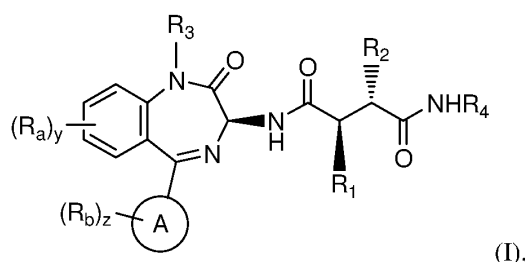


COMPOSITIONS COMPRISING BISFLUOROALKYL-1,4-BENZODIAZEPINONE COMPOUNDS AND METHODS OF USE THEREOF

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),

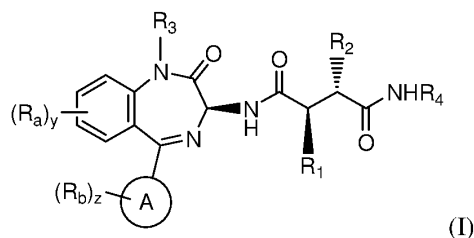
for treating diseases and disorders such as cancer.

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 OF THE INVENTION

- [004] 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 represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

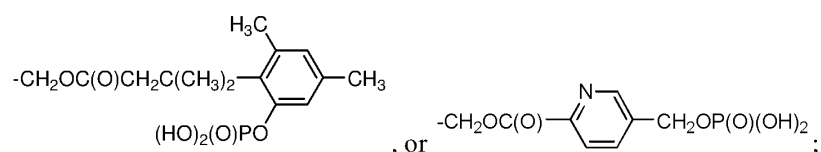
R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

R₃ is H, -CH₃ or R_x;

R₄ is H or R_y;

5 R_x

is: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(CH₃)
)₂)NHC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH₂--OP(O)(OH)₂,



R_y is: -SCH₂CH(NH₂)C(O)OH, -SCH₂CH(NH₂)C(O)OH₃,

10 or -SCH₂CH(NH₂)C(O)OC(CH₃)₃;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH₃, C₁₋₃ alkyl, -CH₂OH, -CF₃,

cyclopropyl, -OCH₃, -O(cyclopropyl) and/or -NHCH₂CH₂OCH₃;

each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

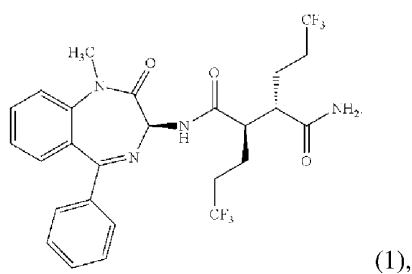
15 y is zero, 1 or 2; and

z is zero, 1, or 2

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

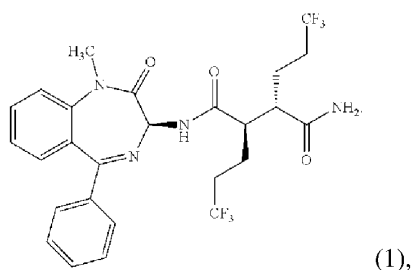
[005] The present invention also provides a method of treating, suppressing or inhibiting a solid tumor in a subject comprising the step of administering to said subject a composition comprising the

20 compound of Formula (1):



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

[006] The present invention 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):



- 5 wherein said compound is administered to said subject intravenously at a dose of 6 mg once every two weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

[007] **Figure 1. Study Design** of Phase I clinical trial, ascending multiple-dose study of intravenous (IV) administration of Compound (1) in patients with advanced or metastatic solid tumors; IV = intravenous; MTD = maximum tolerated dose; QW = once weekly; Q2W = once every 2 weeks.

[008] **Figure 2A. Correlation between Individual Patient C_{max} and Compound (1) Dose - Week 1.** Patients were administered 0.3 mg; 0.6 mg; 1.2 mg; 2.4 mg; 4 mg; 6 mg or 8.4 mg once a week. AUC = area under the curve; C_{max} = maximum concentration; QW = once weekly.

[009] **Figure 2B. Correlation between Individual Patient $AUC_{(0-t)}$ and Compound (1) Dose - Week 1.** Patients were administered 0.3 mg; 0.6 mg; 1.2 mg; 2.4 mg; 4 mg; 6 mg or 8.4 mg once a week. AUC = area under the curve; C_{max} = maximum concentration; QW = once weekly.

[0010] **Figure 3A. Plasma Concentration-Time Profiles per Treatment Group after Compound (1) administration - Week 1.** Patients were administered 0.3 mg; 0.6 mg; 1.2 mg; 2.4 mg; 4 mg; 6 mg or 8.4 mg of Compound (1) once a week, and plasma concentration of Compound (1) was determined via a validated liquid chromatography-mass spectrometry/mass spectrometry assay. QW = once weekly.

[0011] **Figure 3B. Plasma Concentration-Time Profiles per Treatment Group after Compound (1) administration - Week 4.** Patients were administered 0.3 mg; 0.6 mg; 1.2 mg; 2.4 mg; 4 mg; 6 mg or 8.4 mg of Compound (1) once a week, and plasma concentration of Compound (1) was determined via a validated liquid chromatography-mass spectrometry/mass spectrometry assay. QW = once weekly.

[0012] **Figure 3C. Individual Plasma Concentration-Time Profiles after Compound (1) (4 mg) administration – Week 1.** Patients were administered 4 mg Compound (1) once a week, and plasma concentration of Compound (1) was determined via a validated liquid chromatography–mass spectrometry/mass spectrometry assay. The dotted horizontal line shows the EC_{50} = half maximal effective concentration; QW = once weekly.

[0013] **Figure 3D. Individual Plasma Concentration-Time Profiles after Compound (1) (4 mg) administration – Week 4.** Patients were administered 4 mg Compound (1) once a week, and plasma concentration of Compound (1) was determined via a validated liquid chromatography–mass spectrometry/mass spectrometry assay. The dotted horizontal line shows the EC_{50} = half maximal effective concentration; QW = once weekly.

[0014] **Figure 4A. Pharmacodynamic Effect of Compound (1) on Expression of Hes1 – Week 1.** Patients were administered 2.4 mg, 4 mg, 6, mg, and 8.4 mg Compound (1) once a week, and Hes1 expression was determined using quantitative real time polymerase chain reaction. Data presented for subjects one week after receiving 2.4 mg, 4 mg, 6, mg, and 8.4 mg Compound (1) as compared to baseline Hes1 expression. QW = once weekly.

[0015] **Figure 4B. Pharmacodynamic Effect of Compound (1) on Expression of Hes1 – Week 4.** Patients were administered 2.4 mg, 4 mg, 6, mg, and 8.4 mg of Compound (1) once a week, and Hes1 expression was determined at the end of the fourth week using quantitative real time polymerase chain reaction. Data presented as compared to baseline Hes1 expression. QW = once weekly.

[0016] **Figure 5A. Efficacy of Compound (1) Treatment - Tumor Burden.** Tumor burden for three individual patients with desmoid tumors or fibromatosis treated with Compound (1) was assessed over time as percent change from baseline. Horizontal lines denote 20% increase, no change (0%) and 30% decrease from baseline. Subjects with baseline and at least one post-baseline assessment with non-missing value are presented. Subjects meeting more than one qualification are presented only once using their priority qualifying criterion: gene mutation or tumor type. Subject 4-11 continued to Week 243 with PR and then transitioned to named patient program of therapy with Compound (1). Subject 5-14 continued to Week 100 with PR and then transitioned to named patient program of therapy with Compound (1).

[0017] **Figure 5B. Efficacy of Compound (1) Treatment on Tumors with Activated Notch or Wnt Signalling.** Change in tumor burden from baseline for patients with tumors with activated Notch or Wnt signalling after treatment with Compound (1). Dotted line: Breast-APC; Dashed line: GE Junction Notch1 & APC; solid line: Notch1 adenoid cystic carcinoma. Horizontal lines denote 20% increase, no change (0%) and 30% decrease from baseline. ‘+’ – first occurrence of new lesions. Subjects with baseline and at least one post-baseline assessment with non-missing value are

presented. Subjects meeting more than one qualification are presented only once using their priority qualifying criterion: gene mutation or tumor type. Subject 3-37 having GE Junction Adenocarcinoma shows a 100% reduction from baseline at Week 40. Subject 5-14 with abdominal desmoid fibromatosis and reported CTNNB1 mutation is included in the figure for tumor type.

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DETAILED DESCRIPTION OF THE PRESENT INVENTION

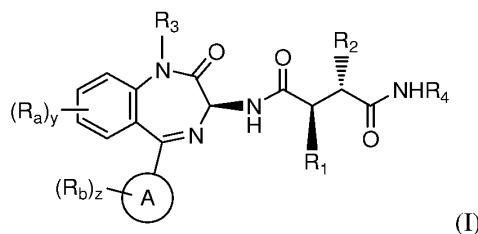
[0018] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as not to obscure the present invention.

[0019] 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, one or more Notch inhibitors, or a combination thereof. In one embodiment, the gamma secretase inhibitor comprises a bisfluoroalkyl-1,4-benzodiazepinone compound.

15

Bisfluoroalkyl-1,4-benzodiazepinone Compounds

[0020] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



20

and/or at least one salt thereof, wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

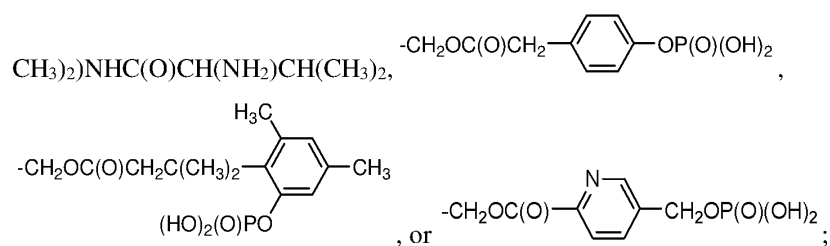
R₃ is H, -CH₃ or R_x;

25

R₄ is H or R_y;

R_x

is: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(



R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OH_3$,

or $-\text{SCH}_2\text{CH}(\text{NH}_2)\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$;

5 Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH₃, C₁₋₃ alkyl, -CH₂OH, -CF₃, cyclopropyl, -OCH₃, -O(cyclopropyl) and/or -NHCH₂CH₂OCH₃;

each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

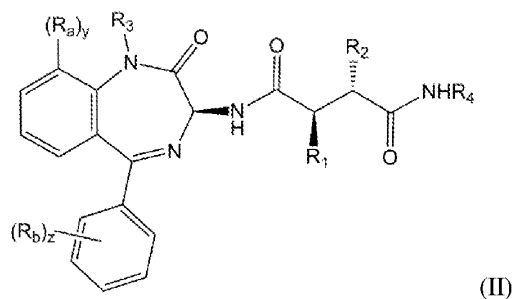
y is zero, 1 or 2; and

10 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.

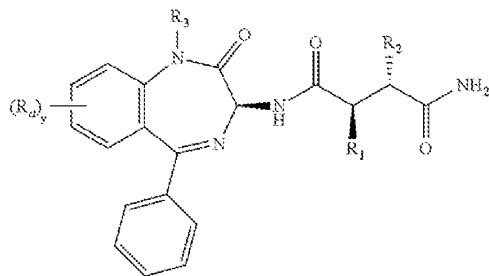
[0022] In one embodiment, the present invention provides compositions comprising compounds

15 represented by the structure of Formula (II):



wherein R₃ is H or -CH₃; and y is zero or 1.

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



(III)

or prodrugs or salts thereof; wherein:

R_1 is $-\text{CH}_2\text{CF}_3$ or $-\text{CH}_2\text{CH}_2\text{CF}_3$;

5 R_2 is $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$;

R_3 is H or $-\text{CH}_3$;

each R_a is independently F, Cl, $-\text{CN}$, $-\text{OCH}_3$, and/or $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$; and

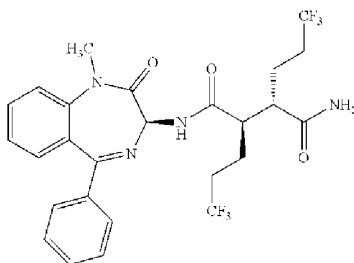
y is zero, 1, or 2.

[0024] In one embodiment, R_1 is $-\text{CH}_2\text{CF}_3$ or $-\text{CH}_2\text{CH}_2\text{CF}_3$ and R_2 is $-\text{CH}_2\text{CF}_3$ or $-\text{CH}_2\text{CH}_2\text{CF}_3$. In

10 another embodiment, R_1 is $-\text{CH}_2\text{CH}_2\text{CF}_3$ and R_2 is $-\text{CH}_2\text{CH}_2\text{CF}_3$. In one embodiment, y is 1 or 2. In another embodiment, y is zero or 1. In one embodiment, y is zero.

