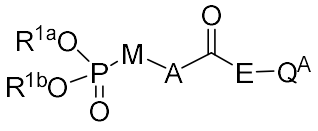
CLAIMS

1. A compound of Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen C_1-C_4 alkyl, aralkyl, and -$CH_2OC(=O)R^{1e}$;

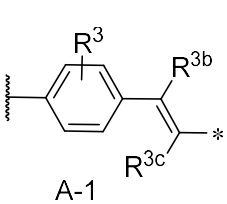
R^{1e} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy;

M is selected from the group consisting of -O- and -$C(R^{2a})(R^{2b})$-;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen and fluoro; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group;

A is selected from the group consisting of:



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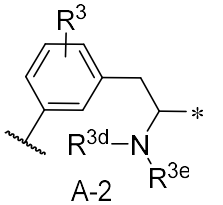

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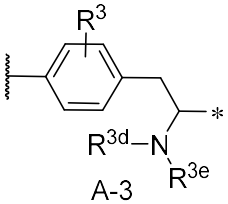

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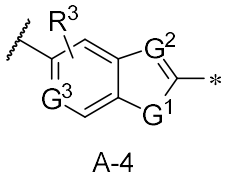

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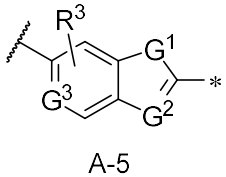

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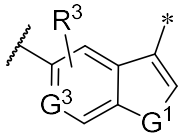

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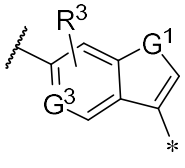

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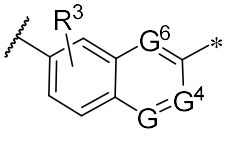

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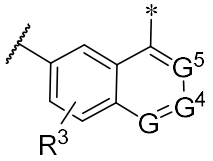

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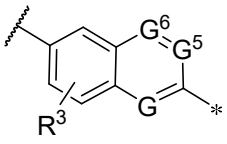

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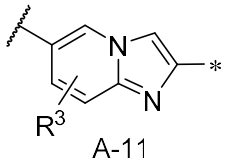

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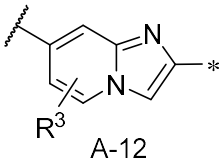

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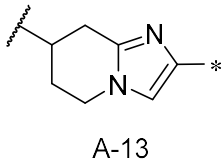

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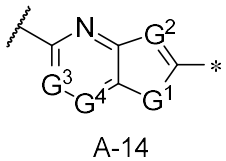

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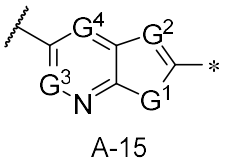

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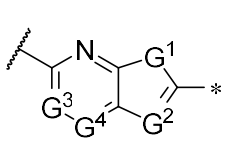

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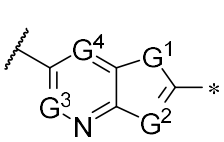

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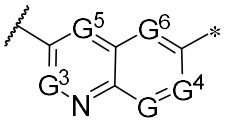

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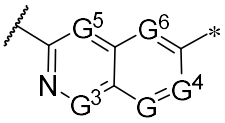

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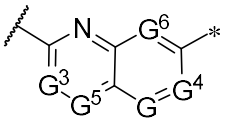

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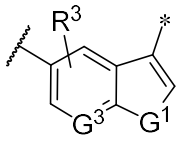

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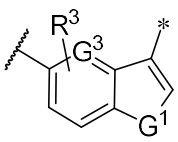


A-22 ;

wherein the bond designated with an "*" is attached to -C(=O)-E-Q^A;

G^1 is selected from the group consisting of -O-, -S-, and -NR^{17}-;

G^2 is selected from the group consisting of -N= and -CR^{18a}=;

G^3 is selected from the group consisting of -N= and -CR^{18b}=;

G^4 is selected from the group consisting of -N= and -CR^{18c}=;

G^5 is selected from the group consisting of -N= and -CR^{18d}=;

G^6 is selected from the group consisting of -N= and -CR^{18e}=;

G is selected from the group consisting of -N= and -CR^{18f}=;

R^3 is selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -C(=O)R^{3a}, and aralkyl;

R^{3a} is C_1-C_4 alkyl;

R^{3b} and R^{3c} are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{3d} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^{3f};

R^{3e} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

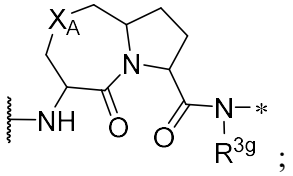
R^{3f} is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_6 alkoxy, and aralkyloxy;

R^{17} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, aralkyl, and -C(=O)R^{17a};

R^{17a} is C_1-C_4 alkyl;

R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, and R^{18f} are each independently selected from the group consisting of hydrogen, halo, and C_1-C_4 alkyl,

E is:



wherein the bond designated with an "*" is attached to Q^A;

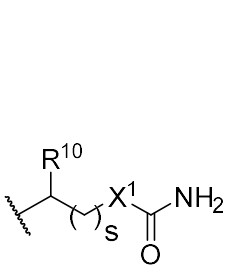
R^{3g} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

X_A is selected from the group consisting of -N(R^8)CH_2-, -CH_2N(R^8)-, and -CH_2CH_2-;

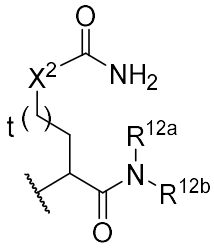
R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, -C(=O)R^9, and -L-B;

R^9 is selected from the group consisting of C_1-C_6 alkyl, amino, C_1-C_6 alkoxy, aralkyloxy, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, optionally substituted aryl, optionally substituted 5- to 10-membered heteroaryl, aralkyl, and (heteroaryl)alkyl;

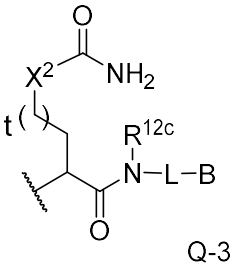
Q^A is selected from the group consisting of:



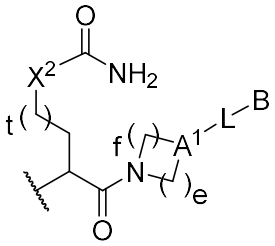
Q-1



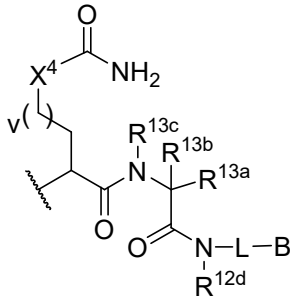
Q-2



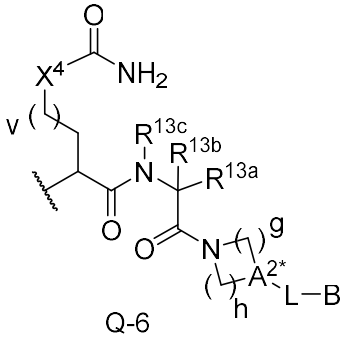
Q-3



Q-4

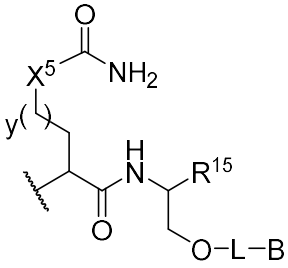


Q-5



Q-6

and



Q-7 ;

