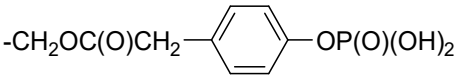
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

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

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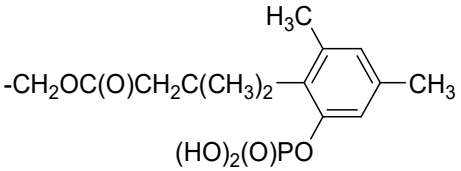
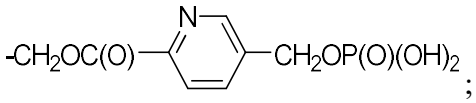


, or 

;

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, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

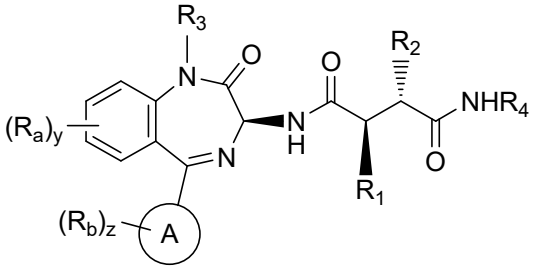
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is ~~zero,~~ 1~~,~~ or 2

in the manufacture of a medicament for treating, suppressing or inhibiting a proliferative disease in a subject, wherein said composition is to be administered at a dose of 4 mg or 6 mg.

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



(I)

and/or at least one salt thereof, wherein:

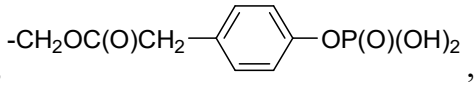
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

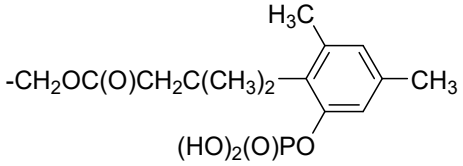
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

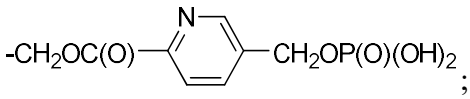
R_3 is H, $-CH_3$ or Rx;

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 $-NHCH_2CH_2OCH_3$;

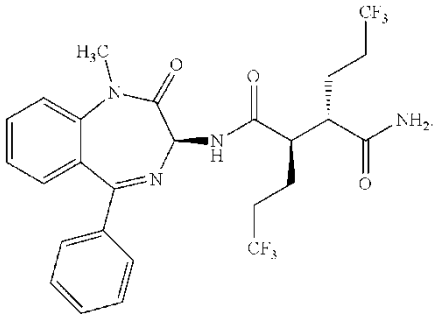
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2

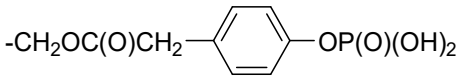
wherein said composition is administered at a dose of 4 mg.

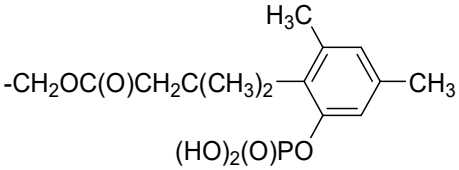
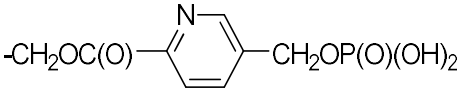
[005] The present disclosure also provides a method of treating, suppressing or inhibiting a solid tumor in a subject comprising the step of administering to said subject a composition comprising the compound of Formula (1):



(1),

wherein said compound is administered to said subject intravenously at a dose of 4 mg once per week.

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

, 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 $-NHCH_2CH_2OCH_3$;

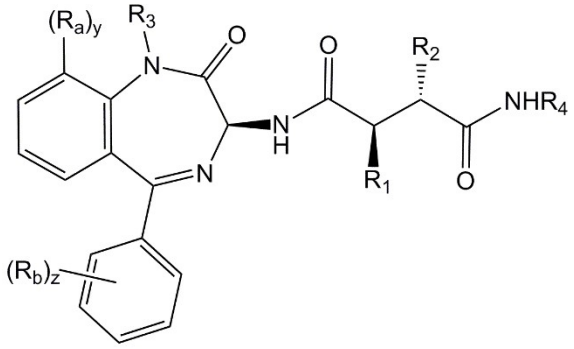
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[0021] In one embodiment, the present invention provides compositions comprising compounds as described herein formulated at a dose of 4 mg. In one embodiment, the present invention provides compositions comprising compounds as described herein formulated for intravenous administration.

