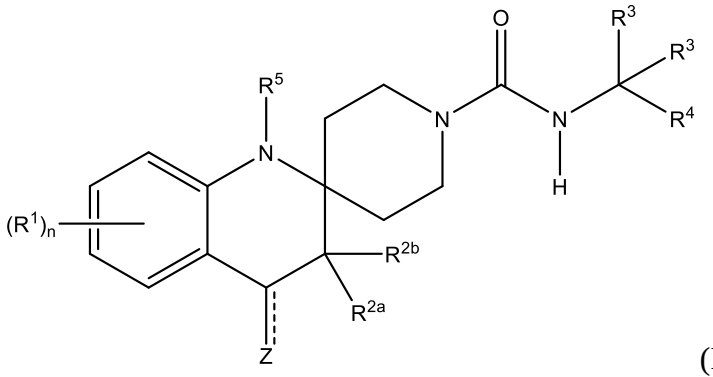
CLAIMS

1. A method of identifying a subject for treatment with a compound of formula (I):



(I),

wherein ------ is a single bond or a double bond;

Z is either OH, when ------ is a single bond; or O, when ------ is a double bond;

each R^1 is independently selected from the group consisting of, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_0\text{-}C_4)$alkyl$N(R^8)_2$, and halo;

R^{2a} and R^{2b} are each independently selected from the group consisting of H, $(C_1\text{-}C_6)$ alkyl, and halo;

each R^3 is independently selected from the group consisting of H, , and halo;

R^4 is selected from the group consisting of aryl, a 5 to 6-membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; and a 9 to 10-membered fused bicyclic heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S; wherein any of the foregoing is optionally substituted with one or more R^6;

R^5 is selected from the group consisting of H; $(C_1\text{-}C_6)$alkyl; $(C_2\text{-}C_6)$alkenyl; $(C_0\text{-}C_4)$alkylOR^8; $(C_1\text{-}C_4)$alkyl$(C_3\text{-}C_{10})$cycloalkyl; halo$(C_1\text{-}C_6)$alkyl; $(C_2\text{-}C_3)$alkynyl; $(C_1\text{-}C_4)$alkyl$N(R^{10})_2$;

each R^6 is independently selected from the group consisting of halo;; (C_1-C_6)alkyl; (C_1-C_6)alkoxy; halo(C_1-C_6)alkyl; OH; aryl; 3 to 6-membered heterocycle; 5- to 6-membered heteroaryl; (C_0-C_4)alkylS(O)$_m$(C_1-C_6)alkyl; halo(C_1-C_6)alkoxy; (C_0-C_4)alkylS(O)$_m$N(R^8)$_2$; (C_0-C_4)alkyl N(R^8)$_2$; (C_0-C_4)alkyl(CO)OR^7; N(R^8)S(O)$_m$(C_1-C_6)alkyl; N(R^8)S(O)$_m$(C_3-C_6)cycloalkyl; OP(O)(OH)$_2$; (C_0-C_3)alkyl(CO)NHR^{11}; (C_0-C_3)alkylOR^7, and (C_3-C_{10})cycloalkyl; wherein each R^6, when not being halo, OH, or OP(O)(OH)$_2$, is optionally substituted with one to three R^9; or two neighboring R^6, together with the atoms to which they attach form a 5 to 7- membered heterocycle or (C_5-C_8)cycloalkyl;

each R^7 and R^8 is independently selected from the group consisting of H or (C_1-C_6)alkyl, that is optionally substituted with one to three R^9;

