

COMBINATION THERAPY INVOLVING MACROCYCLIC INDAZOLE COMPOUNDS

RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 63/510,056, filed June 23, 2023, U.S. Provisional Application No. 63/588,518, filed October 6, 2023, U.S. Provisional Application No. 63/575,674, filed April 6, 2024, and U.S. Provisional Application No. 63/659,580, filed June 13, 2024, the entire disclosures of all of which are incorporated herein by reference.

TECHNICAL FIELD

[002] The present disclosure relates to methods and compositions for treating cancer with a macrocyclic indazole compound in combination with at least one other cancer therapeutic, such as a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, a chemotherapy, an EGFR inhibitor, and the like.

BACKGROUND

[003] Protein kinases are tightly regulated signaling proteins that orchestrate the activation of signaling cascades by phosphorylating target proteins in response to extracellular and intracellular stimuli. The human genome encodes approximately 518 protein kinases (Manning G, et al The protein kinase complement of the human genome. *Science*. 2002, 298:1912–34). Dysregulation of kinase activity is associated with many diseases, including cancers, and cardiovascular, degenerative, immunological, infectious, inflammatory, and metabolic diseases (Levitzi, A. Protein kinase inhibitors as a therapeutic modality. *Acc. Chem. Res.* 2003, 36:462–469). The molecular bases leading to various diseases include kinase gain- and loss-of-function mutations, gene amplifications and deletions, splicing changes, and translocations (Wilson LJ, et al New Perspectives, Opportunities, and Challenges in Exploring the Human Protein Kinome. *Cancer Res.* 2018, 78:15-29). The critical role of kinases in cancer and other diseases makes them attractive targets for drug inventions with 62 small molecule kinase inhibitors have been approved and 55 of them for cancer targeted therapies (Roskoski R Jr, Properties of FDA-approved Small Molecule Protein Kinase Inhibitors: A 2021 Update. *Pharmacol Res* 2021, 165:105463). Although kinase inhibitors have achieved dramatic success in cancer targeted therapies, the development of treatment resistance has remained as a challenge for small molecule kinase inhibitors. Acquired secondary mutations within kinase domain during the treatment often lead to treatment resistance to kinase inhibitors (Pottier C, et al Tyrosine Kinase Inhibitors in Cancer: Breakthrough and Challenges of Targeted Therapy. *Cancers (Basel)*, 2020, 12:731). Resistance

can also arise from subpopulations of tolerant/persister cells that survive in the presence of the treatment. Different processes contribute to the emergence of tolerant persister cells, including pathway rebound through the release of negative feedback loops, transcriptional rewiring mediated by chromatin remodeling and autocrine/paracrine communication among tumor cells and within the tumor microenvironment (Swayden M, et al Tolerant/Persister Cancer Cells and the Path to Resistance to Targeted Therapy. *Cells* 2020, 9, 2601). Therefore, it is necessary to invent kinase inhibitors that can target not only the kinase oncogenic drivers, overcome most frequent resistance mutations, but also tolerant persister cancer cells for overcoming resistance, achieving better efficacy and longer disease control. One such mechanism may occur through alternative splicing. Cdc-like kinases (CLKs) are evolutionary conserved dual-specificity kinases that are able to phosphorylate serine, threonine, and tyrosine residues. CLKs catalyze the phosphorylation of SR proteins, serine, and arginine-rich splicing factors 1-12 (SRSF1-12), which regulate the spliceosome molecular machinery (Martín Moyano P, et al Cdc-Like Kinases (CLKs): Biology, Chemical Probes, and Therapeutic Potential. *Int J Mol Sci* 2020, 21(20):7549). Dysregulation of alternative splicing is a feature of cancer.

[004] An example of cancer having a complex treatment and resistance profile is acute myeloid leukemia (AML), which is a complex malignancy with many cytogenetic or chromosomal aberrations. The most frequently identified mutation in AML is FMS-like tyrosine kinase 3 (*FLT3*) with about 25% of adult patients having *FLT3* internal tandem duplication (*FLT3*-ITD) and 7-10% with point mutations or deletions (Daver N, et al Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia* 2019, 33:299–312). Pro-survival splice isoform switching is a feature of secondary AML leukemia stem cell (LSC), and spliceosome modulators impair AML LSC maintenance in humanized pre-clinical models. (Crews L. A.; et al RNA splicing modulation selectively impairs leukemia stem cell maintenance in secondary human AML. *Cell Stem Cell* 2016, 19: 599–612). Two FLT3 inhibitors have been approved by the Food and Drug Administration (FDA) for AML indications: midostaurin for newly diagnosed *FLT3* mutated AML in combination with standard induction and consolidation chemotherapy and gilteritinib for relapsed or refractory *FLT3* mutated AML as monotherapy. In addition to FLT3 inhibitors, other targets have been pursued for the treatment of AML. For example, venetoclax is an FDA approved Bcl-2 inhibitor for use in AML, as well as chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). Although significant progress has been made in the treatment of AML, leukemia relapse remains to be a major cause of treatment failure.

[005] High-frequency mutations of SF3B1 or SRSF2 have been described in patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia, and acute myeloid leukemia (AML) (Papaemmanuil et al, Genomic classification and prognosis in acute myeloid

leukemia. *N Engl J Med.* 2016, 374:2209 – 2221). Splicing factor gene mutations occur in more than 50% of MDS (Mian S. A., et al Spliceosome mutations exhibit specific associations with epigenetic modifiers and proto-oncogenes mutated in myelodysplastic syndrome. *Haematologica* 2013, 98: 1058-1066) with SF3B1, SRSF2, U2AF1, and ZRSR2 as the most frequently mutated splicing factor genes in MDS. 13% of AML patients have splicing mutations (Kantarjian H, et al, Acute myeloid leukemia: current progress and future directions. *Blood Cancer J.* 2021, 11: 41) with no targeted therapies available. In addition, mutations in splicing-related genes have also been found in various solid cancers, including lung, breast, and pancreatic cancers (Dvinge H, et al RNA splicing factors as oncoproteins and tumour suppressors. *Nat Rev Cancer* 2016, 16: 413 – 430).

[006] Upregulation of pro-survival proteins MCL-1 and BCL-XL by *TP53* mutations and the expansion of FLT3-ITD confers resistance to venetoclax treatment (Xu Y, et al Progress in understanding the mechanisms of resistance to BCL-2 inhibitors. *Experimental Hematology & Oncology* 2022, 11: 31). The modulation of pre-mRNA splicing via inhibition of CLK kinases is an attractive anti-neoplastic strategy, especially for the cancers that exhibit aberrant pre-mRNA splicing.

[007] There is a significant medical need in the art for the satisfactory treatment of cancers having complex resistance mechanisms. One approach for overcoming the non-responsiveness exhibited by resistant cancers is the use of combination treatments.

SUMMARY

[008] One approach to overcoming resistance mechanisms in cancer therapies that result from alternative splicing is to combine a cancer therapeutic with a compound capable of inhibiting a regulator of pre-mRNA splicing, such as a CLK inhibitor.

[009] It has been discovered that the combination of a CLK inhibitor and at least one additional anti-cancer agent provides a robust response in cancers having alternative splicing as a mechanism of resistance.

[010] In one aspect, the disclosure provides a method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a CLK inhibitor, in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[011] In another aspect, the disclosure provides a CLK inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a

therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[012] In another aspect, the disclosure provides use of a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

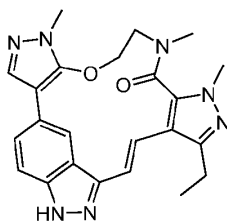
[013] In another aspect, the disclosure provides a composition comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is Bcl-2 inhibitor, a FLT3 inhibitor, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[014] In another aspect, the disclosure provides a medicament comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, combined with a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[015] In another aspect, the disclosure provides a synergistic composition of a CLK inhibitor and a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, where the two components come into contact with each other at a locus.

[016] In another aspect, the disclosure provides a synergistic composition of a CLK inhibitor and a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor, where the two components come into contact with each other only in the human body.

[017] In some embodiments of the above aspects, the CLK inhibitor is (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-13(10*H*)-one (Compound I), having the formula I



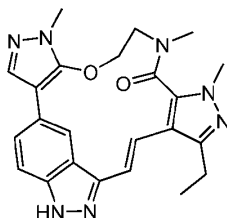
I

[018] or a pharmaceutically acceptable salt thereof. Compound I has been described in International Patent Application No. PCT/US2023/068071 (WO2023240140, published December 14, 2023), the entire contents of which is incorporated herein by reference.

[019] Additional embodiments, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as embodiments in any of the following enumerated clauses. It will be understood that any of the embodiments described herein can be used in connection with any other embodiments described herein to the extent that the embodiments do not contradict one another.

[020] 1. A method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a CLK inhibitor, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[021] 2. The method of clause 1, wherein the CLK inhibitor is of the formula I



I

[022] or a pharmaceutically acceptable salt thereof.

[023] 3. The method of clause 1 or 2, wherein the cancer is a liquid tumor or a solid tumor.

[024] 4. The method of any one of the preceding clauses, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory

myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[025] 5. The method of any one of the preceding clauses, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[026] 6. The method of any one of the preceding clauses, wherein the cancer is acute myeloid leukemia (AML).

[027] 7. The method of any one of clauses 1 to 5, wherein the cancer is chronic lymphocytic leukemia (CLL).

[028] 8. The method of any one of clauses 1 to 5, wherein the cancer is non-small cell lung cancer (NSCLC).

[029] 9. The method of any one of clauses 1 to 5, wherein the cancer is ovarian cancer.

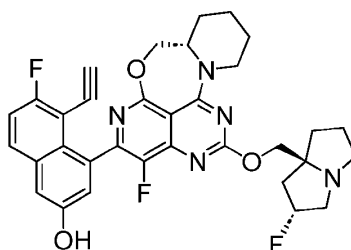
[030] 10. The method of any one of the preceding clauses, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[031] 11. The method of clause 10, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[032] 12. The method of clause 10, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[033] 13. The method of clause 10, wherein the additional anti-cancer agent is a KRAS inhibitor.

[034] 14. The method of clause 13, wherein the KRAS inhibitor is compound II having the formula



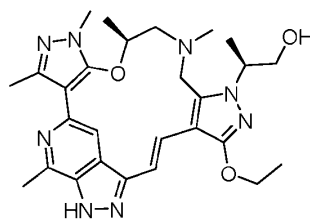
Compound II

[035] or a pharmaceutically acceptable salt thereof.

[036] 15. The method of clause 10, wherein the additional anti-cancer agent is an ALK inhibitor.

[037] 16. The method of clause 10, wherein the additional anti-cancer agent is an EGFR inhibitor.

[038] 17. The method of clause 16, wherein the EGFR inhibitor is compound III having the formula



Compound III

[039] or a pharmaceutically acceptable salt thereof.

[040] 18. The method of clause 16, wherein the EGFR inhibitor is osimertinib.

[041] 19. The method of any one of clauses 1 to 13, 15, or 16, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[042] 20. The method of any one of clauses 1 to 11, or 19, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[043] 21. The method of any one of clauses 1 to 10, 12, or 19, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[044] 22. The method of any one of clauses 1 to 10, 13, or 19, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

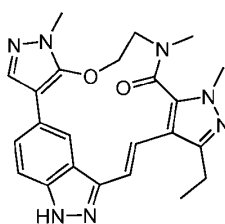
[045] 23. The method of any one of clauses 1 to 10, 13, or 19, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[046] 24. The method of any one of the preceding clauses, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[047] 25. The method of any one of the preceding clauses, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[048] 26. A CLK inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[049] 27. The compound of clause 26, wherein the CLK inhibitor is of the formula I



I

[050] or a pharmaceutically acceptable salt thereof.

[051] 28. The compound of clause 26 or 27, wherein the cancer is a liquid tumor or a solid tumor.

[052] 29. The compound of any one of clauses 26 to 28, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric

cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[053] 30. The compound of any one of clauses 26 to 29, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[054] 31. The compound of any one of clauses 26 to 30, wherein the cancer is acute myeloid leukemia (AML).

[055] 32. The compound of any one of clauses 26 to 30, wherein the cancer is chronic lymphocytic leukemia (CLL).

[056] 33. The compound of any one of clauses 26 to 30, wherein the cancer is non-small cell lung cancer (NSCLC).

[057] 34. The compound of any one of clauses 26 to 30, wherein the cancer is ovarian cancer.

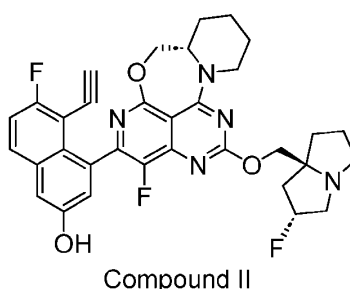
[058] 35. The compound of any one of clauses 26 to 34, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[059] 36. The compound of clause 35, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[060] 37. The compound of clause 35, wherein the additional anti-cancer agent is a FLT3 inhibitor.

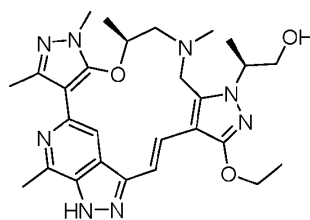
[061] 38. The compound of clause 35, wherein the additional anti-cancer agent is a KRAS inhibitor.

[062] 39. The compound of clause 38, wherein the KRAS inhibitor is compound II having the formula



[063] or a pharmaceutically acceptable salt thereof.

- [064] 40. The compound of clause 35, wherein the additional anti-cancer agent is an ALK inhibitor.
- [065] 41. The compound of clause 35, wherein the additional anti-cancer agent is an EGFR inhibitor.
- [066] 42. The compound of clause 41, wherein the EGFR inhibitor is compound III having the formula

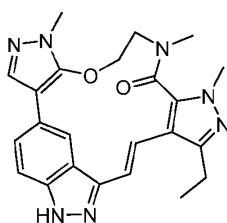


Compound III

- [067] or a pharmaceutically acceptable salt thereof.
- [068] 43. The method of clause 41, wherein the EGFR inhibitor is osimertinib.
- [069] 44. The compound of any one of clauses 26 to 38, 40, or 41, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.
- [070] 45. The compound of any one of clauses 26 to 36, or 44, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.
- [071] 46. The compound of any one of clauses 26 to 35, 37, or 44, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.
- [072] 47. The compound of any one of clauses 26 to 35, 38, or 44, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.
- [073] 48. The compound of any one of clauses 26 to 35, 38, or 44, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.
- [074] 49. The compound of any one of clauses 26 to 48, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.
- [075] 50. The compound of any one of the clauses 26 to 49, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[076] 51. Use of a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[077] 52. The use of clause 51, wherein the CLK inhibitor is of the formula I



I

[078] or a pharmaceutically acceptable salt thereof.

[079] 53. The use of clause 51 or 52, wherein the cancer is a liquid tumor or a solid tumor.

[080] 54. The use of any one of clauses 51 to 53, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[081] 55. The use of any one of clauses 51 to 54, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS),

small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[082] 56. The use of any one of clauses 51 to 55, wherein the cancer is acute myeloid leukemia (AML).

[083] 57. The use of any one of clauses 51 to 55, wherein the cancer is chronic lymphocytic leukemia (CLL).

58. The use of any one of clauses 51 to 55, wherein the cancer is non-small cell lung cancer (NSCLC).

[084] 59. The use of any one of clauses 51 to 55, wherein the cancer is ovarian cancer.

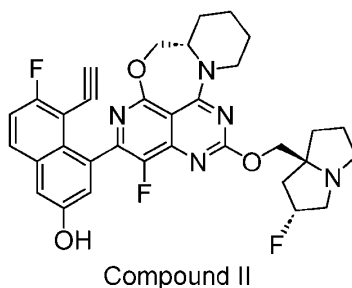
[085] 60. The use of any one of clauses 51 to 59, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[086] 61. The use of clause 60, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[087] 62. The use of clause 60, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[088] 63. The use of clause 60, wherein the additional anti-cancer agent is a KRAS inhibitor.

[089] 64. The use of clause 63, wherein the KRAS inhibitor is compound II having the formula

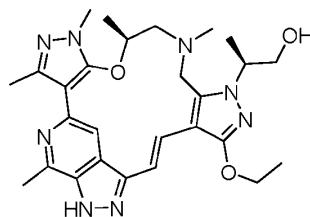


[090] or a pharmaceutically acceptable salt thereof.

[091] 65. The use of clause 60, wherein the additional anti-cancer agent is an ALK inhibitor.

[092] 66. The use of clause 60, wherein the additional anti-cancer agent is an EGFR inhibitor.

[093] 67. The use of clause 66, wherein the EGFR inhibitor is compound III having the formula



Compound III

[094] or a pharmaceutically acceptable salt thereof.

[095] 68. The use of clause 66, wherein the EGFR inhibitor is osimertinib.

[096] 69. The use of any one of clauses 51 to 63, 65, or 66, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[097] 70. The use of any one of clauses 51 to 61, or 69, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[098] 71. The use of any one of clauses 51 to 60, 62, or 69, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[099] 72. The use of any one of clauses 51 to 60, 63, or 69, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

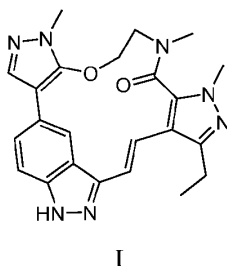
[0100] 73. The use of any one of clauses 51 to 60, 63, or 69, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[0101] 74. The use of any one of clauses 51 to 73, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[0102] 75. The use of any one of clauses 51 to 74, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[0103] 76. A composition comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0104] 77. The composition of clause 76, wherein the CLK inhibitor is of the formula I



[0105] or a pharmaceutically acceptable salt thereof.

[0106] 78. The composition of clause 76 or 77, wherein the cancer is a liquid tumor or a solid tumor.

[0107] 79. The composition of any one of clauses 76 to 78, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0108] 80. The composition of any one of clauses 76 to 79, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0109] 81. The composition of any one of clauses 76 to 80, wherein the cancer is acute myeloid leukemia (AML).

[0110] 82. The composition of any one of clauses 76 to 80, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0111] 83. The composition of any one of clauses 76 to 80, wherein the cancer is non-small cell lung cancer (NSCLC).

[0112] 84. The composition of any one of clauses 76 to 80, wherein the cancer is ovarian cancer.

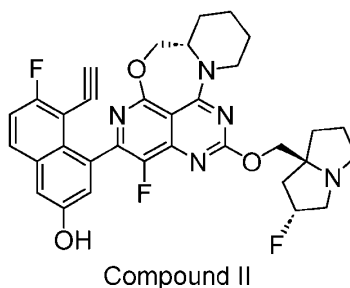
[0113] 85. The composition of any one of clauses 76 to 84, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0114] 86. The composition of clause 85, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0115] 87. The composition of clause 85, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0116] 88. The composition of clause 85, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0117] 89. The composition of clause 88, wherein the KRAS inhibitor is compound II having the formula



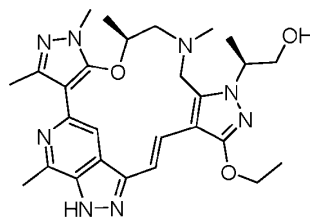
Compound II

[0118] or a pharmaceutically acceptable salt thereof.