[0022] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (II):

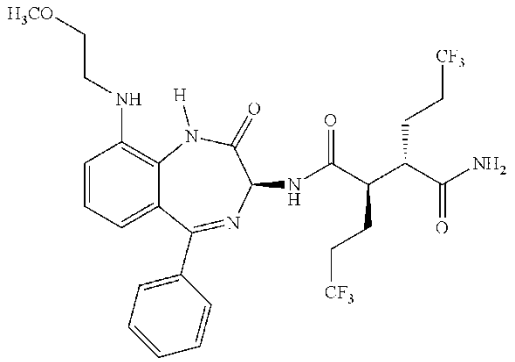


(II)

wherein R_3 is H or $-CH_3$; and y is zero or 1.

[0023] In one embodiment, the present invention provides compositions comprising compounds of Formula (III):

(21)



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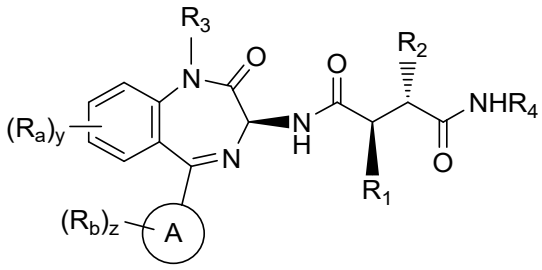
[0035] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

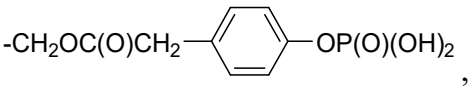
R_1 is $-CH_2CF_3$;

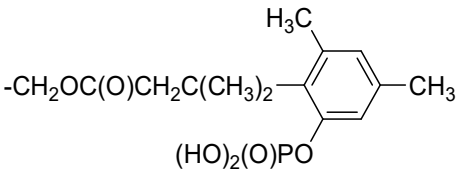
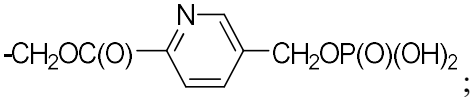
R_2 is $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

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

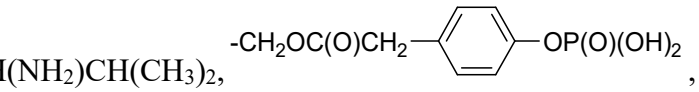
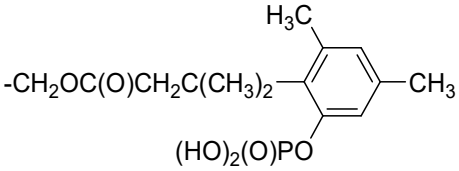
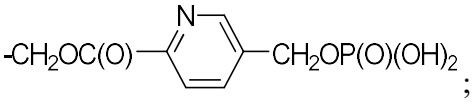
or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently Cl, $C_{1\text{-}3}$ 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 $-OCH_3$;

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, $-OCH_3$, $C_{1\text{-}3}$ 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

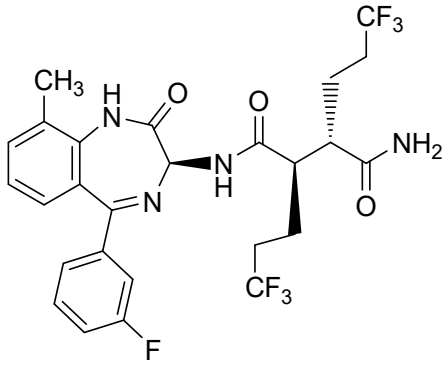
provided that if Ring A is phenyl, z is zero, and y is 1 or 2 then at least one R_a is $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, or -O(cyclopropyl);

provided that if R_3 is R_x then R_4 is H; and

provided that if R_4 is R_y then R_3 is H or $-CH_3$.

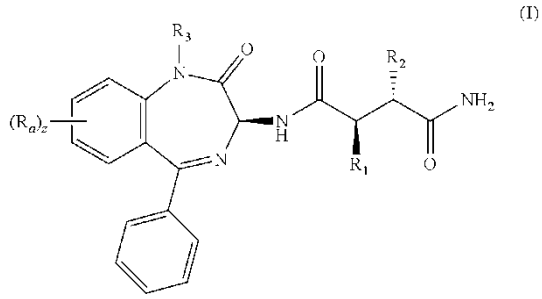
[0041] In another embodiment, the structure as described hereinabove comprises one or more of the following provisos: provided that if Ring A is phenyl, z is zero, and y is 1 or 2 then at least one R_a is $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, or -O(cyclopropyl); provided that if R_3 is R_x then R_4 is H; and provided that if R_4 is R_y then R_3 is H or $-CH_3$.

