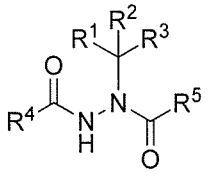
Claims

1. A compound having Formula I:



I

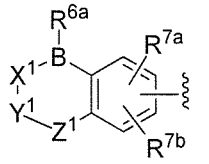
wherein:

R^1 and R^2 are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, and haloalkyl; or

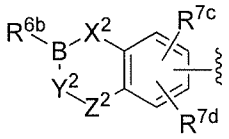
R^1 and R^2 taken together with the carbon atom to which they are attached form a 4- to 8-membered cycloalkyl;

R^3 is selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted aryl, and optionally substituted heteroaryl;

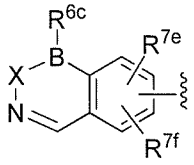
R^4 is selected from the group consisting of:



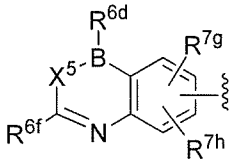
R^4-1



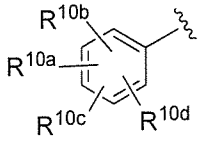
R^4-2



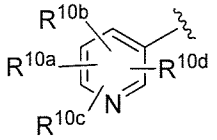
R^4-3



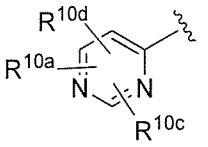
R^4-4



R^4-5

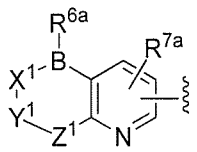


R^4-6



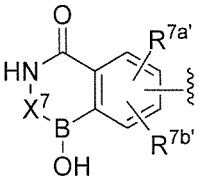
R^4-7

,



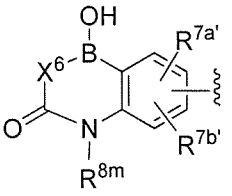
R^4-8

,



R^4-9

and



R^4-10

;

X^1 is selected from the group consisting of -O- and -N(R^{8a})-;

Y^1 is -($CR^{9a}R^{9b}$)$_m$-;

Z^1 is selected from the group consisting of -O- and -N(R^{8b})-, or Z^1 is absent;

R^{6a} is selected from the group consisting of hydroxy, alkyl, and alkoxy; or

R^{6a} forms a hydroxy acid adduct or an amino acid adduct;

R^{7a} and R^{7b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

$R^{7a'}$ and $R^{7b'}$ are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen and alkyl;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen and alkyl;

m is 1, 2, 3, or 4;

X^2 is selected from the group consisting of -O- and -N(R^{8c})-;

Y^2 is -($CR^{9c}R^{9d}$)$_n$-;

Z^2 is selected from the group consisting of -O- and -N(R^{8d})-, or Z^2 is absent;

R^{6b} is selected from the group consisting of hydroxy, alkyl, and alkoxy; or

R^{6b} forms a hydroxy acid adduct or an amino acid adduct;

R^{7c} and R^{7d} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8c} and R^{8d} are each independently selected from the group consisting of hydrogen and alkyl;

R^{9c} and R^{9d} are each independently selected from the group consisting of hydrogen and alkyl;

n is 1, 2, 3, or 4;

X is selected from the group consisting of -O- and -N(R^{8e})-;

R^{6c} is selected from the group consisting of hydroxy, alkyl, and alkoxy; or

R^{6c} forms a hydroxy acid adduct or an amino acid adduct;

R^{7e} and R^{7f} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8e} is selected from the group consisting of hydrogen and alkyl;

R^{6d} is selected from the group consisting of hydroxy, alkyl, and alkoxy; or

R^{6d} forms a hydroxy acid adduct or an amino acid adduct;

R^{6f} is selected from the group consisting of hydrogen, alkyl, amino, and hydroxy;

X^5 is selected from the group consisting of -O- and -N(R^{8k})-;

R^{7g} and R^{7h} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8k} is selected from the group consisting of hydrogen and alkyl;

X^6 is selected from the group consisting of -O- and -N(R^{8l})-;

X^7 is selected from the group consisting of -O- and -N(R^{8n})-;

R^{8l} is selected from the group consisting of hydrogen and alkyl;

R^{8m} is selected from the group consisting of hydrogen and alkyl;

R^{8n} is selected from the group consisting of hydrogen and alkyl;

R^{10a} is selected from the group consisting of hydrogen and -$(CR^{11a}R^{11b})_o$-B(R^{12a})(R^{12b}); and

R^{10b}, R^{10c}, and R^{10d} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, -N(H)CHO, -N(H)CN, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, heteroalkyl, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino; or

R^{10b} is selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, -N(H)CHO, -N(H)CN, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, heteroalkyl, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino; and/or

R^{10c} and R^{10d} taken together with two adjacent carbon atoms form a fused optionally substituted cycloalkyl, optionally substituted heterocyclo, or optionally substituted heteroaryl group;

R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen and alkyl;

R^{12a} and R^{12b} are selected from the group consisting of hydroxy and alkoxy; or

R^{12a} and R^{12b} taken together form a linkage $-O(CR^{13a}R^{13b})_pO-$; or

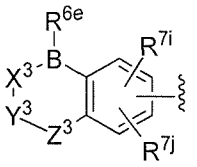
$-B(R^{12a})(R^{12b})$ forms a fluoride adduct;