[0119] 90. The composition of clause 85, wherein the additional anti-cancer agent is an ALK inhibitor.

[0120] 91. The composition of clause 85, wherein the additional anti-cancer agent is an EGFR inhibitor.

[0121] 92. The composition of clause 91, wherein the EGFR inhibitor is compound III having the formula



Compound III

[0122] or a pharmaceutically acceptable salt thereof.

[0123] 93. The composition of clause 91, wherein the EGFR inhibitor is osimertinib.

[0124] 94. The composition of any one of clauses 76 to 88, 90, or 91, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[0125] 95. The composition of any one of clauses 76 to 86, or 94, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0126] 96. The composition of any one of clauses 76 to 85, 87, or 94, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0127] 97. The composition of any one of clauses 76 to 85, 88, or 94, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

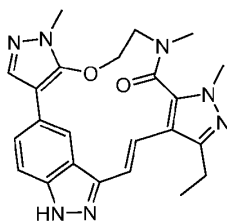
[0128] 98. The composition of any one of clauses 76 to 85, 88, or 94, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[0129] 99. The composition of any one of clauses 76 to 98, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[0130] 100. The composition of any one of clauses 76 to 99, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[0131] 101. A medicament comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, combined with at least one additional anti-cancer agent in fixed or free combination.

[0132] 102. The medicament of clause 101, wherein the CLK inhibitor is of the formula I



I

[0133] or a pharmaceutically acceptable salt thereof.

[0134] 103. The medicament of clause 101 or 102, wherein the cancer is a liquid tumor or a solid tumor.

[0135] 104. The medicament of any one of clauses 101 to 103, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0136] 105. The medicament of any one of clauses 101 to 104, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0137] 106. The medicament of any one of clauses 101 to 105, wherein the cancer is acute myeloid leukemia (AML).

[0138] 107. The medicament of any one of clauses 101 to 105, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0139] 108. The medicament of any one of clauses 101 to 105, wherein the cancer is non-small cell lung cancer (NSCLC).

[0140] 109. The medicament of any one of clauses 101 to 105, wherein the cancer is ovarian cancer.

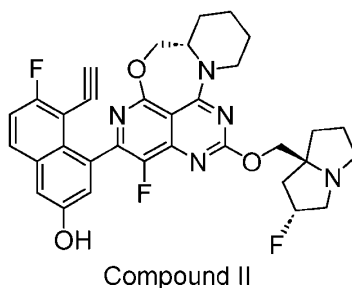
[0141] 110. The medicament of any one of clauses 101 to 109, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0142] 111. The medicament of clause 110, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0143] 112. The medicament of clause 110, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0144] 113. The medicament of clause 110, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0145] 114. The medicament of clause 113, wherein the KRAS inhibitor is compound II having the formula

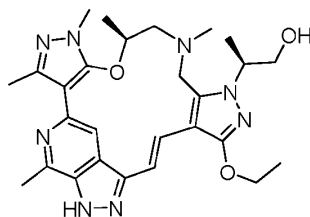


[0146] or a pharmaceutically acceptable salt thereof.

[0147] 115. The medicament of clause 110, wherein the additional anti-cancer agent is an ALK inhibitor.

[0148] 116. The medicament of clause 110, wherein the additional anti-cancer agent is an EGFR inhibitor.

[0149] 117. The medicament of clause 116, wherein the EGFR inhibitor is compound III having the formula



Compound III

[0150] or a pharmaceutically acceptable salt thereof.

[0151] 118. The medicament of clause 116, wherein the EGFR inhibitor is osimertinib.

[0152] 119. The medicament of any one of clauses 101 to 113, 115, or 116, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[0153] 120. The medicament of any one of clauses 101 to 111, or 119, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0154] 121. The medicament of any one of clauses 101 to 110, 112, or 119, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0155] 122. The medicament of any one of clauses 101 to 110, 113, or 119, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

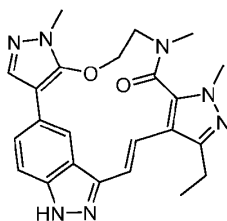
[0156] 123. The medicament of any one of clauses 101 to 110, 113, or 119, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[0157] 124. The medicament of any one of clauses 101 to 123, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[0158] 125. The medicament of any one of clauses 101 to 124, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[0159] 126. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other at a locus.

[0160] 127. The synergistic composition of clause 126, wherein the CLK inhibitor is of the formula I



I

[0161] or a pharmaceutically acceptable salt thereof.

[0162] 128. The synergistic composition of clause 126 or 127, wherein the cancer is a liquid tumor or a solid tumor.

[0163] 129. The synergistic composition of any one of clauses 126 to 128, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0164] 130. The synergistic composition of any one of clauses 126 to 129, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0165] 131. The synergistic composition of any one of clauses 126 to 130, wherein the cancer is acute myeloid leukemia (AML).

[0166] 132. The synergistic composition of any one of clauses 126 to 130, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0167] 133. The synergistic composition of any one of clauses 126 to 130, wherein the cancer is non-small cell lung cancer (NSCLC).

[0168] 134. The synergistic composition of any one of clauses 126 to 130, wherein the cancer is ovarian cancer.

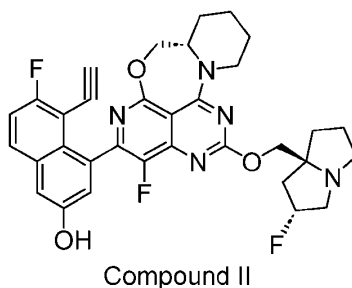
[0169] 135. The synergistic composition of any one of clauses 126 to 134, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0170] 136. The synergistic composition of clause 135, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0171] 137. The synergistic composition of clause 135, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0172] 138. The synergistic composition of clause 135, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0173] 139. The synergistic composition of clause 138, wherein the KRAS inhibitor is compound II having the formula

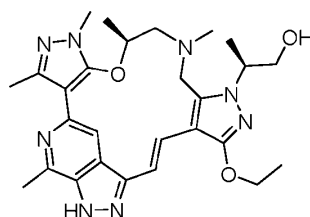


[0174] or a pharmaceutically acceptable salt thereof.

[0175] 140. The synergistic composition of clause 135, wherein the additional anti-cancer agent is an ALK inhibitor.

[0176] 141. The synergistic composition of clause 135, wherein the additional anti-cancer agent is an EGFR inhibitor.

[0177] 142. The synergistic composition of clause 141, wherein the EGFR inhibitor is compound III having the formula



Compound III

[0178] or a pharmaceutically acceptable salt thereof.

[0179] 143. The synergistic composition of clause 141, wherein the EGFR inhibitor is osimertinib.

[0180] 144. The synergistic composition of any one of clauses 126 to 138, 140, or 141, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[0181] 145. The synergistic composition of any one of clauses 126 to 136, or 144, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0182] 146. The synergistic composition of any one of clauses 126 to 135, 137, or 144, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0183] 147. The synergistic composition of any one of clauses 126 to 135, 138, or 144, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

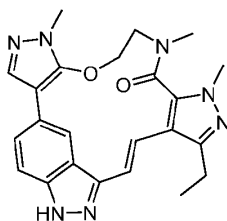
[0184] 148. The synergistic composition of any one of clauses 126 to 135, 138, or 144, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[0185] 149. The synergistic composition of any one of clauses 126 to 148, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[0186] 150. The synergistic composition of any one of clauses 126 to 149, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

[0187] 151. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other only in the human body.

[0188] 152. The synergistic composition of clause 151, wherein the CLK inhibitor is of the formula I



I

[0189] or a pharmaceutically acceptable salt thereof.

[0190] 153. The synergistic composition of clause 151 or 152, wherein the cancer is a liquid tumor or a solid tumor.

[0191] 154. The synergistic composition of any one of clauses 151 to 153, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0192] 155. The synergistic composition of any one of clauses 151 to 154, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0193] 156. The synergistic composition of any one of clauses 151 to 155, wherein the cancer is acute myeloid leukemia (AML).

[0194] 157. The synergistic composition of any one of clauses 151 to 155, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0195] 158. The synergistic composition of any one of clauses 151 to 155, wherein the cancer is non-small cell lung cancer (NSCLC).

[0196] 159. The synergistic composition of any one of clauses 151 to 155, wherein the cancer is ovarian cancer.

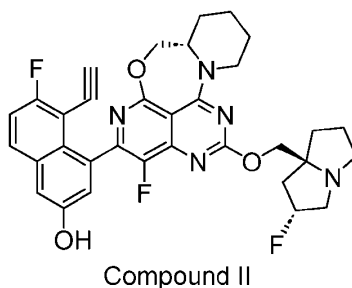
[0197] 160. The synergistic composition of any one of clauses 151 to 159, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0198] 161. The synergistic composition of clause 160, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0199] 162. The synergistic composition of clause 160, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0200] 163. The synergistic composition of clause 160, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0201] 164. The synergistic composition of clause 163, wherein the KRAS inhibitor is compound II having the formula



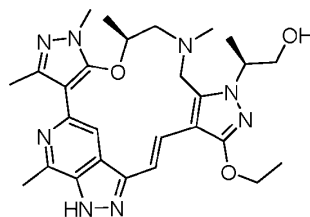
Compound II

[0202] or a pharmaceutically acceptable salt thereof.

[0203] 165. The synergistic composition of clause 160, wherein the additional anti-cancer agent is an ALK inhibitor.

[0204] 166. The synergistic composition of clause 160, wherein the additional anti-cancer agent is an EGFR inhibitor.

[0205] 167. The synergistic composition of clause 166, wherein the EGFR inhibitor is compound III having the formula



Compound III

[0206] or a pharmaceutically acceptable salt thereof.

[0207] 168. The synergistic composition of clause 166, wherein the EGFR inhibitor is osimertinib.

[0208] 169. The synergistic composition of any one of clauses 151 to 163, 165, or 166, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

[0209] 170. The synergistic composition of any one of clauses 151 to 161, or 169, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0210] 171. The synergistic composition of any one of clauses 151 to 160, 162, or 169, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0211] 172. The synergistic composition of any one of clauses 151 to 160, 163, or 169, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0212] 173. The synergistic composition of any one of clauses 151 to 160, 163, or 169, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

[0213] 174. The synergistic composition of any one of clauses 151 to 173, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

[0214] 175. The synergistic composition of any one of clauses 151 to 174, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line

BRIEF DESCRIPTION OF THE DRAWINGS

[0215] FIG. 1 is a graph showing the HSA synergy map for the combination of Compound I with venetoclax in an in vitro proliferation assay matrix combination study in AML cell line

MOLM13. Representative synergistic area score (dark area) at various concentrations of Compound I and venetoclax are shown in Table 1.

[0216] FIG. 2 is a graph showing the HSA synergy map for the combination of Compound I with AMG-510 in an in vitro proliferation assay matrix combination study in NSCLC cell line H358. Representative synergistic area score (dark area) at various concentrations of Compound I and AMG-510 are shown in Table 2.

[0217] FIGs. 3a, b are charts showing the in vivo effect of the combination of Compound I and gilteritinib in a MOLM-13 CDX tumor model. (●) vehicle; (▲) gilteritinib dosed at 25mg/kg QD; (○) Compound I dosed at 25 mg/kg MWF; (▼) Compound I dosed at 25 mg/kg MWF + gilteritinib dosed at 25 mg/kg QD; (□) Compound I dosed at 25 mg/kg QD; (■) Compound I dosed at 25 mg/kg QD + gilteritinib dosed at 25 mg/kg QD. (FIG. 3a) Anti-tumor activity; (FIG. 3b) Body weight.

[0218] FIGs. 4a, b are charts showing the in vivo effect of the combination of Compound I with venetoclax in a MOLM-13 CDX tumor model. (●) vehicle; (▲) venetoclax dosed at 100mg/kg QD; (▼) Compound I dosed at 25 mg/kg MWF; (■) Compound I dosed at 25 mg/kg MWF + venetoclax dosed at 100 mg/kg QD; (◆) Compound I dosed at 25 mg/kg QW + venetoclax dosed at 100 mg/kg QD. (FIG. 4a) Anti-tumor activity; (FIG. 4b) Body weight.

[0219] FIG. 5 is a graph showing the results of 3D spheroid growth assay as measured by brightfield object total area of SW480 cell line treated with DMSO, Compound I, Compound II, or a combination of Compound I and Compound II. (●) DMSO; (■) Compound I dosed at 62 nM; (▲) Compound II dosed at 37 nM; (▼) Compound I dosed at 62 nM + Compound II dosed at 37 nM.

[0220] FIG. 6 is a graph showing the HSA synergy map highlights the synergistic dose regions of Compound I and Compound II in matrix combination study in CRC cell line SW480. Representative synergistic area score (dark area) at various concentrations of Compound I and Compound II are shown in Table 3.

[0221] FIG. 7 is a graph showing proliferation as measured by phase object confluence of H1975 cell line treated with DMSO, Compound I, Compound III, or a combination of Compound I and Compound III. (●) DMSO; (■) Compound III dosed at 11 nM; (▲) Compound I dosed at 50 nM; (▼) Compound I dosed at 50 nM + Compound III dosed at 11 nM.

[0222] FIG. 8 is a graph showing proliferation as measured by phase object confluence of H1975 cell line treated with DMSO, Compound I, Osimertinib, or a combination of Compound I and Osimertinib. (●) DMSO; (■) Osimertinib dosed at 11 nM; (▲) Compound I dosed at 50 nM; (▼) Compound I dosed at 50 nM + Osimertinib dosed at 11 nM.

[0223] FIG. 9 is a graph showing the HSA synergy map highlights the synergistic dose regions of Compound I and MRTX1133 in matrix combination study in PDAC cell line Suit-2. Representative synergistic area score (dark area) at various concentrations of Compound I and MRTX1133 are shown in Table 4.

[0224] FIG. 10 is a graph showing the HSA synergy map highlights the synergistic dose regions of Compound I and MRTX1133 in matrix combination study in CRC cell line GP2D. Representative synergistic area score (dark area) at various concentrations of Compound I and MRTX1133 are shown in Table 5.

[0225] FIG. 11 is a graph showing the HSA synergy map highlights the synergistic dose regions of Compound I and adagrsib in matrix combination study in CRC cell line SW1463. Representative synergistic area score (dark area) at various concentrations of Compound I and adagrsib are shown in Table 6.

[0226] FIGs. 12a, b are charts showing the in vivo effect of the combination of Compound I with venetoclax in MOLM-13 CDX tumor model following pretreatment of venetoclax for 16 days. (■) venetoclax dosed at 100 mg/kg QD + Compound I dosed at 25 mg/kg MWF; (○) venetoclax dosed at 100 mg/kg QD + Compound I dosed at 25 mg/kg QW; (▲) venetoclax dosed at 100 mg/kg QD + gilteritinib dosed at 25 mg/kg QD. (FIG. 12a) Anti-tumor activity; (FIG. 12b) Body weight.

[0227] FIGs. 13a, b are charts showing the in vivo effect of the combination of Compound I with azacitidine in the MOLM-13 CDX tumor model. (●) vehicle; (▲) Compound I dosed at 25 mg/kg QD; (▼) azacitidine dosed at 5mg/kg IP QDx7; (■) Compound I dosed at 25 mg/kg QD + azacitidine dosed at 5mg/kg IP QDx7 with concurrent treatment; (◆) azacitidine dosed at 5mg/kg IP QDx7 followed by Compound I dosed at 25 mg/kg QD. (FIG. 13 a) Anti-tumor activity; (FIG. 13b) Body weight.

[0228] FIGs. 14a, b are charts showing the in vivo effect of the combination of Compound I with carboplatin in the OVCAR3 CDX tumor model. (●) vehicle; (▼) Compound I 25 mg/kg QD; (▲) carboplatin 50mg/kg IP QW; (■) Compound I 25 mg/kg QD + carboplatin 50mg/kg IP QW. (FIG. 14a) Anti-tumor activity; (FIG. 14b) Body weight.

[0229] FIGs. 15a, b are charts showing the in vivo effect of the combination of Compound I with osimertinib in the H1975 CDX tumor model. (●) vehicle; (□) Compound I 25 mg/kg QD; (▲) osimertinib 1 mg/kg QD; (■) Compound I 25 mg/kg QD + osimertinib 1 mg/kg QD. (FIG. 15a) Anti-tumor activity; (FIG. 15b) Body weight.

[0230] FIGs. 16a, b, and c are charts showing the in vivo effect of the combination of Compound I with adagrasib in the SW1463 CDX tumor model. (●) vehicle; (□) Compound I 25 mg/kg QD;

(▲) adagrasib 30 mg/kg QD; (■) Compound I 25 mg/kg QD + adagrasib 30 mg/kg QD. (FIG. 16a) Anti-tumor activity; (FIG. 16b) Survival analysis; (FIG. 16c) Body weight.

[0231] FIGs. 17a, b are charts showing the in vivo effect of the combination of Compound I with cytarabine in the MOLM-13 CDX tumor model. (●) vehicle; (▲) Compound I 25 mg/kg QD; (▼) cytarabine 50 mg/kg QD x7; (■) Compound I 25 mg/kg QD + cytarabine 50 mg/kg QD x 7. (FIG. 17a) Anti-tumor activity; (FIG. 17b) Body weight.

DETAILED DESCRIPTION

[0232] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0233] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entireties. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is herein incorporated by reference, the definition set forth in this section prevails over the definition incorporated herein by reference.

[0234] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0235] As used herein, the terms “including,” “containing,” and “comprising” are used in their open, non-limiting sense.

[0236] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that, whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to

the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

[0237] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0238] Except as otherwise noted, the methods and techniques of the present embodiments are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Loudon, *Organic Chemistry*, Fourth Edition, New York: Oxford University Press, 2002, pp. 360-361, 1084-1085; Smith and March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fifth Edition, Wiley-Interscience, 2001.

[0239] Chemical nomenclature for compounds described herein can be derived using commercially-available software such as ACD/Name 2014 (ACD/Labs) or ChemBioDraw Ultra 13.0 (Perkin Elmer).

[0240] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

[0241] As used herein, the term "therapeutically effective amount" refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a patient, which includes alleviation of the symptoms of the disease or disorder being treated. In one aspect, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors. An exemplary dose is in the range of about from about 0.1 mg to 1.5 g daily, about 0.1 mg to 1 g

daily, or about 1 mg to 50 mg daily, or about 50 to 250 mg daily, or about 250 mg to 1 g daily. The total dosage may be given in single or divided dosage units (e.g., QD, QW, BID, TID, QID).

[0242] A “patient,” “subject,” “host animal,” or “individual” are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

[0243] “Administering” or “administration of” a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0244] Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g., solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

[0245] As used herein, the term “cancer” includes both solid and liquid tumors, where liquid tumors can be cancers of blood cells, bone marrow, or the lymphatic system, and the term cancer includes, but is not limited to, acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma,

head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer. It will be appreciated that the term “cancer” includes both primary cancers or primary tumors and metastatic cancers or metastatic tumors. For example, metastatic NSCLC, metastatic CRC, metastatic pancreatic cancer, metastatic HER2-overexpressing breast cancer, metastatic EGFR-expressing colorectal carcinoma, metastatic HNSCC, and the like. It will be appreciated that the term “cancer” includes cancers that involve the upregulation of certain genes or genetic mutations in certain genes that can lead to disease progression, such up-regulation of epidermal growth factor receptor.