[0042] In another embodiment, the present invention provides compositions comprising compounds represented by the following structure:



(22).

[00132] In another embodiment, the present invention provides a method of treating, suppressing or inhibiting a proliferative disease in a subject, comprising the step of administering to said subject a composition comprising one or more compounds of Formula (I) and/or at least one salt thereof,



(I)

wherein:

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

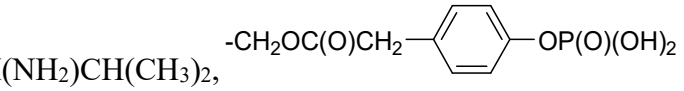
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

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



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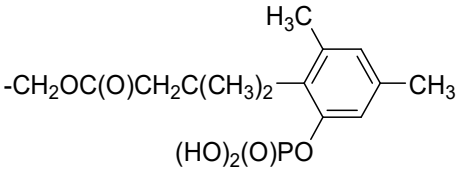

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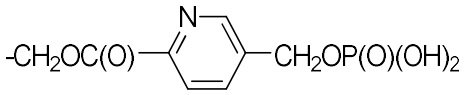


;

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, $-OCH_3$, $C_{1\text{-}3}$ 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.

[00133] In another embodiment, the present invention provides a method of treating, suppressing or inhibiting a proliferative disease in a subject, comprising the step of administering to said subject a composition comprising one or more compounds of Formula (III):

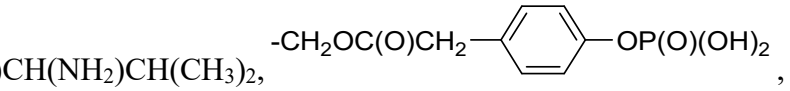
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

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

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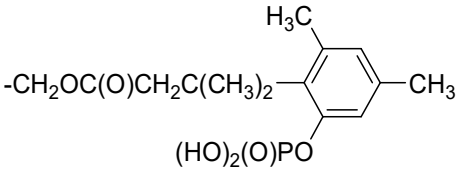
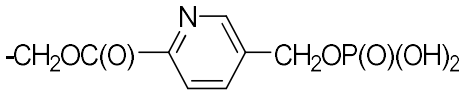


, or 

;

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;

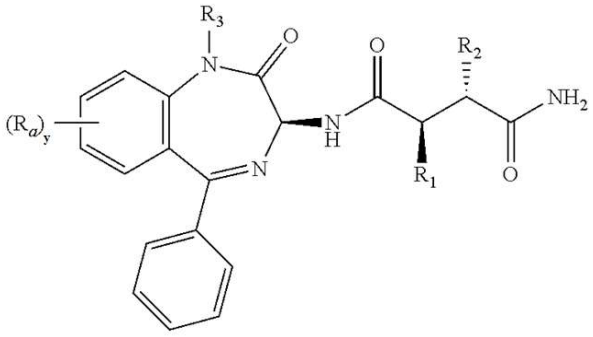
each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

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.

[00162] In another embodiment, the present invention provides a method of treating cancer, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (III):



or prodrugs or salts thereof; wherein:

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

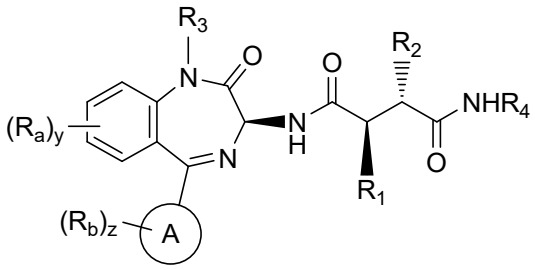
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H or $-CH_3$;

CLAIMS

What is claimed is:

1. Use of 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 $-CH_2CH_2CF_3$;

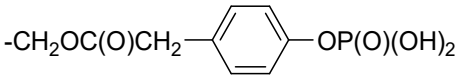
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

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



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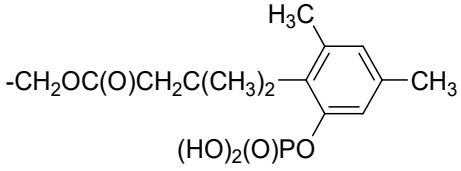