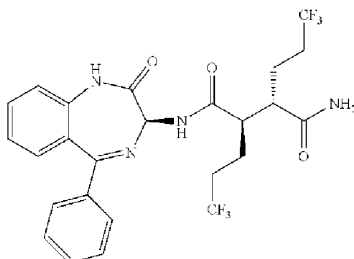
[0025] In one embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide

(1)

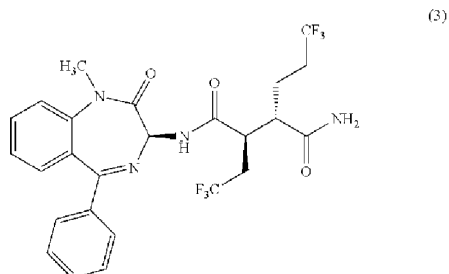


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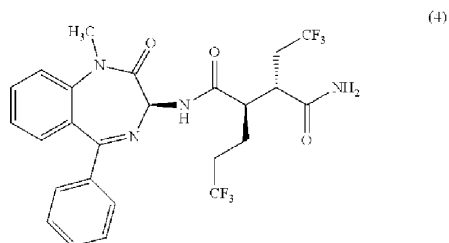
[0026] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (2)



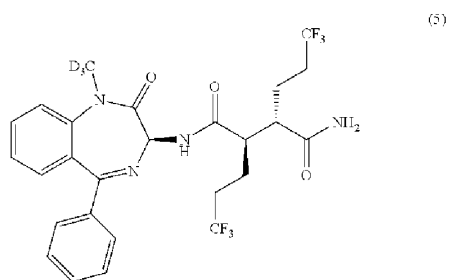
[0027] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2-(2,2,2-trifluoroethyl)-3-(3,3,3-trifluoropropyl)succinamide (3);



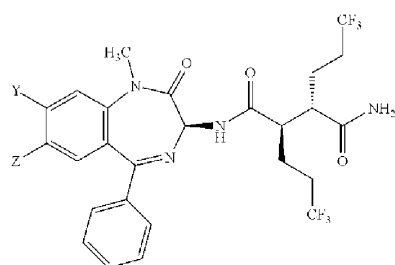
- 5 [0028] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(2,2,2-trifluoroethyl)-2-(3,3,3-trifluoropropyl)succinamide (4);



- [0029] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-1-(²H₃)methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (5);
- 10



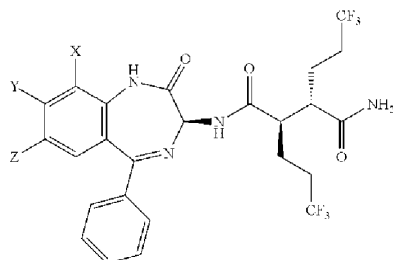
[0030] In another embodiment, the compound of Formula (III) comprises a compound of Formula (VI):



(VI),

which in one embodiment, comprises (2R,3S)—N-((3S)-7-chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (6), i.e. Y=H and Z=Cl; (2R,3S)—N-((3S)-8-methoxy-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (7), i.e. Y=OCH₃ and Z=H; (2R,3S)—N-((3S)-8-fluoro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (8), i.e. Y=F and Z=H; (2R,3S)—N-((3S)-7-methoxy-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (9), Y=H and Z=OCH₃; (2R,3S)—N-((3S)-7-fluoro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (10), i.e. Y=H and Z=F; or (2R,3S)—N-((3S)-8-chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (11), i.e. Y=Cl and Z=H.

[0031] In another embodiment, the compound of Formula (III) comprises a compound of Formula (VII):

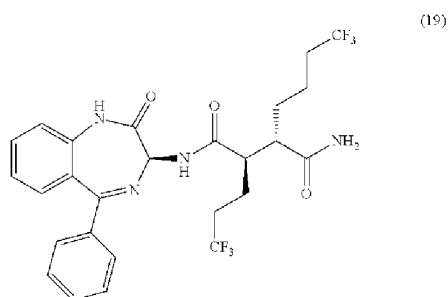


(VII),

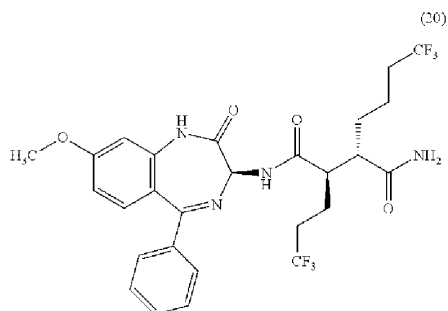
which in one embodiment, comprises (2R,3S)—N-((3S)-9-methoxy-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (12), i.e. X=OCH₃, Y=H and Z=H; (2R,3S)—N-((3S)-8-methoxy-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (13), i.e. X=H, Y=OCH₃ and Z=H; (2R,3S)—N-((3S)-7-methoxy-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (14), i.e. X=H, Y=H and Z=OCH₃; (2R,3S)—N-((3S)-8-cyano-9-methoxy-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (15), i.e. X=OCH₃, Y=CN and Z=H; (2R,3S)—N-((3S)-8,9-dichloro-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide

(16), i.e. X=Cl, Y=Cl and Z=H; (2R,3S)—N-((3S)-9-fluoro-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (17), i.e. X=F, Y=H and Z=H; or (2R,3S)—N-((3S)-9-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (18), i.e. X=Cl, Y=H and Z=H.

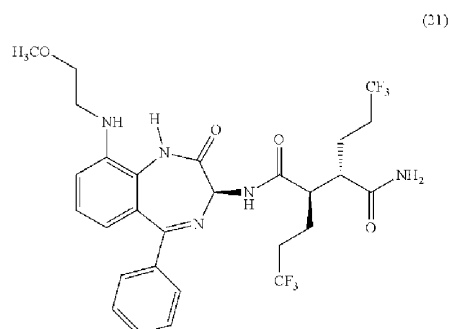
- 5 [0032] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (19);



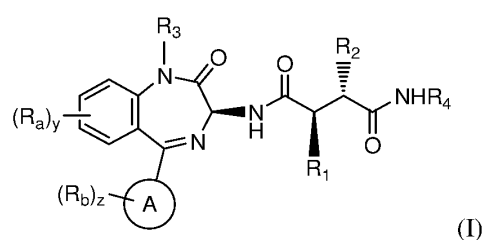
- [0033] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-8-methoxy-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (20)



- [0034] In another embodiment, the compound of Formula (III) comprises: (2R,3S)—N-((3S)-9-((2-methoxyethyl)amino)-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (21)



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



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

R_1 is $-\text{CH}_2\text{CF}_3$;

R_2 is $-\text{CH}_2\text{CH}_2\text{CF}_3$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$;

R_3 is H, $-\text{CH}_3$ or R_x ;

R_4 is H or R_y ;

10 R_x

is: $-\text{CH}_2\text{OC}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}(\text{NH}_2)\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}((\text{CH}(\text{CH}_3)_2)\text{NHC}(\text{O})\text{CH}(\text{NH}_2)\text{CH}(\text{CH}_3)_2)$,

$-\text{CH}_2\text{OC}(\text{O})\text{CH}_2$ -, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_2$ -,

$-\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{C}(\text{CH}_3)_2$ -, $-\text{CH}_2\text{OC}(\text{O})$ -, $-\text{CH}_2\text{OC}(\text{O})$ -;

R_y is: $-\text{SCH}_2\text{CH}(\text{NH}_2)\text{C}(\text{O})\text{OH}$, $-\text{SCH}_2\text{CH}(\text{NH}_2)\text{C}(\text{O})\text{OH}_3$,

15 or $-\text{SCH}_2\text{CH}(\text{NH}_2)\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently Cl, C_{1-3} alkyl, $-\text{CH}_2\text{OH}$, $-\text{CF}_3$, cyclopropyl, $-\text{OCH}_3$,

and/or $-\text{O}(\text{cyclopropyl})$;

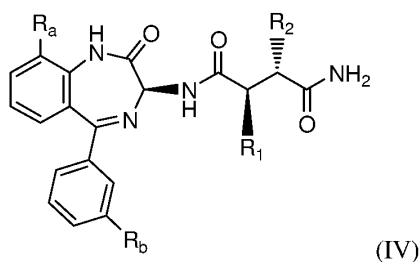
each R_b is independently F, Cl, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CF}_3$, cyclopropyl, and/or $-\text{OCH}_3$;

y is zero, 1 or 2; and

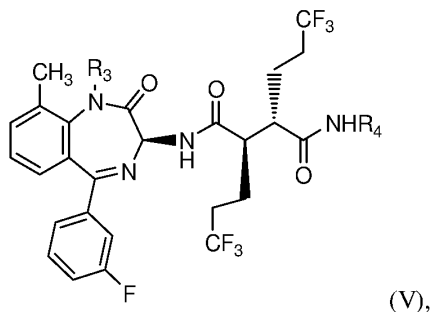
z is 1 or 2.

- [0036] In another embodiment, Ring A is phenyl; and R_3 is H. In another embodiment, R_2 is $-\text{CH}_2\text{CH}_2\text{CF}_3$; and Ring A is phenyl. In another embodiment, R_2 is $-\text{CH}_2\text{CH}_2\text{CF}_3$; Ring A is phenyl;
 5 R_a is C_{1-3} alkyl or $-\text{CH}_2\text{OH}$; each R_b is independently F and/or Cl; and y is 1.

[0037] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (IV):



- [0038] In another embodiment, the present invention provides compositions comprising compounds
 10 represented by the structure of Formula (V):



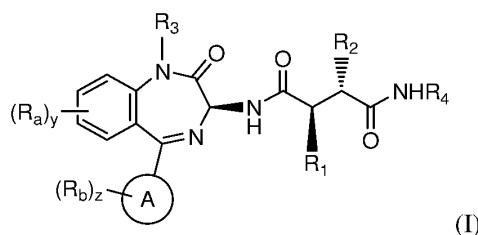
wherein R_3 is H or R_x .

- [0039] In another embodiment, the present invention provides compositions comprising (2R,3S)-N-
 ((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-
 15 trifluoropropyl)succinamide (22); (2R,3S)-N-((3S)-5-(3-chlorophenyl)-9-ethyl-2-oxo-2,3-dihydro-
 1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (23); (2R,3S)-N-((3S)-5-(3-
 chlorophenyl)-9-isopropyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-
 trifluoropropyl)succinamide (24); (2R,3S)-N-(9-chloro-5-(3,4-dimethylphenyl)-2-oxo-2,3-dihydro-
 1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (25);
 20 (2R,3S)-N-(9-chloro-5-(3,5-dimethylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-
 (4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (26); (2R,3S)-N-((3S)-9-ethyl-5-(3-
 methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-
 trifluoropropyl)succinamide (27); (2R,3S)-N-((3S)-5-(3-chlorophenyl)-9-methyl-2-oxo-2,3-dihydro-

1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (28); (2R,3S)-N-((3S)-5-(3-chlorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (29); (2R,3S)-N-((3S)-5-(3-methylphenyl)-2-oxo-9-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (30); (2R,3S)-N-((3S)-9-chloro-5-(3,5-dimethylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (31); (2R,3S)-N-((3S)-5-(3-methylphenyl)-2-oxo-9-(trifluoromethyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (32); (2R,3S)-N-((3S)-9-isopropyl-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (33); (2R,3S)-N-((3S)-9-(cyclopropyloxy)-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (34); (2R,3S)-N-((3S)-9-(cyclopropyloxy)-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (35); (2R,3S)-N-((3S)-9-chloro-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (36); (2R,3S)-N-((3S)-9-methyl-2-oxo-5-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(4,4,4-trifluorobutyl)-2-(3,3,3-trifluoropropyl)succinamide (37); (2R,3S)-N-((3S)-9-methyl-2-oxo-5-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (38); (2R,3S)-N-((3S)-9-chloro-5-(2-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (39); (2R,3S)-N-((3S)-5-(4-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (40); (2R,3S)-N-((3S)-9-chloro-5-(3-cyclopropylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (41); (2R,3S)-N-((3S)-5-(3-chlorophenyl)-9-methoxy-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (42); (2R,3S)-N-((3S)-5-(4-chlorophenyl)-9-methoxy-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (43); (2R,3S)-N-((3S)-9-chloro-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (44); (2R,3S)-N-((3S)-5-(3-methylphenyl)-9-methoxy-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (45); (2R,3S)-N-((3S)-5-(4-(hydroxymethyl)phenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (46); (2R,3S)-N-((3S)-5-(2-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (47); (2R,3S)-N-((3S)-5-(3-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (48); (2R,3S)-N-((3S)-9-methoxy-2-oxo-5-(5-(trifluoromethyl)-2-pyridinyl)-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-

trifluoropropyl)succinamide (49); (2R,3S)-N-((3S)-5-(5-chloro-2-pyridinyl)-9-methoxy-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (50); (2R,3S)-N-((3S)-5-(4-methoxyphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (51); (2R,3S)-N-((3S)-5-(4-methylphenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (52); (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (53); ((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-valinate (54); ((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-alaninate (55); 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-cysteine (56); *tert*-butyl 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 (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.

[0040] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



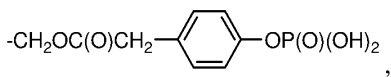
and/or at least one salt thereof, wherein:

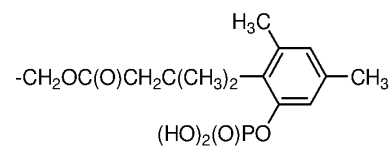
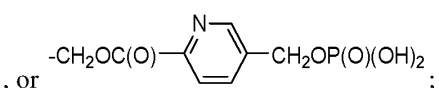
R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

R₃ is H, -CH₃ or R_x;

R₄ is H or R_y;

R_xis: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(CH₃)₂)NHC(O)CH(NH₂)CH(CH₃)₂,
,

, or
;
5 R_y is: -SCH₂CH(NH₂)C(O)OH, -SCH₂CH(NH₂)C(O)OH₃,or -SCH₂CH(NH₂)C(O)OC(CH₃)₃;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH₃, C₁₋₃ alkyl, -CH₂OH, -CF₃,cyclopropyl, -OCH₃, -O(cyclopropyl) and/or -NHCH₂CH₂OCH₃;10 each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

y is zero, 1 or 2; and

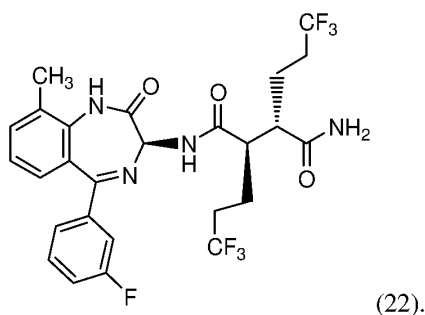
z is zero, 1, or 2

provided that if Ring A is phenyl, z is zero, and y is 1 or 2 then at least one R_a isC₁₋₃ alkyl, -CH₂OH, -CF₃, cyclopropyl, or -O(cyclopropyl);15 provided that if R₃ is R_x then R₄ is H; andprovided that if R₄ is R_y then R₃ is H or -CH₃.