R^{13a} and R^{13b} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

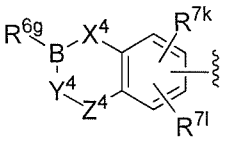
o is 0, 1, 2, 3, 4, or 5;

p is 2, 3, or 4;

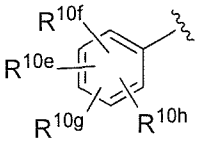
R^5 is R^4-3, R^4-4, R^4-8, R^4-9, or R^4-10; or R^5 is selected from the group consisting of:



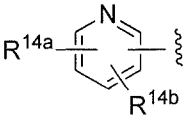
R^5-1 ,



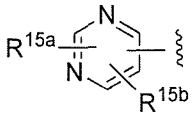
R^5-2 ,



R^5-3 ,



and



R^5-4 R^5-5 ;

X^3 is selected from the group consisting of -O- and -N(R^{8f})-;

Y^3 is -($CR^{9e}R^{9f}$)$_q$-;

Z^3 is selected from the group consisting of -O- and -N(R^{8g})-, or Z^3 is absent;

R^{6e} is selected from the group consisting of hydroxy and alkyl; or

R^{6e} forms a hydroxy acid adduct or an amino acid adduct;

R^{7i} and R^{7j} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8f} and R^{8g} are each independently selected from the group consisting of hydrogen and alkyl;

R^{9e} and R^{9f} are each independently selected from the group consisting of hydrogen and alkyl;

q is 1, 2, 3, or 4;

X^4 is selected from the group consisting of -O- and -N(R^{8h})-;

Y^4 is -($CR^{9g}R^{9h}$)$_r$-;

Z^4 is selected from the group consisting of -O- and -N(R^{8i})-, or Z^4 is absent;

R^{6g} is selected from the group consisting of hydroxy and alkyl; or

R^{6g} forms a hydroxy acid adduct or an amino acid adduct;

R^{7k} and R^{7l} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, and alkylthio;

R^{8h} and R^{8i} are each independently selected from the group consisting of hydrogen and alkyl;

R^{9g} and R^{9h} are each independently selected from the group consisting of hydrogen and alkyl;

r is 1, 2, 3, or 4;

R^{10e} is selected from the group consisting of hydrogen and $-(CR^{11c}R^{11d})_s-B(R^{12c})(R^{12d})$; and

R^{10f}, R^{10g}, and R^{10h} are independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, -N(H)CHO, -N(H)CN, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino; or

R^{10f} is selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, -N(H)CHO, -N(H)CN, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino; and

R^{10g} and R^{10h} taken together with two adjacent carbon atoms form a fused optionally substituted cycloalkyl, optionally substituted heterocyclo, or optionally substituted heteroaryl group; or

R^{11c} and R^{11d} are each independently selected from the group consisting of hydrogen and alkyl;

R^{12c} and R^{12d} are selected from the group consisting of hydroxy and alkoxy; or

R^{12c} and R^{12d} taken together form a linkage $-O(CR^{13c}R^{13d})_tO-$; or

$-B(R^{12c})(R^{12d})$ forms a fluoride adduct;

R^{13c} and R^{13d} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

s is 0, 1, 2, 3, 4, or 5;

t is 2, 3, or 4;

R^{14a} and R^{14b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, -N(H)CHO, -N(H)CN, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino;

R^{15a} and R^{15b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, hydroxy, amino, -N(H)CHO, -N(H)CN, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^{16}$, $-SO_2R^{17}$, $-N(R^{18})COR^{19}$, $-N(R^{18})SO_2R^{20}$ or $N(R^{18})C=N(R^{21})$-amino;

R^{16} is selected from the group consisting of hydrogen, hydroxy, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy, and arylalkyloxy;

R^{17} is selected from the group consisting of haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, and optionally substituted heteroaryl;

R^{18} is selected from the group consisting of hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, and optionally substituted heteroaryl;

R^{19} is selected from the group consisting of hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy, arylalkyloxy, and amino;

R^{20} is selected from the group consisting of haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, and amino;

R^{21} is selected from the group consisting of hydrogen, alkyl, aryl, cyano, and nitro;

with the provisos:

a) when R^4 is R^4-5, R^4-6, or R^4-7 and R^5 is R^5-3, then one of R^{10a} or R^{10e} is not hydrogen; and

b) when R^4 is R^4-5, R^4-6, or R^4-7 and R^5 is R^5-4 or R^5-5, then R^{10a} is not hydrogen,

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein:

R^4 is R^4-1;

R^5 is selected from the group consisting of R^5-3, R^5-4, and R^5-5; and

R^{10e} is hydrogen,

or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 1, wherein:

R^4 is R^4-2;

R^5 is selected from the group consisting of R^5-3, R^5-4, and R^5-5; and

R^{10e} is hydrogen,

or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 1, wherein:

R^4 is R^4-5;

R^5 is selected from the group consisting of R^5-3, R^5-4, and R^5-5; and

R^{10a} is $-(CR^{11a}R^{11b})_o$-$B(R^{12a})(R^{12b})$,

or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of claim 1, wherein:

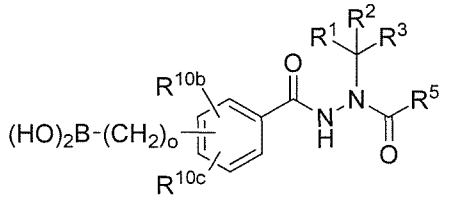
R^4 is R^4-5;