X^1 is selected from the group consisting of -CH_2-, -O-, and -N(R^{11a})-; or

X^1 is absent;

R^{10} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, optionally substituted aralkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, and optionally substituted aryl;

R^{11a} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

s is 1, 2, 3, or 4;

X^2 is selected from the group consisting of -CH_2-, -O-, and -N(R^{11b})-; or

X^2 is absent;

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

R^{11b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{12a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, optionally substituted C_2-C_6 alkynyl, aralkyl, (heteroaryl)alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, optionally substituted aryl, (amido)(aryl)alkyl, (amino)(aryl)alkyl, (amino)(heteroaryl)alkyl, and (cycloalkyl)alkyl;

R^{12b} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, optionally substituted aryl, and aralkyl; or

R^{12a} and R^{12b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered optionally substituted heterocyclo,

R^{12c} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

A^1 is selected from the group consisting of -C(R^{14a})- and -N-;

R^{14a} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

e is 1, 2, or 3;

f is 1, 2, or 3;

X^4 is selected from the group consisting of -CH_2-, -O-, and -N(R^{11d})-; or

X^4 is absent;

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

R^{11d} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{12d} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

R^{13a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted aryl, aralkyl, (heteroaryl)alkyl, (cycloalkyl)alkyl, and optionally substituted 5- to 9-membered heteroaryl;

R^{13b} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{13c} is selected from the group consisting of hydrogen and C_1-C_4 alkyl; or

R^{13a} and R^{13b} taken together form a C_3-C_8 optionally substituted cycloalkyl or C_4-C_9 optionally substituted heterocyclo; or

R^{13b} and R^{13c} taken together form a 4- to 9-membered optionally substituted heterocyclo;

A^{2*} is selected from the group consisting of -C(R^{14b})- and -N-;

R^{14b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

g is 1, 2, or 3;

h is 1, 2, or 3;

X^5 is selected from the group consisting of -CH_2-, -O-, and -N(R^{11e})-; or

X^5 is absent;

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

R^{11e} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{15} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, optionally substituted aryl, and optionally substituted 5- to 9-membered heteroaryl;

L is -J^1-Y^1-J^2-Y^2-J^3-Z-;

J^1 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^1 is absent;

Y^1 is selected from the group consisting of -(CH_2)$_m$-, -C≡C-, -CH=CH-, -N(R^{16a})-, -C(=O)-, -S(=O)$_2$-, -C(=O)O-, -OC(=O)-, -C(=O)N(R^{16b})-, and -N(R^{16b})C(=O)-;

m is 0, 1, 2, or 3;

R^{16a} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

R^{16b} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

J^2 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^2 is absent;

Y^2 is selected from the group consisting of -(CH_2)$_n$-, -C≡C-, -CH=CH-, -N($R^{16a'}$)-, -C(=O)-, -S(=O)$_2$-, -C(=O)O-, -OC(=O)-, -C(=O)N($R^{16b'}$), and -($R^{16b'}$)C(=O)N-;

n is 0, 1, 2, 3, 4, 5, or 6;

$R^{16a'}$ is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

$R^{16b'}$ is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

J^3 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^3 is absent;

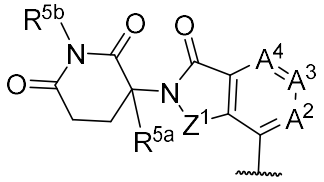
Z is selected from the group consisting of -$(CH_2)_d$-, -C≡C-, -CH=CH-, -C(=O)-, -O-, -S-, -$N(R^{16c})$-, -$C(=O)N(R^{16d})$-, -$N(R^{16d})C(=O)$-, -$N(R^{16e})C(=O)CH_2O$-, and -$N(R^{16f})C(=O)CH_2N(R^{16g})$-;

d is 0, 1, 2, or 3;

R^{16c}, R^{16d}, R^{16e}, R^{16f}, and R^{16g} are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

wherein Z is attached to B;

B is selected from the group consisting of: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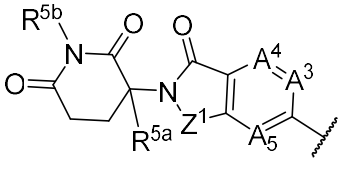
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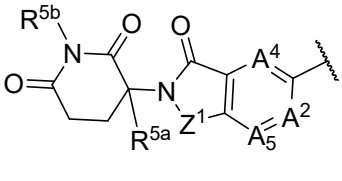
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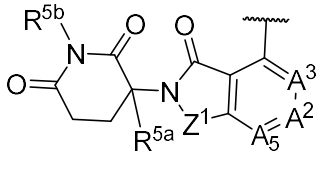
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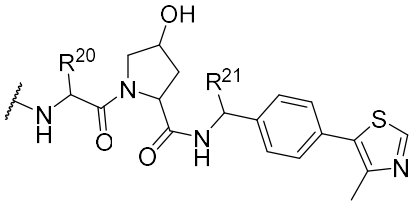
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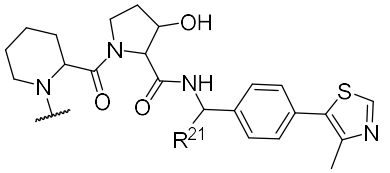
B-6

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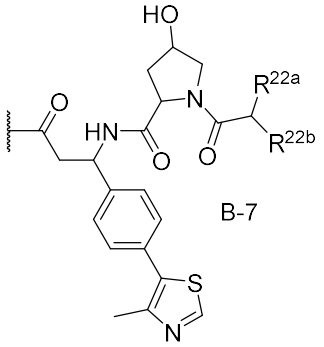
B-7

