

phosphorylation on Cdc2. Thus, entry into mitosis rests on a balance between the opposing activities of Wee1 and Chk1/Cdc25. Wee1 inhibition is thus expected to abrogate G₂-M arrest and propel cells into premature mitosis, a hypothesis confirmed by studies documenting that Wee1 inhibition by either small molecule inhibitors or small interference RNA leads to premature entry into mitosis and consequent cell death through mitotic catastrophe or apoptosis. (S. Muller, *J. Clinical. Oncology*, 2015).

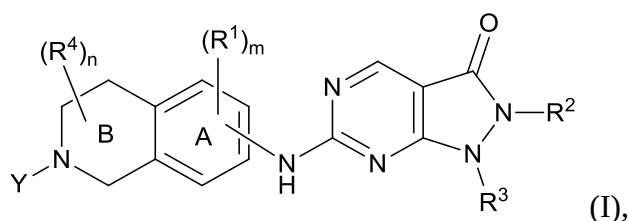
[0006] Recently, a few classes of Wee1 inhibitors have been disclosed. Among them is a selective inhibitor, AZD-1775 (1, 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-((4-(4methylpiperazin-1-yl)phenyl)amino)-1H-pyrazolo[3,4-d]pyrimidin-3(2H)-one). AZD-1775 exhibited antitumor activity in various preclinical studies as a monotherapy or in potentiating chemo- and radiotherapy, and is currently in phase I/II clinical trials.

[0007] Wee1 is highly expressed in several cancer types, including hepatocellular carcinoma, breast cancers, cervical cancers, lung cancers, squamous cell carcinoma, diffuse intrinsic pontine glioma (DIPG), glioblastoma, medulloblastoma, leukemia, melanoma, and ovarian cancers. (P. Reigan *et al.*, *Trends in Pharmacol. Sci.*, 2016).

[0008] There are few Wee1 inhibitors in clinical development. There is scope to improve Wee1 inhibitor selectivity and the properties of the inhibitors to permit targeting of specific cancer types.

BRIEF SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

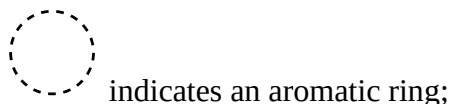
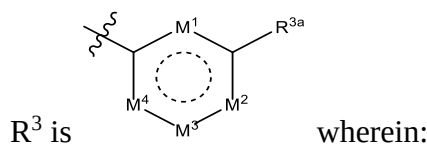
Y is hydrogen or R⁴;

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3, or 4;

R¹ is independently F, Cl, or methyl;

R² is C₁-C₆ alkyl, C₃-C₆ cycloalkyl or -(C₁-C₃ alkylene)CF₃;



M¹ is CH, CR^{3b} or N;

M² is CH, CR^{3b}, N, or absent;

M³ is CH, CR^{3b}, N, O, or S;

M⁴ is CH, CR^{3b}, N, O, or S,

provided that:

(1) when M⁴ is O or S and M² is absent, then M³ is CH, CR^{3b} or N, and

(2) when M³ is O or S and M² is absent, then M⁴ is CH, CR^{3b} or N;

R^{3a} is C₃-C₆ cycloalkyl optionally substituted by C₁-C₆ haloalkyl or -CN, or C₁-C₆ alkyl optionally substituted by halogen, -OH or -CN, provided that when R^{3a} is C₁-C₆ alkyl optionally substituted by halogen, -OH or -CN, then at least one of M¹, M², M³, and M⁴ is CR^{3b};

R^{3b} is halogen or -CN;

each R⁴ is independently oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, -C(O)R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁸, -CN, -Si(C₁-C₆ alkyl)₃, -OR¹⁷, -NR¹⁷R¹⁸, -OC(O)NR¹⁷R¹⁸, -NR¹⁷C(O)R¹⁸, -S(O)₂R¹⁷, -NR¹⁷S(O)₂R¹⁸, -S(O)₂NR¹⁷R¹⁸, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR¹⁷, -(C₁-C₃ alkylene)NR¹⁷R¹⁸, -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)C(O)R¹⁷, -(C₁-C₃ alkylene)C(O)NR¹⁷R¹⁸, -(C₁-C₃ alkylene)NR¹⁷C(O)R¹⁸, -(C₁-C₃ alkylene)S(O)₂R¹⁷, -(C₁-C₃ alkylene)NR¹⁷S(O)₂R¹⁸, -(C₁-C₃ alkylene)S(O)₂NR¹⁷R¹⁸, -(C₁-C₃ alkylene)(C₃-C₆ cycloalkyl) or -(C₁-C₃ alkylene)(3- to 6-membered heterocyclyl), wherein each R⁴ is independently optionally substituted by halogen, oxo, -OR¹⁹, -NR¹⁹R²⁰, or -C(O)R¹⁹,

