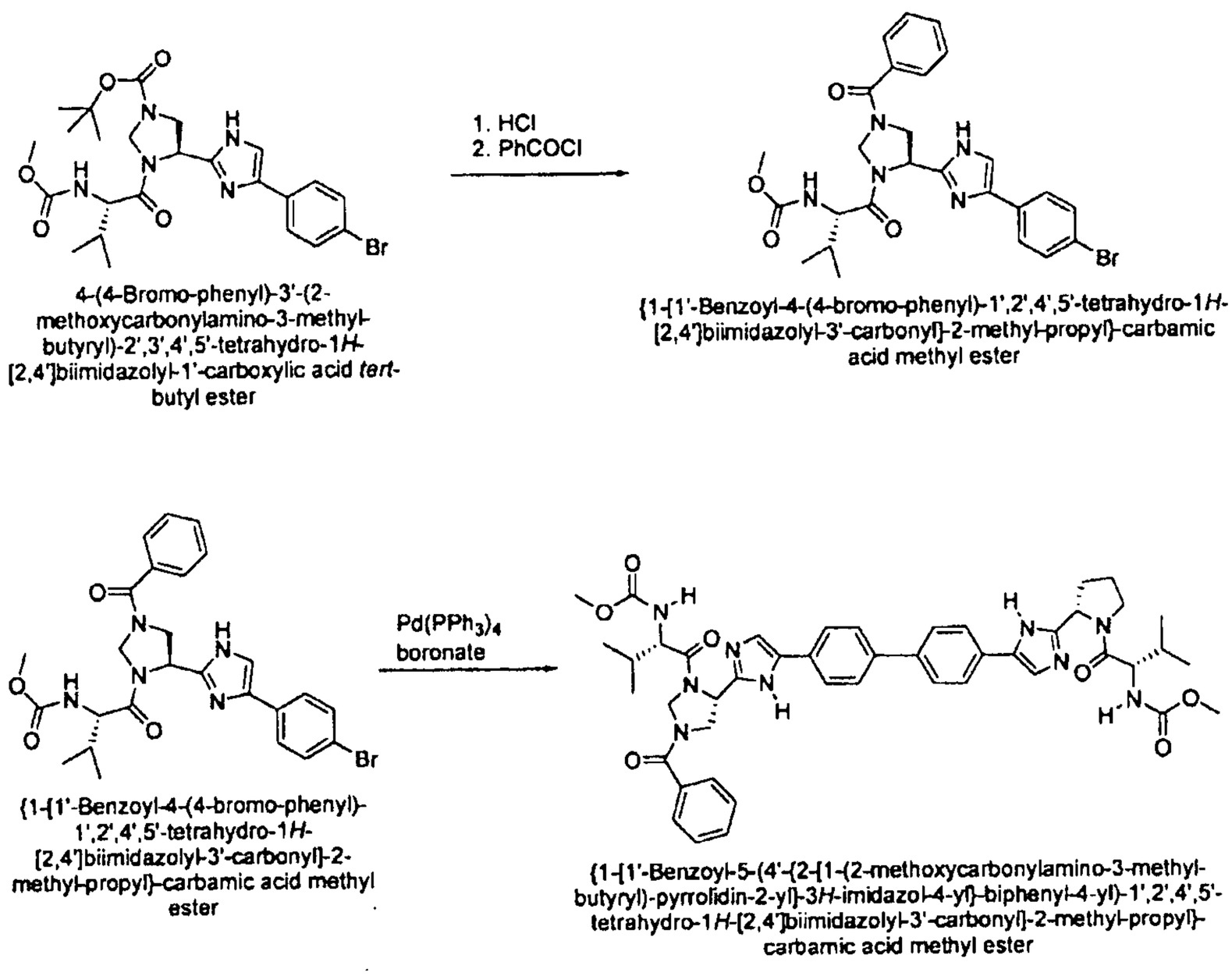
3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid methyl ester

3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid methyl ester: 4-Methylmorpholine (31 μL, 0.28 mmol) was added to a suspension of {1-[2-(5-{4'-[3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-3H,1'H-[2,4']biimidazolyl-4-yl]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (41.1 mg, 0.056 mmol) [prepared via reaction of 3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester with HCl-solution] in dichloromethane (5 mL). Methyl chloroformate (16.5 μL, 0.21 mmol) was added to the resulting solution. After 20 minutes the solvent was removed *in vacuo*. The residue was taken into tetrahydrofuran (4 mL) and methanol (2 mL) and an aqueous solution of sodium hydroxide (2 N, 1 mL) was added. After 2 hours the organic solvents were removed *in vacuo* and the aqueous phase was decanted. The residue was dissolved in dimethylformamide (2 mL) and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA). The product-containing fractions were combined and the solvent was removed by lyophilization to provide 3'-(2-Methoxycarbonylamino-3-methyl-butyryl)-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-

butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid methyl ester (7.5 mg)

$C_{41}H_{51}N_9O_8$ calculated 797.4 observed $[M + 1]^+$ 798.4; ^1H (DMSO-d6): δ = 8.08 (s, 1H), 7.83 (m, 8H), 7.58 (d, J = 8.0 Hz, 1H), 7.29 (s, J = 8.4 Hz,1 H), 5.42 (dd, J = 7.6, 3.6 Hz, 1H), 5.26 (d, J = 4.8 Hz, 1H), 5.18 (d, J = 6.0 Hz, 1H), 5.10 (t, J = 7.2 Hz, 1H), 4.88 (m, 1H), 4.08 (t, J = 7.6 Hz, 2H), 3.94 (m, 1H), 3.82 (m, 4H), 3.65 (s, 3H), 3.52 (s, 3H), 3.51 (s, 3H), 2.36 (m, 1H), 2.01 (m, 5H), 0.83 (m, 12H).

Example BW



4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-1'-carboxylic acid *tert*-butyl ester

{1-[1'-Benzoyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Benzoyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Benzoyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

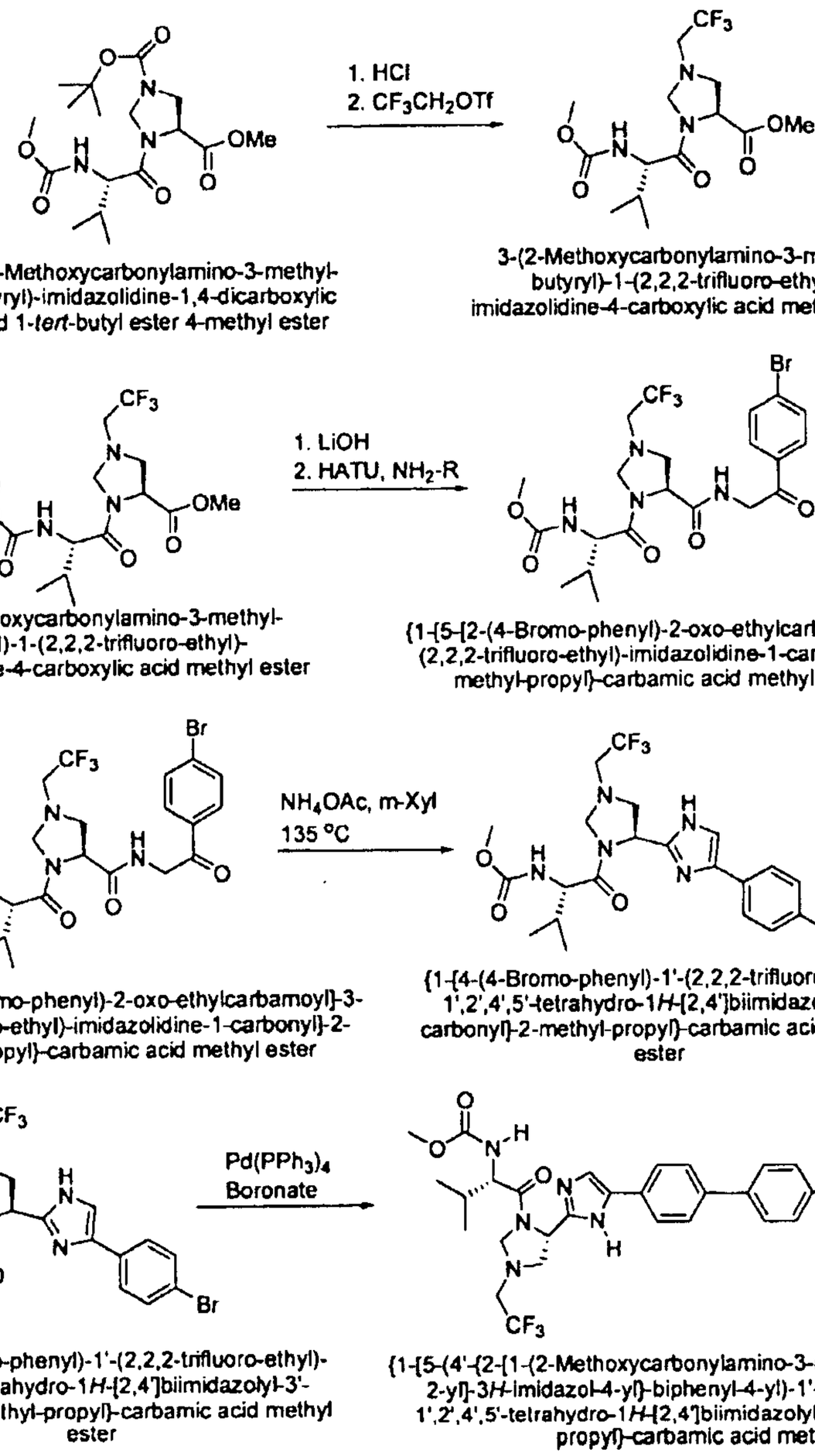
{1-[1'-Benzoyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 4-(4-Bromo-phenyl)-3'-(2-methoxycarbonylamino-3-methyl-butyryl)-2',3',4',5'-tetrahydro-1H-[2,4']biimidazolyl-1'-carboxylic acid tert-butyl ester (55.6 mg, 0.101 mmol) was dissolved in dichloromethane (0.5 mL) and HCl (4M dioxane, 0.5 mL) was added. The resultant suspension was stirred at room temperature for 20 minutes, after which all volatiles were removed *in vacuo*. The crude material was dissolved in THF (1 mL) and di*iso*propyl ethylamine (26.0 mg, 0.202 mmol) was added, followed by benzoyl chloride (15.6 mg, 0.11 mmol). The reaction was stirred at room temperature. After 10 minutes, all starting material was consumed. All volatiles were removed

in vacuo and the crude brown solid {1-[1'-Benzoyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester was used in the coupling reaction without further analysis or purification: LCMS-ESI$^+$: calc'd for $C_{26}H_{28}BrN_5O_4$: 554.4 (M^+); Found: 554.3 / 556.4 ($M+H^+$).

{1-[1'-Benzoyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

{1-[1'-Benzoyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (crude, <0.101 mmol) was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (45.1 mg, 0.091 mmol) under an argon atmosphere. Potassium carbonate (27.8 mg, 0.202 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added, followed by DME (2.0 mL) and water (0.4 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product {1-[1'-Benzoyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (20.7 mg): LCMS-ESI$^+$: calc'd for $C_{46}H_{53}N_9O_7$: 843.9 (M^+); Found: 844.3 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.90-7.84 (m, 10H), 7.66-7.52 (m, 5H), 5.68 (m,1H), 5.59 (m, 1H), 5.49 (m, 1H), 5.26 (m, 1H), 4.24 (d,J= 7.5Hz, 1H), 4.11 (m, 2H), 3.86 (m, 2H), 3.66 (s, 3H), 3.65 (s, 3H), 3.46 (d, J= 5.7Hz, 1H), 2.57 (m, 1H), 2.29-2.09 (m, 5H), 1.01-0.85 (m, 12H).

Example BX



3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester

3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-(2,2,2-trifluoro-ethyl)-imidazolidine-4-carboxylic acid methyl ester

{1-[5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2,2,2-trifluoro-ethyl)-imidazolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-(2,2,2-trifluoro-ethyl)-imidazolidine-4-carboxylic acid methyl ester: 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (160 mg, 0.412 mmol) was dissolved in dichloromethane (0.5 mL) and HCl (4M dioxane, 3 mL) was added. The resultant suspension was stirred at room temperature for 60 minutes, after which all volatiles were removed *in vacuo*. The crude material was dissolved in DMF (1.5 mL) and di*iso*propyl ethylamine (106 mg, 0.824 mmol) was added followed by trifluoroethyl triflate (114.7 mg, 0.494 mmol). After 14 hrs additional di*iso*propyl ethylamine (212 mg, 1.648 mmol) and trifluoroethyl triflate (229.4 mg,

0.988 mmol) were added. Stirring at room temperature was continued. After 40 hours, all volatiles were removed *in vacuo* and the crude material was purified by flash chromatography on silica gel (eluent: EtOAc / hexanes) to yield the product 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-(2,2,2-trifluoro-ethyl)-imidazolidine-4-carboxylic acid methyl ester (95 mg, 0.257 mmol): LCMS-ESI$^+$: calc'd for $C_{14}H_{23}F_3N_3O_5$: 369.3 (M^+); Found: 369.9 (M^+).

{1-[5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2,2,2-trifluoro-ethyl)-imidazolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

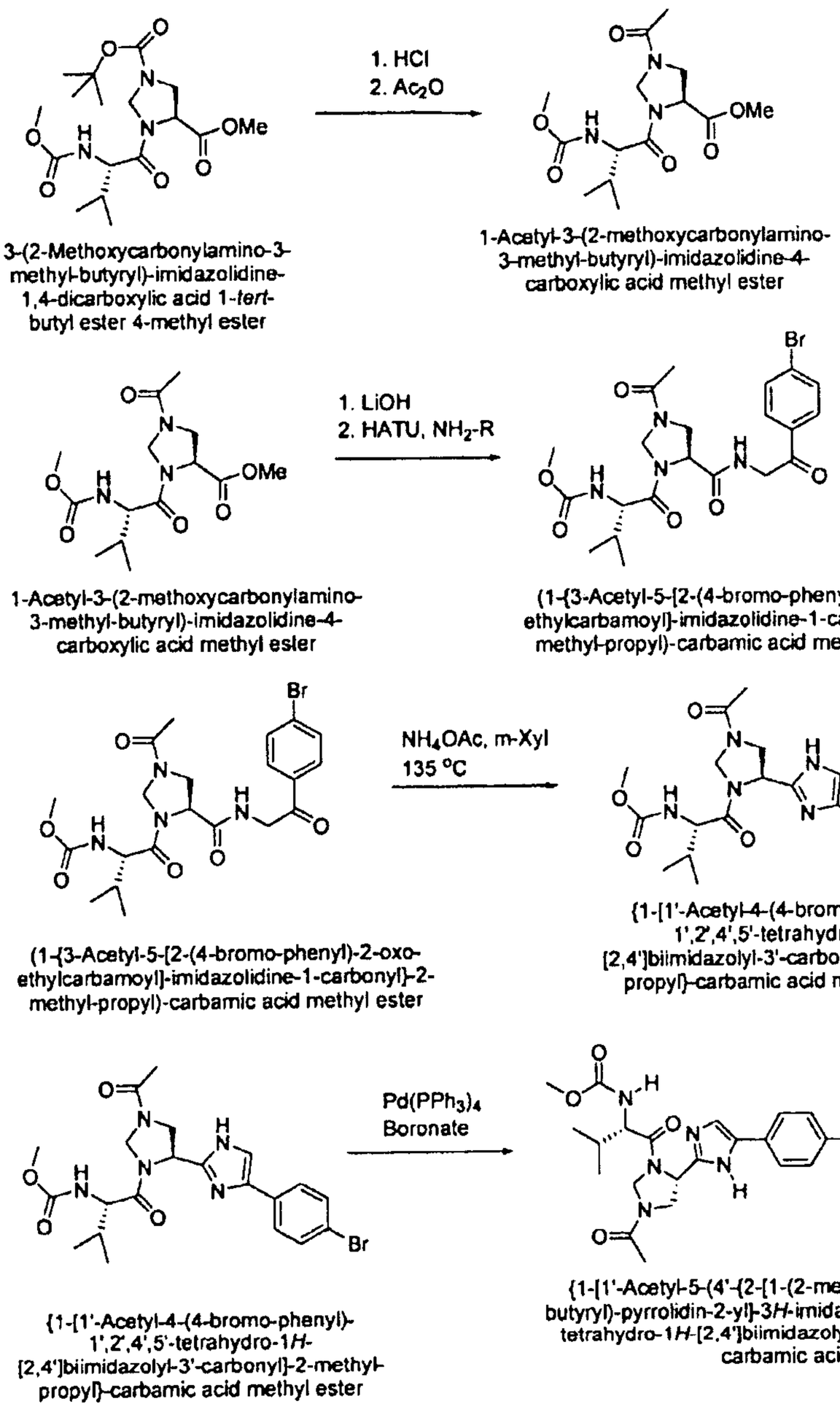
3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-(2,2,2-trifluoro-ethyl)-imidazolidine-4-carboxylic acid methyl ester (95 mg, 0.257 mmol) was dissolved in THF (1.8 mL) and MeOH (0.9 mL). An aqueous solution of LiOH (10.8 mg, 0.208 mmol) was added and stirring at room temperature was continued. After the hydrolysis was complete, the reaction was neutralized with aqueous HCl (1M). The organic solvents were removed *in vacuo* and the aqueous suspension was frozen and lyophilized. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.5 mL) and HATU (97.6 mg, 0.257 mmol) and DIEA (66.3 mg, 0.514 mmol) were added. The reaction was stirred at room temperature for five minutes, after which the amino-(4'bromo) acetophenone hydrochloride salt (64.2 mg, 0.257 mmol) was added. Stirring at room temperature was continued. After 60 minutes, all volatiles were removed *in vacuo* and the crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the slightly impure product {1-[5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2,2,2-trifluoro-ethyl)-imidazolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (148 mg): LCMS-ESI$^+$: calc'd for $C_{21}H_{26}BrF_3N_4O_5$: 551.3 (M^+); Found: 551.2 / 553.2 (M^+).

{1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

{1-[5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-(2,2,2-trifluoro-ethyl)-imidazolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (148 mg, < 257 mmol) was dissolved in m-xylenes (4.0 mL) and heated at 135 °C. Solid ammonium acetate (150 mg, 1.9 mmol) was added and the reaction was stirred at 135 °C. After 60 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via RP-HPLC (eluent: water / MeCN w 0.1 % TFA) to yield the product {1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (15.1 mg) as the TFA salt: LCMS-ESI$^+$: calc'd for $C_{21}H_{25}BrF_3N_5O_3$: 532.3 (M^+); Found: 532.1 / 534.2 (M^+).

{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (13.0 mg, 0.0244 mmol) was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (12.1 mg, 0.0244 mmol) under an argon atmosphere. Potassium carbonate (6.7 mg, 0.048 mmol) and $Pd(PPh_3)_4$ (2.7 mg, 0.0024 mmol) were added, followed by DME (2.0 mL) and water (0.4 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product {1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (6.1 mg, 0.006 mmol) as the TFA salt: LCMS-ESI$^+$: calc'd for $C_{41}H_{50}F_3N_9O_6$: 821.8 (M^+); Found: 823.4 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.89-7.82 (m, 10H), 5.39 (dd, J=6.3, 6.3Hz, 1H), 5.25 (m, 1H), 4.78 (d, J=6.9Hz, 1H), 4.24 (d, J=7.5Hz, 1H), 4.10 (m,1H), 4.00 (d, J=7.5Hz, 1H), 3.88 (m, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.65-3.43 (m, 4H), 2.58 (m, 1H), 2.29-2.01 (m, 5H), 1.03-0.89 (m, 12H).

Example BY



3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester

1-Acetyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester

1-Acetyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester

(1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

(1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

{1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Acetyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

1-Acetyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester: 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (465 mg, 1.2 mmol) was dissolved in dichloromethane (1 mL) and HCl (4M dioxane, 3 mL) was added. The resultant suspension was stirred at room temperature for 30 minutes, after which all volatiles were removed *in vacuo*. The crude material was dissolved in THF and di*iso*propyl ethylamine (154 mg, 1.2 mmol) was added, followed by

acetic anhydride (122 mg, 1.2 mmol). The reaction was stirred at room temperature. After 30 minutes, all volatiles were removed *in vacuo*. The crude material was purified by silica gel chromatography (eluent: DCM / MeOH) to yield the product 1-Acetyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester (273 mg, 0.829 mmol): LCMS-ESI$^+$: calc'd for $C_{14}H_{23}N_3O_6$: 329.4 (M^+); Found: 330.4 ($M+H^+$).

(1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester:

1-Acetyl-3-(2-methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-4-carboxylic acid methyl ester (273 mg, 0.829 mmol) was dissolved in THF (1.8 mL) and MeOH (1.2 mL). An aqueous solution of LiOH (34.8 mg, 0.829 mmol) was added and stirring at room temperature was continued. After the hydrolysis was complete, the reaction was neutralized with aqueous HCl (0.83 mL, 1M). The organic solvents were removed *in vacuo* and the aqueous suspension was frozen and lyophilized. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (3 mL) and HATU (315 mg, 0.829 mmol) and DIEA (106 mg, 0.829 mmol) were added. The reaction was stirred at room temperature for five minutes, after which the amino-(4'bromo) acetophenone hydrochloride salt (207 mg, 0.829 mmol) was added. Stirring at room temperature was continued. After 120 minutes, all volatiles were removed *in vacuo* and the crude material was dissolved in DCM. The organic layer was washed with aqueous HCl (0.5 M), aqueous lithium chloride solution (5%), brine and was dried over sodium sulfate. Filtration and evaporation of solvents yielded crude product which was purified via silica gel chromatography (eluent EtOAc / hexanes) to yield the product (1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (203 mg, 0.397 mmol): LCMS-ESI$^+$: calc'd for $C_{21}H_{27}BrN_4O_6$: 511.4 (M^+); Found: 511.3 / 513.2 ($M+H^+$).

{1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

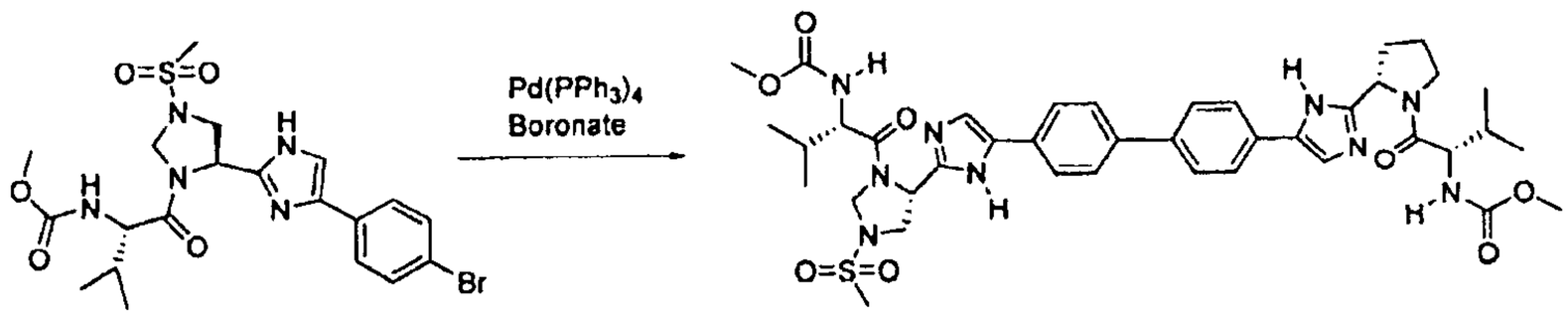
(1-{3-Acetyl-5-[2-(4-bromo-phenyl)-2-oxo-ethylcarbamoyl]-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (203 mg, 0.397 mmol) was dissolved in m-xylenes (4 mL) and heated at 135 °C. Solid ammonium acetate (200 mg, 2.58 mmol) was added and the reaction was stirred at 135 °C. After 120 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc w 10% MeOH/hexanes) to yield the product {1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-

carbamic acid methyl ester (162 mg, 0.329 mmol): LCMS-ESI$^+$: calc'd for $C_{21}H_{26}BrN_5O_4$: 492.4 (M^+); Found: 492.3 / 494.3 ($M+H^+$).

{1-[1'-Acetyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

{1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (150 mg, 0.304 mmol) was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (151 mg, 0.304 mmol) under an argon atmosphere. Potassium carbonate (83.9 mg, 0.608 mmol) and $Pd(PPh_3)_4$ (34 mg, 0.030 mmol) were added, followed by DME (8 mL) and water (2 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product {1-[1'-Acetyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (69.8 mg): LCMS-ESI$^+$: calc'd for $C_{41}H_{51}N_9O_7$: 781.9 (M^+); Found: 782.5 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.91-7.82 (m, 10H), 5.68 (m,1H), 5.59-5.37 (m, 2H), 5.25 (m, 1H), 4.34 (m,1H), 4.24 (d, J= 7.5Hz, 1H), 4.11-4.02 (m, 2H), 3.88 (m, 1H), 3.66 (s, 6H), 3.47 (d, J= 7.2Hz, 1H), 2.60 (m, 1H), 2.29-2.10 (m, 8H), 1.05-0.89 (m, 12H).

Example BZ



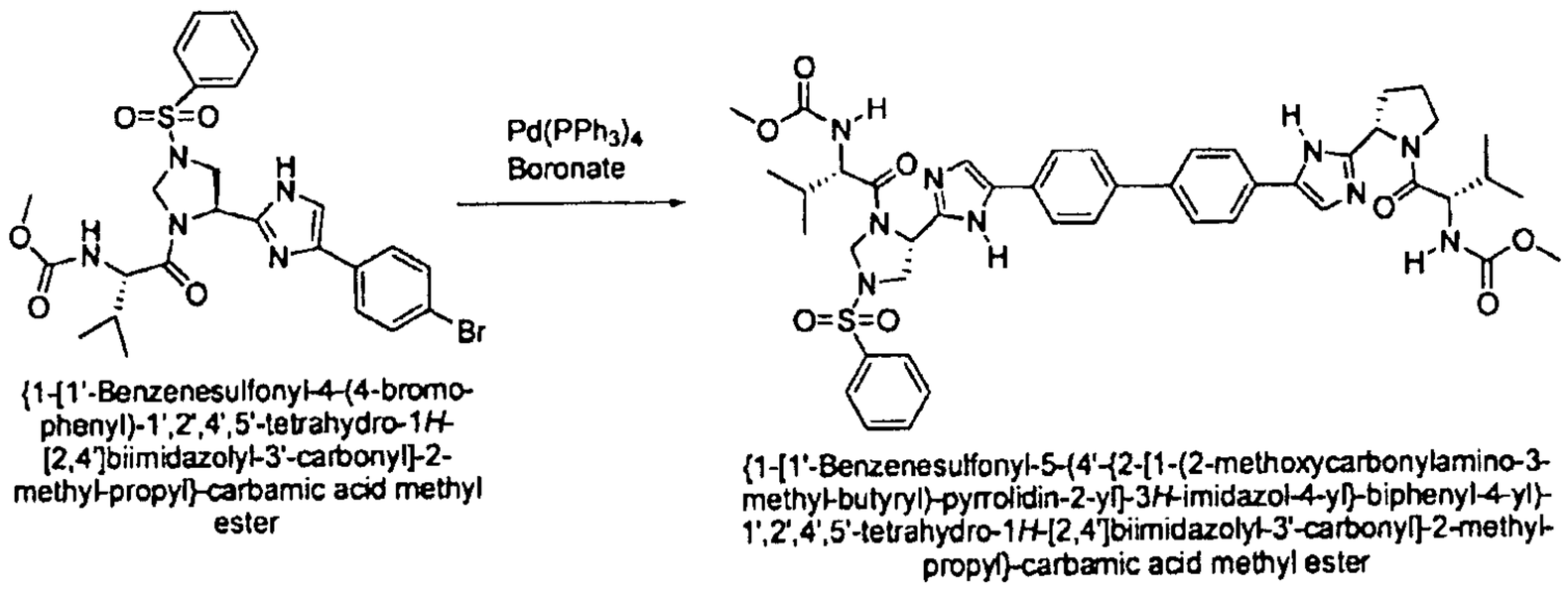
{1-[4-(4-Bromo-phenyl)-1'-methanesulfonyl-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Methanesulfonyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Methanesulfonyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[4-(4-Bromo-phenyl)-1'-methanesulfonyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-

methyl-propyl}-carbamic acid methyl ester (62.9 mg, 0.119 mmol) [prepared as described for the synthesis of {1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl (Example **BY**)]-2-methyl-propyl}-carbamic acid methyl ester substituting the acetic anhydride with methyl sulfonyl chloride] was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (54.6 mg, 0.110 mmol) under an argon atmosphere. Potassium carbonate (33.1 mg, 0.240 mmol) and $Pd(PPh_3)_4$ (12.7 mg, 0.011 mmol) were added, followed by DME (2.0 mL) and water (0.4 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product (20.1 mg): LCMS-ESI$^+$: calc'd for $C_{40}H_{51}N_9O_8S$: 817.9 (M^+); Found: 818.6 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.90-7.81 (m, 10H), 5.69 (d, J=7.5Hz, 1H), 5.48 (dd, J=6.9, 6.9Hz, 1H), 5.27 (dd, J=8.1, 8.1Hz, 1H), 5.17 (d, J=8.4Hz, 1H), 4.41 (dd, J=12.0, 7.8Hz,1H), 4.24 (d, J=7.2Hz, 1H), 4.11 (m, 2H), 4.00 (d, J=8.1Hz, 1H), 3.87 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.17 (s, 3H), 2.57 (m, 1H), 2.29-1.99 (m, 5H), 1.03-0.89 (m, 12H).

Example CA



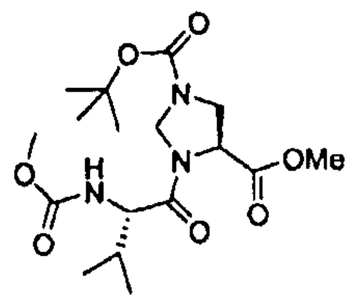
{1-[1'-Benzenesulfonyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Benzenesulfonyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[1'-Benzenesulfonyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[1'-Benzenesulfonyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (63.1 mg, 106.9 mmol) [prepared as described for the synthesis of {1-[1'-Acetyl-4-(4-bromo-phenyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (Example **BY**)] substituting the acetic anhydride with phenyl sulfonyl chloride] was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-

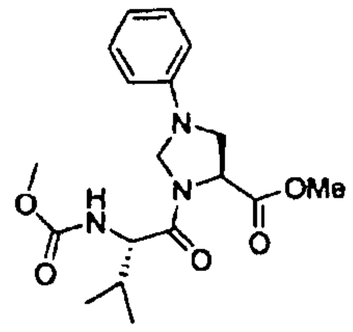
propyl]-carbamic acid methyl ester (53.1 mg, 106.9 mmol) under an argon atmosphere. Potassium carbonate (29.2 mg, 0.212 mmol) and $Pd(PPh_3)_4$ (12.2 mg, 0.0106 mmol) were added, followed by DME (2.5 mL) and water (0.8 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product {1-[1'-Benzenesulfonyl-5-(4'-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (27.9 mg): LCMS-ESI$^+$: calc'd for $C_{45}H_{53}N_9O_8S$: 880.2 (M^+); Found: 881.5 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 8.01 (d, J=7.5Hz, 2H), 7.90-7.76 (m, 11H), 7.65 (t, J=7.8Hz, 2H), 5.59 (d, J=8.7Hz, 1H), 5.25 (dd, J=7.5, 7.5Hz, 1H), 5.19 (d, J=8.7Hz, 1H), 4.67 (dd, J=7.5, 7.5Hz, 1H), 4.32-4.22 (m, 2H), 4.08 (m, 2H), 3.85 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.44 (d, J= 6.6Hz, 1H), 2.57 (m, 1H), 2.29-1.99 (m, 5H), 0.99-0.86 (m, 12H).

Example CB

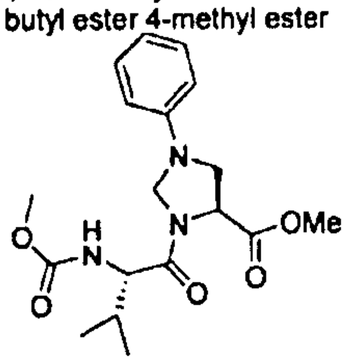


3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester

1. HCl
2. $PhB(OH)_2$, Cu(II)

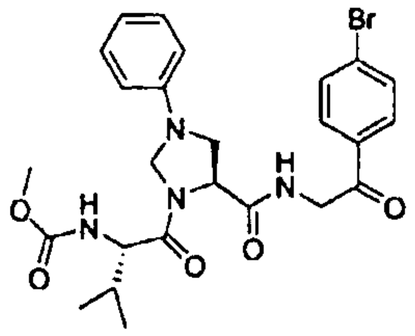


3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-phenyl-imidazolidine-4-carboxylic acid methyl ester

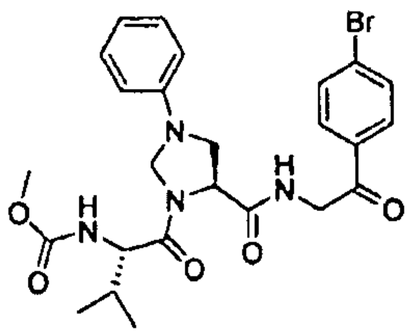


3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-phenyl-imidazolidine-4-carboxylic acid methyl ester

1. LiOH
2. HATU, NH_2-R

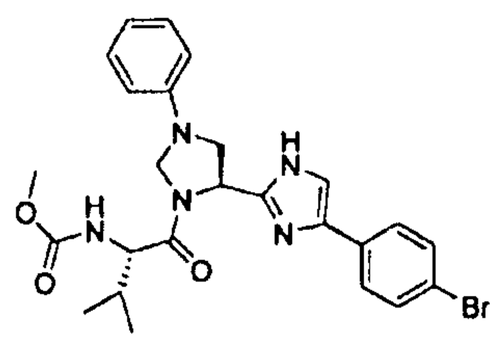


(1-{5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-phenyl-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

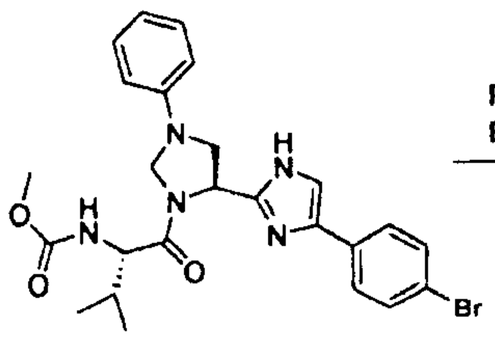


(1-{5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-phenyl-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

NH_4OAc, m-Xyl
135 °C

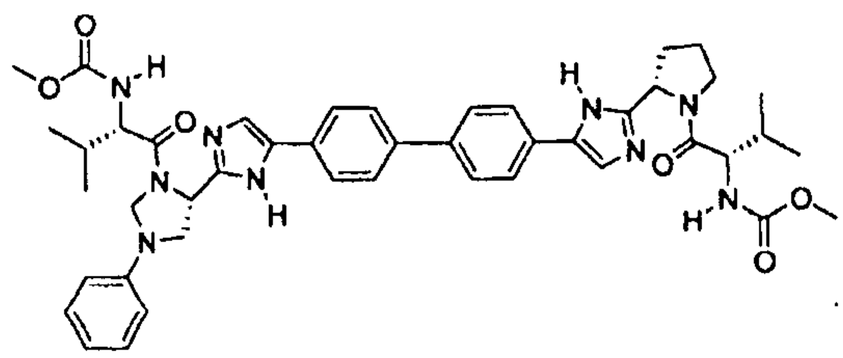


(1-[4-(4-Bromo-phenyl)-1'-phenyl-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester



(1-[4-(4-Bromo-phenyl)-1'-phenyl-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester

$Pd(PPh_3)_4$
Boronate



(1-{5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-yl)-1'-phenyl-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester

3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-phenyl-imidazolidine-4-carboxylic acid methyl ester: 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-imidazolidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (0.20 g, 0.515 mmol) was dissolved in dichloromethane (1.0 mL) and HCl (4M dioxane, 1 mL) was added. The resultant suspension was stirred at room temperature for 60 minutes, after which all volatiles were removed *in vacuo*. The crude material was combined with phenyl boronic acid (188 mg, 1.545 mmol) and DCM (15 mL) was added. Triethylamine (1.2 mL, 8.89 mmol) was added, followed by copper(II) acetate and molecular sieves 4 Å. The reaction was stirred at room temperature. After 24 hrs, the reaction was quenched with aqueous ammonium hydroxide solution (10%) and the organic layer was isolated. The organic layer was washed with aqueous HCl solution (0.5 M), brine, and was dried over sodium sulfate. Filtration and evaporation gave crude material. Purification via flash chromatography on silica gel (eluent: EtOAc / hexanes) yielded the desired product 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-phenyl-imidazolidine-4-carboxylic acid methyl ester (51.0 mg, 0.14 mmol): LCMS-ESI$^+$: calc'd for $C_{18}H_{25}N_3O_5$: 363.4 (M^+); Found: 364.4 ($M+H^+$).

