COMBINATION THERAPIES FOR HIGH AND VERY HIGH RISK MDS

CROSS-REFERENCE

[0001] This patent application claims the benefit of US Provisional Application No. 62/773,490, filed November 30, 2018 which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

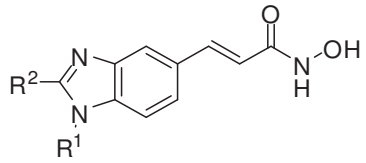
[0002] Local chromatin architecture is generally recognized as an important factor in the regulation of gene expression. The architecture of chromatin, a protein-DNA complex, is strongly influenced by post-translational modifications of the histones which are the protein components. Reversible acetylation of histones is a key component in the regulation of gene expression by altering the accessibility of transcription factors to DNA. In general, increased levels of histone acetylation are associated with increased transcriptional activity, whereas decreased levels of acetylation are associated with repression of gene expression. In normal cells, histone deacetylases (HDACs) and histone acetyltransferase together control the level of acetylation of histones to maintain a balance. Inhibition of HDACs results in the accumulation of acetylated histones, which results in a variety of cell type dependent cellular responses, such as apoptosis, necrosis, differentiation, cell survival, inhibition of proliferation and cytostasis.

[0003] Inhibitors of HDAC have been studied for their therapeutic effects on cancer cells. For example, suberoylanilide hydroxamic acid (SAHA) is a potent inducer of differentiation and/or apoptosis in murine erythroleukemia, bladder, and myeloma cell lines. SAHA has been shown to suppress the growth of prostate cancer cells *in vitro* and *in vivo*. Other inhibitors of HDAC that have been widely studied for their anti-cancer activities are trichostatin A (TSA) and trapoxin B. Trichostatin A is a reversible inhibitor of mammalian HDAC. Trapoxin B is a cyclic tetrapeptide, which is an irreversible inhibitor of mammalian HDAC. However, due to the *in vivo* instability of these compounds they are less desirable as anti-cancer drugs. The in vivo activity of recently disclosed inhibitors can be directly monitored by their ability to increase the amount of acetylated histones in the biological sample. HDAC inhibitors have been reported to interfere with neurodegenerative processes, for instance, HDAC inhibitors arrest polyglutamine-dependent neurodegeneration. In addition, HDAC inhibitors have also been known to inhibit production of cytokines such as TNF, IFN, IL-1 which are known to be implicated in inflammatory diseases and/or immune system disorders.

[0004] Nevertheless, there is still a need to provide further HDAC inhibitor combinations that would be expected to have useful, improved pharmaceutical properties in the treatment of diseases such as cancer, neurodegenerative diseases, disorders involving angiogenesis and inflammatory and/or immune system disorders.

SUMMARY OF THE DISCLOSURE

[0004a] In one aspect, disclosed herein is a use of a DNA hypomethylating agent in the manufacture of a first medicament and use of about 45 mg of a compound of formula (I):



Formula (I)

wherein

R^1 is $-(CR^{20}R^{21})_m—(CR^{22}R^{23})_n—(CR^{24}R^{25})_o—NR^{26}R^{27}$;

R^2 is alkyl, fluoroalkyl, cyano, C_2-C_6alkenyl, C_2-C_6alkynyl, or heteroalkyl optionally substituted with =O;

each R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, and R^{25} is independently H or methyl;

each R^{26} and R^{27} is independently H, hydroxyalkyl, or alkyl; and

m, n, and o are independently integers of 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof.

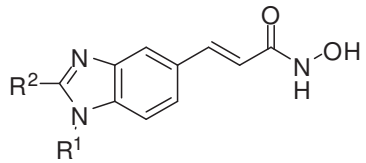
[0004b] In another aspect, disclosed herein is a use of a DNA hypomethylating agent in the manufacture of a first medicament and about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof, wherein pracinostat is to be orally administered to the patient 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

[0004c] In another aspect, provided herein is a use of about 75 mg/m^2 of 5-azacytidine (azacitidine) in the manufacture of a first medicament and use of about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof, wherein 5-azacytidine (azacitidine) is to be administered intravenously or subcutaneously for 7 days of each 28-day cycle; and wherein pracinostat is to be orally administered for 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

[0005] Disclosed herein is a method of treating high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof; the method comprising administering to the patient:

(i) a DNA hypomethylating agent; and

(ii) about 45 mg of a compound of formula (I):



Formula (I)

wherein

R^1 is -$(CR^{20}R^{21})_m$—$(CR^{22}R^{23})_n$—$(CR^{24}R^{25})_o$—$NR^{26}R^{27}$;

R^2 is alkyl, fluoroalkyl, cyano, C_2-C_6alkenyl, C_2-C_6alkynyl, or heteroalkyl optionally substituted with =O;

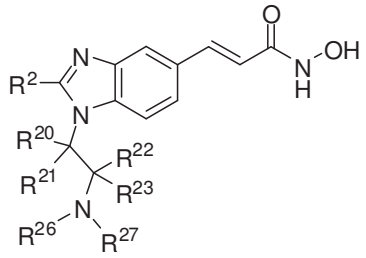
each R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, and R^{25} is independently H or methyl;

each R^{26} and R^{27} is independently H, hydroxyalkyl, or alkyl; and

m, n, and o are independently integers of 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof.