[0246] As used herein, “independently” means that the subsequently described event or circumstance is to be read on its own relative to other similar events or circumstances. For example, in a circumstance where several equivalent hydrogen groups are optionally substituted by another group described in the circumstance, the use of “independently optionally” means that each instance of a hydrogen atom on the group may be substituted by another group, where the groups replacing each of the hydrogen atoms may be the same or different. Or for example, where multiple groups exist all of which can be selected from a set of possibilities, the use of “independently” means that each of the groups can be selected from the set of possibilities separate from any other group, and the groups selected in the circumstance may be the same or different.

[0247] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which counter ions which may be used in pharmaceuticals. See, generally, S.M. Berge, et al., “Pharmaceutical Salts,” J. Pharm. Sci., 1977, 66, 1-19. Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. A compound described herein may possess a sufficiently acidic group, a sufficiently basic group, both types of functional groups, or more than one of each type, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Such salts include:

[0248] (1) acid addition salts, which can be obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as

acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methane sulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like; or

[0249] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, trimethamine, N-methylglucamine, and the like.

[0250] Pharmaceutically acceptable salts are well known to those skilled in the art, and any such pharmaceutically acceptable salt may be contemplated in connection with the embodiments described herein. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

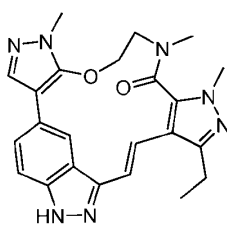
Embodiments

[0251] In some embodiments, the methods described herein relate to the treatment of cancer comprising administering to a patient in need of treatment a therapeutically effective amount of a CLK inhibitor in combination with an additional anti-cancer agent. In some embodiments, additional anti-cancer agents include Bcl-2 inhibitors, an additional anti-cancer agent, a KRAS inhibitor, a FLT3 inhibitor, and the like. In some embodiments, additional anti-cancer agents include a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor. It will be appreciated that an inhibitor is any substance that reduces or suppresses the activity of another substance, such as a cell surface receptor (i.e., a receptor tyrosine kinase), or a kinase (i.e., a non-receptor tyrosine kinase). The definition of an "inhibitor" is well known to one of skill in the art, and the use herein of the general term "inhibitor" is understood to be the usual and customary meaning. It will be appreciated that "a

CLK inhibitor” is a compound that can have affinity for any one or more of the biological targets CLK1, CLK2, CLK3, or CLK4.

[0252] It has been discovered that a compound described herein is an inhibitor of CLK and can be used in combination with an additional anti-cancer agent to treat cancer in a patient in need of such treatment. In some embodiments, the combination of a CLK inhibitor with an additional anti-cancer agent, such as a Bcl-2 inhibitor, an EGFR inhibitor, a KRAS inhibitor, a FLT3 inhibitor, and the like, can provide a synergistic response in a patient in need of treatment for cancer. In some embodiments, the combination of a CLK inhibitor with an additional anti-cancer agent, such as a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, a chemotherapy (e.g., platinum therapy), an EGFR inhibitor, and the like, can provide a synergistic response in a patient in need of treatment for cancer. In some embodiments, methods for treating cancer comprising administering a combination of a therapeutically effective amount of a CLK inhibitor and a therapeutically effective amount of an additional anti-cancer agent. In some embodiments, the CLK inhibitor and the additional anti-cancer agent are co-formulated. In some embodiments, the CLK inhibitor and the additional anti-cancer agent are administered at the same time. In some embodiments, the CLK inhibitor and the additional anti-cancer agent are individually formulated, and administered at the same time. In some embodiments, the CLK inhibitor and the additional anti-cancer agent are individually formulated, and administered in sequence. In some embodiments, the sequential administration of the CLK inhibitor and the additional anti-cancer agent can be accomplished with the CLK inhibitor administered first, and the additional anti-cancer agent administered second. In some embodiments, the sequential administration of the CLK inhibitor and the additional anti-cancer agent can be accomplished with additional anti-cancer agent administered first, and the CLK inhibitor administered second.

[0253] In some embodiments, the CLK inhibitor is of the formula I



I

[0254] or a pharmaceutically acceptable salt thereof. Compound I has been described in International Patent Application No. PCT/US2023/068071 (WO2023240140, published December 14, 2023), the entire contents of which is incorporated herein by reference.

[0255] It will be appreciated that the cancer can be a liquid or solid tumor cancer, such as acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer. In some embodiments, the cancer can be a liquid tumor, such as a hematologic cancer, a bone marrow cancer, or a lymphatic system cancer. In some embodiments, the cancer can be a solid tumor, such as NSCLC, breast cancer, colon cancer, and the like.

[0256] In some embodiments, the present disclosure provides methods of treating disease in a patient that has received a prior treatment with one or more therapeutic agents. In some embodiments, the patient has been previously treated with one or more anti-cancer agents. In still other embodiments, the patient has been previously treated with one or more anti-cancer agents and developed an acquired resistance to the treatment. In still other embodiments, the patient has been previously treated with one or more anti-cancer agents and developed resistance to the treatment. In still other embodiments, the patient has been previously treated with one or more anti-cancer agents and developed resistance to the treatment regulated by Bcl-2, FLT3, KRAS, EGFR, and the like. In still other embodiments, the patient has been previously treated with one or more anti-cancer agents and developed resistance to the treatment regulated by Bcl-2, FLT3, KRAS, ALK, PARP, EGFR, and the like.

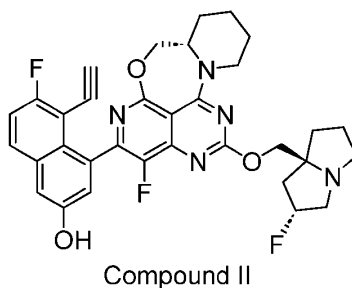
[0257] Other anti-cancer agents which the patient may be treated with prior to treatment with one or more of the compounds described herein include but are not limited to kinase inhibitors, adrenocorticoids and corticosteroids, alkylating agents, peptide and peptidomimetic signal transduction inhibitors, antiandrogens, antiestrogens, androgens, aclamycin and aclamycin

derivatives, estrogens, antimetabolites, platinum compounds, amanitins, plant alkaloids, mitomycins, discodermolides, microtubule inhibitors, epothilones, inflammatory and proinflammatory agents, purine analogs, pyrimidine analogs, camptothecins and dolastatins.

[0258] It will be appreciated that the additional anti-cancer agent for use in connection with the combination therapy described herein can be any additional anti-cancer agent as defined herein. Suitable examples of additional anti-cancer agents include a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor. Suitable examples of additional anti-cancer agents include a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, a chemotherapy (e.g., a platinum-based therapy such as carboplatin or cytarabine), or an EGFR inhibitor. In some embodiments, the additional anti-cancer agent can be a compound, such as venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof. In some embodiments, the additional anti-cancer agent used with the CLK inhibitor (e.g., Compound I) is venetoclax, gilteritinib, Compound II, Compound III, MRTX1133, adagrasib, osimertinib, azacitidine, carboplatin, or cytarabine or pharmaceutically acceptable salts thereof. In some embodiments, the additional anti-cancer agent used with the CLK inhibitor (e.g., Compound I) is venetoclax, gilteritinib, adagrasib, osimertinib, azacitidine, carboplatin, or cytarabine or pharmaceutically acceptable salts thereof.

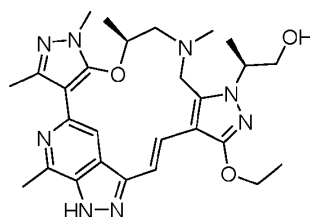
[0259] In some embodiments, the additional anti-cancer agent is a chemotherapy. Chemotherapies include chemical substances such as doxorubicin, 5-Fluorouracil, cytosine arabinoside, cyclophosphamide, thiotepa, busulfan, cytoxin, taxol, methotrexate, cisplatin, melphalan, vinblastine, cytarabine, and carboplatin. Preparation and dosing schedules for such chemotherapeutic agents can be determined according to manufacturers' instructions.

[0260] In some embodiments, the additional anti-cancer agent is a KRAS inhibitor. An example of a KRAS inhibitor for use in combination with a CLK inhibitor as described herein, includes Compound II,



[0261] or a pharmaceutically acceptable salt thereof. Compound II has been described in International Patent Application No. PCT/US2023/027125 (WO2024015262, published January 18, 2024), the entire contents of which is incorporated herein by reference.

[0262] In some embodiments, the additional anti-cancer agent is an EGFR inhibitor. An example of an EGFR inhibitor for use in combination with a CLK inhibitor as described herein, includes Compound III,



Compound III

[0263] or a pharmaceutically acceptable salt thereof. Compound III has been described in International Patent Application No. PCT/US2024/027195, the entire contents of which is incorporated herein by reference.

[0264] In some embodiments, the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent is synergistic. In certain embodiments, the synergism of the combination is determined using a cell proliferation assay in a cancerous cell line (e.g., a cancer cell line such as MOLM13 cells, H358 cells, SW480 cells, Suit-2 cells, GP2D cells, or SW1463 cells). The synergism score may be called an HSA score and have a value of at least about 10, at least about 11, at least about 15, at least about 20, or at least about 25. In some embodiments, the synergism score may be called an HSA score and be in a range of about 10 to about 50, about 10 to about 40, about 10 to about 35, or about 15 to about 35. The synergism score (e.g., the HSA score) may be determined as described in Example 1, 2, 4, 6, 7, or 8, or other known methods in the art.

[0265] In some embodiments, a particular concentration of the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent is synergistic. The particular concentration of the CLK inhibitor may be in a range of about 0.05 nM to about 50 nM, about 0.1 nM to about 50 nM, about 0.05 nM to about 30 nM, about 0.1 nM to about 30 nM, about 1 nM to about 1000 nM, about 1 nM to about 800 nM, about 1 nM to about 300 nM, about 1 nM to about 250 nM, about 2 nM to about 1000 nM, about 2 nM to about 800 nM, about 2 nM to about 300 nM, or about 2 nM to about 250 nM to provide synergism in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0266] In some embodiments, the combinations described herein contain a particular ratio (e.g., a molar ratio) of the concentrations of the CLK inhibitor to the at least one additional anti-cancer agent that is synergistic.

[0267] In certain embodiments, the molar ratio of Compound I to venetoclax is in a range of about 50:1 to about 1:10,000, about 10:1 to about 1:1000, about 5:1 to about 1:100, about 1:1 to about 1:50, or about 1:2 to about 1:20 to provide synergism. For example, the molar ratio of Compound I to venetoclax may be about 1:4 or about 1:10.

[0268] In certain embodiments, the molar ratio of Compound I to AMG510 is in a range of about 1000:1 to about 1:20, about 100:1 to about 1:10, about 50:1 to about 1:1, or about 20:1 to about 2:1 to provide synergism. For example, the molar ratio of Compound I to AMG510 may be about 5:1 or about 10:1.

[0269] In certain embodiments, the molar ratio of Compound I to Compound II is in a range of about 1000:1 to about 1:1000, about 100:1 to about 1:100, about 50:1 to about 1:50, about 20:1 to about 1:10, or about 10:1 to about 1:5 to provide synergism. For example, the molar ratio of Compound I to Compound II may be about 1:2 or about 6:1.

[0270] In certain embodiments, the molar ratio of Compound I to MRTX-1133 is in a range of about 1000:1 to about 1:20, about 100:1 to about 1:10, about 50:1 to about 1:1, or about 20:1 to about 2:1 to provide synergism. For example, the molar ratio of Compound I to MRTX-1133 may be about 5:1, about 10:1, or about 15:1.

[0271] In certain embodiments, the molar ratio of Compound I to adagrasib is in a range of about 1000:1 to about 1:20, about 100:1 to about 1:10, about 50:1 to about 1:1, or about 20:1 to about 2:1 to provide synergism. For example, the molar ratio of Compound I to adagrasib may be about 10:1 or about 15:1.

[0272] In some embodiments, a particular concentration of the CLK inhibitor in combination with a particular concentration of at least one additional anti-cancer agent is administered to the host animal. For example, the host animal may be a human. In certain embodiments, the total daily administration of Compound I can be achieved by any of the dosing schedules provided herein. In certain embodiments, the total daily dose of Compound I present in the combination with at least one additional anti-cancer agent is in a range of about 10 mg to about 500 mg per day, about 25 mg to about 250 mg per day, about 50 mg to about 200 mg per day, or about 100 mg to about 150 mg per day in a human. Administration of Compound I can be performed according to any of the dosing schedules described herein.

[0273] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of gilteritinib in a range of about 0.1 mg/kg to about 10 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg

in combination with a concentration of gilteritinib in a range of about 1 mg/kg to about 5 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of gilteritinib in a range of about 1 mg/kg to about 3 mg/kg may be administered to a human, for example to treat AML. Dosing and dosing schedules for gilteritinib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and gilteritinib can be achieved by any of the dosing schedules provided herein.

[0274] In certain embodiments, Compound I is administered in combination with a total daily dose of gilteritinib in a range of about 10 mg to about 500 mg per day, about 25 mg to about 250 mg per day, about 50 mg to about 200 mg per day, or about 100 mg to about 150 mg per day of gilteritinib in a human, for example to treat AML. Dosing and dosing schedules for gilteritinib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and gilteritinib can be achieved by any of the dosing schedules provided herein.

[0275] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of venetoclax in a range of about 0.1 mg/kg to about 10 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of venetoclax in a range of about 5 mg/kg to about 10 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of venetoclax in a range of about 7 mg/kg to about 9 mg/kg may be administered to a human, for example to treat CLL or SLL. Dosing and dosing schedules for venetoclax can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and venetoclax can be achieved by any of the dosing schedules provided herein.

[0276] In certain embodiments, Compound I is administered in combination with a total daily dose of venetoclax in a range of about 10 mg to about 750 mg per day, about 20 mg to about 600 mg per day, about 100 mg to about 500 mg per day, about 200 mg to about 500 mg per day, or about 300 mg to about 500 mg per day of venetoclax in a human, for example to treat CLL or SLL. Dosing and dosing schedules for venetoclax can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and venetoclax can be achieved by any of the dosing schedules provided herein.

[0277] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of azacitidine in a range of about 0.1 mg/kg to about 10 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of azacitidine in a range of about 0.1 mg/kg to about 5 mg/kg,

or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of azacitidine in a range of about 0.2 mg/kg to about 2 mg/kg may be administered to a human, for example to treat AML. Dosing and dosing schedules for azacitidine can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and azacitidine can be achieved by any of the dosing schedules provided herein.

[0278] In certain embodiments, Compound I is administered in combination with a total daily dose of azacitidine in a range of about 1 mg to about 400 mg per day, about 1 mg to about 300 mg per day, about 1 mg to about 200 mg per day, about 10 mg to about 200 mg per day, about 1 mg to about 100 mg per day, about 5 mg to about 100 mg per day, about 10 mg to about 100 mg per day, or about 10 mg to about 50 mg per day of azacitidine in a human, for example to treat AML. Dosing and dosing schedules for azacitidine can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and azacitidine can be achieved by any of the dosing schedules provided herein.

[0279] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of carboplatin in a range of about 0.1 mg/kg to about 15 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of carboplatin in a range of about 1 mg/kg to about 10 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of carboplatin in a range of about 3 mg/kg to about 7 mg/kg may be administered to a human, for example to treat ovarian cancer. Dosing and dosing schedules for carboplatin can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and carboplatin can be achieved by any of the dosing schedules provided herein.

[0280] In certain embodiments, Compound I is administered in combination with a total dose of carboplatin in a range of about 10 mg to about 800 mg per day, about 25 mg to about 700 mg per administration, about 50 mg to about 600 mg per administration, about 100 mg to about 600 mg per administration, about 200 mg to about 600 mg per administration, about 100 mg to about 500 mg per administration, about 200 mg to about 500 mg per administration, or about 200 mg to about 400 mg per administration of carboplatin in a human, for example to treat ovarian cancer. Dosing and dosing schedules for carboplatin can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and carboplatin can be achieved by any of the dosing schedules provided herein.

[0281] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of osimertinib in a range of about 0.01 mg/kg

to about 5 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of osimertinib in a range of about 0.01 mg/kg to about 2 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of osimertinib in a range of about 0.05 mg/kg to about 0.5 mg/kg may be administered to a human, for example to treat non-small cell lung cancer (NSCLC). Dosing and dosing schedules for osimertinib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and osimertinib can be achieved by any of the dosing schedules provided herein.

[0282] In certain embodiments, Compound I is administered in combination with a total daily dose of osimertinib in a range of about 0.1 mg to about 200 mg per day, about 0.1 mg to about 150 mg per day, about 1 mg to about 100 mg per day, about 5 mg to about 100 mg per day, about 10 mg to about 100 mg per day, about 1 mg to about 50 mg per day, or about 1 mg to about 25 mg per day of osimertinib in a human, for example to treat non-small cell lung cancer (NSCLC). Dosing and dosing schedules for osimertinib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and osimertinib can be achieved by any of the dosing schedules provided herein.

[0283] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of adagrasib in a range of about 1 mg/kg to about 25 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of adagrasib in a range of about 1 mg/kg to about 10 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of adagrasib in a range of about 1 mg/kg to about 5 mg/kg may be administered to a human, for example to treat non-small cell lung cancer (NSCLC). Dosing and dosing schedules for adagrasib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and adagrasib can be achieved by any of the dosing schedules provided herein.

[0284] In certain embodiments, Compound I is administered in combination with a total daily dose of adagrasib in a range of about 10 mg to about 1.5 g per day, about 100 mg to about 1.5 g per day, about 10 mg to about 1 g per day, about 100 mg to about 1 g per day, about 25 mg to about 800 mg per day, about 100 mg to about 600 mg per day, about 100 mg to about 500 mg per day, or about 100 mg to about 300 mg per day of adagrasib in a human, for example to treat non-small cell lung cancer (NSCLC). Dosing and dosing schedules for adagrasib can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and adagrasib can be achieved by any of the dosing schedules provided herein.

[0285] In certain embodiments, a concentration of Compound I in a range of about 0.1 mg/kg to about 10 mg/kg in combination with a concentration of cytarabine in a range of about 0.1 mg/kg to about 10 mg/kg, a concentration of Compound I in a range of about 1 mg/kg to about 5 mg/kg in combination with a concentration of cytarabine in a range of about 1 mg/kg to about 8 mg/kg, or a concentration of Compound I in a range of about 1 mg/kg to about 3 mg/kg in combination with a concentration of cytarabine in a range of about 2 mg/kg to about 5 mg/kg may be administered to a human, for example to treat leukemias and lymphomas. Dosing and dosing schedules for cytarabine can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and cytarabine can be achieved by any of the dosing schedules provided herein.

[0286] In certain embodiments, Compound I is administered in combination with a total dose of cytarabine in a range of about 1 mg to about 500 mg per administration, about 50 mg to about 500 mg per administration, about 100 mg to about 500 mg per administration, about 10 mg to about 400 mg per administration, about 50 mg to about 400 mg per administration, about 100 mg to about 400 mg per administration, about 50 mg to about 300 mg per administration, about 100 mg to about 300 mg per administration, or about 150 mg to about 300 mg per administration of cytarabine in a human, for example to treat leukemias and lymphomas. Dosing and dosing schedules for cytarabine can be according to manufacturers' instructions or as described herein. In certain embodiments, the total daily administration of Compound I and cytarabine can be achieved by any of the dosing schedules provided herein.