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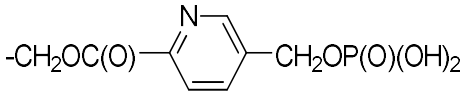


;

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, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

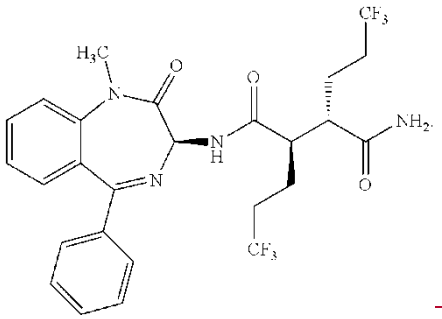
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

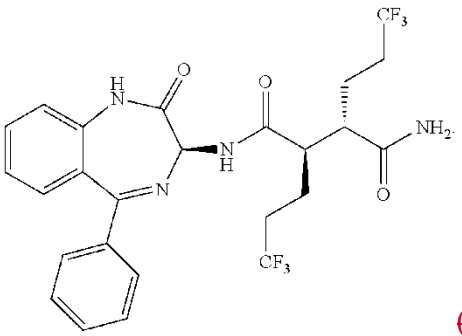
z is ~~zero,~~ 1~~,~~ or 2

in the manufacture of a medicament for treating, suppressing or inhibiting a proliferative disease in a subject, wherein said composition is to be administered at a dose of 4 mg or 6 mg.

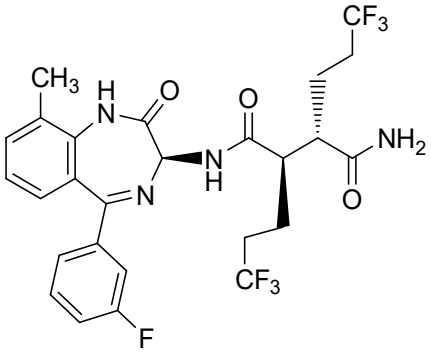
2. The use of claim 1, wherein said proliferative disease is a pre-cancerous condition or a benign proliferative disorder.
3. The use of claim 1, wherein said proliferative disease is a cancer.
4. The use of claim 3, wherein said cancer comprises breast cancer, endometrial cancer, pancreatic adenocarcinoma, or non-small cell lung cancer (NSCLC).
5. The use of claim 4, wherein said breast cancer comprises triple negative breast cancer.
6. The use of claim 3, wherein said cancer comprises multiple myeloma.
7. The use of claim 3, wherein said cancer comprises a Desmoid tumor or fibromatosis.
8. The use of any one of claims 3-7, wherein said cancer comprises a solid tumor.
9. The use of claim 8, wherein said solid tumor is a metastatic or advanced solid tumor.
10. The use of any one of claims 8-9, wherein said solid tumor comprises non-triple negative breast cancer (TNBC), colorectal cancer, gastric cancer, melanoma, squamous, non-squamous, ovarian cancer, or gastroesophageal junction adenocarcinoma.
11. The use of any one of claims 3-10, wherein said cancer comprises a carcinoma, a lymphoma, a leukemia, or a combination thereof.
12. The use of claim 11, wherein said carcinoma comprises Adenoid Cystic Carcinoma (ACC).
13. The use of claim 11, wherein said lymphoma comprises Marginal zone B cell lymphoma, Diffuse large B cell lymphoma, Mantle cell lymphoma, or a combination thereof.
14. The use of claim 11, wherein said leukemia comprises T-cell acute lymphoblastic leukemia (T-ALL), T-lymphoblastic leukemia/lymphoma (TLL), or Chronic Lymphocytic Leukemia (CLL).
15. The use of any one of claims 3-14, wherein said cancer comprises a Notch-activating mutation, a Wnt-activating mutation, or a combination thereof.
16. The use of any one of claims 1-15, wherein said composition is formulated as a monotherapy.
17. The use of any one of claims 1-15, wherein said composition further comprises a second composition comprising an additional cancer therapeutic agent.
18. The use of any one of claims 1-17, wherein said first composition and/or said second composition is formulated for intravenous or oral administration.
19. The use of any one of claims 1-18, wherein the compound of Formula (I) comprises:



~~(1),~~



~~(2), or~~



(22).

20. The use of any one of claims 1-19, wherein said composition is formulated for weekly administration or for administration once every two weeks.