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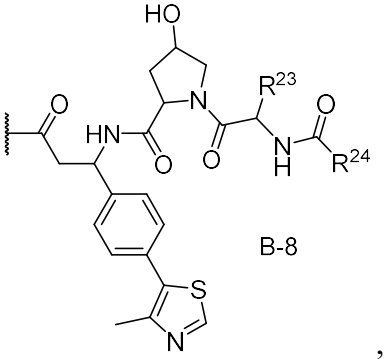
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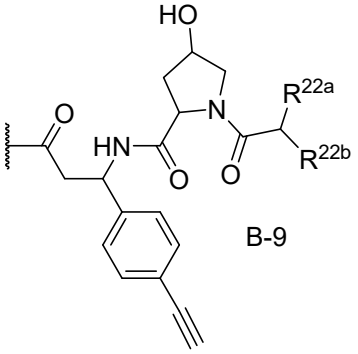
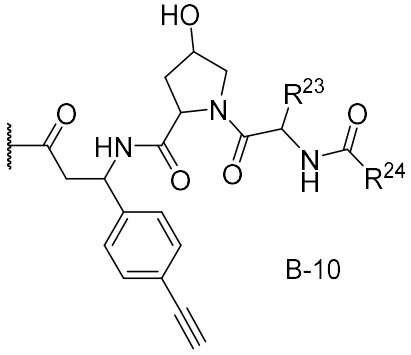

B-9

and


B-10

;

A_5 is selected from the group consisting of -C(R^{19a})= and –N=;

A^2 is selected from the group consisting of -C(R^{19b})= and –N=;

A^3 is selected from the group consisting of -C(R^{19c})= and –N=;

A^4 is selected from the group consisting of -C(R^{19d})= and –N=;

Z^1 is selected from the group consisting of -CH_2 and -C(=O)-;

R^{5a} is selected from the group consisting of hydrogen, methyl, and fluoro;

R^{5b} is selected from the group consisting of hydrogen and methyl;

R^{19a}, R^{19b}, R^{19c}, and R^{19d} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

R^{20} is C_1-C_6 alkyl;

R^{21} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{22a} is selected from the group consisting of C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl;

R^{22b} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{23} is selected from the group consisting of C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl; and

R^{24} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl,

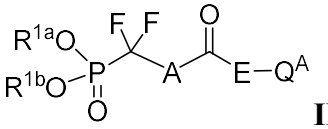
with the provisos:

(1) when X_A is -CH_2CH_2-, then Q^A is selected from the group consisting of Q-3, Q-4, Q-5, Q-6, and Q-7;

(2) when X_A is -N(R^8)CH_2- or -CH_2N(R^8)-, and R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9, then Q^A is selected from the group consisting of Q-3, Q-4, Q-5, Q-6, and Q-7;

(3) when X_A is -N(R^8)CH_2- or -CH_2N(R^8)-, and R^8 is -L-B, then Q^A is selected from the group consisting of Q-1 and Q-2.

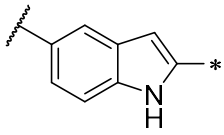
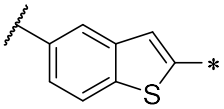
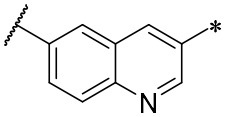
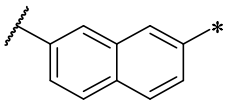
2. The compound of claim 1, wherein the compound of Formula I is a compound of Formula **II**:



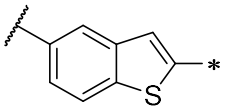
II,

or a pharmaceutically acceptable salt or solvate thereof.

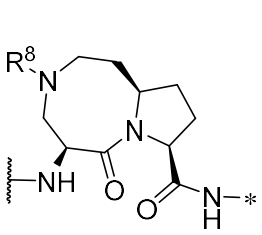
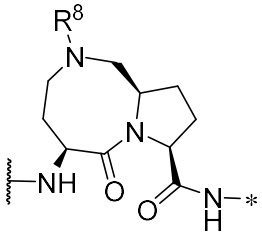
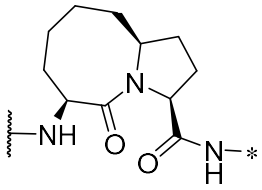
3. The compound of claims 1 or 2, wherein A is selected from the group consisting of:

 ,  ,  , and  .

4. The compound of claim 3, wherein A is:

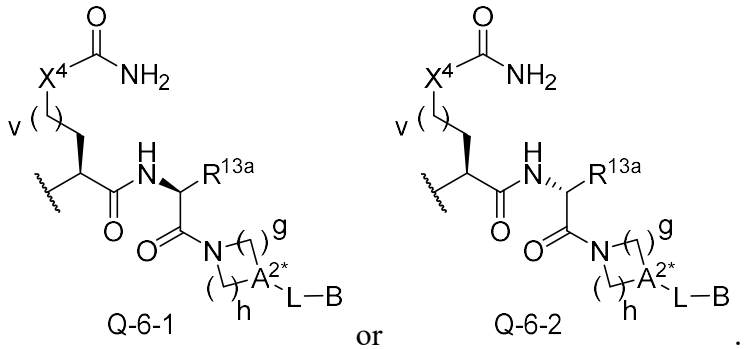
 .

5. The compound of any one of claims 1-4, wherein E is:


E-1-1
, 
E-2-1
, or 
E-3-1
.

6. The compound of any one of claims 1-5, wherein R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9, and Q^A is Q-3, Q-4, Q-5, or Q-6.

7. The compound of claim 6, wherein Q-6 is Q-6-1 or Q-6-2:



Q-6-1 or Q-6-2 .

8. The compound of claim 7, wherein X^4 is $-CH_2-$ and v is 0.

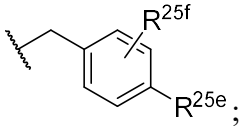
9. The compound of claim 7 or 8, wherein g and h are 2.

10. The compound of any one of claims 7-9, wherein A^{2*} is -C(H)-,.

11. The compound of any one of claims 7-10, wherein R^{13a} is selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, aralkyl, and optionally substituted phenyl.

12 The compound of claim 11, wherein:

R^{13a} is:



;

R^{25e} is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, $-C(=O)NR^{50c}R^{50d}$, C_1-C_6 alkylsulfonyl, arylsulfonyl, $-N(R^{56c})S(=O)_2R^{56d}$, and $-S(=O)_2R^{58}$;

R^{25f} is selected from the group consisting of hydrogen and halo;

R^{50c} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 5- or 6-membered heterocyclo, optionally substituted phenyl, optionally substituted 5- to 9-membered heteroaryl, aralkyl, (heteroaryl)C_1-C_4 alkyl, and (heterocyclo)C_1-C_4 alkyl;

R^{50d} is selected from thre group consisting of hydrogen and C_1-C_3 alkyl; or

R^{50c} and R^{50d} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group;

R^{56c} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{56d} is selected from the group consisting of optionally substituted C_3-C_6 cycloalkyl, optionally substituted phenyl, and optionally substituted 5- to 9-membered heteroaryl; and

R^{58} is optionally substituted C_3-C_6 cycloalkyl.

13. The compound of any one of claims 1-5, wherein R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9, and Q^A is Q-7.

