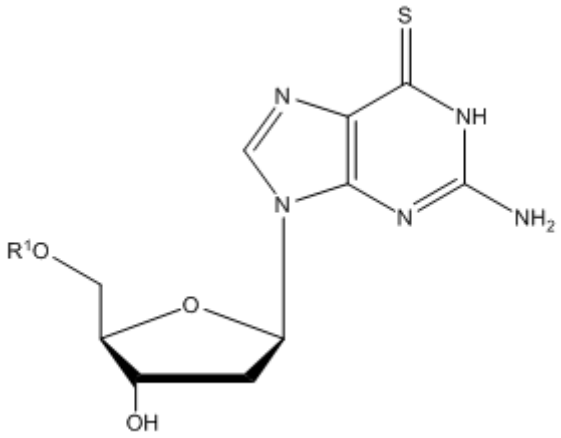
hTERT (telomerase catalytic protein component) and hTR or hTERC (telomerase functional or template RNA component). (Greider CW and Blackburn EH, "Telomeres, telomerase and cancer," Scientific American. 1996;274:92-7.) While most normal somatic human cells do not have telomerase activity, it is detected, almost universally, in primary human cancer cells (~85-90%). Thus, the progressive shortening in normal cells without telomerase activity provide an initial barrier for tumorigenesis.

[0006] Therefore, in cancer cells telomerase and telomeres represent attractive almost universal targets for therapeutic approaches. Because most normal somatic cells do not have telomerase activity, treatments that selectively target telomerase activity can be beneficial. In addition, treatments that can interfere with telomere sequencing during telomerase activity to interfere with the structure or function of the shelterin complex can also be beneficial.

SUMMARY

[0007] The present disclosure relates to the use of the compound 6-mercaptopurine ribonucleoside and analogues thereof for the treatment of tumors, cancer, and hyperproliferative diseases. Specifically, compounds of the present disclosure can be convereted into telomere substrates *in vivo* and can be recognized by telomerase for incorporation into telomeres of telomerase active cells, leading to induction of cell death of the telomerase active cells. While not wishing to be bound by any particular theory, incorporation of the described compounds into the telomere is believed to be an immediate teloemere DNA chain terminator and/or recognized as having telomeric DNA damage due to the altered telomere structure.

[0007a] In an aspect, there is provided the se of a pharmaceutical composition comprising a compound according to formula (III):

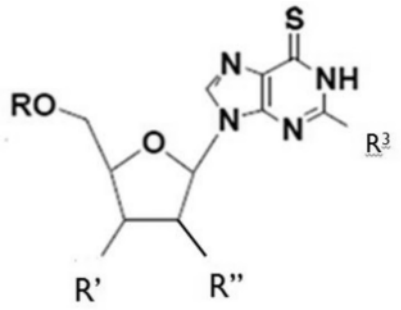


(Formula III)

wherein R^1 is H, a pharmaceutically acceptable salt, or polymorph thereof, in the manufacture of a medicament for treating a telomerase-expressing lung cancer cell or colon cancer cell characterized by an over-activation of telomerase in a subject in need thereof with lung cancer or colon cancer,

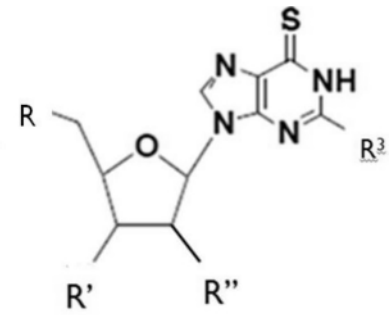
wherein the pharmaceutical composition is to be administered in an amount effective to reduce stability of telomere length and to induce cell death in the telomerase-expressing lung cancer cell or colon cancer cell.

[0008] In accordance with the present disclosure, a compound according to Formula I below can be administered to a subject:



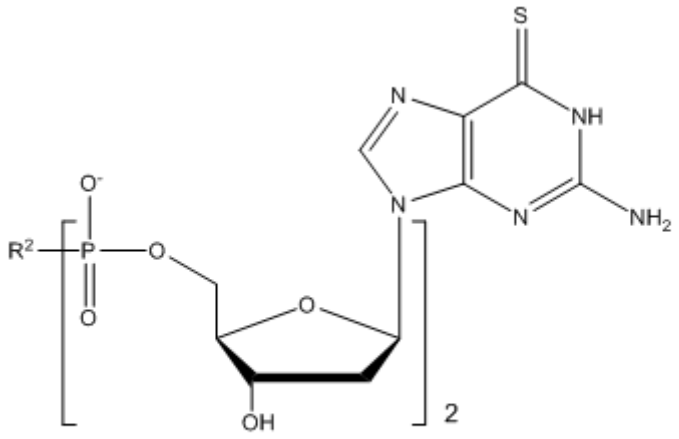
where R can be an H, hydroxyl group, an amino group, an alkyl amino group, a fluoride, an acyl group, a C_1-C_{20} alkyl or ether group, a phosphate, diphosphate, triphosphate, phosphonate, or a phosphodiester group; where R' can be an H, a hydroxyl group, flouride group, a C_1-C_{20} alkyl or ether group; where R" can be a hydroxyl group, a flouride, or an amino group in the ribo or arabino configuration; where R^3 can be an amino group or a alkyl-amino group; and pharmaceutically acceptable salts, solvates or polymorphs thereof. In various examples, R. is H, R' is a hydroxyl group, and R" is H and such compounds are referred to herein as 6-thio-2'-deoxyguanosine.

