METHODS AND COMPOUNDS FOR RESTORING MUTANT p53 FUNCTION

CROSS REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/023,601, filed May 12, 2020, which is 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 May 10, 2021, is named 44727706201SL_1.txt and is 2,540 bytes in size.

BACKGROUND

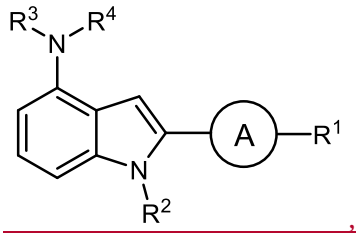
[003] Cancer, an uncontrolled proliferation of cells, is a multifactorial disease characterized by tumor formation, growth, and in some instances, metastasis. Cells carrying an activated oncogene, damaged genome, or other cancer-promoting alterations can be prevented from replicating through an elaborate 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 of the formula:



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wherein:

- A is a substituted or unsubstituted heteroaryl;
- R^1 is alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halo, 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;
- each R^2, 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;

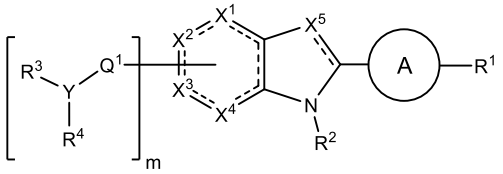
- each R^{19} and R^{20} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, hydrogen,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

[005] In some ~~embodiment~~examples, provided herein is a compound comprising: an indole group, wherein the indole group comprises: a) a haloalkyl group at a 1-position of the indole group; b) a first substituent at a 2-position of the indole group, wherein the first substituent is a cyclic group; and c) a second substituent, wherein the second substituent is substituted with at least halo-; or a pharmaceutically-acceptable salt thereof.

[006] In some ~~embodiment~~examples, provided herein is a compound comprising an indole group, wherein the indole group comprises: a) a substituted or unsubstituted non-cyclic group at a 3-position of the indole group; and b) a substituted or unsubstituted cyclic group at a 2-position of the indole group, wherein the compound increases a stability of a biologically active conformation of a p53 mutant relative to a stability of a biologically-active conformation of the p53 mutant in an absence of the compound, or a pharmaceutically-acceptable salt thereof.

[007] In some ~~embodiment~~examples, provided herein is a compound of the formula:



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wherein:

- each ------- is independently a single bond or a double bond;

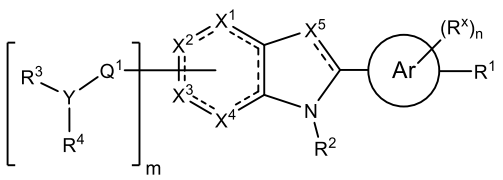
- X^1 is CR^5, CR^5R^6, N, NR^5, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, 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 substituted or unsubstituted ring;
- 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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, provided 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;

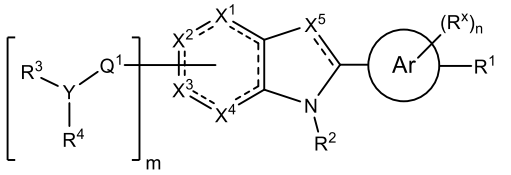
- Ar is unsubstituted or substituted aryl;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- n is 0, 1, 2, 3, or 4;
- Y is N, O, or absent;
- each R^x and R^1 is independently $C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; cyano, halo, or hydrogen; or R^1 and R^x together with Ar form a fused ring;
- 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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.

[009] In some ~~embodiment~~examples, provided 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 formula:

heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen, or a pharmaceutically-acceptable salt thereof.

