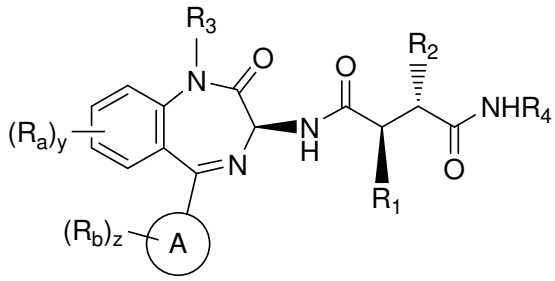
COMPOSITIONS COMPRISING BISFLUOROALKYL-1,4-BENZODIAZEPINONE COMPOUNDS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[001] The present invention provides methods of use for compositions comprising bisfluoroalkyl-1,4-benzodiazepinone compounds, including compounds of Formula (I) or prodrugs thereof;



(I),

for treating diseases and disorders such as cancer.

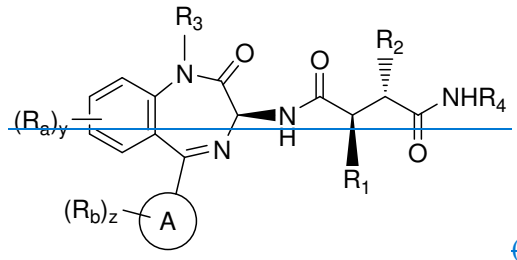
BACKGROUND OF THE INVENTION

[002] Many human solid tumors and hematologic malignancies show a characteristic deregulation of Notch pathway signaling. An important step in activation of Notch receptors is cleavage by gamma secretase, freeing the intracellular signaling domain. Notch inhibition by gamma secretase inhibitors (GSIs) such as benzodiazepinone compounds has potential for having potent antineoplastic effects.

[003] Patients with advanced solid tumors refractory to standard therapies, patients who relapsed after standard therapies or patients with tumors for which there is no known effective treatment require new strategies for treating solid tumors.

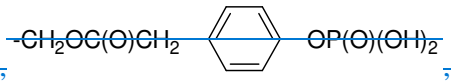
SUMMARY

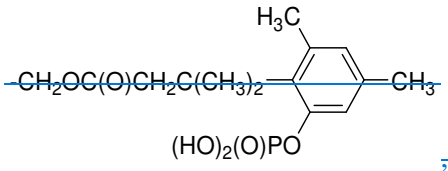
[003a] In one aspect, the present disclosure refers to use of a composition comprising: ~~one or more compounds represented by the structure of Formula (I):~~

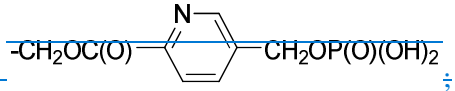


~~(I)~~

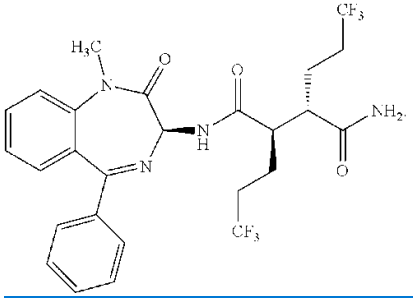
~~and/or at least one salt thereof, wherein:~~

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



~~, or~~  ~~;~~

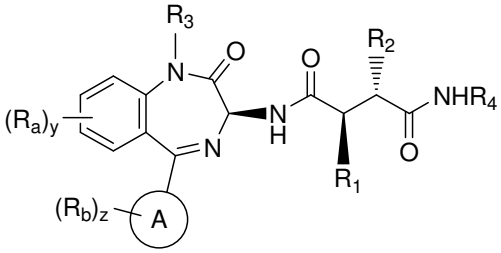
~~R_y is: $SCH_2CH(NH_2)C(O)OH$, $SCH_2CH(NH_2)C(O)OCH_3$,~~
~~or $SCH_2CH(NH_2)C(O)OC(CH_3)_3$;~~
~~Ring A is phenyl or pyridinyl;~~
~~each R_a is independently F, Cl, CN, OCH_3, C_{1-3} alkyl, CH_2OH, CF_3,~~
~~cyclopropyl, OCH_3, O(cyclopropyl) and/or $NHCH_2CH_2OCH_3$;~~
~~each R_b is independently F, Cl, CH_3, CH_2OH, CF_3, cyclopropyl, and/or OCH_3;~~
~~y is zero, 1 or 2; and~~
~~z is 1 or 2~~



(1)

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):



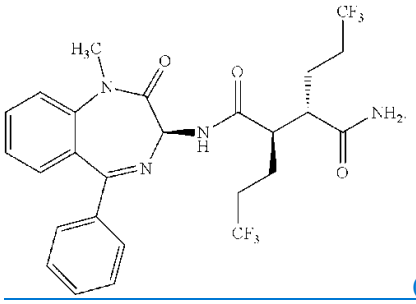
(I)

and/or at least one salt thereof, wherein:

CLAIMS

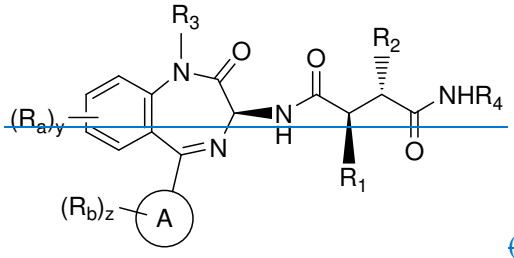
What is claimed is:

1. Use of a composition comprising:



(1)

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 $CH_2CH_2CF_3$;

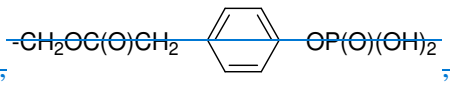
R_2 is CH_2CF_3, $CH_2CH_2CF_3$, or $CH_2CH_2CH_2CF_3$;

R_3 is H, CH_3 or Rx;

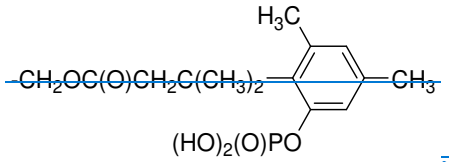
R_4 is H or R_y;

R_x

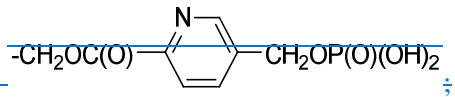
is: $CH_2OC(O)CH(CH_3)NH_2$, $CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



;



, 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;

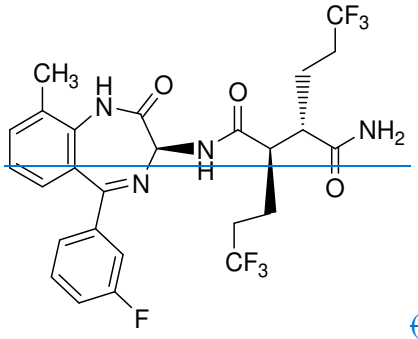
~~y is zero, 1 or 2; and~~

~~z is 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:~~



~~(22).~~

~~20.~~19. The use of any one of claims 1-~~19~~18, wherein said composition is formulated for weekly administration or for administration once every two weeks.