14. The compound of any one of claims 1-13, wherein L is -Y^1-Y^2-Z-.

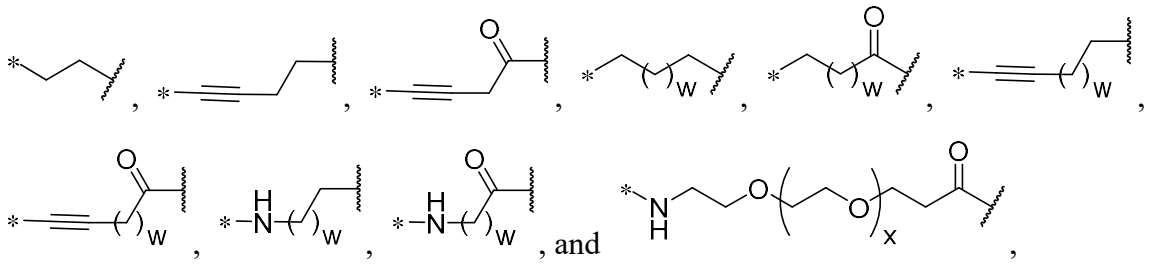
15. The compound of claim 14, wherein Y^1 is selected from the group consisting of -$(CH_2)_m$- and -C(=O)-; m is 1, 2, or 3; Y^2 is -$(CH_2)_n$-; n is 1, 2, 3, 4, 5, or 6; and Z is selected from the group consisting of -(CH_2)-, -C≡C-, and -N(H)-.

16. The compound of claim 15, wherein Z is -C≡C-.

17. The compound of any one of claims 1-5, and 16, wherein:

R^8 is -L-B;

L is selected from the group consisting of:



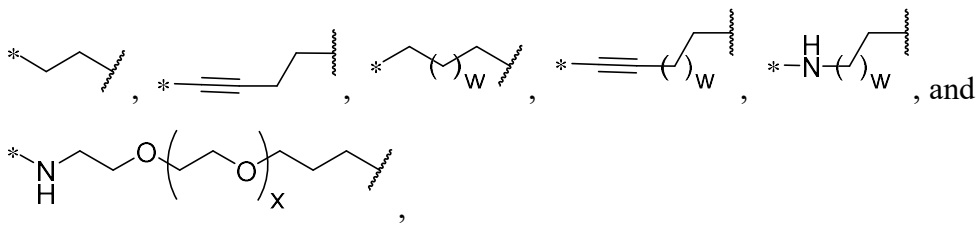
wherein the bond designated with an "*" is attached to B;

w is 1, 2, 3, 4, 5, 6, 7, or 8; and

x is 1, 2, 3, 4, 5, or 6.

18. The compound of any one of claims 1-5, 6-13, and 16, wherein:

L is selected from the group consisting of:

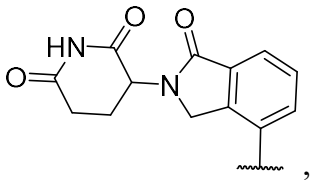


wherein the bond designated with an "*" is attached to B;

w is 1, 2, 3, 4, 5, 6, 7, or 8; and

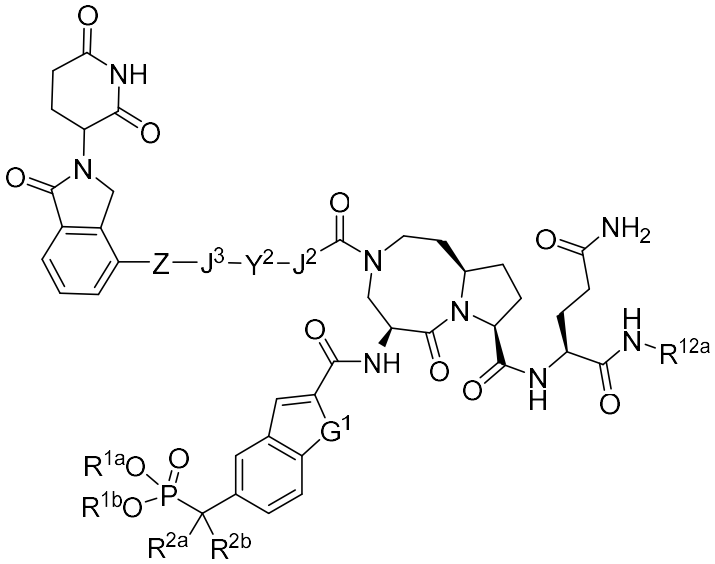
x is 1, 2, 3, 4, 5, or 6.

19. The compound of any one of claims 1-18, wherein B is B-1, and B-1 is:



or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of claim 1, wherein the compound of Formula I is a compound of Formula **IV-A**:

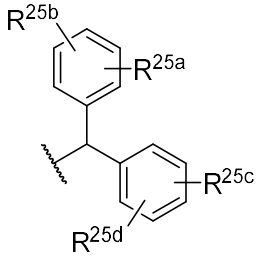


IV-A,

or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of claim 20, wherein:

R^{12a} is:



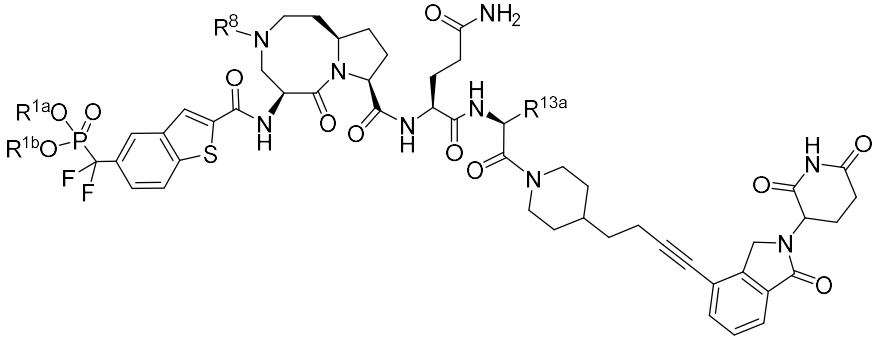
; and

R^{25a}, R^{25b}, R^{25c}, and R^{25d} are each independently selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl, and C_1-C_4 alkoxy.