[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 C₁₋₃ alkyl, -CH₂OH, -CF₃, cyclopropyl, or -O(cyclopropyl); provided that if R₃ is R_x then R₄ is H; and

20 provided that if R₄ is R_y then R₃ is H or -CH₃.

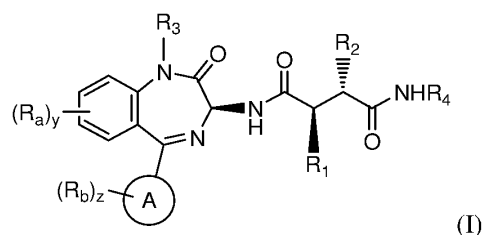
[0042] In another embodiment, the present invention provides compositions comprising compounds represented by the following structure:



[0043] In another embodiment, the compounds as described herein comprise prodrugs of one or more of the compounds.

[0044] U.S. Patent No. 9,273,014, which is incorporated by reference herein in its entirety, discloses various compounds of Formula (I):

5



and/or at least one salt thereof, wherein:

R₁ is -CH₂CH₂CF₃;

R₂ is -CH₂CH₂CF₃ or -CH₂CH₂CH₂CF₃;

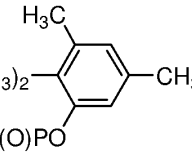
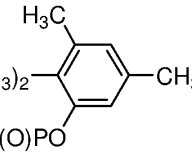
10 R₃ is H, -CH₃, or R_x;

R₄ is H or R_y;

R_x

is: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(CH₃

)₂)NHC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH₂--OP(O)(OH)₂, ,

-CH₂OC(O)CH₂C(CH₃)₂--CH₃,
 15 (HO)₂(O)PO--CH₃, or -CH₂OC(O)--CH₂OP(O)(OH)₂ ;

R_y is: -SCH₂CH(NH₂)C(O)OH, -SCH₂CH(NH₂)C(O)OCH₃,

or -SCH₂CH(NH₂)C(O)OC(CH₃)₃;

Ring A is phenyl or pyridinyl;

each R_a is independently Cl, C₁₋₃ alkyl, -CH₂OH, -CF₃, cyclopropyl, -OCH₃,

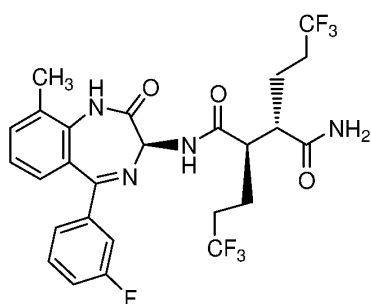
20 and/or -O(cyclopropyl);

each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

y is zero, 1, or 2; and

z is 1 or 2.

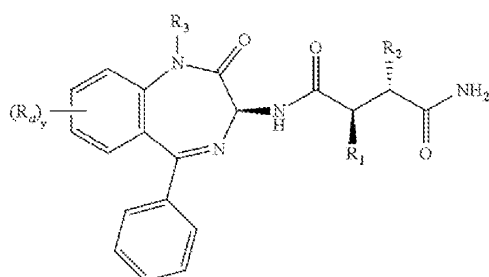
[0045] U.S. Patent No. 9,273,014 also discloses the compound of Formula (22):



(22),

which, in one embodiment, has the chemical name (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide. U.S. Patent No. 9,273,014 also discloses a process for synthesizing the compounds as well as other compounds of Formula (I), which are to be considered as part of the present invention.

[0046] U.S. Patent No. 8,629,136, which is incorporated by reference herein in its entirety, discloses compounds of Formula (III):



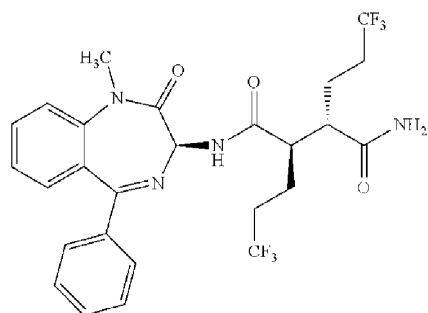
(III)

and/or at least one salt thereof, wherein:

R₃ is H or -CH₃; and

each R_a is independently F, Cl, -CN, -OCH₃ and/or -NHCH₂CH₂OCH₃.

U.S. Patent No. 8,629,136 also discloses the compound of Formula (1):



(1),

15

which, in one embodiment, has the chemical name (2R,3S)—N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide. In one embodiment, the compounds are Notch inhibitors. U.S. Patent No. 8,629,136 discloses a process for synthesizing the compounds as well as other compounds of Formula (I), which are to be considered as part of the present invention.

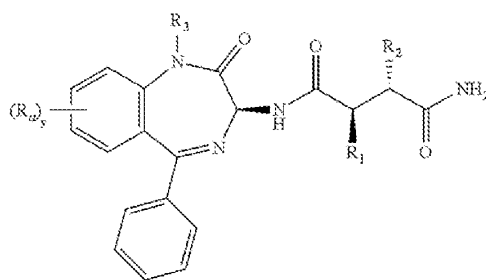
[0047] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of the aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more embodiments. It is also to be understood that each individual element of the embodiments is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

Combined Treatments

[0048] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I) as described herein as monotherapy or in a combination therapy with one or more anti-cancer agents.

[0049] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I) as described herein as monotherapy or in a combination therapy with one or more chemotherapeutic agents.

[0050] In one embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (III) as monotherapy or in a combination therapy with one or more anti-cancer agents:



or prodrugs or salts thereof; wherein:

25 R_1 is $-\text{CH}_2\text{CF}_3$ or $-\text{CH}_2\text{CH}_2\text{CF}_3$;

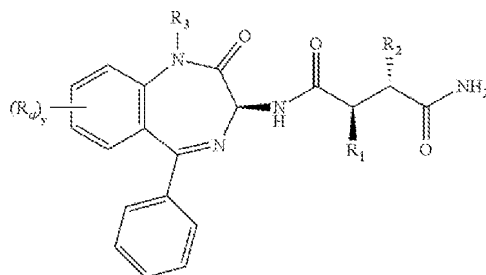
R_2 is $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$;

R_3 is H or $-\text{CH}_3$;

each R_a is independently F, Cl, $-\text{CN}$, $-\text{OCH}_3$, and/or $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$; and

y is zero, 1, or 2.

[0051] In one embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (III) as monotherapy or in a combination therapy with one or more chemotherapeutic agents:



5

or prodrugs or salts thereof; wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

R₃ is H or -CH₃;

10 each R_a is independently F, Cl, -CN, -OCH₃, and/or -NHCH₂CH₂OCH₃; and

y is zero, 1, or 2.

[0052] In one embodiment, compositions of the present invention or for use in the methods of the present invention comprise one or more cancer therapeutic agents in a combination therapy with one or more bisfluoroalkyl-1,4-benzodiazepinone compounds described hereinabove.

15 [0053] In treating cancer, a combination of chemotherapeutic agents and/or other treatments (e.g., radiation therapy) is often advantageous. An additional agent may have the same or different mechanism of action than the primary therapeutic agents. For example, drug combinations may be employed wherein the two or more drugs being administered act in different manners or in different phases of the cell cycle, and/or where the two or more drugs have nonoverlapping toxicities or side effects, and/or where the drugs being combined each has a demonstrated efficacy in treating the

20 particular disease state manifested by the patient.

[0054] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with Eribulin.

25 [0055] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with vinorelbine.

[0056] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with FOLFIRI. In one embodiment, FOLFIRI comprises folinic acid (leucovorin), fluorouracil (5-FU) and irinotecan (Camptosar). In another embodiment, the present invention provides a composition
5 comprising one or more compounds represented by the structure of Formula (I) as described herein and folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (Camptosar), or a combination thereof.

[0057] In one embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein and one or more targeted therapeutics. In one embodiment, said targeted therapeutic comprises an inhibitor of mammalian
10 target of rapamycin (mTOR). In one embodiment, the mTOR inhibitor comprises Everolimus. In another embodiment, the mTOR inhibitor comprises sirolimus (rapamycin). In another embodiment, the mTOR inhibitor comprises temsirolimus.

[0058] In another embodiment, the mTOR inhibitor comprises a dual mammalian target of rapamycin/phosphoinositide 3-kinase inhibitor, which in one embodiment, comprises NVP-BEZ235
15 (dactolisib), GSK2126458, XL765, or a combination thereof.

[0059] In another embodiment, the mTOR inhibitor comprises a second generation mTOR inhibitor, which, in one embodiment, comprises AZD8055, INK128/MLN0128, OSI027, or a combination thereof.

[0060] In another embodiment, the mTOR inhibitor comprises a third generation mTOR inhibitor,
20 which, in one embodiment, comprises RapaLinks.

[0061] In one embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with an mTOR inhibitor and a chemotherapeutic drug. In one embodiment, the mTOR inhibitor comprises everolimus. In one embodiment, the chemotherapeutic drug comprises cisplatin.

25 [0062] In one embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with a PARP (poly ADP-ribose polymerase) inhibitor.

[0063] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein and a polyfunctional
30 alkylating agent. In one embodiment, the polyfunctional alkylating agent comprises a Nitrosourea, Mustard, Nitrogen Mustard, Methanesulphonate, Busulphan, Ethylenimine, or a combination thereof.

[0064] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with steroids.

[0065] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with bisphosphonates.

[0066] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with cancer growth blockers.

[0067] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with proteasome inhibitors.

[0068] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with one or more interferons.

[0069] In another embodiment, a composition of the present invention comprises one or more compounds represented by the structure of Formula (I) as described herein in combination with one or more interleukins.

[0070] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and an alkylating drug. In one embodiment, the alkylating drug comprises Procarbazine (Matulane), Dacarbazine (DTIC), Altretamine (Hexalen), or a combination thereof.

[0071] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and an alkylating-like drug. In one embodiment, the alkylating-like drug comprises Cisplatin (Platinol).

[0072] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and an antimetabolite. In one embodiment, the antimetabolite comprises an antifolic acid compound (Methotrexate), an amino acid antagonists (Azaserine), or a combination thereof.

[0073] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and a purine antagonist. In one embodiment, the purine antagonist comprises Mercaptopurine (6-MP), Thioguanine (6-TG), Fludarabine Phosphate, Cladribine (Leustatin), Pentostatin (Nipent), or a combination thereof.

[0074] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and a pyrimidine antagonist. In one embodiment, the pyrimidine antagonist comprises Fluorouracil (5-FU), Cytarabine (ARA-C), Azacitidine, or a combination thereof.

[0075] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and a plant alkaloid. In one embodiment, the plant alkaloid comprises Vinblastine (Velban), Vincristine (Oncovin), Etoposide (VP-16, VePe-sid), Teniposide (Vumon), Topotecan (Hycamtin), Irinotecan (Camptosar),
5 Paclitaxel (Taxol), Docetaxel (Taxotere), or a combination thereof.

[0076] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and an antibiotic. In one embodiment, the antibiotic comprises Anthracyclines, Doxorubicin (Adriamycin, Rubex, Doxil), Daunorubicin (DaunoXome), Dactinomycin (Cosmegen), Idarubicin (Idamycin), Plicamycin
10 (Mithramycin), Mitomycin (Mutamycin), Bleomycin (Blenoxane), or a combination thereof.

[0077] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a cancer vaccine. In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and an
15 immunotherapeutic. In one embodiment, the immunotherapeutic comprises a monoclonal antibody. In one embodiment, the monoclonal antibody comprises an anti-PD-1 antibody, which in one embodiment comprises nivolumab.

[0078] In another embodiment, the monoclonal antibody comprises alemtuzumab (Campath®), trastuzumab (Herceptin®), Bevacizumab (Avastin®), Cetuximab (Erbix®), or a combination
20 thereof. In another embodiment, the monoclonal antibody comprises a radiolabeled antibody, which, in one embodiment, comprises brentuximab, tiuxetan (Zevalin®), or a combination thereof. In another embodiment, the monoclonal antibody comprises a chemolabeled antibody, which in one embodiment comprises Brentuximab vedotin (Adcetris®), Ado-trastuzumab emtansine (Kadcyla®, also called TDM-1), denileukin difitox (Ontak®), or a combination thereof. In another embodiment,
25 the monoclonal antibody comprises a bispecific antibody, which in one embodiment, comprises blinatumomab (Blinicyto).

[0079] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a hormonal therapy. In another embodiment, the present invention provides a composition comprising
30 one or more compounds represented by the structure of Formula (I) as described herein and a hormonal agent. In one embodiment, the hormonal agent comprises Tamoxifen (Nolvadex), Flutamide (Eulexin), Gonadotropin-Releasing Hormone Agonists, (Leuprolide and Goserelin (Zoladex)), Aromatase Inhibitors, Aminoglutethimide, Anastrozole (Arimidex), or a combination thereof.

[0080] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein and Amsacrine, Hydroxyurea (Hydrea), Asparaginase (El-spar), Mitoxantrone (Novantrone), Mitotane, Retinoic Acid Derivatives, Bone Marrow Growth Factors, Amifostine, or a combination thereof.

5 [0081] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an agent that inhibits one or more cancer stem cell pathways. In one embodiment, such agent comprises an inhibitor of Hedgehog, WNT, BMP, or a combination thereof.

