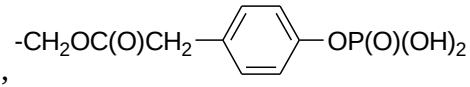
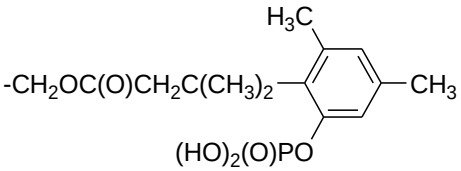
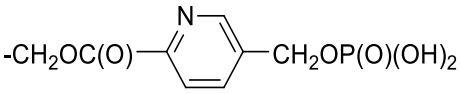
$CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, ,

, 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 $-NHCH_2CH_2OCH_3$;

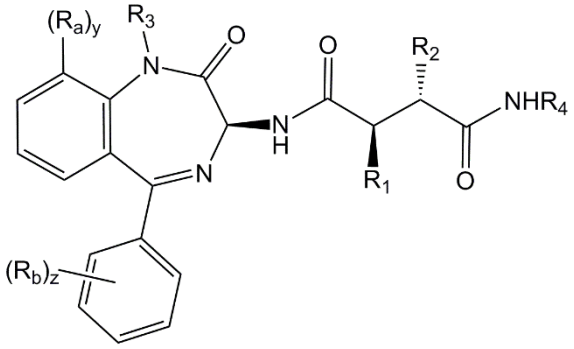
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[0028] 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.

[0029] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (II):

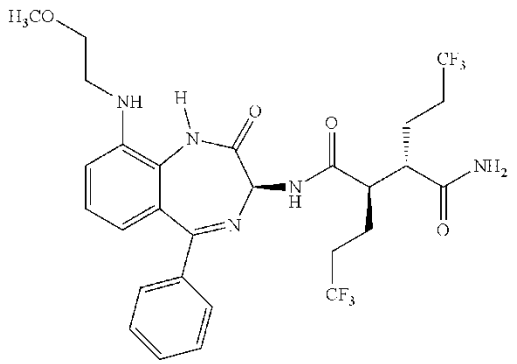


(II)

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

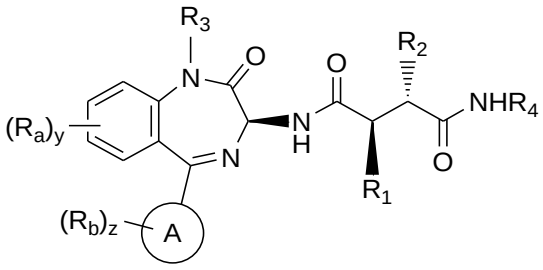
[0030] In one embodiment, the present invention provides compositions comprising compounds of Formula (III):

(21)



.

[0042] 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:

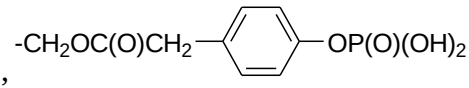
R_1 is $-CH_2CF_3$;

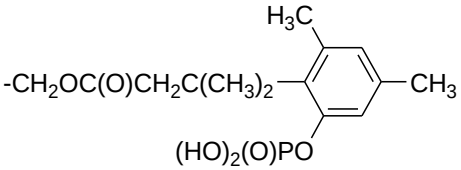
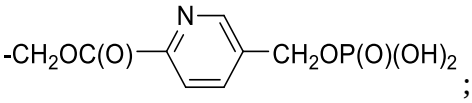
R_2 is $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

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

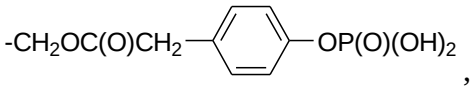
or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

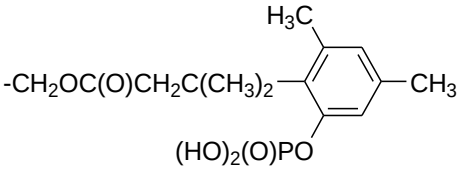
Ring A is phenyl or pyridinyl;

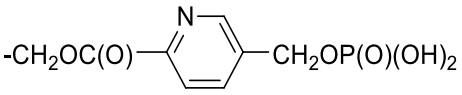
each R_a is independently Cl, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, and/or -O(cyclopropyl);