[0009] In accordance with the present disclosure, a compound according to Formula II below can be administered to a subject:



where R can be an H, an acyl group, a C_1-C_{20} alkyl or ether group, a phosphate, diphosphate, triphosphate, phosphonate, or a phosphodiester group; where R' can be an H, a hydroxyl group, flouride, a C_1-C_{20} alkyl or ether group; where R" can be a hydroxyl group, a flouride, or an amino group in the ribo or arabino configuration; where R^3 can be an amino group or a alkyl-amino group; and pharmaceutically acceptable salts, solvates or polymorphs thereof. In various examples, R is H, R' is a hydroxyl group, and R" is H.

[0010] In accordance with the present disclosure, a pharmaceutical composition can comprise a compound according to Formula III below can be administered to a subject:



where R^2 can be spermine or spermidine and such compounds are referred to herein as 6-thio-2'-deoxyguanosine.

[0013] Pharmaceutical compositions comprising an anti-cancer effective amount of one or more of the compounds of Formula I, II, III, IV, or V, optionally in combination with an effective amount of at least one additional anti-cancer agent or at least one carrier, additive or excipient are additional examples of the present disclosure.

[0014] Further examples of the present disclosure relate to methods for treating cancer and other hyperproliferative diseases, including tumors, especially malignant tumors and cancer, and any cell which possesses an over-activation of telomerase.

[0015] Other examples of the present disclosure comprise a method of treatment comprising administering an effective amount of 6-mercaptopurine ribonucleoside analogue according to the present disclosure and administering a second pharmaceutical composition comprising another anti-cancer agent. Administration can occur simultaneously, in sequential stages, or be administered stages wherein the stages at least partially overlap in time or are spaced apart by an certain interval of time. The multiple anti-cancer agent treatment can provide an additive effect or further a synergistic enhancement of the anticancer activity of one or both of the anti-cancer agents.

[0016] Examples discussed in the context of methods or compositions of the disclosure can be employed with respect to any other method or composition described herein. Thus, an example pertaining to one method or composition may be applied to

other methods and compositions of the disclosure as well. As used herein the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one.

[0017] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." As used herein "another" may mean at least a second or more.

[0018] Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0019] Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred examples of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.]

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

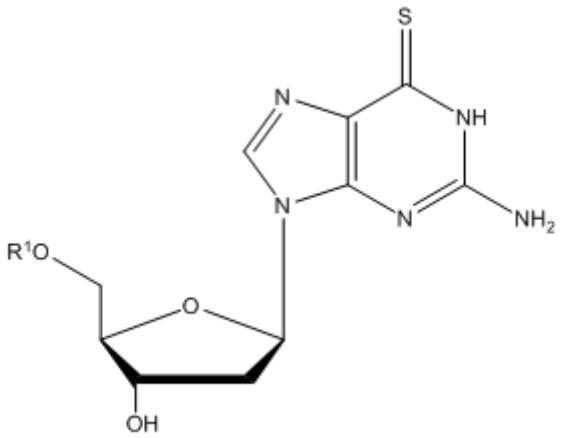
[0021] FIG. 1A The chemical structures of 6-thioguanine (6-thio-G) and 6-thio-deoxyguanosine (6-thio-dG).

[0022] FIG. 1B. A graph demonstrating the cell counts of HCT116 and BJ cells treated with 6-thio-dG (3μM) and 6-thio-G (3μM) for 1 week (every 3 days). (Control; untreated)

[0023] FIG. 2. Time table of HCT116 cells treatment protocols with no drug (--), 6-thio-dG (6dG), GRN163L (Im) or combination of 6-thio-dG and GRN163L (combo). Each week $1x10^6$ cells/sample were collected for TRF analysis. HCT116 cells were treated 10μM 6-thio-dG for 12-16 weeks. After treating with 10μM 6-thio-dG for 12 weeks, the cells were treated

CLAIMS

1. Use of a pharmaceutical composition comprising a compound according to formula (III):



(Formula III)

wherein R^1 is H, a pharmaceutically acceptable salt, or polymorph thereof, in the manufacture of a medicament for treating a telomerase-expressing lung cancer cell or colon cancer cell characterized by an over-activation of telomerase in a subject in need thereof with lung cancer or colon cancer,

wherein the pharmaceutical composition is to be administered in an amount effective to reduce stability of telomere length and to induce cell death in the telomerase-expressing lung cancer cell or colon cancer cell.

2. The use of claim 1, wherein the pharmaceutical composition is to be administered at an amount between 0.5-3 mg per 1 kg of the subject per day.

3. The use of claim 1, wherein the pharmaceutical composition is to be administered at least twice per week for at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, or at least 12 weeks.

4. The use of claim 1, wherein the pharmaceutical composition is to be administered orally or by injection.

5. The use of claim 1, wherein the pharmaceutical composition is to be administered by intratumoral injection.

6. The use of claim 1, wherein the subject is a human being.

7. The use of claim 1, wherein the telomerase-expressing lung cancer cell or colon cancer cell characterized by overactivation of telomerase is a telomerase-expressing tumor cell.

8. The use of claim 7, wherein the amount effective to reduce stability of telomere length and induce cell death in the telomerase-expressing lung cancer cell or colon cancer cell effects a reduction in tumor size of a lung tumor or colon tumor comprising the telomerase-expression lung cancer cell or colon cancer cell or a reduction in tumor growth rate of a lung tumor or colon tumor comprising the telomerase-expressing lung cancer cell or colon cancer cell.