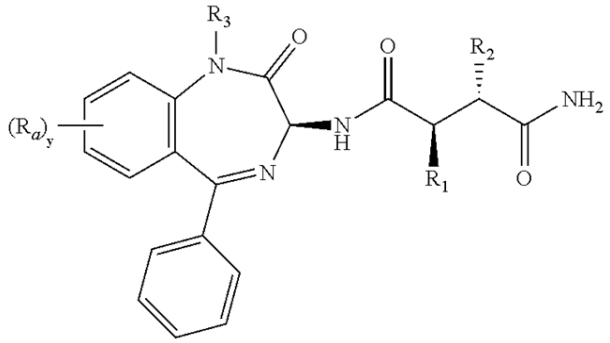
to experience an increased likelihood of distant metastasis and early recurrence within 2 or 3 years after treatment, compared with patients with other subtypes of breast cancer; patients with TNBC also tend to have shorter survival. Notch genetic alterations are potential tumor drivers and have been identified in ~10% of TNBC. Identifying new therapeutic strategies for triple-negative breast cancer (TNBC) would satisfy an unmet need.

SUMMARY

[003] In one example, the present disclosure provides a method of reducing tumor size, suppressing tumor growth, or inhibiting tumor growth having breast cancer characterized by an activated Notch pathway, comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (III):



or prodrugs or salts thereof; wherein:

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

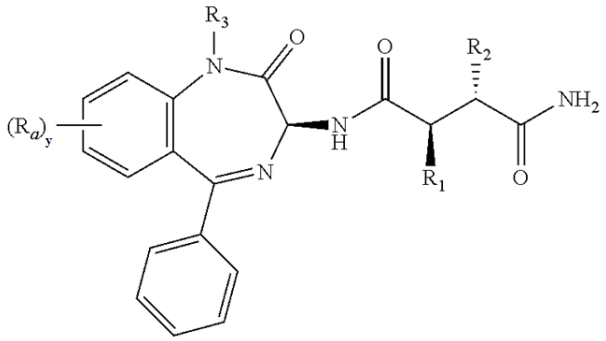
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H or $-CH_3$;

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

y is zero, 1, or 2.

[003a] In one aspect, the present disclosure provides use of a composition for the preparation of a medicament for reducing tumor size, suppressing tumor growth, or inhibiting tumor growth in a subject having breast cancer characterized by an activated Notch pathway, said composition comprising one or more compounds represented by the structure of Formula (III):



or prodrugs or salts thereof; wherein:

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

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

R_3 is H or $-CH_3$;

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

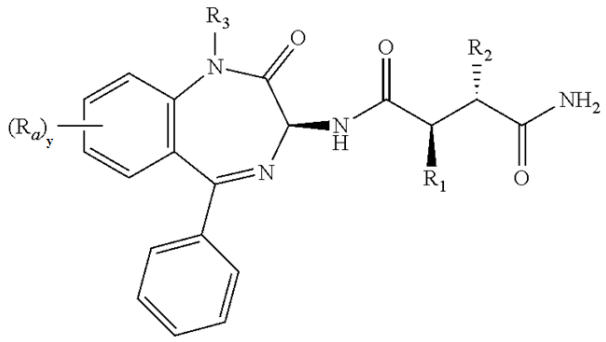
y is zero, 1, or 2.

[004] In another example, the present disclosure also provides a method of reducing tumor size, suppressing tumor growth, or inhibiting tumor growth in a subject having breast cancer characterized by an activated Notch pathway, comprising the step of administering to said subject a first composition comprising a cytotoxic agent and a second composition comprising one or more compounds represented by the structure of Formula (III):

CLAIMS

What is claimed is:

1. Use of a composition for the preparation of a medicament for reducing tumor size, suppressing tumor growth, or inhibiting tumor growth in a subject having breast cancer characterized by an activated Notch pathway, said composition comprising one or more compounds represented by the structure of Formula (III):



or prodrugs or salts thereof; wherein:

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

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

R_3 is H or $-CH_3$;

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

y is zero, 1, or 2.

2. The use of claim 1, wherein:

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

R_2 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$.

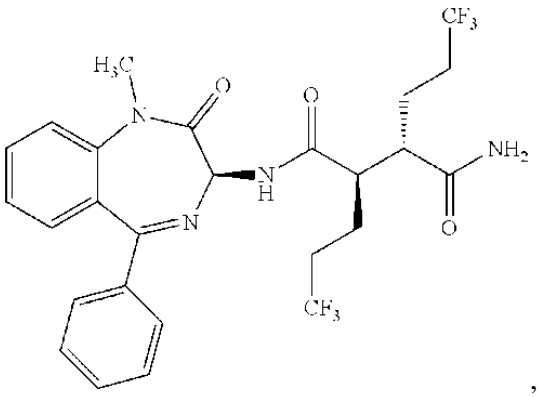
3. The use of claim 1 or 2, wherein:

y is zero or 1.