each R^9 is independently selected from the group consisting of halo; -OH; amino, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, OP(O)(OH)$_2$;(C_1-C_6)alkyl; (C_1-C_3)alkynyl; (C_1-C_6)alkoxy; halo(C_1-C_6)alkyl; (C_0-C_4)alkylS(O)$_m$(C_1-C_6)alkyl; halo(C_1-C_6)alkoxy; 3 to 6-membered heterocycle which is optionally substituted with oxo (=O); (C_0-C_4)alkylS(O)$_m$N(R^{10})$_2$;; (C_0-C_4)alkyl(CO)R^{10}; (C_0-C_4)alkyl(CO)OR^{10}; (C_0-C_4)alkylNR^{10}S(O)$_m$(C_1-C_6)alkyl; (C_0-C_4)alkylOR^{10}; (C_0-C_4)alkylN(R^{10})$_2$; (C_0-C_4)alkylCN; (C_0-C_4)alkylN(R^{10})$_2$; and (C_0-C_4)alkyl(CO)N(R^{10})$_2$;

each R^{10} is independently selected from the group consisting of H, (C_1-C_6)alkyl; or 3 to 6-membered heterocycle, wherin the 3 to 6-membered heterocycle is optionally substituted with one or more of (C_1-C_6)alkyl; and oxo (=O);

each R^{11} is selected from the group consisting of H; 4 to 6-membered heterocycle which is optionally substituted with one to four R^{12}; (C_3-C_6)cycloalkyl which is optionally substituted with one to four R^{12}; (C_0-C_3)alkyl(C_3-C_6)cycloalkyl (C_1-C_3)alkyl which is optionally substituted with halo;; CH_2-aryl which is optionally substituted with one to three R^{12}; (C_1-C_6)alkyl; (C_2-C_6)alkenyl; or (C_2-C_6)alkynyl, wherein each of the (C_1-C_6)alkyl; (C_2-C_6)alkenyl; and (C_2-C_6)alkynyl is optionally substituted with one or more R^{13};

each R^{12} is independently selected from the group consisting of OH, (C_1-C_3)alkoxy, NH_2; or (C_1-C_3)alkyl optionally substituted with one or more OH;

each R^{13} is independently selected from the group consisting of halo, OH, amino, (C_1-C_4)alkylamino, di(C_1-C_4)alkylamino, (C_1-C_3)alkoxy; and C(O)-(C_3-C_8)cycloalkyl;

m is 0, 1, or 2; and

n is 0, 1 or 2,

or a pharmaceutically acceptable salt thereof,

the method comprising determining in a subject sample a level of AKR1C3, wherein an elevated level of AKR1C3 identifies the subject as a subject in need of treatment with the compound of formula (I), or a pharmaceutically acceptable salt thereof.

2. A method of selecting a compound of formula (I), or a pharmaceutically acceptable salt thereof, for treating a subject, the method comprising determining in a subject sample a level of AKR1C3, wherein an elevated level of AKR1C3 identifies the subject as a subject in need of treatment of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

3. A method of determining in a subject a level of AKR1C3, the method comprising:

determining in a subject sample a level of AKR1C3, wherein an elevated level of AKR1C3 identifies the subject as in need of treatment with a compound of formula (I), or a pharmaceutically acceptable salt thereof ,

wherein an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, is to be administered to the subject.

4. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject, wherein an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt

thereof is to be administered to the subject, and wherein a subject sample is characterized as having an elevated level of AKR1C3.

5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

6. The method, use, or compound for use of any one of claims 1-5, wherein the compound of formula (I) is selected from the group consisting of: 6'-fluoro-N-(4-fluorobenzyl)-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-carboxamide; and N-(4-amino-3-fluorobenzyl)-6'-fluoro-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-carboxamide, or a pharmaceutically acceptable salt thereof.

7. The method, use, or compound for use of any one of claims 1-6, wherein the compound of formula (I) is 6'-fluoro-N-(4-fluorobenzyl)-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-carboxamide, or a pharmaceutically acceptable salt thereof.

8. The method, use, or compound for use of any one of claims 1-7, wherein the subject sample comprises a cell, a cell population, a cell lysate, a tissue, or a fluid of the subject.

