COMBINATION THERAPIES WITH OLIG2 INHIBITORS

CROSS-REFERENCE

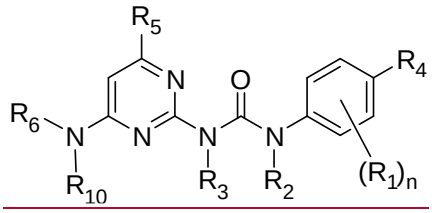
[0001] This application claims the benefit of U.S. Provisional Application No. 63/069,472, filed on August 24, 2020, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Current brain tumor therapeutic agents, which are only able to extend median survival of patients by six months, cause significant systemic toxicity. This toxicity results in serious long term morbidity of the few patients that survive, in terms of cognition, endocrine disorders, and motor effects. Currently brain tumors are essentially incurable with a median survival of fifteen months.

SUMMARY ~~OF THE INVENTION~~

[0002a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure:



Formula (I);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-SR_8$, $-N(R_8)S(=O)_2R_9$, $-S(=O)_2N(R_8)_2$, $-S(=O)R_9$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, $-N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_5 is halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a substituted or unsubstituted 5-, 6-, 7-, or 8-membered heterocyclic ring;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

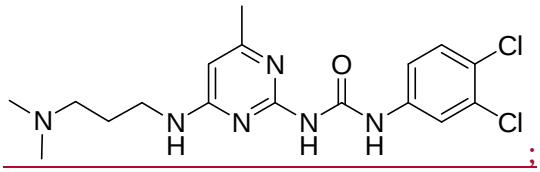
each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H, or C_1-C_4alkyl;

m is 2-6; and

n is 0-4.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent has the structure:



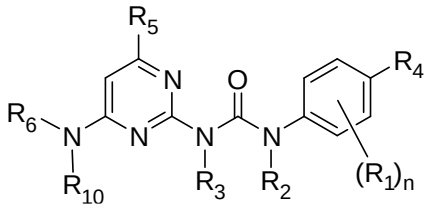
;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0002c] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cancer or Down's Syndrome in a subject.

[0002d] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in therapy.

[0003] In one ~~aspect~~example, described herein is a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure:



Formula (I);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_5 is halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a substituted or unsubstituted 5-, 6-, 7-, or 8-membered heterocyclic ring;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H, or C_1-C_4alkyl;

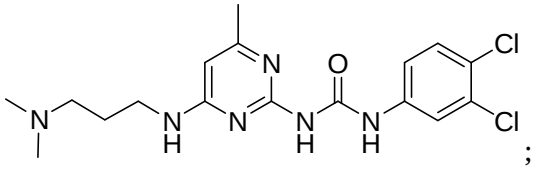
m is 2-6; and

n is 0-4.

[0004] In one ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_2 and R_3 are each H. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{14} and R_{15} are each H. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_{11} and R_{12} are each unsubstituted C_1-C_6alkyl. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_{11}

and R_{12} are each $-CH_3$. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein m is 2. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein m is 3. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_{10} is H or CH_3. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_5 is CH_3. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_5 is CH_2CH_3. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_4 is H, halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-SR_8$, $-N(R_8)S(=O)_2R_9$, $-S(=O)_2N(R_8)_2$, $-S(=O)R_9$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, $-N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_4 is H, halogen, -CN, -OH, $-OCF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_4 is H, halogen, $-OCF_3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein R_4 is halogen. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein each R_1 is independently halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-SR_8$, $-N(R_8)S(=O)_2R_9$, $-S(=O)_2N(R_8)_2$, $-S(=O)R_9$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, $-N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein each R_1 is independently halogen, -CN, -OH, $-OCF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein each R_1 is independently halogen, $-OCF_3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein each R_1 is independently is halogen. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein n is 1. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein n is 0. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein n is 0 and R_4 is H, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-SR_8$, $-N(R_8)S(=O)_2R_9$, $-S(=O)_2N(R_8)_2$, $-S(=O)R_9$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, $-N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl,

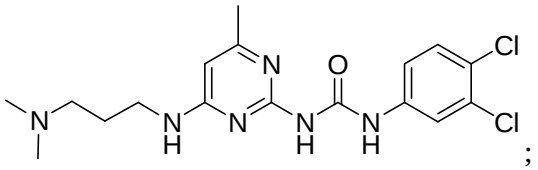
substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein n is 0 and R_4 is H, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another ~~embodiment~~example, the pharmaceutical composition comprises a compound of Formula (I) wherein the compound of Formula (I) has the structure:



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or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0005] In another ~~aspect~~example, is a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent has the structure:



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or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0006] In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor, an ataxia telangiectasia mutated (ATM) kinase inhibitor, an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor, a cyclin-dependent kinase (CDK) 4/6 inhibitor, a checkpoint kinase 1 (Chk1) inhibitor, a signal transducer and activator of transcription 3 (STAT3) inhibitor, a mechanistic target of rapamycin (mTOR) inhibitor, or a Janus Kinase 2 (JAK2) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is an ataxia telangiectasia mutated (ATM) kinase inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor. In another

~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a poly ADP-ribose polymerase (PARP) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a cyclin-dependent kinase (CDK) 4/6 inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a checkpoint kinase 1 (Chk1) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a signal transducer and activator of transcription 3 (STAT3) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a mechanistic target of rapamycin (mTOR) inhibitor. In another ~~embodiment~~example of the aforementioned ~~embodiment~~examples, the pharmaceutical composition comprises a second therapeutic agent, wherein the second therapeutic agent is a Janus Kinase 2 (JAK2) inhibitor.

[0007] In another ~~aspect~~example is a method for treating a disease in a subject comprising administering to the subject in need thereof a pharmaceutical composition described herein, wherein the disease is cancer or Down's Syndrome. In another ~~aspect~~example is a method for treating a disease in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the disease is cancer or Down's Syndrome. In some ~~embodiment~~examples is a method for treating cancer in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In some ~~embodiment~~examples is a method for treating cancer in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia. In some ~~embodiment~~examples is a method for treating Down's Syndrome in a subject

comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0008] In another ~~aspect~~example is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor, an ataxia telangiectasia mutated (ATM) kinase inhibitor, an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor, a cyclin-dependent kinase (CDK) 4/6 inhibitor, a checkpoint kinase 1 (Chk1) inhibitor, a signal transducer and activator of transcription 3 (STAT3) inhibitor, a mechanistic target of rapamycin (mTOR) inhibitor, or a Janus Kinase 2 (JAK2) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is an ataxia telangiectasia mutated (ATM) kinase inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein

the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a poly ADP-ribose polymerase (PARP) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a cyclin-dependent kinase (CDK) 4/6 inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a checkpoint kinase 1 (Chk1) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a signal transducer and activator of transcription 3 (STAT3) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a mechanistic target of rapamycin (mTOR) inhibitor. In some ~~embodiment~~examples is a method for treating cancer or Down's Syndrome in a subject comprising administering to the subject in need thereof a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and the second therapeutic agent is a Janus Kinase 2 (JAK2) inhibitor.

[0009] In another ~~aspect~~example is the use of a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a

pharmaceutically acceptable salt, solvate, or prodrug thereof, in the manufacture of a medicament for the treatment of cancer or Down's Syndrome.

[0010] 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 ~~embodiment~~example**s**, 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

[0011] Disclosed herein is a pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I) described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof. Further disclosed herein is a pharmaceutical composition comprising 1) a first therapeutic agent that is an OLIG2 modulator having the structure of Formula (I) described herein; 2) a second therapeutic agent that is an epidermal growth factor receptor (EGFR) inhibitor, an ataxia telangiectasia mutated (ATM) kinase inhibitor, an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor, a cyclin-dependent kinase (CDK) 4/6 inhibitor, a checkpoint kinase 1 (Chk1) inhibitor, signal transducer and activator of transcription 3 (STAT3) inhibitor, a mechanistic target of rapamycin (mTOR) inhibitor, or a Janus Kinase 2 (JAK2) inhibitor; and 3) at least one pharmaceutically acceptable excipient.

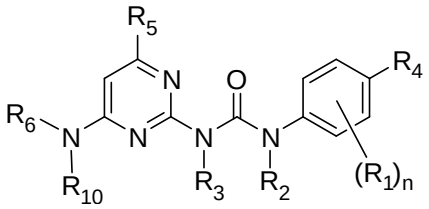
OLIG2 Biology

[0012] The compounds of Formula (I) or (II) 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 trasnscription 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 hetereodimerizes 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

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure:



Formula (I);

wherein:

each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring;

R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 is H, halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_5 is halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a substituted or unsubstituted 5-, 6-, 7-, or 8-membered heterocyclic ring;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

each R_8 is independently H, or substituted or unsubstituted C_1-C_6alkyl;

each R_9 is independently substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H, or C_1-C_4alkyl;

m is 2-6; and

n is 0-4.

2. The pharmaceutical composition of claim 1, wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

3. The pharmaceutical composition of claim 2, wherein R_2 and R_3 are each H.

4. The pharmaceutical composition of claim 1, wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring.

5. The pharmaceutical composition of claim 4, wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring.

6. The pharmaceutical composition of any one of claims 1-5, wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{14} and R_{15} are each H.

