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

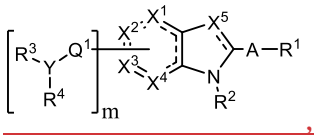
[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

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:



,

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.

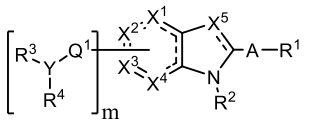
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound in the manufacture of a medicament for the treatment of cancer ~~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 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~~wherein the small molecule compound does not contain arsenic, antimony, or bismuth~~.

2. The ~~method of~~ use according to claim 1, ~~further comprising obtaining~~ wherein the biological sample of the subject is to be obtained, and~~.~~

~~3. The method of claim 1, further comprising performing~~ 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.

~~4. The method of claim 1, wherein the administering of the therapeutically effective amount of the small molecule compound to the subject increases anti-cancer activity of the p53 mutant in the subject.~~

~~5. The method of claim 1, wherein the small molecule compound induces a conformational change in the p53 mutant.~~

~~6~~3. The use according to ~~method of~~ claim 1 or claim 2, wherein ~~the therapeutically effective amount is from~~ about 50 mg to about 3000 mg of the compound is to be administered to the subject in need thereof.

~~7. The method of claim 1, wherein the small molecule compound increases stability of a biologically-active conformation of the p53 mutant relative to the stability of the biologically-active conformation of the p53 mutant in absence of the small molecule compound.~~

~~8. The method of claim 1, wherein the subject has a cancer, wherein the cancer expresses the p53 mutant.~~

~~9. The method of claim 1, wherein the mutation is at amino acid 220.~~

~~10~~4. The use according to any one ~~method~~ of claims 1-3, wherein the p53 mutant is a p53 Y220C.

~~11~~5. The use according to any one ~~method~~ of claims 1-4, wherein the assay is DNA sequencing.

~~12. The method of claim 1, wherein the assay is next-generation DNA sequencing.~~

~~13~~6. The use according to any one ~~method~~ of claims 1-5, wherein the biological sample is a liquid biopsy.

~~14~~7. The use according to any one ~~method~~ of claims 1-5, wherein the biological sample is a solid tumor sample.

~~15. The method of claim 1, wherein the condition is a cancer.~~

~~16~~8. The use according to any one ~~method~~ of claims 1-7, wherein the condition is ovarian cancer, ~~.~~

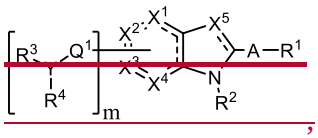
~~17. The method of claim 1, wherein the condition is~~ breast cancer, or~~.~~

~~18. The method of claim 1, wherein the condition is~~ lung cancer.

~~19. The method of claim 1, wherein the administration is oral.~~

~~20. The method of claim 1, wherein the subject is human.~~

21. The method of claim 1, 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 $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halo, each of which is independently substituted or unsubstituted, or hydrogen;
- each R^3 and R^4 is independently $-C(O)R^{19}$, $-C(O)OR^{19}$, $-C(O)NR^{19}R^{20}$, $-SOR^{19}$, $-SO_2R^{19}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, 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 $-C(O)R^{21}$, $-C(O)OR^{21}$, $-C(O)NR^{21}R^{22}$, $-OR^{21}$, $-SR^{21}$, $-NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-OC(O)R^{21}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen or halogen;
- each R^{19} and R^{20} is independently $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or

~~unsubstituted, or hydrogen or halogen;~~

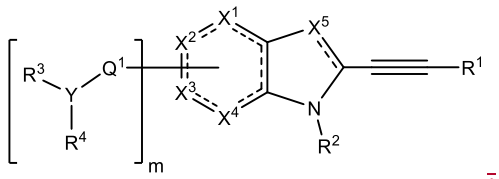
~~each R^{21} and R^{22} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen; and~~

~~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.~~

~~22. The method of claim 21, wherein A is alkylene, alkenylene, or alkynylene, each of which is substituted or unsubstituted.~~