[0006] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I) has the structure:

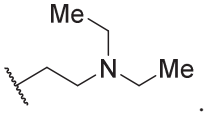


Formula (Ia).

[0007] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), R^{26} and R^{27} are independently H or alkyl.

[0008] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), R^{26} and R^{27} are independently H, methyl, ethyl, isopropyl, propyl, butyl, isobutyl, pentyl, hexyl or heptyl.

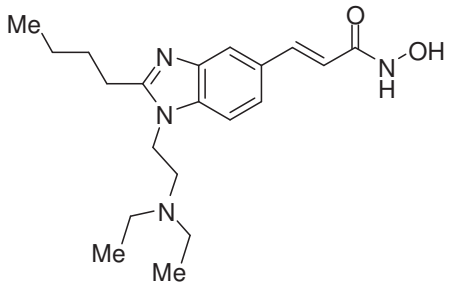
[0009] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), R^1 has the structure



[0010] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), R^2 is ethyl, 1-methyl-ethyl, 2,2,2-trifluoroethyl, propyl, 2-methyl-propyl, 2,2-dimethyl-propyl, 3,3,3-trifluoro-propyl, butyl, 3,3-dimethyl-butyl, pentyl, 2,4,4-trimethyl-pentyl, hexyl or octyl.

[0011] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), R^2 is butyl.

[0012] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I) is pracinostat:



or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof.

[0013] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is 5-azacytidine (azacitidine), 5-azadeoxycytidine (decitabine), SGI-110, zebularine, or procaine.

[0014] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is 5-azacytidine (azacitidine).

[0015] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is 5-azadeoxycytidine (decitabine).

[0016] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the method is for treating high risk myelodysplastic syndromes (MDS).

[0017] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the method is for treating very high risk myelodysplastic syndromes (MDS).

[0018] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the patient in need thereof has not been previously treated with a DNA hypomethylating agent.

[0019] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the patient in need thereof has been previously treated with transfusions, hematopoietic growth factors, or immunosuppressive therapy.

[0020] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the MDS is refractory, non-responsive, or resistant to chemotherapy and/or haploidentical stem cell transplantation.

[0021] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is administered in an amount from about 5 mg/m^2 to about 125 mg/m^2.

[0022] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is administered in an amount of about 75 mg/m^2.

[0023] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, is administered orally and the hypomethylating agent is administered intravenously or subcutaneously.

[0024] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered in cycles of 28 days.

[0025] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 3 cycles.

[0026] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 4 cycles.

[0027] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 5 cycles.

[0028] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 6 cycles.

[0029] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 7 cycles.

[0030] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 8 cycles.

[0031] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 9 cycles.

[0032] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered for at least 10 cycles.

[0033] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are administered until complete remission (CR) is observed.

[0034] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, is administered for 3 days each week for 3 consecutive weeks, followed by 1 week of rest of each 28-day cycle.

[0035] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the method further comprises administering the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, for 3 days each week for 2 consecutive weeks, followed by 2 weeks of rest of each 28-day cycle.

[0036] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is administered for 7 days of each 28-day cycle.

[0037] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent is administered on a 5-2-2 schedule: DNA hypomethylating agent for 5 consecutive days followed by 2 days of rest, followed by DNA hypomethylating agent for 2 consecutive days of each 28-day cycle.

[0038] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the discontinuation rate due to adverse events is less than 25%, less than 20%, less than 15%, less than 10%, less than 8%, less than 5%.

[0039] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the discontinuation rate due to adverse events is about 4%.

[0040] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the adverse event is selected from constipation, nausea, fatigue, decreased appetite, diarrhea, edema peripheral, hypoalbuminemia, dyspnea, hypokalemia, vomiting, dizziness, febrile neutropenia, anemia, neutropenia, and thrombocytopenia.

[0041] Also disclosed herein is a method of treating high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof; the method comprising administering to the patient:

(i) a DNA hypomethylating agent; and

(ii) about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, wherein pracinostat is orally administered to the patient 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

[0042] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 3 cycles.

[0043] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 4 cycles.

[0044] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 5 cycles.

[0045] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 6 cycles.

[0046] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), the DNA hypomethylating agent and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 3 cycles, followed by further

administering pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, for 3 days each week for 2 consecutive weeks, followed by 2 weeks of rest of each 28-day cycle for at least 1 cycle.

[0047] Also disclosed herein is a method of treating high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof; the method comprising administering to the patient:

(i) about 75 mg/m^2 of 5-azacytidine (azacitidine), wherein 5-azacytidine (azacitidine) is administered intravenously or subcutaneously for 7 days of each 28-day cycle; and

(ii) about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, wherein pracinostat is orally administered for 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

[0048] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 3 cycles.