R^5 is R^5-3; and

R^{10e} is $-(CR^{11c}R^{11d})_s$-$B(R^{12c})(R^{12d})$,

or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 4 having Formula **II**:

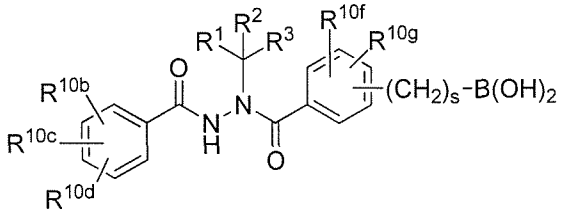


II

or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 6, wherein o is 0 and R^{10b} and R^{10c} are each independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy, or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of claim 6, having Formula **III**:



III

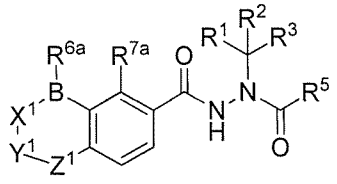
or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of claim 8, wherein s is 0 and R^{10b}, R^{10c}, and R^{10d} are independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; or

R^{10b} is selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^{10c} and R^{10d} taken together with two adjacent carbon atoms form a fused optionally substituted cycloalkyl, optionally substituted heterocyclo, or optionally substituted heteroaryl group, or a pharmaceutically acceptable salt or solvate thereof

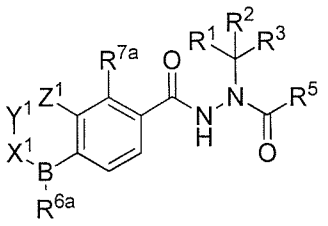
10. The compound of claim 1 having Formula **V**:



V

or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 1 having Formula **VI**:



VI

or a pharmaceutically acceptable salt or solvate thereof.

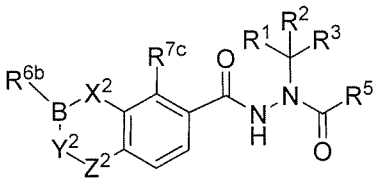
12. The compound of claims 10 or 11, wherein R^{7a} is selected from the group consisting of hydrogen, halogen, and alkyl, or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 12, wherein Z^1 is absent or -O-, or a pharmaceutically acceptable salt or solvate thereof.

14. The compound of claim 12, wherein X^1 is -O-, or a pharmaceutically acceptable salt or solvate thereof.

15. The compound of claim 13, wherein Z^1 is absent, R^{9a} and R^{9b} are selected from the group consisting of hydrogen and methyl, and m is 1, 2, or 3, or a pharmaceutically acceptable salt or solvate thereof.

16. The compound of claim 1 having Formula **VIII**:



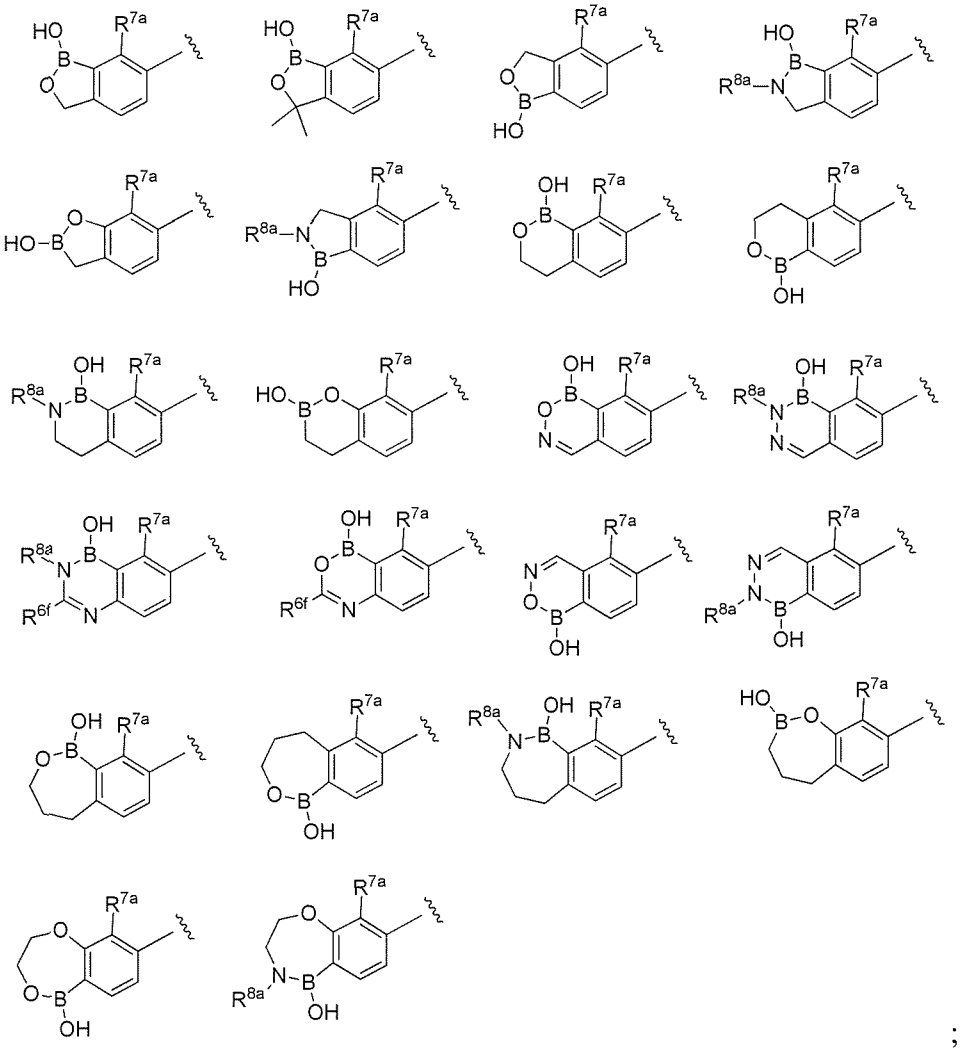
VIII

or a pharmaceutically acceptable salt or solvate thereof.