[0082] In one embodiment, said anti-cancer agent comprises a BCMA-targeted chimeric antigen receptor T-cell immunotherapeutic, p53-HDM2 inhibitor, c-MET inhibitor, BCR-ABL inhibitor, Anti-interleukin-1 beta monoclonal antibody, EGFR mutation modulator, PI3K-alpha inhibitor, JAK1/2 inhibitor, Cortisol synthesis inhibitor, Thrombopoietin, P-selectin inhibitor receptor agonist, Anti-CD20 monoclonal antibody, Anti-PD-1 monoclonal antibody, Signal transduction inhibitor, CDK4/6 inhibitor, BRAF inhibitor + MEK inhibitor, CD19-targeted chimeric antigen receptor T-cell
10 immunotherapeutic, Somatostatin analogue, or a combination thereof. In one embodiment, said anti-cancer agent comprises capmatinib, asciminib, canakinumab, alpelisib, ruxolitinib, osilodrostat, eltrombopag, crizanlizumab, ofatumumab, spartalizumab, midostaurin, ribociclib, dabrafenib + trametinib, tisagenlecleucel, everolimus, pasireotide, or a combination thereof.

[0083] In another embodiment, the present invention provides a composition comprising one or more
20 compounds represented by the structure of Formula (I) as described herein in combination with a hematopoietic stem cell transplant approach.

[0084] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with isolated infusion approaches. In one embodiment, the isolated infusion approach comprises infusion
25 of chemotherapy into a specific tissue in order to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming systemic damage.

[0085] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with targeted delivery mechanisms. In one embodiment, the targeted delivery mechanism increases
30 effective levels of chemotherapy for tumor cells while reducing effective levels for other cells for increased tumor specificity and/or reduced toxicity. In one embodiment, targeted delivery mechanisms comprise a traditional chemotherapeutic agent, or a radioisotope or an immune stimulating factor.

[0086] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with nanoparticles. In one embodiment, nanoparticles are used as a vehicle for poorly-soluble agents such as paclitaxel. In one embodiment, nanoparticles made of magnetic material can also be used to
5 concentrate agents at tumour sites using an externally applied magnetic field.

[0087] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an agent for treating Adenoid Cystic Carcinoma (ACC). In one embodiment, said agent for treating ACC comprises Axitinib, Bortezomib (Velcade), Bortezomib + doxorubicin, Cetuximab, Cetuximab +
10 Intensity modulated radiation therapy (IMRT), Cetuximab + RT + cisplatin, Cetuximab + cisplatin + 5-FU, Chidamide (CS055/HBI-8000), Cetuximab & Carbon Ion, Cisplatin, cisplatin & 5-FU, Cisplatin & Doxorubicin & Bleomycin, Cisplatin & Doxorubicin & Cyclophosphamide, Dasatinib, Dovitinib, Epirubicin, Gefitinib, Gemcitabine, Gemcitabine & Cisplatin, Imatinib, Imatinib + cisplatin, Lapatinib, Mitoxanthrone, MK 2206, Nelfinavir, Paclitaxel, Paclitaxel & Carboplatin,
15 Panitumumab & Radiotherapy, PF-00562271, PF-00299804 & Figitumumab PX-478, PX-866, Regorafenib, Sonpencizumab, Sorafenib, Sunitinib, Vinorelbine, Vinorelbine & Cisplatin, Vorinostat, XL147 & Erlotinib, XL647, or combinations thereof.

[0088] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with
20 pembrolizumab, docetaxel, nivolumab and ipilimumab, PSMA-PET Imaging, chidamide, APG-115, HDM201, DS-3032b, LY3039478, or a combination thereof.

[0089] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an agent for treating triple negative breast cancer (TNBC). In one embodiment, said agent for treating
25 triple-negative breast cancer comprises PARP (poly ADP-ribose polymerase) inhibitors such as olaparib, VEGF (vascular endothelial growth factor) inhibitors such as bevacizumab, EGFR (epidermal growth factor receptor)-targeted therapies such as cetuximab, or a combination thereof.

[0090] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a composition as described herein and administering one or more anti-cancer
30 agents.

[0091] In one embodiment, the phrase “anti-cancer agent” refers to a drug selected from any one or more of the following: alkylating agents (including mustard, nitrogen mustards, methanesulphonate, busulphan, alkyl sulfonates, nitrosoureas, ethylenimine derivatives, and triazenes or combinations thereof); anti-angiogenics (including matrix metalloproteinase inhibitors); antimetabolites (including

adenosine deaminase inhibitors, folic acid antagonists, purine analogues, and pyrimidine analogues); antibiotics or antibodies (including monoclonal antibodies, CTLA-4 antibodies, anthracyclines); aromatase inhibitors; cell-cycle response modifiers; enzymes; farnesyl-protein transferase inhibitors; hormonal and antihormonal agents and steroids (including synthetic analogs, glucocorticoids, estrogens/anti-estrogens [e.g., SERMs], androgens/anti-androgens, progestins, progesterone receptor agonists, and luteinizing hormone-releasing [LHRH] agonists and antagonists); insulin-like growth factor (IGF)/insulin-like growth factor receptor (IGFR) system modulators (including IGFR1 inhibitors); integrin-signaling inhibitors; kinase inhibitors (including multi-kinase inhibitors and/or inhibitors of Src kinase or Src/ab1, cyclin dependent kinase [CDK] inhibitors, panHer, Her-1 and Her-2 antibodies, VEGF inhibitors, including anti-VEGF antibodies, EGFR inhibitors, PARP (poly ADP-ribose polymerase) inhibitors, mitogen-activated protein [MAP] inhibitors, MET inhibitors, MEK inhibitors, Aurora kinase inhibitors, PDGF inhibitors, and other tyrosine kinase inhibitors or serine/threonine kinase inhibitors; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, Platinum-based antineoplastic drugs (platins) such as cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin and satraplatin and the naturally-occurring epothilones and their synthetic and semi-synthetic analogs; microtubule-binding, destabilizing agents (including vinca alkaloids); topoisomerase inhibitors; prenyl-protein transferase inhibitors; platinum coordination complexes; signal transduction inhibitors; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors, and immune modulators.

[0092] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with any one or more of the following: Revlimid, Avastin, Herceptin, Rituxan, Opdivo, Gleevec, Imbruvica, Velcade, Zytiga, Xtandi, Alimta, Gadasil, Ibrance, Perjeta, Tassigna, Xgeva, Afinitor, Jakafi, Tarceva, Keytruda, Sutent, Yervoy, Nexavar, Zoladex, Erbitux, Dazalex, Xeloda, Gazyva, Venclexta, and Tecentriq.

[0093] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with any one or more of the following: abemaciclib, epacadostat, apalutamide, Carfilzomib, Crizotinib (PF-02341066), GDC-0449 (vismodegib), OncoVex, PLX4032 (RG7204), Ponatinib, SGN-35 (brentuximab vedotin), Tivozanib (AV-951), T-DM1 (Trastuzumab-DM1), and XL184 (cabozantinib).

[0094] Accordingly, the compositions of the present invention may be administered in combination with other anti-cancer treatments useful in the treatment of cancer or other proliferative diseases. The

invention herein further comprises use of the compositions of the present invention in preparing medicaments for the treatment of cancer, and/or it comprises the packaging of the compositions of the present invention together with instructions that the compositions be used in combination with other anti-cancer or cytotoxic agents and treatments for the treatment of cancer.

5 [0095] In one embodiment, any of the methods as described herein comprises the step of administering to a subject a composition comprising compounds represented by the structure of Formula (I) as described herein as monotherapy or in a combination therapy with one or more anti-cancer agents. In another embodiment, any of the methods as described herein comprises the step of administering to a subject a composition comprising compounds represented by the structure of
10 Formula (I) as described herein as monotherapy or in a combination therapy with one or more chemotherapeutic agents.

[0096] In another embodiment, any of the methods as described herein comprises the step of administering to a subject a composition comprising compounds represented by the structure of Formula (III) as described herein as monotherapy or in a combination therapy with one or more anti-
15 cancer agents. In another embodiment, any of the methods as described herein comprises the step of administering to a subject a composition comprising compounds represented by the structure of Formula (III) as described herein as monotherapy or in a combination therapy with one or more chemotherapeutic agents.

[0097] In one embodiment, the anti-cancer or chemotherapeutic agent(s) in the methods of the
20 present invention are administered to the subject in a single composition with a compound represented by the structure of Formula (I) or a compound represented by the structure of Formula (III). In another embodiment, the anti-cancer or chemotherapeutic agent(s) are administered to the subject in separate compositions from the composition comprising a compound represented by the structure of Formula (I) or a compound represented by the structure of Formula (III). In one embodiment, the separate
25 compositions are administered to the subject at the same time. In another embodiment, the separate compositions are administered to the subject at separate times, at separate sites of administration, or a combination thereof.

[0098] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I); administering cisplatin; and optionally,
30 administering one or more additional anti-cancer agents.

[0099] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I); administering dasatinib; and optionally, administering one or more additional anti-cancer agents.

[00100] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I); administering paclitaxel; and optionally, administering one or more additional anti-cancer agents.

5 [00101] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I); administering tamoxifen; and optionally, administering one or more additional anti-cancer agents.

[00102] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I), administering a glucocorticoid; and optionally, administering one or more additional anti-cancer agents. An example of a suitable glucocorticoid is
10 dexamethasone.

[00103] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I), administering carboplatin; and optionally, administering one or more additional anti-cancer agents.

[00104] The compounds of the present invention can be formulated or co-administered with other
15 therapeutic agents that are selected for their particular usefulness in addressing side effects associated with the aforementioned conditions. For example, compounds of the invention may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H₁ and H₂ antihistaminics.

[00105] In one embodiment, pharmaceutical compositions are provided comprising a compound of
20 Formula (I) or prodrug thereof; one or more additional agents selected from a kinase inhibitory agent (small molecule, polypeptide, and antibody), an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

[00106] The above other therapeutic agents, when employed in combination with the compounds
25 of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Pharmaceutical Compositions

Formulations

30 [00107] Also embraced within this invention is a class of pharmaceutical compositions comprising the compound of Formula (I) and one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients.

- [00108] The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g., magnesium stearate and a disintegrating agent such as croscopovidone. The carrier mixture may be filled into a gelatin capsule or compressed as a tablet. The pharmaceutical composition may be administered as an oral dosage form or an infusion, for example.
- 5 [00109] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, liquid capsule, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. For example, the pharmaceutical composition may be provided as a tablet or capsule comprising an amount of active ingredient in the range of from about 1 to 2000 mg, preferably from about 1 to 500 mg, and more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but can be determined using routine methods.
- 10 [00110] Any pharmaceutical composition contemplated herein can, for example, be delivered orally via any acceptable and suitable oral preparations. Exemplary oral preparations, include, but are not limited to, for example, tablets, troches, lozenges, aqueous and oily suspensions, dispersible powders or granules, emulsions, hard and soft capsules, liquid capsules, syrups, and elixirs. Pharmaceutical compositions intended for oral administration can be prepared according to any methods known in the art for manufacturing pharmaceutical compositions intended for oral administration. In order to provide pharmaceutically palatable preparations, a pharmaceutical composition in accordance with the invention can contain at least one agent selected from sweetening agents, flavoring agents, coloring agents, demulcents, antioxidants, and preserving agents.
- 15 [00111] A tablet can, for example, be prepared by admixing at least one compound of Formula (I) with at least one non-toxic pharmaceutically acceptable excipient suitable for the manufacture of tablets. Exemplary excipients include, but are not limited to, for example, inert diluents, such as, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as, for example, microcrystalline cellulose, sodium croscarmellose, corn starch, and alginic acid; binding agents, such as, for example, starch, gelatin, polyvinyl-pyrrolidone, and acacia; and lubricating agents, such as, for example, magnesium stearate, stearic acid, and talc. Additionally, a tablet can either be uncoated, or coated by known techniques to
- 20
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either mask the bad taste of an unpleasant tasting drug, or delay disintegration and absorption of the active ingredient in the gastrointestinal tract thereby sustaining the effects of the active ingredient for a longer period. Exemplary water soluble taste masking materials, include, but are not limited to, hydroxypropyl-methylcellulose and hydroxypropyl-cellulose. Exemplary time delay materials, include, but are not limited to, ethyl cellulose and cellulose acetate butyrate.

[00112] Hard gelatin capsules can, for example, be prepared by mixing at least one compound of Formula (I) with at least one inert solid diluent, such as, for example, calcium carbonate; calcium phosphate; and kaolin.

[00113] Soft gelatin capsules can, for example, be prepared by mixing at least one compound of Formula (I) with at least one water soluble carrier, such as, for example, polyethylene glycol; and at least one oil medium, such as, for example, peanut oil, liquid paraffin, and olive oil.

[00114] An aqueous suspension can be prepared, for example, by admixing at least one compound of Formula (I) with at least one excipient suitable for the manufacture of an aqueous suspension. Exemplary excipients suitable for the manufacture of an aqueous suspension, include, but are not limited to, for example, suspending agents, such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinylpyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as, for example, a naturally-occurring phosphatide, e.g., lecithin; condensation products of alkylene oxide with fatty acids, such as, for example, polyoxyethylene stearate; condensation products of ethylene oxide with long chain aliphatic alcohols, such as, for example heptadecaethylene-oxycetanol; condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol, such as, for example, polyoxyethylene sorbitol monooleate; and condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, such as, for example, polyethylene sorbitan monooleate. An aqueous suspension can also contain at least one preservative, such as, for example, ethyl and n-propyl p-hydroxybenzoate; at least one coloring agent; at least one flavoring agent; and/or at least one sweetening agent, including but not limited to, for example, sucrose, saccharin, and aspartame.