or two R^4 , when bound to the same carbon, are taken together with the carbon to which they are attached to form a C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl, each is optionally substituted by R^{19} ; and

each R^{17} , R^{18} , R^{19} , and R^{20} is independently hydrogen, C_3 - C_6 cycloalkyl, 3-6 membered heterocyclyl or C_1 - C_6 alkyl, each of which is optionally substituted by halogen, oxo or $-OH$,

or R^{17} and R^{18} are taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or $-OH$.

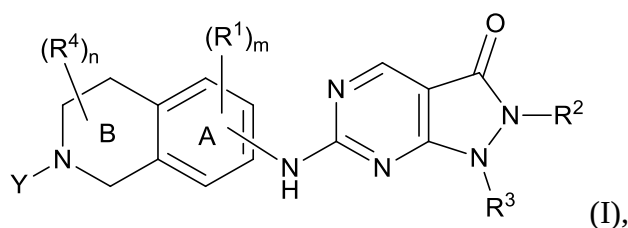
[0008b] In another aspect of the present disclosure, there is provided a compound or a salt thereof, wherein the compound is selected from the group consisting of compounds in Table 1.

[0008c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

[0008d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating cancer.

[0008e] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in treating cancer.

[0009] In one example, provided is a compound of Formula (I):



or a salt thereof, wherein Y , R^1 , R^2 , R^3 , R^4 , m and n are as detailed herein.

[0010] In some examples, the compound of Formula (I) or a salt thereof, is of the Formula (II) or (III), or a salt thereof as detailed herein.

[0011] In another example, provided is a method of treating cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound as detailed herein, such as a compound of Formula (I), (II) or (III) or a

pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting Wee1 in a cell, comprising administering a compound detailed herein, or a salt thereof, to the cell.

[0012] In another example, provided are pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier or excipient. Kits comprising a compound detailed herein or a salt thereof are also provided. A compound as detailed herein, or a salt thereof, is also provided for the manufacture of a medicament for the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0013] “Alkyl” refers to and includes saturated linear and branched univalent hydrocarbon structures and combination thereof, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Particular alkyl groups are those having 1 to 20 carbon atoms (a “C₁-C₂₀ alkyl”). More particular alkyl groups are those having 1 to 8 carbon atoms (a “C₁-C₈ alkyl”), 3 to 8 carbon atoms (a “C₃-C₈ alkyl”), 1 to 6 carbon atoms (a “C₁-C₆ alkyl”), 1 to 5 carbon atoms (a “C₁-C₅ alkyl”), or 1 to 4 carbon atoms (a “C₁-C₄ alkyl”). Examples of alkyl include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

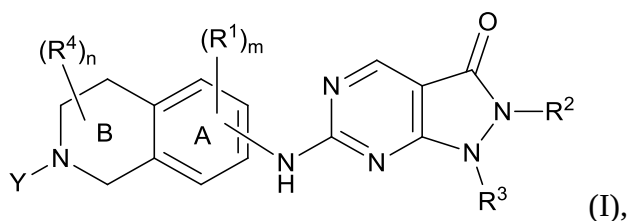
[0014] “Alkenyl” as used herein refers to an unsaturated linear or branched univalent hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and having the number of carbon atoms designated (*i.e.*, C₂-C₁₀ means two to ten carbon atoms). The alkenyl group may be in “cis” or “trans” configurations, or alternatively in “E” or “Z” configurations. Particular alkenyl groups are those having 2 to 20 carbon atoms (a “C₂-C₂₀ alkenyl”), having 2 to 8 carbon atoms (a “C₂-C₈ alkenyl”), having 2 to 6 carbon atoms (a “C₂-C₆ alkenyl”), or having 2 to 4 carbon atoms (a “C₂-C₄ alkenyl”). Examples of alkenyl include, but are not limited to, groups such as ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-dienyl, homologs and isomers thereof, and the like.