22. The compound of claim 20 or 21, wherein J^2 is absent, Y^2 is $-(CH_2)_n-$, n is 3, 4, or 5, and J^3 is absent.

23. The compound of any one of claims 20-22, wherein Z is -C≡C-.

24. The compound of claim 1, wherein the compound of Formula I is a compound of Formula **VII-E**:

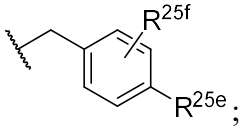


VII-E,

or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of claim 24, wherein:

R^{13a} is:



;

R^{25e} is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, -C(=O)$NR^{50c}R^{50d}$, C_1-C_6 alkylsulfonyl, arylsulfonyl, -N(R^{56c})S(=O)$_2R^{56d}$, and -S(=O)$_2R^{58}$;

R^{25f} is selected from the group consisting of hydrogen and halo;

R^{50c} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 5- or 6-membered heterocyclo, optionally substituted phenyl, optionally substituted 5- to 9-membered heteroaryl, aralkyl, (heteroaryl)C_1-C_4 alkyl, and (heterocyclo)C_1-C_4 alkyl;

R^{50d} is selected from thre group consisting of hydrogen and C_1-C_3 alkyl; or

R^{50c} and R^{50d} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group;

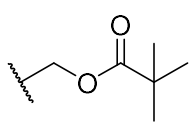
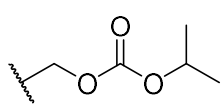
R^{56c} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{56d} is selected from the group consisting of optionally substituted C_3-C_6 cycloalkyl, optionally substituted phenyl, and optionally substituted 5- to 9-membered heteroaryl; and

R^{58} is optionally substituted C_3-C_6 cycloalkyl.

26. The compound of claim 24 or 25, wherein R^8 is selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, alkylsulfonyl, and -C(=O)R^9; and R^9 is selected from the group consisting of C_1-C_4 alkyl, alkylamino, dialkylamino, and C_1-C_4 alkoxy.

27. The compound of any one of claims 1-26, wherein R^{1a} and R^{1b} are hydrogen, C_1-C_4 alkyl,

 , or  .

28. The compound of claim 1, wherein the compound is selected from the compounds of Tables 1.

29. A pharmaceutical composition comprising the compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

30. A compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, for use in treating of cancer.

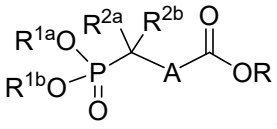
31. The compound for use of claim 30, wherein the cancer is selected from one or more of the cancers of Table 3.

32. Use of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of cancer.

33. The use of claim 32, wherein the cancer is selected from one or more of the cancers of Table 3.

34. A kit comprising the compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administration to a subject having cancer.

35. A compound of Formula **XIII**:



XIII,

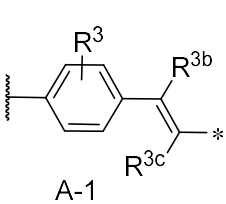
or a pharmaceutically acceptable salt or solvate thereof, wherein:

R is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aralkyl, and optionally substituted phenyl;

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen C_1-C_6 alkyl, and aralkyl;

R^{2a} and R^{2b} are each fluoro; orR^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group;

A is selected from the group consisting of: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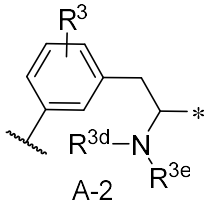
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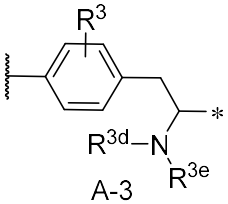
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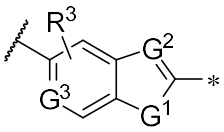
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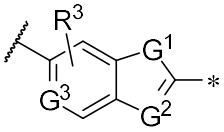
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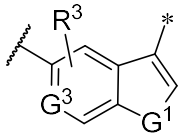
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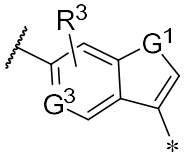
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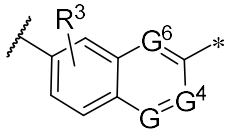
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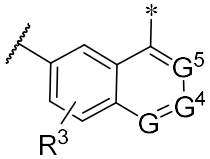
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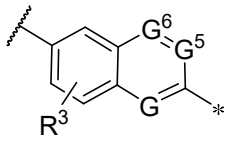
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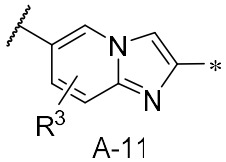
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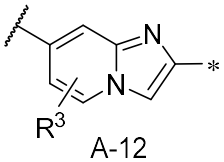
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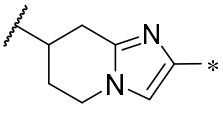
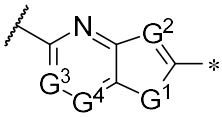

A-13 ,

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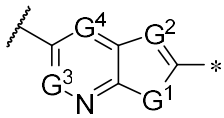
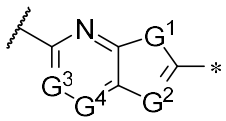
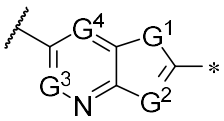
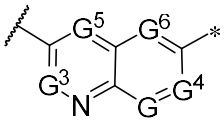

A-15 ,

A-16 ,

A-17 ,

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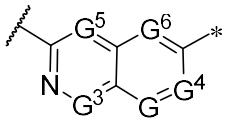
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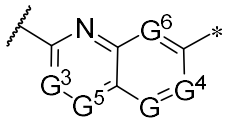

A-20 ;

wherein the bond designated with an "*" is attached to -C(=O)-OR;

G^1 is selected from the group consisting of -O-, -S-, and -NR^{17}-;

G^2 is selected from the group consisting of -N= and -CR^{18a}=;

G^3 is selected from the group consisting of -N= and -CR^{18b}=;

G^4 is selected from the group consisting of -N= and -CR^{18c}=;

G^5 is selected from the group consisting of -N= and -CR^{18d}=;

G^6 is selected from the group consisting of -N= and -CR^{18e}=;

G is selected from the group consisting of -N= and -CR^{18f}=;

R^3 is selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl,

C_3-C_6 cycloalkyl, -C(=O)R^{3a}, and aralkyl;

R^{3a} is C_1-C_4 alkyl;

R^{3b} and R^{3c} are each independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{3d} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^{3f};

R^{3e} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

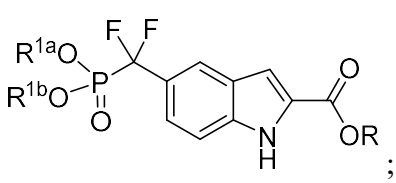
R^{3f} is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_6 alkoxy, and aralkyloxy;

R^{17} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, aralkyl, and -C(=O)R^{17a};