7. The pharmaceutical composition of claim 6, wherein R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl.

8. The pharmaceutical composition of claim 7, wherein R_{11} and R_{12} are each independently unsubstituted C_1-C_6alkyl.

9. The pharmaceutical composition of claim 8, wherein R_{11} and R_{12} are each -CH_3.

10. The pharmaceutical composition of any one of claims 1-9, wherein m is 2.

11. The pharmaceutical composition of any one of claims 1-9, wherein m is 3.

12. The pharmaceutical composition of any one of claims 1-11, wherein R_{10} is H or CH_3.

13. The pharmaceutical composition of any one of claims 1-12, wherein R_5 is substituted or unsubstituted C_1-C_6alkyl.

14. The pharmaceutical composition of claim 13, wherein R_5 is CH_3.

15. The pharmaceutical composition of claim 13, wherein R_5 is CH_2CH_3.

16. The pharmaceutical composition of any one of claims 1-15, wherein R_4 is H, halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

17. The pharmaceutical composition of claim 16, wherein R_4 is H, halogen, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

18. The pharmaceutical composition of claim 16, wherein R_4 is H, halogen, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy.

19. The pharmaceutical composition of claim 16, wherein R_4 is halogen.

20. The pharmaceutical composition of any one of claims 1-19, wherein each R_1 is independently halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

21. The pharmaceutical composition of claim 20, wherein each R_1 is independently halogen, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

22. The pharmaceutical composition of claim 20, wherein each R_1 is independently halogen, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy.

23. The pharmaceutical composition of claim 20, wherein each R_1 is independently is halogen.

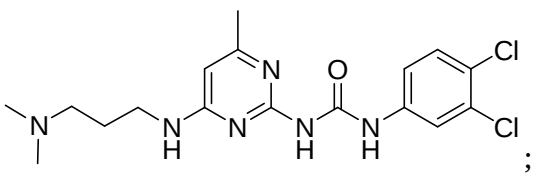
24. The pharmaceutical composition of any one of claims 1-23, wherein n is 1.

25. The pharmaceutical composition of any one of claims 1-19, wherein n is 0.

26. The pharmaceutical composition of any one of claims 1-15, wherein n is 0 and R_4 is H, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl.

27. The pharmaceutical composition of claim 26, wherein R_4 is H, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

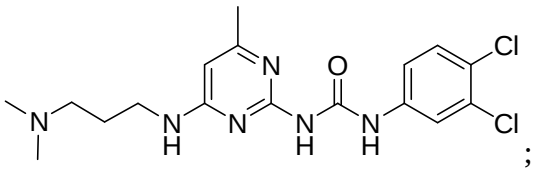
28. The pharmaceutical composition of claim 1, wherein the compound of Formula (I) has the structure:



;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

29. A pharmaceutical composition comprising 1) a first therapeutic agent, 2) a second therapeutic agent, and 3) at least one pharmaceutically acceptable excipient, wherein the first therapeutic agent has the structure:



;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

30. The pharmaceutical composition of any one of claims 1-29, wherein the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor, an ataxia telangiectasia mutated (ATM) kinase inhibitor, an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor, a cyclin-dependent kinase (CDK) 4/6 inhibitor, a checkpoint kinase 1 (Chk1) inhibitor, a signal transducer and activator of transcription 3 (STAT3) inhibitor, a mechanistic target of rapamycin (mTOR) inhibitor, or a Janus Kinase 2 (JAK2) inhibitor.

31. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor.

32. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is an ataxia telangiectasia mutated (ATM) kinase inhibitor.

33. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is an ataxia telengiectasia and Rad3 related (ATR) kinase inhibitor.

34. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a poly ADP-ribose polymerase (PARP) inhibitor.

35. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a cyclin-dependent kinase (CDK) 4/6 inhibitor.

36. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a checkpoint kinase 1 (Chk1) inhibitor.

37. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a signal transducer and activator of transcription 3 (STAT3) inhibitor.

38. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a mechanistic target of rapamycin (mTOR) inhibitor.

39. The pharmaceutical composition of any one of claims 1-30, wherein the second therapeutic agent is a Janus Kinase 2 (JAK2) inhibitor.

40. Use of a pharmaceutical composition of any one of claims 1-39, in the manufacture of a medicament ~~A method~~ for treating cancer or Down's Syndrome in a subject ~~comprising~~

~~administering to the subject in need thereof a pharmaceutical composition of any one of claims 1-39~~.

41. The ~~method~~use of claim 40, wherein the disease is cancer.

42. The ~~method~~use of claim 41, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia.

43. The ~~method~~use of claim 40, wherein the disease is Down's Syndrome.

44. A pharmaceutical composition of any one of claims 1-39, for use in therapy.