[0015] “Alkylene” as used herein refers to the same residues as alkyl, but having bivalency. Particular alkylene groups are those having 1 to 6 carbon atoms (a “C₁-C₆

CLAIMS

What is claimed is:

1. A compound of Formula (I):



or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

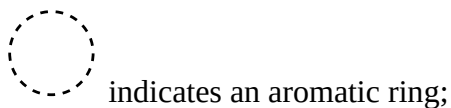
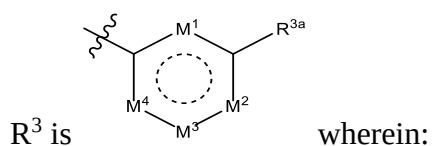
Y is hydrogen or R^4 ;

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3, or 4;

R^1 is independently F, Cl, or methyl;

R^2 is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or $-(C_1$ - C_3 alkylene) CF_3 ;



M^1 is CH, CR^{3b} or N;

M^2 is CH, CR^{3b} , N, or absent;

M^3 is CH, CR^{3b} , N, O, or S;

M^4 is CH, CR^{3b} , N, O, or S,

provided that:

(1) when M^4 is O or S and M^2 is absent, then M^3 is CH, CR^{3b} or N, and

(2) when M^3 is O or S and M^2 is absent, then M^4 is CH, CR^{3b} or N;

R^{3a} is C_3 - C_6 cycloalkyl optionally substituted by C_1 - C_6 haloalkyl or -CN, or C_1 - C_6 alkyl optionally substituted by halogen, -OH or -CN, provided that when R^{3a} is C_1 - C_6 alkyl optionally substituted by halogen, -OH or -CN, then at least one of M^1 , M^2 , M^3 , and M^4 is CR^{3b} ;

R^{3b} is halogen or -CN;

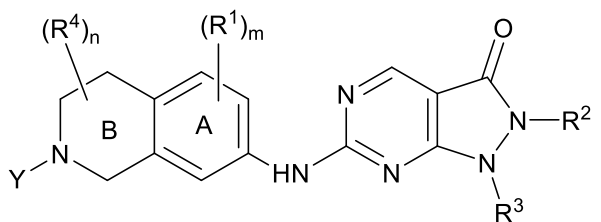
each R^4 is independently oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{18}$, -CN, $-Si(C_1-C_6 \text{ alkyl})_3$, $-OR^{17}$, $-NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-NR^{17}C(O)R^{18}$, $-S(O)_2R^{17}$, $-NR^{17}S(O)_2R^{18}$, $-S(O)_2NR^{17}R^{18}$, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(C_1-C_3 \text{ alkylene})CN$, $-(C_1-C_3 \text{ alkylene})OR^{17}$, $-(C_1-C_3 \text{ alkylene})NR^{17}R^{18}$, $-(C_1-C_3 \text{ alkylene})CF_3$, $-(C_1-C_3 \text{ alkylene})C(O)R^{17}$, $-(C_1-C_3 \text{ alkylene})C(O)NR^{17}R^{18}$, $-(C_1-C_3 \text{ alkylene})NR^{17}C(O)R^{18}$, $-(C_1-C_3 \text{ alkylene})S(O)_2R^{17}$, $-(C_1-C_3 \text{ alkylene})NR^{17}S(O)_2R^{18}$, $-(C_1-C_3 \text{ alkylene})S(O)_2NR^{17}R^{18}$, $-(C_1-C_3 \text{ alkylene})(C_3-C_6 \text{ cycloalkyl})$ or $-(C_1-C_3 \text{ alkylene})(3\text{- to }6\text{-membered heterocyclyl})$, wherein each R^4 is independently optionally substituted by halogen, oxo, $-OR^{19}$, $-NR^{19}R^{20}$, or $-C(O)R^{19}$,

or two R^4 , when bound to the same carbon, are taken together with the carbon to which they are attached to form a C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl, each is optionally substituted by R^{19} ; and

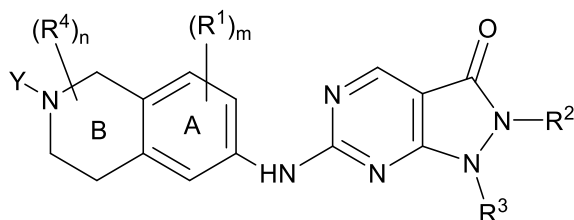
each R^{17} , R^{18} , R^{19} , and R^{20} is independently hydrogen, C_3 - C_6 cycloalkyl, 3-6 membered heterocyclyl or C_1 - C_6 alkyl, each of which is optionally substituted by halogen, oxo or -OH,

or R^{17} and R^{18} are taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or -OH.