(1-{5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-phenyl-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 3-(2-Methoxycarbonylamino-3-methyl-butyryl)-1-phenyl-imidazolidine-4-carboxylic acid methyl ester (51 mg, 0.14 mmol) was dissolved in THF (1.2 mL) and MeOH (0.8 mL). An aqueous solution of LiOH (6.0 mg, 0.14 mmol) was added and stirring at room temperature was continued. After the hydrolysis was complete, the reaction was neutralized with aqueous HCl (1M). The organic solvents were removed *in vacuo* and the aqueous suspension was frozen and lyophilized. The crude material was used in the next step without further purification. The crude material was dissolved in DMF (1.5 mL) and HATU (54.3 mg, 0.14 mmol) and DIEA (36.9 mg, 0.28 mmol) were added. The reaction was stirred at room temperature for five minutes, after which the amino-(4'bromo) acetophenone hydrochloride salt (35.7 mg, 0.14 mmol) was added. Stirring at room temperature was continued. After 10 minutes, all volatiles were removed *in vacuo* and the crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the slightly impure product (95 mg): LCMS-ESI$^+$: calc'd for $C_{25}H_{29}BrN_4O_5$: 545.4 (M^+); Found: 545.2 / 547.4 ($M+H^+$).

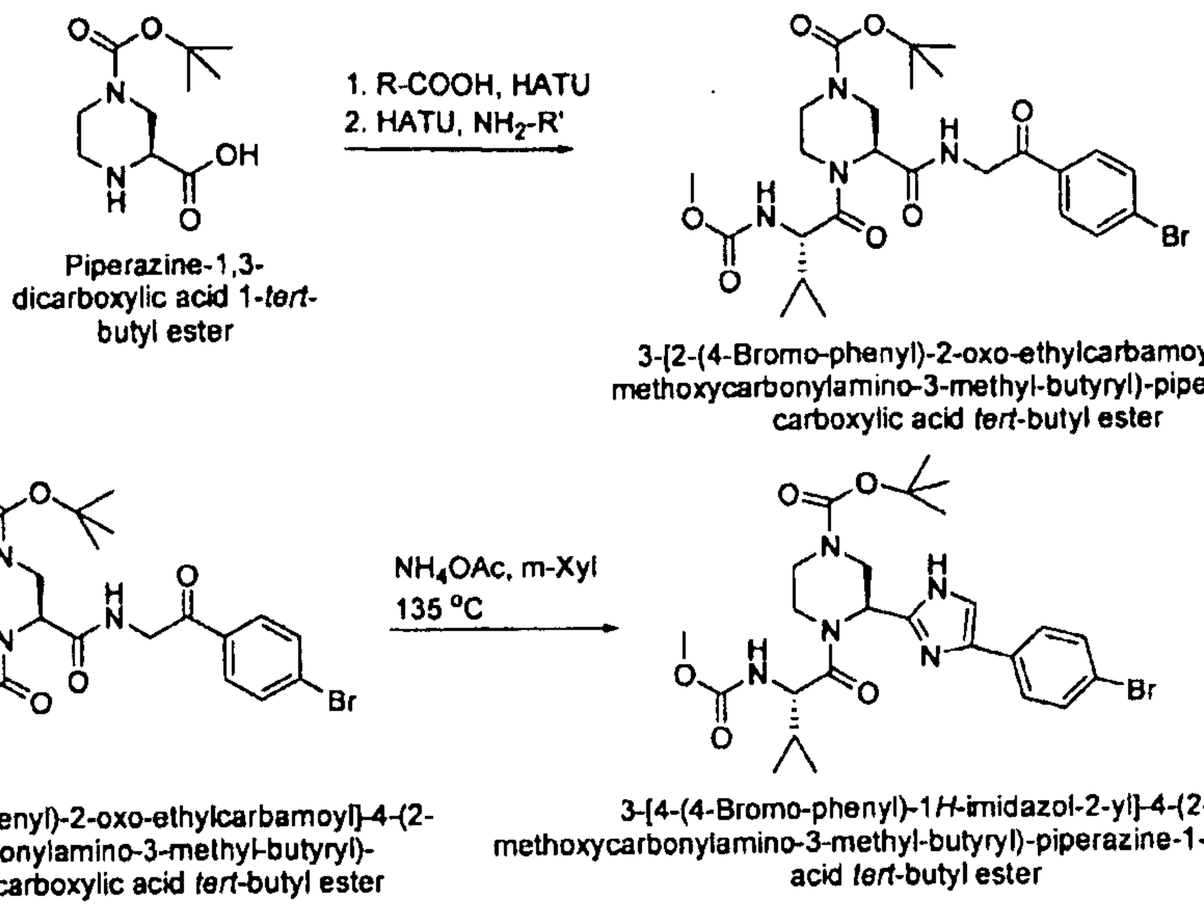
{1-[4-(4-Bromo-phenyl)-1'-phenyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (1-{5-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-3-phenyl-imidazolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl

ester (90 mg) was dissolved in m-xylenes (3 mL) and heated at 135 °C. Solid ammonium acetate (100 mg, 1.29 mmol) was added and the reaction was stirred at 135 °C. After 120 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc / hexanes) to yield the product {1-[4-(4-Bromo-phenyl)-1'-phenyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (40.2 mg, 0.0764 mmol): LCMS-ESI$^+$: calc'd for $C_{25}H_{28}BrN_5O_3$: 526.4 (M^+); Found: 526.4 / 528.3 ($M+H^+$).

{1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1'-phenyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester:

{1-[4-(4-Bromo-phenyl)-1'-phenyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (40 mg, 0.076 mmol) was combined with [2-Methyl-1-(2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (37.6 mg, 0.076 mmol) under an argon atmosphere. Potassium carbonate (20.9 mg, 0.152 mmol) and $Pd(PPh_3)_4$ (8.7 mg, 0.0076 mmol) were added, followed by DME (1.8 mL) and water (0.3 mL). The mixture was heated under microwave conditions for 20 minutes at 120 °C. All volatiles were removed *in vacuo* and the crude material was dissolved in DMF and purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product {1-[5-(4'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-biphenyl-4-yl)-1'-phenyl-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (5.4 mg): LCMS-ESI$^+$: calc'd for $C_{45}H_{53}N_9O_6$: 815.9 (M^+); Found: 816.5 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.89-7.86 (m, 10H), 7.35 (m, 2H), 7.18 (m, 1H), 6.94 (m, 2H), 5.67 (m, 1H), 5.37 (m, 1H), 5.25 (m, 1H), 5.12 (m, 1H), 4.31-4.08 (m, 3H), 4.01-3.79 (m, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.58 (m, 1H), 2.29-1.99 (m, 5H), 0.99-0.89 (m, 12H).

Example CD



Piperazine-1,3-dicarboxylic acid 1-*tert*-butyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester

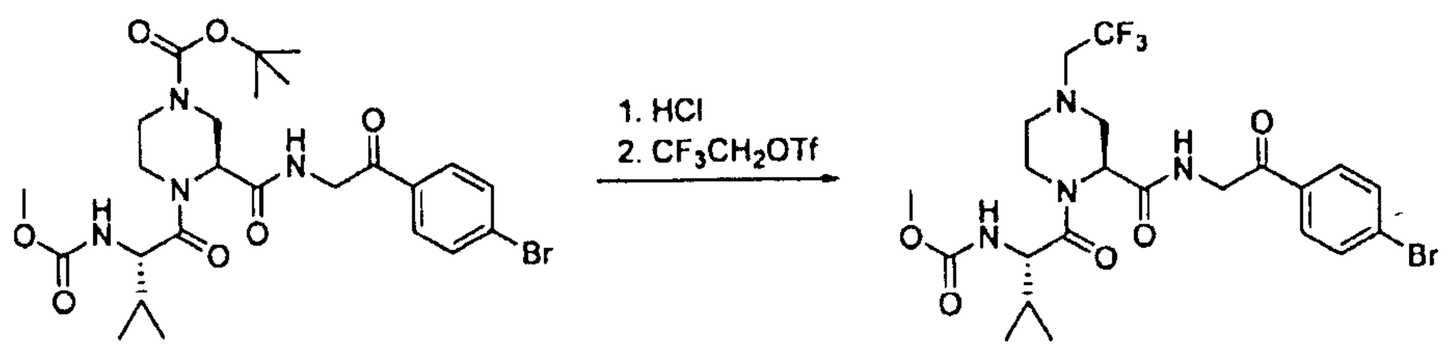
3-[4-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester

3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester: N-(Methylcarbamoyl)(*L*)-valine (2.0 g, 11.4 mmol) was dissolved in DMF (15 mL) at room temperature. HATU (4.34 g, 11.4 mmol) and di*iso*propyl ethylamine (1.47 g, 11.4 mmol) were added and stirring was continued. After 10 minutes, solid piperazine-1,3-dicarboxylic acid 1-*tert*-butyl ester (2.62 g, 11.4 mmol) was added. To the resultant suspension was added DMF (10 mL) and di*iso*propyl ethylamine (1.47 g, 11.4 mmol). Stirring at room temperature was continued. After 45 min, HATU (4.34 g, 11.4 mmol) and di*iso*propyl ethylamine (1.47 g, 11.4 mmol) were added to the resultant yellow solution followed by amino-(4'bromo) acetophenone hydrochloride salt (2.85 g, 11.4 mmol). After 30 minutes all volatiles were removed *in vacuo*. The crude material was taken into EtOAc and the organic layer was washed with aqueous HCl (1 M), aqueous LiCl (5%), aqueous bicarbonate solution, brine and was dried over sodium sulfate. Filtration and evaporation of solvents *in vacuo* yielded crude material, which was purified by flash chromatography on silica gel (eluent: EtOAc w MeOH 10%/ hexanes) to yield the product 3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester (3.62 g): LCMS-ESI$^+$: calc'd for $C_{25}H_{35}BrN_4O_7$: 583.4 (M^+); Found: 583.2 / 585.2 ($M+H^+$).

3-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester:

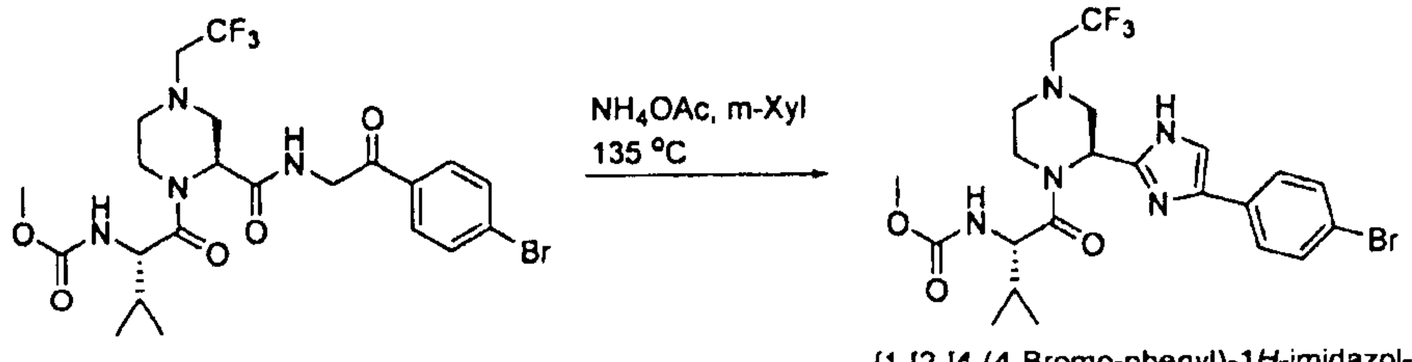
3-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.0 g, 3.43 mmol) was dissolved in m-xylenes (18 mL) and heated at 135 °C. Solid ammonium acetate (1.70 g, 22.0 mmol) was added and the reaction was stirred at 135 °C. After 120 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc w MeOH 10% / hexanes) to yield the product 3-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester (674 mg, 1.19 mmol): LCMS-ESI$^+$: calc'd for $C_{25}H_{34}BrN_5O_5$: 564.5 (M^+); Found: 564.2 / 566.2 ($M+H^+$).

Example CE



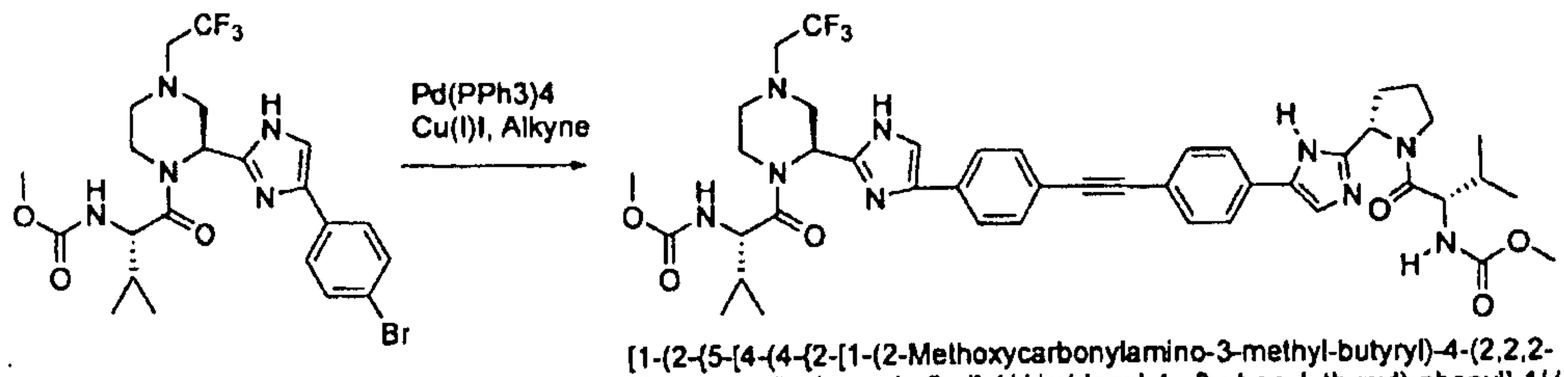
3-[4-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester

{1-[2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



{1-[2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

{1-[2-[4-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



{1-[2-[4-(4-Bromo-phenyl)-1*H*-imidazol-2-yl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

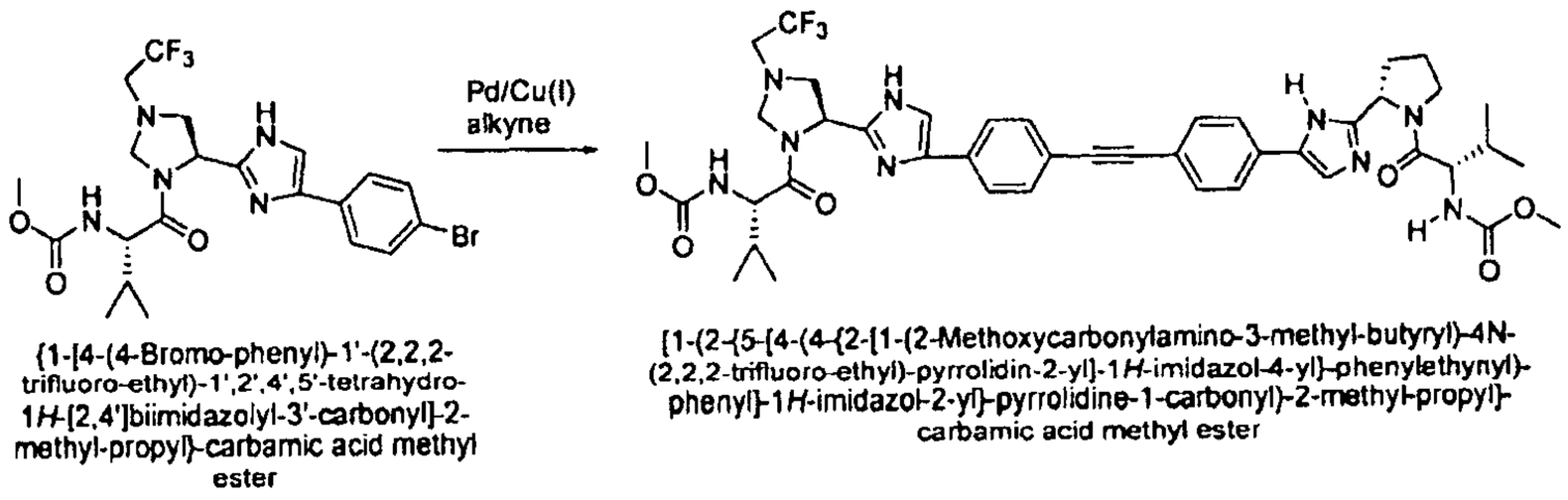
[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(2,2,2-trifluoro-ethyl)-piperazin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

{1-[2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: 3-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2-methoxycarbonylamino-3-methyl-butyryl)-piperazine-1-carboxylic acid *tert*-butyl ester (400 mg, 0.686 mmol) was dissolved in dichloromethane (1.0 mL) and HCl (4M dioxane, 2 mL) was added. The resultant suspension was stirred at room temperature for 20 minutes, after which all volatiles were removed *in vacuo*. The crude material was dissolved in DMF (1.0 mL) / THF (1.0 mL) and di*iso*propyl ethylamine (88.5 mg, 0.686 mmol) was added followed by trifluoroethyl triflate (114.7 mg, 0.494 mmol). Stirring at room temperature was continued. After 14 hours, all volatiles were removed *in vacuo* and the crude material was purified by flash chromatography on silica gel (eluent: EtOAc w MeOH 10% / hexanes) to yield the product {1-[2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (192 mg, 0.34 mmol): LCMS-ESI$^+$: calc'd for $C_{22}H_{28}BrF_3N_4O_5$: 565.3 (M^+); Found: 565.2 / 567.2 ($M+H^+$).

{1-[2-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: {1-[2-[2-(4-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (192 mg, 0.34 mmol) was dissolved in m-Xylenes (2 mL) and heated at 135 °C. Solid ammonium acetate (128 mg, 1.66 mmol) was added and the reaction was stirred at 135 °C. After 110 minutes, the reaction was cooled to room temperature and the volatiles were removed *in vacuo*. The crude material was purified via silica gel chromatography (eluent: EtOAc w MeOH 10%/hexanes) to yield the product {1-[2-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (98.7 mg, 0.181 mmol): LCMS-ESI$^+$: calc'd for $C_{22}H_{27}BrF_3N_5O_3$: 546.4 (M^+); Found: 546.0 / 548.2 ($M+H^+$).

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(2,2,2-trifluoro-ethyl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: {1-[2-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-4-(2,2,2-trifluoro-ethyl)-piperazine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (98.7 mg, 0.181 mmol) was combined with (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (71.2 mg, 0.181 mmol) and $Pd(PPh_3)_4$ (21.5 mg, 0.018 mmol) under an argon atmosphere. DMF (degassed with Argon) was added followed by triethylamine (181 mg, 1.8 mmol) and copper(I) iodide (3.5 mg, 0.018 mmol). The mixture was heated at 80 °C. After 20 minutes, volatiles were removed *in vacuo* and the crude material was semi-purified via chromatography on silica gel (eluent EtOAc w MeOH 10% / hexanes) and further purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product [1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4-(2,2,2-trifluoro-ethyl)-piperazin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (12.4 mg): LCMS-ESI$^+$: calc'd for $C_{44}H_{52}F_3N_9O_6$: 859.9 (M^+); Found: 860.5 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.91-7.68 (m, 10H), 6.06 (m, 2H), 5.24 (m, 1H), 4.43 (m, 1H), 4.23 (d, J=7.8Hz, 1H), 4.11 (m, 1H), 3.85 (m,1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.49-3.45 (m, 2H), 3.15-3.02 (m, 3H), 2.77 (m, 1H), 2.58 (m, 1H), 2.29-2.01 (m, 5H), 1.07-0.83 (m, 12H).

Example CF



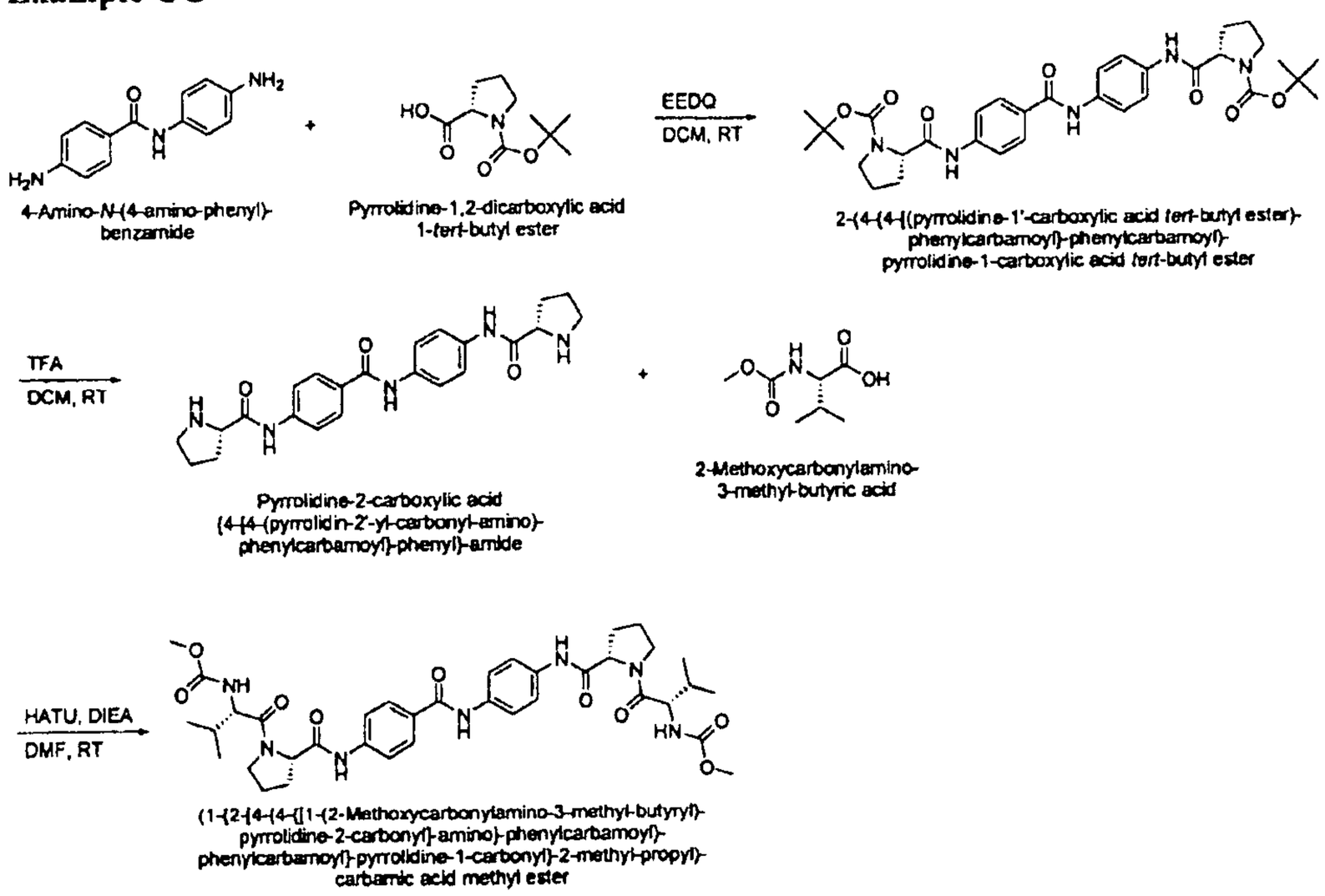
{1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1*H*-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4N-(2,2,2-trifluoro-ethyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-phenylethynyl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4N-(2,2,2-trifluoro-ethyl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: {1-[4-(4-Bromo-phenyl)-1'-(2,2,2-trifluoro-ethyl)-1',2',4',5'-tetrahydro-1H-[2,4']biimidazolyl-3'-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (55.0 mg, 0.103 mmol) was combined with (1-{2-[5-(4-Ethynyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (37.5 mg, 0.095 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.010 mmol) under an argon atmosphere. DMF (2.0 mL, degassed with Argon) was added followed by triethylamine (104

mg, 1.03 mmol) and copper(I) iodide (1.9 mg, 0.01 mmol). The mixture was heated at 80 °C. After 240 minutes, volatiles were removed *in vacuo* and the crude material was semi-purified via chromatography on silica gel (eluent EtOAc w MeOH 10% / hexanes) and further purified via RP-HPLC (eluent: water/ MeCN w 0.1% TFA) to yield the product [1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-4N-(2,2,2-trifluoro-ethyl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-phenylethynyl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (4.9 mg): LCMS-ESI$^+$: calc'd for $C_{43}H_{50}F_3N_9O_6$: 845.9 (M^+); Found: 846.4 ($M+H^+$); ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 7.91-7.68 (m, 10H), 5.35 (dd, J=6.3, 6.3Hz, 1H), 5.24 (m, 1H), 4.76 (d, J=6.9Hz, 1H), 4.23 (d, J=7.5Hz, 1H), 4.09 (m,1H), 4.00 (d, J=7.8Hz, 1H), 3.87 (m, 1H), 3.66 (s, 6H), 3.65-3.42 (m, 4H), 2.56 (m, 1H), 2.29-2.06 (m, 5H), 0.99-0.88 (m, 12H).

Example CG



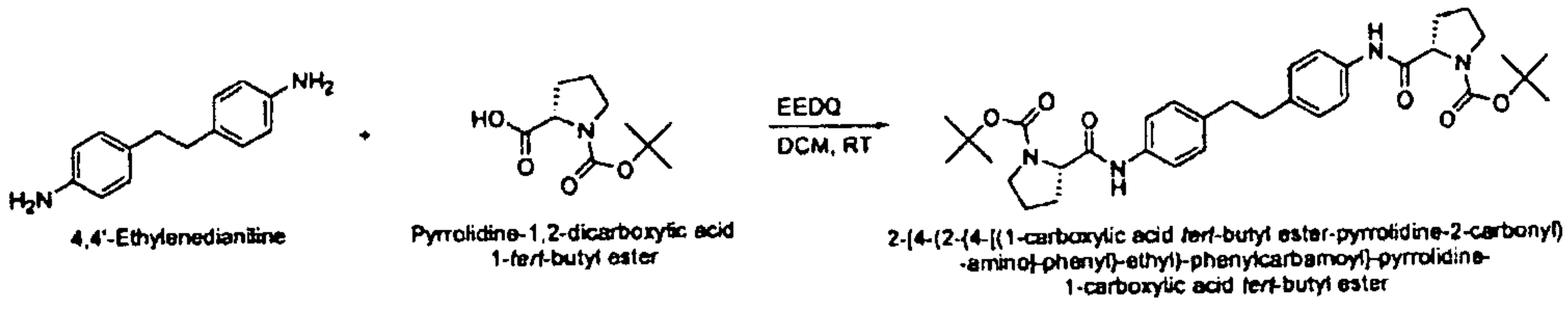
2-(4-{4-[(pyrrolidine-1'-carboxylic acid *tert*-butyl ester)-phenylcarbamoyl}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-Amino-N-(4-amino-phenyl)-benzamide (3.00 g) and pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (6.55 g) were dissolved in DCM (90 mL), and 1-ethoxycarbonyl-1,2-dihydroquinoline (7.88 g) was added. The reaction mixture was stirred at ambient temperature for 17 hours and evaporated under vacuum. Oil was dissolved in ethyl acetate, forming a precipitate, which was collected by vacuum filtration and dried under vacuum, giving 2-(4-{4-[(pyrrolidine-1'-carboxylic acid *tert*-

butyl ester)-phenylcarbamoyl}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (7.64 g, 93%) as a white solid.

Pyrrolidine-2-carboxylic-acid{4-[4-(pyrrolidin-2'-yl-carbonyl-amino)-phenylcarbamoyl]-phenyl}-amide: 2-(4-{4-[(pyrrolidine-1'-carboxylic acid *tert*-butyl ester)-phenylcarbamoyl}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.01 g) was dissolved in DCM (46 mL), and trifluoroacetic acid (6 mL) was added. The reaction mixture was stirred at ambient temperature for 3.5 hours and evaporated under vacuum. Solid was dissolved in DCM and extracted twice with saturated $NaHCO_3$ solution. Solid was collected by vacuum filtration, washed with ethyl acetate, and dried under vacuum, giving pyrrolidine-2-carboxylic acid {4-[4-(pyrrolidin-2'-yl-carbonyl-amino)-phenylcarbamoyl]-phenyl}-amide (1.18 g, 87%) as a white solid.

(1-{2-[4-(4-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenylcarbamoyl)-phenylcarbamoyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid {4-[4-(pyrrolidin-2'-yl-carbonyl-amino)-phenylcarbamoyl]-phenyl}-amide (0.305 g), 2-methoxycarbonylamino-3-methyl-butyric acid (0.277 g), and HATU (0.621 g) were dissolved in anhydrous DMF (8 mL), and diisopropylethylamine (0.496 mL) was added. The reaction mixture was stirred at ambient temperature for 1 hour and evaporated under vacuum. The oil was dissolved in DCM and purified by chromatography (0-20% ethyl acetate:hexane), giving (1-{2-[4-(4-{[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenylcarbamoyl)-phenylcarbamoyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.324 g, 58%) as a white solid: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ:10.3 (s, 1H), 10.1 (s, 1H), 10.0 (s, 1H), 7.9 (d, J=9.9, 2H), 7.7 (m, 4H), 7.5 (d, J=9.9, 2H), 7.3 (d, J=9.9, 2H), 4.5 (m, 2H), 4.0 (m, 2H), 3.8 (m, 2H), 3.6 (m, 2H), 3.5 (s, 6H), 2.2 (m, 2H), 1.9 (m, 8H), 0.9 (m, 12H); MS (ESI) *m/z* 736 $[M + H]^+$.

Example CH



4,4'-Ethylenedianiline

Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

2-[4-(2-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenyl}-ethyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

Pyrrolidine-2-carboxylic acid (4-{2-[4-(pyrrolidinecarbonyl-amino)-phenyl]-ethyl}-phenyl)-amide

2-Methoxycarbonylamino-3-methyl-butyric acid

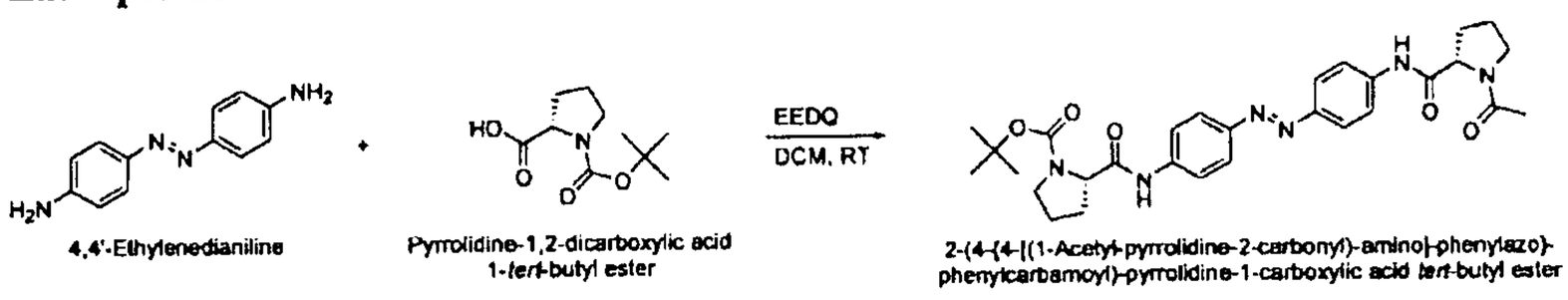
[1-(2-{4-[2-(4-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenyl)-ethyl]-phenylcarbamoyl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

2-[4-(2-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenyl}-ethyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4,4'-Ethylenedianiline (2.98 g) and pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (7.09 g) were dissolved in DCM (90 mL), and 1-ethoxycarbonyl-1,2-dihydroquinoline (8.38 g) was added. The reaction mixture was stirred at ambient temperature for 3 hours and evaporated under vacuum. Oil was dissolved in ethyl acetate, forming a precipitate, which was collected by vacuum filtration and dried under vacuum, giving 2-[4-(2-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenyl}-ethyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (8.30 g, 97%) as a white solid.

