concomitant and maintenance temozolomide. Despite its use to treat this newly defined disease in adults, this regimen's efficacy has not been evaluated specifically in adult mutant H3 K27M glioma patients.

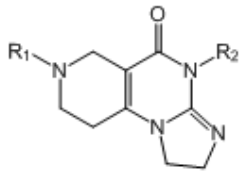
[0005] The functions of histones are predominantly protein-DNA and protein-protein interactions; they do not function as enzymes, which represent the bulk of targeted cancer therapy (kinases, HDAC inhibitors, etc.). Thus, no therapies directly target the mutant H3 proteins itself (such as the case for mutant BRAF); instead, therapeutic efforts have focused on targeting features of tumor cells with H3 K27M mutations, such as their epigenetic- and transcription-dependency. Inhibition of proteins involved in epigenetics such as histone de-acetylates, histone de-methylases, or bromodomains have yielded efficacy in preclinical models, however their ability to improve clinical outcome has not been shown.

[0006] A major challenge for effective H3 K27M glioma therapies is the need to penetrate the blood-brain barrier, a rare feature of current cancer therapies. This is further enhanced by the location of these tumors in midline brain structures, which has been shown to be harder to penetrate than other brain locations. The H3 K27M mutation also tends to occur in midline gliomas with dopamine present and DRD2 expression prevalent in the tumor environment.

[0007] The lack of treatments for H3 K27M glioma leave a large unmet medical need with respect to disease control, symptom relief, and survival rates. Patients with recurrent disease following radiation, are left with no treatment options with a demonstrated survival benefit.

SUMMARY

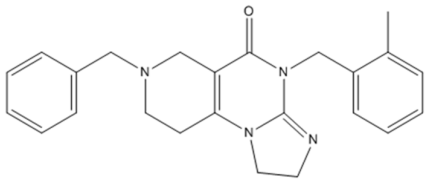
[0008] In one example, provided herein are compounds of formula (**10**):



(10)

, wherein R_1 and R_2 are independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, and acyl radicals. In one example, when R_1 is CH_2Ph, R_2 is not CH_2-(2-CH_3-Ph). In one example, R_1 is CH_2Ph and R_2 is CH_2-(2-CH_3-Ph) (ONC201). In one example, R_1 is CH_2Ph and R_2 is CH_2-(2,4-di F-Ph) (ONC206). In one example, R_1 is CH_2Ph and R_2 is CH_2-(4-CF_3-Ph) (ONC212). In one example, R_1 is CH_2Ph and R_2 is CH_2-(3,4-di F-Ph) (ONC213). In one example, R_1 is CH_2-(3,4-di-Cl-Ph) and R_2 is CH_2-(4-CF_3-Ph) (ONC234). In one example, R_1 is CH_2-3-thienyl and R_2 is CH_2-(4-CF_3-Ph) (ONC236).

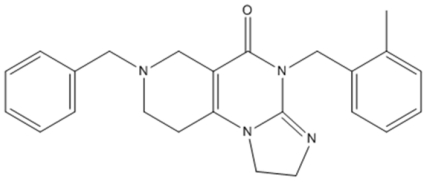
[0009] In another example, provided herein are methods to treat or prevent cancer in a subject in need thereof, comprising: administering to the subject in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount compound (**1**)



(**1**)

or a pharmaceutically acceptable salt thereof, wherein the cancer involves a midline structure of the brain and has a histone H3 K27M mutation.

[0009a] In one aspect, provided herein is a use of a pharmaceutical composition comprising a therapeutically effective amount compound (**1**)



(**1**)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer involves a midline structure of the brain and has a histone H3 K27M mutation.

[0010] In another example, provided herein are methods to treat or prevent cancer in a subject in need thereof, comprising: administering to the subject in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof, wherein the cancer has a histone H3 mutation.

[0010a] In one aspect, provided herein is a use of a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer has a histone H3 mutation.

[0011] In another example, provided herein are methods to treat or prevent cancer in a subject in need thereof, comprising: administering to the subject in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount a compound of

formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof, wherein the cancer involves a midline structure of the brain.

[0011a] In one aspect, provided herein is a use of a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer involves a midline structure of the brain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The above summary, as well as the following detailed description of embodiments of the invention, will be better understood when read in conjunction with the appended drawings. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown. In the drawings:

[0013] Figure **1**.Antagonism of dopamine receptors (DRD1, DRD2S, DRD2L, DRD3, DRD4, and DRD5) by ONC201.

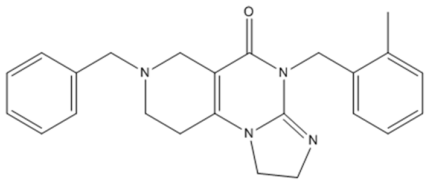
[0014] Figure **2**. Tumor type sensitivity of the Genomic of Drug Sensitivity in Cancer program (GDSC) cell line collection. The average sensitivity was determined by average estimated IC_{50} values from cell viability assays conducted at 72 hours post-treatment. Numbers above the bar indicates indicate the number of cell lines per tumor type.