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_{1-3} 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

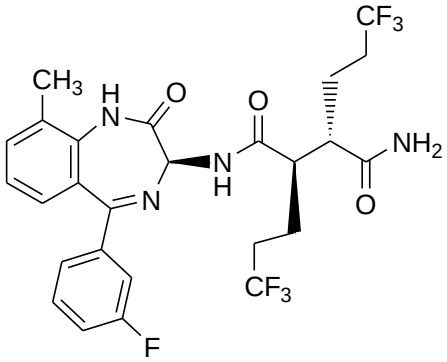
provided that if Ring A is phenyl, z is zero, and y is 1 or 2 then at least one R_a is C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, or -O(cyclopropyl);

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

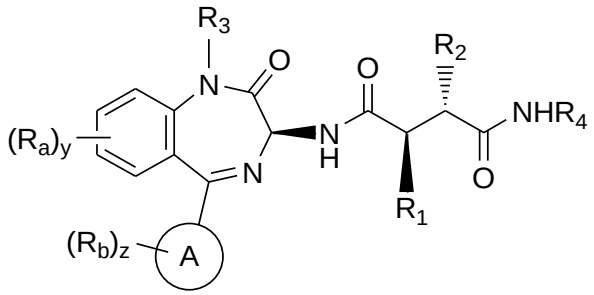
provided that if R_4 is R_y then R_3 is H or $-CH_3$.

[0048] 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_{1-3} 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 $-CH_3$.

[0049] In another embodiment, the present invention provides compositions comprising compounds represented by the following structure:



(22).



(I),

wherein:

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

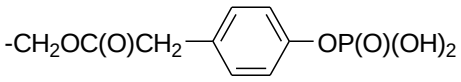
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

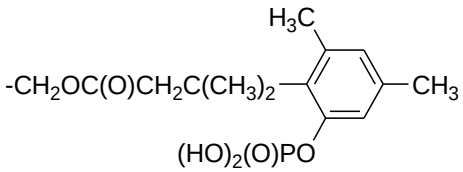
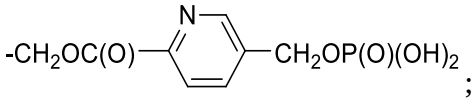
R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

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

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

, 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 $-NHCH_2CH_2OCH_3$;

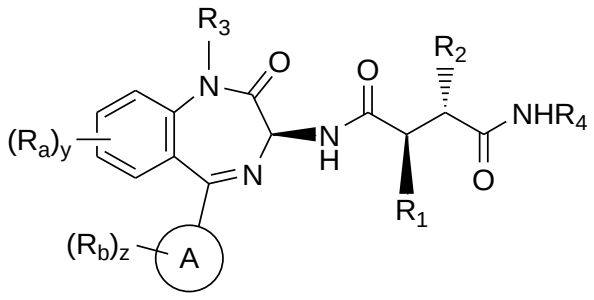
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[00140] 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):

administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) and/or at least one salt thereof,



(I),

wherein:

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

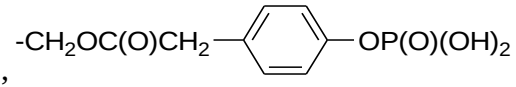
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

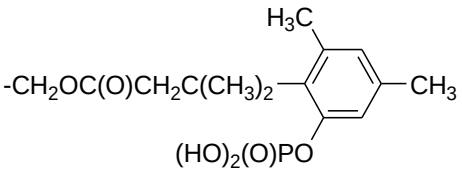
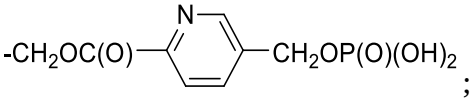
R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

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

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

, 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 $-NHCH_2CH_2OCH_3$;

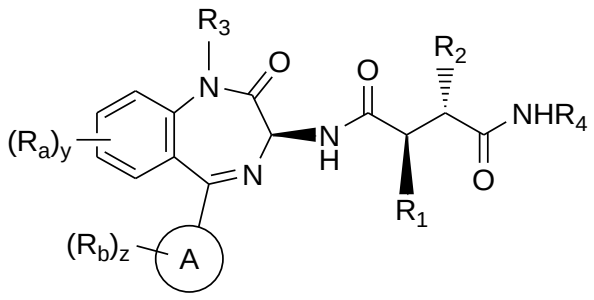
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[00165] In another embodiment, the present invention provides a method of treating cancer, wherein said cancer comprises one or more Notch-activating genetic alterations, comprising the step

