METHODS AND COMPOUNDS FOR RESTORING MUTANT p53 FUNCTION

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 62/904,369, filed September 23, 2019; and U.S. Provisional Application No. 63/038,388, filed June 12, 2020, which are incorporated herein by reference.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing, which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 18, 2020, is named 44727-705.601 Sequence Listing.txt and is 2,578 bytes in size.

BACKGROUND

[003] 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

[004] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY ~~OF THE INVENTION~~

[004a] In an aspect of the present disclosure, there is provided a compound comprising:
a heterocyclyl group comprising a halogen substituent,
wherein the compound binds a mutant p53 protein and increases wild-type p53 activity of the mutant p53 protein.

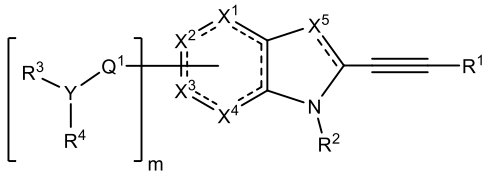
[004b] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for inducing apoptosis in a cell, wherein the compound binds a p53 mutant, and wherein the cell is to be contacted with a therapeutically-effective amount of the compound.

[004c] In a further aspect of the present disclosure, there is provided a use of compound disclosed herein, in the manufacture of a medicament for treating cancer, wherein a therapeutically-effective amount of a compound is to be administered to a subject in need thereof, and wherein the compound has an SC_{150} value for p53 Y220C of less than 1 μM as measured by a homogeneous time-resolved fluorescence (HTRF) assay.

[004d] In another aspect of the present disclosure, there is provided a compound disclosed herein, for use in therapy.

[005] In some ~~embodiment~~examples, described herein is a compound, the compound comprising: a heterocyclyl group comprising a halo substituent, wherein the compound binds a mutant p53 protein and increases wild-type p53 activity of the mutant p53 protein.

[006] In some ~~embodiment~~examples, described herein is a compound 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};

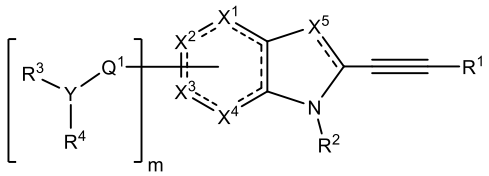
wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- 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)N$R^{16}R^{17}$, -OR^{16}, -SR^{16}, -N$R^{16}R^{17}$, -NR^{16}C(O)R^{16}, -OC(O)R^{16}, C=O, C=S, -CN, -Si$R^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, 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)N$R^{19}R^{20}$, -SOR^{19}, -SO_2R^{19}, alkyl, alkylene, alkenyl, alkenylene, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen, or R^3 and R^4 together with the Y 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)N$R^{21}R^{22}$, -OR^{21}, -SR^{21}, -N$R^{21}R^{22}$, -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 C(O)R^{23}, -C(O)OR^{23}, -C(O)N$R^{23}R^{24}$, -OR^{23}, -SR^{23}, -N$R^{23}R^{24}$, -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, wherein the compound is not a compound of Table 1.

[007] In some ~~embodiment~~examples, described herein is a compound 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;

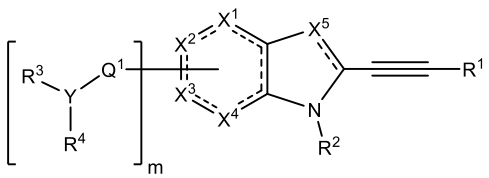
- Q^1 is C=O, C=S, C=$CR^{14}R^{15}$, C=NR^{14}, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;

- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, C=O, C=S, -CN, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, 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, alkylene, alkenyl, alkenylene, 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, wherein at least one of R^3 and R^4 is alkyl, alkylene, alkenyl, alkenylene, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is substituted at least with halo-;
- 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 $C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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.

[008] In some ~~embodiment~~examples, described herein is a compound, the compound comprising: a heterocyclyl group comprising a halogenated substituent, wherein the compound binds a mutant p53 protein and increases wild-type p53 activity of the mutant p53.

[009] In some ~~embodiment~~examples, described herein is a method of treating a cancer, the method comprising administering to a subject in need thereof a compound of Formula (I):



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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};

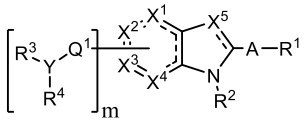
wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- 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 $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, C=O, C=S, -CN, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, 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, alkylene, alkenyl, alkenylene, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen, or R^3 and R^4 together with the Y 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 $C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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;

wherein the compound has an SC_{150} value for p53 Y220C of less than 1 μM as measured by a homogeneous time-resolved fluorescence (HTRF) assay.

[010] In some ~~embodiment~~examples, described herein is a compound 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;

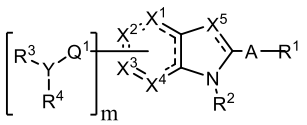
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^5 is CR^{13}, N, or NR^{13};

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; wherein at least one of R^3 and R^4 is alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, aryl, heteroaryl, or heterocyclyl, each of which is substituted with at least halo;
- 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

[011] In some ~~embodiment~~examples, described herein is a compound 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, wherein the compound is not a compound of Table 1.