2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (II):



3. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (III):



4. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is C₁-C₆ alkyl.

5. The compound of claim 4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is isopropyl or ethyl.

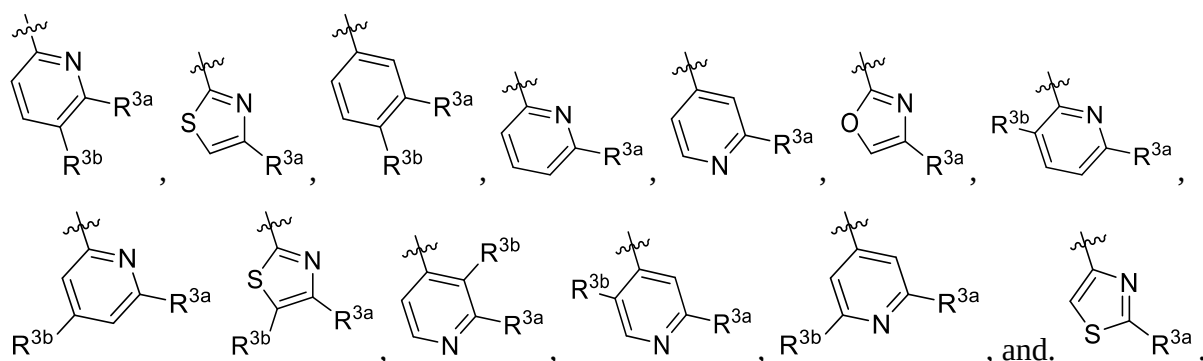
6. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is C₃-C₆ cycloalkyl.

7. The compound of claim 6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is cyclopropyl.

8. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is -(C₁-C₃ alkylene)CF₃.

9. The compound of claim 8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is -CH₂CF₃.

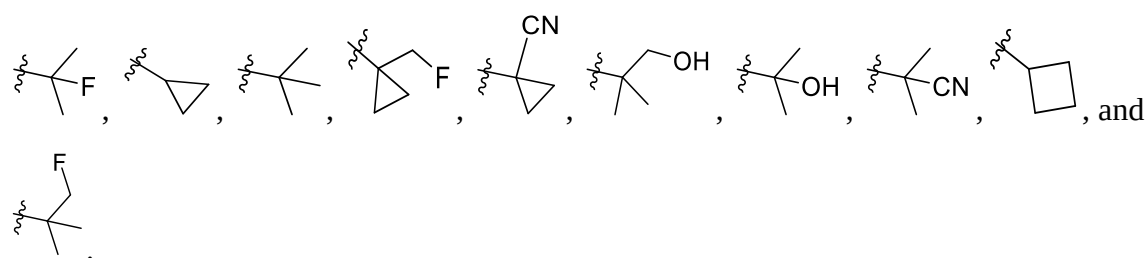
10. The compound of any one of claims 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is selected from the group consisting of:



11. The compound of any one of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{3a} is C₃-C₆ cycloalkyl optionally substituted by C₁-C₆ haloalkyl or -CN.

12. The compound of any one of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{3a} is C₁-C₆ alkyl optionally substituted by halogen, -OH or -CN.

