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

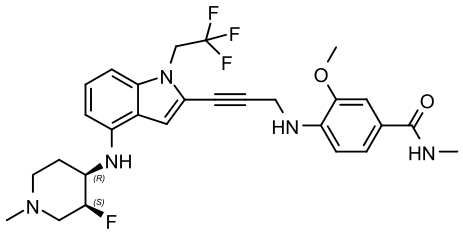
[003] Cancer, an uncontrolled proliferation of cells, is a multifactorial disease characterized by tumor formation, growth, and in some instances, metastasis. Cells carrying an activated oncogene, damaged genome, or other cancer-promoting alterations can be prevented from replicating through an elaborate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

[004a] there is provided a compound which is:



, or a pharmaceutically-acceptable salt thereof.

[004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[004c] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt thereof, for use in therapy.

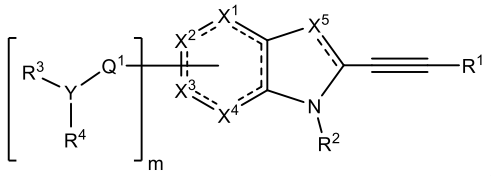
[004d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for inducing apoptosis in a cell, wherein the compound binds a p53 mutant, and wherein the cell is to be contacted with a therapeutically-effective amount of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

compound.

[004e] 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.

[005] In some 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 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};

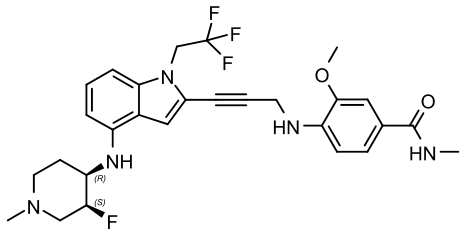
wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- 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;

CLAIMS

WHAT IS CLAIMED IS:

1. A compound which is:



, or a pharmaceutically-acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
3. A compound as defined in claim 1 or a pharmaceutically acceptable salt thereof, for use in therapy.
4. Use of a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof, 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.
5. The use according to claim 4, wherein the cell expresses the p53 mutant.
6. The use according to claim 4 or claim 5, wherein the p53 mutant is p53 Y220C.
7. The use according to any one of claims 4-6, wherein the therapeutically-effective amount is from about 50 mg to about 3000 mg.
8. Use of compound as defined in claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.
9. The use according to claim 8, wherein the therapeutically-effective amount is from about 20 mg to about 2000 mg.
10. The use according to claim 8 or claim 9, wherein the compound is to be orally or intravenously administered.
11. The use according to any one of claims 8-10, wherein the cancer is breast cancer.
12. The use according to any one of claims 8-10, wherein the cancer is lung cancer.
13. The use according to any one of claims 8-10, wherein the cancer is ovarian cancer.
14. The use according to any one of claims 8-10, wherein the cancer is prostate cancer.