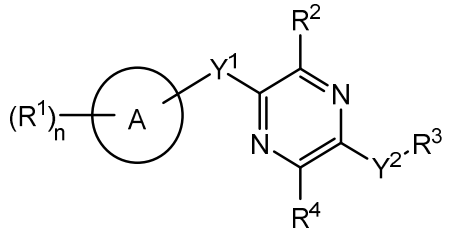
CLAIMS

1. An inhibitor of SHP2 for use for treating a disease or disorder comprising a cell containing a mutation encoding the $KRAS^{G12C}$ variant, wherein said inhibitor of SHP2 is a compound of Formula I-V2:



I-V2

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, and/or isomer thereof, wherein:

A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are 5- to 12-membered monocyclic or 5- to 12-membered polycyclic;

Y^1 is –S–, a direct bond, –NH–, $–S(O)_2–$, $–S(O)_2–NH–$, $–C(=CH_2)–$, –CH–, or –S(O)–;

Y^2 is $–NR^a–$, wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3;

R^3 is combined with R^a to form a 3- to 12-membered polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more $–C_1$-C_6alkyl, halogen, –OH, $–OR^b$, $–NH_2$, $–NHR^b$, heteroaryl, heterocyclyl, $–(CH_2)_nNH_2$, $–(CH_2)_nOH$, $–COOR^b$, $–CONHR^b$, $–CONH(CH_2)_nCOOR^b$, $–NHCOOR^b$, $–CF_3$, $–CHF_2$, $–CH_2F$, or =O;

R^1 is independently, at each occurrence, –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, –OH, $–OR^6$, halogen, $–NO_2$, –CN, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, $–C(O)R^5$,$–CO_2R^5$, $–C(O)NR^5R^6$, $–NR^5C(O)R^6$, monocyclic or polycyclic heterocyclyl, spiroheterocyclyl, heteroaryl, or oxo, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, spiroheterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, =O,

–CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^2 is independently –NH_2, –OR^b, –CN, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, halogen, –$C(O)OR^b$, –C_3-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^b is independently, at each occurrence, –H, –D, –OH, –C_1-C_6alkyl, –C_3-C_8cycloalkyl, –C_2-C_6alkenyl, –$(CH_2)_n$-aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, cycloalkyl, alkenyl, heterocycle, heteroaryl, or –$(CH_2)_n$-aryl is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, –$C(O)NR^5R^6$, –$NR^5C(O)R^6$, heterocycle, aryl, heteroaryl, –$(CH_2)_n$OH, –C_1-C_6alkyl, –CF_3, –CHF_2, or –CH_2F;

R^4 is independently –H, –D, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –C_1-C_6hydroxyalkyl, –CF_2OH, –CHFOH, –NH-NHR^5, –NH-OR^5, –O-NR^5R^6, –NHR^5, –OR^5, –$NHC(O)R^5$, –$NHC(O)NHR^5$, –$NHS(O)_2R^5$, –$NHS(O)_2NHR^5$, –$S(O)_2OH$, –$C(O)OR^5$, –$NH(CH_2)_n$OH, –$C(O)NH(CH_2)_n$OH, –$C(O)NH(CH_2)_nR^b$, –$C(O)R^b$, –NH_2, –OH, –CN, –$C(O)NR^5R^6$, –$S(O)_2NR^5R^6$, C_3-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with one or more –OH, –NH_2, –OR^b, halogen, or oxo; wherein each aryl or heteroaryl is optionally substituted with one or more –OH, –NH_2, or halogen;

R^5 and R^6 are independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, –OR^7, –SR^7, halogen, –NR^7R^8, –NO_2, –CF_3, or –CN;

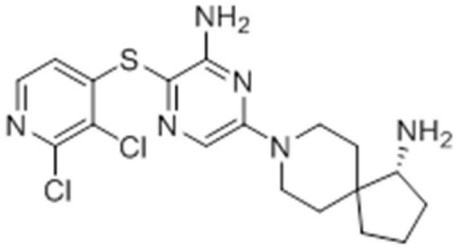
R^7 and R^8 are independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, –OR^b, or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more –OH, –SH, –NH_2, –NO_2, or –CN; and

n is independently, at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

2. The inhibitor of SHP2 for use according to claim 1, wherein said inhibitor of SHP2 is selected from a compound of Formula I-V2 wherein Y1 is -S- or a direct bond, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, and/or isomer thereof.

