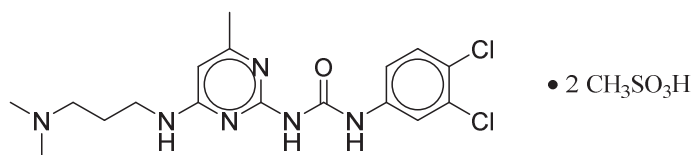


R_6 is H, unsubstituted C_1 - C_6 alkyl, $-(C(R_{14})(R_{15}))_mR_{17}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, $-(C(R_{14})(R_{15}))_mOR_{13}$, $-(C(R_{14})(R_{15}))_nR_{16}$, or $-OR_{22}$;
 R_7 is substituted or unsubstituted phenoxy or $-C(=O)R_{23}$;
each R_8 is independently H or substituted or unsubstituted C_1 - C_6 alkyl;
each R_9 is independently substituted or unsubstituted C_1 - C_6 alkyl;
 R_{10} is H or unsubstituted C_1 - C_4 alkyl;
 R_{11} is H, substituted or unsubstituted C_1 - C_6 alkyl, $-C(=O)R_{19}$, or $-S(=O)_2R_{19}$;
 R_{12} is H or substituted or unsubstituted C_1 - C_6 alkyl;
 R_{13} is H or substituted or unsubstituted C_1 - C_6 alkyl;
each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1 - C_6 alkyl;
 R_{16} is substituted or unsubstituted C_2 - C_7 heterocycloalkyl or $-C(=O)N(R_{18})_2$;
 R_{17} is $-C(=O)R_{20}$, $-CO_2R_{21}$, $-C(=O)N(R_{21})_2$, or substituted or unsubstituted C_2 - C_9 heteroaryl;
each R_{18} is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_7 heterocycloalkyl, or substituted or unsubstituted C_3 - C_8 cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;
 R_{19} is substituted or unsubstituted C_1 - C_6 alkyl;
 R_{20} is substituted or unsubstituted C_1 - C_6 alkyl;
each R_{21} is independently H, or substituted or unsubstituted C_1 - C_6 alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;
 R_{22} is H, or substituted or unsubstituted C_1 - C_6 alkyl;
 R_{23} is substituted or unsubstituted C_6 - C_{10} aryl;
m is 2-6;
n is 1-5; and
p is 0-4; or
a pharmaceutically acceptable salt thereof.

[0017b] In another aspect is a compound having the structure of:



; or a pharmaceutically acceptable salt

thereof.

[0017c] In another aspect is a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[0017d] In another aspect is a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease in a subject; wherein the disease is cancer or Down's Syndrome.

[0018] Other objects, features and advantages of the compounds, compositions, methods, and uses described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent from this detailed description.

DETAILED DESCRIPTION

[0019] The compounds described herein are modulators or inhibitors of the neural and GBM (glioblastoma multiforme) stem cell transcriptional repressor OLIG2 (e.g. NM_005806, NP_005797 for human). OLIG2 (also written herein as Olig2) is the oligodendrocyte transcription factor 2. This protein is a member of the bHLH (basic helix-loop-helix) family. The bHLH family is a family of transcription factors that contain the structure motif characterized by two alpha helices connected by a loop. The transcription factors containing bHLH domains are generally dimeric. Generally one of the helices contains basic amino acid residues that facilitate binding to DNA. OLIG2 is normally restricted to the central nervous system (CNS) in non-disease states, where it is an essential regulator of progenitor cell fate. OLIG2 homodimerizes and heterodimerizes with the E12 or E47 proteins to then bind and repress the p21 gene promoter among other effects. P21 is a stem cell and tumor suppressor, and is directly repressed by OLIG2. P21 is activated by the tumor suppressor p53. p53 occurs in the intact, wild type form in nearly 70% of primary GBM patient samples. OLIG2 is highly expressed in all diffuse gliomas, and is found in virtually 100% of GBM cells positive for the

CD133 stem cell marker. Importantly, OLIG2 is typically not found in normal brain and in tissues outside the CNS unless they are malignant, such as T-cell leukemia, melanoma, lung and breast cancer. No other neural or glial marker gene, and no other transcriptional repressor displays as consistent a link to brain cancers. In contrast, membrane receptors (EGFR, PDGFR, etc) are not uniformly expressed among patients, and various approaches to targeting them has been met with limited success in GBM treatment.