Pyrrolidine-2-carboxylic acid (4-{2-[4-(pyrrolidinecarbonyl-amino)-phenyl]-ethyl}-phenyl)-amide: 2-[4-(2-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenyl}-ethyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.01 g) was dissolved in DCM (45 mL), and trifluoroacetic acid (15 mL) was added. The reaction mixture was stirred at ambient temperature for 4 hours and evaporated under vacuum. Solid was dissolved in DCM and extracted twice with saturated $NaHCO_3$ solution. Solid was collected by vacuum filtration, washed with ethyl acetate, and dried under vacuum, giving pyrrolidine-2-carboxylic acid (4-{2-[4-(pyrrolidinecarbonyl-amino)-phenyl]-ethyl}-phenyl)-amide (1.86 g, 93%) as a light gray solid.

[1-(2-{4-[2-(4-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenyl)-ethyl]-phenylcarbamoyl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid (4-{2-[4-(pyrrolidinecarbonyl-amino)-phenyl]-ethyl}-phenyl)-amide (0.299 g), 2-methoxycarbonylamino-3-methyl-butyric acid (0.296 g), and HATU (0.648 g) were dissolved in anhydrous DMF (5 mL), and diisopropylethylamine (0.513 mL) was added. The reaction mixture was stirred at ambient temperature for 1 hour and evaporated under vacuum. The oil was dissolved in DCM and purified by chromatography (0-100% ethyl acetate:hexane), giving [1-(2-{4-[2-(4-{[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenyl)-ethyl]-phenylcarbamoyl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.254 g, 48%) as a white solid: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 9.9 (s, 2H), 8.2 (broad s, 2H), 7.4 (d, J=9.9, 4H), 7.3 (d, J=9.9, 2H), 7.1 (d, J=9.9, 4H), 4.4 (m, 2H), 4.0 (t, J=7.5, 2H), 3.8 (m, 2H), 3.6 (m, 8H), 3.5 (s, 6H), 3.1 (m, 8H), 2.8 (s, 4H), 2.1 (m, 2H), 1.9 (m, 8H), 0.9 (m, 12H); MS (ESI) *m/z* 721 $[M + H]^+$.

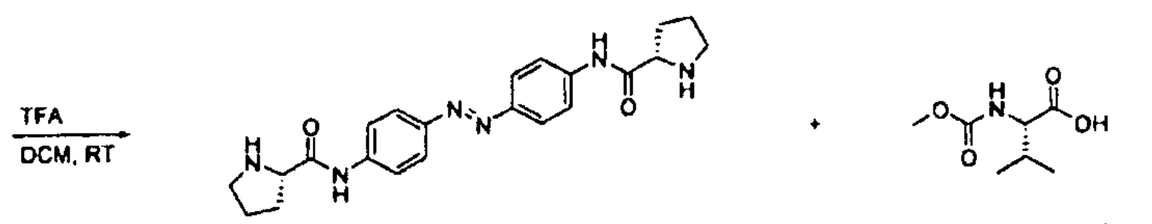
Example CI



4,4'-Ethylenedianiline

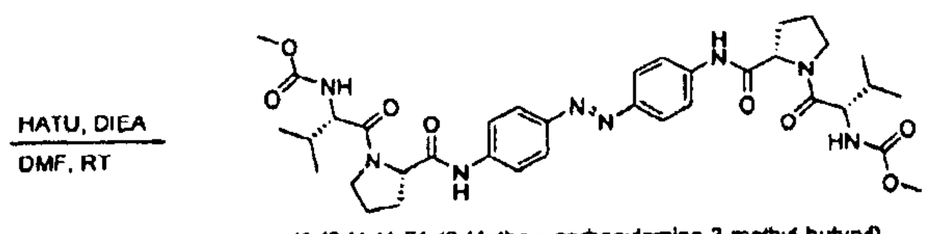
Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

2-(4-{4-[(1-Acetyl-pyrrolidine-2-carbonyl)-amino]-phenylazo}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



Pyrrolidine-2-carboxylic acid (4-[4-(pyrrolidinecarbonyl-amino)-phenylazo]-phenyl)-amide

2-Methoxycarbonylamino-3-methyl-butyric acid



(1-{2-[4-(4-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenylazo)-phenylcarbamoyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

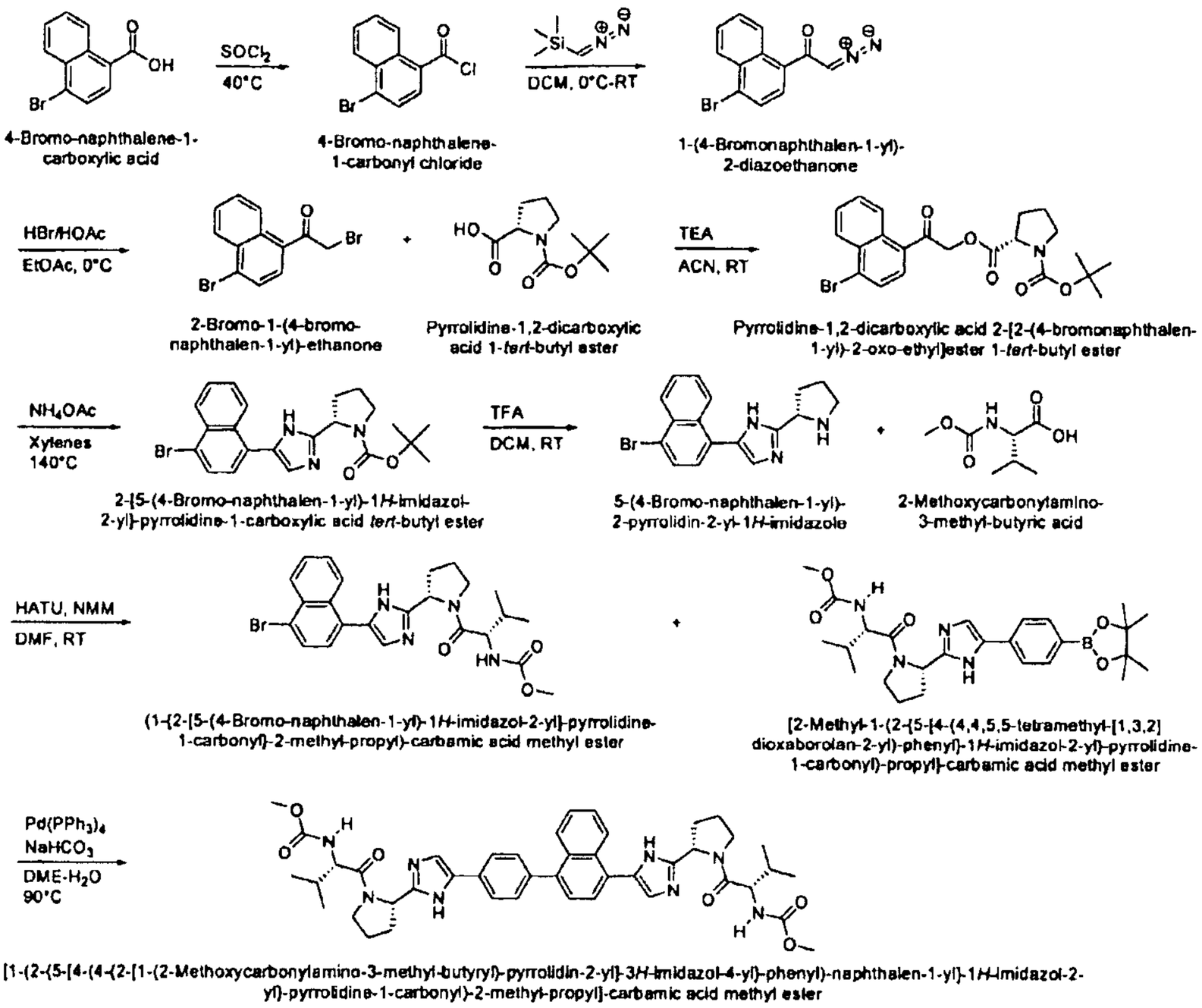
2-(4-{4-[(1-Acetyl-pyrrolidine-2-carbonyl)-amino]-phenylazo}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 4-(4-aminophenylazo)-phenylamine (3.02 g) and pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (7.00 g) were dissolved in DCM (90 mL), and 1-ethoxycarbonyl-1,2-dihydroquinoline (8.45 g) was added. The reaction mixture was stirred at ambient temperature for 19 hours and evaporated under vacuum. Oil was dissolved in

ethyl acetate, forming a precipitate, which was collected by vacuum filtration and dried under vacuum, giving 2-(4-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenylazo}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9.28 g) as a brown solid.

Pyrrolidine-2-carboxylic acid {4-[4-(pyrrolidinecarbonyl-amino)-phenylazo]-phenyl}-amide: 2-(4-{4-[(1-carboxylic acid *tert*-butyl ester-pyrrolidine-2-carbonyl)-amino]-phenylazo}-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9.28 g, crude) was dissolved in DCM (75 mL), and trifluoroacetic acid (25 mL) was added. The reaction mixture was stirred at ambient temperature for 3 hours and evaporated under vacuum. Solid was dissolved in DCM and extracted twice with saturated $NaHCO_3$ solution. The solution was evaporated under vacuum, giving pyrrolidine-2-carboxylic acid {4-[4-(pyrrolidinecarbonyl-amino)-phenylazo]-phenyl}-amide (6.18 g, crude) as a red solid.

(1-{2-[4-(4-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenylazo)-phenylcarbamoyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid {4-[4-(pyrrolidinecarbonyl-amino)-phenylazo]-phenyl}-amide (0.302 g), 2-methoxycarbonylamino-3-methyl-butyric acid (0.284 g), and HATU (0.643 g) were dissolved in anhydrous DMF (5 mL), and N-methylmorpholine (0.324 mL) was added. The reaction mixture was stirred at ambient temperature for 2 hours and evaporated under vacuum. The oil was dissolved in DCM and purified by chromatography (0-100% ethyl acetate:hexane), giving (1-{2-[4-(4-{[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-phenylazo)-phenylcarbamoyl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.158 g, 30%) as a yellow solid: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 10.4 (s, 2H), 7.8.(m, 8H), 7.4 (d, J=9.9, 2H), 4.5 (m, 2H), 4.0 (t, J=7.5, 2H), 3.8 (m, 2H), 3.6 (m, 8H), 3.5 (s, 6H), 2.2 (m, 2H), 2.0 (m, 8H), 0.9 (m, 12H); MS (ESI) *m/z* 721 $[M + H]^+$.

Example CJ



4-Bromo-naphthalene-1-carbonyl chloride: 4-Bromonaphthalene-1-carboxylic acid (9.80 g) was suspended in thionyl chloride (80 mL) and stirred at 40°C for 16 hours and evaporated under vacuum. Solid was dissolved in DCM (20 mL) and evaporated under vacuum, giving 4-bromonaphthalene-1-carbonyl chloride (13.8 g, crude) as a white solid.

1-(4-Bromonaphthalen-1-yl)-2-diazoethanone: 4-Bromo-naphthalene-1-carbonyl chloride (13.8 g) was dissolved in dichloromethane (130 mL) and cooled to 0°C. TMS diazomethane solution (40 mL, 2 M in DCM) was added, and ice bath was removed. Reaction mixture was stirred for 18 hours and evaporated under vacuum, giving 1-(4-bromonaphthalen-1-yl)-2-diazoethanone (13.8 g, crude) as a brown oil.

2-Bromo-1-(4-bromo-naphthalen-1-yl)-ethanone: 1-(4-Bromonaphthalen-1-yl)-2-diazoethanone (13.8 g) was dissolved in ethyl acetate (200 mL), and hydrobromic acid solution (8.4 mL, 5.7 M in acetic acid) was added at 0°C. Reaction mixture was stirred 15 minutes, $NaHCO_3$ solution (100 mL) was added, and mixture was stirred 10 minutes. Ethyl acetate

solution was extracted twice with $NaHCO_3$ solution (50 mL), once with brine (50 mL), and evaporated under vacuum. The oil was dissolved in DCM and purified by chromatography (0-20% ethyl acetate:hexane), giving 2-bromo-1-(4-bromo-naphthalen-1-yl)-ethanone (6.67 g, 51%) as a tan solid.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromonaphthalen-1-yl)-2-oxo-ethyl]ester 1-*tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (4.85 g) was dissolved in acetonitrile (65 mL), and triethylamine (3.09 mL) was added. A solution of 2-bromo-1-(4-bromonaphthalen-1-yl)-ethanone (6.60 g) in acetonitrile (35 mL) was added. Reaction mixture was stirred 90 minutes and evaporated under vacuum. Oil was dissolved in DCM (50 mL), extracted once with water (20 mL) and once with $NaHCO_3$ solution (20 mL), and evaporated under vacuum to a concentrated liquid. Solution was purified by chromatography (0-50% ethyl acetate:hexane) and evaporated under vacuum, giving pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromonaphthalen-1-yl)-2-oxo-ethyl]ester 1-*tert*-butyl ester (8.95 g, 95%) as a tan solid.

2-[5-(4-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromonaphthalen-1-yl)-2-oxo-ethyl]ester 1-*tert*-butyl ester (8.80 g) and ammonium acetate (7.51 g) were suspended in xylenes. The reaction mixture was stirred at 140°C for 15 hours and evaporated under vacuum. Solid was dissolved in ethyl acetate (50 mL) and extracted twice with water (20 mL) and once with brine (20 mL). The oil was dissolved in DCM, purified by chromatography (0-50% ethyl acetate:hexanes), and evaporated under vacuum, giving 2-[5-(4-bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.34 g, 52%) as a tan solid.

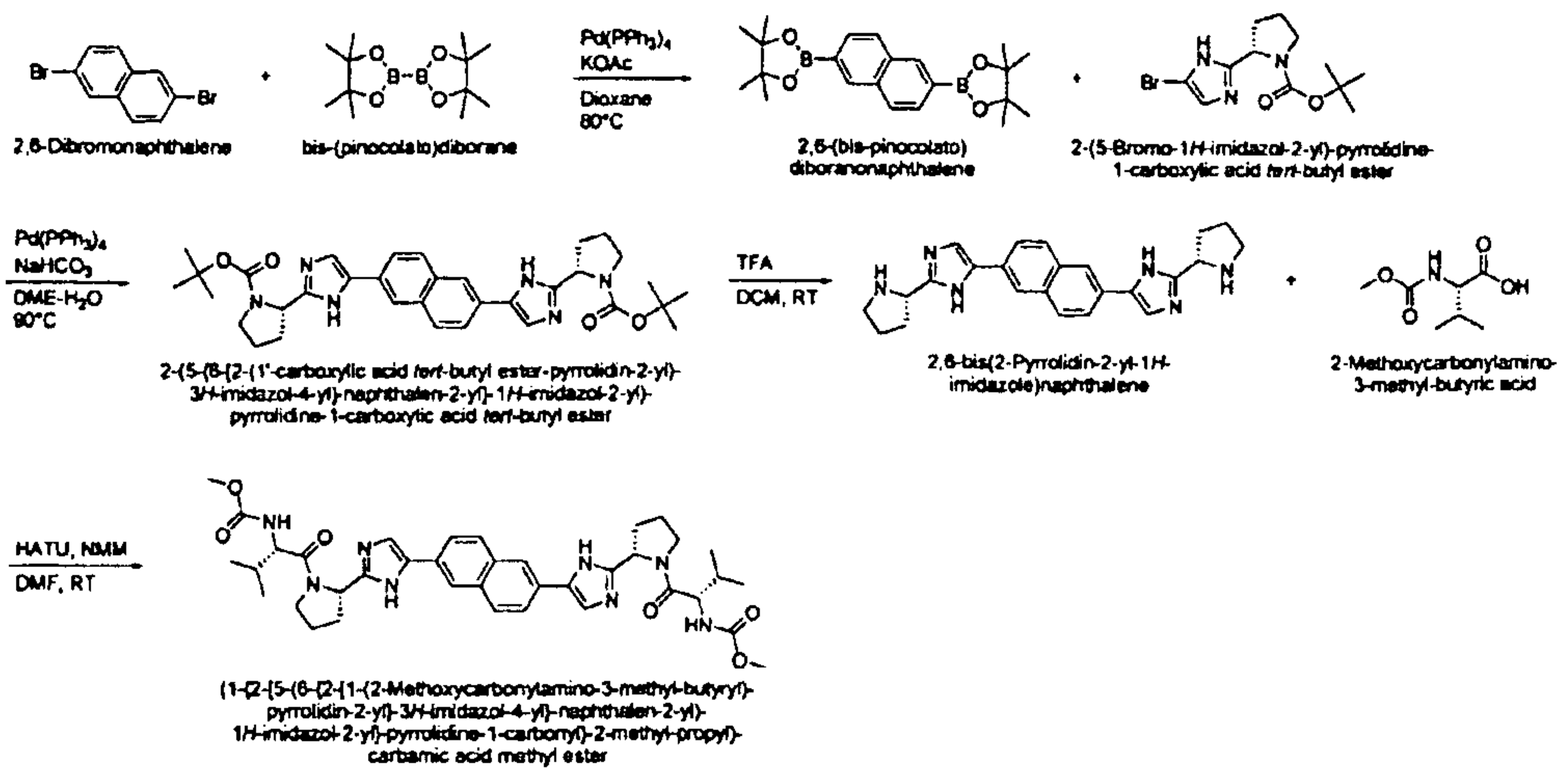
5-(4-Bromo-naphthalen-1-yl)-2-pyrrolidin-2-yl-1H-imidazole: 2-[5-(4-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.00 g) was dissolved in DCM (12 mL), and trifluoroacetic acid (4 mL) was added. The reaction mixture was stirred at ambient temperature for 3 hours and evaporated under vacuum. Solid was dissolved in DCM (10 mL) and extracted with saturated $NaHCO_3$ solution (30 mL). A solid was collected by vacuum filtration, washed with DCM, and dried under vacuum, giving 5-(4-bromo-naphthalen-1-yl)-2-pyrrolidin-2-yl-1H-imidazole (0.940 g, crude) as an off-white solid.

(1-{2-[5-(4-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 5-(4-bromo-naphthalen-1-yl)-2-pyrrolidin-2-yl-1H-imidazole (0.925 g), 2-methoxycarbonylamino-3-methyl-butyric acid (0.441 g), and HATU

(1.00 g) were dissolved in anhydrous DMF (15 mL), and N-methylmorpholine (0.497 mL) was added. The reaction mixture was stirred at ambient temperature for 30 minutes and evaporated under vacuum. The oil was dissolved in DCM, purified by chromatography (0-100% ethyl acetate:hexanes), and evaporated under vacuum, giving (1-{2-[5-(4-bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.814 g, 72%) as an off-white solid.

[1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-1-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester: (1-{2-[5-(4-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.115 g), [2-Methyl-1-(2-{5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (0.111 g), and $NaHCO_3$ (0.0623 g) were dissolved in a mixture of 1,2-dimethoxyethane (3 mL) and water (1 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0114 g) was added. The reaction mixture was stirred at 85°C for 16 hours and evaporated under vacuum. Solid was dissolved in ethyl acetate (10 mL) and extracted twice with water (10 mL) and once with brine (10 mL). Solution was evaporated, dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving [1-(2-{5-[4-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-naphthalen-1-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (0.037 g, 21%) as a white solid: ^{1}H-NMR: 300 MHz, ($CHCl_3$-d_1) δ: 8.9 (m, 1H), 7.6 (m, 2H), 7.4 (m, 5H), 7.0 (m, 2H), 6.8 (m, 2H), 5.8 (m, 2H), 5.3 (m, 2H), 4.3 (m, 2H), 4.0 (m, 4H), 3.6 (s, 6H), 2.4 (m, 6H), 2.0 (m, 6H), 0.8 (m, 12H); MS (ESI) *m/z* 789 $[M + H]^+$.

Example CJ



2,6-(bis-pinocolato) Diboranonaphthalene: 2,6-Dibromonaphthalene (10.2 g), bis-(pinocolato)diborane (37.3 g), and potassium acetate (18.0 g) were dissolved in 1,4-dioxane (250 mL), and solution was degassed with nitrogen. $Pd(PPh_3)_4$ (3.13 g) was added, and the reaction mixture was stirred at 80°C for 20 hours. The suspension was vacuum filtered, and the solid was washed with ethyl acetate, giving 2,6-(bis-pinocolato)diboranonaphthalene (7.71 g, 58%) as a yellow solid.

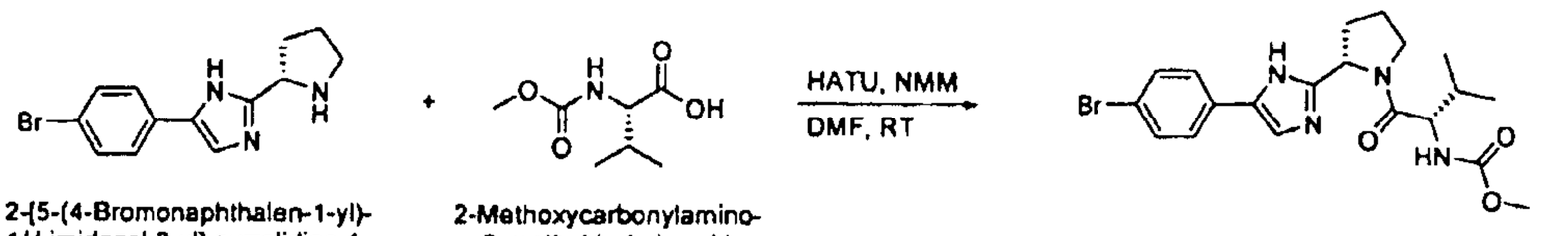
2-(5-{6-[2-(1'-carboxylic acid *tert*-butyl ester-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 2,6-(bis-pinocolato)diboranonaphthalene (0.501 g), 2-(5-bromo-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.885 g), and $NaHCO_3$ (0.562 g) were dissolved in a mixture of 1,2-dimethoxyethanedichloromethane (15 mL) and water (5 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0935 g) was added. The reaction mixture was stirred at 90°C for 16 hours and evaporated under vacuum. Solid was dissolved in DCM (20 mL) and extracted twice with water and once with brine. Solution was evaporated, recrystallized from ethyl acetate, and dried under vacuum, giving 2-(5-{6-[2-(1'-carboxylic acid *tert*-butyl ester-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.365 g, 46%) as a white solid.

2,6-bis(2-Pyrrolidin-2-yl-1H-imidazole)naphthalene: 2-(5-{6-[2-(1'-carboxylic acid *tert*-butyl ester-pyrrolidin-2-yl)-3H-imidazol-4-yl]-naphthalen-2-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.365 g) was dissolved in dichloromethane (3 mL), and trifluoroacetic acid (1 mL) was added. The reaction mixture was stirred at ambient temperature

for 27 hours, heated to 40°C for 3 hours, and evaporated under vacuum. Solid was dissolved in DCM (10 mL) and extracted with saturated $NaHCO_3$ solution (30 mL). A solid was collected by vacuum filtration, washed with DCM, and dried under vacuum, giving 2,6-bis(2-pyrrolidin-2-yl-1H-imidazole)naphthalene (0.180 g, 74%) as a yellow solid.

(1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2,6-bis(2-Pyrrolidin-2-yl-1H-imidazole)naphthalene (0.170 g), 2-methoxycarbonylamino-3-methyl-butyric acid (0.168 g), and HATU (0.378 g) were dissolved in anhydrous DMF (3 mL), and N-methylmorpholine (0.188 mL) was added. The reaction mixture was stirred at ambient temperature for 30 minutes and evaporated under vacuum. The oil was dissolved in DMF and purified by reverse phase HPLC (5-70% acetonitrile:water) and lyophilized, giving (1-{2-[5-(6-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.051 g, 17%) as a white solid: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.3 (s, 2H), 8.1 (s, 2H), 8.0 (m, 4H), 7.3 (d, J=11.2, 2H), 5.1 (m, 2H), 4.1 (m, 2H), 3.9 (m, 4H), 3.5 (s, 6H), 2.4 (m, 1H), 2.0 (m, 5H), 0.8 (m, 12H); MS (ESI) *m/z* 713 $[M + H]^+$.

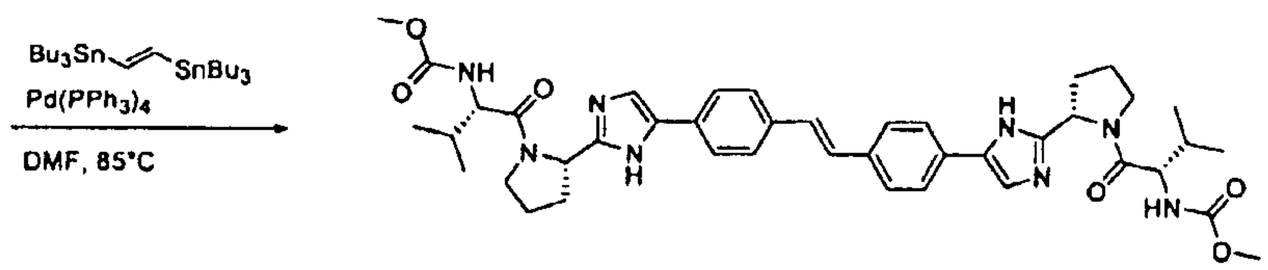
Example CK



2-[5-(4-Bromonaphthalen-1-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

2-Methoxycarbonylamino-3-methyl-butyric acid

(1-{2-[5-(4-Bromonaphthalen-1-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



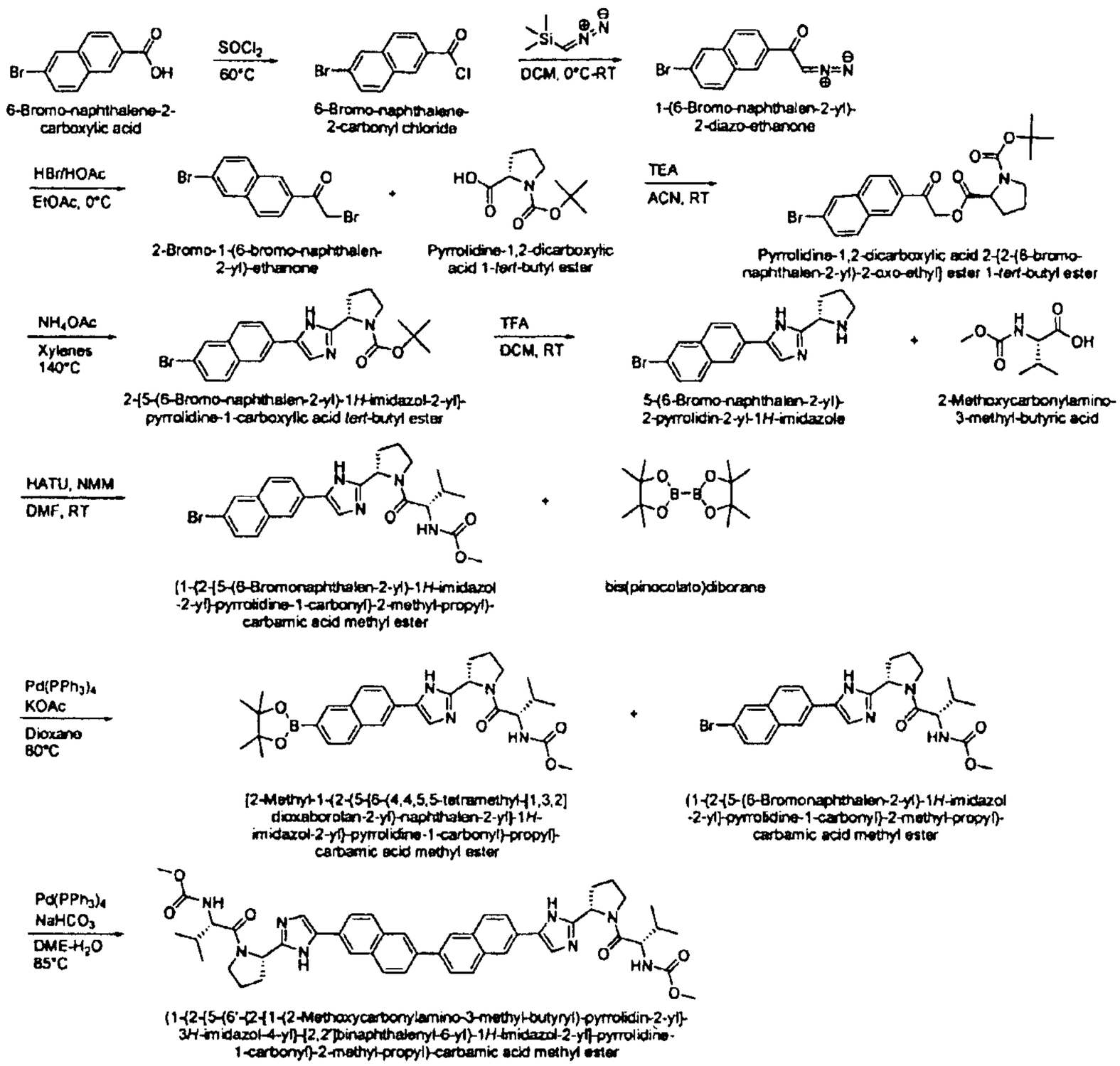
{1-[2-(5-{4-[2-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

(1-{2-[5-(4-Bromonaphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 2-[5-(4-Bromonaphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.80 g), 2-methoxycarbonylamino-3-methyl-

butyric acid (2.57 g), and HATU (5.88 g) were dissolved in anhydrous DMF (85 mL), and N-methylmorpholine (2.86 mL) was added. The reaction mixture was stirred at ambient temperature for 22 hours and evaporated under vacuum. The oil was dissolved in dichloromethane, purified by chromatography (0-50% ethyl acetate:hexanes), and evaporated under vacuum, giving (1-{2-[5-(4-bromonaphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (6.10 g, crude) as a tan solid.

{1-[2-(5-{4-[2-(4-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester: (1-{2-[5-(4-Bromonaphthalen-1-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (1.01 g) was dissolved in anhydrous DMF (13 mL), and (E)-bis(tributylstannyl)ethene (0.585 mL) was added. The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0401 g) was added. The reaction mixture was stirred at 85°C for 17 hours and evaporated under vacuum. Solid was dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving {1-[2-(5-{4-[2-(4-{2-[1-(2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-phenyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (25 mg, 1.5%) as a white solid: ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.0 (s, 2H), 7.8 (m, 8H), 7.4 (s, 2H), 7.3 (d, J=9.9, 2H), 5.1 (t, J=6.9, 2H), 4.1 (t, J=6.9, 2H), 3.8 (m, 4H), 3.8 (m, 2H), 3.5 (s, 6H), 2.4 (m, 2H), 2.0 (m, 6H), 0.8 (m, 12H); MS (ESI) *m/z* 765 $[M + H]^+$.

Example CL



6-Bromo-naphthalene-2-carbonyl chloride: 6-Bromonaphthalene-2-carboxylic acid (25.1 g) was suspended in thionyl chloride (200 mL), stirred at 60°C for 16 hours and evaporated under vacuum. Solid was dissolved in dichloromethane (50 mL) and evaporated under vacuum, giving 6-bromonaphthalene-2-carbonyl chloride (27.0 g, crude) as a white solid.

1-(6-Bromo-naphthalen-2-yl)-2-diazo-ethanone: 6-Bromonaphthalene-2-carbonyl chloride (27.0 g, crude) was dissolved in dichloromethane (330 mL) and cooled to 0°C. TMS diazomethane solution (100 mL, 2 M in DCM) was added, and ice bath was removed. Reaction mixture was stirred for 16 hours and evaporated under vacuum, giving 1-(6-bromonaphthalen-2-yl)-2-diazoethanone (34.7 g, crude) as an orange solid.

2-Bromo-1-(6-bromo-naphthalen-2-yl)-ethanone: 1-(6-Bromonaphthalen-2-yl)-2-diazoethanone (34.7 g) were dissolved in ethyl acetate (500 mL), and hydrobromic acid solution (21.1 mL, 5.7 M in acetic acid) was added at 0°C. Reaction mixture was stirred 3 hours,

$NaHCO_3$ solution (200 mL) was added, and mixture was stirred 10 minutes. Ethyl acetate solution was extracted twice with $NaHCO_3$ solution (50 mL), once with brine (50 mL), and evaporated under vacuum, giving 2-bromo-1-(6-bromonaphthalen-2-yl)-ethanone (33.0 g, crude) as a tan solid.

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (24.0 g) was dissolved in acetonitrile (330 mL), and triethylamine (15.6 mL) was added. A solution of 2-bromo-1-(6-bromonaphthalen-2-yl)-ethanone (33.0 g) in acetonitrile (170 mL) were added. Reaction mixture was stirred over 3 days and evaporated under vacuum. Oil was dissolved in dichloromethane (100 mL), extracted with water (50 mL) and with $NaHCO_3$ solution (50 mL), and evaporated under vacuum to a concentrated liquid. Solution was purified by chromatography (0-30% ethyl acetate:hexane) and evaporated under vacuum, giving pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromo-naphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (39.2 g, 84%) as a tan solid.

2-[5-(6-Bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: Pyrrolidine-1,2-dicarboxylic acid 2-[2-(6-bromonaphthalen-2-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (39.0 g) and ammonium acetate (40.1 g) were suspended in xylenes (420 mL). The reaction mixture was stirred at 140°C for 15 hours and evaporated under vacuum. Solid was dissolved in dichloromethane (300 mL), extracted twice with water (50 mL) and once with brine (50 mL), and evaporated under vacuum, giving 2-[5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (30.3 g, 81%) as an off-white solid.

5-(6-Bromo-naphthalen-2-yl)-2-pyrrolidin-2-yl-1H-imidazole: 2-[5-(6-Bromonaphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5.03 g) was dissolved in dichloromethane (75 mL), and trifluoroacetic acid (25 mL) was added. The reaction mixture was stirred at ambient temperature for 5 hours and evaporated under vacuum. Solid was dissolved in dichloromethane (50 mL) and extracted with saturated $NaHCO_3$ solution (50 mL). Solid was collected by vacuum filtration, washed with dichloromethane, and dried under vacuum, giving 5-(6-Bromo-naphthalen-2-yl)-2-pyrrolidin-2-yl-1H-imidazole (98%) as an off-white solid.