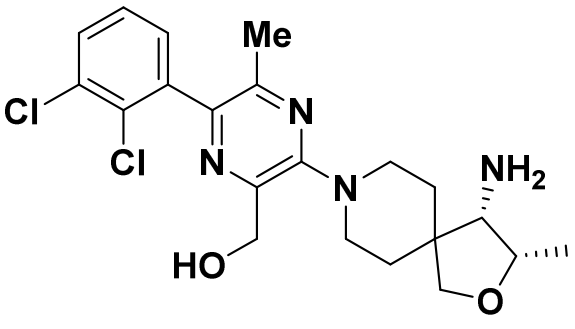
3. The inhibitor of SHP2 for use according to claim 1 or 2, wherein said inhibitor of SHP2 is:

Compound A having the structure:



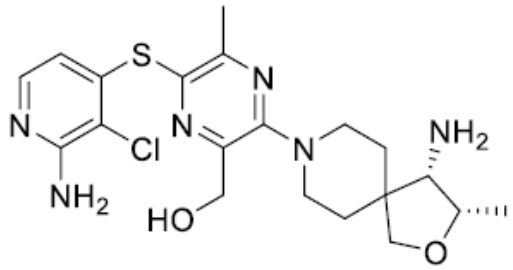
;

Compound B having the structure:



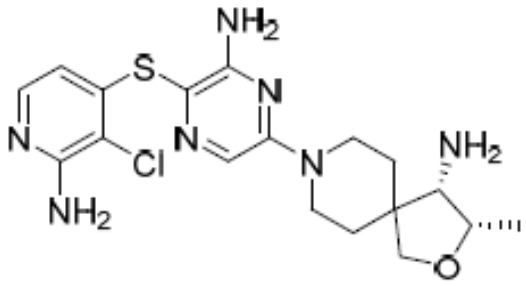
;

the compound of the following structure:



; or

TNO155 having the structure:



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4. An inhibitor of SHP2 for use for treating a disease or disorder comprising a cell with a mutation encoding an NF1 loss of function ($NF1^{LOF}$) variant, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

5. An inhibitor of SHP2 for use for treating a disease or disorder associated with a RAS pathway mutation in a cell of a subject that renders the cell at least partially dependent on signaling flux through SHP2,wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

6. The inhibitor for use according to claim 5, wherein the RAS pathway mutation is selected from a KRAS mutation, an NRAS mutation, a SOS mutation, a BRAF Class III mutation, a Class I MEK1 mutation, a Class II MEK1 mutation, and an NF1 mutation.

7. The inhibitor for use according to claim 6, wherein the KRAS mutation is selected from a $KRAS^{G12A}$ mutation, a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12F}$ mutation, a $KRAS^{G12I}$ mutation, a $KRAS^{G12L}$ mutation, a $KRAS^{G12R}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, a $KRAS^{G12Y}$ mutation, and a $KRAS^{G13D}$ mutation.

8. The inhibitor for use according to claim 6 or 7, wherein the KRAS mutation is $KRAS^{G12C}$, $KRAS^{G12S}$, or $KRAS^{G12V}$.

9. The inhibitor for use according to claim 6, wherein the BRAF Class III mutation is selected from one or more of the following amino acid substitutions in human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E.

10. The inhibitor for use according to claim 6, wherein the NF1 mutation is a loss of function mutation ($NF1^{LOF}$).

11. The inhibitor for use according to claim 6, wherein the Class I MEK1 mutation is selected from one or more of the following amino acid substitutions in human MEK1: D67N; P124L; P124S; and L177V.

12. The inhibitor for use according to claim 6, wherein the Class II MEK1 mutation is selected from one or more of the following amino acid substitutions in human MEK1: ΔE51-Q58; ΔF53-Q58; E203K; L177M; C121S; F53L; K57E; Q56P; and K57N.

13. The inhibitor for use according to any one of claims 1-12, further comprising providing to the subject an inhibitor of the RAS pathway.

14. The inhibitor for use according to claim 13, wherein the inhibitor of the RAS pathway is a MAPK inhibitor.

15. The inhibitor for use according to claim 13, wherein the inhibitor of the RAS pathway is a MEK inhibitor or ERK inhibitor.

16. The inhibitor for use according to claim 13, wherein the inhibitor of the Ras pathway is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib, and Abemaciclib.

17. The inhibitor for use according to any one of claims 1-16, wherein the disease or condition is a cancer.

18. The inhibitor for use according to any one of claims 1-17, wherein the disease or condition is a tumor.

19. The inhibitor for use according to claim 18, wherein the tumor is selected from an NSCLC, a colon cancer, an oesophageal cancer, a rectal cancer, JMML, breast cancer, melanoma, Schwannoma, and a pancreatic cancer.

