COMPANION DIAGNOSTIC TOOL FOR MUTANT P53 REACTIVATING COMPOUNDS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/043,307, filed June 24, 2020; and U.S. Provisional Application No. 63/162,812, filed March 18, 2021, which are incorporated herein by reference.

BACKGROUND

[0002] Cancer, an uncontrolled proliferation of cells, is a multifactorial disease characterized by tumor formation, growth, and in some instances, metastasis. Cells carrying an activated oncogene, damaged genome, or other cancer-promoting alterations can be prevented from replicating through an elaborate tumor suppression network. A central component of this tumor suppression network is p53, one of the most potent tumor suppressors in the cell. Both the wild-type and mutant conformations of p53 are implicated in the progression of cancer.

INCORPORATION BY REFERENCE

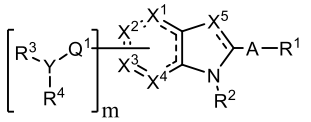
[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a use of a compound in the manufacture of a medicament for the treatment of cancer in a subject in need thereof,

wherein the subject has been previously determined to have a mutation in a TP53 gene that encodes a p53 mutant in the subject based on an assay performed on a biological sample of the subject,

wherein the compound is of the formula:



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wherein:

- each ------- is independently a single bond or a double bond;
- X^1 is CR^5, CR^5R^6, N, NR^5, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, O, S, C=O, C=S, or a carbon atom connected to

Q^1;

- X^5 is CR^{13}, N, or NR^{13};

wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- A is a linking group;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halogen, each of which is independently substituted or unsubstituted, or -$C(O)R^{16}$, -$C(O)OR^{16}$, -$C(O)NR^{16}R^{17}$, -OR^{16}, -SR^{16}, -$NR^{16}R^{17}$, -$NR^{16}C(O)R^{16}$, -$OC(O)R^{16}$, -$SiR^{16}R^{17}R^{18}$, or hydrogen;
- each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{19}$, -$C(O)OR^{19}$, -$C(O)NR^{19}R^{20}$, -SOR^{19}, -SO_2R^{19}, or hydrogen, or R^3 and R^4 together with the nitrogen atom to which R^3 and R^4 are bound form a ring, wherein the ring is substituted or unsubstituted, or R^3 is absent;
- each R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{21}$, -$C(O)OR^{21}$, -$C(O)NR^{21}R^{22}$, -OR^{21}, -SR^{21}, -$NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OC(O)R^{21}$, hydrogen, or halogen;
- each R^{19} and R^{20} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{23}$, -$C(O)OR^{23}$, -$C(O)NR^{23}R^{24}$, -OR^{23}, -SR^{23}, -$NR^{23}R^{24}$, -$NR^{23}C(O)R^{24}$, -$OC(O)R^{23}$, hydrogen, or halogen;
- each R^{21} and R^{22} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen; and
- each R^{23} and R^{24} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen,

or a pharmaceutically-acceptable salt thereof.

[0004] Provided herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a small molecule compound, wherein the subject has been previously determined to have a mutation in a TP53 gene that encodes a p53 mutant protein in the subject based on an assay performed on a

biological sample of the subject, wherein the small molecule compound does not contain arsenic, antimony, or bismuth.

[0005] Also provided herein is a method of treating a condition in a subject in need thereof, the method comprising: a) based on a result of an assay performed on a biological sample of the subject, determining that the subject harbors a mutation in a TP53 gene that encodes a p53 mutant protein; b) based on the result of the assay, administering to the subject a therapeutically-effective amount of a small molecule compound, wherein the small molecule compound does not contain arsenic, antimony, or bismuth.

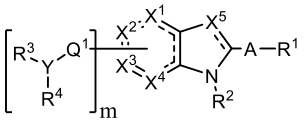
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound in the manufacture of a medicament for the treatment of cancer in a subject in need thereof,

wherein the subject has been previously determined to have a mutation in a TP53 gene that encodes a p53 mutant in the subject based on an assay performed on a biological sample of the subject,

wherein the compound is of the formula:



,

wherein:

- each ------- is independently a single bond or a double bond;
- X^1 is CR^5, CR^5R^6, N, NR^5, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^5 is CR^{13}, N, or NR^{13};

wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- A is a linking group;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halogen, each of which is independently substituted or unsubstituted, or -$C(O)R^{16}$, -$C(O)OR^{16}$, -$C(O)NR^{16}R^{17}$, -OR^{16}, -SR^{16}, -$NR^{16}R^{17}$, -$NR^{16}C(O)R^{16}$, -$OC(O)R^{16}$, -$SiR^{16}R^{17}R^{18}$, or hydrogen;
- each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{19}$, -$C(O)OR^{19}$, -$C(O)NR^{19}R^{20}$, -SOR^{19}, -SO_2R^{19}, or hydrogen, or R^3 and R^4 together with the nitrogen atom to which R^3 and R^4 are bound form a ring, wherein the ring is substituted or unsubstituted, or R^3 is absent;
- each R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is independently

alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or $-C(O)R^{21}$, $-C(O)OR^{21}$, $-C(O)NR^{21}R^{22}$, $-OR^{21}$, $-SR^{21}$, $-NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-OC(O)R^{21}$, hydrogen, or halogen;