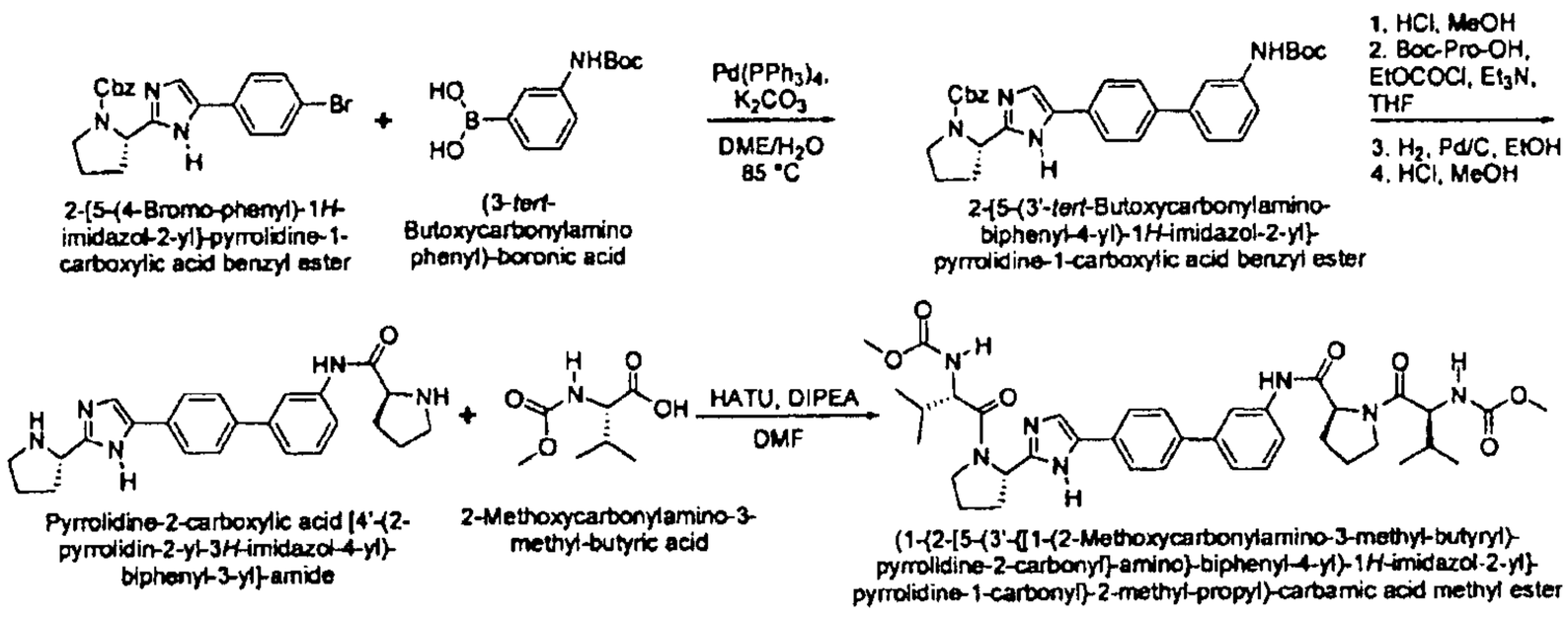
(1-{2-[5-(6-Bromonaphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: 5-(6-Bromo-naphthalen-2-yl)-2-pyrrolidin-2-yl-1H-imidazole (3.80 g), 2-methoxycarbonylamino-3-methyl-butyric acid (2.21 g), and HATU (5.06 g) were dissolved in anhydrous DMF (75 mL), and N-methylmorpholine (2.68 mL) was added. The reaction mixture was stirred at ambient temperature for 16 hours and evaporated under vacuum. The oil was dissolved in dichloromethane, purified by chromatography (0-100% ethyl acetate:hexanes), and evaporated under vacuum, giving (1-{2-[5-(6-bromo-naphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.814 g, 72%) as an off-white solid.

[2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester: (1-{2-[5-(6-Bromonaphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (3.02 g), bis-(pinocolato)diborane (3.18 g), and potassium acetate (1.52 g) were dissolved in 1,4-dioxane (40 mL), and solution was degassed with nitrogen. $Pd(PPh_3)_4$ (0.285 g) was added, and the reaction mixture was stirred at 80°C for 20 hours and evaporated under vacuum. Solid was dissolved in dichloromethane (50 mL), extracted with saturated $NaHCO_3$ solution (50 mL), and evaporated under vacuum. The oil was dissolved in dichloromethane, purified by chromatography (0-10% isopropanol:dichloromethane), and evaporated under vacuum, giving [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (3.65 g, crude) as a yellow solid.

(1-{2-[5-(6'-{2-[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[2,2']binaphthalenyl-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: (1-{2-[5-(6-Bromonaphthalen-2-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.174 g), [2-Methyl-1-(2-{5-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (0.202 g), and $NaHCO_3$ (0.108 g) were dissolved in a mixture of 1,2-dimethoxyethane (6 mL) and water (2 mL). The solution was degassed with nitrogen, and $Pd(PPh_3)_4$ (0.0176 g) was added. The reaction mixture was stirred at 85°C for 16 hours and evaporated under vacuum. Solid was dissolved in ethyl acetate (10 mL) and extracted twice with water (10 mL) and once with brine (10 mL). Solution was evaporated, dissolved in DMF, purified by reverse phase HPLC (5-70% acetonitrile:water), and lyophilized, giving (1-{2-[5-(6'-{2-[1-(2-Methoxycarbonylamino-3-

methyl-butyryl)-pyrrolidin-2-yl]-3H-imidazol-4-yl}-[2,2']binaphthalenyl-6-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (0.050 g, 16%) as a white solid: ^{1}H-NMR: 300 MHz, (MeOH-d_4) δ: 8.3 (m, 4H), 8.1 (m, 6H), 8.0 (s, 2H), 7.8 (d, J=9.4, 2H), 5.3 (m, 2H), 4.3 (d, J=9.0, 2H), 4.1 (m, 2H), 3.9 (m, 2H), 3.7 (s, 6H), 2.6 (m, 2H), 2.2 (m, 6H), 0.9 (m, 12H); MS (ESI) *m/z* 839 $[M + H]^+$.

Example CM



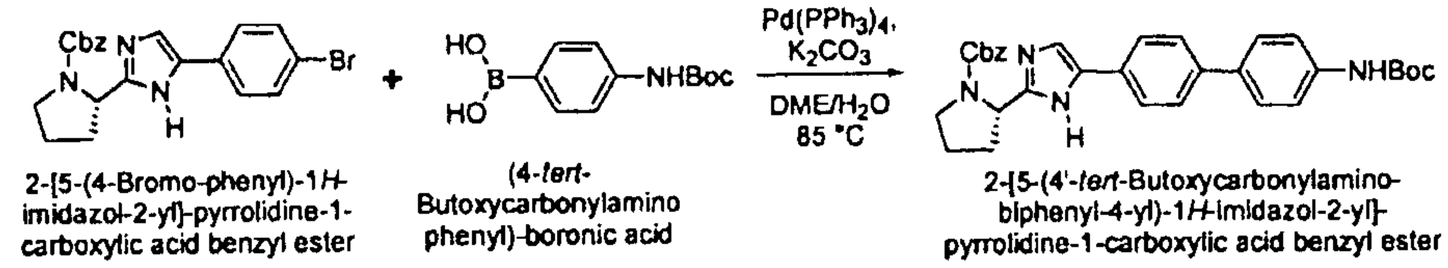
2-[5-(3'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (2.14 g, 5.01 mmol), (3-*tert*-Butoxycarbonylaminophenyl)-boronic acid (1.19 g, 5.01 mmol), $Pd(PPh_3)_4$ (289 mg, 0.251 mmol) and K_2CO_3 (5.5 mL of 2 M aqueous solution, 11.02 mmol) were combined with 1,2-dimethoxyethane (20 mL). The suspension was stirred while N_2 was bubbled through the solution for 24 min. A reflux condenser was attached and the suspension was heated to 85°C for 17 hours. It was then cooled, diluted with ethyl acetate (150 mL), washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide 2-[5-(3'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.73 g, 64%).

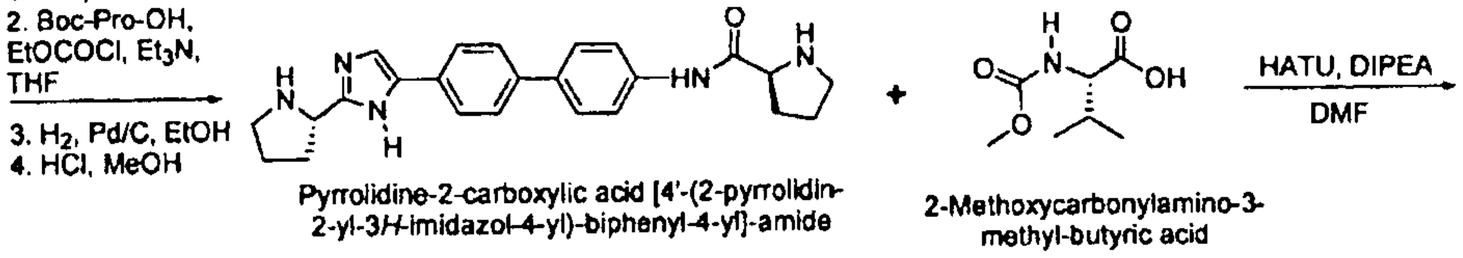
Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-3-yl]-amide: 2-[5-(3'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.75 g, 3.25 mmol) was dissolved in methanol (40 mL) and concentrated HCl (2 mL) was added. The solution was stirred at 50°C for 19 hours before being concentrated to a volume of 10 mL, poured into saturated $NaHCO_3$ (60 mL). The organic phase was extracted 3 times with 30 mL dichloromethane. The combined organic phases were dried with sodium sulfate and concentrated. A portion of the resulting residue (515 mg, 1.17 mmol)

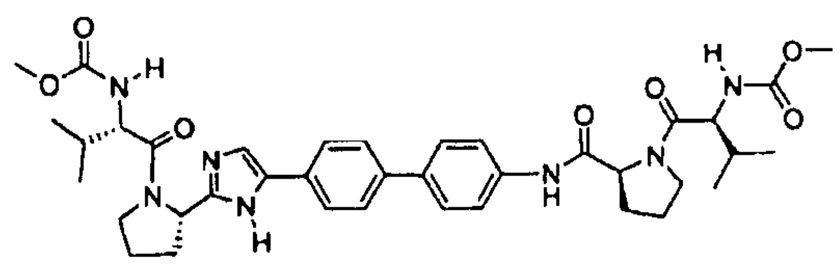
was dissolved in THF (2 mL). In a separate flask, ethylchloroformate (0.134 mL, 1.41 mmol) was added dropwise to a stirred 0°C solution of Boc-Pro-OH (303 mg, 1.41 mmol) and triethylamine (0.197 mL, 1.41 mmol) in THF (4 mL). After 10 minutes, the solution of biphenyl compound was added by cannula followed by a 2 mL rinse with THF. Following addition, the mixture was warmed to RT. After 70 min, the mixture was diluted with ethyl acetate (60 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide the Boc-Pro compound (470 mg, 63%). This material was dissolved in ethanol (40 mL) and 10% Pd/C (300 mg) was added before the flask was sealed and a bladder containing hydrogen gas was attached. A venting needle was placed in the septum for 30 s to allow hydrogen to bubble through the solution. After 13 h, the mixture was filtered over CELITE and concentrated. A portion of this residue (177 mg, 0.353 mmol) was dissolved in methanol (20 mL) and concentrated HCl (2 mL) was added. The mixture was stirred at 60°C before being concentrated to provide Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-3-yl]-amide (142 mg, 100%).

(1-{2-[5-(3'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-3-yl]-amide (142 mg, 0.353 mmol), 2-Methoxycarbonylamino-3-methyl-butyric acid (124 mg, 0.706 mmol) and HATU (295 mg, 0.777 mmol) were suspended in DMF (7 mL) and cooled to 0°C before DIPEA (0.615 mL, 3.53 mmol) was added. After 80 min, the mixture was warmed to RT then filtered and purified by reverse phase preparative HPLC, giving (1-{2-[5-(3'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (50 mg, 20%): ^{1}H NMR (DMSO-d6, 400 MHz) 10.11 (s, 1H), 7.92 (s, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.80-7.56 (m, 3H), 7.41-7.29 (m, 4H), 5.90 (m, 1H), 4.47 (m, 1H), 4.05 (m, 2H), 3.82 (m, 3H), 3.64 (m, 2H), 3.54 (m, 6H), 2.18 (m, 2H), 2.02-1.92 (m, 6H), 0.96-0.82 (m, 12H); MS (ESI) *m/z* 716 $[M + H]^+$.

Example CN







2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester: 2-[5-(4-Bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (2.31 g, 5.42 mmol), (4-*tert*-Butoxycarbonylaminophenyl)-boronic acid (1.28 g, 5.42 mmol), $Pd(PPh_3)_4$ (313 mg, 0.271 mmol) and K_2CO_3 (6 mL of 2 M aqueous solution, 11.92 mmol) were combined with 1,2-dimethoxyethane (20 mL). The suspension was stirred while N_2 was bubbled through the solution for 14 min. A reflux condenser was attached and the suspension was heated to 85°C for 15 hours. It was then cooled, diluted with ethyl acetate (150 mL), washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide 2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.20 g, 41%).

Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide: 2-[5-(4'-*tert*-Butoxycarbonylamino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid benzyl ester (1.75 g, 3.25 mmol) was dissolved in methanol (40 mL) and concentrated HCl (2 mL) was added. The solution was stirred at 50°C for 19 hours before being concentrated to a volume of 10 mL, poured into saturated $NaHCO_3$ (60 mL). The organic phase was extracted 3 times with 30 mL dichloromethane. The combined organic phases were dried with sodium sulfate and concentrated. A portion of the resulting residue (963 mg, 2.20 mmol)

was dissolved in THF (4 mL). In a separate flask, ethylchloroformate (0.231 mL, 2.24 mmol) was added dropwise to a stirred 0°C solution of Boc-Pro-OH (568 mg, 2.64 mmol) and triethylamine (0.368 mL, 2.69 mmol) in THF (6 mL). After 10 minutes, the solution of biphenyl compound was added by cannula followed by a 2 mL rinse with THF. Following addition, the mixture was warmed to RT. After 70 min, the mixture was diluted with ethyl acetate (60 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by silica column chromatography (25% to 50% EtOAc/hexanes) to provide the Boc-Pro compound (470 mg, 63%). This material was dissolved in ethanol (40 mL) and 10% Pd/C (300 mg) was added before the flask was sealed and a bladder containing hydrogen gas was attached. A venting needle was placed in the septum for 30 s to allow hydrogen to bubble through the solution. After 14 h, the mixture was filtered over CELITE and concentrated. A portion of this residue (169 mg, 0.337 mmol) was dissolved in methanol (20 mL) and concentrated HCl (2 mL) was added. The mixture was stirred at 60°C before being concentrated to provide Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide (135 mg, 100%).

(1-{2-[5-(4'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester: Pyrrolidine-2-carboxylic acid [4'-(2-pyrrolidin-2-yl-3H-imidazol-4-yl)-biphenyl-4-yl]-amide (135 mg, 0.337 mmol), 2-Methoxycarbonylamino-3-methyl-butyric acid (118 mg, 0.674 mmol) and HATU (282 mg, 0.741 mmol) were suspended in DMF (6 mL) and cooled to 0°C before DIPEA (0.470 mL, 2.70 mmol) was added. After 60 min, the mixture was warmed to RT then filtered and purified by reverse phase preparative HPLC, giving (1-{2-[5-(4'-{[1-(2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (136 mg, 56%). ^{1}H NMR (DMSO-d6, 400 MHz) 10.16 (s, 1H), 8.07 (s, 1H), 7.80 (d, J = 4.5 Hz, 4H), 7.70 (d, J = 4.5 Hz, 4H), 7.30 (m, 1H), 5.09 (m, 1H), 4.44 (m, 1H), 4.08 (m, 1H), 4.02 (m, 1H), 3.85-3.77 (m, 3H), 3.61 (m, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 2.37 (m, 1H), 2.16-1.84 (m, 10H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (d, 6.5 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 716 $[M + H]^+$.

Claims

1. A compound of formula (I):

J-Y-J (I)

wherein:

Y is –L-L-, –M-W-M- or Y^y;

J is T-P-, -P-T or $-J^m$;

W is a bond or $–W^r$-;

L is –M-A-, -A-M-, or $–L^n$;

T is R9-Z-, -Z-R9, or $–T^p$;

R9 is E-V-, or –V-E, or $–R9^q$;

each A is selected from $–A^s$;

each M is selected from $–M^t$;

each P is selected from $–P^u$;

each Z is selected from $–Z^v$;

each V is selected from $–V^w$;

each E is selected from $–E^x$;

each m is 1

each n is 0, 1, 2, 3, 4, 5, 6, 7, 9, or 10;

each p is 1, 2, 3, 4, 5, 6, 7, or 8;

each q is 0, 1, 2, or 3;

each r is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

each s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21;

each t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19;

each v is 0, 1, 2, 3, 4, 5, or 6;

each w is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

each x is 0, 1, 2, 3, 4, 5, 6, or 7;

each y is 0, 1, or 2;

wherein the sum of m, n, p, q, r, s, t, u, v, w, x, and y is not 0; P is connected to M, L, or Y^y; A is connected to A or L; M is connected to P or J; Z is connected to P; V is connected to Z; and when W is a bond M is connected to M;

each Y^1 is independently:
a fused nine-ring system with up to thirty-five atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

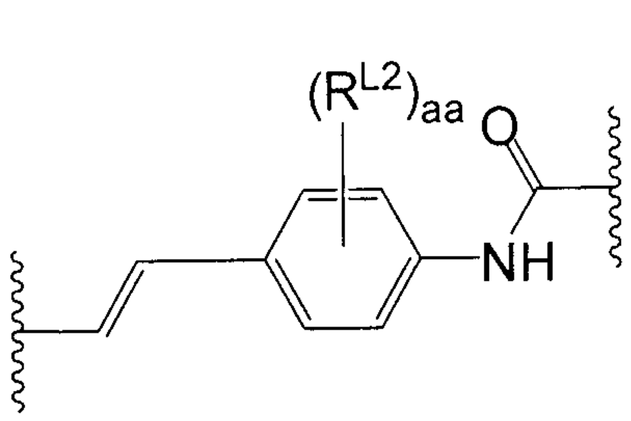
each Y^2 is independently:
a fused five to eight ring system with up to thirty-two atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

each J^1 is independently a fused bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is substituted with one or more $-N(R^{L7})C(=O)OR^{L7}$, and that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,$-CN$, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^0 is independently:

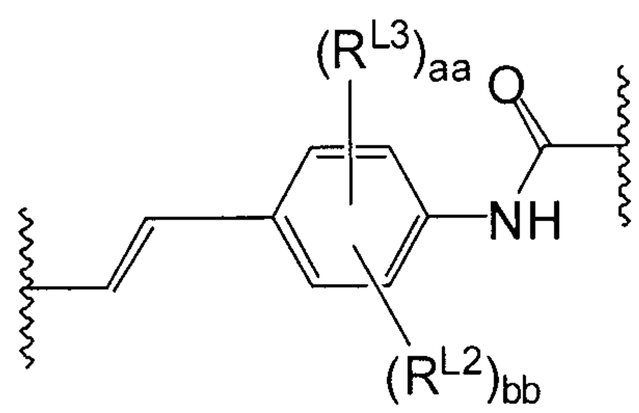


wherein:

each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl; and

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

each L^1 is independently:



wherein:

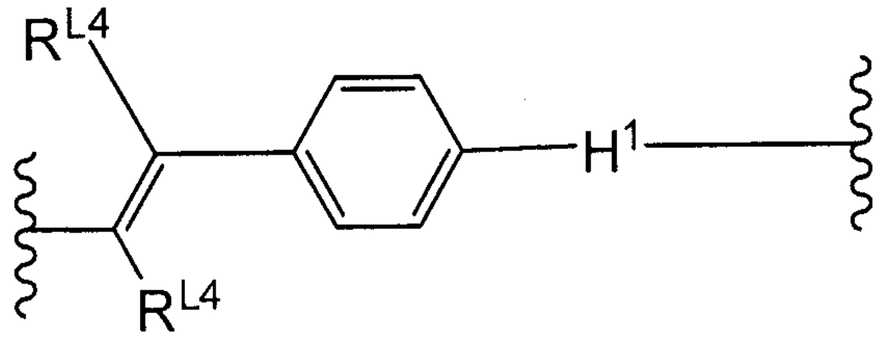
each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl;

each R^{L3} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

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

each L^2 is independently:



wherein:

the phenyl ring shown in L^2 is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{L4} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

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

each H^1 is a 5 membered saturated, partially unsaturated, or aromatic ring comprising one or more heteroatoms.

each L^3 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

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

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

each L^4 is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle,

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

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

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

each L^5 is independently a –CR=CR-fusedbicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

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

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

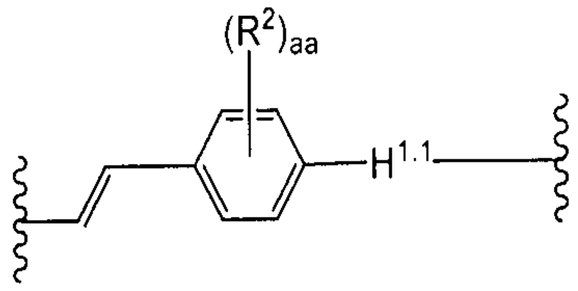
each L^6 is independently a –CR=CR-fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

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

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

each L^7 is independently:



wherein:

each $H^{1.1}$ is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^2;

each R^2 is independently selected from halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-N(R^{L7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, and $-S(=O)_2NR^{L7}$;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and

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

each L^9 is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^{10} is independently a fused-pentacyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, -

$OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^{11} is independently a six-ring fused saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each $R9^0$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

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

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

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

each $R9^1$ is independently $-N(R^{9a})$-$NHC(=O)O$-R^{9b}, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and wherein arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

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

part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each $R9^2$ is independently –$N(R^{9a})$-$NHC(=O)NR^{9b}{}_2$; wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl,

arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, (NR^XR^Y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl

part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

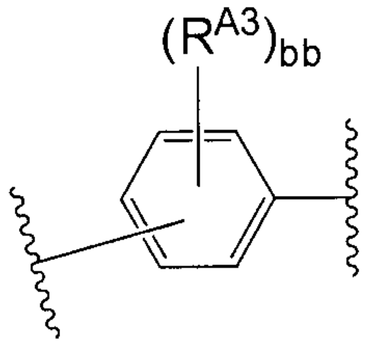
each $R9^3$ is independently –$N(R^{9a})$-$NHC(=O)R^{9b}$, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^XR^Y, -(NR^XR^Y)alkyl, and oxo, wherein the

alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each A^0 is independently:



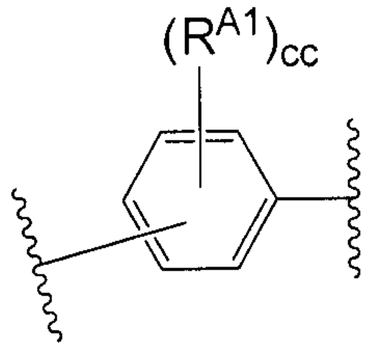
wherein:

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

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

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

each A^1 is independently:



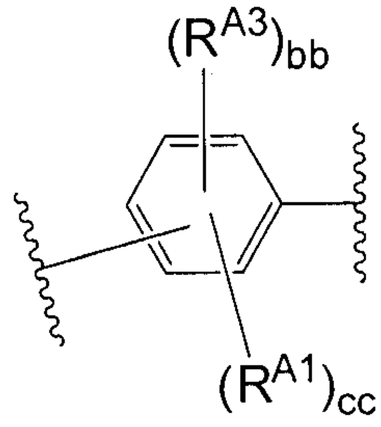
wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

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

each A^2 is independently:



wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

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

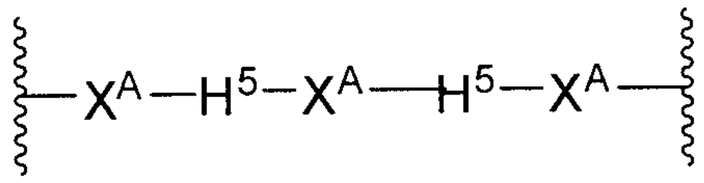
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

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

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

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

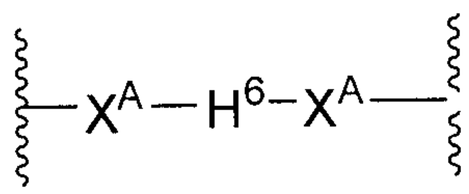
each A^4 is independently:



wherein:

each H^5 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^5 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

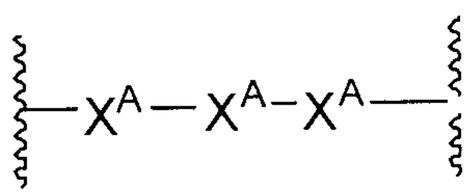
each A^5 is independently:



wherein:

each H^6 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^6 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

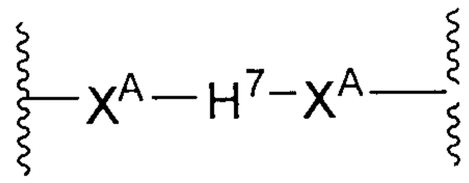
each A^6 is independently:



wherein:

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

each A^7 is independently:

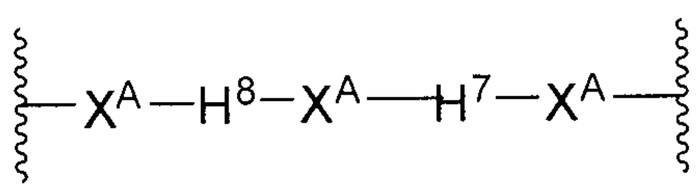


wherein:

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

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

each A^8 is independently:



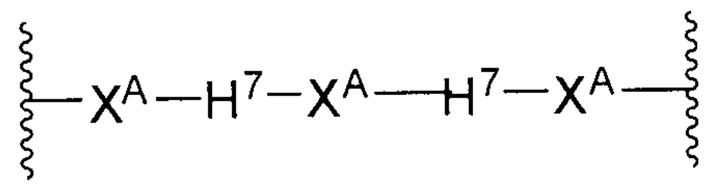
wherein:

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

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^9 is independently:

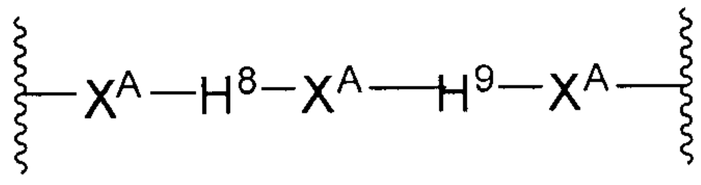


wherein:

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

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

each A^{10} is independently:



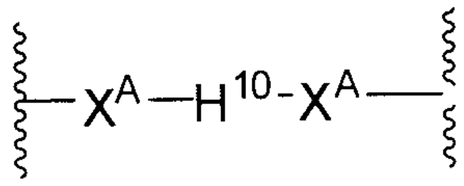
wherein:

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^9 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{11} is independently:



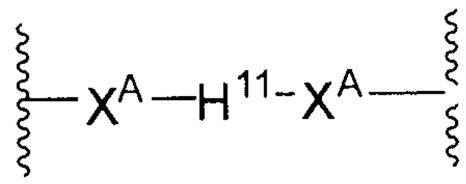
wherein:

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

each H^{10} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that is optionally fused to an aryl, which H^{10} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{12} is independently:



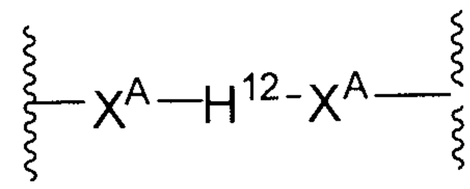
wherein:

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

each H^{11} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms that is optionally fused to an aryl, which H^{11} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{13} is independently:

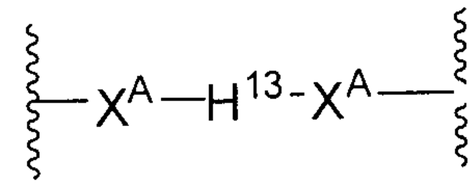


wherein:

each H^{12} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{14} is independently:

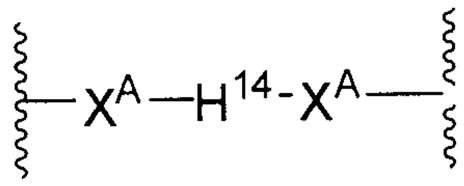


wherein:

each H^{13} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{15} is independently:

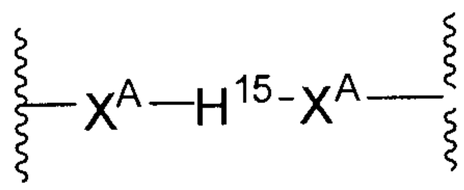


wherein:

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

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

each A^{16} is independently:

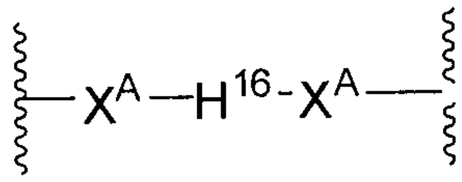


wherein:

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

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

each A^{17} is independently:

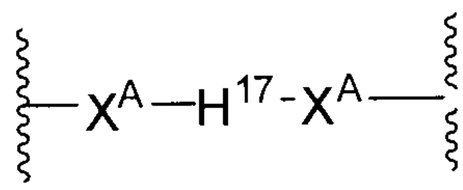


wherein:

each H^{16} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each A^{18} is independently:

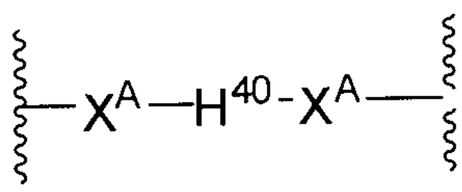


wherein:

each H^{17} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each A^{21} is independently:



wherein:

each H^{40} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

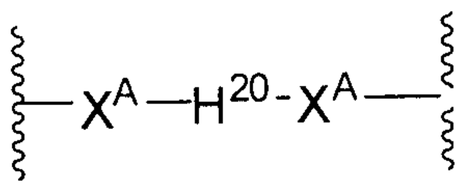
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^1 is independently $-X^A-$:

wherein:

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

each W^2 is independently:

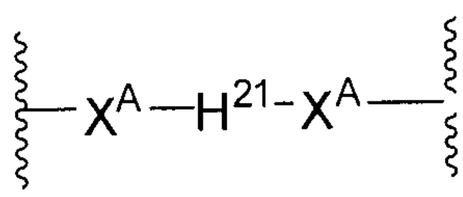


wherein:

each H^{20} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^3 is independently:

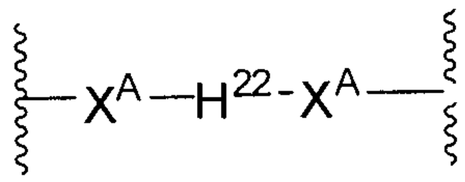


wherein:

each H^{21} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^4 is independently:

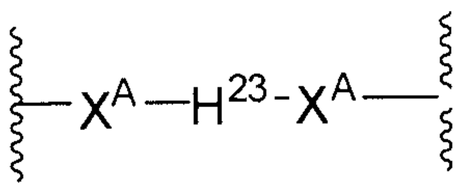


wherein:

each H^{22} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^5 is independently:

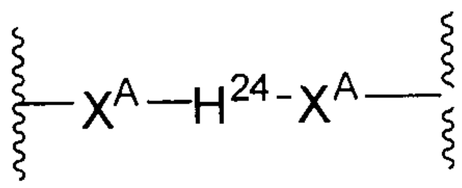


wherein:

each H^{23} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^6 is independently:

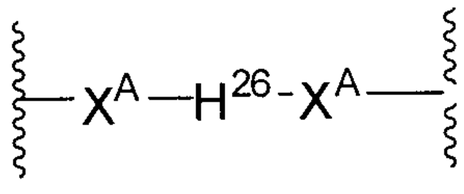


wherein:

each H^{24} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle, which is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^7 is independently:

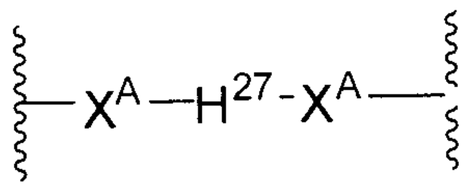


wherein:

each H^{26} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^8 is independently:

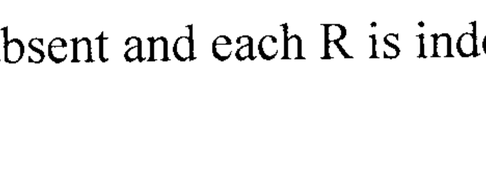


wherein:

each H^{27} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^9 is independently:



wherein:

each H^{29} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms; and

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

each W^{10} is independently $-H^{30}=C=H^{31}-$

wherein each of $-H^{30}$ and H^{31} is independently a saturated 6-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{11} is independently $-H^{32}=C=H^{33}-$

wherein each of $-H^{32}$ and H^{33} is independently a saturated 5-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{12} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{13} is independently a phenyl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{14} is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{15} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic carbocyclic ring, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{16} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{17} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{18} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{19} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

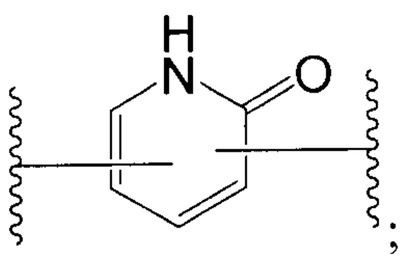
each W^{20} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each M^0 is independently a five membered heteroaryl group optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl and trialkylsilylalkoxyalkyl;

each M^1 is independently selected from –C(=O)NH-, –C(=O)NH-$C(R^M)_2$-, -NHC(=O) -, -$C(R^M)_2$NHC(=O)-, –NHC(=O)N R^M -, –NHC(=O)O -; wherein each R^M is independently selected from H and alkyl;

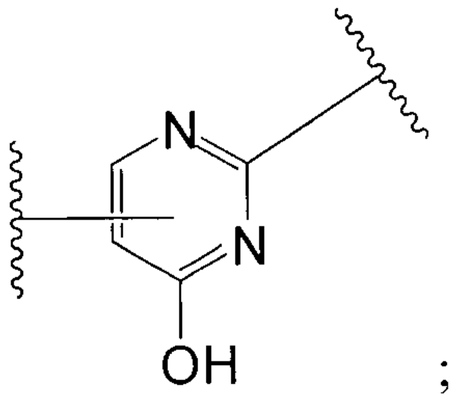
each M^2 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each M^3 is independently:



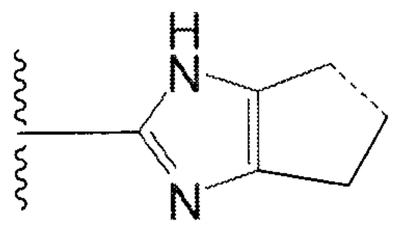
;

each M^4 is independently:



;

each M^5 is independently:



wherein the bond designated with --- is fused to a ring defined for P;

each M^6 is independently a bicyclic bridged ring system comprising 5-15 atoms wherein at least one of the atoms is a heteroatom;

each M^7 is independently a pyrid-di-yl;

each M^8 is independently partially saturated or a saturated five-membered ring that comprises one or more heteroatoms and that is optionally substituted with one or two oxo;

each M^9 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^{P11};

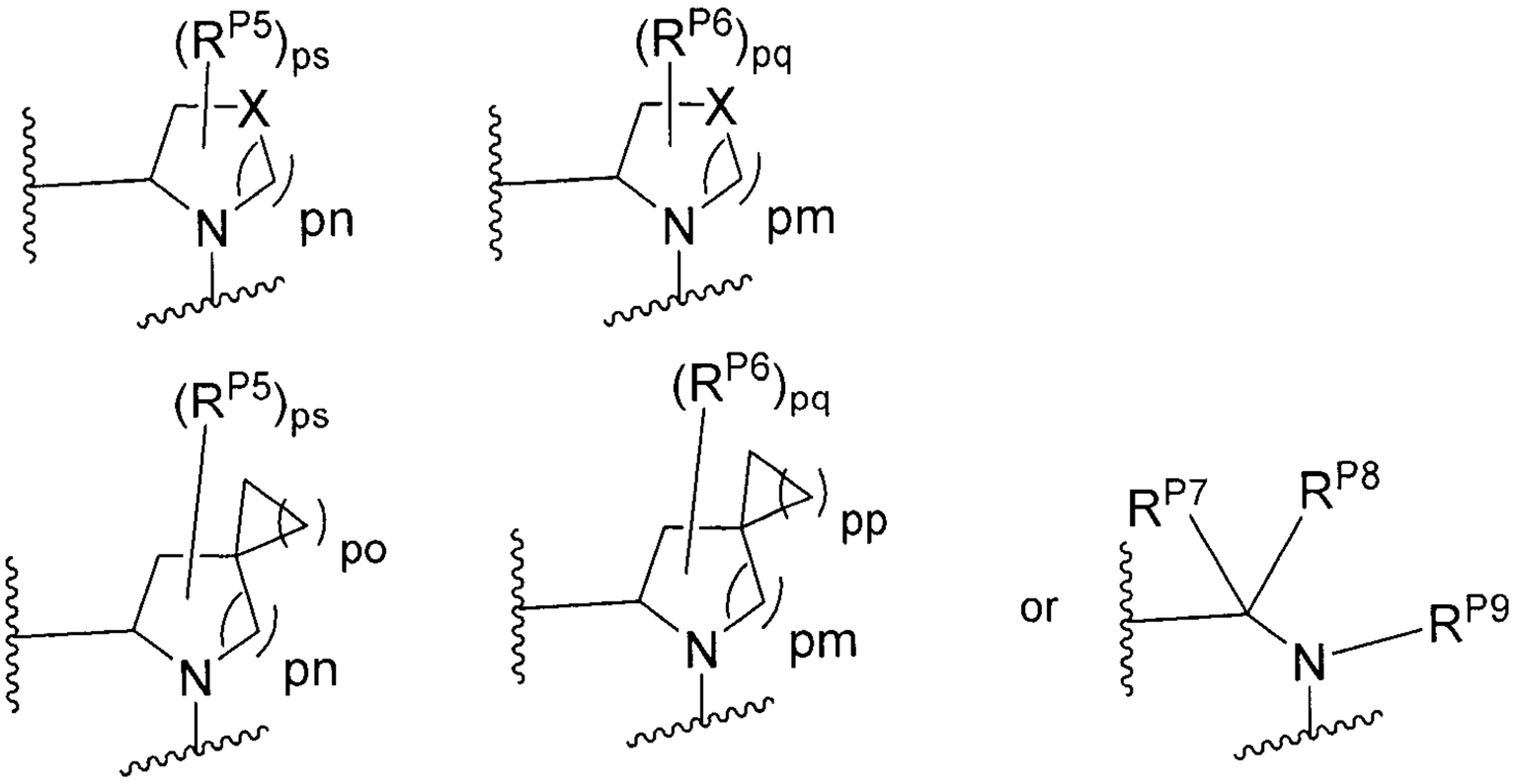
each M^{10} is independently a five membered heteroaryl group substituted with at least one alkoxy, cycloalkyl, cyano, alkylsulfonyl, arylsulfonyl, NR^hR^h, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkoxy, haloalkoxyalkyloxy, cycloalkoxyalkoxy, aryloxyalkoxy, heteroaryloxyalkoxy, heterocyclyloxyalkyloxy, (NR^hR^h)alkoxy, cyanoalkoxy, cycloalkoxy, heterocyclyl, alkoxyalkyl, cycloalkoxyalkyl, (NR^hR^h)alkyl, wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyloxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, and sulfonylalkyl; and

wherein the five membered ring is also optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl;

each M^{11} is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo, halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$; each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each M^{12} is independently a fused-pentacyclic, hexacyclic, or heptacyclic partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$;
each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each P^0 is independently:



wherein:

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

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

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

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

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

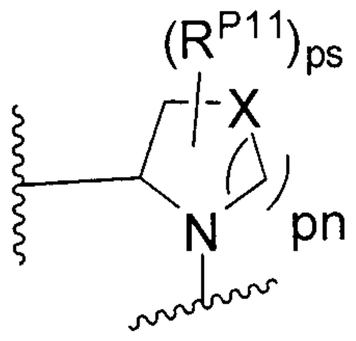
pm and pn are independently 0, 1, or 2;

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

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

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

each P^1 is independently:



wherein:

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

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

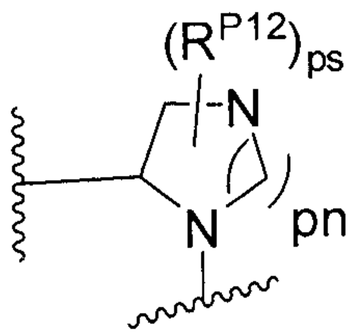
at least one R^{P11} is independently selected from cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy,

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

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^2 is independently:



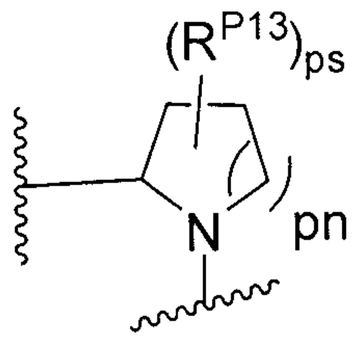
wherein:

each R^{P12} is independently selected from R^{P5}, R^{P11},-C(=O)OR^h, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

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



wherein:

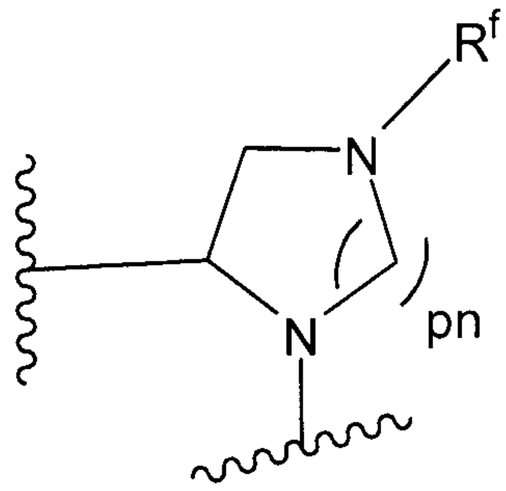
the ring is substituted with one or more oxo group;

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

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

pn is 0, 1, or 2;

each P^4 is independently a ring of the formula:



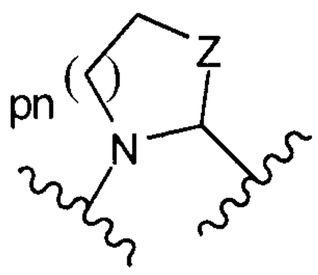
wherein:

the ring is optionally substituted with one or more groups R^{P14} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P14} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

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

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



wherein:

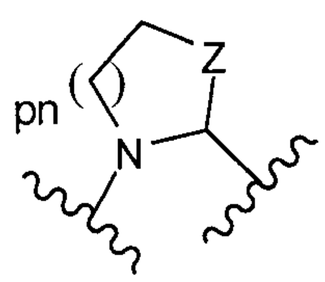
the ring is optionally substituted with one or more groups R^{P15} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered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

pn is 0, 1, or 2;

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

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

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



wherein:

the ring is substituted with one or more oxo and is optionally substituted with one or more groups R^{P16} that are independently selected from alkoxy, alkyl, aryl, halo,

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

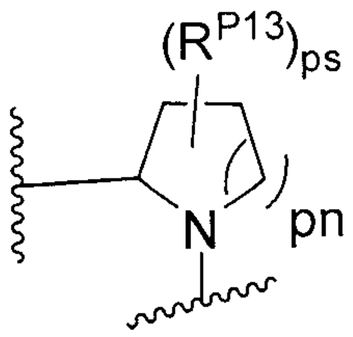
Z is O, S, S(=O), $S(=O)_2$, or NR^f;

pn is 0, 1, or 2;

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

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

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



wherein:

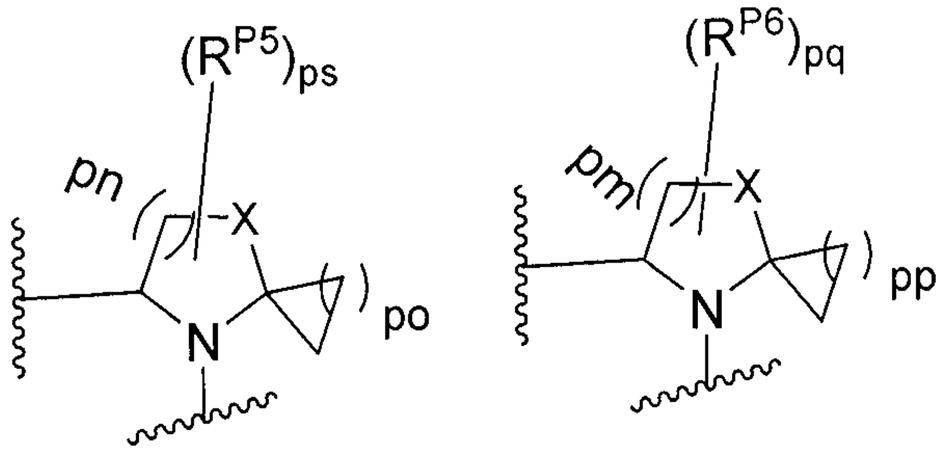
ps is 2, 3, 4, 5, or 6;

pn is 0, 1 or 2;

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

R^{P13} that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each P^{10} is independently:



wherein:

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

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

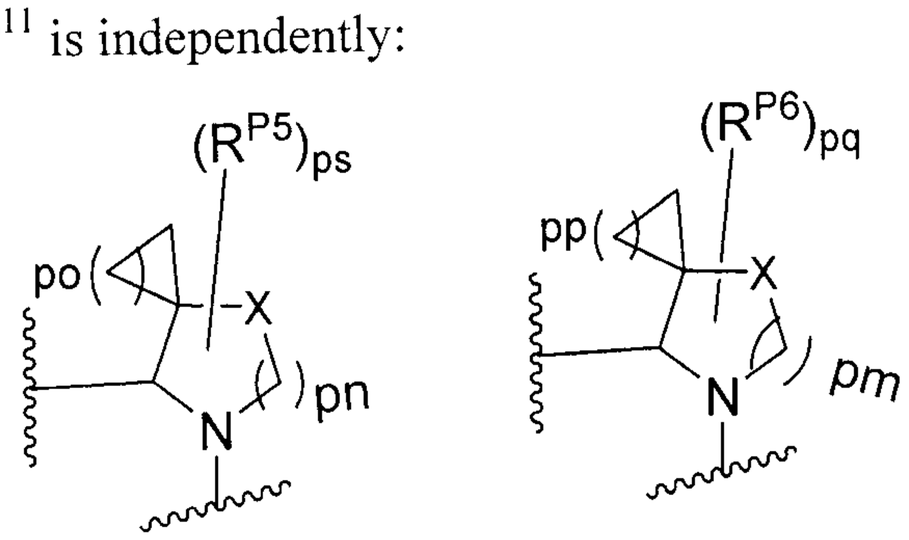
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{11} is independently:



wherein:

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

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

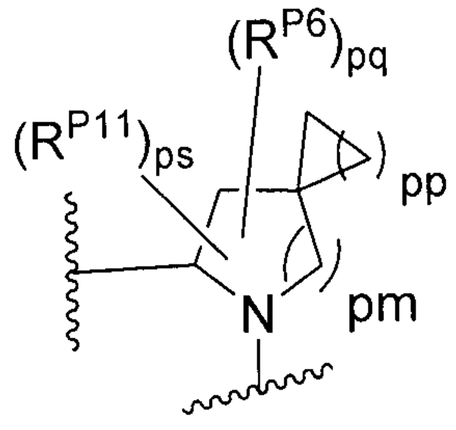
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{12} is independently:



wherein:

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

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

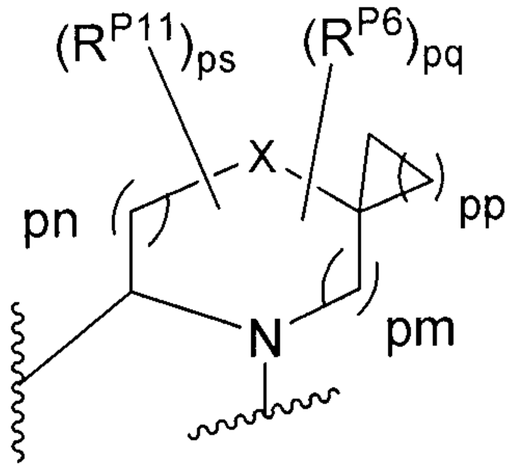
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

each P^{13} is independently:



wherein:

X is selected from O, S, S(O), SO_2, or NR^h;

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

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

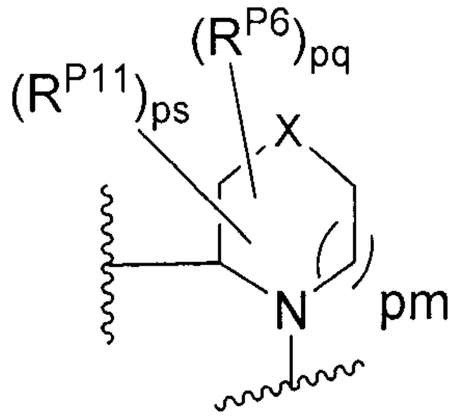
pm and pn are independently 0, 1, or 2 but the sum of pn and pm is greater than zero;

pp are independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

each P^{14} is independently:



wherein:

the ring is substituted with one or more oxo group;

X is NR^f;

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

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

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

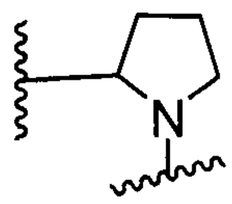
pm is independently 0, 1, or 2;

ps is 1, 2, 3, or 4;

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

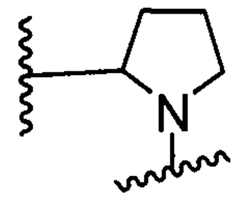
present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

each P^{15} is:



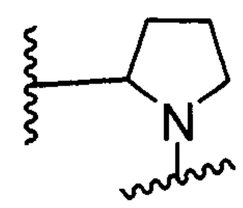
which is substituted with one or two groups independently selected from alkoxyalkyl, haloalkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, cyanoalkyl, and cycloalkylalkyl.

each P^{16} is:



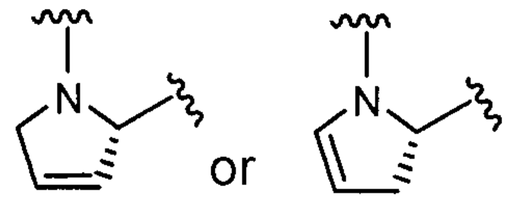
which is substituted with methylene;

each P^{17} is:



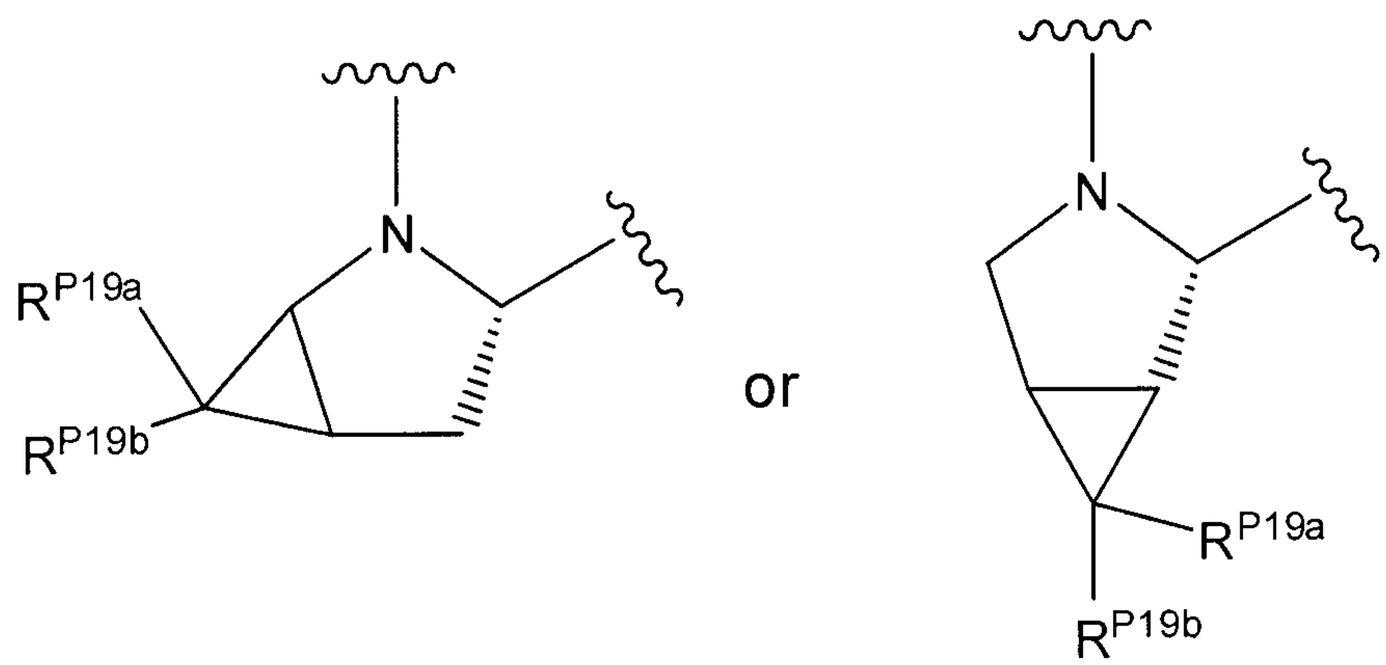
which is substituted with one or two groups independently selected from alkenyl, alkynyl, cycloalkyl, cycloalkylalkenyl, and cycloalkylalkynyl.

each P^{18} is:



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

each P^{19} is:



wherein each R^{P19a} is independently selected from H and halo; and each R^{P19b} is independently selected from halo;

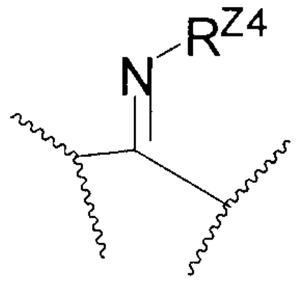
each $-Z^0-$ is $-C(=O)-$ or $-C(=S)-$;

each $-Z^1-$ is independently a bond, or $-C(R^{Z1})_2-$; wherein each R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each $-Z^2-$ is independently saturated or partially unsaturated (C_3-C_8)cycloalkyl that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

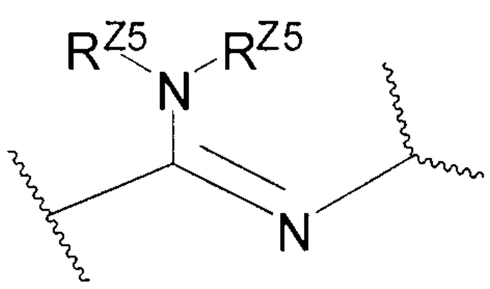
each $-Z^3-$ is independently saturated, partially unsaturated, or aromatic 4-8 membered heterocyclic or heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^4-$ is independently:



wherein each R^{Z4} is independently H, alkyl, cyano, aryl, or heteroaryl;

each $-Z^5-$ is independently:



wherein each R^{Z5} is independently H, alkyl, cyano, aryl, or heteroaryl; or two R^{Z5}s together with the nitrogen to which they are attached form a 4-8 membered heterocyclic ring that is optionally substituted with one or more oxo and with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^6-$ is independently $-C(R^{Z1})-$ and is doublebonded to a carbocyclic P; wherein R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

R^{Ec} and R^{Ed} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl,

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

each E^1 is independently $-OC(=O)NR^{Ee}R^{Ef}$ wherein each R^{Ee} and R^{Ef} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and - $C(NCN)NR^XR^Y$, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; or wherein R^{Ee} and R^{Ef}, together with the nitrogen atom to which they are attached, form a heterocycle;

each E^2 is independently $-NR^aR^b$, wherein R^a is haloalkyl and R^b is H, alkyl, alkoxycarbonyl. or haloalkyl;

each E^3 is independently $-NR^{Ec}R^{E3a}$, wherein R^{E3a} is (C_3-C_6)cycloalkyloxycarbonyl;

each E^4 is independently $-OC(=O)OR^{E4a}$, wherein R^{E4a} is cycloalkyl, aryl, or alkyl;

each E^5 is independently $-NR^{Ec}S(=O)_2OR^{E5a}$, wherein R^{E5a} is is cycloalkyl, aryl or alkyl;

each E^6 is independently $-NR^{Ec}S(=O)_2R^{E6a}$, wherein R^{E6a} is cycloalkyl, aryl, or alkyl;

each E^7 is independently $-NR^{Ec}OR^{E7a}$, wherein R^{E7a} is cycloalkyl, aryl, alkyl, haloalkyl, cycloalkylalkyl or heteroaryl;

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

the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro;

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; wherein R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^6 is independently arylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^7 is independently heterocyclosulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^8 is independently spirocycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^9 is independently spirocycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{10} is independently fusedbicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{11} is independently fusedbicycliccycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{12} is independently bridged-bicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{13} is independently bridged-bicyclic-cycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl,

heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{14} is independently aryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{15} is independently arylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{16} is independently cycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{17} is independently cycloalkylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{18} is independently heterocyclooxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{19} is independently heterocycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{20} is independently heteroaryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{21} is independently heteroarylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{22} is independently cycloalkenylalkyl;

each V^{23} is independently arylalkyl, wherein the aryl is substituted with one or more groups independently selected from cycloalkyl, alkenyl, cycloalkylalkyl, cyanoalkyl, cycloalkoxy, hydroxyalkoxy, $-C(=O)NR^XR^Y$, $S(=O)_2NR^XR^Y$, alkylsulfanyl, alkylsulfonyl, haloalkylsulfanyl, haloalkylsulfonyl, alkylsulfonylalkyl, alkylsulfonylalkyl, arylsulfanyl, arylsulfonyl, alkoxyalkoxy, alkynyl, aryloxy, heteroaryloxy, alkylsulfonylamino;

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

each V^{24} is independently heterocycloalkyl, wherein the heterocycle is substituted with one or more groups independently selected from cycloalkyl, alkenyl, cycloalkylalkyl, cyanoalkyl, cycloalkoxy, hydroxyalkoxy, $-C(=O)NR^XR^Y$, $S(=O)_2NR^XR^Y$, alkylsulfanyl, alkylsulfonyl, haloalkylsulfanyl, haloalkylsulfonyl, alkylsulfonylalkyl, alkylsulfonylalkyl, arylsulfanyl, arylsulfonyl, alkoxyalkyoxy, alkynyl, aryloxy, heteroaryloxy, alkylfulfonylamino;

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

each T^1 is independently a spiro, branched or fused bicycloalkyl;

each T^2 is independently aryl;

each T^3 is independently heteroaryl;

each T^4 is independently arylalkyl;

each T^5 is independently haloalkyl;

each T^6 is independently heteroarylalkyl;

each T^7 is independently heterocycle; and

each T^8 is independently heterocycloalkyl;

or a pharmaceutically acceptable salt, or prodrug thereof.

2. A compound of formula (I):

J-Y-J (I)

wherein:

Y is –L-L-, –M-W-M- or Y^y;

J is T-P-, -P-T or $-J^m$;

W is a bond or $–W^r$-;

L is –M-A-, -A-M-, or $–L^n$;

T is R9-Z-, -Z-R9, or $–T^p$;

R9 is E-V-, or –V-E, or $–R9^q$;

each A is selected from $–A^s$;

each M is selected from $–M^t$;

each P is selected from $–P^u$;

each Z is selected from $–Z^v$;

each V is selected from $–V^w$;

each E is selected from $–E^x$;

each m is 1

each n is 0, 1, 2, 3, 4, 5, 6, 7, 9, or 10;

each p is 1, 2, 3, 4, 5, 6, 7, or 8;

each q is 0, 1, 2, or 3;

each r is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

each s is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 21;

each t is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, or 14;

each v is 0, 1, 2, 3, 4, 5, or 6;

each w is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21;

each x is 0 or 1;

each y is 0, 1, or 2;

wherein the sum of m, n, p, q, r, s, t, u, v, w, x, and y is not 0; P is connected to M, L, or Y^y; A is connected to A or L; M is connected to P or J; Z is connected to P; V is connected to Z; and when W is a bond M is connected to M;

each Y^1 is independently:

a fused nine-ring system with up to thirty-five atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S, and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3}; each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

each Y^2 is independently:

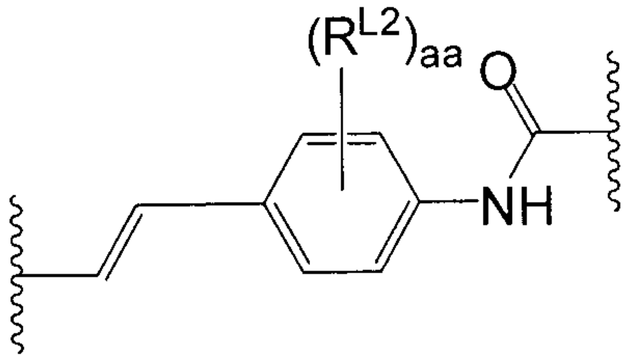
a fused five to eight ring system with up to thirty-two atoms that may be fully aromatic or partially saturated and contains atoms selected from C, N, O, and S, and which ring system is optionally substituted with one or more groups independently selected from H, oxo, R^{A1} and R^{A3};

each J^1 is independently a fused bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is substituted with one or more $-N(R^{L7})C(=O)OR^{L7}$, and that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^0 is independently:

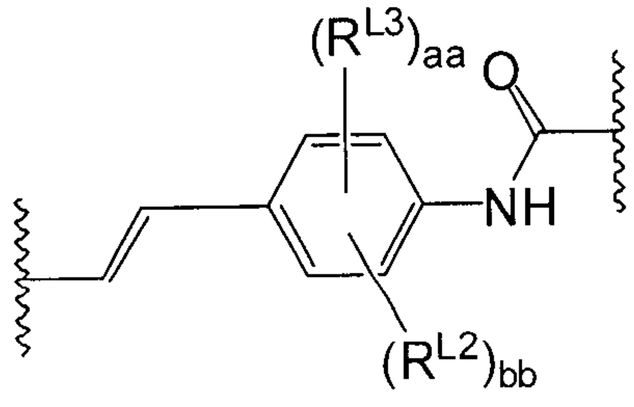


wherein:

each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl; and

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

each L^1 is independently:



wherein:

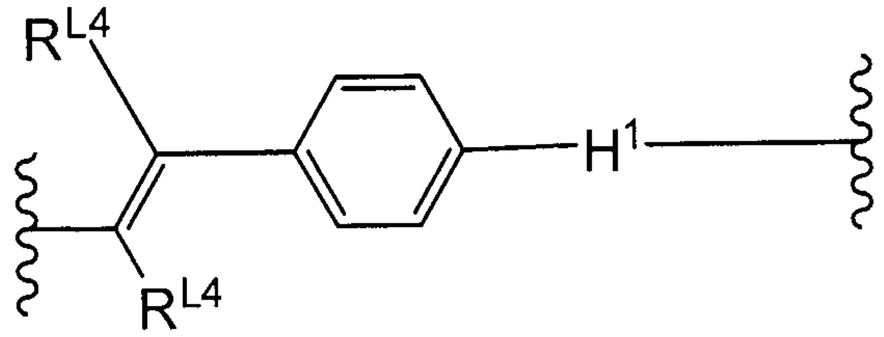
each R^{L2} is independently selected from hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl;

each R^{L3} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

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

each L^2 is independently:



wherein:

the phenyl ring shown in L^2 is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R^{L4} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

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

each H^1 is a 5 membered saturated, partially unsaturated, or aromatic ring comprising one or more heteroatoms.

each L^3 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4,

SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

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

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

each L^4 is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

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

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

each L^5 is independently a –CR=CR-fusedbicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

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

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

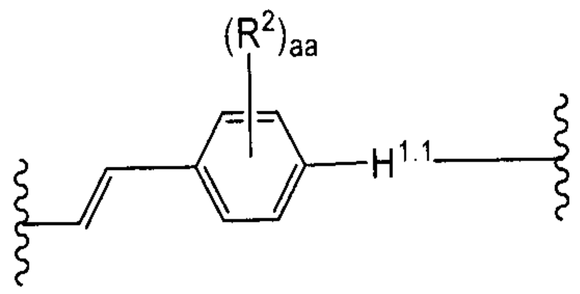
each L^6 is independently a –CR=CR-fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo;

each R is independently selected from H or alkyl;

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

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

each L^7 is independently:



wherein:

each $H^{1.1}$ is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^2;

each R^2 is independently selected from halo, -R^{L7}, -OR^{L7}, -SR^{L7}, -$N(R^{L7})_2$, -CF_3, -CCl_3, -OCF_3,-CN, -NO_2, -$N(R^{L7})C(=O)R^{L7}$, -$C(=O)R^{L7}$, -$OC(=O)R^{L7}$, -$C(O)OR^{L7}$, -$C(=O)NR^{L7}$, -$S(=O)R^{L7}$, -$S(=O)_2OR^{L7}$, -$S(=O)_2R^{L7}$, -$OS(=O)_2OR^{L7}$, and -$S(=O)_2NR^{L7}$;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle; and

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

each L^9 is independently a fused-tetracyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, -R^{L7}, -OR^{L7}, -SR^{L7}, -CF_3, -CCl_3, -OCF_3,-CN, -NO_2, -$N(R^{L7})C(=O)R^{L7}$, -$C(=O)R^{L7}$, -$OC(=O)R^{L7}$, -$C(O)OR^{L7}$, -$C(=O)NR^{L7}$, -$S(=O)R^{L7}$, -$S(=O)_2OR^{L7}$, -$S(=O)_2R^{L7}$, -

$OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^{10} is independently a fused-pentacyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each L^{11} is independently a six-ring fused saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more groups independently selected from oxo, halo, $-R^{L7}$, $-OR^{L7}$, $-SR^{L7}$, $-CF_3$, $-CCl_3$, $-OCF_3$,-CN, $-NO_2$, $-N(R^{L7})C(=O)R^{L7}$, $-C(=O)R^{L7}$, $-OC(=O)R^{L7}$, $-C(O)OR^{L7}$, $-C(=O)NR^{L7}$, $-S(=O)R^{L7}$, $-S(=O)_2OR^{L7}$, $-S(=O)_2R^{L7}$, $-OS(=O)_2OR^{L7}$, $-S(=O)_2NR^{L7}$, alkoxyalkyl, arylalkoxycarbonyl, halo, haloalkyl, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

each R^{L7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

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

each $R9^0$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl,

(cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

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

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

each $R9^1$ is independently –$N(R^{9a})$-NHC(=O)O-R^{9b}, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups

independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl
part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each $R9^2$ is independently $-N(R^{9a})$-$NHC(=O)NR^{9b}{}_2$; wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO2alkyl, cycloalkylalkylSO2alkyl, cyanoalkyl, haloalkyl, cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from hydrogen and alkyl;
and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups

independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

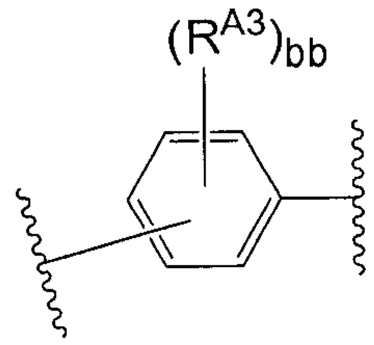
and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl
part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each $R9^3$ is independently $-N(R^{9a})$-$NHC(=O)R^{9b}$, wherein each R^{9a} is independently arylalkyl, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkoxy, halocycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkoxy, alkylSO_2alkyl, cycloalkylalkylSO_2alkyl, cyanoalkyl, haloalkyl cycloalkylalkyl, cycloalkyl, alkoxyalkyl, alkoxyalkylcarbonylalkyl, alkoxycarbonylalkyl, alkylsulfanylalkyl, aryalkoxyalkylcarbonylalkyl, carboxyalkyl, heterocyclylalkyl, heterocyclylcarbonylalkyl, hydroxyalkyl, NRRCOalkyl, wherein each R is independently selected from H or alkyl; and where in arylalkyl the alkyl can be substituted with up to three aryl groups, and the alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkyocarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy;

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

and the heterocyclyl can be substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^XR^Y$, $-(NR^XR^Y)$alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl; the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro; R^{9b} is independently H, alkyl, aryl, haloalkyl, or arylalkyl;

each A^0 is independently:



wherein:

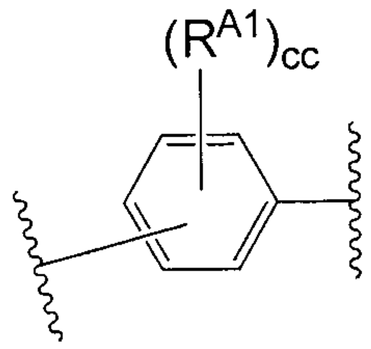
each R^{A3} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; R^a and R^b are each independently selected from the group

consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; and each

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

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

each A^1 is independently:



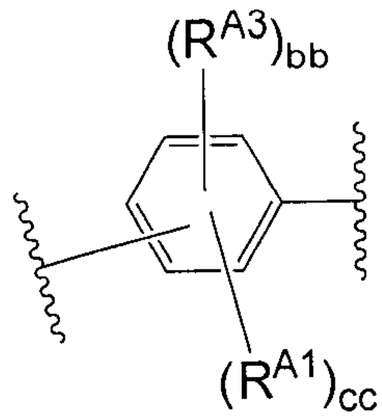
wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

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

each A^2 is independently:



wherein:

each R^{A1} is independently selected from cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl,

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

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

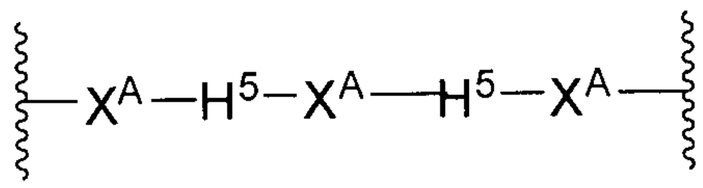
each R^4 is independently selected from H, alkyl, haloalkyl, aryl, and arylalkyl;

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

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

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

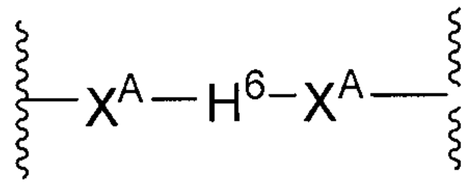
each A^4 is independently:



wherein:

each H^5 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^5 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

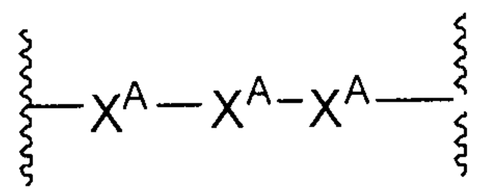
each A^5 is independently:



wherein:

each H^6 is independently a phenyl ring or a six-membered heteroaromatic ring, which H^6 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent; provided that at least one X^A is present and each R is independently selected from H or alkyl;

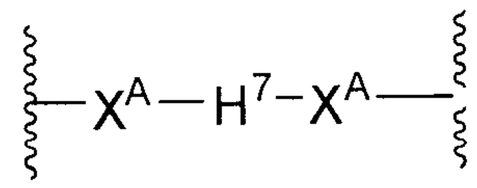
each A^6 is independently:



wherein:

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

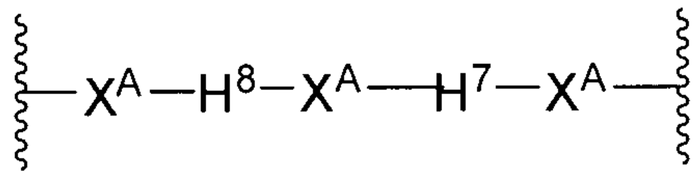
each A^7 is independently:



wherein:

each H^7 is independently a five-membered heteroaromatic ring, which H^7 is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each A^8 is independently:



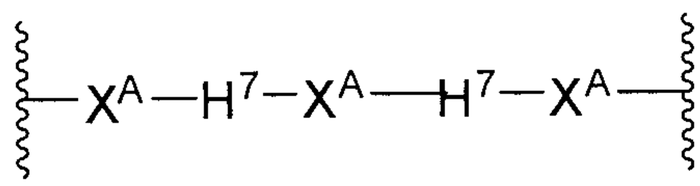
wherein:

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

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^9 is independently:

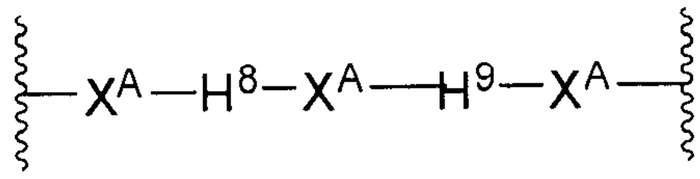


wherein:

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

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

each A^{10} is independently:



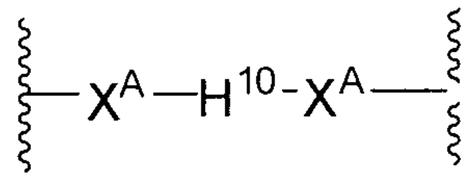
wherein:

each H^8 is independently a phenyl ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each H^9 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{11} is independently:



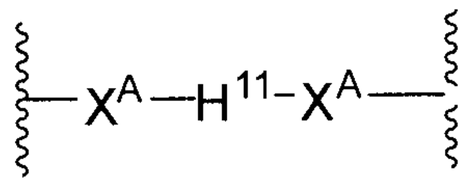
wherein:

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

each H^{10} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that is optionally fused to an aryl, which H^{10} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{12} is independently:



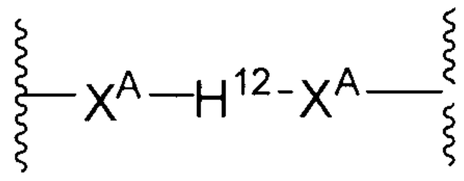
wherein:

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

each H^{11} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms that is optionally fused to an aryl, which H^{11} is optionally substituted with one or more groups independently selected from oxo, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl, cyano, nitro, SOR^4, SO_2R^4, -alkylSO_2R^4, haloalkoxy, cyanoalkyl, $NR^4SO_2R^4$, cycloalkyl, (halo)cycloalkyl, heterocycle, (cycloalkyl)alkyl, and (heterocycle)alkyl, wherein each alkyl, heterocycle and cycloalkyl is optionally substituted with one or more halo; and

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

each A^{13} is independently:

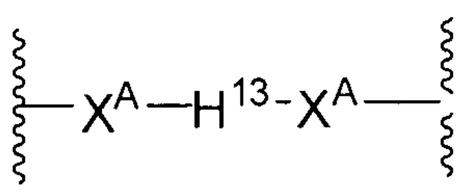


wherein:

each H^{12} is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{14} is independently:

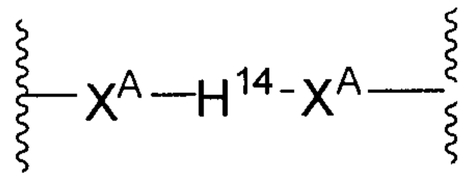


wherein:

each H^{13} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each A^{15} is independently:

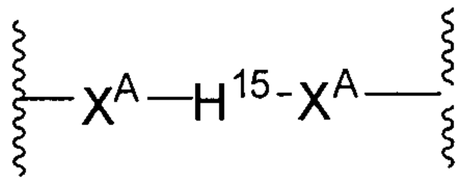


wherein:

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

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

each A^{16} is independently:

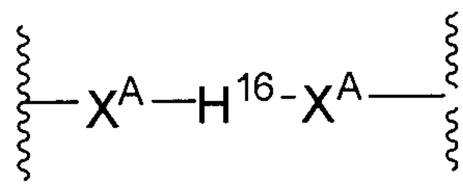


wherein:

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

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

each A^{17} is independently:

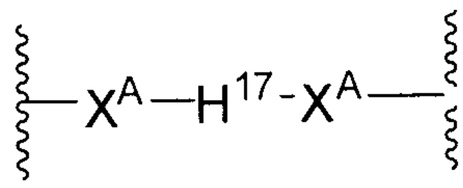


wherein:

each H^{16} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each A^{18} is independently:

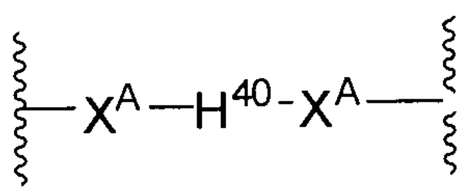


wherein:

each H^{17} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each A^{21} is independently:



wherein:

each H^{40} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

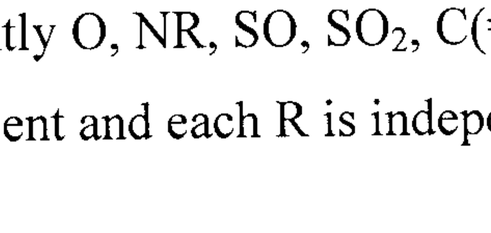
each X^A is independently O, NR, SO, SO_2, C(=O), NRC(=O), C(=O)NR, CR=CR, NRC(=O)NR, allenyl, alkynyl, or absent and each R is independently selected from H or alkyl;

each W^1 is independently $-X^A-$:

wherein:

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

each W^2 is independently:

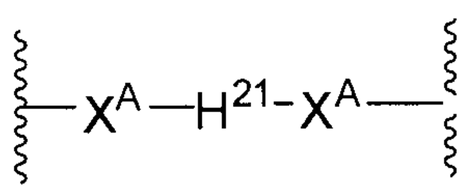


wherein:

each H^{20} is independently is independently a fused aromatic bicyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^3 is independently:

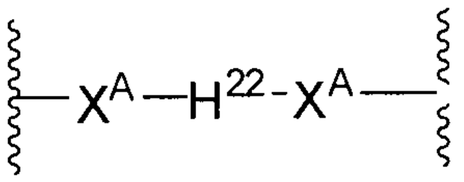


wherein:

each H^{21} is independently a fused bicyclic carbocyclic ring system wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^4 is independently:

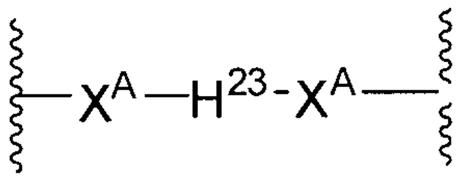


wherein:

each H^{22} is independently a fused aromatic bicyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^5 is independently:

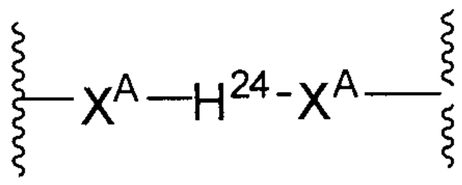


wherein:

each H^{23} is independently a fused bicyclic ring system comprising at least one heteroatom, wherein one ring is aromatic and another ring is partially or fully saturated, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^6 is independently:

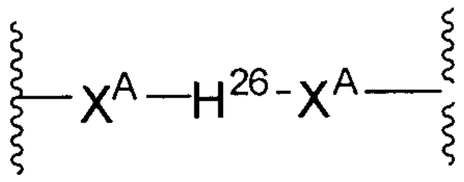


wherein:

each H^{24} is independently a fused unsaturated, partially unsaturated or saturated tricyclic carbocycle, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^7 is independently:

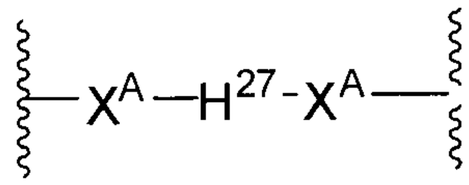


wherein:

each H^{26} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3}; and

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

each W^8 is independently:

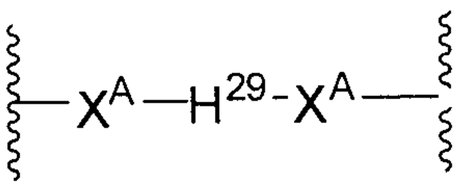


wherein:

each H^{27} is independently a fused unsaturated, partially unsaturated or saturated tricyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3}; and

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

each W^9 is independently:



wherein:

each H^{29} is independently a 5-15 carbon unsaturated, partially unsaturated or saturated bicyclic ring system that contains one or more heteroatoms; and

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

each W^{10} is independently $-H^{30}=C=H^{31}-$

wherein each of $-H^{30}$ and H^{31} is independently a saturated 6-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{11} is independently $-H^{32}=C=H^{33}-$

wherein each of $-H^{32}$ and H^{33} is independently a saturated 5-membered heterocyclic ring comprising one or more heteroatoms, which ring is optionally substituted with oxo;

each W^{12} is independently an anti-aromatic monocyclic or fused carbocyclic ring system, which carbocyclic ring system is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{13} is independently a phenyl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{14} is independently a 5 or 6 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each W^{15} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic carbocyclic ring, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{16} is independently a fused unsaturated, partially unsaturated or saturated tetracyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{17} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{18} is independently a fused unsaturated, partially unsaturated or saturated pentacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each W^{19} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic carbocyclic ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

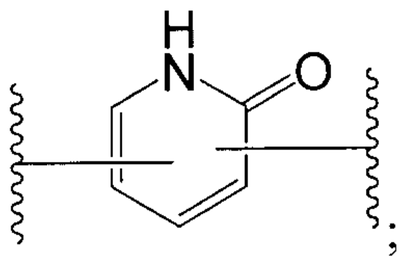
each W^{20} is independently a fused unsaturated, partially unsaturated or saturated hexacyclic heterocycle that comprises at least one heteroatom in the ring system, which ring system is optionally substituted with one or more groups independently selected from oxo, R^{A1} and R^{A3};

each M^0 is independently a five membered heteroaryl group optionally substituted with one or more alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl and trialkylsilylalkoxyalkyl;

each M^1 is independently selected from –C(=O)NH-, –C(=O)NH-$C(R^M)_2$-, -NHC(=O) -, -$C(R^M)_2$NHC(=O)-, –NHC(=O)N R^M -, –NHC(=O)O -; wherein each R^M is independently selected from H and alkyl;

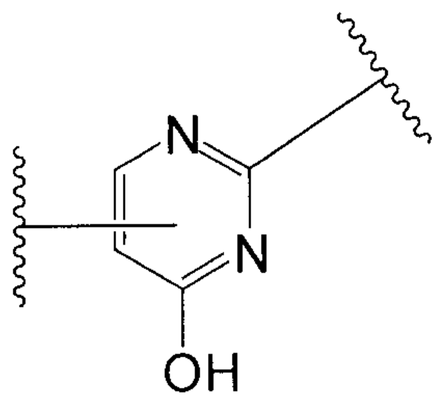
each M^2 is independently a six-membered heteroaromatic ring, which is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each M^3 is independently:



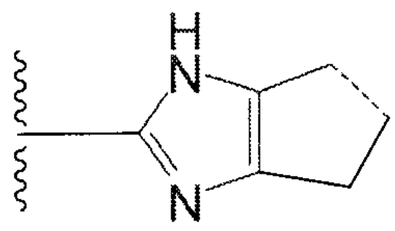
;

each M^4 is independently:



;

each M^5 is independently:



wherein the bond designated with --- is fused to a ring defined for P;

each M^6 is independently a bicyclic bridged ring system comprising 5-15 atoms wherein at least one of the atoms is a heteroatom;

each M^7 is independently a pyrid-di-yl;

each M^8 is independently partially saturated or a saturated five-membered ring that comprises one or more heteroatoms and that is optionally substituted with one or two oxo;

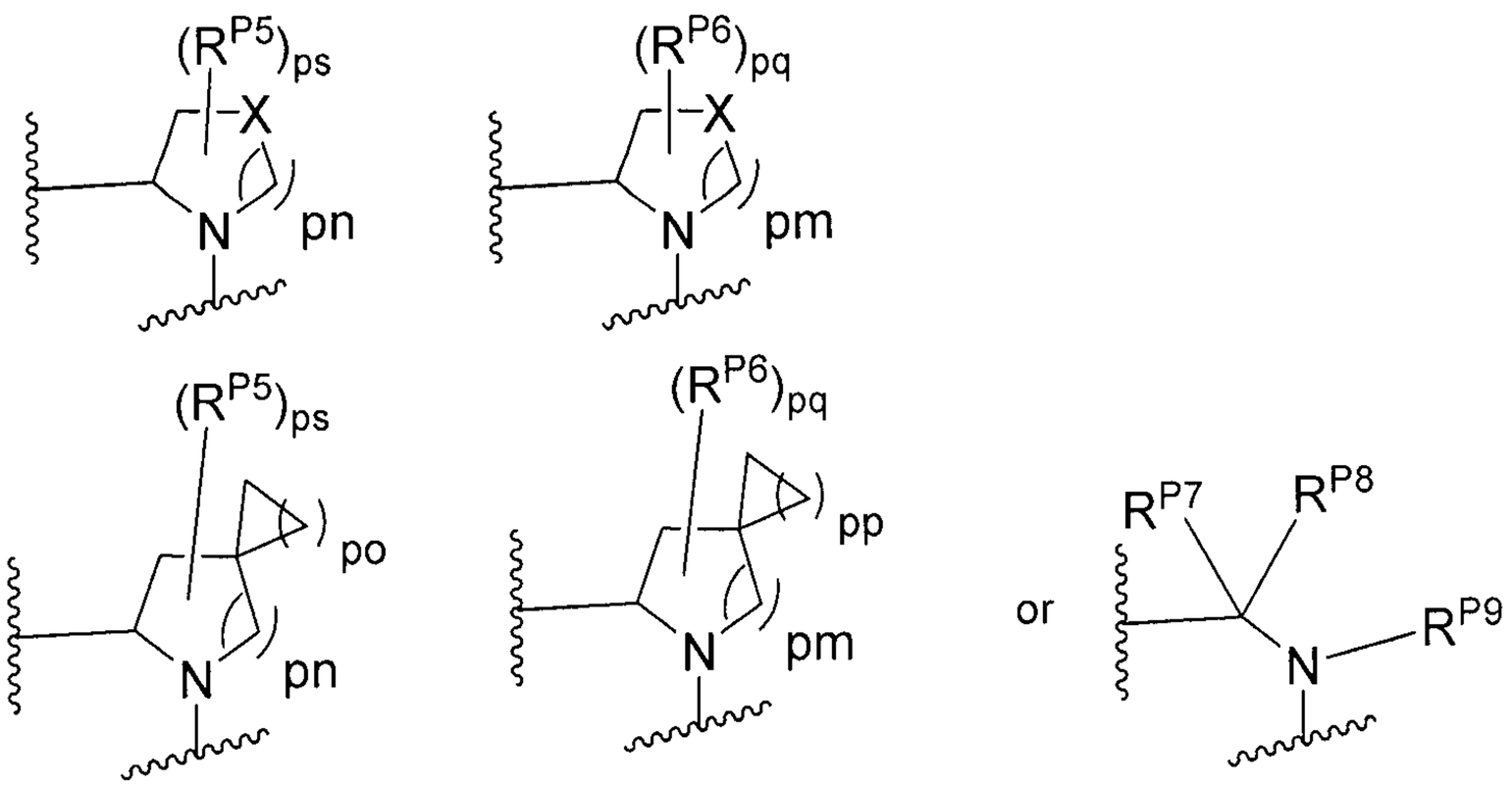
each M^9 is independently a fused-bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more R^{P11};

each M^{10} is independently a five membered heteroaryl group;

each M^{11} is independently a fused-tricyclic saturated, partially unsaturated, or aromatic heterocyclic ring system that is optionally substituted with one or more oxo, halo, $-R^{M7}$, $-OR^{M7}$, $-SR^{M7}$, $-N(R^{M7})_2$, $-CF_3$, $-CCl_3$, $-OCF_3$,$-CN$, $-NO_2$, $-N(R^{M7})C(=O)R^{M7}$, $-C(=O)R^{M7}$, $-OC(=O)R^{M7}$, $-C(O)OR^{M7}$, $-C(=O)NR^{M7}$, $-S(=O)R^{M7}$, $-S(=O)_2OR^{M7}$, $-S(=O)_2R^{M7}$, $-OS(=O)_2OR^{M7}$, or $-S(=O)_2NR^{M7}$;

each R^{M7} is independently -H, alkyl, aryl, arylalkyl, or heterocycle;

each P^0 is independently:



wherein:

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

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

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

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

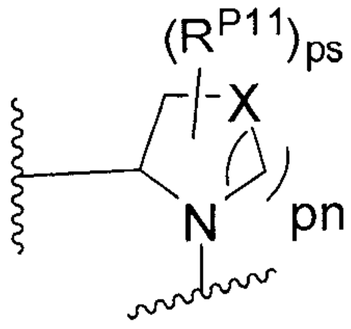
pm and pn are independently 0, 1, or 2;

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

R^{P7} and R^{P8} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and $(NR^{Pa}R^{Pb})$alkyl; or R^{P7} and R^{P8}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^{Pz}, 0, and S; wherein R^{Pz} is selected from hydrogen and alkyl;

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

each P^1 is independently:



wherein:

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

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

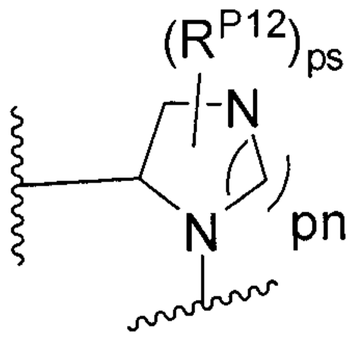
membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

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

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

each P^2 is independently:



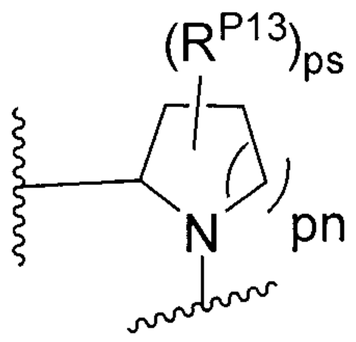
wherein:

each R^{P12} is independently selected from R^{P5}, R^{P11},-C(=O)OR^h, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy, cyanoalkoxy, cyanocycloalkyloxy, cycloalkyloxy, oxo, heterocyclyl; wherein each R^h is independently -H, alkyl, alkoxyamino, aryl, arylalkyl, heterocycle, heterocyclyoxy, alkenyl, alkenyloxy, alkynyl, alkoxyalkyl, haloalkyl, cyanoalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonylalkyl; and when two R^h groups are present then they may come together with the atoms to which they are bound to form a 4-15 membered heterocyclic ring;

ps is 1, 2, 3, or 4;

pn is 0, 1, or 2;

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



wherein:

the ring is substituted with one or more oxo group;

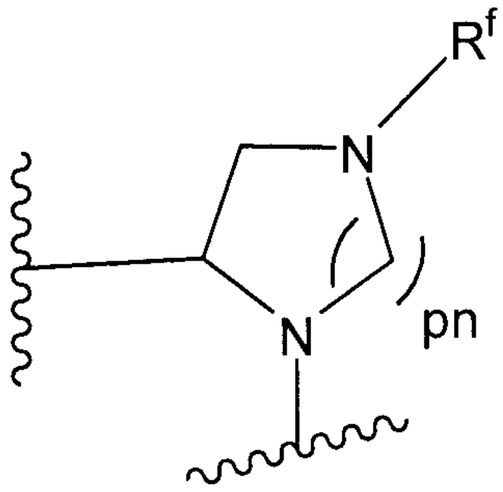
each R^{P13} is independently selected from R^{P5}, cyano, alkylsulfonyl, arylsulfonyl, (NR^hR^h)sulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, haloalkoxy, alkoxyalkyloxy, haloalkoxyalkyloxy, cycloalkyoxyalkyloxy, aryloxyalkyloxy, heteroaryloxyakyloxy, heterocyclooxyalkyloxy, (NR^hR^h)alkyloxy,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

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

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

pn is 0, 1, or 2;

each P^4 is independently a ring of the formula:



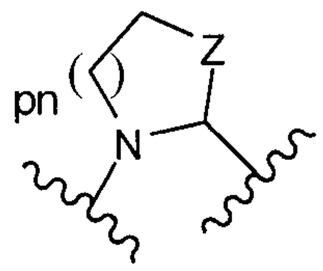
wherein:

the ring is optionally substituted with one or more groups R^{P14} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; and where two groups R^{P14} that are attached to the same carbon when taken together with the carbon to which they are attached can form a 3-6 membered carbocyclic or heterocyclic ring;

pn is 0, 1, or 2;

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

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



wherein:

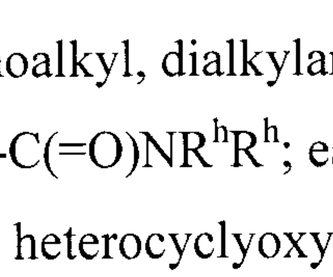
the ring is optionally substituted with one or more groups R^{P15} that are independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered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

pn is 0, 1, or 2;

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

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

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



wherein:

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

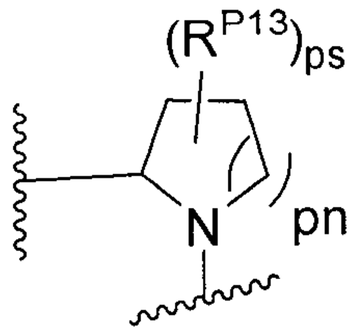
Z is O, S, S(=O), $S(=O)_2$, or NR^f;

pn is 0, 1, or 2;

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

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

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



wherein:

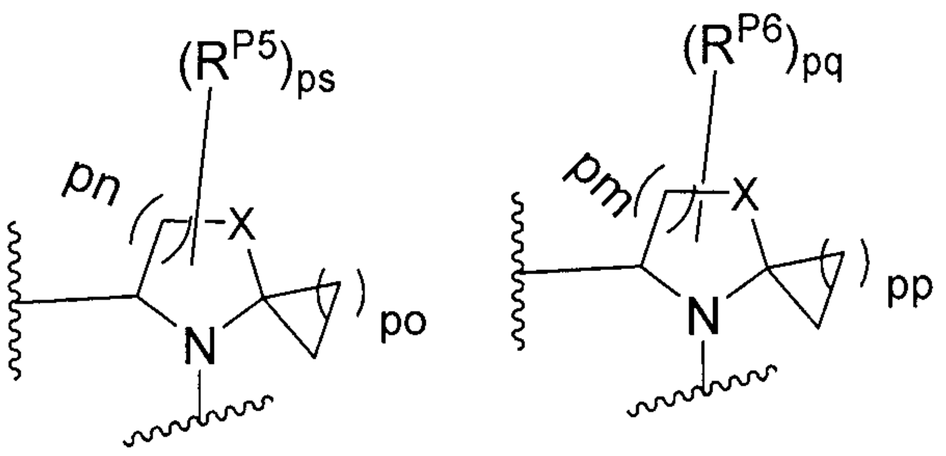
ps is 2, 3, 4, 5, or 6;

pn is 0, 1, or 2;

each R^{P13} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to

six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups; where in at least one case two groups R^{P13} that are attached to the same carbon are taken together with the carbon to which they are attached and form a 4-6 membered heterocyclic ring;

each P^{10} is independently:



wherein:

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

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

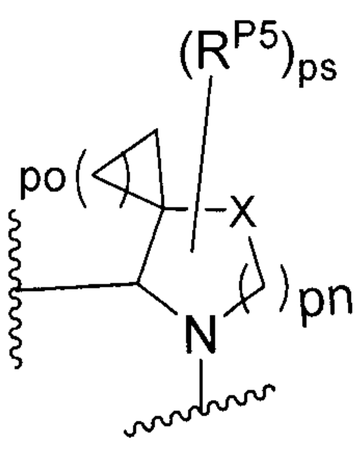
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

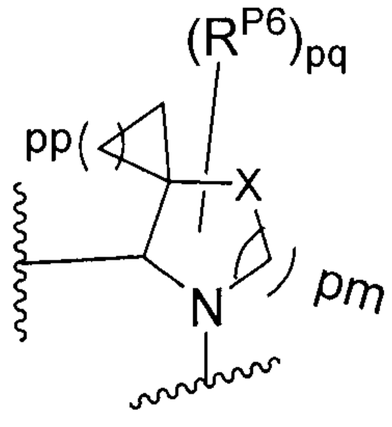
pq and ps are independently 0, 1, 2, 3, or 4;

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

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

each P^{11} is independently:





wherein:

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

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

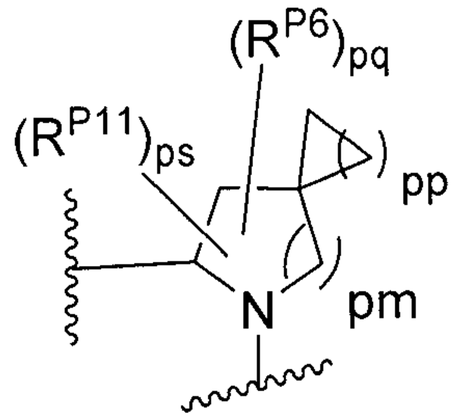
each R^{P5} and R^{P6} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^{Pa}R^{Pb}$, wherein the alkyl can optionally form a fused three-to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one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

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

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

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

each P^{12} is independently:



wherein:

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

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

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

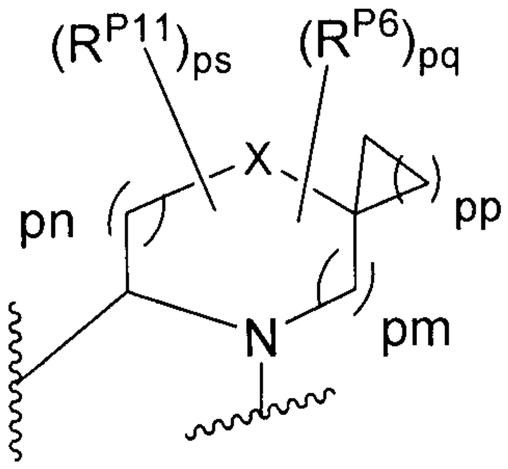
pm is independently 0, 1, or 2;

pp is independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

each P^{13} is independently:



wherein:

X is selected from O, S, S(O), SO_2, or NR^h;

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

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

pm and pn are independently 0, 1, or 2 but the sum of pn and pm is greater than zero;

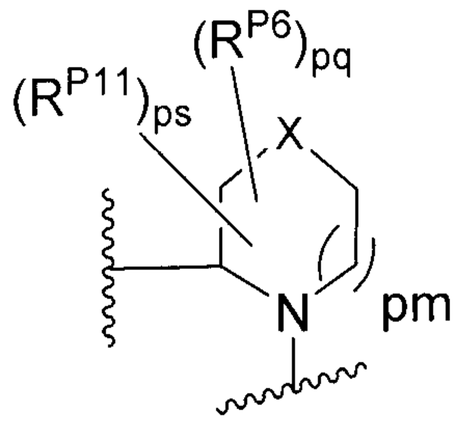
pp are independently 1, 2, or 3;

ps is 1, 2, 3, or 4;

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

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

each P^{14} is independently:



wherein:

the ring is substituted with one or more oxo group;

X is NR^f;

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

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

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

pm is independently 0, 1, or 2;

ps is 1, 2, 3, or 4;

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

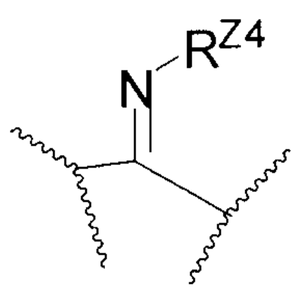
each $-Z^0-$ is $-C(=O)-$ or $-C(=S)-$;

each $-Z^1-$ is independently a bond, or $-C(R^{Z1})_2-$; wherein each R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each $-Z^2-$ is independently saturated or partially unsaturated (C_3-C_8)cycloalkyl that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

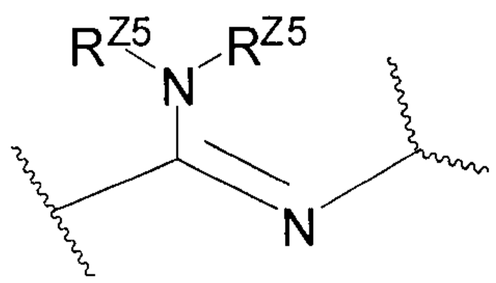
each $-Z^3-$ is independently saturated, partially unsaturated, or aromatic 4-8 membered heterocyclic or heteroaryl ring that is optionally substituted with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^4-$ is independently:



wherein each R^{Z4} is independently H, alkyl, cyano, aryl, or heteroaryl;

each $-Z^5-$ is independently:



wherein each R^{Z5} is independently H, alkyl, cyano, aryl, or heteroaryl; or two R^{Z5}s together with the nitrogen to which they are attached form a 4-8 membered heterocyclic ring that is optionally substituted with one or more oxo and with one or more groups independently selected from R^{A1} and R^{A3};

each $-Z^6-$ is independently $-C(R^{Z1})-$ and is doublebonded to a carbocyclic P; wherein R^{Z1} is independently H, alkyl, haloalkyl, or halo;

each E^0 is independently $-NR^{Ec}R^{Ed}$ wherein

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

each E^1 is independently $-OC(=O)NR^{Ee}R^{Ef}$ wherein each R^{Ee} and R^{Ef} are each independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl,

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

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

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

each V^1 is independently cyanoalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^2 is independently haloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^3 is independently alkyl, which is substituted with one or more oxo, and which is optionally substituted with one or more groups independently selected from cycloalkyl, halo, aryl, alkenyl, and cyano;

each V^4 is independently haloalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^5 is independently alkylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^6 is independently arylsulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^7 is independently heterocyclosulfonylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^8 is independently spirocycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^9 is independently spirocycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{10} is independently fusedbicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{11} is independently fusedbicycliccycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{12} is independently bridged-bicycliccycloalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle,

heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{13} is independently bridged-bicyclic-cycloalkylalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{14} is independently aryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{15} is independently arylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{16} is independently cycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{17} is independently cycloalkylalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{18} is independently heterocyclooxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle,

heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{19} is independently heterocycloalkyloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{20} is independently heteroaryloxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each V^{21} is independently heteroarylalkylalkoxyalkyl, which is optionally substituted with one or more groups independently selected from cycloalkyl, alkoxy, haloalkoxy, cycloalkenyl, heterocycle, heteroaryl, hydroxy, and $NR^{Va}R^{Vb}C(=O)O$-; R^{Va} and R^{Vb} are each independently selected from hydrogen, alkenyl, and alkyl;

each T^1 is independently a spiro, branched or fused bicycloalkyl;

each T^2 is independently aryl;

each T^3 is independently heteroaryl;

each T^4 is independently arylalkyl;

each T^5 is independently haloalkyl;

each T^6 is independently heteroarylalkyl;

each T^7 is independently heterocycle; and

each T^8 is independently heterocyclealkyl.

3. The compound of claim 1, which comprises M^0-W-M^0, M^0-W-M^9, M^9-W-M^0, or M^9-W-M^9, M^{10}-W-M^0, M^0-W-M^{10}, M^{10}-W-M^9, M^9-W-M^{10}, or M^{10}-W-M^{10}.