[0020] The expression of Olig2 in diffuse gliomas likely results from the transformed stem cell origin of these tumors. It has been found that a small cohort of the cells present in patient GBM expresses neural stem cell markers including CD133 and nestin, among others. The CD133(+) cells isolated from existing GBM are highly tumorigenic when orthotopically implanted into mice. In one study, as few as 100 of the CD133(+) cells extracted from a patient GBM produced an invasive tumor when transplanted into the brain of a recipient mouse, while 100,000 CD133(-) GBM cells were unable to generate a tumor. Consistent with these findings, a strikingly high percentage of GBM occur in close proximity to the neural stem cell germinal zones in the brain, i.e., neural stem cells undergo malignant transformation and migrate some distance from the germinal zones and establish a GBM.

[0021] Another significant finding with respect to GBM cancer stem cells (CSCs) is that the CD133(+) cells are significantly more resistant to radiation and cytotoxic agents used to treat GBM than the bulk of the tumor mass which is comprised of CD133(-) cells. This suggests that conventional radio/chemotherapy spares the CSCs within a GBM, and unless these cells are targeted, the tumor invariably is resurgent, with lethal effect. Moreover, the very few patients that survive GBM suffer lifelong morbidity from chemo- and radio-toxicity, in terms of cognition, endocrine balance, and other functions.

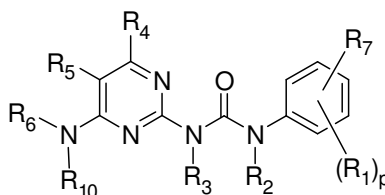
[0022] Olig2 is highly expressed in GBM CSCs, but is only expressed in low levels by normal brain and is not detected in tissues outside the nervous system. Olig2 inhibitors would offer a therapeutic margin superior to conventional chemotherapy. Low systemic toxicity would be much more compatible with long-term clinical management of GBM than is the case with currently used treatment approaches.

[0023] High rates of mortality for patients with brain cancers make this disease a leading cause of cancer related death in men, women and children. Primary brain tumors are actually the most common solid tumor of childhood and the second leading cause of cancer death after leukemia. The toxicity of current treatments causes serious life-long morbidity in the few patients that survive. The development of small molecule, orally available drugs with low toxicity effective in brain cancers would represent a significant advance. Moreover, the compounds may also be effective in other cancers that are stem cell driven and which highly express Olig2. These

Claims

WHAT IS CLAIMED IS:

1. A compound of Formula (III):



Formula (III);

wherein:

each R₁ is independently halogen, -CN, -NO₂, -OH, -OCF₃, -OCH₂F, -OCF₂H, -CF₃, -SR₈, -N(R₈)S(=O)₂R₉, -S(=O)₂N(R₈)₂, -S(=O)R₉, -S(=O)₂R₉, -C(=O)R₉, -CO₂R₈, -N(R₈)₂, -C(=O)N(R₈)₂, -N(R₈)C(=O)R₉, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₇heteroaryl;

R₂ and R₃ are each independently H, -CN, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₂-C₇heterocycloalkyl; or R₂ and R₃ are taken together to form a 5- or 6-membered heterocyclic ring;

R₄ and R₅ are independently H, halogen, -CN, -OH, -CF₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₉heteroaryl;

R₆ is H, unsubstituted C₁-C₆alkyl, -(C(R₁₄)(R₁₅))_mR₁₇, -(C(R₁₄)(R₁₅))_mN(R₁₁)(R₁₂), -(C(R₁₄)(R₁₅))_mOR₁₃, -(C(R₁₄)(R₁₅))_nR₁₆, or -OR₂₂;

