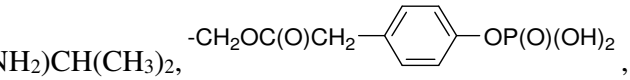
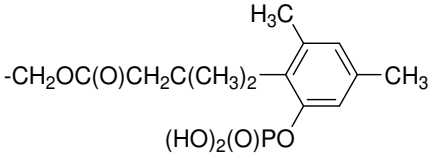
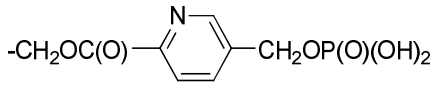
R_3 is H, -CH_3 or Rx;

R_4 is H or R_y;

R_x

is: -$CH_2OC(O)CH(CH_3)NH_2$, -$CH_2OC(O)CH(NH_2)CH(CH_3)_2$, -$CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: -$SCH_2CH(NH_2)C(O)OH$, -$SCH_2CH(NH_2)C(O)OCH_3$,

or -$SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH_3, C_{1-3} alkyl, -CH_2OH, -CF_3, cyclopropyl, -OCH_3, -O(cyclopropyl) and/or -$NHCH_2CH_2OCH_3$;

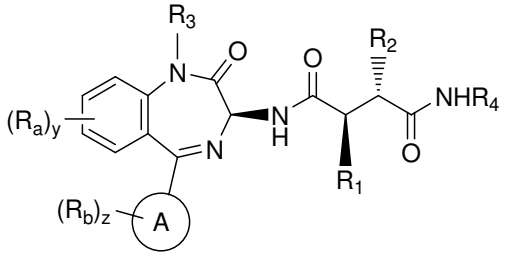
each R_b is independently F, Cl, -CH_3, -CH_2OH, -CF_3, cyclopropyl, and/or -OCH_3;

y is zero, 1 or 2; and

z is zero, 1, or 2

in combination with an additional cancer therapeutic agent.

[003a] In one aspect, the present disclosure refers to a composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

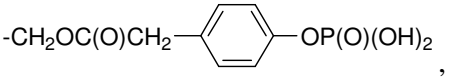
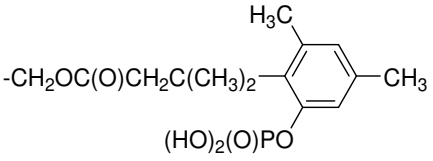
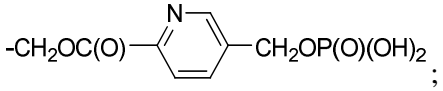
R_1 is -CH_2CF_3 or -$CH_2CH_2CF_3$;

R_2 is -CH_2CF_3, -$CH_2CH_2CF_3$, or -$CH_2CH_2CH_2CF_3$;

R_3 is H, -CH_3 or Rx;

R_4 is H or R_y;

R_x

is: -$CH_2OC(O)CH(CH_3)NH_2$, -$CH_2OC(O)CH(NH_2)CH(CH_3)_2$, -$CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: -$SCH_2CH(NH_2)C(O)OH$, -$SCH_2CH(NH_2)C(O)OCH_3$, or -$SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH_3, C_{1-3} alkyl, -CH_2OH, -CF_3, cyclopropyl, -OCH_3, -O(cyclopropyl) and/or -$NHCH_2CH_2OCH_3$;

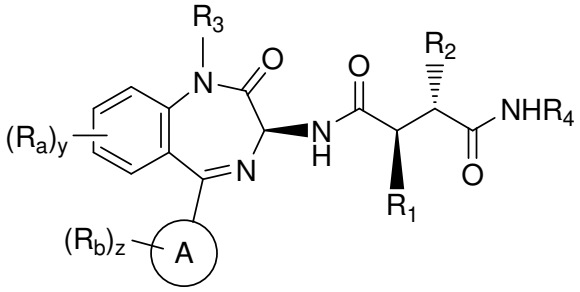
each R_b is independently F, Cl, -CH_3, -CH_2OH, -CF_3, cyclopropyl, and/or -OCH_3;

y is zero, 1 or 2; and

z is zero, 1, or 2,

in combination with a composition comprising a CDK 4/6 inhibitor, sorafenib, regorafenib, Venclexta, or Vorinostat, ~~Venclexta, a tyrosine kinase inhibitor, a retinoic acid derivative, an anti-PD1 antibody, an EGFR inhibitor,~~ or a combination thereof.