20. An inhibitor of SHP2 for use for treating a disease associated with an NF1 loss of function mutation, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

21. The inhibitor for use according to claim 20, wherein the disease is a tumor comprising cells with an NF1 loss of function mutation.

22. The inhibitor for use according to claim 21, wherein the tumor is an NSCLC or melanoma tumor.

23. The inhibitor for use according to claim 20, wherein the disease is selected from neurofibromatosis type I, neurofibromatosis type II, schwannomatosis, and Watson syndrome.

24. The inhibitor for use according to any one of claims 20-23, further comprising providing to the subject an inhibitor of the RAS pathway.

25. The inhibitor for use according to claim 24, wherein the RAS pathway inhibitor is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib, and Abemaciclib.

26. An inhibitor of SHP2 for use for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a KRAS mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a $KRAS^{G12C}$ mutant, a $KRAS^{G12D}$ mutant, a $KRAS^{G12S}$ mutant, or a $KRAS^{G12V}$ mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

27. An inhibitor of SHP2 for use for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as an $NF1^{LOF}$ mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as an $NF1^{LOF}$ mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

28. An inhibitor of SHP2 for use for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class 3 BRAF mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class 3 BRAF mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

29. An inhibitor of SHP2 for use for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class I MEK1 mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class I MEK1 mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

30. An inhibitor of SHP2 for use for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class II MEK1 mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class II MEK1 mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

31. An inhibitor for use for treating or preventing drug resistance to a RAS pathway inhibitor in a subject receiving administration of a RAS pathway inhibitor, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

32. The inhibitor for use according to claim 31, wherein the subject comprises a tumor containing cells with an $NF1^{LOF}$ mutation.

33. The inhibitor for use according to claim 31 or 32, wherein the subject comprises a tumor containing a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12A}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, or a $KRAS^{G13D}$ mutation.

34. The inhibitor for use according to any one of claims 31-33, wherein the RAS pathway inhibitor is a MEK inhibitor.

35. The inhibitor for use according to claim 34, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704) , CH5126766, MAP855, and GSK1120212.

36. The inhibitor for use according to any one of claims 31-33, wherein the RAS pathway inhibitor is an ERK inhibitor.

37. The inhibitor for use according to claim 36, wherein the ERK inhibitor is selected from LY3214996; Ulixertinib; and BVD523.

38. A combination therapy comprising a RAS pathway inhibitor and an inhibitor of SHP2, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

39. The combination therapy of claim 38, wherein the RAS pathway inhibitor is a MEK inhibitor.

40. The combination therapy of claim 39, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), CI-1040; PD-0325901, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704), CH5126766, MAP855, and GSK1120212.

41. The combination therapy of claim 38, wherein the RAS pathway inhibitor is the $KRAS^{G12C}$-specific inhibitor ARS-853.

42. The combination therapy of any one of claims 38-41, for use in the treatment of a tumor.

43. The combination therapy of claim 42, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

44. A pharmaceutical composition comprising a RAS pathway inhibitor, an inhibitor of SHP2, and one or more pharmaceutically acceptable carrier, excipient, diluent, and/or surfactant, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

45. The pharmaceutical composition of claim 44, wherein the RAS pathway inhibitor is selected from one or more of Trametinib (GSK1120212) Selumetinib (AZD6244); Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; Refametinib (RDEA 119/BAY 86-9766); RO5126766, AZD8330 (ARRY-424704/ARRY-704); GSK1120212, Ulixertinib; and Abemaciclib.

46. The pharmaceutical composition of claim 44 or 45, for use in the treatment of a tumor.

47. The pharmaceutical composition of claim 46, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

48. The inhibitor for use according to any one of claims 18, 20, 21, 26-30, and 32-37, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung

cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

49. An inhibitor of SHP2 for use for inhibiting the growth or proliferation of a cell containing a RAS pathway mutation, wherein the RAS pathway mutation renders the cell at least partially dependent on signaling flux through SHP2, the method comprising contacting the cell with an inhibitor of SHP2, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

50. The inhibitor of SHP2 for use according to claim 49, wherein the RAS pathway mutation is selected from a KRAS mutation, an NRAS mutation, an HRAS mutation, a SOS mutation, a Class III BRAF mutation, and an NF1 loss of function mutation.