R₇ is substituted or unsubstituted phenoxy or -C(=O)R₂₃;

each R₈ is independently H or substituted or unsubstituted C₁-C₆alkyl;

each R₉ is independently substituted or unsubstituted C₁-C₆alkyl;

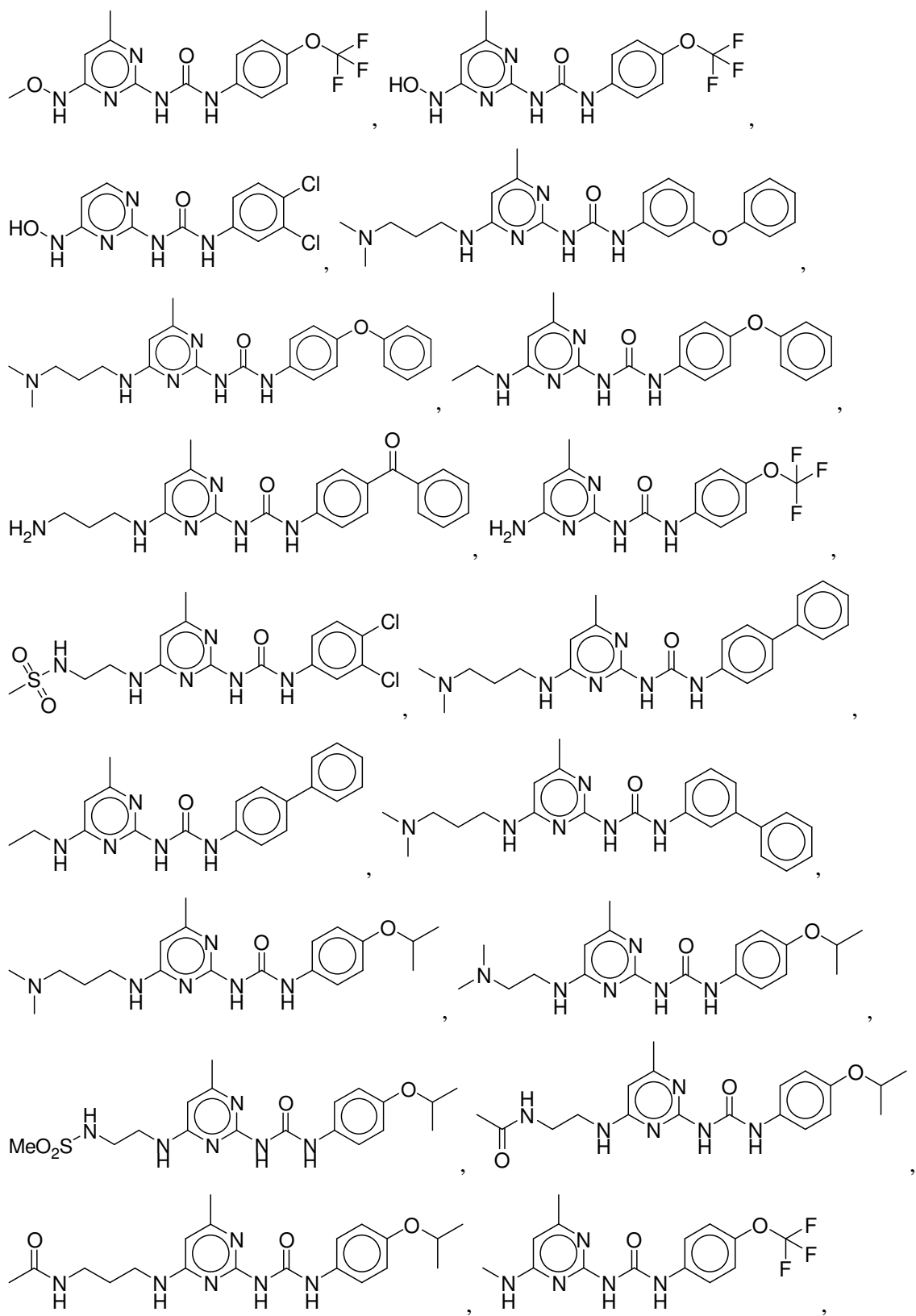
R₁₀ is H or unsubstituted C₁-C₄alkyl;