[010] In some ~~embodiment~~examples, provided 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, 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;

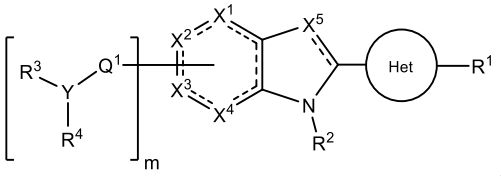
- Ar is unsubstituted or substituted aryl;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- n is 0, 1, 2, 3, or 4;
- Y is N, O, or absent;
- each R^x and R^1 is independently $C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, $-SiR^{16}R^{17}R^{18}$, alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; cyano, halo, or hydrogen; or R^1 and R^x together with Ar form a fused ring;
- 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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, disclosed 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;

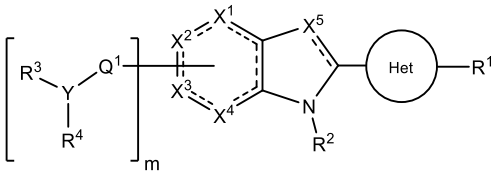
- Het is substituted or unsubstituted heteroaryl;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $OC(O)R^{16}$, $-SiR^{16}R^{17}R^{18}$, 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, -

$NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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.

[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 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;

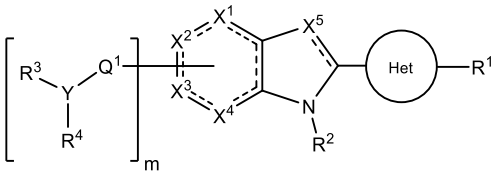
- Het is substituted or unsubstituted heteroaryl;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is $-C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-SR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $OC(O)R^{16}$, $-SiR^{16}R^{17}R^{18}$, 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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.

[013] In some ~~embodiment~~examples, disclosed 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, wherein the compound is of the formula:



,

wherein:

- each $\overline{\text{-------}}$ 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;

- Het is substituted or unsubstituted heteroaryl;
- 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 $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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.

[014] In some ~~embodiment~~examples, disclosed 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.

[015] In some ~~embodiment~~examples, disclosed 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 disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[016] **FIG. 1** shows a ^{1}H NMR spectrum of 4-((2-(4-(aminomethyl)phenyl)-1-(2,2,2-trifluoroethyl)-1H-indol-4-yl)amino)tetrahydro-2H-thiopyran 1,1-dioxide.

[017] **FIG. 2** shows a ^{1}H NMR spectrum of 4-((2-(4-chlorophenyl)-1-(2,2,2-trifluoroethyl)-1H-indol-4-yl)amino)tetrahydro-2H-thiopyran 1,1-dioxide.

[018] **FIG. 3** shows a ^{1}H NMR spectrum of 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)benzoic acid.

[019] **FIG. 4** shows a ^{1}H NMR spectrum of 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)-N-methylbenzamide.

[020] **FIG. 5** shows a ^{1}H NMR spectrum of 4-((2-(4-(hydroxymethyl)phenyl)-1-(2,2,2-trifluoroethyl)-1H-indol-4-yl)amino)tetrahydro-2H-thiopyran 1,1-dioxide.

[021] **FIG. 6** shows a ^{1}H NMR spectrum of 2-(4-(((4-(methylsulfonyl)phenyl)amino)methyl)phenyl)-N-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-indol-4-amine.

[022] **FIG. 7** shows a ^{1}H NMR spectrum of 6-methyl-N-(4-(5-(((1-methylpiperidin-4-yl)amino)methyl)-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)benzyl)pyridin-3-amine.

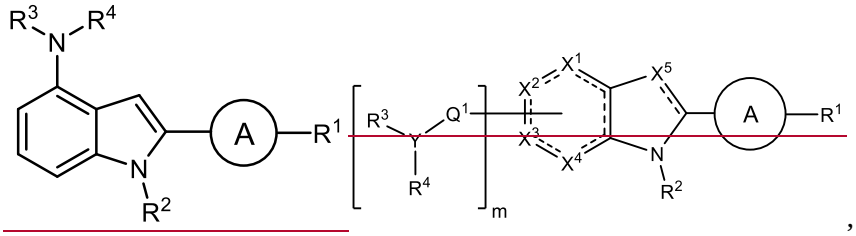
[023] **FIG. 8** shows a ^{1}H NMR spectrum of N-(1-methylpiperidin-4-yl)-2-(4-(1-((6-(methylsulfonyl)pyridin-3-yl)amino)ethyl)phenyl)-1-(2,2,2-trifluoroethyl)-1H-indol-4-amine.