51. The inhibitor of SHP2 for use according to claim 50, wherein the KRAS mutation is selected from a $KRAS^{G12A}$ mutation, a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12F}$ mutation, a $KRAS^{G12I}$ mutation, a $KRAS^{G12L}$ mutation, a $KRAS^{G12R}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, a $KRAS^{G12Y}$ mutation, and a $KRAS^{G13D}$ mutation.

52. The inhibitor of SHP2 for use according to claim 51, wherein the KRAS mutation is $KRAS^{G12C}$, $KRAS^{G12S}$, or $KRAS^{G12V}$.

53. The inhibitor of SHP2 for use according to claim 50, wherein the Class 3 BRAF mutation is selected from one or more of the following amino acid substitutions in

human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E.

54. The inhibitor of SHP2 for use according to any one of claims 49-53, further comprising contacting the cell with an inhibitor of the RAS pathway.

55. The inhibitor of SHP2 for use according to claim 54, wherein the inhibitor of the RAS pathway is a MAPK inhibitor.

56. The inhibitor of SHP2 for use according to claim 54, wherein the inhibitor of the RAS pathway is a MEK inhibitor or ERK inhibitor.

57. The inhibitor of SHP2 for use according to claim 54, wherein the inhibitor of the Ras pathway is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib; and Abemaciclib.

58. The inhibitor for use according to any one of claims 1-37 and 48-57, further comprising contacting the cell with a SOS inhibitor.

59. The inhibitor for use according to claim 58, wherein the SOS inhibitor is administered to a cell comprising higher than normal SOS levels or SOS activity.

60. The inhibitor for use according to claim 18, wherein the tumor is from a NSCLC tumor.

61. The inhibitor for use according to claim 18, wherein the tumor is a colon cancer tumor.

62. The inhibitor for use according to claim 18, wherein the tumor is an oesophageal cancer tumor.

63. The inhibitor for use according to claim 18, wherein the tumor is a rectal cancer tumor.

64. The inhibitor for use according to claim 18, wherein the tumor is a JMML tumor.

65. The inhibitor for use according to claim 18, wherein the tumor is a breast cancer tumor.

66. The inhibitor for use according to claim 18, wherein the tumor is a melanoma tumor.

67. The inhibitor for use according to claim 18, wherein the tumor is a Schwannoma tumor.

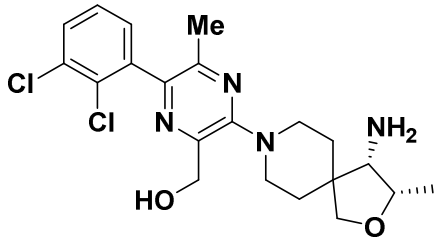
68. The inhibitor for use according to claim 18, wherein the tumor is a pancreatic cancer tumor.

69. The combination therapy of claim 39, for use ininhibiting the growth of a tumor cell, comprising contacting the tumor cell with said combination therapy.

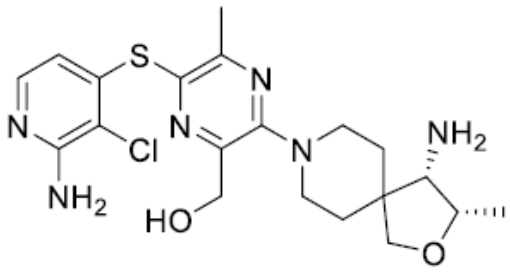
70. The combination therapy of claim 69, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), CI-1040; PD-0325901, CH5126766, MAP855, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704), and GSK1120212.

71. The combination therapy of claim 69 or 70, wherein the MEK inhibitor is Trametinib (GSK1120212).

72. The combination therapy of any one of claims 69-71, wherein the inhibitor of SHP2 is Compound B having the structure

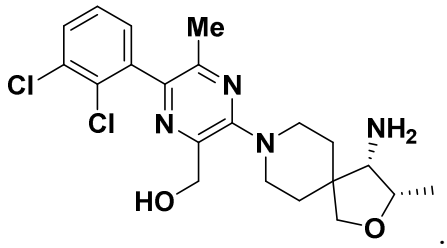


or the compound of the following structure



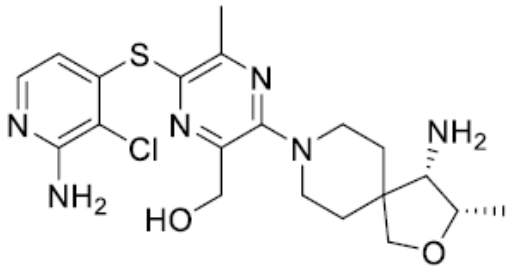
.