- each R^{19} and R^{20} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, hydrogen, or halogen;
- each R^{21} and R^{22} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen; and
- each R^{23} and R^{24} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen,

or a pharmaceutically-acceptable salt thereof.

2. The use according to claim 1, wherein the biological sample of the subject is to be obtained, and the assay is performed on the biological sample of the subject to detect the mutation in the TP53 gene that encodes the p53 mutant in the subject.

3. The use according to claim 1 or claim 2, wherein about 50 mg to about 3000 mg of the compound is to be administered to the subject in need thereof.

4. The use according to any one of claims 1-3, wherein the p53 mutant is a p53 Y220C.

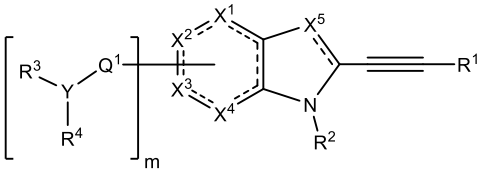
5. The use according to any one of claims 1-4, wherein the assay is DNA sequencing.

6. The use according to any one of claims 1-5, wherein the biological sample is a liquid biopsy.

7. The use according to any one of claims 1-5, wherein the biological sample is a solid tumor sample.

8. The use according to any one of claims 1-7, wherein the condition is ovarian cancer, breast cancer, or lung cancer.

9. The use according to any one of claims 1-8, wherein the compound is of the formula:



wherein:

Q^1 is a bond;

Y is N;

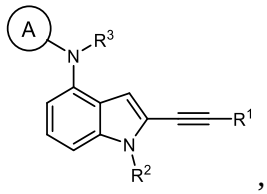
m is 1; and

each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; or hydrogen,

or a pharmaceutically acceptable salt thereof.

10. The use according to any one of claims 1-9, wherein R^3 is H; and R^4 is aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted.

11. The use according to any one of claims 1-9, wherein the compound is of the formula:



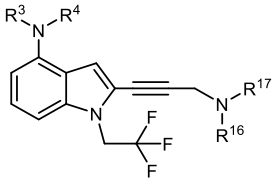
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wherein ring A is aryl, heteroaryl, or heterocyclyl, each of which is substituted or unsubstituted.

12. The use according to any one of claims 1-11, wherein R^1 is alkyl or alkenyl, each of which is unsubstituted or substituted; or $-C(O)R^{16}$, $-C(O)OR^{16}$, or $-C(O)NR^{16}R^{17}$.

13. The use according to any one of claims 1-11, wherein R^1 is alkyl substituted with $NR^{16}R^{17}$.

14. The use according to any one of claims 1-10, wherein the compound is of the formula:



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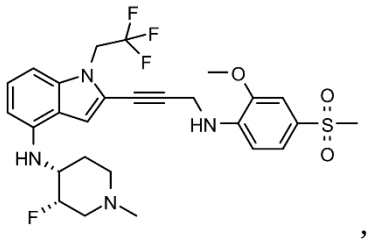
15. The use according to any one of claims 1-14, wherein each R^{16} and R^{17} is independently alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, each of which is independently substituted or

unsubstituted; or hydrogen.

16. The use according to any one of claims 1-14, wherein R^{16} is hydrogen or alkyl.

17. The use according to any one of claims 1-15, wherein R^{17} is phenyl substituted with a sulfoxide group, carboxyl group, amide group, amino group, alkyl, alkoxy, hydroxy, or heterocyclyl, each of which is independently substituted or unsubstituted, or halo or cyano.

18. The use according to claim 1, wherein the compound is



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or a pharmaceutically-acceptable salt thereof.

19. The use according to claim 1, wherein the compound is 4-((3-(4-(((3S,4R)-3-fluoro-1-methylpiperidin-4-yl)amino)-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)prop-2-yn-1-yl)amino)-3-methoxy-N-methylbenzamide.

20. The use according to claim 1, wherein the compound is N-(2,3-dihydroxypropyl)-4-{[3-(4-{[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]amino}-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)prop-2-yn-1-yl]amino}-3-methoxybenzamide, or a pharmaceutically-acceptable salt thereof.