Pharmaceutical Compositions

[0287] For treatment purposes, pharmaceutical compositions comprising the compounds described herein may further comprise one or more pharmaceutically-acceptable excipients. A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In preferred embodiments, pharmaceutical compositions according to the invention are sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art.

[0288] Sterile compositions are also contemplated by the invention, including compositions that are in accord with national and local regulations governing such compositions.

[0289] The pharmaceutical compositions and compounds described herein may be formulated as solutions, emulsions, suspensions, or dispersions in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. Pharmaceutical compositions of the invention may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. Preferably, the compositions are formulated for intravenous or oral administration.

[0290] For oral administration, the compounds the invention may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds of the invention may be formulated to yield a dosage of, *e.g.*, from about 0.1 mg to 1 g daily, or about 1 mg to 50 mg daily, or about 50 to 250 mg daily, or about 250 mg to 1 g daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0291] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil, such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0292] Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, *e.g.*, oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or

propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[0293] For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the agents of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampoules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 $\mu\text{g/kg/minute}$ of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

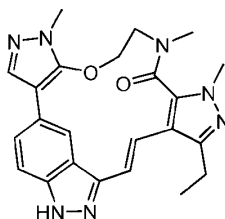
[0294] For nasal, inhaled, or oral administration, the inventive pharmaceutical compositions may be administered using, for example, a spray formulation also containing a suitable carrier. The inventive compositions may be formulated for rectal administration as a suppository.

[0295] For topical applications, the compounds of the present invention are preferably formulated as creams or ointments or a similar vehicle suitable for topical administration. For topical administration, the inventive compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the agents of the invention may utilize a patch formulation to effect transdermal delivery.

Alternative Embodiments

[0296] 1. A method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a CLK inhibitor, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0297] 2. The method of embodiment 1, wherein the CLK inhibitor is of the formula I



I

[0298] or a pharmaceutically acceptable salt thereof.

[0299] 3. The method of embodiment 1 or 2, wherein the cancer is a liquid tumor or a solid tumor.

[0300] 4. The method of any one of the preceding embodiments, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0301] 5. The method of any one of the preceding embodiments, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0302] 6. The method of any one of the preceding embodiments, wherein the cancer is acute myeloid leukemia (AML).

[0303] 7. The method of any one of embodiments 1 to 5, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0304] 8. The method of any one of embodiments 1 to 5, wherein the cancer is non-small cell lung cancer (NSCLC).

[0305] 9. The method of any one of embodiments 1 to 5, wherein the cancer is ovarian cancer.

[0306] 10. The method of any one of the preceding embodiments, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0307] 11. The method of embodiment 10, wherein the additional anti-cancer agent is a Bcl-

2 inhibitor.

[0308] 12. The method of embodiment 10, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0309] 13. The method of embodiment 10, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0310] 14. The method of embodiment 10, wherein the additional anti-cancer agent is an ALK inhibitor.

[0311] 15. The method of any one of the preceding embodiments, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

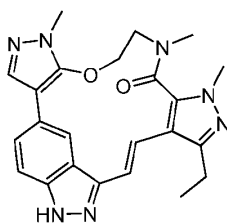
[0312] 16. The method of any one of embodiments 1 to 11, or 15, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0313] 17. The method of any one of embodiments 1 to 10, 12, or 15, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0314] 18. The method of any one of embodiments 1 to 10, 13, or 15, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0315] 19. A CLK inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0316] 20. The compound of embodiment 19, wherein the CLK inhibitor is of the formula I



I

[0317] or a pharmaceutically acceptable salt thereof.

[0318] 21. The compound of embodiment 19 or 20, wherein the cancer is a liquid tumor or a solid tumor.

[0319] 22. The compound of any one of embodiments 19 to 21, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-

small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CMML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0320] 23. The compound of any one of embodiments 19 to 22, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0321] 24. The compound of any one of embodiments 19 to 23, wherein the cancer is acute myeloid leukemia (AML).

[0322] 25. The compound of any one of embodiments 19 to 23, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0323] 26. The compound of any one of embodiments 19 to 23, wherein the cancer is non-small cell lung cancer (NSCLC).

[0324] 27. The compound of any one of embodiments 19 to 23, wherein the cancer is ovarian cancer.

[0325] 28. The compound of any one of embodiments 19 to 27, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0326] 29. The compound of embodiment 28, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0327] 30. The compound of embodiment 28, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0328] 31. The compound of embodiment 28, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0329] 32. The compound of embodiment 28, wherein the additional anti-cancer agent is an ALK inhibitor.

[0330] 33. The compound of any one of embodiments 19 to 32, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

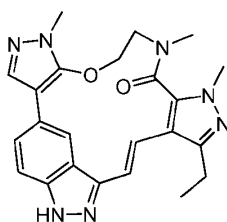
[0331] 34. The compound of any one of embodiments 19 to 29, or 33, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0332] 35. The compound of any one of embodiments 19 to 28, 30, or 33, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0333] 36. The compound of any one of embodiments 19 to 28, 31, or 33, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0334] 37. Use of a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0335] 38. The use of embodiment 37, wherein the CLK inhibitor is of the formula I



I

[0336] or a pharmaceutically acceptable salt thereof.

[0337] 39. The use of embodiment 37 or 38, wherein the cancer is a liquid tumor or a solid tumor.

[0338] 40. The use of any one of embodiments 37 to 39, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast,

colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0339] 41. The use of any one of embodiments 37 to 40, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0340] 42. The use of any one of embodiments 37 to 41, wherein the cancer is acute myeloid leukemia (AML).

[0341] 43. The use of any one of embodiments 37 to 41, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0342] 44. The use of any one of embodiments 37 to 41, wherein the cancer is non-small cell lung cancer (NSCLC).

[0343] 45. The use of any one of embodiments 37 to 41, wherein the cancer is ovarian cancer.

[0344] 46. The use of any one of embodiments 37 to 45, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0345] 47. The use of embodiment 46, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0346] 48. The use of embodiment 46, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0347] 49. The use of embodiment 46, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0348] 50. The use of embodiment 46, wherein the additional anti-cancer agent is an ALK inhibitor.

[0349] 51. The use of any one of embodiments 37 to 50, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

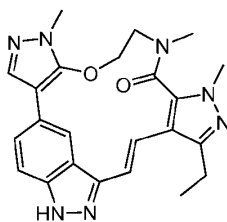
[0350] 52. The use of any one of embodiments 37 to 46, or 51, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0351] 53. The use of any one of embodiments 37 to 46, 48, or 51, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0352] 54. The use of any one of embodiments 37 to 46, 49, or 51, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0353] 55. A composition comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[0354] 56. The composition of embodiment 55, wherein the CLK inhibitor is of the formula I



I

[0355] or a pharmaceutically acceptable salt thereof.

[0356] 57. The composition of embodiment 55 or 56, wherein the cancer is a liquid tumor or a solid tumor.

[0357] 58. The composition of any one of embodiments 55 to 57, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic

nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0358] 59. The composition of any one of embodiments 55 to 58, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0359] 60. The composition of any one of embodiments 55 to 59, wherein the cancer is acute myeloid leukemia (AML).

[0360] 61. The composition of any one of embodiments 55 to 59, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0361] 62. The composition of any one of embodiments 55 to 59, wherein the cancer is non-small cell lung cancer (NSCLC).

[0362] 63. The composition of any one of embodiments 55 to 59, wherein the cancer is ovarian cancer.

[0363] 64. The composition of any one of embodiments 55 to 63, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0364] 65. The composition of embodiment 64, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0365] 66. The composition of embodiment 64, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0366] 67. The composition of embodiment 64, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0367] 68. The composition of embodiment 64, wherein the additional anti-cancer agent is an ALK inhibitor.

[0368] 69. The composition of any one of embodiments 55 to 68, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts

thereof.

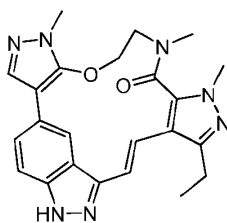
[0369] 70. The composition of any one of embodiments 55 to 65 or 69, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0370] 71. The composition of any one of embodiments 55 to 64, 66, or 69, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0371] 72. The composition of any one of embodiments 55 to 64, 67, or 69, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0372] 73. A medicament comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, combined with at least one additional anti-cancer agent in fixed or free combination.

[0373] 74. The medicament of embodiment 73, wherein the CLK inhibitor is of the formula I



I

[0374] or a pharmaceutically acceptable salt thereof.

[0375] 75. The medicament of embodiment 73 or 74, wherein the cancer is a liquid tumor or a solid tumor.

[0376] 76. The medicament of any one of embodiments 73 to 75, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin

cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0377] 77. The medicament of any one of embodiments 73 to 76, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0378] 78. The medicament of any one of embodiments 73 to 77, wherein the cancer is acute myeloid leukemia (AML).

[0379] 79. The medicament of any one of embodiments 73 to 77, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0380] 80. The medicament of any one of embodiments 73 to 77, wherein the cancer is non-small cell lung cancer (NSCLC).

[0381] 81. The medicament of any one of embodiments 73 to 77, wherein the cancer is ovarian cancer.

[0382] 82. The medicament of any one of embodiments 73 to 81, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0383] 83. The medicament of embodiment 82, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0384] 84. The medicament of embodiment 82, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0385] 85. The medicament of embodiment 82, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0386] 86. The medicament of embodiment 82, wherein the additional anti-cancer agent is an ALK inhibitor.

[0387] 87. The medicament of any one of embodiments 73 to 86, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

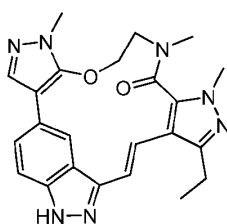
[0388] 88. The medicament of any one of embodiments 73 to 83 or 87, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0389] 89. The medicament of any one of embodiments 73 to 82, 84, or 87, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0390] 90. The medicament of any one of embodiments 73 to 82, 85, or 87, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0391] 91. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other at a locus.

[0392] 92. The synergistic composition of embodiment 90, wherein the CLK inhibitor is of the formula I



I

[0393] or a pharmaceutically acceptable salt thereof.

[0394] 93. The synergistic composition of embodiment 91 or 92, wherein the cancer is a liquid tumor or a solid tumor.

[0395] 94. The synergistic composition of any one of embodiments 91 to 93, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder

cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

[0396] 95. The synergistic composition of any one of embodiments 91 to 94, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0397] 96. The synergistic composition of any one of embodiments 91 to 95, wherein the cancer is acute myeloid leukemia (AML).

[0398] 97. The synergistic composition of any one of embodiments 91 to 95, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0399] 98. The synergistic composition of any one of embodiments 91 to 95, wherein the cancer is non-small cell lung cancer (NSCLC).

[0400] 99. The synergistic composition of any one of embodiments 91 to 95, wherein the cancer is ovarian cancer.

[0401] 100. The synergistic composition of any one of embodiments 91 to 99, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0402] 101. The synergistic composition of embodiment 100, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0403] 102. The synergistic composition of embodiment 100, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0404] 103. The synergistic composition of embodiment 100, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0405] 104. The synergistic composition of embodiment 100, wherein the additional anti-cancer agent is an ALK inhibitor.

[0406] 105. The synergistic composition of any one of embodiments 91 to 104, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

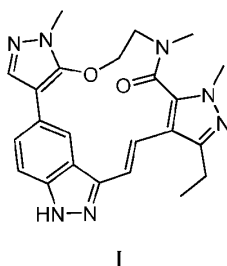
[0407] 106. The synergistic composition of any one of embodiments 91 to 101 or 105, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0408] 107. The synergistic composition of any one of embodiments 91 to 100, 102, or 105, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

[0409] 108. The synergistic composition of any one of embodiments 91 to 100, 103, or 105, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

[0410] 109. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other only in the human body.

[0411] 110. The synergistic composition of embodiment 109, wherein the CLK inhibitor is of the formula I



[0412] or a pharmaceutically acceptable salt thereof.

[0413] 111. The synergistic composition of embodiment 109 or 110, wherein the cancer is a liquid tumor or a solid tumor.

[0414] 112. The synergistic composition of any one of embodiments 109 to 111, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney

cancer, liver cancer and lung cancer.

[0415] 113. The synergistic composition of any one of embodiments 109 to 112, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

[0416] 114. The synergistic composition of any one of embodiments 109 to 113, wherein the cancer is acute myeloid leukemia (AML).

[0417] 115. The synergistic composition of any one of embodiments 109 to 113, wherein the cancer is chronic lymphocytic leukemia (CLL).

[0418] 116. The synergistic composition of any one of embodiments 109 to 113, wherein the cancer is non-small cell lung cancer (NSCLC).

[0419] 117. The synergistic composition of any one of embodiments 109 to 113, wherein the cancer is ovarian cancer.

[0420] 118. The synergistic composition of any one of embodiments 109 to 117, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

[0421] 119. The synergistic composition of embodiment 118, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

[0422] 120. The synergistic composition of embodiment 118, wherein the additional anti-cancer agent is a FLT3 inhibitor.

[0423] 121. The synergistic composition of embodiment 118, wherein the additional anti-cancer agent is a KRAS inhibitor.

[0424] 122. The synergistic composition of embodiment 118, wherein the additional anti-cancer agent is an ALK inhibitor.

[0425] 123. The synergistic composition of any one of embodiments 109 to 118, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, or decitabine or pharmaceutically acceptable salts thereof.

[0426] 124. The synergistic composition of any one of embodiments 109 to 119 or 123, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

[0427] 125. The synergistic composition of any one of embodiments 109 to 118, 120, or 123, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

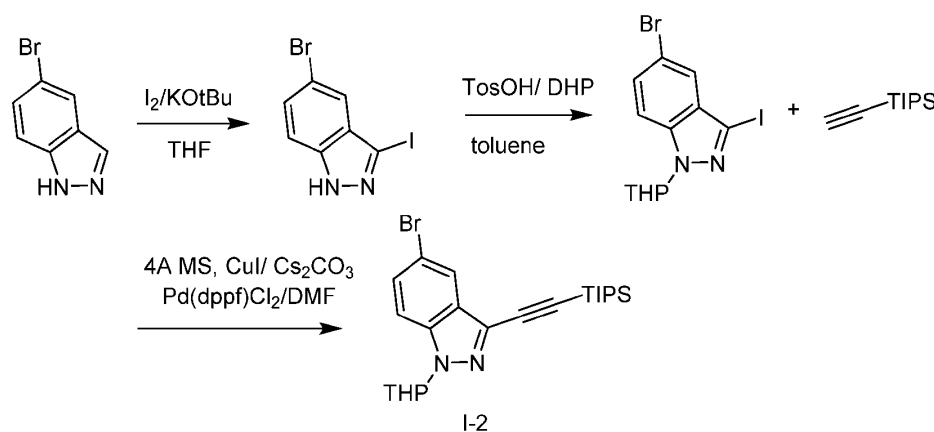
[0428] 126. The synergistic composition of any one of embodiments 109 to 118, 121, or 123, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

Examples

Chemicals and reagents

[0429] Compound I was prepared according to the methods described in International Patent Application No. PCT/US2023/068071 (WO2023240140, published December 14, 2023), see specifically the preparation of Ex. 6 as described therein as General Method B. International Patent Application No. PCT/US2023/068071 (WO2023240140, published December 14, 2023) is incorporated herein by reference for the preparation of Ex. 6 as described therein.

[0430] Preparation of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropylsilane (I-2)



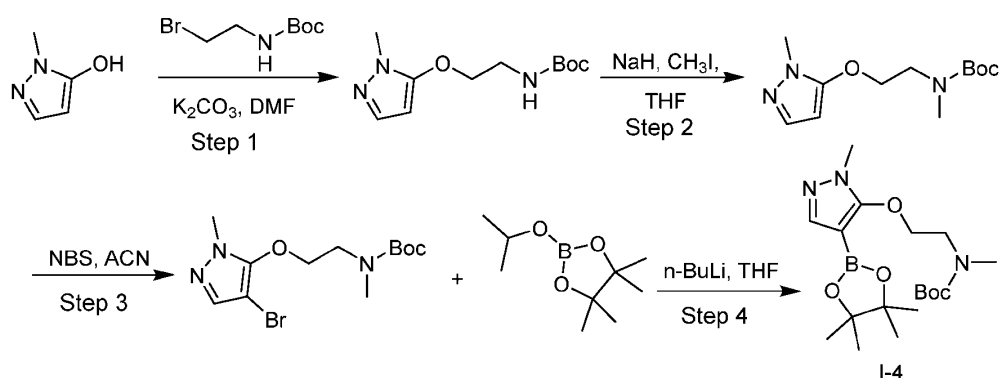
[0431] Step 1. A solution of commercially available 5-bromo-1H-indazole (21.0 g, 107 mmol, 1 eq) in THF (250 mL) was cooled down on an ice bath and KOtBu (35.9 g, 320 mmol, 3 eq) was added portion wise. The resulting slurry was stirred at 0 °C and a solution of I₂ (54.1 g, 213 mmol, 42.9 mL, 2 eq) in THF (250 mL) was added dropwise. The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL*3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1H-indazole (120 g, 350 mmol, 82% yield, 94% purity) as a white solid. LCMS: 324.7 (M+1).

[0432] Step 2. To a mixture of 5-bromo-3-iodo-1H-indazole (25.0 g, 77.4 mmol, 1 eq) and 3,4-dihydro-2H-pyran (13.0 g, 155 mmol, 2 eq) in toluene (250 mL) was added 4-

methylbenzenesulfonic acid (2.67 g, 15.5 mmol, 0.2 eq). The mixture was stirred at 90 °C for 12 hours. On completion, the reaction was diluted with H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (24.0 g, 58.9 mmol, 76% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.64 (d, *J* = 1.6 Hz, 1H), 7.54 - 7.44 (m, 2H), 5.68 (dd, *J* = 3.2, 9.1 Hz, 1H), 4.04 - 3.95 (m, 1H), 3.79 - 3.66 (m, 1H), 2.58 - 2.46 (m, 1H), 2.20 - 2.03 (m, 2H), 1.87 - 1.54 (m, 3H).

[0433] Step 3. To a mixture of 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (23.0 g, 56.5 mmol, 1 eq) and ethynyl(triisopropyl)silane (11.3 g, 62.2 mmol, 1.1 eq) in DMF (250 mL) was added Cs₂CO₃ (55.2 g, 170 mmol, 3 eq), Pd(dppf)Cl₂ (2.48 g, 3.39 mmol, 0.06 eq) and CuI (646 mg, 3.39 mmol, 0.06 eq) under N₂. The mixture was stirred at 25 °C for 3 hours. On completion, the reaction was diluted with H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford compound 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-2, 38.0 g, 79.9 mmol, 70% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.87 (s, 1H), 7.57 - 7.43 (m, 2H), 5.70 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.02 (bd, *J* = 11.2 Hz, 1H), 3.80 - 3.65 (m, 1H), 2.59 - 2.41 (m, 1H), 2.14 (d, *J* = 3.2 Hz, 1H), 2.08 (s, 1H), 1.79 - 1.70 (m, 2H), 1.67 (s, 1H), 1.22 - 1.18 (m, 18H), 1.18 - 1.14 (m, 3H).