~~23~~9. The use according to any one ~~method~~ of claims 1-8 ~~21~~, wherein the compound is of the formula:



~~24. The method of claim 21, wherein Q^1 is C_1 alkylene.~~

~~25. The method of claim 21,~~ wherein:

Q^1 is a bond;~~.~~

~~26. The method of claim 21, wherein m is 1.~~

~~27. The method of claim 21, wherein~~ Y is N;~~.~~

m is 1; and

~~28. The method of claim 21, wherein~~ each R^3 and R^4 is independently alkyl, ~~alkylene,~~ alkenyl, ~~alkenylene,~~ alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; or hydrogen,

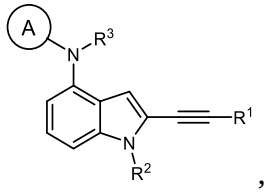
or a pharmaceutically acceptable salt thereof.

~~29~~10. The use according to any one ~~method~~ of claims 1-9 ~~28~~, wherein R^3 is H; and R^4 is aryl,

heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted.

~~30. The method of claim 21, wherein R^{13} is hydrogen.~~

~~31~~11. The use according to any one ~~method~~ of claims 1-9 ~~21~~, wherein the compound is of the formula:



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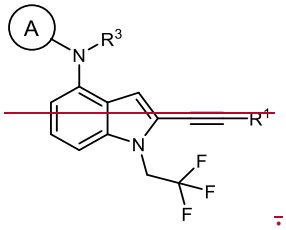
wherein ring A is ~~a cyclic group that~~ aryl, heteroaryl, or heterocyclyl, each of which is substituted or unsubstituted.

~~32. The method of claim 21, wherein R^2 is substituted or unsubstituted alkyl.~~

~~33. The method of claim 32, wherein R^2 is substituted ethyl.~~

~~34. The method of claim 33, wherein R^2 is trifluoroethyl.~~

~~35. The method of claim 34, wherein the compound is of the formula:~~



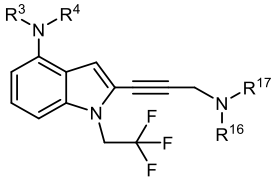
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~~36. The method of claim 35, wherein ring A is aryl, heteroaryl, or heterocyclyl, each of which is substituted or unsubstituted.~~

~~37~~12. The use according to any one ~~method~~ of claims 1-11 ~~21~~, wherein R^1 is alkyl or~~,~~ alkenyl, ~~-C(O)R^{16}, -C(O)OR^{16}, or -C(O)$NR^{16}R^{17}$,~~ each of which is unsubstituted or substituted; or -C(O)R^{16}, -C(O)OR^{16}, or -C(O)$NR^{16}R^{17}$.

~~38~~13. The use according to any one ~~method~~ of claims 1-11 ~~37~~, wherein R^1 is alkyl substituted with $NR^{16}R^{17}$.

~~39~~14. The use according to any one ~~method~~ of claims 1-10~~-38~~, wherein the compound is of the formula:



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.

~~40~~16. The use according to any one ~~method~~ of claims 1-14~~-21~~, wherein R^{16} is hydrogen or alkyl.

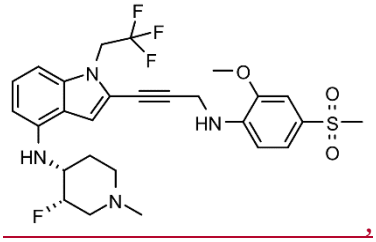
~~41. The method of claim 21, wherein R^{17} is aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted.~~

~~42. The method of claim 41, wherein R^{17} is substituted aryl.~~

~~43. The method of claim 41, wherein R^{17} is substituted phenyl.~~

~~44~~17. The use according to any one ~~method~~ of claims 1-15~~-43~~, wherein R^{17} is phenyl substituted with a sulfoxide group, carboxyl group, amide group, amino group, alkyl, alkoxy, hydroxy, ~~halo, cyano,~~ 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



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.