9. The method, use, or compound for use of claim 8, wherein the cell is a cancerous cell.

10. The method, use, or compound for use of claim 9, wherein the cancerous cell is a tumor cell.

11. The method, use, or compound for use of claim 10, wherein the tumor cell is selected from the group consisting of a lung cancer tumor cell, a non-small cell lung cancer tumor cell, a lung adenocarcinoma tumor cell, a lung squamous cell carcinoma cell, a bladder tumor cell, a cervical tumor cell, an esophageal tumor cell, a head and neck tumor cell, a kidney tumor cell, and a liver tumor cell.

12. The method, use, or compound for use of claim 8, wherein the cell is a lung cell.

13. The method, use, or compound for use of claim 8, wherein the fluid is selected from the group consisting of blood, plasma, and lymphatic fluid.

14. The method, use, or compound for use of any one of claims 1-13, wherein the subject is diagnosed with a disease or disorder selected from the group consisting of a non-small cell lung cancer, a lung adenocarcinoma, a lung squamous cell carcinoma, a bladder cancer, a cervical cancer, an esophageal cancer, a head and neck cancer, a kidney cancer, and a liver cancer.

15. The method, use, or compound for use of any one of claims 1-14, wherein the subject tumor genome comprises a somatic mutation in one or more of the NFE2L2, KEAP1, and CUL3 gene sequences.

16. The method, use, or compound for use of any one of claims 1-15, wherein the level of AKR1C3 of the subject sample is elevated relative to a control level of AKR1C3.

17. The method, use, or compound for use of claim 16, wherein the control level comprises a level of AKR1C3 of a control sample or a control data set.

18. The method, use, or compound for use of claim 17, wherein the control sample comprises a sample selected from the group consisting of a non-cancerous cell of the subject, a non-cancerous cell population of the subject, a non-cancerous tissue of the subject, a non-cancerous fluid of the subject, a non-cancerous cell of a control subject, a non-cancerous cell population of a control subject, a non-cancerous tissue of a control subject, and a non-cancerous fluid of a control subject.

19. The method, use, or compound for use of claim 17, wherein the control data set comprises biomarker level data from a source selected from the group consisting of a non-cancerous cell of the subject, a non-cancerous cell population of the subject, a non-cancerous tissue of the subject, a non-cancerous fluid of the subject, a non-cancerous cell of a control subject, a non-cancerous cell population of a control subject, a non-cancerous tissue of a control subject, a non-cancerous fluid of a control subject, and a combination thereof.

20. The method, use, or compound for use of any one of claims 1-19, wherein the level of AKR1C3 is a protein level of AKR1C3.

21. The method, use, or compound for use of claim 1-19, wherein the level of AKR1C3 is an RNA level of AKR1C3.

22. The method, use, or compound for use of claim 21, wherein the RNA level of AKR1C3 is an mRNA level of AKR1C3.

23. A method of identifying a subject in need of treatment with a compound of formula (I), or a pharmaceutically acceptable salt thereof, the method comprising detecting in a subject sample a somatic mutation in at least one of the following genes: NFE2L2, KEAP1, or CUL3.

24. A method of selecting a compound of formula (I), or a pharmaceutically acceptable salt thereof, for treating a subject, the method comprising detecting in a subject sample a somatic mutation in at least one of the following genes: NFE2L2, KEAP1, or CUL3.

25. A method of detecting in a subject a somatic mutation, the method comprising:

detecting in a subject sample a somatic mutation in at least one of the following genes: NFE2L2, KEAP1, or CUL3, wherein said detecting identifies the subject as in need of treatment with a compound of formula (I), or a pharmaceutically acceptable salt thereof,

wherein an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, is to be administered to the subject.

26. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject, wherein an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof is to be administered to the subject, and wherein a subject sample is characterized by the presence of a somatic mutation in at least one of the following genes: NFE2L2, KEAP1, or CUL3.