[0434] Preparation of tert-butyl N-methyl-N-[3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (I-4)



[0435] Step 1: To a mixture of commercially available 2-methylpyrazol-3-ol (5 g, 50.9 mmol, 1 eq) and tert-butyl N-(2-bromoethyl)carbamate (13.7 g, 61.1 mmol, 1.2 eq) in DMF (50 mL) was added K₂CO₃ (21.1 g, 152 mmol, 3 eq). The mixture was stirred at 80 °C for 2 hours. On completion, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (40

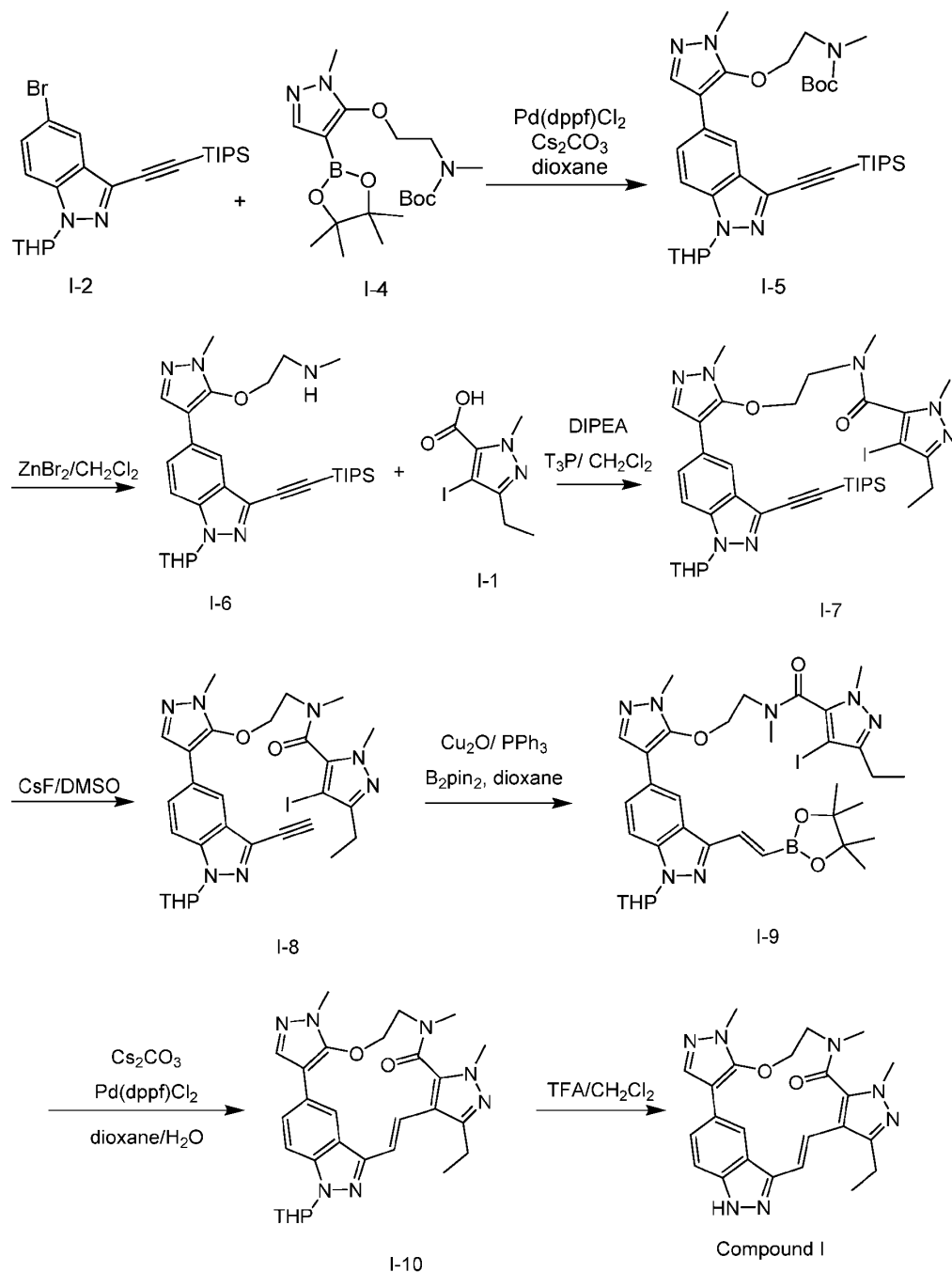
mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl N-[2-(2-methylpyrazol-3-yl)oxyethyl]carbamate (11 g, 45.5 mmol, 89.45% yield) as black oil. LCMS: (M+1:242.2)

[0436] Step 2: To a solution of tert-butyl N-[2-(2-methylpyrazol-3-yl)oxyethyl]carbamate (2 g, 8.29 mmol, 1 *eq*) in THF (20 mL) was added NaH (497 mg, 12.4 mmol, 60% purity, 1.5 *eq*) at 0 °C, the mixture was stirred at 25 °C for 0.5 hours, and CH₃I (1.41 g, 9.95 mmol, 619 uL, 1.2 *eq*) was then added at 25 °C. The mixture was stirred at 25 °C for 3 hours. On completion, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (25 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl N-methyl-N-[2-(2-methylpyrazol-3-yl)oxyethyl]carbamate (2 g, 7.83 mmol, 94.51% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.20 (d, *J* = 2.0 Hz, 1H), 5.65 (d, *J* = 2.0 Hz, 1H), 4.17 - 4.10 (m, 2H), 3.58 - 3.48 (m, 5H), 2.85 (d, *J* = 6.4 Hz, 3H), 1.37 (d, *J* = 19.2 Hz, 9H).

[0437] Step 3: To a solution of tert-butyl N-methyl-N-[2-(2-methylpyrazol-3-yl)oxyethyl]carbamate (2 g, 7.83 mmol, 1 *eq*) in ACN (20 mL) was added NBS (1.44 g, 8.07 mmol, 1.03 *eq*). The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:0 to 1:1) to give tert-butyl N-[2-(4-bromo-2-methylpyrazol-3-yl)oxyethyl]-N-methyl-carbamate (1.73 g, 5.18 mmol, 66.08% yield) as red oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.32 (s, 1H), 4.24 (t, *J* = 5.6 Hz, 2H), 3.54 (s, 3H), 3.48 (t, *J* = 5.6 Hz, 2H), 2.81 (s, 3H), 1.31 (d, *J* = 4.0 Hz, 9H).

[0438] Step 4. To a solution of tert-butyl N-[2-(4-bromo-2-methylpyrazol-3-yl)oxyethyl]-N-methyl-carbamate (I-3, 20.0 g, 59.8 mmol, 1 *eq*), which was prepared according to the methods described in WO2022/133037, the entirety of which is incorporated herein by reference, and specifically for the preparation of N-[2-(4-bromo-2-methylpyrazol-3-yl)oxyethyl]-N-methyl-carbamate, in THF (200 mL) was added *n*-BuLi (2.5 M, 23.9 mL, 1 *eq*) at -78 °C, the mixture was stirred at this temperature for 30 mins followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22.2 g, 119 mmol, 2 *eq*) dropwise at -78 °C. The mixture was stirred at -78 °C for 2 hr. On completion, the mixture was quenched with water (200 mL) and extracted with ethyl acetate (250 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography to give I-4 (21.2 g, 55.6 mmol, 92% yield) as a yellow oil. LCMS: *m/z* 381.9 (M+1).

[0439] Preparation of (17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-13(10*H*)-one (Compound I)



[0440] Step 1. A mixture of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-2, 5.00 g, 10.83 mmol, 1 eq), *tert*-butyl N-methyl-N-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (I-4, 4.96 g, 13.00 mmol, 1.2 eq), Pd(dppf)Cl_2 (1.59 g, 2.17 mmol, 0.2 eq), Cs_2CO_3 (2 M, 16.25 mL, 3 eq) in

dioxane (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 5 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography to provide I-5 (5.00 g, 7.86 mmol, 72.6% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.82 (s, 1H), 7.65 - 7.55 (m, 3H), 5.72 (dd, *J* = 2.8, 9.2 Hz, 1H), 4.00 (s, 2H), 3.76 (s, 3H), 3.56 - 3.47 (m, 2H), 2.99 - 2.93 (m, 3H), 2.62 - 2.48 (m, 1H), 2.16 (dd, *J* = 3.6, 8.4 Hz, 1H), 1.83 - 1.59 (m, 5H), 1.47 (s, 3H), 1.41 - 1.31 (m, 6H), 1.21 - 1.18 (m, 21H).

[0441] Step 2. To a solution of I-5 (1 g, 1.57 mmol, 1 eq) in CH₂Cl₂ (10 mL) was added ZnBr₂ (1.77 g, 7.86 mmol, 5 eq). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography to give I-6 (800 mg, 1.49 mmol, 95.0% yield) as a yellow solid. LCMS: *m/z* 536.1 (*M*+1).

[0442] Step 3. To a solution of I-6 (1.5 g, 2.80 mmol, 1 eq) and 5-ethyl-4-iodo-2-methylpyrazole-3-carboxylic acid (commercially available, 705 mg, 2.52 mmol, 0.9 eq) in CH₂Cl₂ (30 mL) were added DIPEA (2.89 g, 22.4 mmol, 8 eq) and T₃P (3.56 g, 5.60 mmol, 50% purity, 2 eq). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was partitioned between H₂O (50 mL) and CH₂Cl₂ (30 mL). The organic phase was separated, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography to give I-7 (1.15 g, 1.37 mmol, 49.0% yield, 95.1% purity) as a yellow gum. LCMS: (*M*+1: 798.4).

[0443] Step 4. To a solution of I-7 (1.15 g, 1.44 mmol, 1 eq) in DMSO (12 mL) was added CsF (438 mg, 2.88 mmol, 2 eq). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was partitioned between H₂O (10 mL) and EtOAc (10 mL). The organic phase was separated, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give I-8 (650 mg, 1.01 mmol, 70.3% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.87 - 7.43 (m, 4H), 5.93 - 5.85 (m, 1H), 4.55 (d, *J* = 7.6 Hz, 1H), 4.22 - 4.09 (m, 1H), 3.94 - 3.61 (m, 8H), 3.58 - 3.46 (m, 2H), 3.16 - 3.00 (m, 3H), 2.56 - 2.52 (m, 3H), 2.40 - 2.28 (m, 1H), 2.09 - 1.95 (m, 2H), 1.81 - 1.68 (m, 1H), 1.65 - 1.55 (m, 2H), 1.20 - 1.13 (m, 3H).

[0444] Step 5. A mixture of I-8 (650 mg, 1.01 mmol, 1 eq), Pin₂B₂ (257 mg, 1.01 mmol, 1 eq), PPh₃ (266 mg, 1.01 mmol, 1 eq) and Cu₂O (72.5 mg, 0.507 mmol, 0.5 eq) in dioxane (12 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12

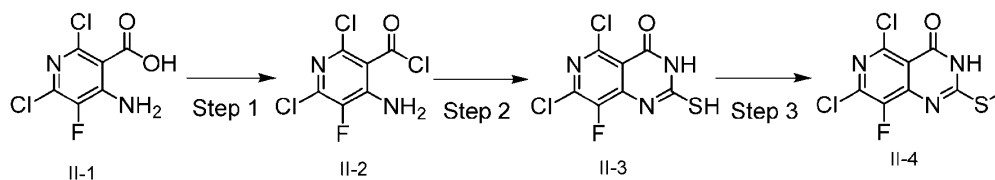
hours under N₂ atmosphere. The reaction mixture was partitioned between H₂O (30 mL) and EtOAc (30 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give I-9 (750 mg, 0.974 mmol, 96.2% yield) as a yellow solid. LCMS: m/z 770.4 (M+1).

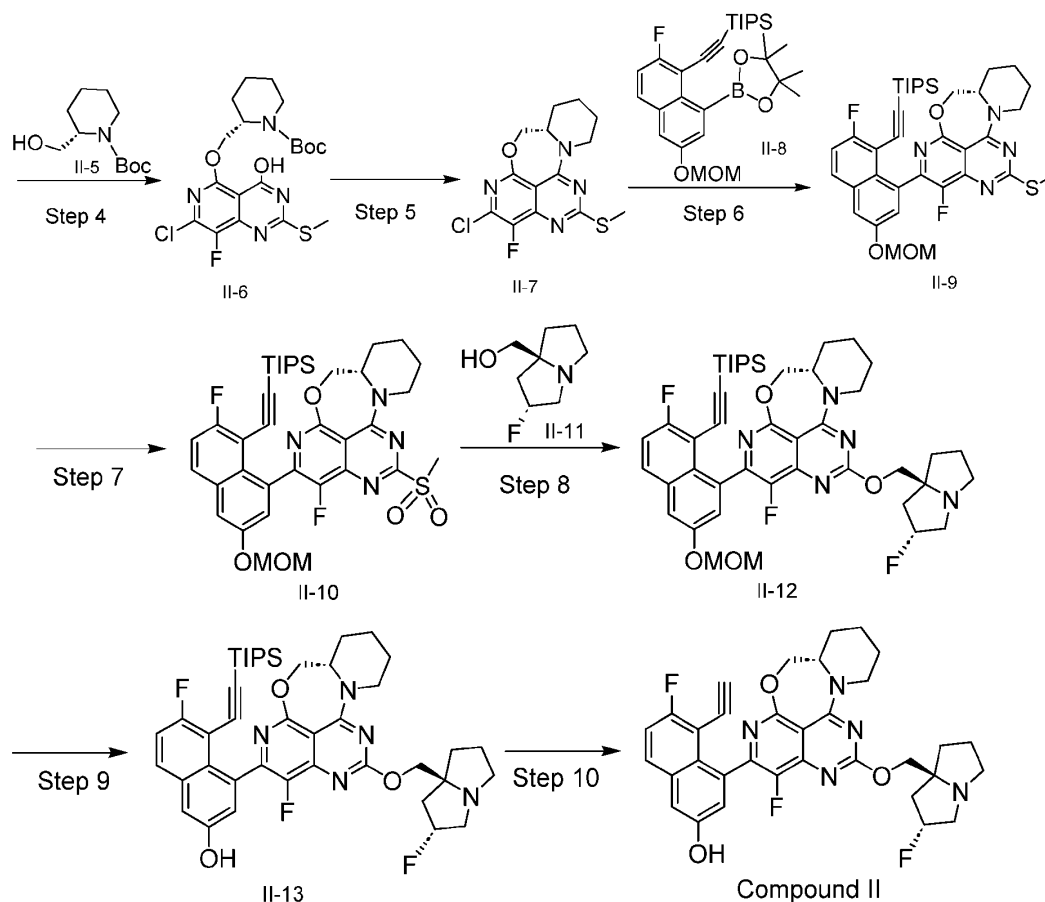
[0445] Step 6. A mixture of I-9 (700 mg, 0.91 mmol, 1 eq), Cs₂CO₃ (889 mg, 2.73 mmol, 3 eq) and Pd(dppf)Cl₂ (66.6 mg, 0.91 mmol, 0.1 eq) in dioxane (12 mL) and H₂O (1.2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 12 hours under N₂ atmosphere. The reaction mixture was partitioned between H₂O (10 mL) and EtOAc (10 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give I-10 (140 mg, 0.271 mmol, 29.7% yield) as a yellow oil. LCMS: m/z 516.3 (M+1).

[0446] Step 7. To a solution of I-10 (140 mg, 0.271 mmol, 1 eq) in CH₂Cl₂ (2 mL) was added TFA (1 mL). The mixture was stirred at 15 °C for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (5 mL × 2). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to provide Compound I (56.9 mg, 0.130 mmol, 48.0% yield) as an off-white solid.

[0447] Compound II was prepared according to the methods described in International Patent Application No. PCT/US2023/027125 (WO2024015262, published January 18, 2024), see specifically the preparation of Ex. 1 as described therein. International Patent Application No. PCT/US2023/027125 (WO2024015262, published January 18, 2024) is incorporated herein by reference for the preparation of Ex. 1 as described therein.

[0448] Preparation of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-de]naphthalen-5-yl)naphthalen-2-ol (Compound II)





[0449] Step 1. Commercially available 4-amino-2,6-dichloro-5-fluoropyridine-3-carboxylic acid (II-1, 2.9 g, 12.89 mmol, 1 eq.) was added to SOCl_2 (82.00 g, 689.25 mmol, 53.48 eq) and the mixture was stirred at 50 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to remove SOCl_2 to give 4-amino-2,6-dichloro-5-fluoropyridine-3-carbonyl chloride (II-2, 2.2 g, 9.04 mmol, crude) as brown oil.

[0450] Step 2. To a solution of 4-amino-2,6-dichloro-5-fluoropyridine-3-carbonyl chloride (II-2, 2.1 g, 8.63 mmol, 1 eq) in acetone (60 mL) was added NH_4SCN (1.97 g, 25.88 mmol, 3 eq). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was concentrated to remove solvent to give 5,7-dichloro-8-fluoro-2-sulfanylprido[4,3-*d*]pyrimidin-4(3*H*)-one (II-3, 1.2 g, 4.51 mmol, crude) as brown solid. LCMS: m/z 263.1 ($M+1$).

[0451] Step 3. To a solution of 5,7-dichloro-8-fluoro-2-sulfanylprido[4,3-*d*]pyrimidin-4(3*H*)-one (II-3, 1.1 g, 4.13 mmol, 1 eq) in MeOH (7.5 mL) was added NaOH (0.1 M, 82.68 mL, 2 eq) and MeI (1.17 g, 8.27 mmol, 2 eq). The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was diluted with water (50 mL), added 6M HCl to adjust pH to 6, filtered and the filtrate

was concentrated under reduced pressure to remove MeOH to give 5,7-dichloro-8-fluoro-2-(methylsulfanyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (II-4, 1.1 g, 3.93 mmol, crude) as gray solid. LCMS: *m/z* 279.9 (*M*+1)

[0452] Step 4. To a solution of commercially available *tert*-butyl (2*S*)-2-(hydroxymethyl)piperidine-1-carboxylate (II-5, 845.46 mg, 3.93 mmol, 1 eq) in THF (10 mL) was added NaH (314.14 mg, 7.85 mmol, 60% purity, 2 eq) at 0 °C and stirred for 0.5 h, and then 5,7-dichloro-8-fluoro-2-(methylsulfanyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (II-4, 1.1 g, 3.93 mmol, 1 eq) was added at 0 °C. The mixture was stirred at 25 °C for 1.5 h. On completion, the reaction mixture was quenched by addition of saturated solution of NH₄Cl in water (10 mL) at 0 °C. And the residue was diluted with H₂O (50) mL and extracted with ethyl acetate (30 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH=1/0 to 0/1) to give *tert*-butyl (2*S*)-2-([7-chloro-8-fluoro-4-hydroxy-2-(methylsulfanyl)pyrido[4,3-*d*]pyrimidin-5-yl]oxy)methyl)piperidine-1-carboxylate (II-6, 650 mg, 1.42 mmol, 36% yield) as yellow solid. LCMS: *m/z* 358.9 (*M*-100+1).