17. The compound of claim 16, wherein R^{7c} is selected from the group consisting of hydrogen, halogen, and alkyl; Z^2 is absent; X^2 is -O-; R^{9c} and R^{9d} are selected from the group consisting of hydrogen and methyl; and n is 1, 2, or 3, or a pharmaceutically acceptable salt or solvate thereof.

18. The compound of claim 1, wherein:

R^4 is selected from the group consisting of



;

R^5 is selected from the group consisting of R^5-3, R^5-4, and R^5-5; and

R^{10e} is hydrogen,

or a pharmaceutically acceptable salt or solvate thereof.

19. The compound of claim 18, wherein

R^{7a} is selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

R^{8a} is selected from the group consisting of hydrogen and C_{1-4} alkyl; and

R^{6f} is selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy, and $-NH_2$,

or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of claim 1, wherein:

R^1 is optionally substituted C_{1-6} alkyl;

R^2 is selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; and

R^3 is optionally substituted C_{1-6} alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of claim 20, wherein:

R^1 is selected from the group consisting of methyl, ethyl, n-propyl, and n-butyl; and

R^2 is selected from the group consisting of hydrogen and methyl,

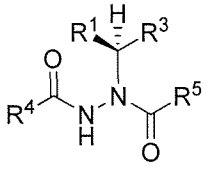
or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of claim 21, wherein R^3 is selected from the group consisting of methyl and tert-butyl, or a pharmaceutically acceptable salt or solvate thereof.

23. The compound of claim 1, wherein R^1 is optionally substituted C_{1-6} alkyl; R^2 is hydrogen; and R^3 is selected from the group consisting of optionally substituted phenyl, optionally substituted pyridyl, and optionally substituted pyrimidinyl, or a pharmaceutically acceptable salt or solvate thereof.

24. The compound of claim 22, wherein R^1, R^2, and R^3 are each methyl, or a pharmaceutically acceptable salt or solvate thereof.

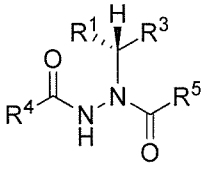
25. The compound of claim 1 having Formula **X**



X

wherein R^1 does not equal R^3, or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of claim 1 having Formula **XI**

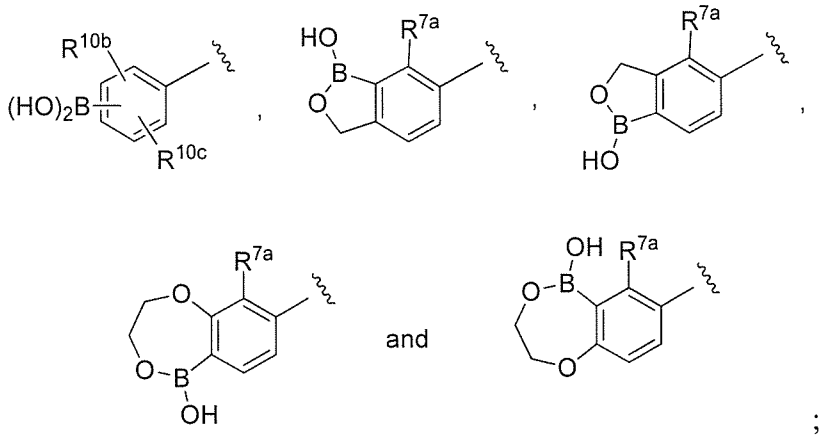


XI

wherein R^1 does not equal R^3, or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of claim 25 or 26, wherein:

R^4 is selected from the group consisting of:



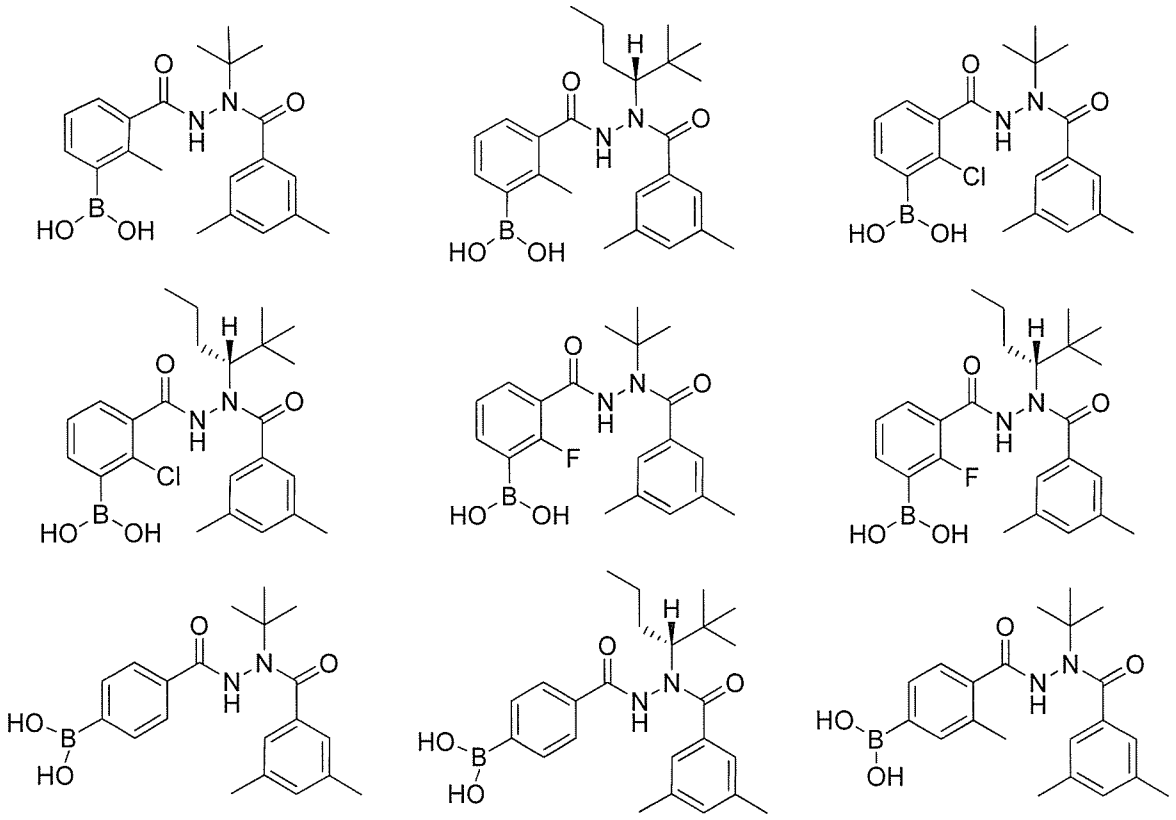
;

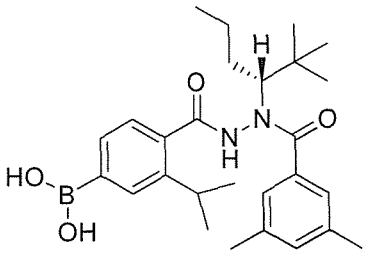
R^5 is selected from the group consisting of R^5-3, R^5-4, and R^5-5; and

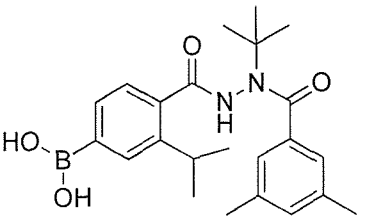
R^{10e} is hydrogen,

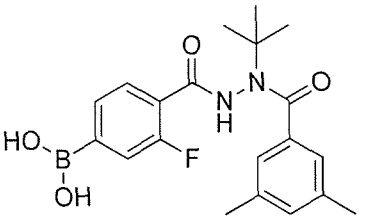
or a pharmaceutically acceptable salt or solvate thereof.

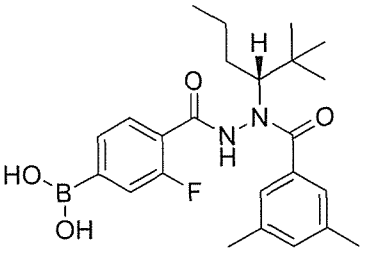
28. The compound of claim 1 selected from the group consisting of:

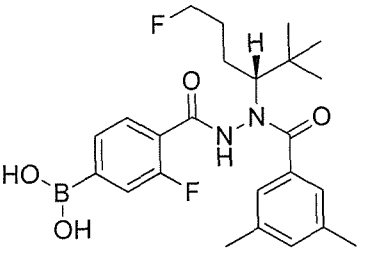


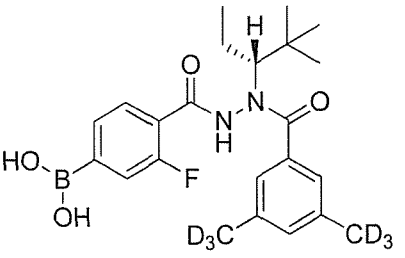


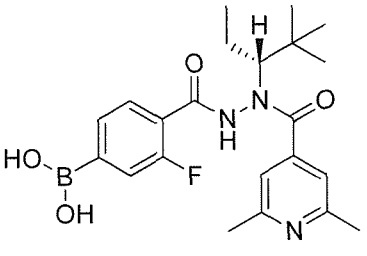


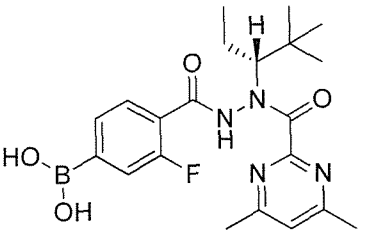


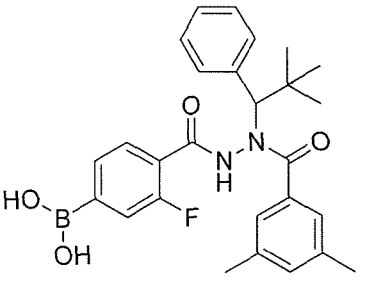


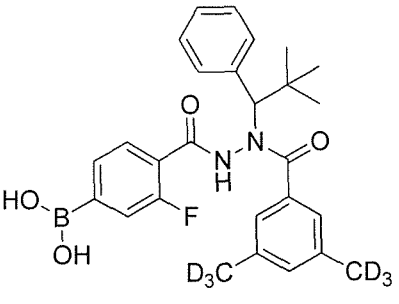


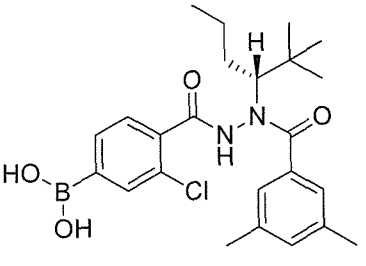


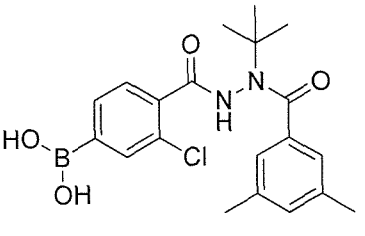


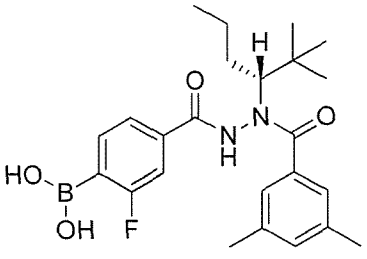


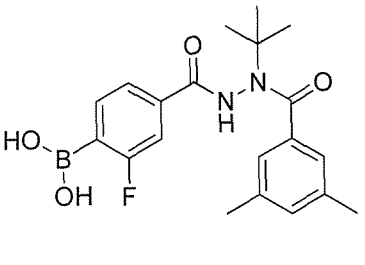


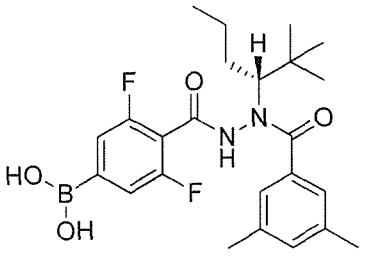


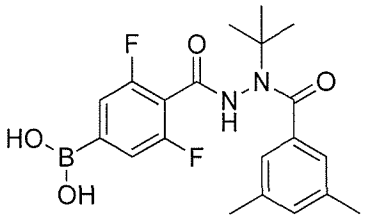


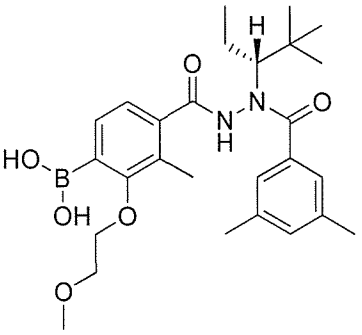


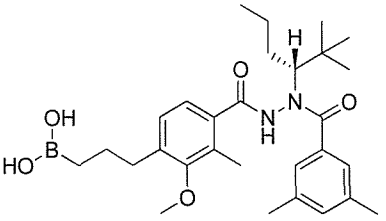


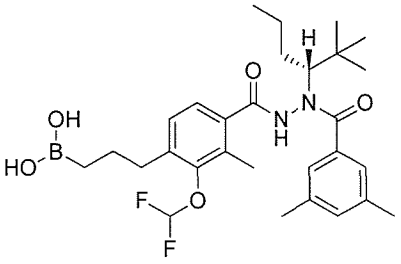


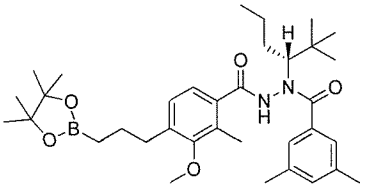


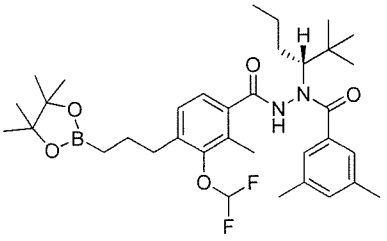


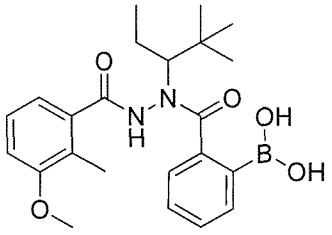