[00168] In one embodiment, the present invention provides a method of treating a carcinoma, wherein said carcinoma comprises one or more Notch-activating genetic alterations, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) and/or at least one salt thereof,



(I),

wherein:

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

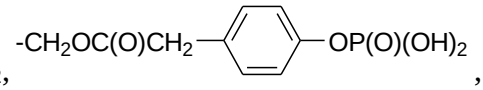
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

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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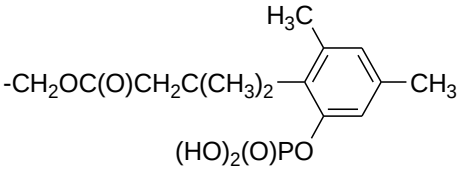
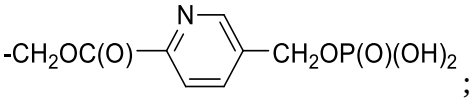


, or 

;

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;

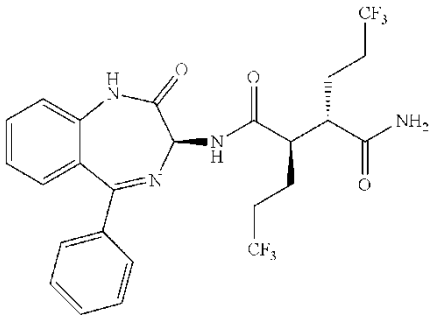
each R_a is independently F, Cl, -CN, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$,

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

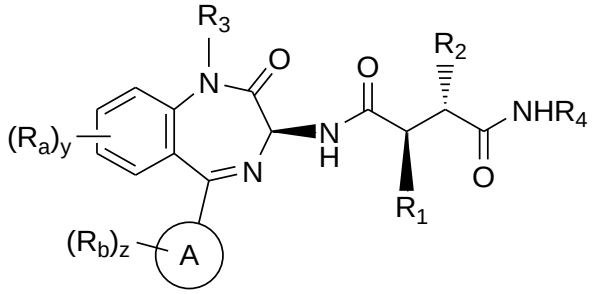
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.



[00172] In one embodiment, the present invention provides a method of treating ACC, wherein said ACC comprises one or more Notch-activating genetic alterations, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) and/or at least one salt thereof,



(I),

wherein:

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

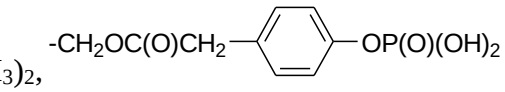
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

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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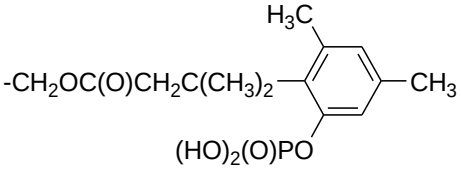
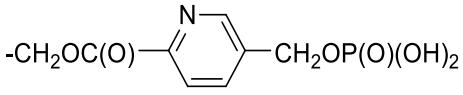


, or



;

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

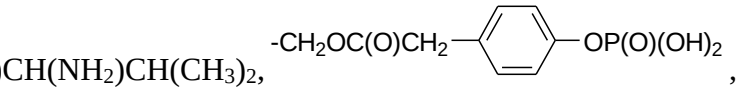
or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

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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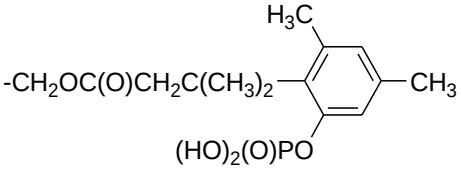
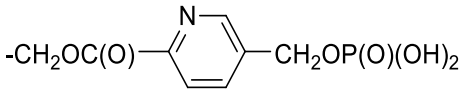


, or 

;

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, $-CH_2OH$, $-CF_3$,

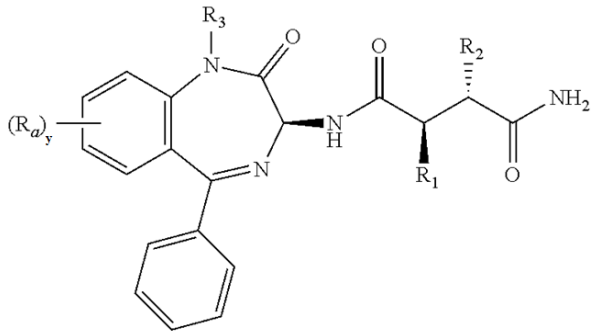
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

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.