[0015] Figure **3**. GBM cell lines with higher DRD2 or lower DRD5 expression are more responsive to ONC201. (A) Inhibition of NCI60 GBM cell lines as a function of ONC201 concentration. (B) Log ONC201 GI_{50} (M) vs DRD2 expression for each GBM cell line. R^2 =

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition comprising a therapeutically effective amount compound (**1**)



(**1**)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer involves a midline structure of the brain and has a histone H3 K27M mutation.

2. The use according to claim **1**, wherein the cancer involves the thalamus, medulla, hypothalamus, basal ganglia, pineal gland, midbrain, cerebellum, pons, or spinal cord.

3. The use according to claim **1**, wherein the histone H3 K27M mutation is H3.3 K27M or H3.1 K27M.

4. The use according to claim **1**, wherein the histone H3 K27M mutation is in one or more histone genes selected from *H3F3A, H3F3B, HIST1H3A, HIST1H3B, HIST1H3C, HIST1H3D, HIST1H3E, HIST1H3F, HIST1H3G, HIST1H3H, HIST1H3I,* or *HIST1H3J*.

5. The use according to claim **1**, wherein in cancerous tissue DRD2 is overexpressed, DRD5 is underexpressed, or both.

6. The use according to claim **1**, wherein the subject is a human.

7. The use according to claim **1**, wherein the subject is a domesticated pet.

8. The use according to claim **1**, wherein the subject is a pediatric subject.

9. Use of a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer has a histone H3 mutation.

10. The use according to claim **9**, wherein the cancer is selected from the group consisting of a central nervous system tumor, a brain tumor, a peripheral nervous system tumor, a pheochromocytoma, a paraganglioma, an adrenal cortical carcinoma, an adrenal tumor, and a neuroendocrine tumor.

11. The use according to claim **9**, wherein the cancer comes from glial cells and is selected from the group consisting of meningioma, ependymoma, oligodendrogliomas, astrocytoma, optic nerve glioma, pineal tumors, rhabdoid tumors, and diffuse intrinsic pontine glioma; or wherein the cancer comes from neural cells and is selected from the group consisting of medulloblastoma, neuroblastoma, ganglioma, primitive neuro-ectodermal tumors, and schwannoma.

12. The use according to claim **9**, wherein the cancer involves the thalamus, medulla, hypothalamus, basal ganglia, pineal gland, midbrain, cerebellum, pons, or spinal cord.

13. The use according to claim **9**, wherein the histone H3 mutation is H3.3 K27M or H3.1 K27M.

14. The use according to claim **9**, wherein the cancer has a K27M mutation in one or more histone genes selected from *H3F3A, H3F3B, HIST1H3A, HIST1H3B, HIST1H3C, HIST1H3D, HIST1H3E, HIST1H3F, HIST1H3G, HIST1H3H, HIST1H3I,* or *HIST1H3J*.

15. The use according to claim **9**, wherein DRD2 is overexpressed in cancerous tissue, DRD5 is underexpressed, or both.

16. The use according to claim **9**, wherein the subject is a human.

17. The use according to claim **9**, wherein the subject is a domesticated pet.

18. The use according to claim **9**, wherein the compound is ONC201.

19. The use according to claim **9**, wherein the subject is a pediatric subject.

20. Use of a pharmaceutical composition comprising a therapeutically effective amount a compound of formula (**10**) or an analog thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof, wherein the cancer involves a midline structure of the brain.

21. The use according to claim **20**, wherein the cancer involves the thalamus, medulla, hypothalamus, basal ganglia, pineal gland, midbrain, cerebellum, pons, or spinal cord.

22. The use according to claim **20**, wherein the cancer has a histone H3 mutation, wherein the histone H3 mutation is H3.3 K27M or H3.1 K27M.

23. The use according to claim **20**, wherein the cancer has a histone H3 K27M mutation in one or more histone genes selected from *H3F3A, H3F3B, HIST1H3A, HIST1H3B, HIST1H3C, HIST1H3D, HIST1H3E, HIST1H3F, HIST1H3G, HIST1H3H, HIST1H3I,* or *HIST1H3J*.

24. The use according to claim **20**, wherein DRD2 is overexpressed in cancerous tissue, DRD5 is underexpressed, or both.

25. The use according to claim **20**, wherein the subject is a human.

26. The use according to claim **20**, wherein the subject is a domesticated pet.

27. The use according to claim **20**, wherein the compound is ONC201.

28. The use according to claim **20**, wherein the subject is a pediatric subject.