[024] **FIG. 9** shows a ^{1}H NMR spectrum of 6-(4-((1-(2-hydroxy-3-methoxypropyl)piperidin-4-

CLAIMS

WHAT IS CLAIMED IS:

1. 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 substituted or unsubstituted heteroaryl~~ring~~;

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

- each R^{19} and R^{20} is independently ~~$-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$,~~ alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or $-C(O)R^{23}$, $-C(O)OR^{23}$, $-C(O)NR^{23}R^{24}$, $-OR^{23}$, $-SR^{23}$, $-NR^{23}R^{24}$, $-NR^{23}C(O)R^{24}$, $-OC(O)R^{23}$, 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 compound of claim 1, wherein A is substituted or unsubstituted aryl, heteroaryl, heterocyclyl, cycloalkylene.~~

~~3. The compound of claim 1, wherein A is substituted aryl.~~

~~4. The compound of claim 3, wherein A is substituted phenyl.~~

~~5. The compound of claim 4, wherein A is phenyl substituted with alkyl, cycloalkyl, alkoxy, an amine group, a carboxyl group, a carboxylic acid group, a carbamide group, or an amide group, each of which is substituted or unsubstituted; cyano, halo , or hydrogen.~~

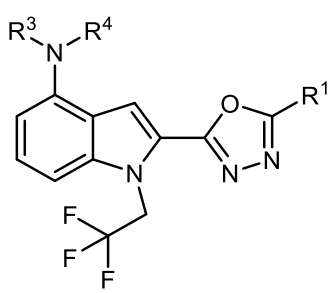
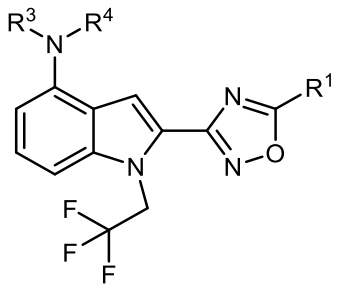
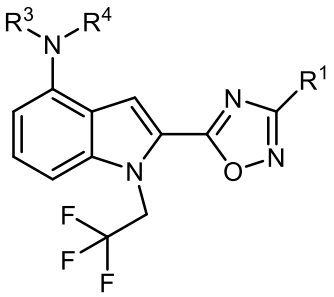
~~6. The compound of claim 1, wherein A is substituted heteroaryl.~~

~~7.~~2. The compound of claim 1, wherein A is an unsubstituted or substituted aromatic 5-membered, 6-membered, 7-membered, or 8-membered monocyclic ring system comprising 1, 2, or 3 heteroatoms as ring members, wherein each heteroatom is independently selected from O, N, or S.

~~8.~~3. The compound of claim 1 or claim 2~~7~~, wherein A is pyridinyl, pyrimidinyl, thiadiazolyl, thiazolyl, pyrazolyl, thiophenyl, or oxadiazolyl, each of which is independently substituted or unsubstituted.

~~9.~~4. The compound of any one of claims 1-3~~claim 8~~, wherein A is 1,3,5-thiadiazol-2-yl.

~~10.~~5. The compound of any one of claims 1-3~~claim 8~~, wherein ~~A is 1,3,4-oxadiazol-2-yl or 1,2,4-oxadiazol-2-yl~~the compound is of the formula:


,

, or

.

~~11.~~6. The compound of any one of claims 1-3~~claim 8~~, wherein A is pyridinyl.

~~12.~~7. The compound of claim 1~~8~~, wherein A is an unsubstituted or substituted aromatic 8-membered, 9-membered, 10-membered, 11-membered, or 12-membered bicyclic ring system comprising 1, 2, 3, 4, 5, or 6 heteroatoms, wherein each heteroatom is independently selected from O, N, or S.

~~13. The compound of claim 1, wherein m is 1.~~

~~14. The compound of claim 1, wherein Q^1 is alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond.~~

~~15. The compound of claim 14, wherein Q^1 is a bond.~~

~~16. The compound of claim 1, wherein Y is N.~~

~~17.~~8. The compound of any one of claims 1-4, 6, and 7~~claim 1~~, wherein R^2 is hydrogen.