[004] The present disclosure also provides a method of treating, suppressing or inhibiting a proliferative disease in a subject comprising the step of administering to said subject a first composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

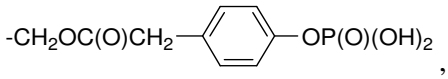
R_1 is -CH_2CF_3 or -$CH_2CH_2CF_3$;

R_2 is -CH_2CF_3, -$CH_2CH_2CF_3$, or -$CH_2CH_2CH_2CF_3$;

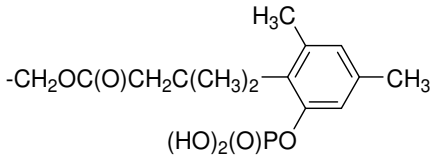
R_3 is H, -CH_3 or Rx;

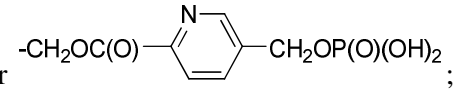
R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, 

,



, or 

;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$,

cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

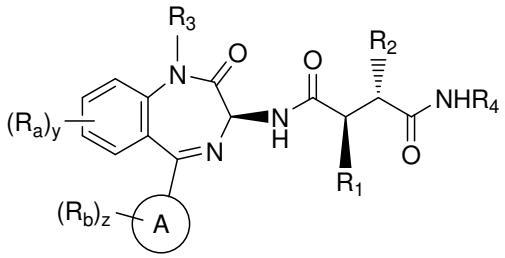
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2

in combination with a second composition comprising an additional cancer therapeutic agent.

[004a] In one aspect, the present disclosure refers to use of a first composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

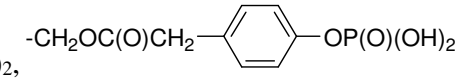
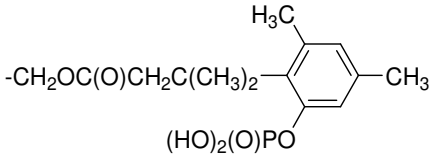
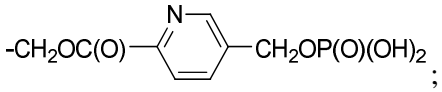
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2

and a second composition comprising a CDK 4/6 inhibitor, sorafenib, regorafenib, Venclexta, or Vorinostat, or a combination thereof, in the manufacture of a medicament for treating, suppressing, or inhibiting a proliferative disease in a subject~~, wherein the first composition is to be administered with a second composition comprising Venclexta, a tyrosine kinase inhibitor, a retinoic acid derivative, an anti-PD1 antibody, an EGFR inhibitor, or a combination thereof~~.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

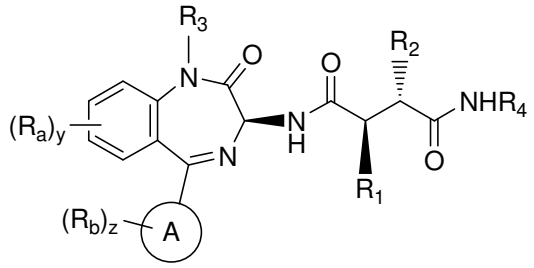
[005] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as not to obscure the present invention.

[006] In one embodiment, compositions of the present invention or for use in the methods of the present invention comprise one or more gamma secretase inhibitors. In one embodiment, the gamma secretase inhibitor comprises a bisfluoroalkyl-1,4-benzodiazepinone compound.

[007] In one embodiment, compositions of the present invention or for use in the methods of the present invention comprise one or more NOTCH inhibitors. In one embodiment, the NOTCH inhibitor comprises a bisfluoroalkyl-1,4-benzodiazepinone compound.