4. The compound of claim 3, wherein W is W^2.

5. The compound of claim 3, wherein W is W^8.

6. The compound of claim 3, wherein W is W^{15}.

7. The compound of claim 3, wherein W is W^{16}.

8. The compound of claim 3, wherein W is W^{18}.

9. The compound of claim 2, which comprises M^0-A-A-M^0, M^0-A-A-M^9, M^9- A-A-M^0, or M^9-A-A-M^9. M^{10}- A-A-M^0, M^0-A-A-M^{10}, M^{10}- A-A-M^9, M^9- A-A-M^{10}, or M^{10}- A-A-M^{10}

10. The compound of claim 9, wherein –A-A- is $-A^0$-A^5-.

11. The compound of claim 9, wherein –A-A- is $-A^0$-A^{13}-.

12. The compound of claim 9, wherein –A-A- is $-A^{13}$-A^{13}-.

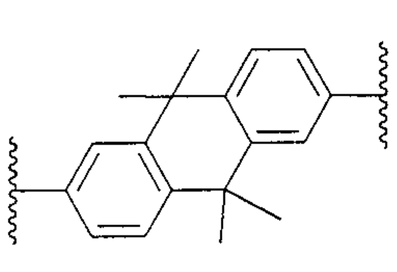
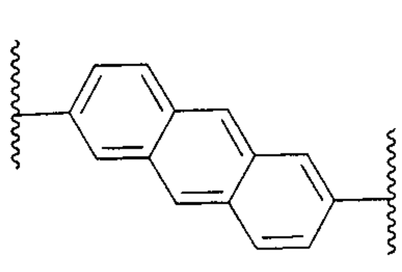
13. The compound of claim 9, wherein –A-A- is $-A^0$-A^{11}-.

14. The compound of claim 9, wherein –A-A- is $-A^{13}$-A^6-.

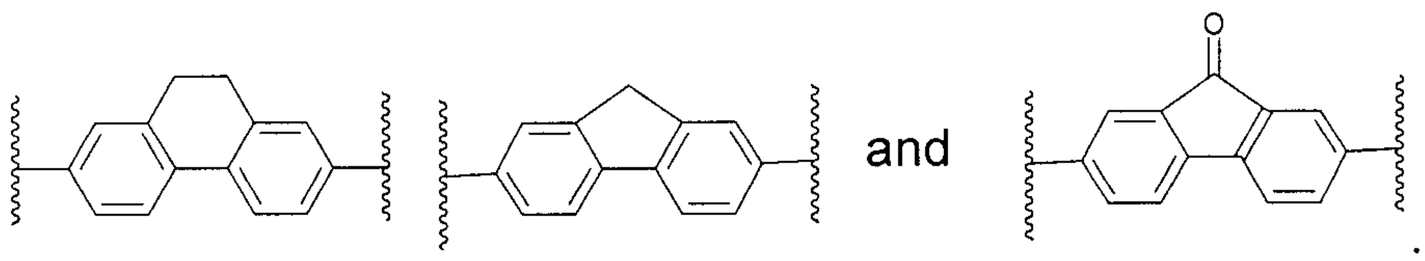
15. The compound of claim 2, wherein W is W^6.

16. The compound of claim 15, wherein each X^A is absent.

17. The compound of claim 15 or 16, wherein W^6 is selected from:


and

.

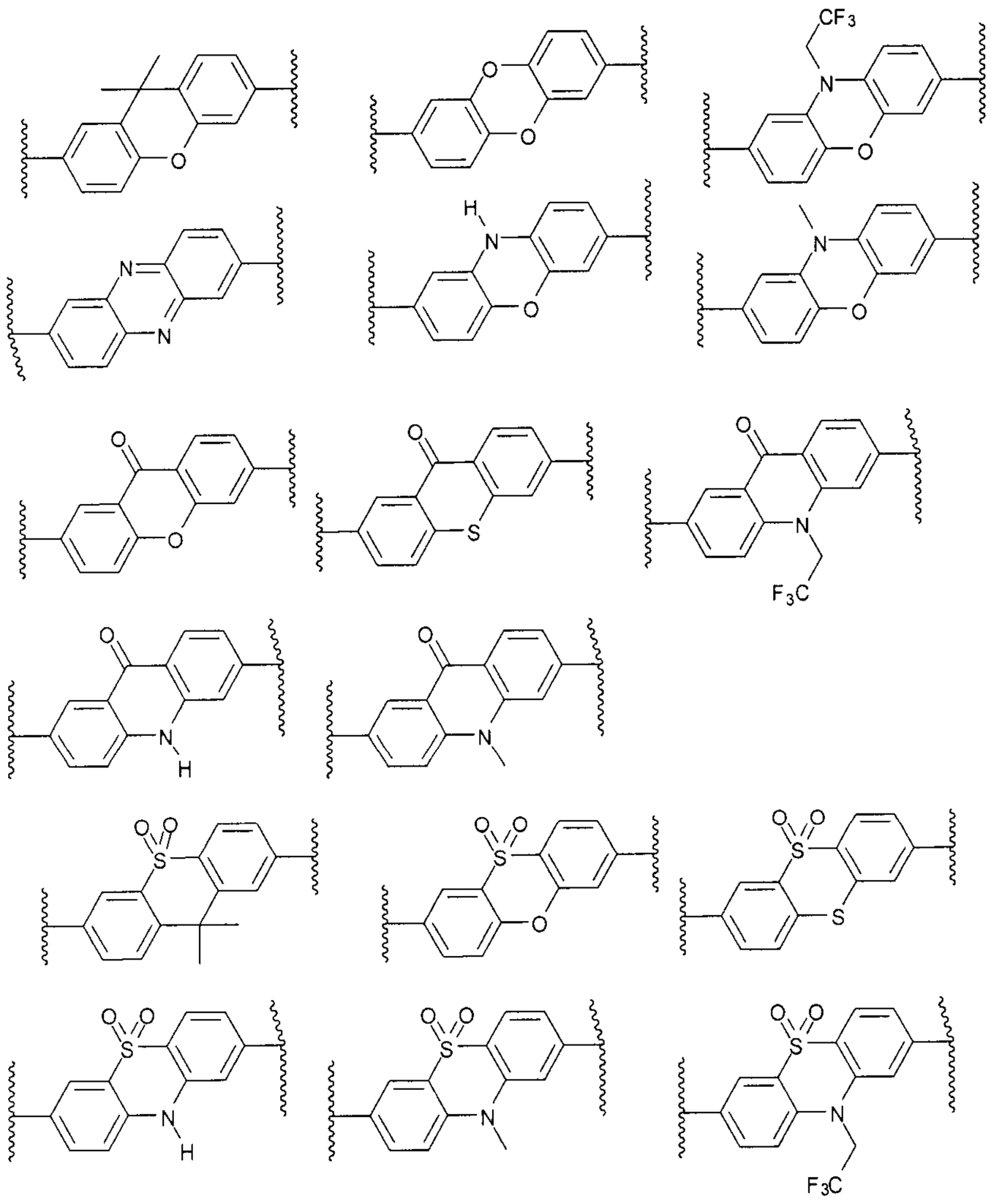
18. The compound of claim 15 or 16, wherein W^6 is selected from:

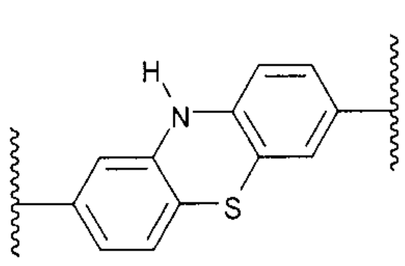
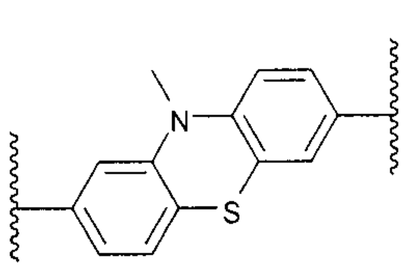


19. The compound of claim 2, wherein W is W^8.

20. The compound of claim 19, wherein each X^A is absent.

21. The compound of claim 19 or 20, wherein W^8 is selected from:

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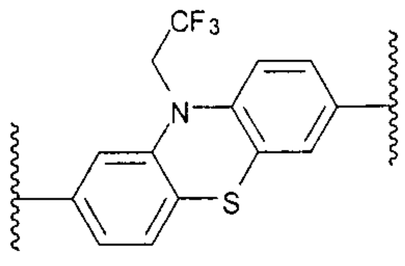
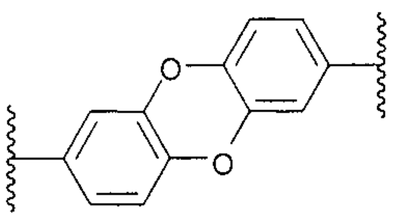
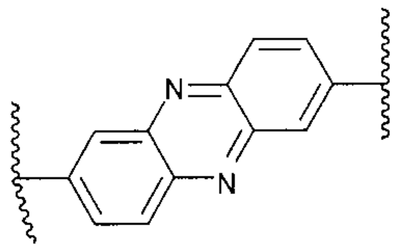
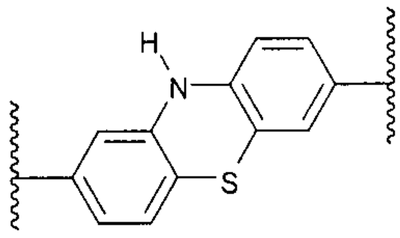
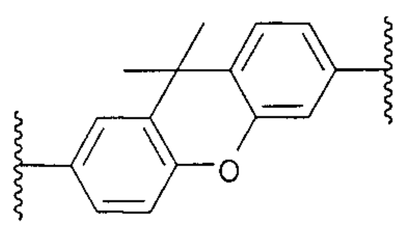
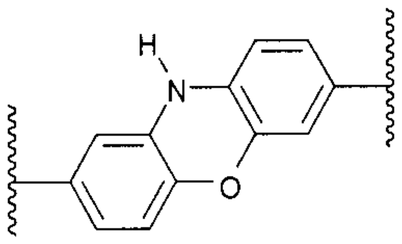
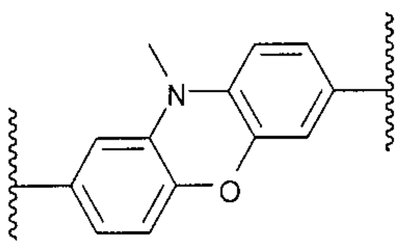
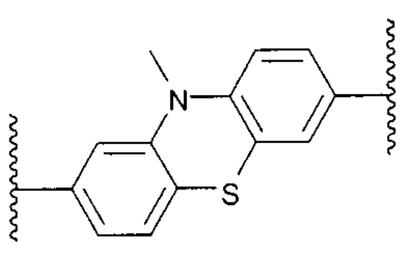
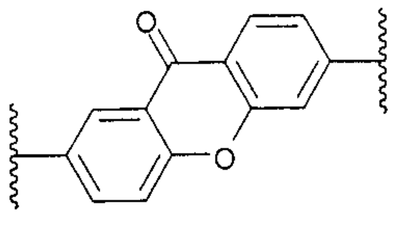
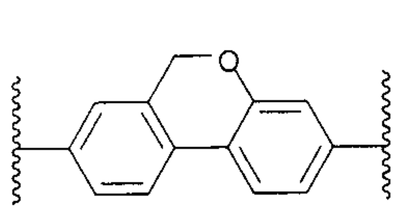
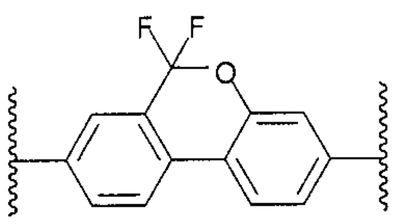
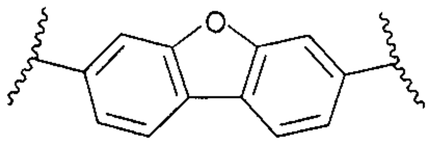
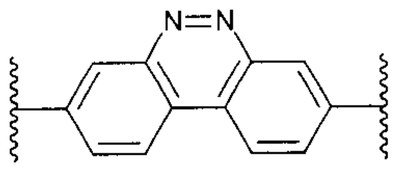


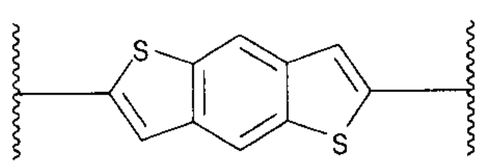
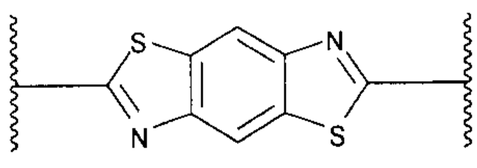
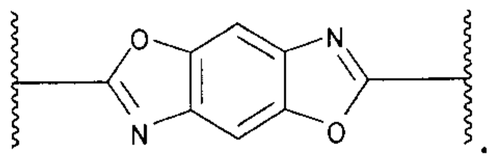
22. The compound of claim 19 or 20, wherein W^8 is selected from:








and


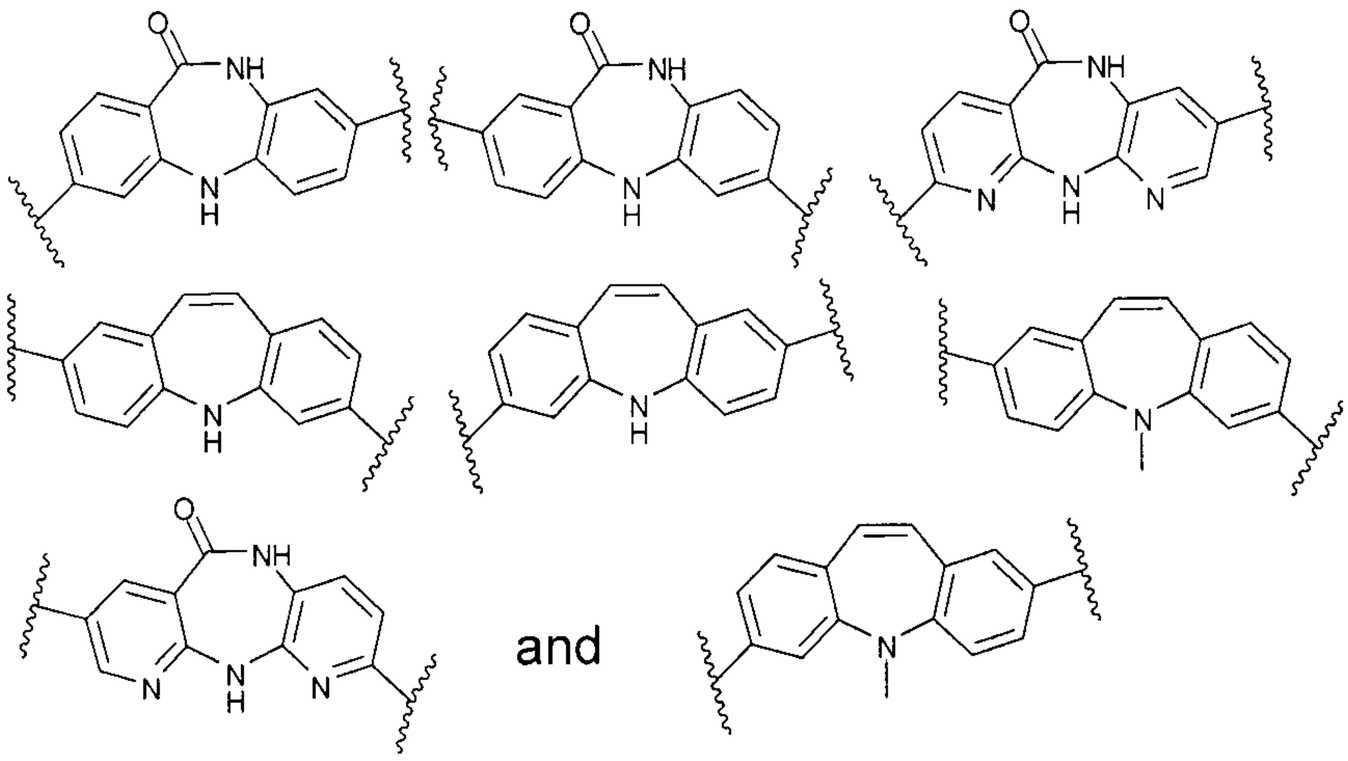
23. The compound of claim 19 or 20, wherein W^8 is selected from:




and


24. The compound of claim 19 or 20, wherein W^8 is selected from:

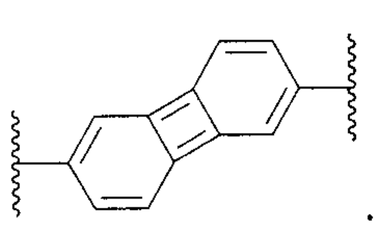


and


25. The compound of claim 19 or 20, wherein W^8 is selected from:



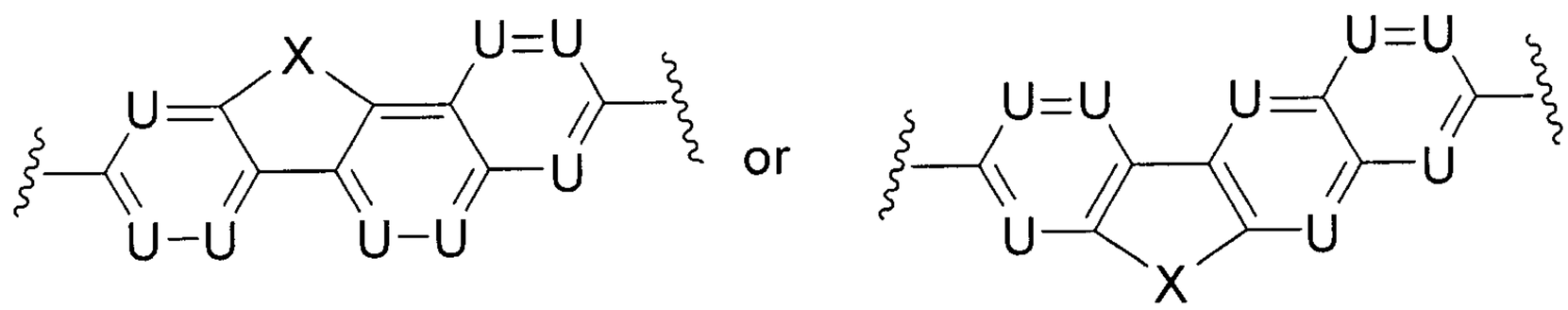
26. The compound of claim 2, wherein W is W^8 that is unsubstituted.

27. The compound of claim 19 or 20, wherein W^{12} is:



28. The compound of claim 2, wherein W is W^{15} or W^{16}.

29. The compound of claim 2, wherein W is a ring system of formula:



wherein :

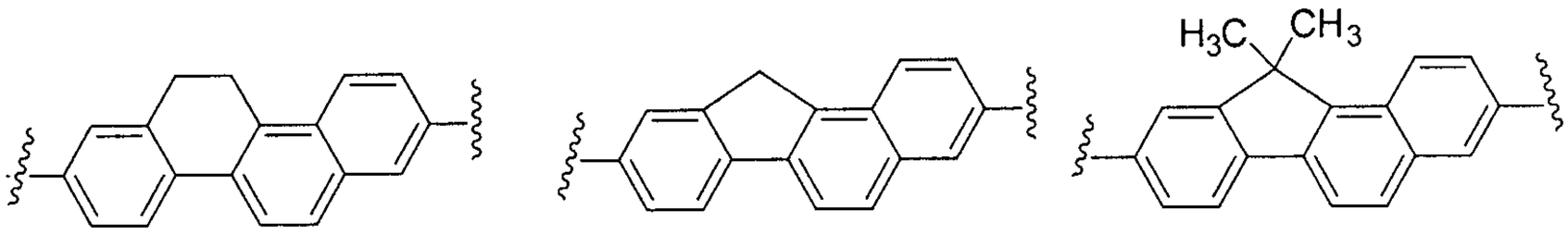
U is CH or N; and

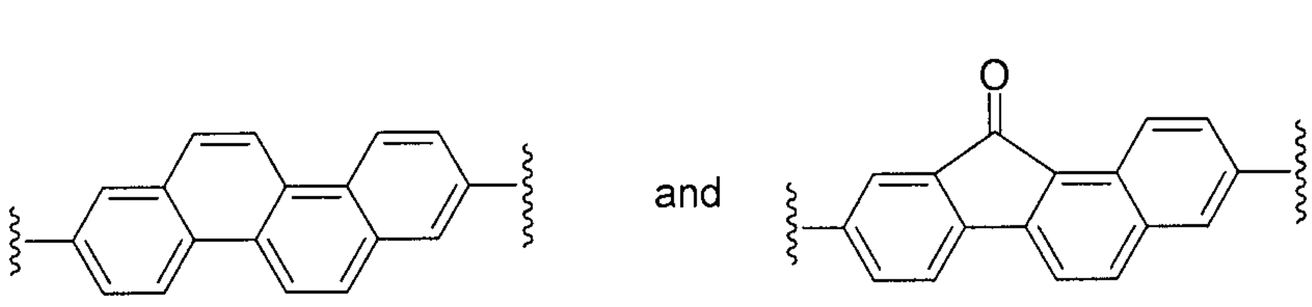
X is $-CH_2-$, $-C(=O)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$;

wherein the ring system is optionally substituted with one or more R^1 or R^3.

30. The compound of claim 2, wherein W is W^{15}.

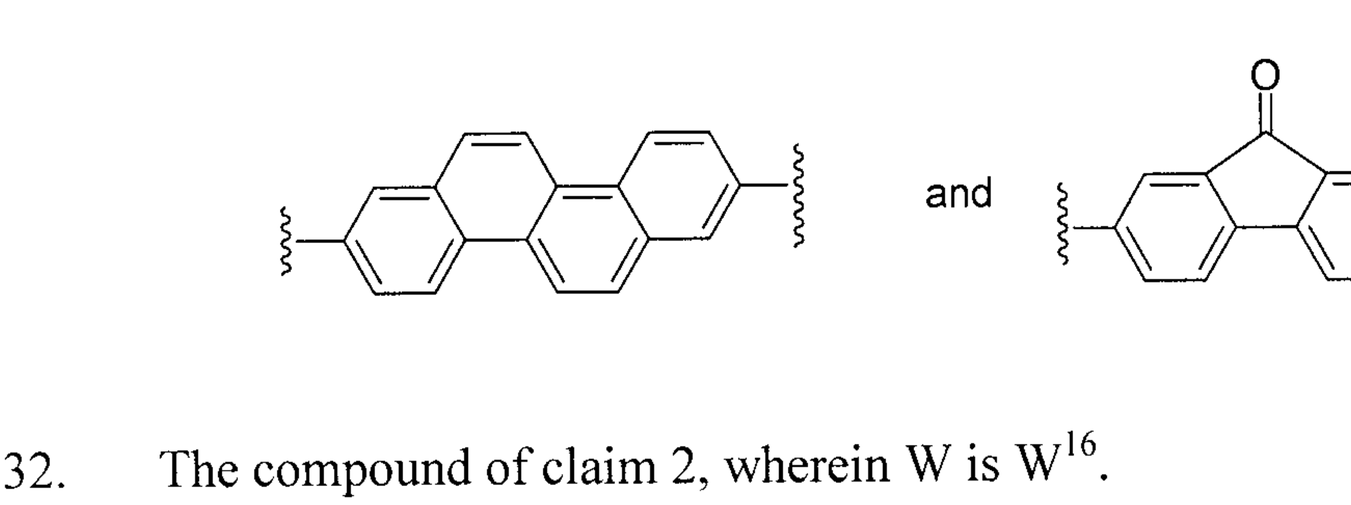
31. The compound of claim 2, wherein W is selected from:





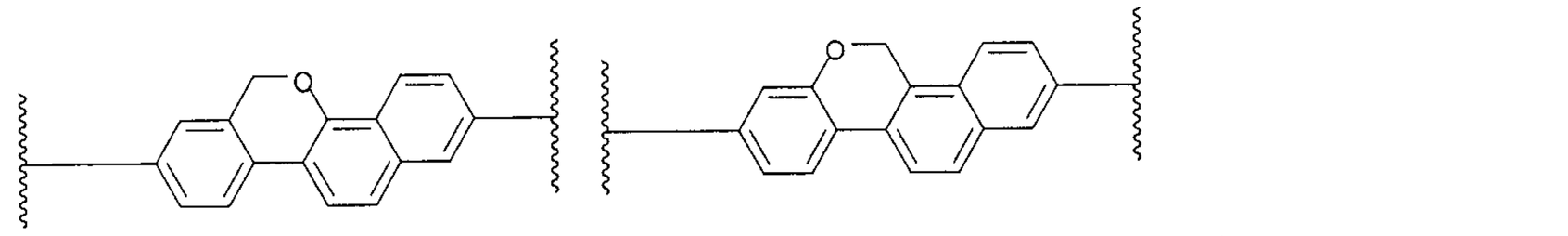
32. The compound of claim 2, wherein W is W^{16}.

33. The compound of claim 2, wherein W is selected from:



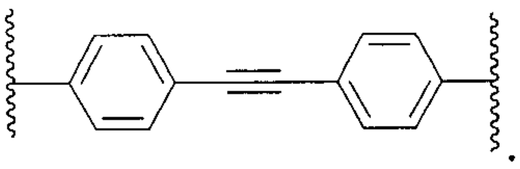
34. The compound of claim 2, wherein W is W^{18}.

35. The compound of claim 2, wherein W is selected from:



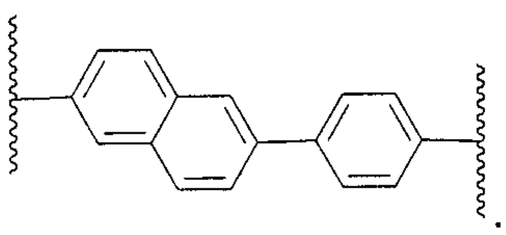
36. The compound of claim 2, wherein one A is A^0 and one A is A^5, wherein one X^A in the A^5 is absent and the other X^A in the A^5 is alkynyl.

37. The compound of claim 2 or 10, wherein $-A^0-A^5-$ has the following structure:



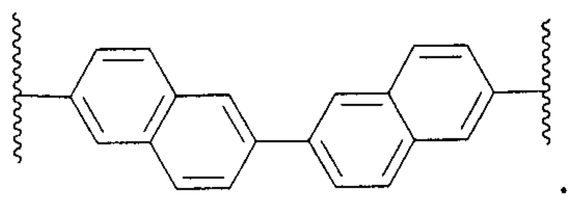
38. The compound of claim 2, wherein one A is A^0 and one A is A^{13}, wherein both X^A in the A^{13} are absent.

39. The compound of claim 2 or 11, wherein $-A^0-A^{13}-$ has the following structure:



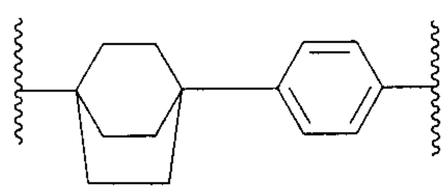
40. The compound of claim 2, that comprises $A^{13}-A^{13}$, wherein all X^A in both A^{13} are absent.

41. The compound of claim 2 or 12, wherein $-A^{13}-A^{13}-$ has the following structure:



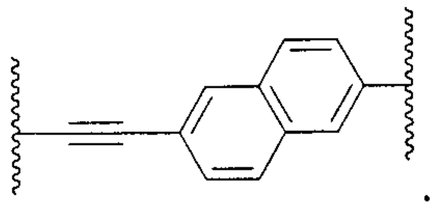
42. The compound of claim 2, that comprises A^0-A^{11} wherein all X^A in both the A^0 and the A^{11}, are absent or alkynyl.

43. The compound of claim 2 or 13, wherein $-A^0-A^{11}-$ has the following structure:



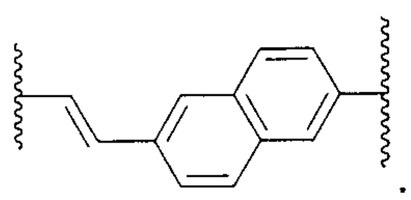
44. The compound of claim 2, that comprises one A^{13} and one A^6 wherein all X^A in the A^{13} are bonds.

45. The compound of claim 2 or 14, wherein $-A^{13}-A^6-$ has the following structure:



46. The compound of claim 2, wherein W is W^2 and within the W^2 one X^A is absent and one X^A is RC=CR.

47. The compound of claim 2, wherein W^2 has the following structure:

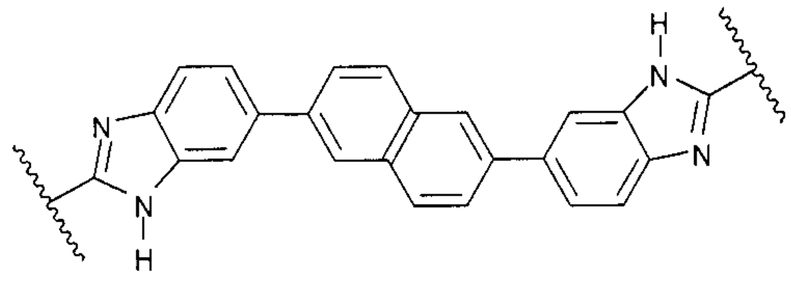


48. The compound of claim 2, wherein W is W^2 and within the W^2 one X^A is absent and one X^A is selected from absent, alkynyl, or RC=CR; and M is selected from M^0 or M^9.

49. The compound of claim 48, wherein M^0 is imidazolyl and M^9 is benzimidazolyl.

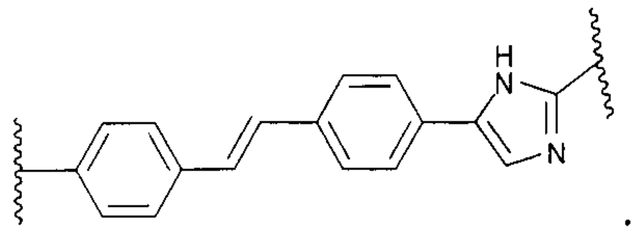
50. The compound of claim 2, that comprises a group M^9-W^2-M^9.

51. The compound of claim 50, wherein the group M^9- W^2-M^9 has the following structure:



52. The compound of claim 2, wherein A is A^0 and L is L^2.

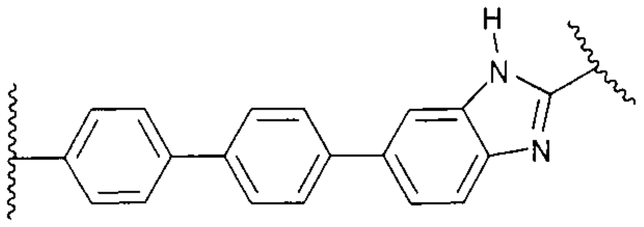
53. The compound of claim 52, wherein A^0-L^2 has the following structure:



54. The compound of claim 2, that comprises two A^0 and one M is M^9.

55. The compound of claim 2, that comprises two A^0 and one M is M^0 and another M is M^9.

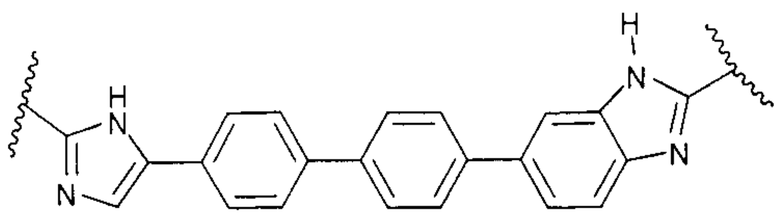
56. The compound of claim 55, wherein A^0-A^0-M^9 has the following structure:



.

57. The compound of claim 2, that comprises M^0-A^0-A^0-M^9.

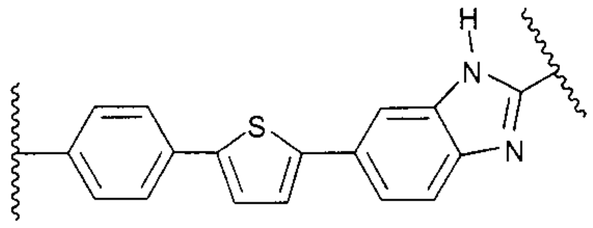
58. The compound of claim 57, wherein M^0-A^0-A^0-M^9 has the following structure:



.

59. The compound of claim 2, that comprises A^0-A^7-M^9.

60. The compound of claim 59, wherein A^0-A^7-M^9 has the following structure:



.

61. The compound of claim 2, that comprises one or two M and each M is M^0.

62. The compound of claim 2, that comprises one or two M and each M is imidazolyl.

63. The compound of claim 2, that comprises one or two M and each M is M^9.

64. The compound of claim 2, that comprises one or two M and each M is benzimidazolyl.

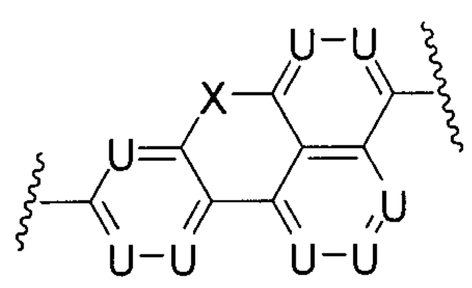
65. The compound of claim 2, that comprises two M wherein one M is M^0 and one M is M^9.