R^{17a} is C_1-C_4 alkyl; and

R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, and R^{18f} are each independently selected from the group consisting of hydrogen, halo, and C_1-C_4 alkyl;

with the proviso that the compound is not: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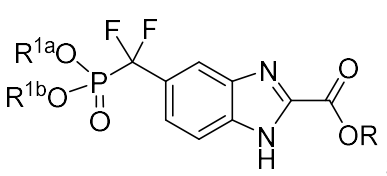
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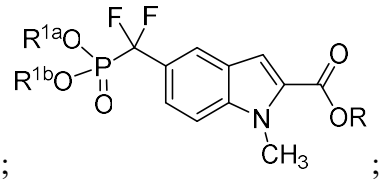
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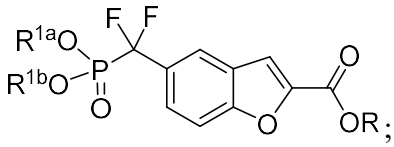
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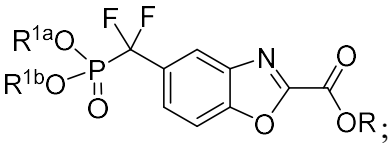
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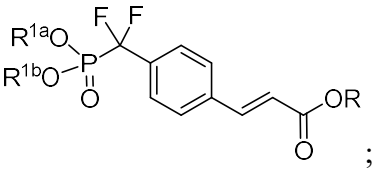
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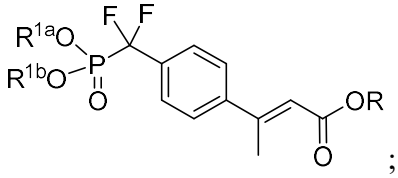
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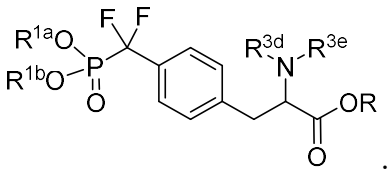
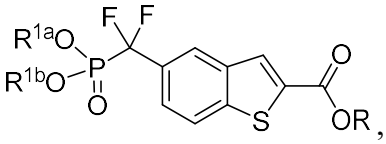

.

36. The compound of claim 35 selected from the group consisting of: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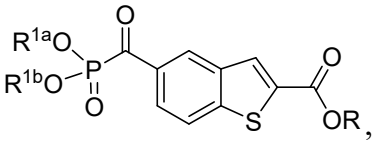
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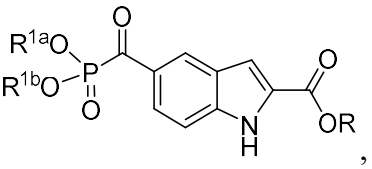
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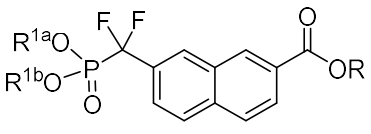
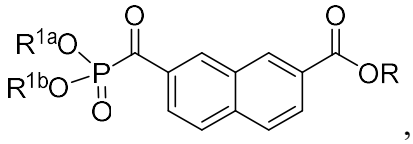
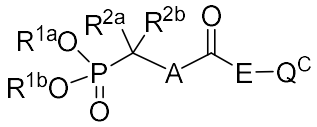

, and

,

or a pharmaceutically acceptable salt or solvate thereof.

37. A compound of Formula **XVI**:



XVI,

or a salt or solvate thereof, wherein:

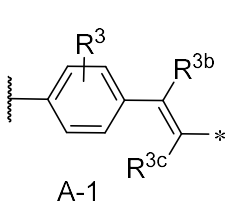
R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen C_1-C_4 alkyl, aralkyl, and -$CH_2OC(=O)R^{1e}$;

R^{1e} is C_1-C_6 alkyl;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen and fluoro; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group;

A is selected from the group consisting of:



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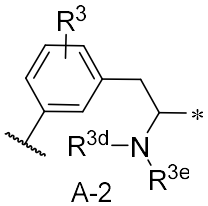

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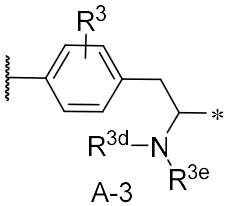

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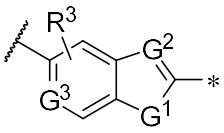

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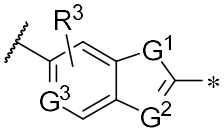

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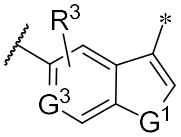

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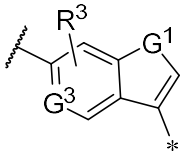

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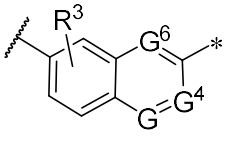

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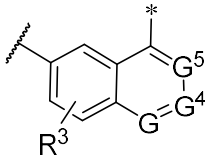

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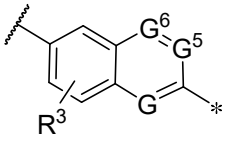

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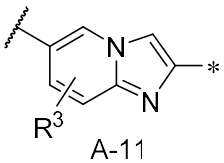

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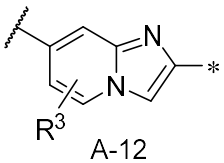

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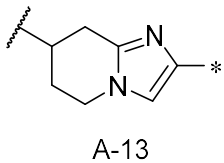

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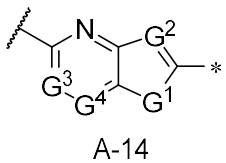

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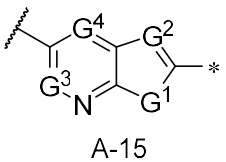

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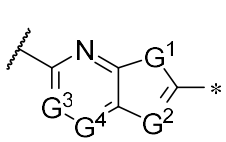
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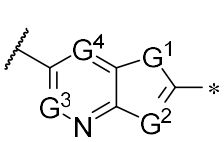
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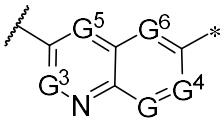
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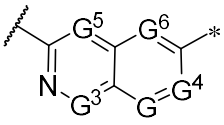
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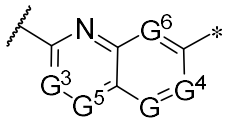

A-20 ;

wherein the bond designated with an "*" is attached to -C(=O)-E-Q^C;

G^1 is selected from the group consisting of -O-, -S-, and -NR^{17}-;

G^2 is selected from the group consisting of -N= and -CR^{18a}=;

G^3 is selected from the group consisting of -N= and -CR^{18b}=;

G^4 is selected from the group consisting of -N= and -CR^{18c}=;

G^5 is selected from the group consisting of -N= and -CR^{18d}=;

G^6 is selected from the group consisting of -N= and -CR^{18e}=;

G is selected from the group consisting of -N= and -CR^{18f}=;

R^3 is selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -C(=O)R^{3a}, and aralkyl;

R^{3a} is C_1-C_4 alkyl;

R^{3b} and R^{3c} are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{3d} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^{3f};