Bisfluoroalkyl-1,4-benzodiazepinone Compounds

[008] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

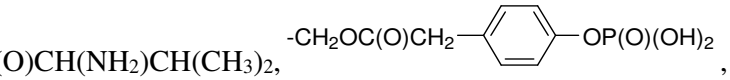
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

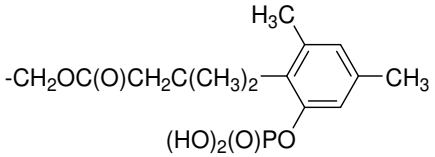
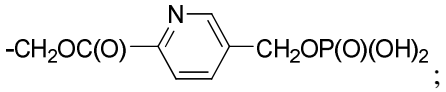
R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH($

$CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, ,

, or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$,

cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

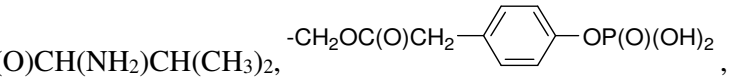
[009] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (II):

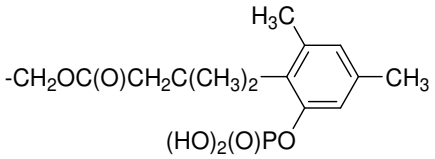
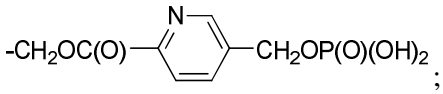
R_3 is H, -CH_3 or Rx;

R_4 is H or R_y;

R_x

is: -$CH_2OC(O)CH(CH_3)NH_2$, -$CH_2OC(O)CH(NH_2)CH(CH_3)_2$, -$CH_2OC(O)CH((CH($

$CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, ,

, or ;

R_y is: -$SCH_2CH(NH_2)C(O)OH$, -$SCH_2CH(NH_2)C(O)OCH_3$,

or -$SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently Cl, C_{1-3} alkyl, -CH_2OH, -CF_3, cyclopropyl, -OCH_3, and/or -O(cyclopropyl);

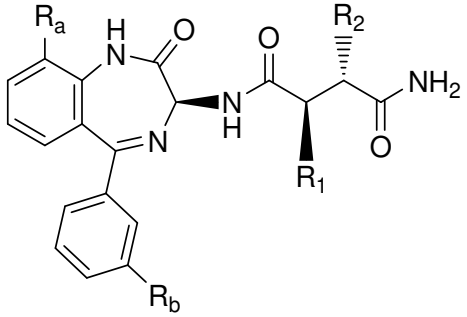
each R_b is independently F, Cl, -CH_3, -CH_2OH, -CF_3, cyclopropyl, and/or -OCH_3;

y is zero, 1 or 2; and

z is 1 or 2.

[0023] In another embodiment, Ring A is phenyl; and R_3 is H. In another embodiment, R_2 is -$CH_2CH_2CF_3$; and Ring A is phenyl. In another embodiment, R_2 is -$CH_2CH_2CF_3$; Ring A is phenyl; R_a is C_{1-3} alkyl or -CH_2OH; each R_b is independently F and/or Cl; and y is 1.

[0024] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (IV):

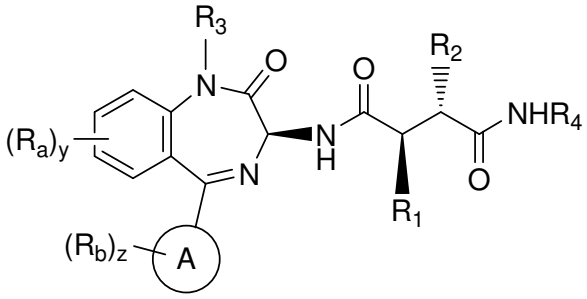


(IV)

[0025] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (V):

(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)carbamoyl)-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-L-cysteinate (57); methyl S-(((2S,3R)-6,6,6-trifluoro-3-(((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)carbamoyl)-2-(3,3,3-trifluoropropyl) hexanoyl)amino)-L-cysteinate (58); ((3S)-3-(((2R,3S)-3-carbamoyl-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)methyl (4-(phosphonooxy)phenyl)acetate (59); and ((3S)-3-(((2R,3S)-3-carbamoyl-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)methyl L-valyl-L-valinate (60); and salts thereof.