66. The compound of claim 2, that comprises two M wherein one M is imidazolyl and one M is benzimidazolyl.

67. The compound of claim 2, that comprises one or two L wherein each L is L^3.

68. The compound of claim 2, that comprises one or two L wherein each L is benzimidazolyl.

69. The compound of claim 2, wherein W is a ring system of formula:



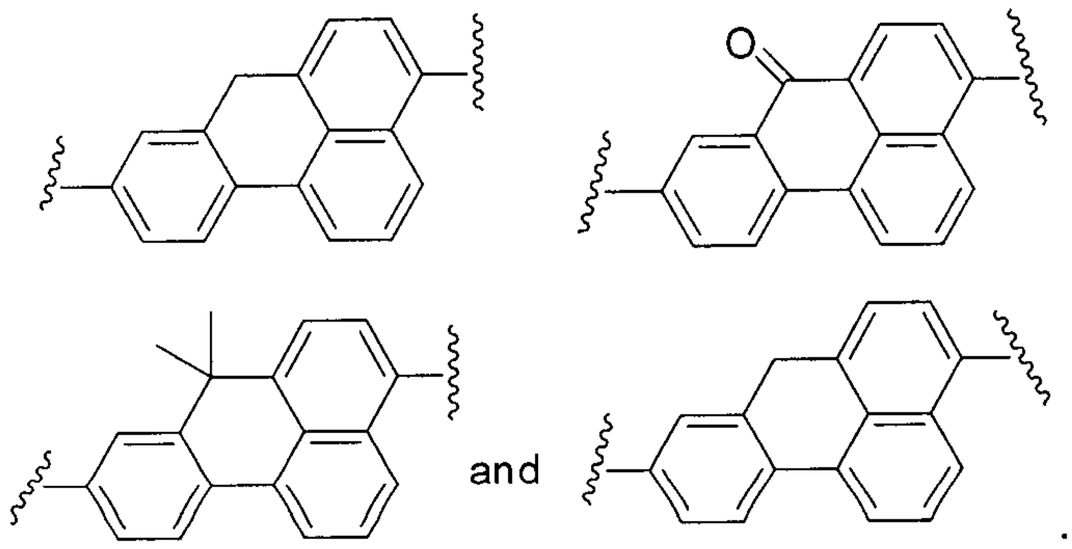
wherein :

U is CH or N; and

X is $-CH_2-$, $-C(=O)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$;

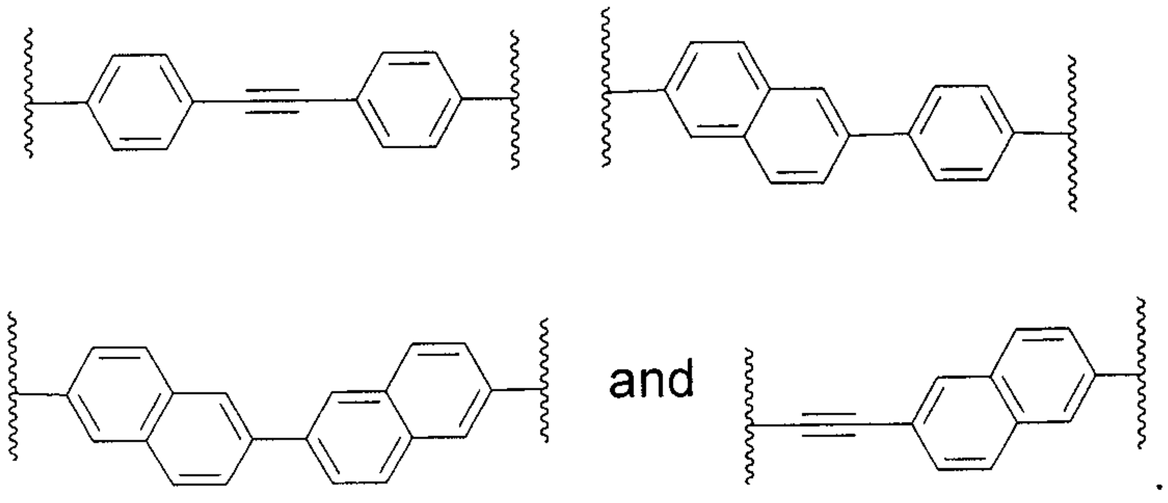
wherein the ring system is optionally substituted with one or more R^1 or R^3.

70. The compound of claim 2, wherein W is selected from:



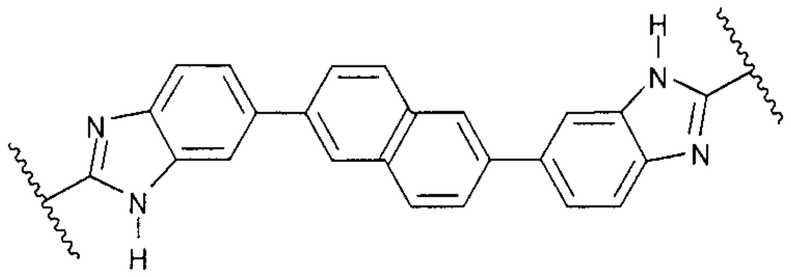
.

71. The compound of claim 2, wherein A-A is selected from:

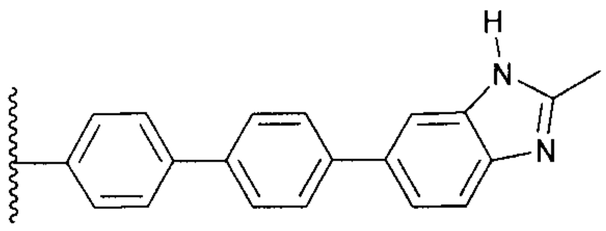


.

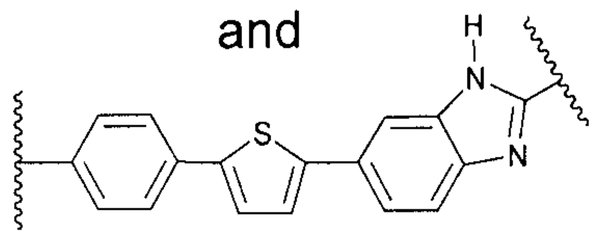
72. The compound of claim 2, wherein M-W-M is:



73. The compound of claim 2, wherein -A-L- is selected from:

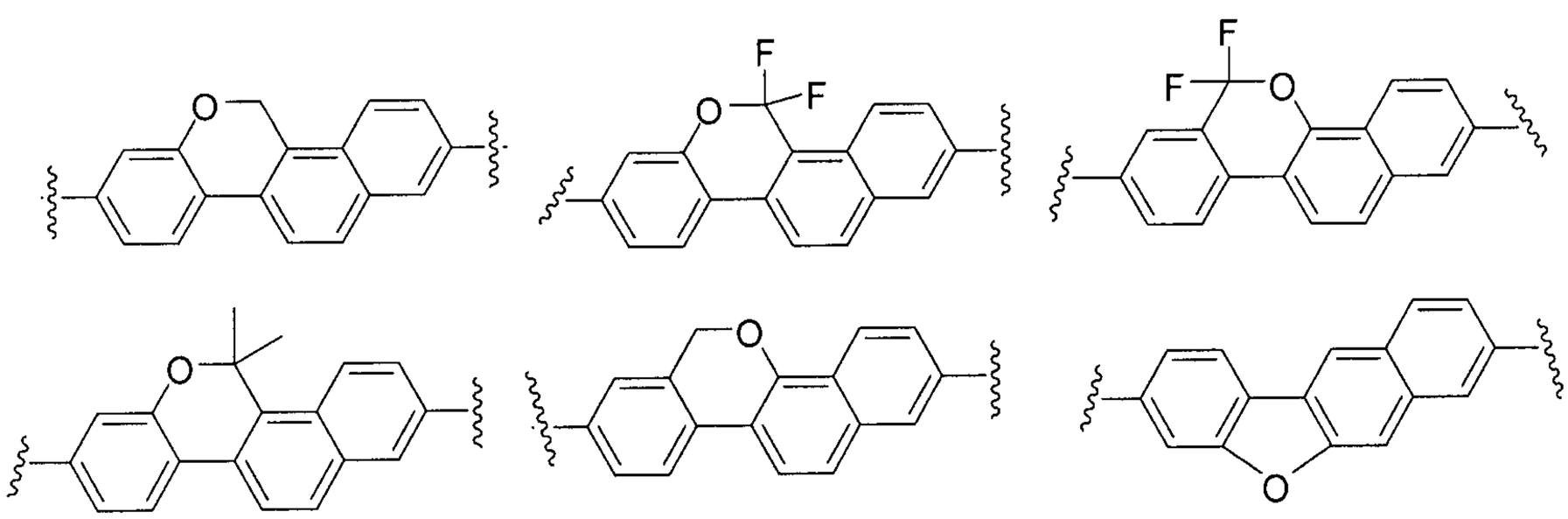


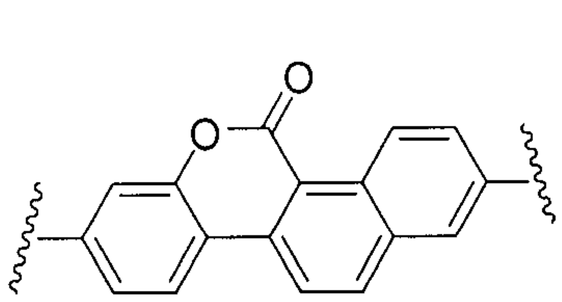
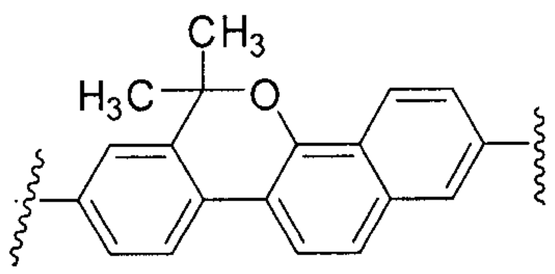
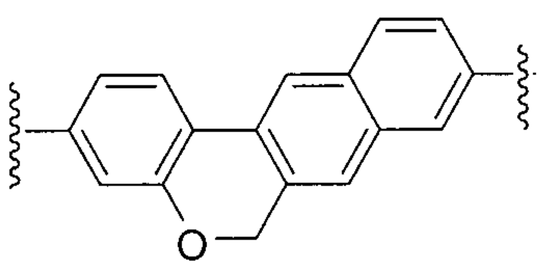
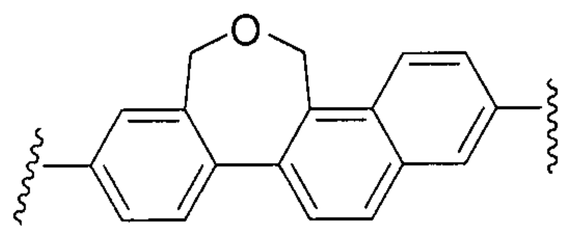
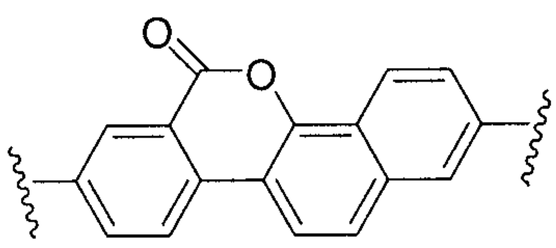
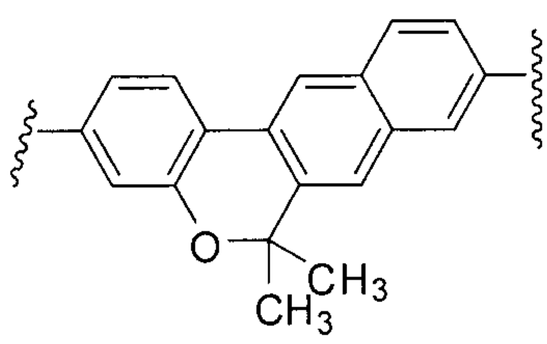
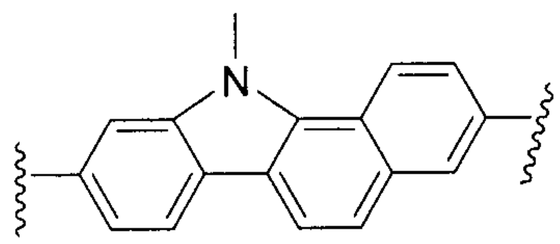
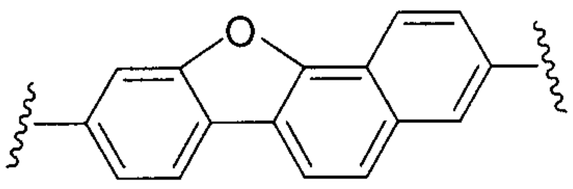
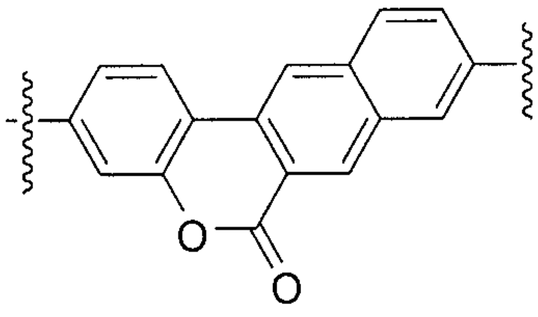
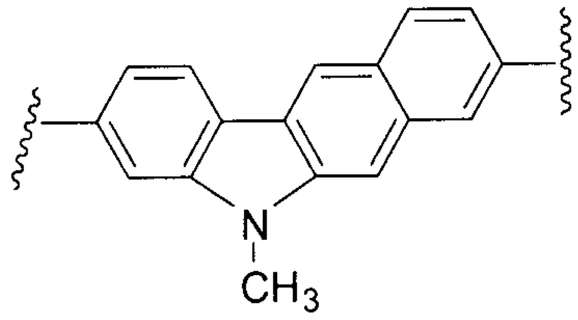
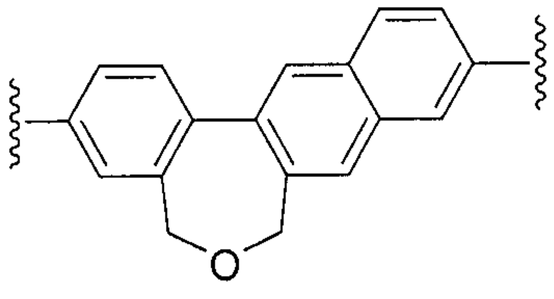
and



74. The compound of claim 2, wherein the compound of formula I has the formula E-V-Z-P-M-A-L-P-Z-V-E .

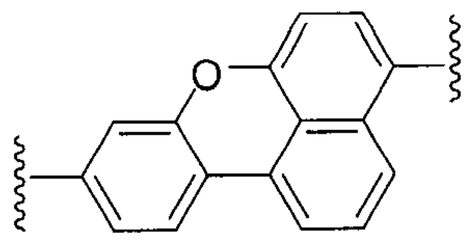
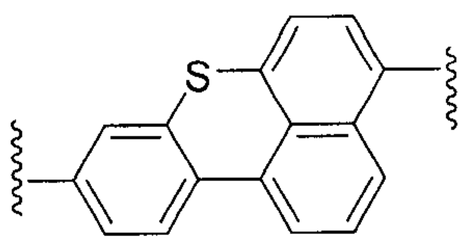
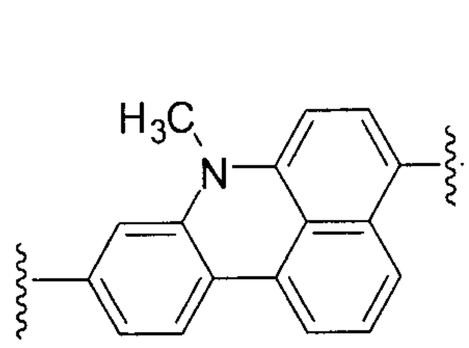
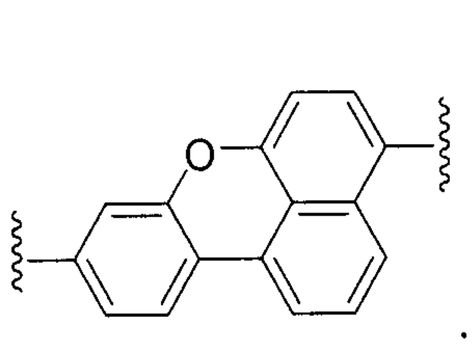
75. The compound of claim 2, wherein W is selected from:













and


76. The compound of claim 2, wherein W is W^{17}.

77. The compound of claim 2, wherein W is selected from:




and


78. The compound of claim 2, wherein the compound of formula I has the formula J-M-W-M-J.

79. The compound of claim 2, wherein the compound of formula I has the formula E-V-Z-P-M-W-M- P-Z-V-E.

80. The compound of claim 2, wherein the compound of formula I has the formula E-V-Z-P-M-W-M-P-Z-V-E.

81. The compound of claim 2, wherein the compound of formula I has the formula E-V-Z-P-M-A-A-M-P-Z-V-E.

82. The compound of claim 2, having the structure E-V-Z-P-M-A-L-P-Z-V-E

83. The compound of claim 2, having the structure E-V-Z-P-M-W-M-P-Z-V-E

84. The compound of claim 83, wherein –M-W-M- is selected from M^0-W-M^0, M^0-W-M^9, M^9-W-M^0, and M^9-W-M^9.

85. The compound of claim 83, wherein –M-W-M- is selected from M^{10}-W-M^0, M^0-W-M^{10}, M^{10}-W-M^9, M^9-W-M^{10}, and M^{10}-W-M^{10}.

86. The compound of claim 81, wherein –M-A-A-M- is selected from M^0-A-A-M^0, M^0-A-A-M^9, M^9-A-A-M^0, and M^9-A-A-M^9.

87. The compound of claim 81, wherein –M-A-A-M- is selected from M^{10}-A-A-M^0, M^0-A-A-M^{10}, M^{10}-A-A-M^9, M^9-A-A-M^{10}, and M^{10}-A-A-M^{10}.

88. The compound of any one of claims 2-87, wherein each E is E^0.

89. The compound of any one of claims 2-87, wherein each E is -NHC(=O)Oalkyl.

90. The compound of any one of claims 2-87, wherein each E is methoxycarbonylamino.

91. The compound of any one of claims 2-90, wherein each V is V^0.

92. The compound of any one of claims 2-90, wherein each V is alkyl.

93. The compound of any one of claims 2-90, wherein each V is isopropyl.

94. The compound of any one of claims 2-90, wherein each V is V^2.

95. The compound of any one of claims 2-90, wherein each V is haloalkyl.

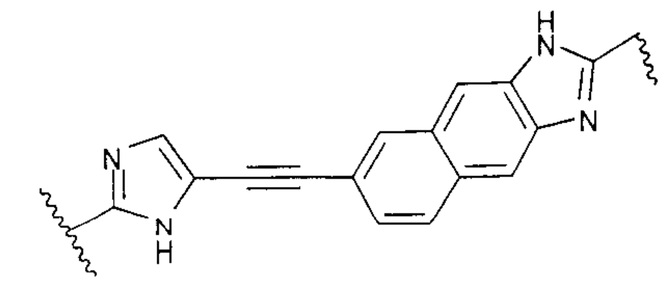
96. The compound of any one of claims 2-95, wherein each Z is Z^0.

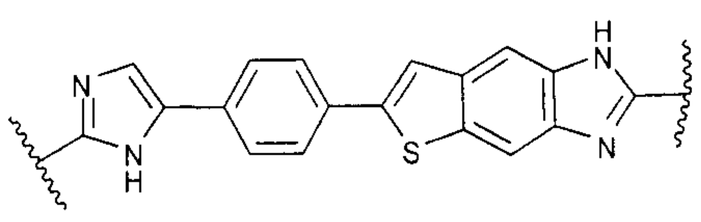
97. The compound of any one of claims 2-95, wherein each Z is –C(=O)-.

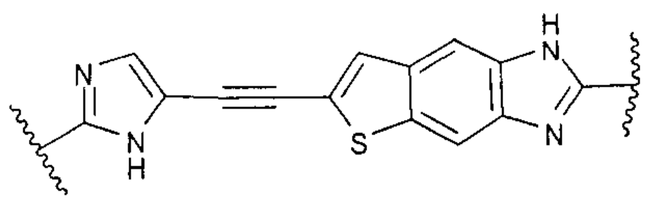
98. The compound of any one of claims 2-97, wherein each M is independently a 5-membered heteroaryl ring.

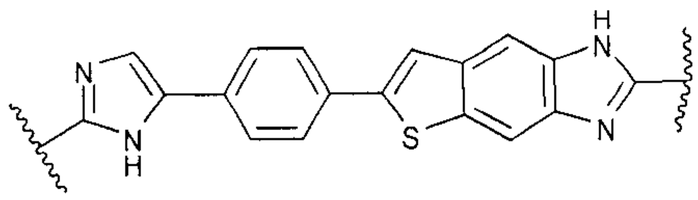
99. The compound of any one of claims 2-97, wherein each M is 2,5-imidazoldiyl.

100. The compound of any one of claims 2 and 88-97 wherein -M-A-L- is selected from:

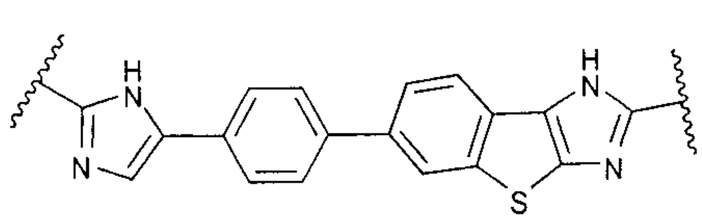








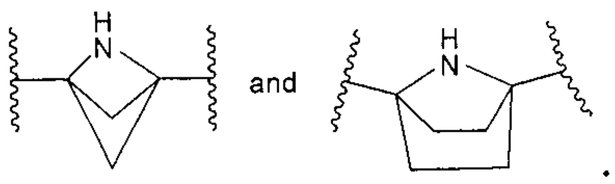
and



.

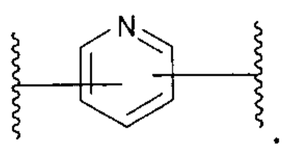
101. The compound of any one of claims 2 and 88-97, wherein M is M^6.

102. The compound of any one of claims 21 and 88-97, wherein M is selected from:



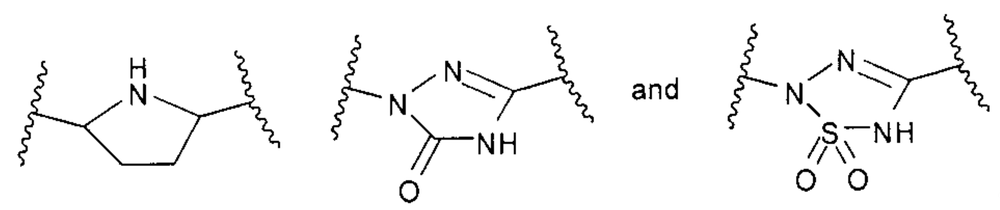
103. The compound of any one of claims 2 and 88-97, wherein M is M^7.

104. The compound of any one of claims 2 and 88-97, wherein M is:



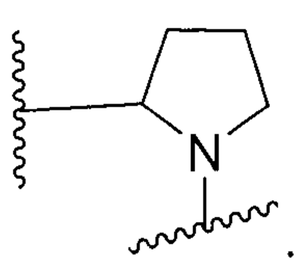
105. The compound of any one of claims 2 and 88-97, wherein M is M^8.

106. The compound of any one of claims 2 and 88-97, wherein M is:

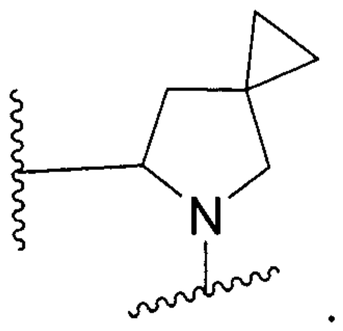


107. The compound of any one of claims 2-106, wherein P is P^0.

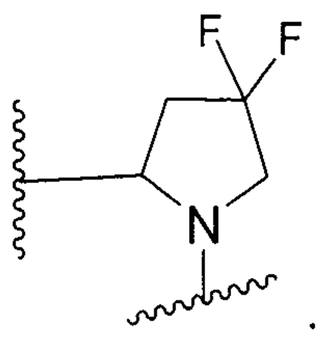
108. The compound of any one of claims 2-106, wherein P is



109. The compound of any one of claims 2-106, wherein P is



110. The compound of any one of claims 2-106, wherein P is



111. The compound of any one of claims 2-106, wherein P is P^1.

112. The compound of any one of claims 2-106, wherein P is P^2.

113. The compound of any one of claims 2-106, wherein P is P^2; and pn is 1.

114. The compound of any one of claims 2-106, wherein P is P^2; pn is 1; and R^{P12} is independently selected from alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, heteroarylsulfonyl, $-C(=O)R^h$, $-C(=O)NR^hR^h$; $-C(=O)OR^h$, and haloalkyl.

115. The compound of any one of claims 2-106, wherein P is P^3; pn is 1 and ps is zero.

116. The compound of any one of claims 2-106, wherein P is P^5.

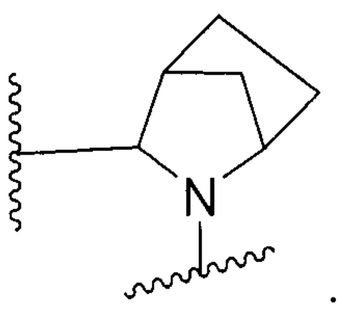
117. The compound of any one of claims 2-106, wherein P is P^5; pn is 1; and Z is O, S, S(=O), $S(=O)_2$, or NR^f.

118. The compound of any one of claims 2-106, wherein P is P^6.

119. The compound of any one of claims 2-106, wherein P is P^6; pn is 1; and Z is O, S, S(=O), $S(=O)_2$, or NR^f.

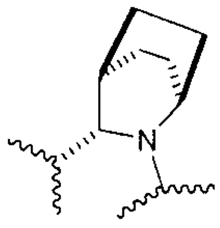
120. The compound of any one of claims 2-106, wherein P is P^7 wherein P^7 is a [2.2.1] or a [2.2.2] ring system.

121. The compound of any one of claims 2-106, wherein P is



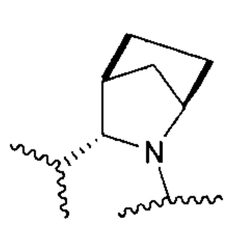
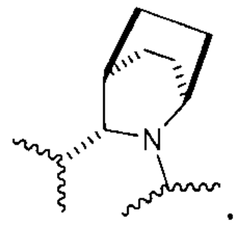
optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

122. The compound of any one of claims 2-106, wherein P is



optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

123. The compound of any one of claims 2-106, wherein P is


or

.

optionally substituted with one or more groups independently selected from R^{P6} and R^{P11}.

124. The compound of any one of claims 2-106, wherein P is P^8.

125. The compound of any one of claims 2-106, wherein P is P^8; and pn is 1.

126. The compound of any one of claims 2-106, wherein P is P^8; pn is 1; and ps is 2.

127. The compound of any one of claims 2-106, wherein P is P^{10}.

128. The compound of any one of claims 2-106, wherein P is P^{10}; pn is 1; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

129. The compound of any one of claims 2-106, wherein P is P^{10}; pn is 1; po is 1; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

130. The compound of any one of claims 2-106, wherein P is P^{10}; pn is 1; po is 1; ps is 0; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

131. The compound of any one of claims 2-106, wherein P is P^{11}.

132. The compound of any one of claims 2-106, wherein P is P^{11}; pn is 1; po is 1; ps is 0; and X is O, S, S(=O), $S(=O)_2$, CHR^{P10}, or $C(R^{P10})_2$.

133. The compound of any one of claims 2-106, wherein P is P^{12}.

134. The compound of any one of claims 2-106, wherein P is P^{12}; pm is 1; and pp is 1.

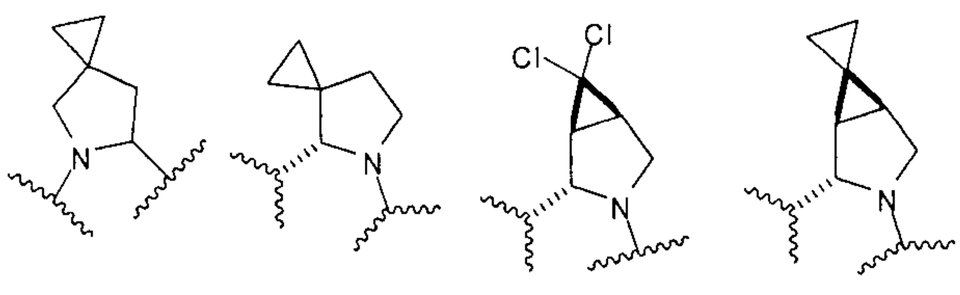
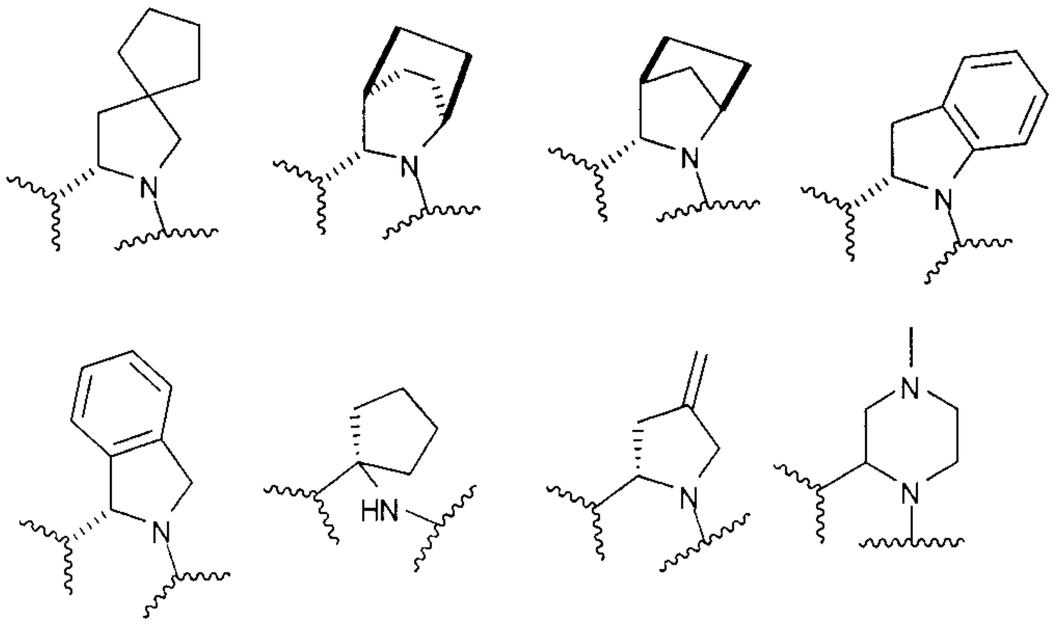
135. The compound of any one of claims 2-106 wherein P is P^{13}.

136. The compound of any one of claims 2-106, wherein P is P^{13}; pm is 1; po is 0; ps is 0; pp is 1; pq is 0; and X is O, S, or $S(=O)_2$.

137. The compound of any one of claims 2-106, wherein P is P^{14}.

138. The compound of any one of claims 2-106, wherein P is P^{14}; pm is 0; and pq is 0.

139. The compound of any one of claims 2-106, wherein P is selected from:

and

.

140. The compound of formula I as described in claim 2, which is a compound having a formula selected from: T-P-Y-P-T; T-P-Y-J; J-Y-J; T-P-Y-P-Z-R9; R9-Z-P-Y-P-Z-R9; J-Y-P-Z-R9; T-P-Y-P-Z-V-E; E-V-Z-P-Y-P-Z-V-E; J-Y-P-Z-V-E; R9-Z-P-Y-P-Z-V-E; T-P-L-L-P-T; T-P-L-L-J; J-L-L-J; T-P-L-L- P-Z-R9; R9-Z-P-L-L-P-Z-R9; J-L-L-P-Z-R9; T-P-L-L-P-Z-V-E; E-V-Z-P-L-L-P-Z-V-E; J-L-L-P-Z-V-E; R9-Z-P-L-L-P-Z-V-E; T-P-M-A-L-P-T; T-P-M-A-L-J; J-M-A-L-J; T-P-M-A-L-P-Z-R9; R9-Z-P-M-A-L-P-Z-R9; J-M-A-L-P-Z-R9; T-P-M-A-L-P-Z-V-E; E-V-Z-P-M-A-L-P-Z-V-E; J-M-A-L-P-Z-V-E; J-M-A-L-P-T; R9-Z-P-M-A-L-J; R9-Z-P-M-A-L-P-T; R9-Z-P-M-A-L-P-Z-V-E; E-V-Z-P-M-A-L-J; E-V-Z-P-M-A-L-P-T; E-V-Z-P-M-A-L-P-Z-R9; T-P-M-A-A-M-P-T; T-P-M-A-A-M-J; J-M-A-A-M-J; T-P-M-A-A-M-P-Z-R9; R9-Z-P-M-A-A-M-P-Z-R9; J-M-A-A-M-P-Z-R9; T-P-M-A-A-M-P-Z-V-E; E-V-Z-P-M-A-A-M-P-Z-V-E; J-M-A-A-M-P-Z-V-E; R9-Z-P-M-A-A-M-P-Z-V-E; T-P-M-W-M-P-T; T-P-M-W-M-J; J-M-W-M-J; T-P-M-W-M-P-Z-R9; R9-Z-P-M-W-M-P-Z-R9; J-M-W-M-P-Z-R9; T-P-M-W-M-P-Z-V-E; E-V-Z-P-M-W-M-P-Z-V-E; J-M-

W-M-P-Z-V-E; R9-Z-P-M-W-M-P-Z-V-E; T-P-M-M-P-T; T-P-M-M-J; J-M-M-J; T-P-M-M-P-Z-R9; R9-Z-P-M-M-P-Z-R9; J-M-M-P-Z-R9; T-P-M-M-P-Z-V-E; E-V-Z-P-M-M-P-Z-V-E; J-M-M-P-Z-V-E; R9-Z-P-M-M-P-Z-V-E; or a pharmaceutically acceptable salt thereof.

141. The compound of any one of claims 1-140, wherein the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), or (Ie).

142. The compound of any one of claims 1-141, which is a prodrug or a pharmaceutically acceptable salt thereof.

143. A pharmaceutical composition comprising the compound as described in any one of claims 1-141 or a pharmaceutically acceptable salt, or prodrug thereof; and at least one pharmaceutically acceptable carrier.

144. The pharmaceutical composition according to claim 143 for use in treating disorders associated with HCV.

145. The pharmaceutical composition of claim 143, further comprising at least one additional therapeutic agent.

146. The pharmaceutical composition of claim 145, wherein said additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

147. The pharmaceutical composition according to claim 146, further comprising a nucleoside analogue.

148. The pharmaceutical composition according to claim 147, further comprising an interferon or pegylated interferon.

149. The pharmaceutical composition according to claim 148, wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, a L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated interferon.

150. A compound as described in any one of claims 1-141 or a pharmaceutically acceptable salt, or prodrug thereof for use in medical therapy.

151. Use of a compound as described in any one of claims 1-141 or a pharmaceutically acceptable salt, or prodrug thereof for preparing a medicament for treating hepatitis C or a hepatitis C associated disorder in an animal.

152. Use of a compound as described in any one of claims 1-141 or a pharmaceutically acceptable salt, or prodrug thereof for treating hepatitis C or a hepatitis C associated disorder in an animal.

153. A compound as described in any of claims 1-141 or a pharmaceutically acceptable salt, or prodrug thereof for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.