[00115] Oily suspensions can, for example, be prepared by suspending at least one compound of Formula (I) in either a vegetable oil, such as, for example, arachis oil; olive oil; sesame oil; and coconut oil; or in mineral oil, such as, for example, liquid paraffin. An oily suspension can also contain at least one thickening agent, such as, for example, beeswax; hard paraffin; and cetyl alcohol. In order to provide a palatable oily suspension, at least one of the sweetening agents already described hereinabove, and/or at least one flavoring agent can be added to the oily suspension. An oily

suspension can further contain at least one preservative, including, but not limited to, for example, an antioxidant, such as, for example, butylated hydroxyanisol, and alpha-tocopherol.

[00116] Dispersible powders and granules can, for example, be prepared by admixing at least one compound of Formula (I) with at least one dispersing and/or wetting agent; at least one suspending agent; and/or at least one preservative. Suitable dispersing agents, wetting agents, and suspending agents are as already described above. Exemplary preservatives include, but are not limited to, for example, anti-oxidants, e.g., ascorbic acid. In addition, dispersible powders and granules can also contain at least one excipient, including, but not limited to, for example, sweetening agents; flavoring agents; and coloring agents.

[00117] An emulsion of at least one compound of Formula (I) can, for example, be prepared as an oil-in-water emulsion. The oily phase of the emulsions comprising compounds of Formula (I) may be constituted from known ingredients in a known manner. The oil phase can be provided by, but is not limited to, for example, a vegetable oil, such as, for example, olive oil and arachis oil; a mineral oil, such as, for example, liquid paraffin; and mixtures thereof. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Suitable emulsifying agents include, but are not limited to, for example, naturally-occurring phosphatides, e.g., soy bean lecithin; esters or partial esters derived from fatty acids and hexitol anhydrides, such as, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, such as, for example, polyoxyethylene sorbitan monooleate. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. An emulsion can also contain a sweetening agent, a flavoring agent, a preservative, and/or an antioxidant. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

[00118] In another embodiment, the compounds of Formula (I) can be formulated as a nanoparticle, lipid nanoparticle, microparticle or liposome.

[00119] The compounds of Formula (I) can, for example, also be delivered intravenously, subcutaneously, and/or intramuscularly via any pharmaceutically acceptable and suitable injectable form. Exemplary injectable forms include, but are not limited to, for example, sterile aqueous solutions comprising acceptable vehicles and solvents, such as, for example, water, Ringer's solution, and isotonic sodium chloride solution; sterile oil-in-water microemulsions; and aqueous or oleaginous

suspensions. For example, the composition may be provided for intravenous administration comprising an amount of active ingredient in the range of from about 0.2 to 150 mg. In another embodiment, the active ingredient is present in the range of from about 0.3 to 10 mg. In another embodiment, the active ingredient is present in the range of from about 4 to 8.4 mg. In one
5 embodiment, the active ingredient is administered at a dose of about 4 mg. In another embodiment, the active ingredient is administered at a dose of about 6 mg. In another embodiment, the active ingredient is administered at a dose of about 8.4 mg.

[00120] In another embodiment, the active ingredient is administered at a dose of about 0.3 mg. In another embodiment, the active ingredient is administered at a dose of about 0.6 mg. In another
10 embodiment, the active ingredient is administered at a dose of about 1.2 mg. In another embodiment, the active ingredient is administered at a dose of about 2.4 mg.

[00121] Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in
15 the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a
20 composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (i.e., CAPTISOL®), cosolvent solubilization (i.e., propylene glycol) or micellar solubilization (i.e., Tween 80).

[00122] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol.
25 Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

30 [00123] A sterile injectable oil-in-water microemulsion can, for example, be prepared by 1) dissolving at least one compound of Formula (I) in an oily phase, such as, for example, a mixture of soybean oil and lecithin; 2) combining the Formula (I) containing oil phase with a water and glycerol mixture; and 3) processing the combination to form a microemulsion.

[00124] A sterile aqueous or oleaginous suspension can be prepared in accordance with methods already known in the art. For example, a sterile aqueous solution or suspension can be prepared with a non-toxic parenterally-acceptable diluent or solvent, such as, for example, 1,3-butane diol; and a sterile oleaginous suspension can be prepared with a sterile non-toxic acceptable solvent or suspending medium, such as, for example, sterile fixed oils, e.g., synthetic mono- or diglycerides; and fatty acids, such as, for example, oleic acid.

[00125] Pharmaceutically acceptable carriers, adjuvants, and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-alpha-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, polyethoxylated castor oil such as CREMOPHOR® surfactant (BASF), or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as alpha-, beta-, and gamma-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

[00126] The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

[00127] The amounts of compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, gender, the medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.001 to 100 mg/kg body weight, preferably between about 0.005 and

about 50 mg/kg body weight and most preferably between about 0.01 to 10 mg/kg body weight, may be appropriate.

[00128] For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

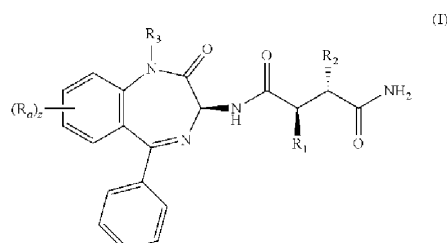
[00129] Pharmaceutical compositions of this invention comprise at least one compound of Formula (I) and/or at least one salt thereof, and optionally an additional agent selected from any pharmaceutically acceptable carrier, adjuvant, and vehicle. Alternate compositions of this invention comprise a compound of the Formula (I) described herein, or a prodrug thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00130] The compound in accordance with Formula (I) can be administered by any means suitable for the condition to be treated, which can depend on the need for site-specific treatment or quantity of Formula (I) compound to be delivered. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, or parentally including intravascularly, intraperitoneally, subcutaneously, intramuscularly, and intrasternally. In one embodiment, the compounds and compositions of the present invention are administered intravenously.

Methods of Use

[00131] In one embodiment, the present invention provides the use of the described compounds or compositions for treating, suppressing or inhibiting a proliferative disease in a subject comprising one or more compounds of Formula (I) and/or at least one salt thereof, as described herein. In one embodiment, the present invention provides the use of the described compounds or compositions for treating, suppressing or inhibiting a proliferative disease in a subject consisting essentially of one or more compounds of Formula (I) and/or at least one salt thereof, as described herein. In one embodiment, the present invention provides the use of the described compounds or compositions for treating, suppressing or inhibiting a proliferative disease in a subject consisting of one or more compounds of Formula (I) and/or at least one salt thereof, as described herein.

[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,



wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

R₃ is H, -CH₃ or R_x;

R₄ is H or R_y;

R_x

is: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(

CH₃)₂)NHC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH₂--OP(O)(OH)₂,

-CH₂OC(O)CH₂C(CH₃)₂-, or -CH₂OC(O)--CH₂OP(O)(OH)₂;

R_y is: -SCH₂CH(NH₂)C(O)OH, -SCH₂CH(NH₂)C(O)OH₃,

or -SCH₂CH(NH₂)C(O)OC(CH₃)₃;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH₃, C₁₋₃ alkyl, -CH₂OH, -CF₃,

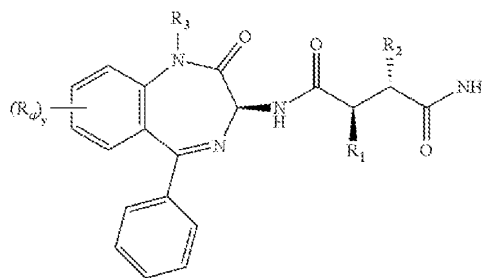
cyclopropyl, -OCH₃, -O(cyclopropyl) and/or -NHCH₂CH₂OCH₃;

each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

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):



wherein:

R₁ is —CH₂CF₃ or —CH₂CH₂CF₃;

R₂ is —CH₂CF₃, —CH₂CH₂CF₃, or —CH₂CH₂CH₂CF₃;

5 R₃ is H or —CH₃;

each R_a is independently F, Cl, —CN, —OCH₃, and/or —NHCH₂CH₂OCH₃; and

y is zero, 1, or 2.

[00134] In one embodiment, the compound is administered at a dose of approximately 0.3, 0.6, 1.2, 2.4, 4, 6, or 8.4 mg.

10 [00135] In one embodiment, the compound is administered intravenously at a dose of approximately 0.3, 0.6, 1.2, 2.4, 4, 6, or 8.4 mg. In another embodiment, the compound is administered weekly at a dose of approximately 0.3, 0.6, 1.2, 2.4, 4, 6, or 8.4 mg.

[00136] 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
15 composition comprising one or more compounds represented by the structure of Formula (I) as described hereinabove, wherein said compound is administered at a dose of about 4 mg. In one embodiment, the compound is administered intravenously at a dose of approximately 4 mg. In another embodiment, the compound is administered weekly at a dose of approximately 4 mg.

[00137] In another embodiment, the present invention provides a method of treating, suppressing
20 or inhibiting a proliferative disease in a subject comprising the step of administering to said subject a composition consisting essentially of one or more compounds represented by the structure of Formula (I) as described hereinabove, wherein said compound is administered at a dose of approximately 0.3, 0.6, 1.2, 2.4, 4, 6, or 8.4 mg. In another embodiment, the present invention provides a method of treating, suppressing or inhibiting a proliferative disease in a subject comprising the step of
25 administering to said subject a composition consisting of one or more compounds represented by the structure of Formula (I) as described hereinabove, wherein said compound is administered at a dose of approximately 0.3, 0.6, 1.2, 2.4, 4, 6, or 8.4 mg.

[00138] In one embodiment, the present invention provides the use of a therapeutically acceptable amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a therapeutically effective amount of one or more compounds or compositions as described
5 herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a synergistically effective amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a synergistically therapeutically effective amount of one or more compounds or compositions as
10 described herein for treating, suppressing or inhibiting a proliferative disease in a subject.

[00139] In one embodiment, the proliferative disease comprises a Desmoid tumor.

[00140] In one embodiment, the proliferative disease comprises a pre-cancerous condition or a benign proliferative disorder.

[00141] In one embodiment, the term "pre-cancerous" or, alternatively, "pre-malignant" as used
15 herein interchangeably refers to diseases, syndromes or other conditions associated with an increased risk of cancer. Pre-cancerous conditions in the context of the present invention include, but are not limited to: breast calcifications, vaginal intra-epithelial neoplasia, Barrett's esophagus, atrophic gastritis, dyskeratosis congenital, sideropenic dysphagia, lichen planus, oral submucous fibrosis, actinic keratosis, solar elastosis, cervical dysplasia, leukoplakia and erythroplakia.

[00142] In one embodiment, the term "benign hyperproliferative disorder" as used herein refers to a condition in which there is an abnormal growth and differentiation of cells and an increase in the amount of organic tissue that results from cell proliferation. The benign hyperproliferative disorder may be attributed to lack of response or inappropriate response to regulating factors, or alternatively to dysfunctional regulating factors. Non-limiting examples of benign hyperproliferative disorder are
25 psoriasis and benign prostatic hyperplasia (BPH).

[00143] In another embodiment, the proliferative disease comprises a cancer.

[00144] In one embodiment, the cancer comprises a solid tumor. In another embodiment, the cancer comprises a hematological malignancy.

[00145] In one embodiment, a subject as described herein has cancer. In one embodiment, the term
30 "cancer" in the context of the present invention includes all types of neoplasm whether in the form of solid or non-solid tumors and includes both malignant and premalignant conditions as well as their metastasis.

[00146] In one embodiment, the cancer is a carcinoma, sarcoma, myeloma, leukemia, or lymphoma. In another embodiment, the cancer is a mixed type.

[00147] In one embodiment, mixed type cancers comprise several types of cells. The type components may be within one category or from different categories. Some examples are: adenosquamous carcinoma; mixed mesodermal tumor; carcinosarcoma; teratocarcinoma

[00148] In another embodiment, the carcinoma comprises Adenoid Cystic Carcinoma (ACC).

5 [00149] In another embodiment, the carcinoma comprises Gastro-esophageal junction carcinoma.

[00150] In one embodiment, the carcinoma is an adenocarcinoma. In another embodiment, the carcinoma is a squamous cell carcinoma.

[00151] In one embodiment, the sarcoma comprises osteosarcoma or osteogenic sarcoma (bone); Chondrosarcoma (cartilage); Leiomyosarcoma (smooth muscle); Rhabdomyosarcoma (skeletal
10 muscle); Mesothelial sarcoma or mesothelioma (membranous lining of body cavities); Fibrosarcoma (fibrous tissue); Angiosarcoma or hemangioendothelioma (blood vessels); Liposarcoma (adipose tissue); Glioma or astrocytoma (neurogenic connective tissue found in the brain); Myxosarcoma (primitive embryonic connective tissue); and Mesenchymous or mixed mesodermal tumor (mixed connective tissue types).

15 [00152] In one embodiment, the cancer comprises myeloma, which, in one embodiment, is cancer that originates in the plasma cells of bone marrow. The plasma cells produce some of the proteins found in blood. In one embodiment, the cancer comprises multiple myeloma.

[00153] In another embodiment, the cancer comprises leukemia ("non-solid tumor" or "blood cancer"), which in one embodiment, is a cancer of the bone marrow (the site of blood cell production).

20 In one embodiment, leukemia comprises myelogenous or granulocytic leukemia (malignancy of the myeloid and granulocytic white blood cell series); Lymphatic, lymphocytic, or lymphoblastic leukemia (malignancy of the lymphoid and lymphocytic blood cell series); and Polycythemia vera or erythremia (malignancy of various blood cell products, but with red cells predominating).