[0049] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 4 cycles.

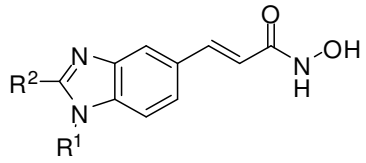
[0050] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 5 cycles.

[0051] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 6 cycles.

[0052] In some examples of a method of treating high or very high risk myelodysplastic syndromes (MDS), 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are administered for at least 3 cycles, followed by further administering pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, for 3 days each week for 2 consecutive weeks, followed by 2 weeks of rest of each 28-day cycle for at least 1 cycle.

CLAIMS

1. Use of a DNA hypomethylating agent in the manufacture of a first medicament and use of about 45 mg of a compound of formula (I):



Formula (I)

wherein

R^1 is $-(CR^{20}R^{21})_m—(CR^{22}R^{23})_n—(CR^{24}R^{25})_o—NR^{26}R^{27}$;

R^2 is alkyl, fluoroalkyl, cyano, C_2-C_6alkenyl, C_2-C_6alkynyl, or heteroalkyl optionally substituted with =O;

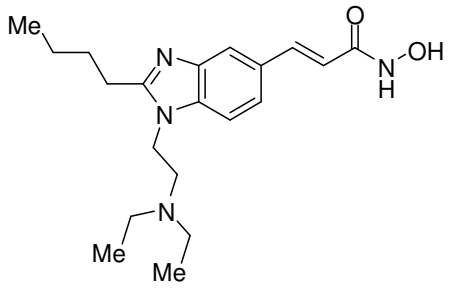
each R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, and R^{25} is independently H or methyl;

each R^{26} and R^{27} is independently H, hydroxyalkyl, or alkyl; and

m, n, and o are independently integers of 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof.

2. The use of claim 1, wherein the compound of formula (I) is pracinostat:



or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof.

3. The use of claim 1 or 2, wherein the DNA hypomethylating agent is 5-azacytidine (azacitidine), 5-azadeoxycytidine (decitabine), SGI-110, zebularine, or procaine.

4. The use of any one of claims 1-3, wherein the DNA hypomethylating agent is 5-azacytidine (azacitidine).

5. The use of any one of claims 1-4, wherein the patient in need thereof has not been previously treated with a DNA hypomethylating agent.

6. The use of any one of claims 1-5, wherein the patient in need thereof has been previously treated with transfusions, hematopoietic growth factors, or immunosuppressive therapy.

7. The use of any one of claims 1-6, wherein the MDS is refractory, non-responsive, or resistant to chemotherapy and/or haploidentical stem cell transplantation.

8. The use of any one of claims 1-7, wherein the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, is to be administered orally and the hypomethylating agent is to be administered intravenously or subcutaneously.
9. The use of any one of claims 1-8, wherein the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are to be administered in cycles of 28 days.
10. The use of any one of claims 1-9, wherein the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are to be administered for at least 3 cycles.
11. The use of any one of claims 1-10, wherein the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, and the DNA hypomethylating agent are to be administered until complete remission (CR) is observed.
12. The use of any one of claims 1-11, wherein the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, is to be administered for 3 days each week for 3 consecutive weeks, followed by 1 week of rest of each 28-day cycle.
13. The use of any one of claims 1-12, wherein the DNA hypomethylating agent is to be administered for 7 days of each 28-day cycle.
14. The use of any one of claims 1-13, wherein the DNA hypomethylating agent is to be administered on a 5-2-2 schedule: DNA hypomethylating agent for 5 consecutive days followed by 2 days of rest, followed by DNA hypomethylating agent for 2 consecutive days of each 28-day cycle.
15. The use of any one of claims 1-14, wherein the discontinuation rate due to adverse events is less than 25%, less than 20%, less than 15%, less than 10%, less than 8%, less than 5%.
16. The use of any one of claims 1-15, wherein the discontinuation rate due to adverse events is about 4%.
17. Use of a DNA hypomethylating agent in the manufacture of a first medicament and about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof, wherein pracinostat is to be orally administered to the patient 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.
18. Use of about 75 mg/m^2 of 5-azacytidine (azacitidine) in the manufacture of a first medicament and use of about 45 mg of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat high or very high risk myelodysplastic syndromes (MDS) in a patient in need thereof,
wherein 5-azacytidine (azacitidine) is to be administered intravenously or subcutaneously for 7 days of each 28-day cycle; and

wherein pracinostat is to be orally administered for 3 days each week for 3 consecutive weeks, followed by 1 week of rest, in 28-day cycles.

19. The use of claim 18, wherein 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are to be administered for at least 3 cycles.

20. The use of claim 19, wherein 5-azacytidine (azacitidine) and pracinostat or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, are to be administered for at least 3 cycles, followed by further administration of pracinostat, or a pharmaceutically acceptable salt, isotopic variant, or prodrug thereof, for 3 days each week for 2 consecutive weeks, followed by 2 weeks of rest of each 28-day cycle for at least 1 cycle.