[0453] Step 5. A solution of *tert*-butyl (2*S*)-2-([7-chloro-8-fluoro-4-hydroxy-2-(methylsulfanyl)pyrido[4,3-*d*]pyrimidin-5-yl]oxy)methyl)piperidine-1-carboxylate (II-6, 500 mg, 1.09 mmol, 1 eq) in POCl₃ (16.50 g, 107.61 mmol, 98.77 eq) was stirred at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove POCl₃. Then CH₂Cl₂ (10 mL) was added, and DIEA (422.42 mg, 3.27 mmol, 3 eq) was added at 0 °C and stirred for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give (8*aS*)-5-chloro-4-fluoro-2-(methylsulfanyl)-8,8*a*,9,10,11,12-hexahydro-7-oxa-1,3,6,12*a*-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-7, 180 mg, 0.528 mmol, 49% yield) as white solid. LCMS: *m/z* 340.9 (*M*+1).

[0454] Step 6. To a solution of (8*aS*)-5-chloro-4-fluoro-2-(methylsulfanyl)-8,8*a*,9,10,11,12-hexahydro-7-oxa-1,3,6,12*a*-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-7, 90 mg, 0.264 mmol, 1 eq) in THF (1 mL) and H₂O (0.2 mL) was added K₃PO₄ (168.17 mg, 0.792 mmol, 3 eq), commercially available {[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl]ethynyl}tri(propan-2-yl)silane (II-8, 203.03 mg, 0.396 mmol, 1.5 eq) and [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butylphosphane;methanesulfonate (19.23 mg, 0.0264 mmol, 0.1 eq) under N₂. The mixture was stirred at 80 °C for 2 hr under microwave. On completion, the reaction mixture was quenched with water (20ml), and extracted with ethyl acetate (10 mL×3). The combined organic phase were dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by

column chromatography (SiO₂, Petroleum ether/Ethyl acetate=4:1 to 1:1) to give (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-[[tri(propan-2-yl)silyl]ethynyl]naphthalen-1-yl]-2-(methylsulfanyl)-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-9, 94 mg, 0.136 mmol, 52% yield) as brown solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.69 - 7.56 (m, 1H), 7.41 - 7.32 (m, 1H), 7.30 - 7.24 (m, 1H), 7.20 - 7.11 (m, 2H), 5.22 - 5.13 (m, 2H), 4.40 - 4.24 (m, 2H), 3.47 - 3.33 (m, 3H), 2.04 - 1.90 (m, 2H), 1.88 - 1.80 (m, 2H), 1.79 - 1.70 (m, 2H), 1.67 - 1.56 (m, 2H), 1.55 - 1.49 (m, 3H), 1.04 - 0.65 (m, 21H). LCMS: *m/z* 691.4 (M+1)

[0455] Step 7. To a solution of (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-[[tri(propan-2-yl)silyl]ethynyl]naphthalen-1-yl]-2-(methylsulfanyl)-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-9, 84 mg, 0.122 mmol, 1 eq) in CH₂Cl₂ (1 mL) was added *m*-CPBA (61.71 mg, 0.304 mmol, 85% purity, 2.5 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched by addition of saturated solution of Na₂SO₃ in water (30 mL) at 0 °C, extracted with CH₂Cl₂ (10 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=1/0 to 0/1) to give (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-[[tri(propan-2-yl)silyl]ethynyl]naphthalen-1-yl]-2-(methanesulfonyl)-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-10, 65 mg, 0.0899 mmol, 74% yield) as brown oil. LCMS: *m/z* 723.4 (M+1).

[0456] Step 8. A mixture of (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-[[tri(propan-2-yl)silyl]ethynyl]naphthalen-1-yl]-2-(methanesulfonyl)-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-10, 65 mg, 0.0899 mmol, 1 eq), *t*-BuOK (30.27 mg, 0.270 mmol, 3 eq) in Tol. (0.5 mL) was degassed and purged with N₂ for 3 times at 0 °C, and then commercially available [(2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methanol (II-11, 42.94 mg, 0.270 mmol, 3 eq) was added at 0 °C, the mixture was stirred at 25 °C for 1 h under N₂ atmosphere. On completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (10 mL×3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=4:1 to 0:1) to give (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-[[tri(propan-2-yl)silyl]ethynyl]naphthalen-1-yl]-2-[[2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methoxy}-8,8a,9,10,11,12-

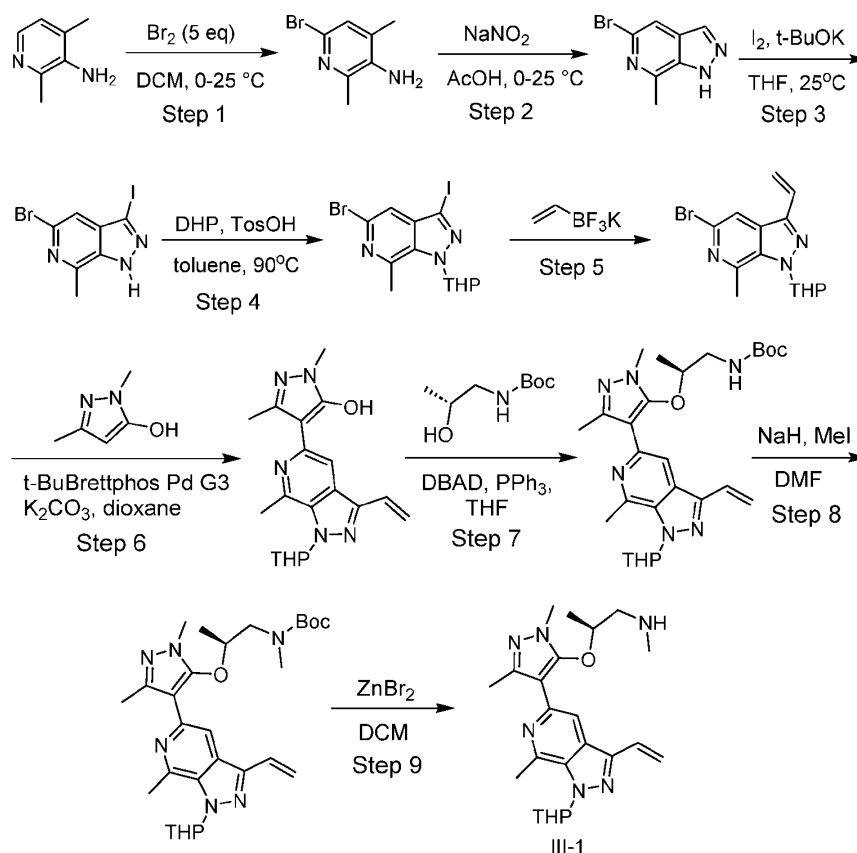
hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-12, 75 mg, 0.0888 mmol, 99% yield) as white solid. LCMS: *m/z* 802.4 (M+1).

[0457] Step 9. To a solution of (8a*S*)-4-fluoro-5-[7-fluoro-3-(methoxymethoxy)-8-{[tri(propan-2-yl)silyl]ethynyl}naphthalen-1-yl]-2-[[*(2R,7aS)*-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methoxy]-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalene (II-12, 68 mg, 0.0848 mmol, 1 eq) in CH₂Cl₂ (1 mL) was added HCl/dioxane (4 M, 0.2 mL, 9.44 eq). The mixture was stirred at 25 °C for 0.5 h. On completion, the reaction mixture was concentrated under reduced pressure to give 6-fluoro-4-[(8a*S*)-4-fluoro-2-[[*(2R,7aS)*-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methoxy]-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalen-5-yl]-5-{[tri(propan-2-yl)silyl]ethynyl}naphthalen-2-ol (II-13, 55 mg, crude). LCMS: *m/z* 758.3 (M+1).

[0458] Step 10. To a solution of 6-fluoro-4-[(8a*S*)-4-fluoro-2-[[*(2R,7aS)*-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methoxy]-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalen-5-yl]-5-{[tri(propan-2-yl)silyl]ethynyl}naphthalen-2-ol (II-13, 55 mg, 0.0726 mmol, 1 eq) in DMSO (0.5 mL) was added CsF (66.14 mg, 0.435 mmol, 6 eq). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; B%: 22%-42%, 58 min) to give 5-ethynyl-6-fluoro-4-[(8a*S*)-4-fluoro-2-[[*(2R,7aS)*-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl]methoxy]-8,8a,9,10,11,12-hexahydro-7-oxa-1,3,6,12a-tetraazabenz[4,5]cyclohepta[1,2,3-*de*]naphthalen-5-yl]naphthalen-2-ol (Compound II, 16.59 mg, 0.0256 mmol, 35.30% yield as formic acid salt) as brown gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.29 - 9.99 (m, 1H), 7.99 - 7.93 (m, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.18 - 7.12 (m, 1H), 5.38 - 5.19 (m, 1H), 4.52 - 4.38 (m, 2H), 4.06 (s, 2H), 4.01 - 3.91 (m, 2H), 3.13 - 3.07 (m, 2H), 3.03 (br s, 2H), 2.87 - 2.79 (m, 1H), 2.15 - 2.05 (m, 2H), 2.03 - 1.98 (m, 1H), 1.95 - 1.66 (m, 10H). LCMS: *m/z* 602.2 (M+1).

[0459] Preparation of (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12,20-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-5,3-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Compound III); also described in International Patent Application No. PCT/US2024/027195, the entire contents of which is incorporated herein by reference.

[0460] Part I: Preparation of (2*S*)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinylpyrazolo[3,4-*c*]pyridin-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-1-amine (III-1)



[0461] Step 1. To a mixture of 2,4-dimethylpyridin-3-amine (25.0 g, 204.64 mmol, 1 *eq*) in CH_2Cl_2 (500 mL) was added a solution of Br_2 (163 g, 1.02 mol, 52.75 mL, 5 *eq*) in CH_2Cl_2 (300 mL) dropwise at 0°C , the mixture was stirred at 25°C for 12 hours. To the mixture was added aq. Na_2SO_3 (300 mL) and the mixture was stirred at 25°C for 1 h. Then the mixture was adjusted to $\text{pH} = 7$ by addition of NaHCO_3 slowly. The mixture was extracted with CH_2Cl_2 (300 mL $\times$ 3). The combined organic phase was washed with brine (50 mL), dried with Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether : Ethyl acetate = 1:1) to afford 6-bromo-2,4-dimethylpyridin-3-amine (62.0 g, 308 mmol, 75.3% yield, 100% purity) as a yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.02 (s, 1H), 3.45 (d, J = 16.4 Hz, 2H), 2.37 (s, 3H), 2.13 (s, 3H).

[0462] Step 2. To a mixture of 6-bromo-2,4-dimethylpyridin-3-amine (30.0 g, 149 mmol, 1 *eq*) in AcOH (300 mL) was added NaNO_2 (11.3 g, 164 mmol, 1.1 *eq*) at 0°C , the mixture was stirred at 25°C for 12 hours. The reaction mixture was concentrated in vacuum. The residue was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (50 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated under reduced

pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% FA condition) to afford Compound 5-bromo-7-methyl-1H-pyrazolo[3,4-c]pyridine (20.0 g, 94.3 mmol, 63.2% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 11.63 - 11.02 (m, 1H), 8.09 (s, 1H), 7.71 (s, 1H), 2.84 (s, 3H).

[0463] Step 3. To a solution of 5-bromo-7-methyl-1H-pyrazolo[3,4-c]pyridine (34.0 g, 160 mmol, 1 *eq*) in THF (450 mL) was added t-BuOK (54.0 g, 481 mmol, 3 *eq*), was added I₂ (40.7 g, 160 mmol, 32.3 mL, 1 *eq*). The mixture was stirred at 25 °C for 3 hr. On completion, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by combi flash (12 g silica gel column, THF in PE 0~100%) to give 5-bromo-3-iodo-7-methyl-1H-pyrazolo [3, 4-c] pyridine (51.0 g, 151 mmol, 94.1% yield) as yellow solid. LCMS: (M+1:337.9).

[0464] Step 4. To a solution of 5-bromo-3-iodo-7-methyl-1H-pyrazolo[3,4-c]pyridine (3.10 g, 9.17 mmol, 1 *eq*) in toluene (31 mL) was added TsOH (316 mg, 1.83 mmol, 0.2 *eq*) and 3,4-dihydro-2H-pyran (1.93 g, 22.9 mmol, 2.10 mL, 2.5 *eq*). The mixture was stirred at 90 °C for 16 hr, filtered and the filtrate was concentrated in vacuum. The residue was purified by combi flash (12 g silica gel column, EtOAc in PE 0-100%). 5-bromo-3-iodo-7-methyl-1-tetrahydropyran-2-yl-pyrazolo [3, 4-c] pyridine (2.57 g, 6.09 mmol, 66.38% yield) was obtained as light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.53 (s, 1H), 6.12 (dd, *J* = 9.2, 2.2 Hz, 1H), 3.88 (d, *J* = 11.6 Hz, 1H), 3.73 (d, *J* = 2.4 Hz, 1H), 2.90 (s, 3H), 2.45 - 2.37 (m, 1H), 2.12 - 2.03 (m, 2H), 1.81 - 1.66 (m, 2H), 1.47 - 1.43 (m, 1H). LCMS: (M+1:421.9).

[0465] Step 5. To a solution of potassium hydride;trifluoro(vinyl)boron (816 mg, 6.09 mmol, 1 *eq*), 5-bromo-3-iodo-7-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-c]pyridine (2.57 g, 6.09 mmol, 1 *eq*) in a mixture solvent of dioxane (25 mL) and H₂O (5 mL) was added Pd(dppf)Cl₂ (445 mg, 609 μmol, 0.1 *eq*) and Na₂CO₃ (1.94 g, 18.3 mmol, 3 *eq*). The mixture was stirred at 80 °C for 16 hr under N₂. Dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by combi flash (20 silica gel column, CH₂Cl₂ 100%) to give 5-bromo-7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo [3, 4-c] pyridine (1.00 g, 3.10 mmol, 50.9% yield) as black, brown solid. LCMS: (M+1: 322.0).

[0466] Step 6. To a mixture of 5-bromo-7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridine (1.10 g, 3.41 mmol, 1 *eq*), commercially available 2,5-dimethylpyrazol-3-ol (498 mg, 4.44 mmol, 1.3 *eq*), K₂CO₃ (1.42 g, 10.24 mmol, 3 *eq*) in dioxane (11 mL) was added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (117 mg, 136 μmol, 0.04 *eq*) and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 1.5 h under N₂ atmosphere. On completion, the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a

residue. The residue was purified by combi flash (20 g silica gel column, THF in PE from 0-100%) to give 2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-ol (0.990 g, 2.80 mmol, 82% yield) as a yellow oil. LCMS: (M+1:354.1).

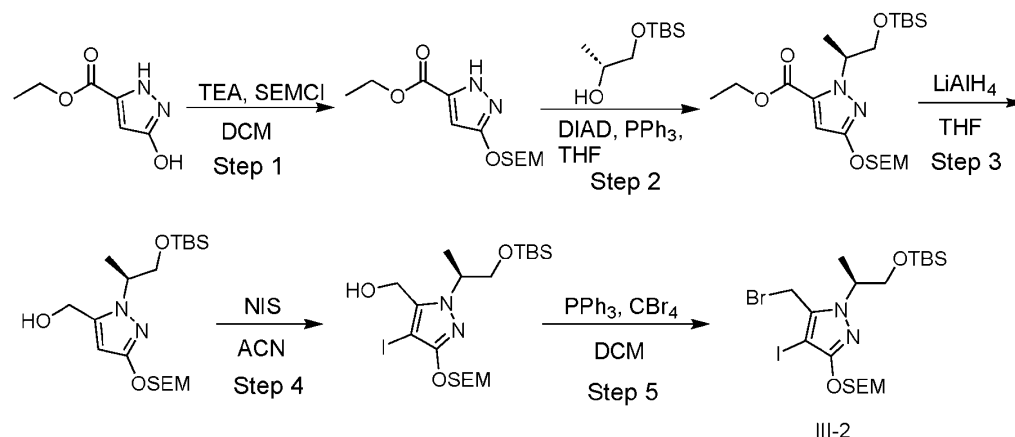
[0467] Step 7. To a solution of 2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-ol (970 mg, 2.74 mmol, 1 *eq*) in THF (10 mL) was added commercially available tert-butyl N-[(2R)-2-hydroxypropyl]carbamate (962 mg, 5.49 mmol, 2 *eq*) and PPh₃ (1.44 g, 5.49 mmol, 2 *eq*) and DBAD (948 mg, 4.12 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (20 g silica gel column, THF in PE from 0-100%) to give tert-butyl N-[(2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxypropyl]carbamate (1.75 g, crude) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 6.79 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.16 (br d, *J* = 8.0 Hz, 1H), 5.59 (d, *J* = 3.6 Hz, 1H), 5.37 (s, 2H), 4.06 (s, 6H), 1.58 (q, *J* = 7.6 Hz, 3H), 0.49 - 0.25 (m, 17H). LCMS: (M+1:511.6).

[0468] Step 8. To a solution of tert-butyl N-[(2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxypropyl]carbamate (1.70 g, 3.33 mmol, 1 *eq*) in DMF (17 mL) was added NaH (399 mg, 9.99 mmol, 60% purity, 3 *eq*) and CH₃I (709 mg, 4.99 mmol, 311 μL, 1.5 *eq*). The mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was quenched by addition H₂O (70 mL) at 25 °C, and extracted with ethyl acetate (50 mL *3). The combined organic layers were washed with H₂O (40 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue the residue was purified by combi flash (20 g silica gel column, THF in PE from 0-100%) to give tert-butyl N-[(2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxypropyl]-N-methyl-carbamate (1.76 g, 1.68 mmol, 50% yield, 50% purity) as a yellow solid. LCMS: (M+1:525.3).

[0469] Step 9. To a solution of tert-butyl N-[(2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxypropyl]-N-methyl-carbamate (1.70 g, 3.24 mmol, 1 *eq*) in CH₂Cl₂ (17 mL) was added ZnBr₂ (3.65 g, 16.2 mmol, 811 μL, 5 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the reaction mixture was quenched by addition H₂O (25 mL) at 25 °C, and extracted with CH₂Cl₂ (15 mL * 4), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (20 g silica gel column, THF in PE from 0-100%) to give (2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-1-amine (III-1, 550 mg, 1.30 mmol, 40% yield) as a white solid. ¹H NMR (400 MHz, MeOD-*d*₄) δ = 7.82 (d, *J* = 3.2 Hz, 1H), 7.05 (dd, *J* = 11.6, 18.0 Hz, 1H), 6.16

(d, $J = 18.0$ Hz, 1H), 6.07 - 6.01 (m, 1H), 5.59 (d, $J = 11.6$ Hz, 1H), 4.42 - 4.32 (m, 1H), 4.04 - 3.95 (m, 1H), 3.90 - 3.80 (m, 1H), 3.71 (s, 3H), 3.17 - 3.10 (m, 1H), 3.03 - 2.98 (m, 4H), 2.70 - 2.61 (m, 1H), 2.58 (d, $J = 2.4$ Hz, 3H), 2.25 (d, $J = 1.2$ Hz, 3H), 2.22 - 2.15 (m, 2H), 1.92 - 1.78 (m, 1H), 1.75 - 1.61 (m, 2H), 1.14 (dd, $J = 2.8, 6.4$ Hz, 3H). LCMS: (M+1:425.2).