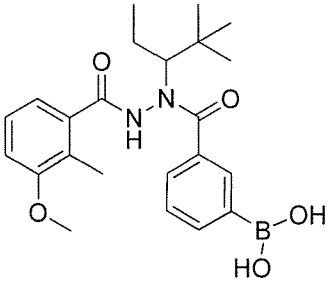


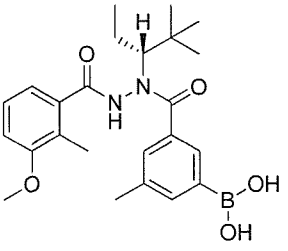


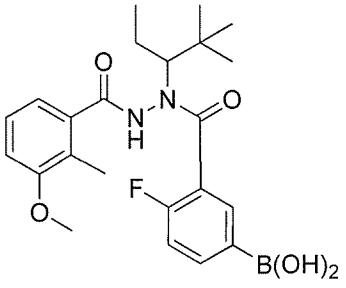


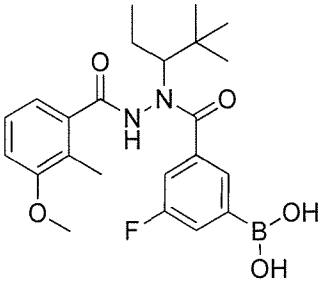


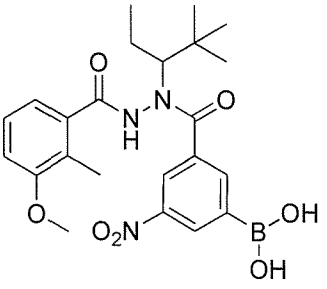


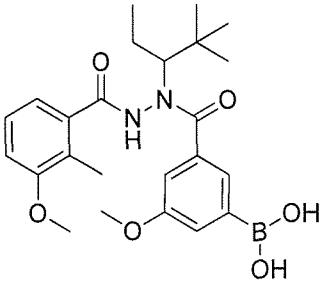


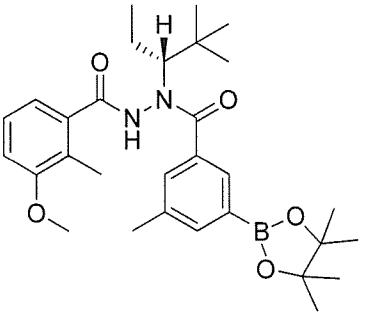


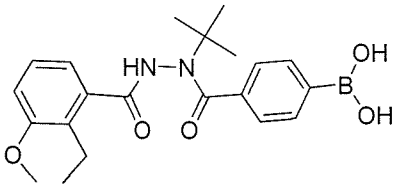


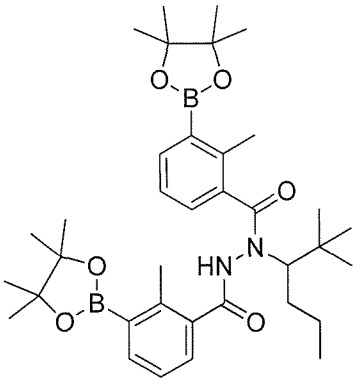


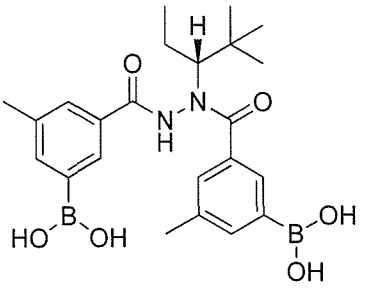


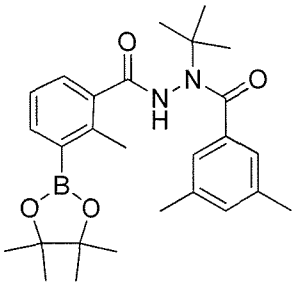


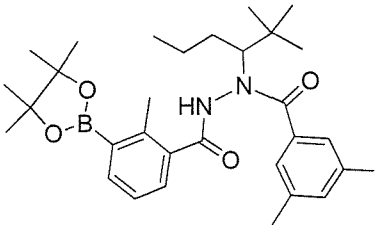


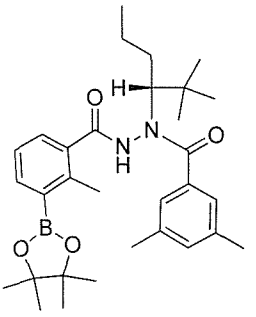


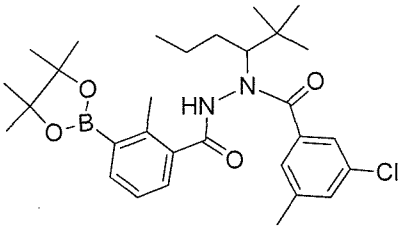


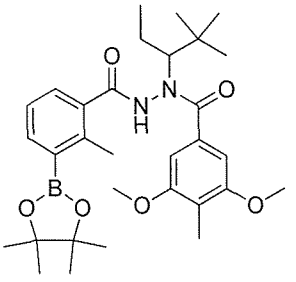


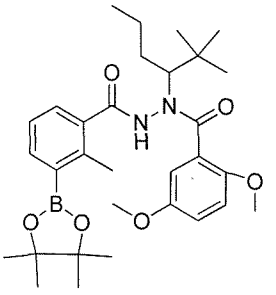


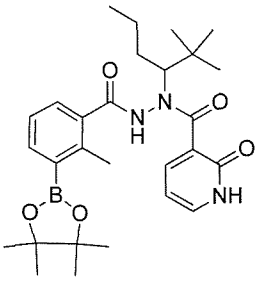


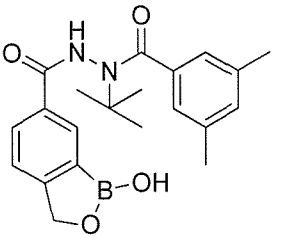