[012] In some ~~embodiment~~examples, described herein is a method of inducing apoptosis in a cell, the method comprising contacting the cell with a therapeutically-effective amount of a compound of the disclosure that binds a p53 mutant, wherein the compound increases the ability of the p53 mutant to bind DNA, wherein the cell expresses the p53 mutant.

[013] In some ~~embodiment~~examples, described herein is a method of treating a cancer, the method comprising administering to a subject in need thereof a therapeutically-effective amount of a compound of the

CLAIMS

WHAT IS CLAIMED IS:

1. A compound comprising:

   a heterocyclyl group comprising a halogen substituent,

   wherein the compound binds a mutant p53 protein and increases wild-type p53 activity of the mutant p53 protein.

2. The compound of claim 1, wherein the compound further comprises an indole group attached to the heterocyclyl group.

3. The compound of claim 2, wherein the indole group has a 1,1,1-trifluoroethyl substituent at a 1-position of the indole group.

4. The compound of claim 2, wherein the indole group has a propargyl substituent at a 2-position of the indole group.

5. The compound of claim 4, wherein the propargyl substituent is attached to the indole group via an sp carbon atom of the propargyl substituent.

6. The compound of claim 4, wherein the propargyl substituent is attached to a nitrogen atom of an aniline group via a methylene group of the propargyl substituent.

7. The compound of claim 2, wherein the indole group comprises an amino substituent at a 4-position of the indole group.

8. The compound of claim 7, wherein the amino substituent is attached to the heterocyclyl group.

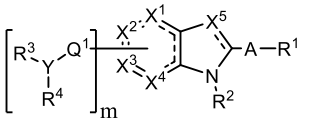
9. The compound of claim 1, wherein the heterocyclyl group is a piperidine group.

10. The compound of claim 9, wherein the heterocyclyl group is a methylpiperidine group that is unsubstituted or substituted.

11. The compound of claim 10, wherein the heterocyclyl group is 3-fluoro-1-methylpiperidin-4-yl.

12. The compound of claim 6, wherein, the aniline group is substituted with a hydroxyl group, sulfhydryl group, halogens, amino group, nitro group, nitroso group, cyano group, azido group, sulfoxide group, sulfone group, sulfonamide group, carboxyl group, carboxaldehyde group, imine group, alkyl group, halo-alkyl group, cyclic alkyl group, alkenyl group, halo-alkenyl group, alkynyl group, halo-alkynyl group, alkoxy group, aryl group, aryloxy group, aralkyl group, arylalkoxy group, heterocyclyl group, acyl group, acyloxy group, carbamate group, amide group, urethane group, and ester group.

13. The compound of claim 1, wherein the compound has 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 $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, C=O, C=S, -CN, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen;
- R^3 is H;
- R^4 is heterocyclyl substituted at least with halo-;
- 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 $C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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, wherein the compound is not a compound of Table 1.

14. Use of a compound of any one of claims 1-13, in the manufacture of a medicament for ~~A method of~~ inducing apoptosis in a cell, ~~the method comprising contacting~~ wherein the compound binds a p53 mutant, and wherein the cell is to be contacted with a therapeutically-effective amount of ~~a~~ the compound ~~that binds a p53 mutant, wherein the compound is a compound of any one of claims 1-13~~.

15. The ~~method~~ use of claim 14, wherein the compound increases the ability of the p53 mutant to bind to

DNA.

16. The ~~method~~ use of claim 14, wherein the p53 mutant is p53 Y220C.

17. The ~~method~~ use of claim 14, wherein the compound induces a conformational change in the p53 mutant.

18. The ~~method~~ use of claim 14, wherein the compound increases a stability of a biologically-active conformation of the p53 mutant relative to a stability of the biologically-active conformation of the p53 mutant in an absence of the compound.

19. Use of compound of any one of claims 1-13, in the manufacture of a medicament for ~~A method of~~ treating cancer, ~~the method comprising administering to a subject in need thereof~~ wherein a therapeutically-effective amount of a compound is to be administered to a subject in need thereof~~of any one of claims 1-13~~, and wherein the compound has an SC_{150} value for p53 Y220C of less than 1 μM as measured by a homogeneous time-resolved fluorescence (HTRF) assay.

20. The ~~method~~ use of claim 19, wherein the compound is to be intravenously administered~~administration is intravenous~~.

21. The ~~method~~ use of claim 19, wherein the compound is to be orally administered~~administration is oral~~.

22. The ~~method~~ use of claim 19, wherein the therapeutically effective amount is from about 20 mg/kg to about 400 mg/kg.

23. The ~~method~~ use of claim 19, wherein the cancer is breast cancer.

24. The ~~method~~ use of claim 19, wherein the cancer is lung cancer.

25. The ~~method~~ use of claim 19, wherein the compound increases a stability of a biologically-active conformation of the p53 mutant relative to a stability of the biologically-active conformation of the p53 mutant in an absence of the compound.

26. The ~~method~~ use of claim 19, wherein the compound has an SC_{150} value of less than 0.05 μM.

27. A compound of any one of claims 1-13, for use in therapy.