~~18.~~9. The compound of any one of claims~~claim~~ 1-4, 6, and 7, wherein R^2 is substituted or unsubstituted alkyl.

~~19.~~10. The compound of any one of claims 1-4, 6, 7, and 9~~claim 18~~, wherein R^2 is trifluoroethyl.

~~20.~~11. The compound of any one of claims 1-4, 6, and 7~~claim 18~~, wherein R^2 is cycloalkyl.

~~21.~~12. The compound of any one of claims~~claim~~ 1-11, wherein R^1 is ~~$C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$,~~ alkyl, alkoxy, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; or $C(O)R^{16}$, $-C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-OR^{16}$, $-NR^{16}R^{17}$, $-NR^{16}C(O)R^{16}$, $-OC(O)R^{16}$, cyano~~cyano, halo~~, or halogen.

~~22.~~13. The compound of any one of claims 1-12~~claim 21~~, wherein R^1 is $-NR^{16}R^{17}$.

~~23.~~14. The compound of any one of claims 1-12~~claim 21~~, wherein R^1 is substituted alkyl.

~~24.~~15. The compound of any one of claims~~claim~~ 1-14, wherein each R^3 and R^4 is independently aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; or hydrogen.

~~25.~~16. The compound of any one of claims 1-15~~claim 24~~, wherein R^3 is hydrogen, and R^4 is heterocyclyl substituted at least with halo-.

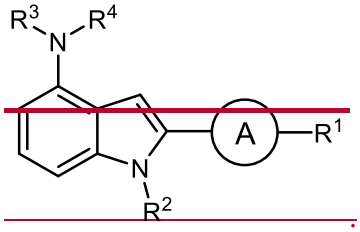
~~26.~~17. The compound of any one of claims 1-16~~claim 25~~, wherein R^4 is heterocyclyl substituted with fluoro-.

~~27.~~18. ~~-~~The compound of any one of claims 1-16~~claim 25~~, wherein R^4 is heterocyclyl substituted with chloro-.

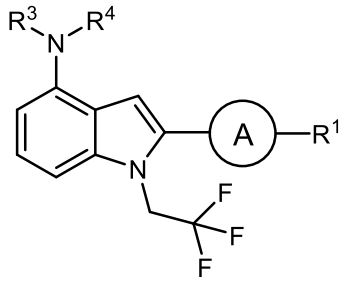
~~28. The compound of claim 1, wherein R^{13} is alkyl, alkenyl, hydrogen, or halogen.~~

~~29. The compound of claim 28, wherein R^{13} is hydrogen.~~

~~30. The compound of claim 1, wherein the compound has the formula:~~



~~31.~~19. ~~-~~The compound of any one of claims 1-4, 6, and 7~~-30~~, wherein the compound has the formula:

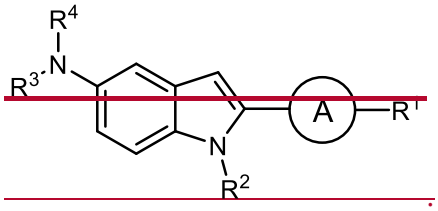


.

20. The compound of claim 12, wherein R^1 is alkyl substituted with $NR^{16}R^{17}$.

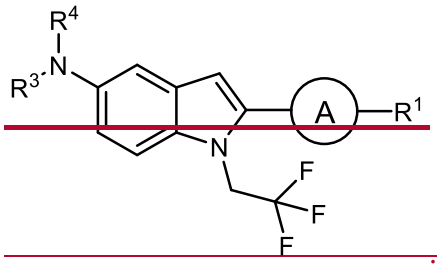
21. The compound of claim 12, wherein R^1 is methyl substituted with $NR^{16}R^{17}$, wherein R^{16} is hydrogen, and R^{17} is $C(O)R^{21}$, wherein R^{21} is heteroaryl that is substituted or unsubstituted.

~~32. The compound of claim 1, wherein the compound has the formula:~~



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~~33. The compound of claim 32, wherein the compound has the formula:~~



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