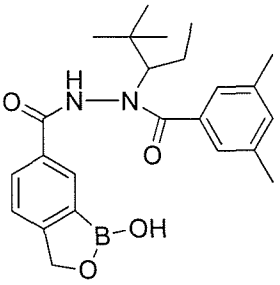


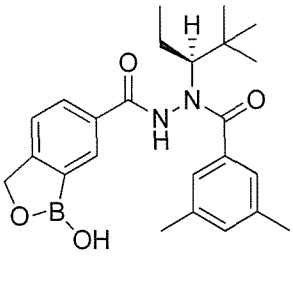


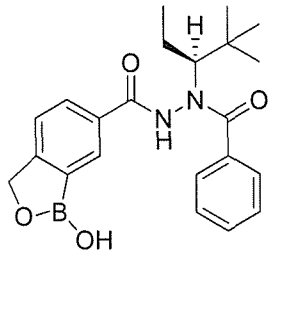


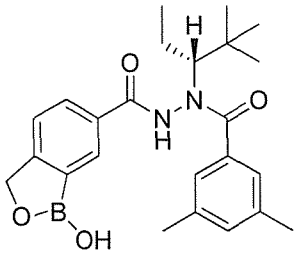


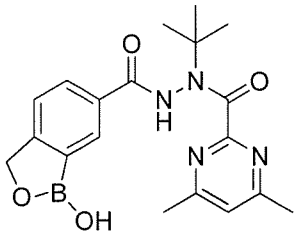


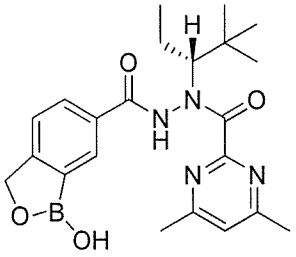


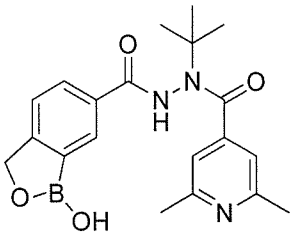


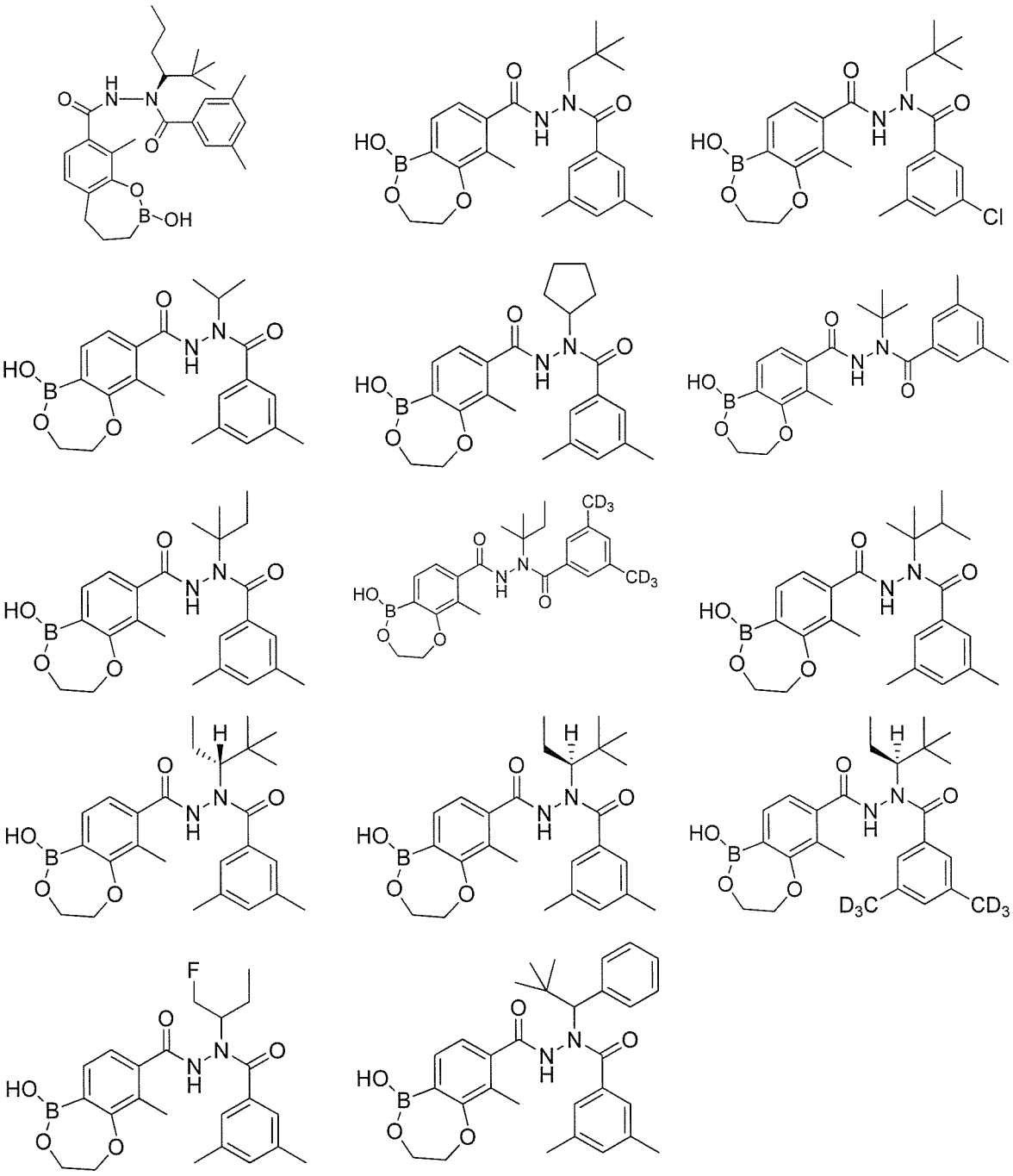












or a pharmaceutically acceptable salt or solvate thereof.

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

30. A method of regulating gene expression of a gene of interest in an isolated host cell, the method comprising contacting said host cell with the compound of claims 1 or 28, or a pharmaceutically acceptable salt thereof.

31. A kit comprising the compound of claims 1 or 28, or a pharmaceutically acceptable salt or solvate thereof.