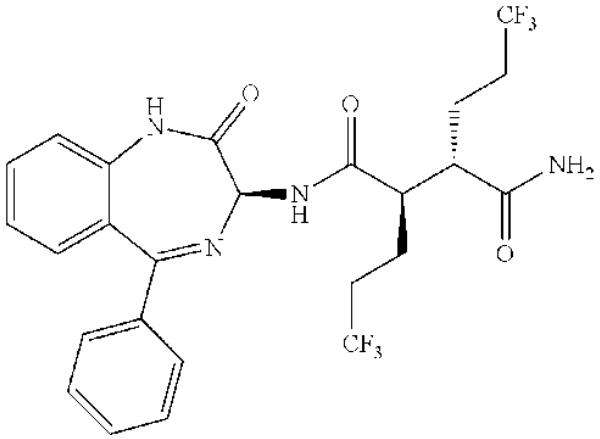
4. The use of any one of claims 1-3, wherein said compound comprises: (2R,3S)—N-((3S)-1-Methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (1); (2R,3S)—N-((3S)-2-Oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide (2); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); (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); or (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).

5. The use of claim 1, wherein said compound comprises:



, or



6. The use of any one of claims 1-5, wherein said breast cancer comprises triple negative breast cancer (TNBC).

7. The use of claim 6, wherein the TNBC comprises luminal androgen receptor (LAR) TNBC, basal-like TNBC, immunomodulatory (IM) TNBC, mesenchymal (M) TNBC, mesenchymal stem like (MSL) TNBC, or unstable (UNS) TNBC.

8. The use of claim 7, wherein said basal-like TNBC comprises BL1 TNBC or BL2 TNBC.

9. The use of any one of claims 1-8, wherein said activated Notch pathway is identified by assessing (i) genetic alterations in one or more Notch-regulated genes, (ii) gene expression profile or mRNA levels of one or more Notch genes or Notch-regulated genes, (iii) levels of one or more Notch proteins or Notch-regulated proteins, or a combination thereof.

10. The use of claim 9, wherein said genetic alteration comprises a gain of function (GOF) activating mutation in one or more Notch-related genes, an internal deletion within one or more Notch genes, a functional inactivation of the negative regulatory region (NRR) in one or more Notch-related genes, a functional inactivation of the proline, glutamic acid,

serine and threonine rich (PEST) domain in one or more Notch-related genes, a fusion in one or more Notch-related genes, a gene rearrangement in the ectodomain of a Notch gene, or a combination thereof.

11. The use of claim 9, wherein said Notch-regulated gene comprises HEY1, NOTCH1, HEYL, NOTCH2, OLFM4, MYC, CDK6, HEY2, KIT, NRARP, MVP, HES6, CDKN2D, NOTCH4, NOTCH3, HES4, HES5, CCND1, HES1, CDKN1B, HES2, or a combination thereof.

12. The use of claim 9, wherein said Notch protein comprises cleaved Notch1 protein or the level of Notch2 protein, Notch3 protein, Notch4 protein, or a combination thereof.

13. The use of any one of claims 1-12, wherein said composition is to be administered at a dose of 0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg, 4 mg, 6 mg, or 8.4 mg; is to be administered once a week or once every two weeks; is to be administered intravenously; or a combination thereof.

14. The use of any one of claims 1-13, wherein a glucocorticoid, a cytotoxic agent, one or more additional therapeutic agents, or a combination thereof is to be further administered.

15. The use of claim 14, wherein said glucocorticoid comprises dexamethasone, which is to be optionally administered prophylactically.

16. The use of claim 15, wherein said dexamethasone is to be administered (i) every 6 hours for up to 72 hours, (ii) at a dose of 4-8 mg, (iii) orally or intravenously, or (iv) a combination thereof.

17. The use of claim 14, wherein said cytotoxic agent comprises eribulin, vinorelbine, sacituzumab govitecan, or a combination thereof.

18. The use of any one of claims 1-17, wherein said tumor growth comprises tumor outgrowth after treatment withdrawal.

19. The use of any one of claims 1-18, wherein said subject is exposed to two or more treatment cycles and wherein the tumor growth inhibition is in the second treatment cycle for said subject.