R^{3e} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

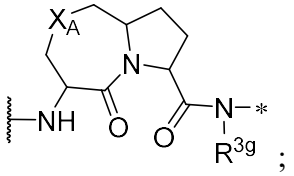
R^{3f} is selected from the group consisting of C_1-C_{12} alkyl, C_1-C_6 alkoxy, and aralkyloxy;

R^{17} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, aralkyl, and -C(=O)R^{17a};

R^{17a} is C_1-C_4 alkyl;

R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, and R^{18f} are each independently selected from the group consisting of hydrogen, halo, and C_1-C_4 alkyl;

E is:



wherein the bond designated with an "*" is attached to Q^C;

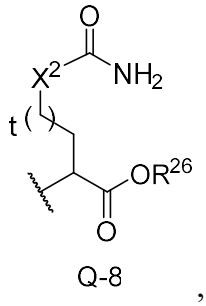
R^{3g} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

X_A is selected from the group consisting of -N(R^8)CH_2-, -CH_2N(R^8)-, and -CH_2CH_2-;

R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, -C(=O)R^9, alkylsulfonyl, and -L-B;

R^9 is selected from the group consisting of C_1-C_6 alkyl, amino, C_1-C_6 alkoxy, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, optionally substituted aryl, optionally substituted 5- to 10-membered heteroaryl, aralkyl, and (heteroaryl)alkyl;

Q^C is:



Q-8

,

X^2 is selected from the group consisting of -CH_2-, -O-, and -N(R^{11b})-; or

X^2 is absent;

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

R^{11b} is selected from the group consisting of hydrogen and C_1-C_3 alkyl; and

R^{26} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and aralkyl;

L is -J^1-Y^1-J^2-Y^2-J^3-Z-;

J^1 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^1 is absent;

Y^1 is selected from the group consisting of -$(CH_2)_m$-, -C≡C-, -CH=CH-, -N(R^{16a})-, -C(=O)-, -$S(=O)_2$-, -C(=O)O-, -OC(=O)-, -C(=O)N(R^{16b})-, and -N(R^{16b})C(=O)-;

m is 0, 1, 2, or 3;

R^{16a} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

R^{16b} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

J^2 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^2 is absent;

Y^2 is selected from the group consisting of $-(CH_2)_n-$, -C≡C-, -CH=CH-, $-N(R^{16a})-$, -C(=O)-, $-S(=O)_2-$, -C(=O)O-, -OC(=O)-, $-C(=O)N(R^{16b})$, and $-(R^{16b})C(=O)N-$;

n is 0, 1, 2, 3, 4, 5, or 6;

R^{16a} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

R^{16b} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

J^3 is selected from the group consisting of alkylenyl, heteroalkylenyl, cycloalkylenyl, heterocyclenyl, phenylenyl, and heteroarylenyl; or

J^3 is absent;

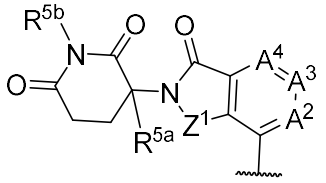
Z is selected from the group consisting of $-(CH_2)_d-$, -C≡C-, -CH=CH-, -C(=O)-, -O-, -S-, $-N(R^{16c})-$, $-C(=O)N(R^{16d})-$, $-N(R^{16d})C(=O)-$, $-N(R^{16e})C(=O)CH_2O-$, and $-N(R^{16f})C(=O)CH_2N(R^{16g})-$;

d is 0, 1, 2, or 3;

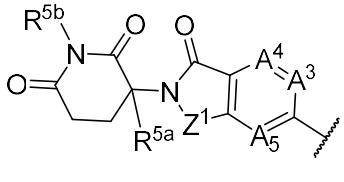
R^{16c}, R^{16d}, R^{16e}, R^{16f}, and R^{16g} are each independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aralkyl;

wherein Z is attached to B;

B is selected from the group consisting of:



B-1 ,



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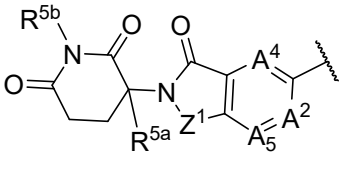
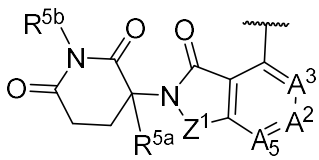
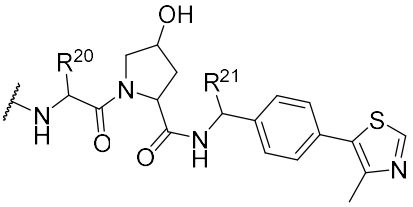


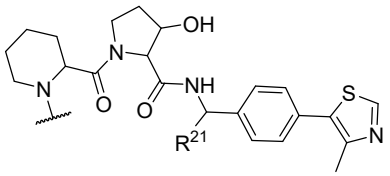
B-3 ,



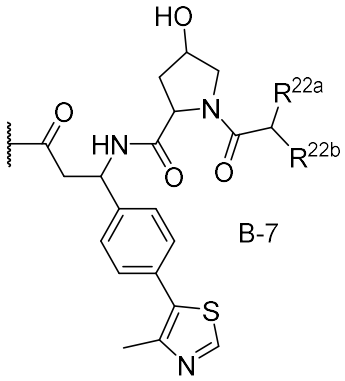
B-4 ,



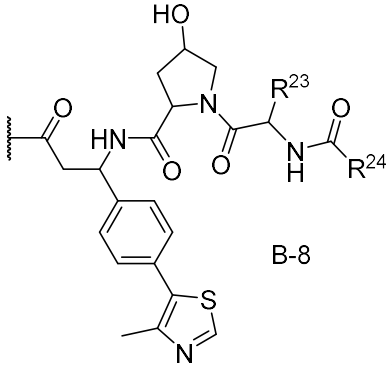
B-5 ,



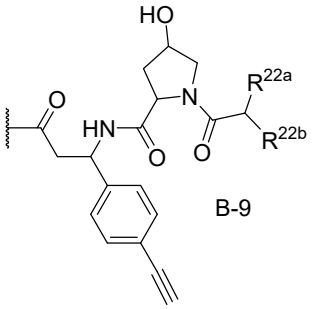
B-6 ,



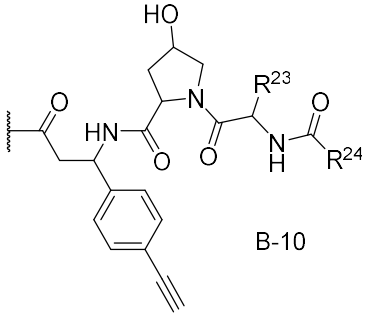
B-7 ,



B-8 ,



B-9 and



B-10 ;

A_5 is selected from the group consisting of -C(R^{19a})= and –N=;