73. The combination therapy of claim 69, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is Compound B having the structure



.

74. The combination therapy of claim 69, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is the compound of the following structure



.

75. The combination therapy of any one of claims 69-74, wherein the tumor cell is a cell from a tumor selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid

leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

76. The combination therapy of any one of claims 69-75, wherein the tumor is from a NSCLC tumor.

77. The combination therapy of any one of claims 69-76, wherein the contacting occurs *in vivo* in a subject.

78. The combination therapy of claim 77, wherein the subject is a human.

79. The combination therapy of any one of claims 69-78, wherein the contacting of the tumor cell with the combination therapy results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of the respective MEK and inhibitor of SHP2 separately.

80. The combination therapy of any one of claims 69-79, wherein the MEK inhibitor and the inhibitor of SHP2 do not contact the tumor cell simultaneously.

81. The combination therapy of any one of claims 69-79, wherein the MEK inhibitor and the inhibitor of SHP2 contact the tumor cell simultaneously.

82. The combination therapy of any one of claims 69-81, wherein the contacting is via administration of the MEK inhibitor and the inhibitor of SHP2 to the subject.

83. The combination therapy of claim 82, wherein the administration of the MEK inhibitor precedes the administration of the inhibitor of SHP2.

84. The combination therapy of claim 82, wherein the administration of the inhibitor of SHP2 precedes the administration of the MEK inhibitor.

85. The combination therapy of claim 82, wherein the administration of the inhibitor of SHP2 and the administration of the MEK inhibitor occurs simultaneously.

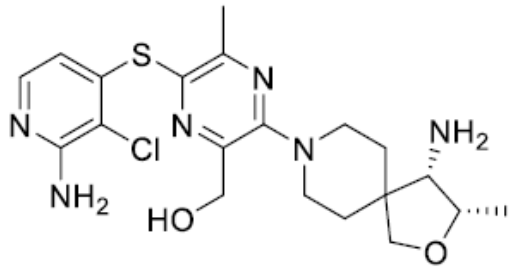
86. The combination therapy of claim 85, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as a single pharmaceutical composition.

87. The combination therapy of claim 85, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as separate pharmaceutical compositions.

88. The combination therapy of any one of claims 69-87, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

89. A combination therapy for use in inhibiting the growth of a tumor cell, comprising contacting the tumor cell with a combination therapy comprising trametinib

(GSK1120212) and an inhibitor of SHP2 of the following structure



.

90. The combination therapy of claim 89, wherein the tumor cell is from a NSCLC tumor.

91. The combination therapy of claim 89 or 90, wherein the contacting occurs *in vivo* in a subject.

92. The combination therapy of claim 91, wherein the subject is a human.

93. The combination therapy of any one of claims 89-92, wherein the contacting of the tumor cell with said combination therapy results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of trametinib (GSK1120212) and the inhibitor of SHP2 separately.

94. The combination therapy of any one of claims 89-93, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

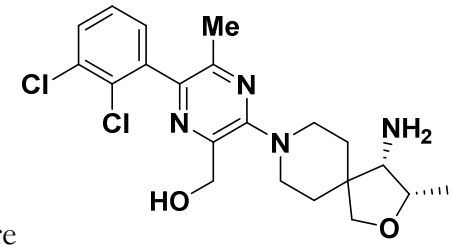
95. The combination therapy for use according to claim 39, for use in treating a tumor, comprising contacting a tumor cell in the tumor in a subject with said combination therapy.

96. The combination therapy of claim 95, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212); Selumetinib (AZD6244); Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655

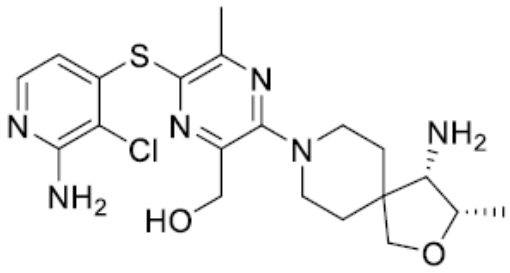
(CH4987655), CI-1040; PD-0325901; CH5126766; MAP855; Refametinib (RDEA 119/BAY 86-9766); RO5126766, AZD8330 (ARRY-424704/ARRY-704); and GSK1120212.