[0470] Part II: Preparation of 2-[[5-(bromomethyl)-1-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-pyrazol-3-yl]oxymethoxy]ethyl-trimethyl-silane (III-2)



[0471] Step 1. Commercially available 5-hydroxy-1H-pyrazole-3-carboxylic acid ethyl ester (10.0 g, 64 mmol, 1 *eq*), SEM-Cl (42.7 g, 256 mmol, 4 *eq*), and TEA (38.9 g, 384 mmol, 6 *eq*) were mixed in CH₂Cl₂ (100 mL) at 0 °C and the mixture was stirred at 25 °C for 1 h. On completion, the mixture was diluted with water (500 mL) and extracted with CH₂Cl₂ (100 mL × 3). The combined organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography on silica gel (120 g silica gel, ethyl acetate in Petroleum ether from 0% to 100%) to give ethyl 3-(2-trimethylsilylethoxymethoxy)-1H-pyrazole-5-carboxylate (10.6 g, 35.8 mmol, 56% yield) as a colorless oil. LCMS: (M+1-28: 259.0)

[0472] Step 2. To the mixture of ethyl 3-(2-trimethylsilylethoxymethoxy)-1H-pyrazole-5-carboxylate (10.0 g, 34.9 mmol, 1 *eq*), (2R)-1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (13.3 g, 69.8 mmol, 2 *eq*) and PPh₃ (20.1 g, 76.8 mmol, 2.2 *eq*) in THF (230 mL), was added DIAD (17.7 g, 87.3 mmol, 2.5 *eq*) at 0 °C, and the resulting mixture was stirred for another 2 h at 25 °C under N₂. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (80 g silica gel, ethyl acetate in Petroleum ether from 0% to 100%) to give ethyl 2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-(2-trimethylsilylethoxymethoxy)pyrazole-3-carboxylate (16.1 g, 31.6 mmol, 90% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 6.33 - 6.28 (m, 1H), 5.38 - 5.28 (m, 1H), 5.21 - 5.16 (m,

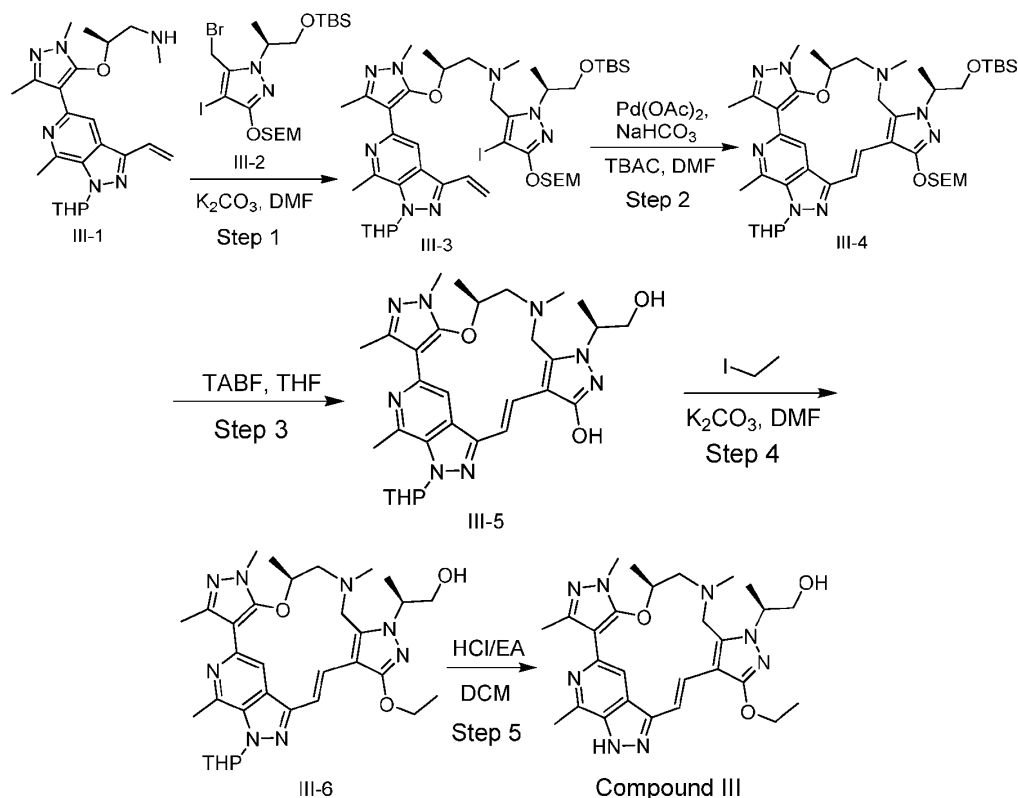
2H), 4.29 - 4.21 (m, 2H), 3.72 - 3.65 (m, 4H), 0.92 - 0.83 (m, 6H), 0.73 (s, 9H), 0.05 - 0.02 (m, 2H), -0.01 - -0.04 (m, 9H), -0.09 (s, 3H), -0.17 (s, 3H).

[0473] Step 3. To a solution of ethyl 2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-(2-trimethylsilylethoxymethoxy)pyrazole-3-carboxylate (15.5 g, 33.8 mmol, 1 *eq*) in THF (155 mL) was added LiAlH₄ (2.50 M, 13.5 mL, 1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was quenched by slow addition of water (1.5 mL), 15% sodium hydroxide solution (1.5 mL) and water (5 mL) at 0 °C. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (40 g silica gel, ethyl acetate in Petroleum ether from 0% to 100%) to give [2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methanol (7.25 g, 17.3 mmol, 51% yield) as a colorless oil. LCMS: (M+1: 417.1)

[0474] Step 4. To a solution of [2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methanol (6.70 g, 16.1 mmol, 1 *eq*) in ACN (70 mL) was added NIS (3.98 g, 17.7 mmol, 1.1 *eq*) at 0 °C for 0.5 h. The mixture was then stirred at 25 °C for 1.5 h. On completion, the reaction mixture was quenched by addition of saturated sodium sulfite solution (70 mL) at 0 °C, and then diluted with H₂O (260 mL) and extracted with ethyl acetate (100 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g silica gel, ethyl acetate in Petroleum ether from 0% to 100%) to give [2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methanol (7.60 g, 13.6 mmol, 85% yield) as a colorless oil. LCMS: (M+1: 543.1)

[0475] Step 5. To a solution of [2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methanol (7.00 g, 12.9 mmol, 1 *eq*), CBr₄ (5.13 g, 15.5 mmol, 1.2 *eq*) in CH₂Cl₂ (70 mL) was added PPh₃ (4.06 g, 15.5 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1.5 h. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (40 g silica gel, ethyl acetate in Petroleum ether from 0% to 100%) to give 2-[[5-(bromomethyl)-1-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-pyrazol-3-yl]oxymethoxy]ethyl-trimethylsilane (III-2, 3.50 g crude of ~62% purity) as a colorless oil. LCMS: (M+1: 607.0). This crude is used directly to the next alkylation reaction.

[0476] Part III: Preparation of (2S)-2-[(10S,17E)-16-ethoxy-6,8,10,12,20-pentamethyl-2,8,10,11,12,13-hexahydro-14H-5,3-(azenometheno)tripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Compound III)



[0477] Step 1. To a solution of (2S)-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-1-amine (III-1, 190 mg, 447 μ mol, 1 *eq*) and 2-[[5-(bromomethyl)-1-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-pyrazol-3-yl]oxymethoxy]ethyl-trimethyl-silane (III-2, 325 mg, 537 μ mol, 1.2 *eq*) in DMF (2 mL) was added K_2CO_3 (186 mg, 1.34 mmol, 3 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the reaction mixture was quenched by addition H_2O (8 mL) at 25 °C and extracted with ethyl acetate (8 mL * 3). The combined organic layers were washed with H_2O (10 mL * 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (4 g silica gel column, THF in PE from 0-100%) to give (2S)-N-[[2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methyl]-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridin-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-1-amine (III-3, 340 mg, 358 μ mol, 80% yield) as a brown oil. LCMS: (M+1: 949.7).

[0478] Step 2. A mixture of (2S)-N-[[2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methyl]-2-[2,5-dimethyl-4-(7-methyl-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-c]pyridine-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-

1-amine (III-3, 330 mg, 348 μmol , 1 *eq*), TBAC (96.6 mg, 348 μmol , 97.2 μL , 1 *eq*), NaHCO_3 (73.0 mg, 869 μmol , 33.8 μL , 2.5 *eq*) and $\text{Pd}(\text{OAc})_2$ (15.6 mg, 69.5 μmol , 0.2 *eq*) in DMF (16.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 130 °C for 1.5 h under N_2 atmosphere. On completion, the reaction mixture was quenched by addition H_2O (30 mL) at 25 °C and extracted with ethyl acetate (15 mL * 3). The combined organic layers were washed with H_2O (20 mL * 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (12 g silica gel column, THF in PE from 0-100%) to give (10*S*,17*E*)-14-[(2*S*)-1-[[*tert*-butyl(dimethyl)silyl]oxy]propan-2-yl]-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-16-{[2-(trimethylsilyl)ethoxy]methoxy}-2,10,11,12,13,14-hexahydro-8*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (III-4, 275 mg, 335 μmol , 96% yield) as a brown oil. LCMS: (M+1: 821.8).

[0479] Step 3. To a solution of (10*S*,17*E*)-14-[(2*S*)-1-[[*tert*-butyl(dimethyl)silyl]oxy]propan-2-yl]-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-16-{[2-(trimethylsilyl)ethoxy]methoxy}-2,10,11,12,13,14-hexahydro-8*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (III-4, 260 mg, 317 μmol , 1 *eq*) in THF (2.6 mL) was added TBAF (1 M, 1.90 mL, 6 *eq*). The mixture was stirred at 70 °C for 3 hr. On completion, the reaction mixture was quenched by addition H_2O (10 mL) at 25 °C and extracted with ethyl acetate (8 mL * 3). The combined organic layers were washed with H_2O (10 mL * 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give (10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (III-5, 200 mg, 243 μmol , 77% yield, 70% purity) as a brown oil. LCMS: (M+1: 577.2).

[0480] Step 4. To a solution of (10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (III-5, 90.0 mg, 156 μmol , 1 *eq*) in DMF (2 mL) was added K_2CO_3 (43.1 mg, 312 μmol , 2 *eq*) and iodoethane (29.2 mg, 187 μmol , 15.0 μL , 1.2 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the reaction mixture was quenched by addition H_2O (8 mL) at 25 °C, and extracted with ethyl acetate (5 mL * 3). The combined organic layers were washed with H_2O (6 mL * 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (III-6, 90.0 mg, 149 μmol , 95% yield) as a brown oil. LCMS: (M+1: 605.3).

[0481] Step 5. To a solution of (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12,20-pentamethyl-2-(oxan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (III-6, 80.0 mg, 132 μ mol, 1 *eq*) in CH₂Cl₂ (2 mL) was added HCl/EtOAc (4 M, 1 mL, 30.2 *eq*). The mixture was stirred at 25 °C for 0.25 h. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um;mobile phase: [water(FA)-ACN];gradient:16%-46% B over 10 min) to give (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12,20-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-5,3-(azenometheno)tripyrzolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Compound III, 4.63 mg, 7.96 μ mol, 6.02% yield, 97.42% purity, FA) as a yellow solid. ¹H NMR (400 MHz, MeOD-*d*₄) δ = 8.28 - 8.19 (m, 2H), 7.24 (d, *J* = 16.8 Hz, 1H), 4.93 - 4.89 (m, 1H), 4.52 - 4.42 (m, 1H), 4.41 - 4.31 (m, 2H), 4.01 - 3.93 (m, 1H), 3.86 - 3.78 (m, 2H), 3.71 - 3.67 (m, 4H), 2.97 - 2.82 (m, 2H), 2.79 (s, 3H), 2.56 (s, 3H), 2.43 (s, 3H), 1.48 (t, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H). LCMS: (M+1: 521.2).

[0482] Venetoclax was purchased from MedChemExpress. Gilteritinib was purchased from Selleckchem. AMG-510 (sotorasib) was purchased from Selleckchem. Osimertinib was purchased from MedChemExpress. MRTX1133 was purchased from MedChemExpress. Adagrasib was purchased from Sellechem.

[0483] The doses used in the following mouse studies can be converted between animals and humans according to Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016 Mar;7(2):27-31. For example, the human equivalent dose (HED) can be calculated by multiplying the dosage administered in a mouse by a factor of 0.081. A 25 mg/kg dose in a mouse, for example, corresponds to a 2.0 mg/kg dose in a human.

[0484] Cell lines

	Cell Line Name	Tumor Type, Disease	Source, Catalog #	Culture Medium
1	MOLM13	Acute myeloid leukemia	DSMZ, ACC 554	90% RPMI 1640 + 10% h.i. FBS
2	H358	Bronchioalveolar carcinoma NSCLC	ATCC, CRL-5807	90% RPMI 1640 + 10% h.i. FBS
3	SW480	Colorectal cancer	ATCC,CCL-228	90% RPMI 1640 + 10% h.i. FBS
4	H1975	NSCLC	ATCC, CRL-5908	90% RPMI 1640 + 10% h.i. FBS

5	Suit-2	Pancreatic ductal adenocarcinoma	JCRB cell bank, JCRB1094	90% RPMI 1640 + 10% h.i. FBS
6	GP2D	Colorectal cancer	Sigma, 95090714-1VL	DMEM + 10% h.i. FBS
7	SW1463	Colorectal cancer	ATCC, CCL-234	DMEM + 10% h.i. FBS

In-Vitro Assays

[0485] Example 1: Venetoclax and Compound I combination synergy analysis by in vitro proliferation assay

[0486] Matrix combination synergy assay (Compound I and Venetoclax) was carried out in AML cell line MOLM13. 2000 cells/100 μ L per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. Venetoclax was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM and 0.15 nM horizontally. Compound I was added at 50 nM, 12.5 nM, 3.13 nM, 0.78 nM and 0.2 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 μ L per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map can be found in FIG. 1 and HSA synergy scores for the most synergistic area concentrations can be found in Table 1.

Table 1

Venetoclax (nM)	Cpd I (nM)	Relative inhibition (%)	HSA Synergy Score
12.4	3.1	75.5	35.0
37.0	3.1	92.8	29.2
37.0	0.8	80.6	17.3

[0487] Synergy score interpretation:

[0488] Less than -10: the interaction between two drugs is likely to be antagonistic.

[0489] From -10 to 10: the interaction between two drugs is likely to be additive.

[0490] Larger than 10: the interaction between two drugs is likely to be synergistic.

[0491] Example 2: AMG-510 (sotorasib) and Compound I combination synergy analysis by in vitro proliferation assay

[0492] Matrix combination synergy assay (Compound I and AMG-510) was carried out in NSCLC cell line H358. 1000 cells/100 μ L per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. AMG-510 was added at 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM, 0.15 nM and 0.05 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 μ L per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map can be found in FIG. 2 and HSA synergy scores for the most synergistic area concentrations can be found in Table 2.

Table 2

AMG-510 (nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
4.1	15.6	51.5	19.2
4.1	62.5	65.8	30.0
12.3	62.5	81.3	20.9

[0493] Synergy score interpretation:

[0494] Less than -10: the interaction between two drugs is likely to be antagonistic.

[0495] From -10 to 10: the interaction between two drugs is likely to be additive.

[0496] Larger than 10: the interaction between two drugs is likely to be synergistic.

[0497] Example 3: IncuCyte™ S3 3D spheroid growth assay in CRC cell line SW480

[0498] IncuCyte™ S3 3D spheroid growth assay (Compound I and Compound II) was carried out in CRC cell line SW480. 2000 cells/200 μ l per well were seeded in 96 well ultra-low

attachment plates (Corning #7007). Compounds were added using Tecan D300e Digital Dispenser in matrix format. Compound II was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM and 0.15 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for up to 9 days at 37°C and 5% CO₂ with media change every week. 3D spheroids were measured using IncuCyte™ S3 Live-Cell Analysis System (Sartorius, Ann Arbor, MI). Scans were taken every 12 hours using phase and brightfield channel at 4X magnification. Brightfield object total area was used to measure cell proliferation in 3D spheroid form and image analysis was done based on manufacturer's recommendations. The graphs of brightfield object total area ($\mu\text{m}^2/\text{image}$) with DMSO, single agent and combination at indicated concentration can be found in FIG. 5.

[0499] Example 4: Compound I and Compound II combination synergy analysis by in vitro proliferation assay

[0500] Matrix combination synergy assay (Compound I and Compound II) was carried out in CRC cell line SW480. 2000 cells/200 μl per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. Compound II was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM and 0.15 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 μl per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map can be found in FIG. 6 (having an average HSA synergy score of 1.161 over all tested concentrations) and HSA synergy scores for the most synergic area concentrations can be found in Table 3.

Table 3

Compound II (nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
12.4	62.5	72.4	26.7
37.0	62.5	59.2	10.9

111.1	62.5	74.4	26.6
333.3	62.5	83.8	17.6

[0501] Example 5: IncuCyte™ S3 3D spheroid growth assay in NSCLC cell line H1975

[0502] IncuCyte™ S3 cell proliferation and confluence assay (Compound I and Compound III or Osimertinib) was carried out in NSCLC cell line H1975. 500 cells/200 µl per well were seeded in 96 well clear plates (Corning #3585). Compounds were added using Tecan D300e Digital Dispenser in matrix format. Compound III or Osimertinib was added at 300 nM, 100 nM, 33 nM, 11 nM, 4.12 nM, 3.7 nM, and 1.2 nM horizontally. Compound I was added at 50 nM, 100 nM and 200 nM vertically. Plates were incubated for up to 21 days at 37 °C and 5% CO₂ with media change every week. After the first week, the media was changed, and the compounds were removed from the plates. After the second week, the media was changed, and the compounds were added back to the plates. Cell proliferation and confluence was measured using IncuCyte™ S3 Live-Cell Analysis System (Sartorius, Ann Arbor, MI). Scans were taken every 12 hours, 4 images per well at 10X magnification using adherent cell-by-cell scan type. Confluency was used to measure cell proliferation and image analysis was done based on manufacturer's recommendations. The graphs of phase object confluence (%) with DMSO, single agent and combination can be found in FIG. 7 and 8, respectively.

[0503] Example 6: MRTX1133 and Compound I combination synergy analysis by in vitro proliferation assay

[0504] Matrix combination synergy assay (Compound I and MRTX1133) was carried out in PDAC cell line Suit-2. 2000 cells/100 µL per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. MRTX1133 was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM, and 0.15 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 µL per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map

can be found in FIG. 9 (having an average HSA synergy score of 4.145 over all tested concentrations) and HSA synergy scores for the most synergistic area concentrations can be found in Table 4.

Table 4

MRTX1133(nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
4.1	62.5	43.0	21.1
12.4	62.5	61.2	19.6
37.0	250.0	90.3	19.3

- [0505] Synergy score interpretation:
- [0506] Less than -10: the interaction between two drugs is likely to be antagonistic.
- [0507] From -10 to 10: the interaction between two drugs is likely to be additive.
- [0508] Larger than 10: the interaction between two drugs is likely to be synergistic.