27. The method or use of any one of claims 23-**Error! Reference source not found.**26, wherein the compound of formula (I) is selected from the group consisting of: 6'-fluoro-N-(4-fluorobenzyl)-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-

carboxamide; and N-(4-amino-3-fluorobenzyl)-6'-fluoro-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-carboxamide, or a pharmaceutically acceptable salt thereof.

28. The method or use of any one of claims 23-27, wherein the compound of formula (I) is 6'-fluoro-N-(4-fluorobenzyl)-4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline]-1-carboxamide, or a pharmaceutically acceptable salt thereof.

29. The method or use of any one of claims 23-28, wherein the somatic mutation is selected from the group consisting of an amplification of the NFE2L2 gene sequence or a portion thereof, a deletion of the KEAP1 gene sequence or a portion thereof, and a deletion of the CUL3 gene sequence or a portion thereof.

30. The method or use of any one of claims 23-28, wherein the somatic mutation comprises a mutation selected from the group consisting of a nonsense mutation, a missense mutation, a substitution mutation, a frameshift mutation, a point mutation, an insertion mutation, a deletion mutation, an inversion mutation, and a gene amplification mutation.

31. The method or use of any one of claims 23-28, wherein the somatic mutation comprises a single nucleotide polymorphism (SNP).

32. The method or use of any one of claims 23-31, wherein the subject sample comprises a cell, a cell population, a cell lysate, a tissue, or a fluid of the subject.

33. The method or use of claim 32, wherein the subject sample comprises genomic DNA of the cell, the cell population, the cell lysate, the tissue, or the fluid of the subject.

34. The method or use of claim 32 or 33, wherein the cell is a cancerous cell.

35. The method or use of claim 34, wherein the cancerous cell is a tumor cell.

36. The method or use of claim 35, wherein the tumor cell is selected from the group consisting of a lung cancer tumor cell, a non-small cell lung cancer tumor cell, a lung adenocarcinoma tumor cell, a lung squamous cell carcinoma cell, a bladder tumor cell, a

cervical tumor cell, an esophageal tumor cell, a head and neck tumor cell, a kidney tumor cell, and a liver tumor cell.

37. The method or use of claim 32 or 33, wherein the cell is a lung cell.

38. The method or use of claim 32 or 33, wherein the fluid is selected from the group consisting of blood, plasma, and lymphatic fluid.

39. The method or use of any one of claims 23-38, wherein the subject is diagnosed with a disease or disorder selected from the group consisting of a non-small cell lung cancer, a lung adenocarcinoma, a lung squamous cell carcinoma , a bladder cancer, a cervical cancer, an esophageal cancer, a head and neck cancer, a kidney cancer, and a liver cancer.

40. The method or use of any one of claims 23-39, wherein the somatic mutation is absent from a control sample or a control data set.

41. The method or use of claim 40, wherein the control sample comprises a sample selected from the group consisting of a non-cancerous cell of the subject, a non-cancerous cell population of the subject, a non-cancerous tissue of the subject, a non-cancerous fluid of the subject, a non-cancerous cell of a control subject, a non-cancerous cell population of a control subject, a non-cancerous tissue of a control subject, and a non-cancerous fluid of a control subject.

42. The method or use of claim 41, wherein the control sample comprises genomic DNA of: the non-cancerous cell of the subject, the non-cancerous cell population of the subject, the non-cancerous tissue of the subject, the non-cancerous fluid of the subject, the non-cancerous cell of a control subject, the non-cancerous cell population of a control subject, the non-cancerous tissue of a control subject, or the non-cancerous fluid of a control subject.

43. The method or use of claim 40, wherein the control data set comprises genomic sequence data from a source selected from the group consisting of a non-cancerous cell of the subject, a non-cancerous cell population of the subject, a non-cancerous tissue of the

subject, a non-cancerous fluid of the subject, a non-cancerous cell of a control subject, a non-cancerous cell population of a control subject, a non-cancerous tissue of a control subject, a non-cancerous fluid of a control subject, and a combination thereof.