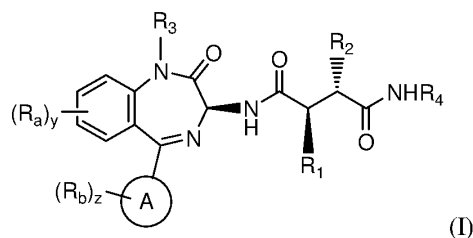
[00154] In another embodiment, the cancer comprises T-cell acute lymphoblastic leukemia (T-ALL). In another embodiment, the cancer comprises T-lymphoblastic leukemia/lymphoma (TLL). In
25 another embodiment, the cancer comprises Chronic Lymphocytic Leukemia (CLL).

[00155] In another embodiment, the cancer comprises a lymphoma. In one embodiment, the lymphoma comprises an extranodal lymphoma. In one embodiment, the lymphoma comprises a Hodgkin lymphoma. In another embodiment, the lymphoma comprises a Non-Hodgkin lymphoma.

30 In one embodiment, the lymphoma comprises a marginal zone B cell lymphoma, a diffuse large B cell lymphoma, or a mantle cell lymphoma.

[00156] In another embodiment, the cancer comprises a breast cancer. In one embodiment, the breast cancer comprises triple negative breast cancer.

- [00157] In one embodiment, a cancer as described herein comprises a Notch activating alteration. In another embodiment, a cancer as described herein comprises a Notch activating genetic alteration. In another embodiment, a cancer as described herein comprises a Notch activating mutation. In another embodiment, a cancer as described herein comprises a Notch activating genetic mutation. In another embodiment, a cancer as described herein comprises a Notch mutation. In another embodiment, a cancer as described herein comprises a Notch altering mutation.
- [00158] In one embodiment, the cancer or tumor is dependent upon Notch activation. In another embodiment, the cancer or tumor is not dependent upon Notch activation. In another embodiment, the cancer or tumor comprises cells comprising a Notch-activating mutation. In another embodiment, the cancer or tumor comprises cells comprising activated Notch signaling. In another embodiment, the cancer or tumor comprises cells comprising activated Wnt signaling. In another embodiment, the cancer or tumor comprises cells comprising dysregulated Notch signalling, Wnt signalling, or a combination thereof.
- [00159] In one embodiment, the Notch-activating mutation comprises a Notch 1 mutation, a Notch 2 mutation, a Notch 3 mutation, a Notch 4 mutation, or a combination thereof.
- [00160] In another embodiment, the Notch-activating genetic alteration comprises a missense mutation. In another embodiment, the Notch-activating genetic alteration comprises a nonsense mutation. In another embodiment, the Notch-activating genetic alteration comprises an insertion. In another embodiment, the Notch-activating genetic alteration comprises a deletion. In another embodiment, the Notch-activating genetic alteration comprises a duplication. In another embodiment, the Notch-activating genetic alteration comprises a frameshift mutation. In another embodiment, the Notch-activating genetic alteration comprises a repeat expansion. In another embodiment, Notch-activating genetic alteration comprises a gene fusion. In another embodiment, Notch-activating genetic alteration comprises a splice site.
- [00161] In one 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 (I) and/or at least one salt thereof,



wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

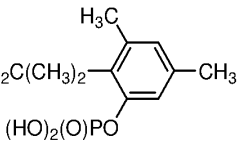
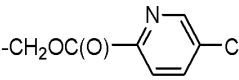
R₃ is H, -CH₃ or R_x;

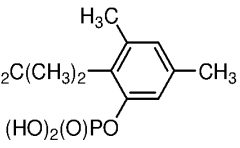
R₄ is H or R_y;

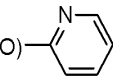
5

R_x

is: -CH₂OC(O)CH(CH₃)NH₂, -CH₂OC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH((CH(

CH₃)₂)NHC(O)CH(NH₂)CH(CH₃)₂, -CH₂OC(O)CH₂--OP(O)(OH)₂,
 , or
 ;

-CH₂OC(O)CH₂C(CH₃)₂-

, or -CH₂OC(O)--CH₂OP(O)(OH)₂;

R_y is: -SCH₂CH(NH₂)C(O)OH, -SCH₂CH(NH₂)C(O)OH₃,

10

or -SCH₂CH(NH₂)C(O)OC(CH₃)₃;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH₃, C₁₋₃ alkyl, -CH₂OH, -CF₃,

cyclopropyl, -OCH₃, -O(cyclopropyl) and/or -NHCH₂CH₂OCH₃;

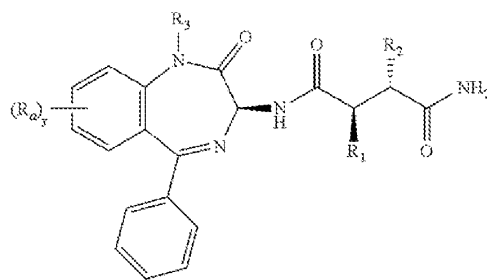
each R_b is independently F, Cl, -CH₃, -CH₂OH, -CF₃, cyclopropyl, and/or -OCH₃;

15

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):



20

or prodrugs or salts thereof; wherein:

R₁ is -CH₂CF₃ or -CH₂CH₂CF₃;

R₂ is -CH₂CF₃, -CH₂CH₂CF₃, or -CH₂CH₂CH₂CF₃;

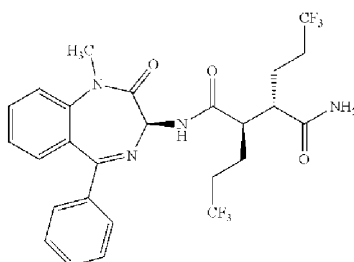
R₃ is H or -CH₃;

each R_a is independently F, Cl, -CN, -OCH₃, and/or -NHCH₂CH₂OCH₃; and

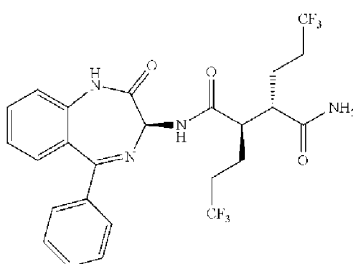
y is zero, 1, or 2.

[00163] In another embodiment, the present invention provides a method of treating cancer, comprising the step of administering to said subject a composition comprising a compound of

5 Formula (1):



[00164] In another embodiment, the present invention provides a method of treating cancer, comprising the step of administering to said subject a composition comprising a compound of Formula (2):



10

[00165] In one embodiment, the present invention provides a method of treating a carcinoma, 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, as described herein.

15 [00166] In another embodiment, the present invention provides a method of treating a carcinoma, 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, as described herein.

20 [00167] In another embodiment, the present invention provides a method of treating a carcinoma, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

[00168] In another embodiment, the present invention provides a method of treating a carcinoma, comprising the step of administering to said subject a composition comprising a compound of Formula (2), as described herein.

[00169] In one embodiment, the present invention provides a method of treating ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

- 5 [00170] In another embodiment, the present invention provides a method of treating ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

- [00171] In another embodiment, the present invention provides a method of treating ACC,
10 gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

- [00172] In another embodiment, the present invention provides a method of treating ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising
15 the step of administering to said subject a composition comprising a compound of Formula (2), as described herein.

- [00173] In one embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having cancer, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) and/or
20 at least one salt thereof, as described herein.

[00174] In one embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having a carcinoma, 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, as described herein.

- 25 [00175] In one embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

- 30 [00176] In another embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

[00177] In another embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

- 5 [00178] In another embodiment, the present invention provides a method of reducing tumor size or tumor volume in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (2), as described herein.

- [00179] In one embodiment, reducing tumor size or tumor volume comprises decreasing tumor size
10 by 25%-95%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 25%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 30%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 35%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 40%. In another embodiment, reducing tumor size or
15 tumor volume comprises decreasing tumor size by 45%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 50%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 55%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 60%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 65%. In another
20 embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 70%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 75%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 80%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 85%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor
25 size by 90%. In another embodiment, reducing tumor size or tumor volume comprises decreasing tumor size by 95%.

- [00180] In one embodiment, the present invention provides a method of suppressing tumor growth in a subject having a tumor, 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
30 salt thereof, as described herein.

[00181] In one embodiment, the present invention provides a method of suppressing tumor growth in a subject having a carcinoma, 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, as described herein.

- [00182] In one embodiment, the present invention provides a method of suppressing tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.
- [00183] In another embodiment, the present invention provides a method of suppressing tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.
- [00184] In another embodiment, the present invention provides a method of suppressing tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein:
- [00185] In another embodiment, the present invention provides a method of suppressing tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (2), as described herein.
- [00186] In one embodiment, administration of a composition as described herein suppresses tumor growth by 20-99% compared to untreated tumors, or compared to tumors treated with another anti-cancer therapy. In another embodiment, tumor growth is suppressed by 20-35%. In another embodiment, tumor growth is suppressed by 35-50%. In another embodiment, tumor growth is suppressed by 50-75%. In another embodiment, tumor growth is suppressed by 75-90%. In another embodiment, tumor growth is suppressed by 90-99%.
- [00187] In another embodiment, tumor growth is suppressed by 20%. In another embodiment, tumor growth is suppressed by 25%. In another embodiment, tumor growth is suppressed by 30%. In another embodiment, tumor growth is suppressed by 35%. In another embodiment, tumor growth is suppressed by 40%. In another embodiment, tumor growth is suppressed by 45%. In another embodiment, tumor growth is suppressed by 50%. In another embodiment, tumor growth is suppressed by 55%. In another embodiment, tumor growth is suppressed by 60%. In another embodiment, tumor growth is suppressed by 65%. In another embodiment, tumor growth is suppressed by 70%. In another embodiment, tumor growth is suppressed by 75%. In another embodiment, tumor growth is suppressed by 80%. In another embodiment, tumor growth is suppressed by 85%. In another embodiment, tumor growth is suppressed by 90%. In another

embodiment, tumor growth is suppressed by 95%. In another embodiment, tumor growth is suppressed by 99%.

[00188] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having a tumor, 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, as described herein.

[00189] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having a carcinoma, 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, as described herein.

[00190] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

[00191] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

[00192] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

[00193] In one embodiment, the present invention provides a method of inhibiting tumor growth in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

[00194] In one embodiment, inhibiting tumor growth comprises decreasing the growth of the tumor in comparison to control by 100%.

[00195] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having a tumor, 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, as described herein.

[00196] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having a carcinoma, 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, as described herein.

5 [00197] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

10 [00198] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, 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, as described herein.

15 [00199] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

[00200] In one embodiment, the present invention provides a method of prolonging progression-free survival or overall survival in a subject having ACC, gastroesophageal junction adenocarcinoma, a Desmoid tumor, or a combination thereof, comprising the step of administering to said subject a composition comprising a compound of Formula (1), as described herein.

[00201] In another embodiment, the cancer comprises astrocytoma, bladder cancer, breast cancer, cholangiocarcinoma (CCA), colon cancer, colorectal cancer, colorectal carcinoma, epithelial carcinoma, epithelial ovarian cancers, fibrosarcoma, gall bladder cancer, gastric cancer, glioblastoma, glioma, head and neck cancer, hepatocellular carcinoma, kidney cancer, liver cancer, lung cancer including non-small cell lung cancer (NSCLC), malignant fibrous histiocytoma (MFH), malignant pleural mesothelioma (MPM), medulloblastoma, melanoma, mesothelioma, neuroblastoma, osteosarcoma, ovarian adenocarcinoma, ovarian cancer, pancreatic adenocarcinoma, pancreatic cancer, prostate cancer, renal cell carcinoma (RCC), rhabdomyosarcoma, seminal vesicle cancer, endometrial cancer, and thyroid cancer.

[00202] As used herein, the term "cancer" includes the above categories of carcinoma, sarcoma, myeloma, leukemia, lymphoma and mixed type tumors. In particular, the term cancer includes: lymphoproliferative disorders, breast cancer, ovarian cancer, prostate cancer, cervical cancer,

endometrial cancer, lung cancer, bone cancer, liver cancer, stomach cancer, bladder cancer, colon cancer, colorectal cancer, pancreatic cancer, cancer of the thyroid, head and neck cancer, cancer of the central nervous system, brain cancer, cancer of the peripheral nervous system, skin cancer, kidney cancer, as well as metastases of all the above. More particularly, as used herein the term may refer to:

5 hepatocellular carcinoma, hematoma, hepatoblastoma, rhabdomyosarcoma, esophageal carcinoma, thyroid carcinoma, ganglioblastoma, glioblastoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, Ewing's tumor, leiomyosarcoma, rhabdotheliosarcoma, invasive ductal carcinoma, papillary adenocarcinoma, melanoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma (well differentiated,

10 moderately differentiated, poorly differentiated or undifferentiated), renal cell carcinoma, hypernephroma, hypernephroid adenocarcinoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, testicular tumor, lung carcinoma including small cell, non-small and large cell lung carcinoma, bladder carcinoma, glioma, astrocyoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, retinoblastoma, neuroblastoma, colon carcinoma,

15 rectal carcinoma, hematopoietic malignancies including all types of leukemia and lymphoma including: acute myelogenous leukemia, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, mast cell leukemia, multiple myeloma, myeloid lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Waldenstrom's Macroglobulinemia, or a combination thereof.

20 [00203] In another embodiment, the administration of the any of the compositions as described herein reduces growth of the cells of a solid tumor or hematological malignancy by 40%, 50%, 60%, 70%, 80%, 90% or 95% compared to growth of the cells of the solid tumor or hematological malignancy that have not been treated with the compositions. In the case of combination treatments, the administration of any of the described combinations reduces growth of the cells of a solid tumor

25 or hematological malignancy compared to subjects treated with either one of the compositions, via a different cancer treatment, or who have not been treated.