[0027] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

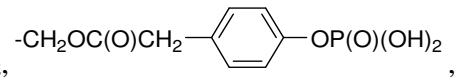
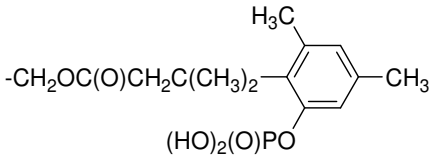
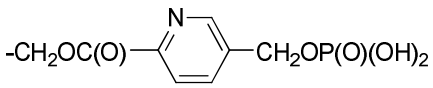
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

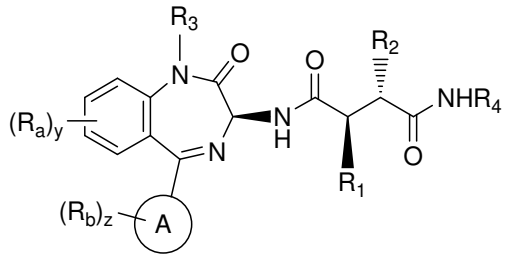
or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

CLAIMS

What is claimed is:

1. A composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

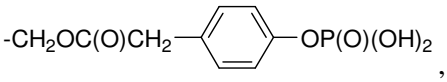
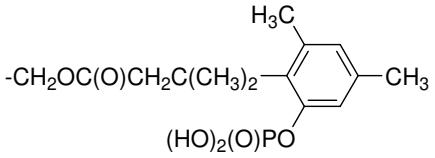
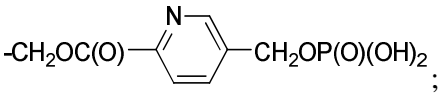
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

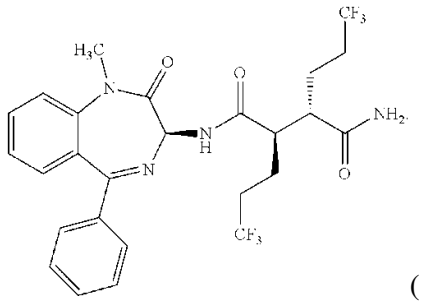
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2,

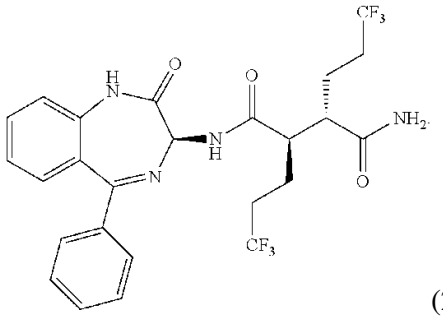
in combination with a composition comprising ~~Venclexta, a tyrosine kinase inhibitor, a retinoic acid derivative, an anti-PD1 antibody, an EGFR inhibitor,~~ a CDK 4/6 inhibitor, sorafenib, regorafenib, Venclexta, or Vorinostat, or a combination thereof.

2. The composition of claim 1, wherein one of the compound of Formula (I) is represented by ~~the structure of~~ Compound (1) having the structure of:



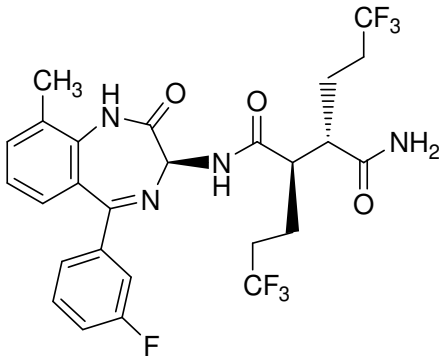
(1); or

~~by the structure of~~ Compound (2) having the structure of:



(2); or

~~by the structure of~~ Compound (22) having the structure of:



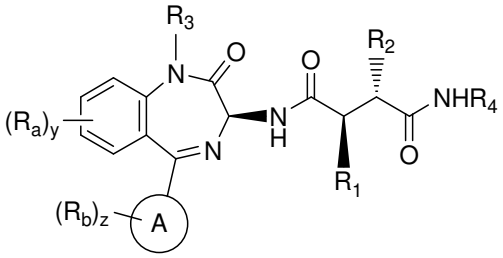
(22).

~~3. The composition of any one of claims 1-2, wherein said anti-PD1 antibody comprises Pembrolizumab.~~

~~4. The composition of any one of claims 1-3, wherein said tyrosine kinase inhibitor comprises Sorafenib.~~

3. The composition of claim 1 or 2, wherein said CDK 4/6 inhibitor comprises IBRANCE, ribociclib, or abemaciclib, or a combination thereof.