97. The combination therapy of claim 96, wherein the MEK inhibitor is Trametinib (GSK1120212).

98. The combination therapy of any one of claims 95-97, wherein the inhibitor of SHP2 is Compound B having the structure

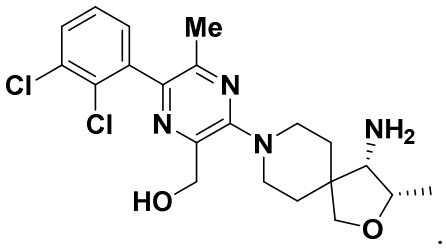


or the compound of the following structure



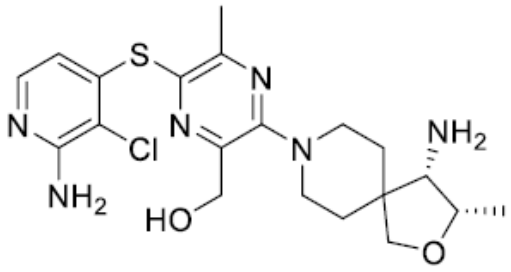
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99. The combination therapy of claim 95, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is Compound B having the structure



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100. The combination therapy of claim 95, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is the compound of the following structure



.

101. The combination therapy of any one of claims 95-100, wherein the tumor cell is a cell from a tumor selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

102. The combination therapy of any one of claims 95-101, wherein the tumor cell is from a NSCLC tumor.

103. The combination therapy of any one of claims 95-102, wherein the contacting occurs *in vivo* in a subject.

104. The combination therapy of claim 103, wherein the subject is a human.

105. The combination therapy of any one of claims 95-104, wherein the contacting of the tumor cell with the combination therapy results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of the respective MEK and inhibitor of SHP2 separately.

106. The combination therapy of any one of claims 95-105, wherein the MEK inhibitor and the inhibitor of SHP2 do not contact the tumor cell simultaneously.

107. The combination therapy of any one of claims 95-105, wherein the MEK inhibitor and the inhibitor of SHP2 contact the tumor cell simultaneously.

108. The combination therapy of any one of claims 95-107, wherein the contacting is via administration of the MEK inhibitor and the inhibitor of SHP2 to the subject.

109. The combination therapy of claim 108, wherein the administration of the MEK inhibitor precedes the administration of the inhibitor of SHP2.

110. The combination therapy of claim 108, wherein the administration of the inhibitor of SHP2 precedes the administration of the MEK inhibitor.

111. The combination therapy of claim 108, wherein the administration of the inhibitor of SHP2 and the administration of the MEK inhibitor occurs simultaneously.

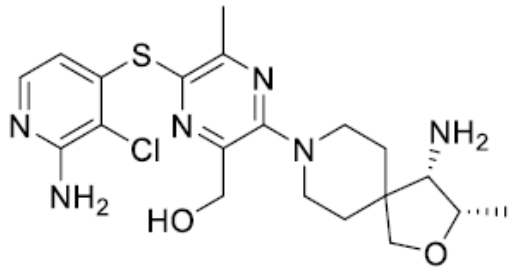
112. The combination therapy of claim 111, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as a single pharmaceutical composition.

113. The combination therapy of claim 111, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as separate pharmaceutical compositions.

114. The combination therapy of any one of claims 95-113, wherein the treatment inhibits the growth of the tumor cell.

115. The combination therapy of claim 114, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

116. A combination therapy for use for treating a tumor, comprising contacting a tumor cell of the tumor in a subject with a combination therapy comprising trametinib (GSK1120212) and an inhibitor of SHP2 of the following structure



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117. The combination therapy of claim 116, wherein the tumor cell is from a NSCLC tumor.

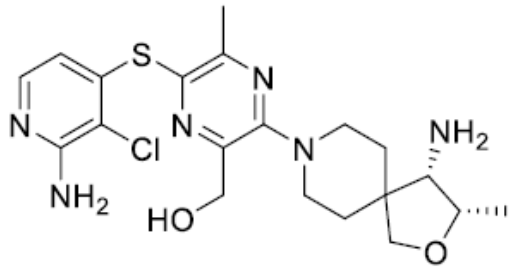
118. The combination therapy of claim 116 or 117, wherein the contacting occurs *in vivo* in a subject.

119. The combination therapy of claim 118, wherein the subject is a human.

120. The combination therapy of any one of claims 116-119, wherein the contacting of the tumor cell with the combination therapy results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of trametinib (GSK1120212) and the inhibitor of SHP2 separately.

121. The combination therapy of any one of claims 116-120, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

122. The pharmaceutical composition of any one of claims 44-47, wherein the inhibitor of SHP2 is the compound of the following structure



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