[00204] In another embodiment, the present invention provides methods of increasing or lengthening survival of a subject having a neoplasia. As used herein, the term "neoplasia" refers to a disease characterized by the pathological proliferation of a cell or tissue and its subsequent migration

30 to or invasion of other tissues or organs. Neoplasia growth is typically uncontrolled and progressive, and occurs under conditions that would not elicit, or would cause cessation of, multiplication of normal cells. Neoplasias can affect a variety of cell types, tissues, or organs, including but not limited to an organ selected from the group consisting of bladder, colon, bone, brain, breast, cartilage, glia, esophagus, fallopian tube, gallbladder, heart, intestines, kidney, liver, lung, lymph node, nervous

tissue, ovaries, pleura, pancreas, prostate, skeletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroid, trachea, urogenital tract, ureter, urethra, uterus, and vagina, or a tissue or cell type thereof. Neoplasias include cancers, such as sarcomas, carcinomas, or plasmacytomas (malignant tumor of the plasma cells).

- 5 [00205] In one embodiment, a subject as described herein is being treated with or has been previously treated with radiation therapy, chemotherapy, transplantation, immunotherapy, hormone therapy, or photodynamic therapy.

Definitions

- [00206] Unless specifically stated otherwise herein, references made in the singular may also
10 include the plural. For example, “a” and “an” may refer to either one, or one or more.

[00207] The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

- [00208] Listed below are definitions of various terms used to describe the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise
15 limited in specific instances) either individually or as part of a larger group.

[00209] As used herein, the term “administering” refers to bringing in contact with a compound of the present invention. In one embodiment, the compositions are applied locally. In another embodiment, the compositions are applied systemically. Administration can be accomplished to cells or tissue cultures, or to living organisms, for example humans.

- 20 [00210] As used herein, the terms “administering,” “administer,” or “administration” refer to deliver one or more compounds or compositions to a subject parenterally, enterally, or topically. Illustrative examples of parenteral administration include, but are not limited to, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and
25 intrasternal injection and infusion. Illustrative examples of enteral administration include, but are not limited to oral, inhalation, intranasal, sublingual, and rectal administration. Illustrative examples of topical administration include, but are not limited to, transdermal and vaginal administration. In particular embodiments, an agent or composition is administered parenterally, optionally by intravenous administration or oral administration to a subject.

- 30 [00211] In one embodiment, a composition of the present invention comprises a pharmaceutically acceptable composition. In one embodiment, the phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and

animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00212] In one embodiment, a composition of the present invention is administered in a therapeutically effective amount. In one embodiment, a “therapeutically effective amount” is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to act as an inhibitor to a Notch receptor, effective to inhibit gamma secretase, or effective to treat or prevent proliferative diseases such as cancer. In one embodiment, a “therapeutically effective amount” of a composition of the invention is that amount of composition which is sufficient to provide a beneficial effect to the subject to which the composition is administered.

[00213] As used herein, “treating” or “treatment” cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

[00214] In one embodiment, “treating” refers to, in one embodiment, therapeutic treatment and, in another embodiment, prophylactic or preventative measures. In one embodiment, the goal of treating is to prevent or lessen the targeted pathologic condition or disorder as described hereinabove. Thus, in one embodiment, treating may include directly affecting or curing, suppressing, inhibiting, preventing, reducing the severity of, delaying the onset of, reducing symptoms associated with the disease, disorder or condition, or a combination thereof. Thus, in one embodiment, “treating” refers inter alia to delaying progression, expediting remission, inducing remission, augmenting remission, speeding recovery, increasing efficacy of or decreasing resistance to alternative therapeutics, or a combination thereof. In one embodiment, “preventing” refers, inter alia, to delaying the onset of symptoms, preventing relapse to a disease, decreasing the number or frequency of relapse episodes, increasing latency between symptomatic episodes, or a combination thereof. In one embodiment, “suppressing” or “inhibiting”, refers inter alia to reducing the severity of symptoms, reducing the severity of an acute episode, reducing the number of symptoms, reducing the incidence of disease-related symptoms, reducing the latency of symptoms, ameliorating symptoms, reducing secondary symptoms, reducing secondary infections, prolonging patient survival, or a combination thereof.

[00215] In one embodiment, the term “decreasing the size of the tumor” as used herein is assessed using the “Response Evaluation Criteria In Solid Tumors” (RECIST). In one embodiment, RECIST measures reduction in tumor size by measuring the longest dimension of a target lesion. In one

embodiment, the target lesion is selected on the basis of its size (lesion with the longest diameter) and its suitability for accurate repeated measurements (either by imaging techniques or clinically). In one embodiment, all other lesions (or sites of disease) are identified as non-target lesions and are also recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each is noted throughout follow-up.

[00216] In one embodiment, the term “decreasing the volume of the tumor” as used herein is assessed using the radiological tumor response evaluation criteria. In one embodiment, the maximum diameter (width) of the tumor is measured in two dimensions in the translation plane and its largest perpendicular diameter on the same image (thickness), according to the World Health Organization (WHO).

[00217] According to any of the methods of the present invention and in one embodiment, a subject as described herein is human. In another embodiment, the subject is a mammal. In another embodiment, the subject is a primate, which in one embodiment, is a non-human primate. In another embodiment, the subject is murine, which in one embodiment is a mouse, and, in another embodiment is a rat. In another embodiment, the subject is canine, feline, bovine, equine, caprine, ovine, porcine, simian, ursine, vulpine, or lupine. In one embodiment, the subject is a chicken or fish.

[00218] In one embodiment, the compositions as described herein comprise the components of the composition (i.e., one or more compounds of Formula (I)) as described herein. In another embodiment, the compositions as described herein consist of the components of the composition (i.e., one or more compounds of Formula (I)) as described herein. In another embodiment, the compositions as described herein consist essentially of the components of the composition (i.e., one or more compounds of Formula (I)) as described herein.

[00219] It is to be understood that the compositions and methods of the present invention comprising the elements or steps as described herein may, in another embodiment, consist of those elements or steps, or in another embodiment, consist essentially of those elements or steps. In some embodiments, the term “comprise” refers to the inclusion of the indicated active agents, such as the gamma secretase inhibitor, as well as inclusion of other active agents, and pharmaceutically or physiologically acceptable carriers, excipients, emollients, stabilizers, etc., as are known in the pharmaceutical industry. In some embodiments, the term “consisting essentially of” refers to a composition, whose only active ingredients are the indicated active ingredients. However, other compounds may be included which are for stabilizing, preserving, etc. the formulation, but are not involved directly in the therapeutic effect of the indicated active ingredients. In some embodiments, the term “consisting essentially of” may refer to components which facilitate the release of the active

ingredient. In some embodiments, the term “consisting” refers to a composition, which contains the active ingredients and a pharmaceutically acceptable carrier or excipient.

Timing and Site of Administration

5 [00220] In one embodiment, in the methods of the present invention, the administration of one or more anti-cancer agents occurs prior to the administration of the compound of Formula (I). In another embodiment, in the methods of the present invention, the administration of one or more anti-cancer agents occurs concurrent with the administration of the compound of Formula (I). In another embodiment, in the methods of the present invention, the administration of one or more anti-cancer agents occurs following the administration of the compound of Formula (I). In one embodiment, concurrent administration comprises administering a single composition comprising the anti-cancer agent and compound of Formula (I). In another embodiment, concurrent administration comprises administering separate compositions.

[00221] In one embodiment, the administration of the anti-cancer agents occurs at the same site as the administration of the compound of Formula (I).

[00222] In one embodiment, the compound of Formula (I) is administered several days before and after the administration of the anti-cancer agent. In one embodiment, the compound of Formula (I) is administered 1, 2, 3, 4, or 5 days prior to the administration of the anti-cancer agent. In one embodiment, the compound of Formula (I) is administered 1, 2, 3, 4, or 5 days subsequent to the administration of the anti-cancer agent. In another embodiment, the compound of Formula (I) is administered one day before and up to 9 days following anti-cancer agent administration. In another embodiment, the compound of Formula (I) is administered one day before and on days 1, 8, and 9 following anti-cancer agent administration. In another embodiment, the compound of Formula (I) is administered one day before and 9 days following anti-cancer agent administration. In another embodiment, the compound of Formula (I) is administered one day before and daily for 9 days following anti-cancer agent administration. In another embodiment, the compound of Formula (I) is administered one day before and on day 9 following anti-cancer agent administration.

[00223] In some embodiments, one or more compositions of the present invention are administered at least once during a treatment cycle. In some embodiments, the compositions of the present invention are administered to the subject on the same days. In some embodiments, the compositions of the present invention are administered to the subject on the different days. In some embodiments, one or more compositions of the present invention are administered to the subject on the same days and on different days according to treatment schedules.

[00224] In particular embodiments, one or more compositions of the present invention are administered to the subject over one or more treatment cycles. A treatment cycle can be at least two, at least three, at least four, at least five, at least six, at least seven, at least 14, at least 21, at least 28, at least 48, or at least 96 days or more. In one embodiment, a treatment cycle is 28 days. In certain
5 embodiments, the compositions are administered over the same treatment cycle or concurrently over different treatment cycles assigned for each composition. In various embodiments, the treatment cycle is determined by a health care professional based on conditions and needs of the subject.

[00225] In some embodiments, a composition is administered on at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, at least seven days, at least
10 eight days, at least nine days, at least ten days, at least eleven days, at least twelve days, at least 13 days, at least 14 days, at least 21 days, or all 28 days of a 28 day treatment cycle. In particular embodiments, a composition is administered to a subject once a day. In other particular embodiments, a composition is administered twice a day.

[00226] In one embodiment, one or more of the compositions as described herein are administered
15 in one to four doses per day. In one embodiment, one or more of the compositions as described herein are administered once per day. In another embodiment, one or more of the compositions as described herein are administered twice per day. In another embodiment, one or more of the compositions as described herein are administered three times per day. In another embodiment, one or more of the compositions as described herein are administered four times per day. In another embodiment, one or
20 more of the compositions as described herein are administered once every two days, once every three days, twice a week, once a week, once every 2 weeks, once every 3 weeks.

[00227] In one embodiment, one or more of the compositions as described herein are administered for 7 days to 28 days. In another embodiment, one or more of the compositions as described herein are administered for 7 days to 8 weeks. In another embodiment, one or more of the compositions as
25 described herein are administered for 7 days to 50 days. In another embodiment, one or more of the compositions as described herein are administered for 7 days to six months. In another embodiment, one or more of the compositions as described herein are administered for 7 days to one and half years. In another embodiment, one or more of the compositions as described herein are administered for 14 days to 12 months. In another embodiment, one or more of the compositions as described herein are
30 administered for 14 days to 3 years. In another embodiment, one or more of the compositions as described herein are administered for several years. In another embodiment, one or more of the compositions as described herein are administered for one month to six months.

[00228] In one embodiment, one or more of the compositions as described herein are administered for 7 days. In another embodiment, one or more of the compositions as described herein are

administered for 14 days. In another embodiment, one or more of the compositions as described herein are administered for 21 days. In another embodiment, one or more of the compositions as described herein are administered for 28 days. In another embodiment, one or more of the compositions as described herein are administered for 50 days. In another embodiment, one or more of the compositions as described herein are administered for 56 days. In another embodiment, one or more of the compositions as described herein are administered for 84 days. In another embodiment, one or more of the compositions as described herein are administered for 90 days. In another embodiment, one or more of the compositions as described herein are administered for 120 days.

[00229] The number of times a composition is administered to a subject in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the subject's response to the formulation. In some embodiments, a composition disclosed herein is administered once to a subject in need thereof with a mild acute condition. In some embodiments, a composition disclosed herein is administered more than once to a subject in need thereof with a moderate or severe acute condition. In the case wherein the subject's condition does not improve, upon the doctor's discretion the composition may be administered chronically, that is, for an extended period of time, including throughout the duration of the subject's life in order to ameliorate or otherwise control or limit the symptoms of the subject's disease or condition.

[00230] In the case wherein the subject's status does improve, upon the doctor's discretion the composition may administered continuously; or, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday may be from 10%- 100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

Kits

[00231] The present invention further comprises combinations of the compositions of the present invention and, optionally, one or more additional agents in kit form, e.g., where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

[00232] In certain embodiments, the kit comprises a therapeutic or prophylactic composition containing an effective amount of the compound of Formula (I) or Formula (III) or Formula (1), as

described herein, which in one embodiment, comprises 4 mg of the compound of Formula (I). In certain embodiments, the kit comprises a sterile container which contains therapeutic or prophylactic agents; such containers can be boxes, ampules, bottles, vials, tubes, bags, pouches, blister-packs, or other suitable container forms known in the art. Such containers can be made of plastic, glass, laminated paper, metal foil, or other materials suitable for holding medicaments.

[00233] If desired, the composition(s) are provided together with instructions for administering the composition(s) to a subject having or at risk of developing a neoplasia (e.g., multiple myeloma). The instructions will generally include information about the use of the composition for the treatment or prevention of a neoplasia (e.g., multiple myeloma). In other embodiments, the instructions include at least one of the following: description of the therapeutic agent; dosage schedule and administration for treatment or prevention of a neoplasia (e.g., multiple myeloma) or symptoms thereof; precautions; warnings; indications; counter-indications; overdosage information; adverse reactions; animal pharmacology; clinical studies; and/or references. The instructions may be printed directly on the container (when present), or as a label applied to the container, or as a separate sheet, pamphlet, card, or folder supplied in or with the container.

EXAMPLES

METHODS

[00234] A phase I, ascending multiple-dose study of intravenous (IV) administration of Compound (1) in patients with advanced or metastatic solid tumors was conducted (**Figure 1**).