[00179] In another embodiment, the present invention provides a method of reducing tumor size in a subject having ACC, wherein one or more cells of the ACC comprises one or more Notch-activating genetic alterations, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (III):

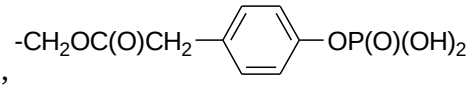


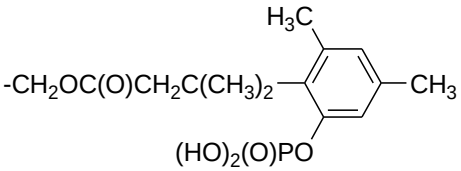
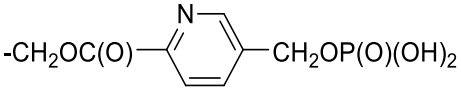
or prodrugs or salts thereof; wherein:

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 $-CH_3$;

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

, 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, $-CH_2OH$, $-CF_3$,

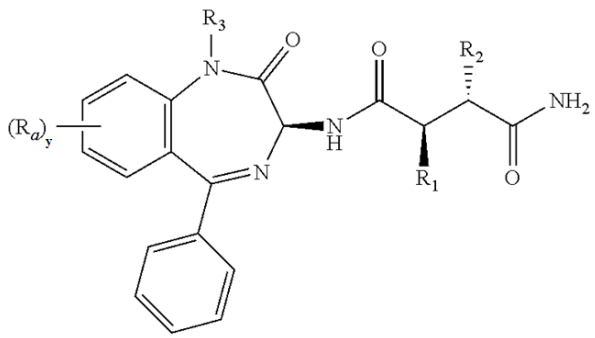
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

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.

[00186] In another embodiment, the present invention provides a method of reducing tumor volume in a subject having ACC, wherein one or more cells of the ACC comprises one or more Notch-activating genetic alterations, 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 $-CH_2CH_2CH_2CF_3$;

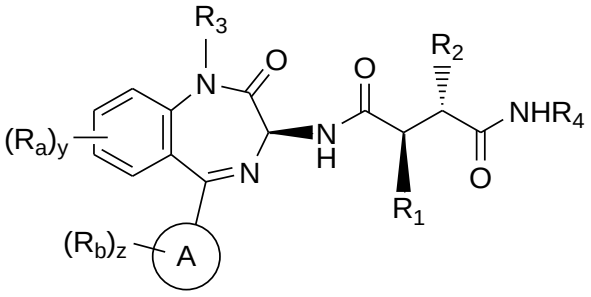
R_3 is H or $-CH_3$;

each R_a is independently F, Cl, -CN, $-OCH_3$, and/or $-NHCH_2CH_2OCH_3$; and

y is zero, 1, or 2.

[00187] In another embodiment, the present invention provides a method of reducing tumor volume in a subject having ACC, wherein one or more cells of said ACC comprises one or more

comprises one or more Notch-activating genetic alterations, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) and/or at least one salt thereof,



(I),

wherein:

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

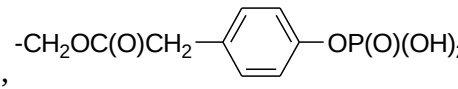
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

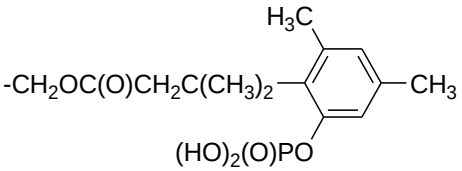
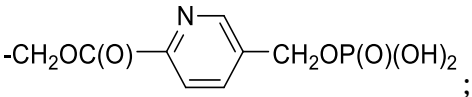
R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

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

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

, 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.

[00208] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having ACC, wherein one or more cells of the ACC