R₁₁ is H, substituted or unsubstituted C₁-C₆alkyl, -C(=O)R₁₉, or -S(=O)₂R₁₉;

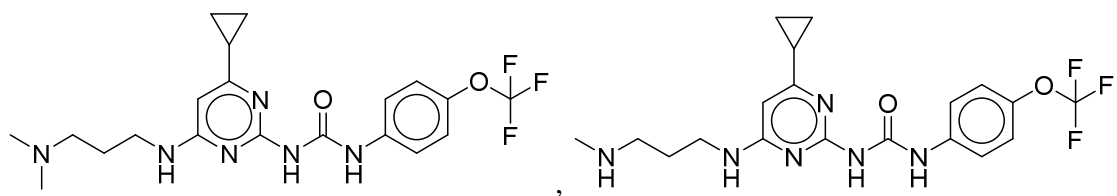
R₁₂ is H or substituted or unsubstituted C₁-C₆alkyl;

R₁₃ is H or substituted or unsubstituted C₁-C₆alkyl;

- each R₁₄ and R₁₅ is each independently H, halogen, or substituted or unsubstituted C₁-C₆alkyl;
- R₁₆ is substituted or unsubstituted C₂-C₇heterocycloalkyl or -C(=O)N(R₁₈)₂;
- R₁₇ is -C(=O)R₂₀, -CO₂R₂₁, -C(=O)N(R₂₁)₂, or substituted or unsubstituted C₂-C₉heteroaryl;
- each R₁₈ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, or substituted or unsubstituted C₃-C₈cycloalkyl; or two R₁₈ are taken together to form a heterocycloalkyl ring;
- R₁₉ is substituted or unsubstituted C₁-C₆alkyl;
- R₂₀ is substituted or unsubstituted C₁-C₆alkyl;
- each R₂₁ is independently H, or substituted or unsubstituted C₁-C₆alkyl; or two R₂₁ are taken together to form a heterocycloalkyl ring;
- R₂₂ is H, or substituted or unsubstituted C₁-C₆alkyl;
- R₂₃ is substituted or unsubstituted C₆-C₁₀aryl;
- m is 2-6;
- n is 1-5; and
- p is 0-4; or
- a pharmaceutically acceptable salt thereof.
2. The compound of claim 1, wherein R₂ and R₃ are each independently H, -CN, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₂-C₇heterocycloalkyl.
 3. The compound of claims 1 or 2, R₅ is H.
 4. The compound of any one of claims 1-3, wherein R₄ is halogen, -CN, -OH, -CF₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl.
 5. The compound of any one of claims 1-4, wherein R₁₀ is H.
 6. The compound of any one of claims 1-5, wherein R₇ is substituted or unsubstituted phenoxy.
 7. The compound of any one of claims 1-5, wherein R₇ is -C(=O)R₂₃.
 8. The compound of claim 1, wherein the compound is selected from:

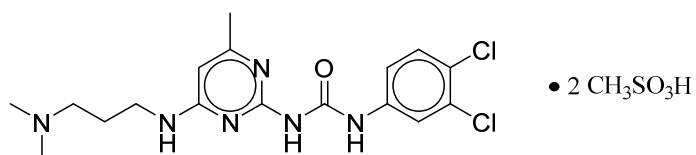






and ; or a pharmaceutically acceptable salt thereof.

9. A compound having the structure of:



; or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

11. Use of a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease in a subject; wherein the disease is cancer or Down's Syndrome.