[00235] Patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent.

Primary objective

[00236] The primary objective was to assess the safety and tolerability of multiple doses of Compound (1), and to establish the recommended phase 2 dose (RP2D).

Secondary objectives

[00237] One of the secondary objectives was to assess the pharmacokinetics (PK) of Compound (1) and its equally active metabolite after the first IV dose and after repeated doses.

[00238] Another secondary objective was to assess pharmacodynamic (PD) changes in the expression of Notch pathway-related genes, such as Hes1 and Deltex1, in surrogate tissues (peripheral blood cells and plucked hair follicles) and tumor biopsies after treatment.

[00239] Another secondary objective was to describe the antitumor activity of Compound (1).

Selected inclusion criteria

- [00240] Patients aged ≥ 18 years with solid tumors refractory to or who relapsed after standard therapies or for which there is no known effective treatment.
- [00241] Dose escalation: advanced or metastatic nonhematologic solid tumors.
- [00242] Dose expansion:
- 5
 - TNBC
 - Squamous NSCLC
 - Advanced or metastatic solid tumors with Notch pathway activation demonstrated by commercially available next-generation sequencing of the patient's tumor or reported in the current literature for the tumor type
 - 10 [00243] Biopsy accessible tumor
 - [00244] Life expectancy ≥ 3 months
 - [00245] Eastern Cooperative Oncology Group performance status 0-1
- Selected exclusion criteria
- [00246] Active infection
 - 15 [00247] Inadequate bone marrow function
 - Absolute neutrophil count (ANC) $< 1,500$ cells/mm³
 - Platelet count $< 100,000$ cells/mm³
 - Hemoglobin < 9.0 g/dL
 - [00248] Inadequate hepatic function
 - 20
 - Total bilirubin > 1.5 x institutional upper limit of normal (ULN)
 - Alanine transaminase (ALT) or aspartate transaminase (AST) > 3 x institutional ULN
 - [00249] Inadequate renal function: blood creatinine > 1.5 x institutional ULN
 - [00250] Gastrointestinal disease within 3 months of treatment causing or increasing the risk of diarrhea
 - 25
 - [00251] Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
 - [00252] Dose limiting toxicity (DLT) was defined using the following criteria, if occurring during the 4-week DLT period:
 - 30
 - Grade 4 neutropenia (ANC < 500 /mm³) lasting ≥ 5 days.
 - Grade 3 febrile neutropenia lasting > 24 hours, or grade 4 febrile neutropenia of any duration.
 - Grade 4 thrombocytopenia, or grade 3 thrombocytopenia with significant bleeding
 - AST or ALT > 5 x institutional ULN

- Grade 3 diarrhea lasting >24 hours despite appropriate medical management
 - Grade 3 infusion-related reactions that recurred despite appropriate medical management
 - Any other drug-related $\geq$ grade 3 nonhematologic adverse event except hyperlipidemia in patients not receiving maximum medical management or electrolyte abnormalities that may be managed with supplements.
- [00253] Maximum tolerated dose (MTD) was defined as the highest dose administered at which <1/3 of patients experienced a DLT; determination of RP2D also considered rate/nature of AEs beyond the DLT period.
- [00254] Tumor assessments were performed at baseline, every 8 weeks, and at end of treatment if not assessed within the prior 8 weeks and were reported using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- [00255] PK plasma samples were analyzed for Compound (1) and its metabolite by a validated liquid chromatography–mass spectrometry/mass spectrometry assay.
- [00256] PD assessments of changes in Hes1 and Deltex1 mRNA or protein were determined using quantitative real time polymerase chain reaction and immunohistochemistry, respectively.

RESULTS

- [00257] 94 patients were enrolled in the study (**Figure 1**). The baseline characteristics of all treated patients are shown in **Table 1**. There were three patients with desmoid tumors/fibromatosis (**Table 1**). The two patients with desmoid tumors were previously treated with imatinib, tamoxifen, and doxorubicin (1 patient) and tamoxifen, imatinib, sorafenib, methotrexate plus vinblastine, crizotinib, and dasatinib (1 patient). The one patient with fibromatosis was previously treated with methotrexate plus vinorelbine.

[00258] **Table 1. Baseline Characteristics of Patients Treated with Compound (1)**

Baseline characteristics	All treated patients (n = 94)
Median age, y (range)	57.0 (18-85)
Male/Female, n/n	43/51
Tumor type, n (%)	2 (2)
Adenocystic carcinoma	14 (15)
Breast (TNBC)	3 (3)
Breast (non-TNBC)	20 (21)
CRC	3 (3)

Baseline characteristics	All treated patients (n = 94)
Desmoid/fibromatosis	2 (2)
Gastric	3 (3)
Melanoma	6 (6)
NSCLC (squamous)	6 (6)
NSCLC (non-squamous)	5 (5)
Ovarian	31 (33)
Other	
Prior therapy,^a n (%)	
Surgery	88 (94)
Radiotherapy	54 (57)
Systemic therapy	94 (100)
1	16 (17)
2	12 (13)
3	24 (26)
≥4	42 (45)

^a Patients may have had more than one type of prior therapy.

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QW = once weekly; Q2W = once every 2 weeks; TNBC = triple negative breast cancer.

5 [00259] The median duration of Compound (1) treatment was 5.9 weeks (range: 1.00-238.29 weeks).

[00260] 66 (70%) patients discontinued treatment because of disease progression (**Table 2**). After treatment, 57 (61%) continued in the follow-up period.

[00261] Overall, 28 (30%) patients died: 22 because of disease, 1 because of AEs, 2 because of
10 other causes, and 2 because of causes unknown.

[00262] Nine (10%) patients died within 30 days of the last study dose.

[00263] **Table 2. Patient Disposition**

	All treated patients (n = 94)
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Reasons for discontinuing treatment, n (%)	
Disease progression	66 (70)
AE unrelated to study drug	8 (9)
Study drug toxicity	7 (7)
Patient withdrew consent	5 (5)
Patient request to discontinue	3 (3)
Maximum clinical benefit	2 (2)
Lost to follow-up	1 (1)
Other ^a	2 (2)
Patients continuing in the follow-up period, n (%)	57 (61)

^aTwo patients continue to receive treatment with Compound (1) through expanded access.

AE = adverse event; QW = once weekly; Q2W = once every 2 weeks.

5 Safety

[00264] The most common drug-related adverse events (AEs) are listed in **Table 3**.

[00265] Drug-related diarrhea was common (n = 59, 63%), consistent with reports of Notch pathway inhibition.

[00266] The majority of events were grade 1/2 (n = 41, 44%) and were manageable with protocol guidelines.

[00267] Grade 3/4 drug-related AEs were reported in approximately half of treated patients (n = 49, 51%).

[00268] Only one grade 5 drug-related AE was reported (hepatic failure) in a patient who received 8.4 mg Compound (1) QW.

[00269] 7 Dose-limited toxicities (DLTs) were reported in the QW arm: 4 patients receiving 6 mg and 3 receiving 8.4 mg Compound (1) (**Table 4**).

[00270] Maximum tolerated dose (MTD) in the QW arm was 4 mg Compound (1); this dose was used in the expansion phase.

[00271] One DLT was reported in the Q2W arm in a patient receiving 6 mg Compound (1) (**Table 4**).

[00272] MTD in the Q2W arm was 6 mg Compound (1).

[00273] **Table 3. Drug-related Adverse Events Reported in ≥10% of Treated Patients**

Drug-related AEs reported in ≥10% of treated patients	All treated patients (n = 94)		Patients treated with Compound (1) QW (n = 83)		Patients treated with Compound (1) Q2W (n = 11)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea, n (%)	59 (63)	18 (19)	50 (60)	17 (20)	9 (82)	1 (9)
Hypophosphatemia, n (%)	50 (53)	33 (35)	47 (57)	31 (37)	3 (27)	2 (18)
Fatigue, n (%)	42 (45)	1 (1)	37 (45)	0	5 (45)	1 (9)
Nausea, n (%)	41 (44)	1 (1)	35 (42)	1 (1)	6 (55)	0
Vomiting, n (%)	28 (30)	4 (4)	25 (30)	4 (5)	3 (27)	0
Decreased appetite, n (%)	25 (27)	0	22 (27)	0	3 (27)	0
Hypokalemia, n (%)	15 (16)	6 (6)	15 (18)	6 (7)	0	0
Dysgeusia, n (%)	13 (14)	0	13 (16)	0	0	0
Dermatitis acneliform, n (%)	11 (12)	0	10 (12)	0	1 (9)	0
Rash, n (%)	11 (12)	0	10 (12)	0	1 (9)	0
Anemia, n (%)	10 (11)	1 (1)	10 (12)	1 (1)	0	0
AST increased, n (%)	10 (11)	3 (3)	8 (10)	3 (4)	2 (18)	0
Pruritus, n (%)	9 (10)	1 (1)	7 (8)	1 (1)	2 (18)	0

AE = adverse event; AST = aspartate aminotransferase; QW = once weekly; Q2W = once every 2 weeks.

Treatment schedule	Compound (1) dose levels	Patients treated, n	Patients evaluable for DLTs, n	DLTs, n	Individual DLTs
QW	0.3 mg	4	4	0	-
	0.6 mg	3	3	0	-
	1.2 mg	4	4	0	-
	2.4 mg	4	3	0	-
	4 mg	7	7	0	-
	6 mg	14	10	4	• Grade 3 vomiting/lipase elevation • Grade 3 diarrhea • Grade 3 diarrhea/colonic ulceration • Grade 3 diarrhea/grade 4 dehydration
	8.4 mg	11	6	3	• Recurrent grade 3 infusion reaction • Grade 3 vomiting • Grade 5 liver failure
Q2W	4 mg	4	4	0	-
	6 mg	7	6	1	• Grade 3 diarrhea

DLT = dose-limiting toxicity; QW = once weekly; Q2W = once every 2 weeks.

Pharmacokinetics

[00275] $C_{\max}$ (**Figure 2A**) and $AUC_{(0-t)}$ (**Figure 2B**) increased in a dose-dependent manner at week 1.

[00276] Plasma concentration of Compound (1) was also largely dose-dependent at week 1 (**Figure 3A**). By week 4, plasma concentrations of Compound (1) ≥ 4 mg QW were above the half maximal effective concentration (EC_{50}) for at least 3 days (**Figure 3D**) compared to approximately one day after 1 week of treatment (**Figure 3C**).

[00277] EC_{50} was determined using concentration response modelling of human PD data from this study.

10

Pharmacodynamics

[00278] Dose-related reduction in Hes1 expression in peripheral blood was observed (**Figures 4A-4B**).

[00279] At Compound (1) doses of 4 mg QW and higher, $>80\%$ peak Hes1 inhibition was observed and $>50\%$ inhibition was sustained 3-7 days post-dose after 4 weeks of treatment (**Figure 4B**).

15

Efficacy

[00280] Confirmed responses occurred in 4 patients, with a confirmed objective response rate of 4% (**Table 5**).

[00281] One patient with gastroesophageal junction adenocarcinoma with Notch1 mutations (2 missense and 1 splice site) and an APC splice site mutation who received Compound (1) 4 mg QW: confirmed complete response (CR) ongoing >1 year.

20

[00282] One patient with a desmoid tumor who received Compound (1) 8.4 mg QW: confirmed partial response (PR) ongoing >1 year.

[00283] One patient with a desmoid tumor who received Compound (1) 6 mg Q2W: confirmed PR ongoing >3 year.

25

[00284] One patient with adenoid cystic carcinoma with Notch1 mutation who received Compound (1) 4 mg QW: confirmed PR with progressive disease at 8 months.

[00285] Ten patients had a best response of stable disease (SD; **Table 5**), including three patients with colorectal cancer and one patient each with NSCLC/appendiceal carcinoma, fibromatosis, immature malignant teratoma, metastatic adenoid cystic carcinoma, metastatic cholangiocarcinoma, renal clear cell adenocarcinoma, and synovial sarcoma.

30

[00286] **Table 5. Best Overall Response**

	All treated patients (n = 94)	Patients treated with Compound (1) QW (n = 83)	Patients treated with Compound (1) Q2W (n = 11)
BOR, n (%)			
CR	1 (1)	1 (1)	0
PR	3 (3)	2 (2)	1 (9)
SD	10 (11)	9 (11)	1 (9)
PD	64 (68)	55 (66)	9 (82)
ND	16 (17)	16 (19)	0
Confirmed ORR,^a n (%)			
95% CI	4 (4) 1.2, 10.5	3 (4) 0.8, 10.2	1 (9) 0.2, 41.3

^aConfirmed complete response plus confirmed partial response.

BOR = best overall response; CI = confidence interval; CR = complete response; ND = not determined; ORR = overall response rate; PD = progressive disease;

5 PR = partial response; SD = stable disease; QW = once weekly; Q2W = once every 2 weeks.

[00287] Treatment with Compound (1) decreased tumor burden for some patients with desmoid tumors/fibromatosis (**Figure 5A**) and decreased tumor burden in patients having tumors with activated Notch or Wnt signalling (**Figure 5B**).

10 [00288] These results suggest that Compound (1) was generally well tolerated in heavily pretreated patients at doses with sustained Notch inhibition.

[00289] Drug-related diarrhea was typically low grade.

[00290] Weekly dosing of Compound (1) led to continuous Notch inhibition in peripheral blood at doses ≥ 4 mg.

15 [00291] Compound (1) demonstrated clinical activity across different solid tumor types.

[00292] 1 CR and 3 PRs were achieved in patients with gastroesophageal junction adenocarcinoma, desmoid tumors, and adenoid cystic carcinoma.

[00293] Responses were seen in tumors with dysregulated Notch and Wnt signalling.