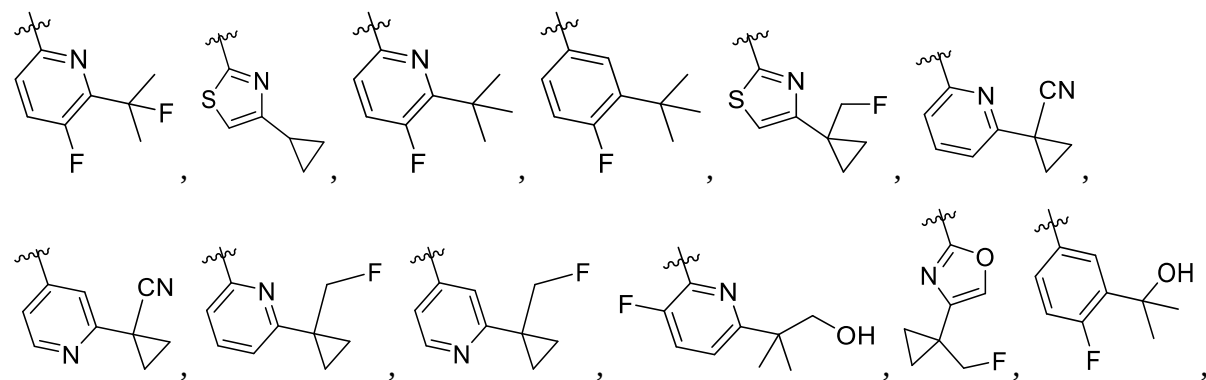
13. The compound of any one of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{3a} is selected from the group consisting of:

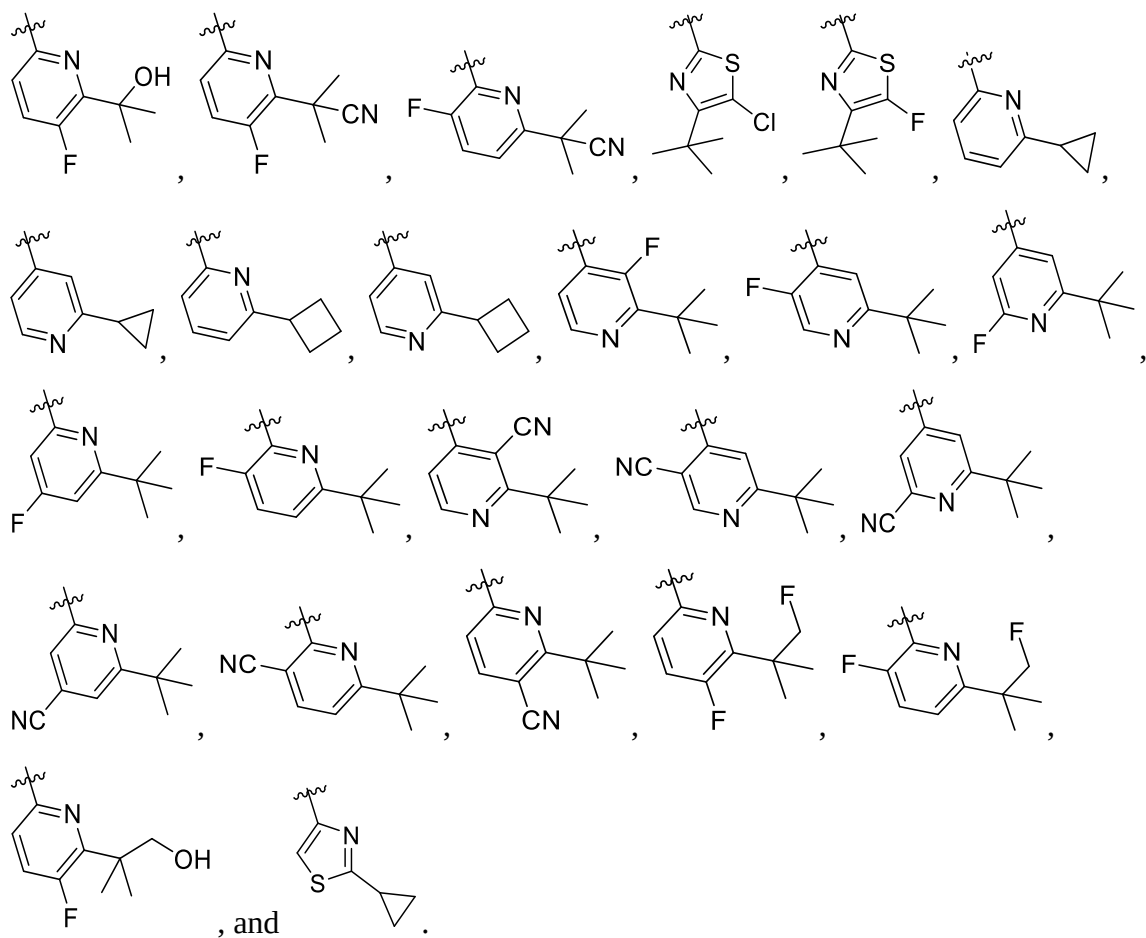


14. The compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{3b} is halogen.

15. The compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{3b} is -CN.

16. The compound of any one of claims 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is selected from the group consisting of:

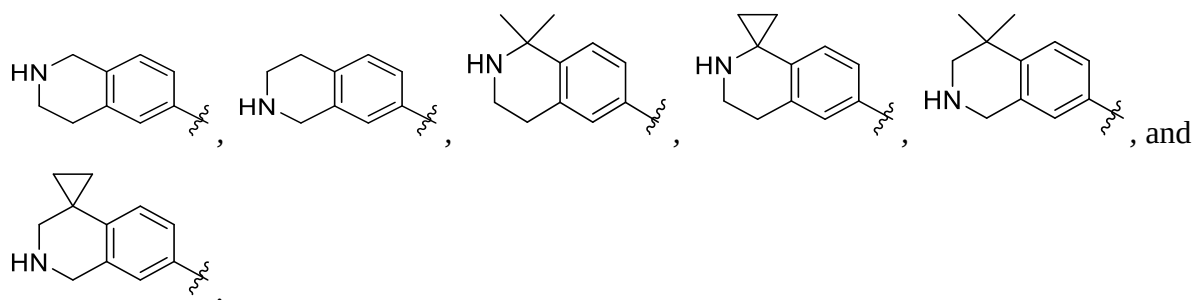




17. The compound of any one of claims 1-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m is 0.
18. The compound of any one of claims 1-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m is 1.
19. The compound of any one of claims 1-18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y is hydrogen.
20. The compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 0.
21. The compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 1.
22. The compound of any one of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein n is 2.
23. The compound of any one of claims 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R⁴ is independently

C₁-C₆ alkyl, or two R⁴, when bound to the same carbon, are taken together with the carbon to which they are attached to form a C₃-C₆ cycloalkyl.

24. The compound of any one of claims 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring A, ring B, R¹, and R⁴ are taken together to form a moiety selected from the group consisting of:



25. A compound or a salt thereof, wherein the compound is selected from the group consisting of compounds in Table 1.

26. The compound of claim 25, wherein the compound is a pharmaceutically acceptable salt of a compound in Table 1.

27. A pharmaceutical composition comprising a compound of any one of claims 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

28. Use of a compound of any one of claims 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating cancer.

29. The use of claim 28, wherein a radiation therapy is to be further administered to the individual.

30. The use of claim 28 or 29, wherein a therapeutically effective amount of an additional therapeutic agent is to be further administered to the individual.

31. The use of claim 30, wherein the additional therapeutic agent is a cancer immunotherapy agent or a chemotherapeutic agent.

32. The use of claim 30 or 31, wherein the additional therapeutic agent is a DNA alkylating agent, a platinum-based chemotherapeutic agent, a kinase inhibitor or a DNA damage repair (DDR) pathway inhibitor.

33. The use of any one of claims 28-32, wherein the cancer comprises a mutant *TP53* gene.
34. The use of any one of claims 28-33, the use further comprising selecting the individual for treatment based on (i) the presence of one or more mutations in the *TP53* gene in the cancer, or (ii) expression of mutant p53 in the cancer.
35. The use of any one of claims 30-32, wherein the additional therapeutic agent is a DNA targeted agent, a topoisomerase inhibitor, a Topoisomerase I inhibitor, a Topoisomerase II inhibitor, an anthracycline, a histone deacetylase inhibitor, a bromodomain inhibitor, an epigenetic inhibitor, a taxane, an anti-angiogenic inhibitor, a nucleotide analog or precursor analog, or a combination of any of the foregoing.36. The use of any one of claims 30-32, wherein the additional therapeutic agent is cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, temozolomide, a nitrosourea, irinotecan, topotecan, etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin, vorinostat, romidepsin, paclitaxel, docetaxel, bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, vismodegib, azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, 5 fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, tioguanine, cisplatin, carboplatin, oxaliplatin, pemetrexed, or a combination of any of the foregoing.
37. A compound of any one of claims 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in treating cancer.