~~5.~~4. Use of a first composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

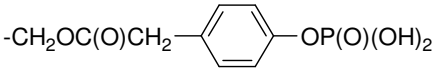
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

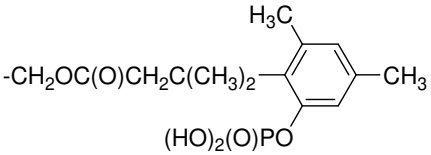
R_4 is H or R_y;

R_x

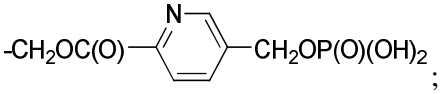
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

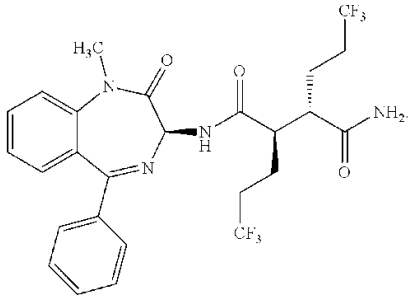
y is zero, 1 or 2; and

z is zero, 1, or 2

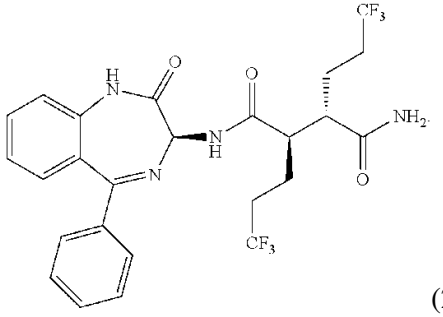
and a second composition comprising a CDK 4/6 inhibitor, sorafenib, regorafenib, Venclexta, or Vorinostat, or a combination thereof, in the manufacture of a medicament for treating, suppressing, or inhibiting a proliferative disease in a subject~~,~~ ~~wherein the first composition is to be administered with a second composition comprising Venclexta, a tyrosine kinase inhibitor, a retinoic acid derivative, an anti-PD1 antibody, an EGFR inhibitor, or a combination thereof~~.

5. The use of claim 4, wherein said CDK 4/6 inhibitor comprises IBRANCE, ribociclib, or abemaciclib, or a combination thereof.

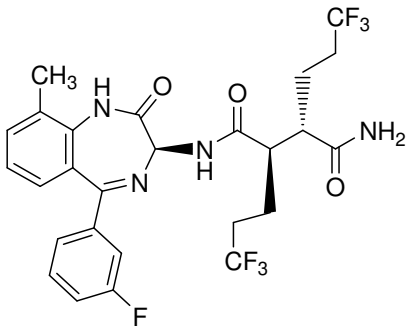
6. The use of claim ~~5~~4, wherein said proliferative disease is a pre-cancerous condition or a benign proliferative disorder.
7. The use of claim ~~5~~4, wherein said proliferative disease is a cancer.
8. The use of claim 7, wherein said cancer comprises Adenoid Cystic Carcinoma (ACC).
9. The use of claim 7, wherein said cancer comprises a Desmoid tumor.
10. The use of claim ~~9~~7, wherein said cancer comprises breast cancer.
11. The use of claim 10, wherein said breast cancer comprises triple negative breast cancer.
12. The use of claim 7, wherein said cancer comprises endometrial cancer.
13. The use of claim 7, wherein said cancer comprises non-small cell lung cancer (NSCLC).
14. The use of claim 7, wherein said cancer comprises multiple myeloma, lymphoma, or leukemia.
15. The use of claim 14, wherein said leukemia comprises T-cell acute lymphoblastic leukemia (T-ALL) or T-lymphoblastic leukemia/lymphoma (TLL).
16. The use of any one of claims 7-15, wherein said cancer comprises a Notch-activating mutation.
17. The use of any one of claims ~~7~~4-16, wherein said first composition and/or said second composition is formulated for intravenous or oral administration.
18. The use of any one of claims ~~7~~4-17, wherein one of the compound of Formula (I) comprises:



(1);



(2); or



(22).

~~19. The use of any one of claims 7-18, wherein said anti-PD1 antibody comprises Pembrolizumab.~~

~~20. The use of any one of claims 7-19, wherein said tyrosine kinase inhibitor comprises Sorafenib.~~