A^2 is selected from the group consisting of -C(R^{19b})= and –N=;

A^3 is selected from the group consisting of -C(R^{19c})= and –N=;

A^4 is selected from the group consisting of -C(R^{19d})= and –N=;

Z^1 is selected from the group consisting of -CH_2 and -C(=O)-;

R^{5a} is selected from the group consisting of hydrogen, methyl, and fluoro;

R^{5b} is selected from the group consisting of hydrogen and methyl;

R^{19a}, R^{19b}, R^{19c}, and R^{19d} are each independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

R^{20} is C_1-C_6 alkyl;

R^{21} is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^{22a} is selected from the group consisting of C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl;

R^{22b} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^{23} is selected from the group consisting of C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl; and

R^{24} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl,

with the provisos that:

(1) when X_A is $-CH_2CH_2-$, then:

(i) A is selected from the group consisting of A-2, A-5, A-6, A-7, A-8, A-9, A-10, A-11, A-12, A-13, A-14, A-15, A-16, A-17, A-18, A-19, and A-20;

(ii) A is A-4 and G^1 is -S-; or

(iii) R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group;

(2) when X_A is $-N(R^8)CH_2-$ and R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and $-C(=O)R^9$, then:

(i) A is selected from the group consisting of A-1, A-2, A-4, A-5, A-6, A-7, A-8, A-9, A-10, A-11, A-12, A-13, A-14, A-15, A-16, A-17, A-18, A-19, and A-20; or

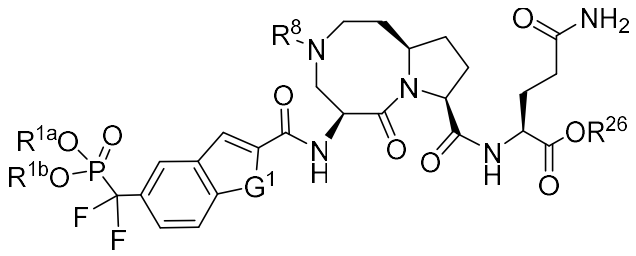
(ii) R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group; or

(3) when X_A is $-CH_2N(R^8)-$ and R^8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and $-C(=O)R^9$, then:

(i) A is selected from the group consisting of A-1, A-2, A-4, A-5, A-6, A-7, A-8, A-9, A-10, A-11, A-12, A-13, A-14, A-15, A-16, A-17, A-18, A-19, and A-20; or

(ii) R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a -C(=O)- group.

38. A compound of Formula **XVI-A**:



or a salt or solvate thereof, wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

G^1 is selected from the group consisting of -S- and -N(H)-;

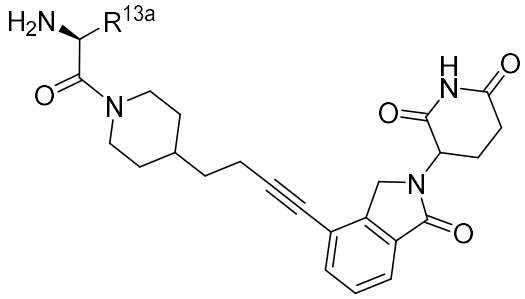
R^8 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9;

R^9 is selected from the group consisting of C_1-C_3 alkyl, alkylamino, dialkylamino, and C_1-C_3 alkoxy; and

R^{26} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and aralkyl.

39. The compound of claim 38 selected from one or more of the compounds of Table 2A, or a salt or solvate thereof.

40. A compound of Intermediate Formula **2**:

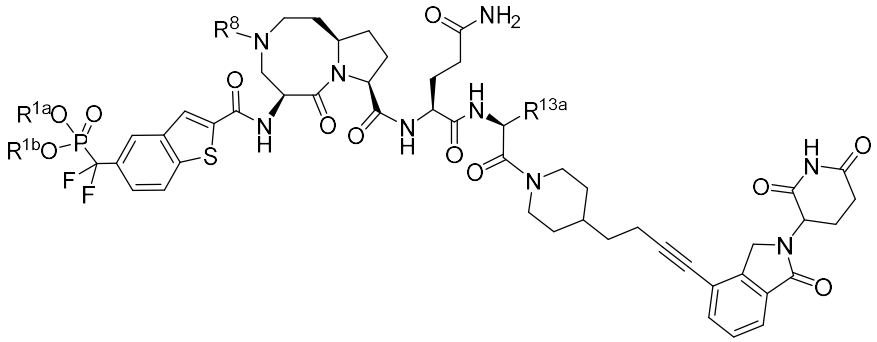


2,

or a salt or solvate thereof, wherein R^{13a} is selected from the group consisting optionally substituted C_3-C_{12} cycloalkyl, optionally substituted aryl, aralkyl, (heteroaryl)alkyl, (cycloalkyl)alkyl, and optionally substituted 5- to 9-membered heteroaryl.

41. The compound of claim 40 selected from one or more of the compounds of Table 2B, or a salt or solvate thereof.

42. A method of making a compound of Formula **VII-E**:



VII-E,

wherein:

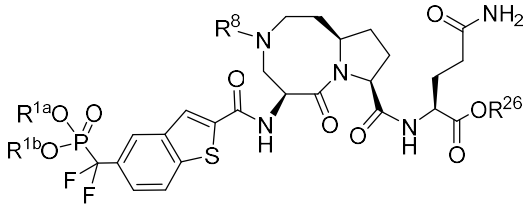
R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^8 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9;

R^9 is selected from the group consisting of C_1-C_3 alkyl, alkylamino, dialkylamino, and C_1-C_3 alkoxy; and

R^{13a} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted aryl, aralkyl, (heteroaryl)alkyl, (cycloalkyl)alkyl, and optionally substituted 5- to 9-membered heteroaryl,

the method comprising reacting a compound of Formula **XVI-A**:



XVI-A,

wherein:

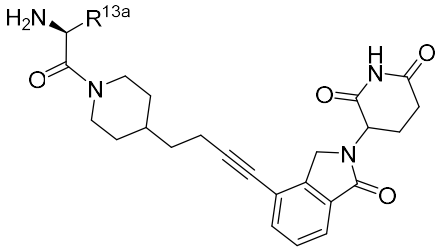
R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

R^8 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, (heterocyclo)alkyl, alkylsulfonyl, and -C(=O)R^9; and

R^9 is selected from the group consisting of C_1-C_3 alkyl, alkylamino, dialkylamino, and C_1-C_3 alkoxy; and

R^{26} is hydrogen,

with a compound of Intermediate Formula **2**:



2,

wherein:

R^{13a} is selected from the group consisting of C_1-C_6 alkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted aryl, aralkyl, (heteroaryl)alkyl, (cycloalkyl)alkyl, and optionally substituted 5- to 9-membered heteroaryl,

in the presence of a coupling agent in a solvent.