[0509] Example 7: MRTX1133 and Compound I combination synergy analysis by in vitro proliferation assay

[0510] Matrix combination synergy assay (Compound I and MRTX1133) was carried out in CRC cell line GP2D. 1000 cells/100 µL per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. MRTX1133 was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM, and 0.15 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 µL per well following the manufacturer’s protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map can be found in FIG. 10 (having an average HSA synergy score of 5.304 over all tested concentrations) and HSA synergy scores for the most synergistic area concentrations can be found in Table 5.

Table 5

MRTX1133(nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
0.46	15.6	59.73	22.59
1.37	15.6	79.32	20.43
4.12	15.6	87.22	11.4

[0511] Synergy score interpretation:

[0512] Less than -10: the interaction between two drugs is likely to be antagonistic.

[0513] From -10 to 10: the interaction between two drugs is likely to be additive.

[0514] Larger than 10: the interaction between two drugs is likely to be synergistic.

[0515] Example 8: Adagrasib and Compound I combination synergy analysis by in vitro proliferation assay

[0516] Matrix combination synergy assay (Compound I and adagrasib) was carried out in CRC cell line SW1463. 2000 cells/100 μ L per well were seeded in 96 well black plate with a clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser in matrix format. Adagrasib was added at 1000 nM, 333 nM, 111 nM, 37 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM, and 0.15 nM horizontally. Compound I was added at 1000 nM, 250 nM, 62.5 nM, 15.6 nM and 3.9 nM vertically. Plates were incubated for 5 days at 37 °C and 5% CO₂. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 μ L per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. Percent of viability was calculated using DMSO as control. Data was analyzed using SynergyFinder 2.0. (Ianevski, A., Giri, K. A., Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. Nucleic Acids Research. gkaa216, <https://doi.org/10.1093/nar/gkaa216>). The HSA model, which states that the expected combination effect is the maximum of the single drug responses at corresponding concentrations was used to calculate the synergy scores. The HSA synergy map can be found in FIG. 11 (having an average HSA synergy score of 7.443 over all tested concentrations) and HSA synergy scores for the most synergic area concentrations can be found in Table 6.

Table 6

Adagrasib (nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
4.12	62.5	72.06	36.98
1.37	62.5	61.03	36.84

Adagrasib (nM)	Compound I (nM)	Relative inhibition (%)	HSA Synergy Score
0.46	15.63	36.35	25.72

[0517] Synergy score interpretation:

[0518] Less than -10: the interaction between two drugs is likely to be antagonistic.

[0519] From -10 to 10: the interaction between two drugs is likely to be additive.

[0520] Larger than 10: the interaction between two drugs is likely to be synergistic.

[0521] Example 9: In Vivo experiments

[0522] Tumor cells were cultured using standard techniques described above and were harvested and pelleted by centrifugation at 1000 rpm for 5 minutes. The pelleted cells were washed once with serum-free medium followed by subsequent re-suspension in the serum-free medium supplemented with 50% matrigel (Corning, Inc). Five million tumor cells were implanted subcutaneously to the right flank of each immune-compromised mouse, followed by tumor volume and body weight measurement once or twice per week with an electronic caliper (Fowler) and a balance, respectively. In general, when the average tumor size reaches a pre-determined volume, the mice were grouped and treated with vehicle, Compound I, an FDA approved agent, or Compound I together with the FDA approved agent to evaluate the anti-tumor activity. In specific studies, the treatment scheme and the treatment sequence could vary and additional dose levels could be added. Compound I was administered orally and the FDA approved agent was dosed through either PO or IP route. During treatment, mice were monitored daily by cage side observation. The tumor volume (TV) and body weight will be measured twice or three times per week during the treatment. Study ended either after 4-5 weeks of treatment or tumor volume of mice reaches 1000 to 2000 mm³. Tumor growth inhibition (TGI) will be calculated as follows: $100\% * \{1 - [(TV_{\text{Treated Last Day of Treatment}} - TV_{\text{Treated First Day of Treatment}}) / (TV_{\text{Control on Last Day of Treatment}} - TV_{\text{Control on First Day of Treatment}})]\}$ when $TV_{\text{Treated Last Day of Treatment}} > TV_{\text{Treated First Day of Treatment}}$. In the case of $TV_{\text{Treated Last Day of Treatment}} < TV_{\text{Treated First Day of Treatment}}$, TGI was calculated as $100\% * (2 - TV_{\text{Treated Last Day of Treatment}} / TV_{\text{Treated First Day of Treatment}})$.

[0523] Example 10: Anti-tumor effect of Compound I in combination with gilteritinib in the MOLM-13 cell-derived xenograft (CDX) tumor model

[0524] MOLM-13 is an AML cell line carrying an FLT3-ITD mutation. Gilteritinib is an FLT3 inhibitor targeting FLT3 mutations in AML. In this study, six groups of mice bearing MOLM-13 tumors were treated with vehicle QD (once per day), gilteritinib 25 mg/kg QD, Compound I

25 mg/kg QD, Compound I 25 mg/kg QD together with gilteritinib 25 mg/kg QD, Compound I 25 mg/kg MWF (once a day on Monday, Wednesday, and Friday), and Compound I 25 mg/kg MWF together with gilteritinib 25 mg/kg QD, respectively. On day 14, gilteritinib treatment, Compound I QD treatment and Compound I MWF treatment resulted in TGIs of 94%, 94%, and 37%, respectively; whereas the Compound I QD treatment combined with gilteritinib and Compound I MWF treatment combined with gilteritinib induced tumor regression and resulted in TGIs of 138% and 114%, respectively (FIG. 3a). The treatment scheme continued for groups treated with gilteritinib, Compound I QD, Compound I QD combined with gilteritinib, and Compound I MWF combined with gilteritinib. On day 24 of the treatment, tumor volumes increased to about 585% and 555% of baseline in the gilteritinib and Compound I QD treatment groups, respectively (FIG. 3a). In contrast, the combination Compound I with gilteritinib resulted in deep tumor regression. Treatment of Compound I QD combined with gilteritinib and Compound I MWF combined with gilteritinib resulted in TGIs of 192% and 154%, respectively (FIG. 3a). The mice were monitored for toxicity by body weight measurement through the course of treatment, and no apparent toxicity based on body weight loss was observed for the mice during treatment (FIG. 3b).

[0525] Example 11: Anti-tumor effect of Compound I in combination with venetoclax in the MOLM-13 CDX tumor model

Venetoclax is a BCL2 inhibitor used in combination with other agents in AML patients. In this study, five groups of mice bearing MOLM-13 tumors were treated with vehicle QD, venetoclax 100 mg/kg QD, Compound I 25 mg/kg MWF, Compound I 25 mg/kg MWF together with venetoclax 100 mg/kg QD, Compound I 25 mg/kg QW (once a week) together with venetoclax 100 mg/kg QD, respectively. On day 14, venetoclax treatment at 100mg/kg QD, Compound I treatment at 25mg/kg on MWF schedule resulted in TGIs of 38% and 34%, respectively (FIG. 4a). In contrast, Compound I MWF combined with venetoclax resulted in 195% TGI (i.e., 95% tumor regression) on day 14 and reached 200% TGI (i.e. complete tumor regression) on day 18 as treatment continued. The combination treatment was extended to day 28 with no tumor regrowth being observed. In addition, combination treatment of Compound I QW with venetoclax resulted in 95% TGI on day 14 (FIG. 4a). No obvious body weight loss was observed during treatment (FIG. 4b)

[0526] Example 12: Anti-tumor effect of Compound I in combination with venetoclax in the venetoclax pretreated MOLM-13 CDX tumor model

[0527] The combination effect of Compound I and venetoclax was accessed after pretreatment of venetoclax at 100mg/kg QD for 16 days. Mice were then randomized into three groups and treated with Compound I 25mg/kg MWF in combination with venetoclax 100mg/kg QD, Compound I 25mg/kg QW in combination with venetoclax, and gilteritinib 25mg/kg QD in combination with venetoclax for 9 days. Using the average tumor volume on day 9 as baseline for each group, the Compound I MWF and venetoclax combination resulted in 42% decrease of average tumor volume (i.e., 142% TGI), whereas average tumor volume in the Compound I QW and venetoclax combination group increased to 122% of baseline and average tumor volume in gilteritinib and venetoclax combination group increased to 346% of baseline (FIG. 12a). No apparent toxicity based on body weight loss was observed during treatment (FIG. 12b).

[0528] Example 13: Anti-tumor effect of Compound I in combination with azacitidine in the MOLM-13 CDX tumor model

Azacitidine is a standard of care medicine used for treating AML patients. In this study, five groups of mice bearing MOLM-13 tumors were treated with vehicle QD, Azacitidine 5 mg/kg QD for 7 days (QDx7), Compound I 25 mg/kg QD, Compound I 25 mg/kg QD together with azacitidine starting at the same time as azacitidine treatment (concurrent combination), and Compound I 25 mg/kg QD together with azacitidine starting on the day after the completion of azacitidine treatment (sequential combination), respectively. On day 11, Compound I and azacitidine treatment resulted in TGIs of 75% and 67%, respectively (FIG. 13a). In contrast, Compound I and azacitidine concurrent combination and sequential combination resulted in TGIs of 98% and 96%, respectively (FIG. 13a). There was no significant body weight loss being observed during treatment (FIG. 13b).

[0529] Example 14: Anti-tumor effect of Compound I in combination with carboplatin in the OVCAR3 CDX tumor model

OVCAR3 is a cell line established from the malignant ascites of a patient with progressive adenocarcinoma of the ovary. Carboplatin is a standard of care medicine to treat ovarian cancers. In this study, four groups of mice bearing OVCAR3 tumors were treated with vehicle QD, carboplatin 50 mg/kg QW, Compound I 25 mg/kg QD, and Compound I 25 mg/kg QD together with carboplatin 50 mg/kg QW. On day 28, Compound I treatment and carboplatin treatment resulted in TGIs of 77% and 56%, respectively (FIG. 14a). In contrast, the Compound I and carboplatin combination resulted in 97% TGI (FIG. 14a). There was no significant body weight loss being observed during treatment (FIG. 14b).

[0530] Example 15: Anti-tumor effect of Compound I in combination with osimertinib in the H1975 CDX tumor model

H1975 is a non-small cell lung cancer (NSCLC) cell line carrying a RBM10 mutation in addition to the EGFR L858R/T790M mutation. Osimertinib is a medicine to treat NSCLC patients with EGFR classical mutations. In this study, four groups of mice bearing H1975 tumors were treated with vehicle QD, osimertinib 1 mg/kg QD, Compound I 25 mg/kg QD, and Compound I 25 mg/kg QD together with osimertinib 1 mg/kg QD. On day 22, Compound I and osimertinib treatment resulted in TGIs of 65% and 26%, respectively (FIG. 15a). In contrast, Compound I and osimertinib combination resulted in 108% TGI (FIG. 15a) and induced tumor regression in 6 out of 10 mice. There was no significant body weight loss being observed during treatment (FIG. 15b).

[0531] Example 16: Anti-tumor effect of Compound I in combination with adagrasib in the SW1463 CDX tumor model.

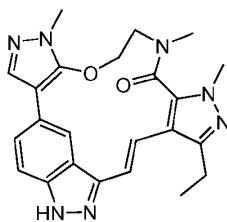
SW1463 is a colorectal cancer (CRC) cell line carrying the KRAS G12C mutation. Adagrasib is medicine targeting the KRAS G12C mutation in NSCLC and is being investigated in clinical studies to target CRC patients with the KRAS G12C mutation. In this study, four groups of mice bearing SW1643 tumors were treated with vehicle QD, adagrasib 30 mg/kg QD, Compound I 25 mg/kg QD, and Compound I 25 mg/kg QD together with adagrasib 30 mg/kg QD. On day 15, adagrasib treatment did not show any tumor growth inhibition at all (FIG. 16a). Compound I treatment resulted in TGI of 24%, whereas the Compound I treatment combined with adagrasib resulted in TGI of 56% (FIG. 16a). Using the tumor size of 2000 mm³ as the criteria for death, the combined treatment of Compound I and adagrasib led to longest median survival of 21 days, significant longer than that of 15 days in vehicle treated group (FIG. 16b). There is no apparent body weight loss observed for the mice during treatment (FIG. 16c).

[0532] Example 17: Anti-tumor effect of Compound I in combination with cytarabine in the MOLM-13 CDX tumor model.

Cytarabine is a standard of care medicine used for treating AML patients. In this study, four groups of mice bearing MOLM-13 tumors were treated with vehicle QD, cytarabine 50 mg/kg QD for 7 days (QDx7, IP), Compound I 25 mg/kg QD, Compound I 25 mg/kg QD together with cytarabine 50 mg/kg QD for 7 days (QDx7, IP) starting at the same time, respectively. On day 11, Compound I and cytarabine treatment resulted in TGIs of 75% and 33%, respectively (FIG. 17a). In contrast, Compound I and cytarabine combination resulted in TGIs of 95% (FIG. 17a). There was no significant body weight loss being observed during treatment (FIG. 17b).

WHAT IS CLAIMED IS:

1. A method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a CLK inhibitor, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.
2. The method of claim 1, wherein the CLK inhibitor is of the formula I



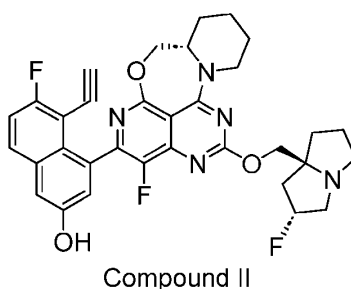
I

or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or 2, wherein the cancer is a liquid tumor or a solid tumor.
4. The method of any one of the preceding claims, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.
5. The method of any one of the preceding claims, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS),

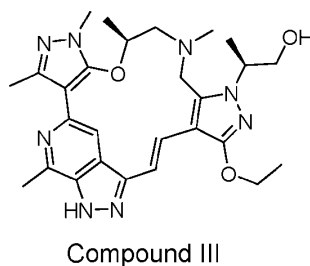
small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

6. The method of any one of the preceding claims, wherein the cancer is acute myeloid leukemia (AML).
7. The method of any one of claims 1 to 5, wherein the cancer is chronic lymphocytic leukemia (CLL).
8. The method of any one of claims 1 to 5, wherein the cancer is non-small cell lung cancer (NSCLC).
9. The method of any one of claims 1 to 5, wherein the cancer is ovarian cancer.
10. The method of any one of the preceding claims, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.
11. The method of claim 10, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.
12. The method of claim 10, wherein the additional anti-cancer agent is a FLT3 inhibitor.
13. The method of claim 10, wherein the additional anti-cancer agent is a KRAS inhibitor.
14. The method of claim 13, wherein the KRAS inhibitor is compound II having the formula



or a pharmaceutically acceptable salt thereof.

15. The method of claim 10, wherein the additional anti-cancer agent is an ALK inhibitor.
16. The method of claim 10, wherein the additional anti-cancer agent is an EGFR inhibitor.
17. The method of claim 16, wherein the EGFR inhibitor is compound III having the formula



or a pharmaceutically acceptable salt thereof.

18. The method of claim 16, wherein the EGFR inhibitor is osimertinib.

19. The method of any one of claims 1 to 13, 15, or 16, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

20. The method of any one of claims 1 to 11, or 19, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

21. The method of any one of claims 1 to 10, 12, or 19, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

22. The method of any one of claims 1 to 10, 13, or 19, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

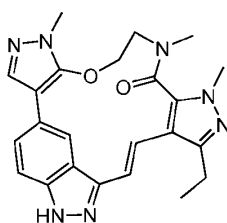
23. The method of any one of claims 1 to 10, 13, or 19, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

24. The method of any one of the preceding claims, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

25. The method of any one of the preceding claims, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

26. A CLK inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

27. The compound of claim 26, wherein the CLK inhibitor is of the formula I



I

or a pharmaceutically acceptable salt thereof.

28. The compound of claim 26 or 27, wherein the cancer is a liquid tumor or a solid tumor.

29. The compound of any one of claims 26 to 28, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL),

myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

30. The compound of any one of claims 26 to 29, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

31. The compound of any one of claims 26 to 30, wherein the cancer is acute myeloid leukemia (AML).

32. The compound of any one of claims 26 to 30, wherein the cancer is chronic lymphocytic leukemia (CLL).

33. The compound of any one of claims 26 to 30, wherein the cancer is non-small cell lung cancer (NSCLC).

34. The compound of any one of claims 26 to 30, wherein the cancer is ovarian cancer.

35. The compound of any one of claims 26 to 34, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

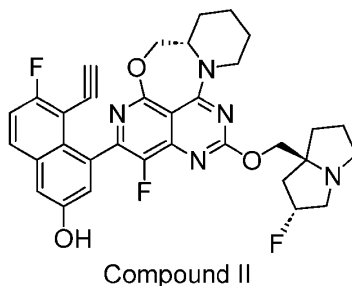
36. The compound of claim 35, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

37. The compound of claim 35, wherein the additional anti-cancer agent is a FLT3 inhibitor.

38. The compound of claim 35, wherein the additional anti-cancer agent is a KRAS inhibitor.

39. The compound of claim 38, wherein the KRAS inhibitor is compound II having the

formula

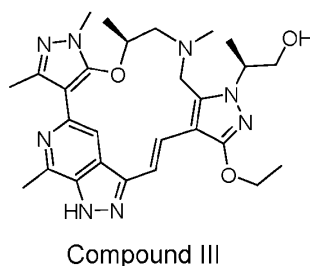


or a pharmaceutically acceptable salt thereof.

40. The compound of claim 35, wherein the additional anti-cancer agent is an ALK inhibitor.

41. The compound of claim 35, wherein the additional anti-cancer agent is an EGFR inhibitor.

42. The compound of claim 41, wherein the EGFR inhibitor is compound III having the formula



or a pharmaceutically acceptable salt thereof.

43. The compound of claim 41, wherein the EGFR inhibitor is osimertinib.

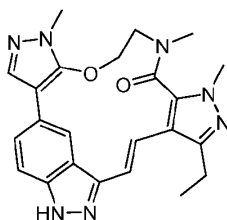
44. The compound of any one of claims 26 to 38, 40, or 41, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

45. The compound of any one of claims 26 to 36, or 44, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

46. The compound of any one of claims 26 to 35, 37, or 44, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

47. The compound of any one of claims 26 to 35, 38, or 44, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

48. The compound of any one of claims 26 to 35, 38, or 44, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.
49. The compound of any one of claims 26 to 48, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.
50. The compound of any one of the claims 26 to 49, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.
51. Use of a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent.
52. The use of claim 51, wherein the CLK inhibitor is of the formula I



melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

55. The use of any one of claims 51 to 54, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

56. The use of any one of claims 51 to 55, wherein the cancer is acute myeloid leukemia (AML).

57. The use of any one of claims 51 to 55, wherein the cancer is chronic lymphocytic leukemia (CLL).

58. The use of any one of claims 51 to 55, wherein the cancer is non-small cell lung cancer (NSCLC).

59. The use of any one of claims 51 to 55, wherein the cancer is ovarian cancer.

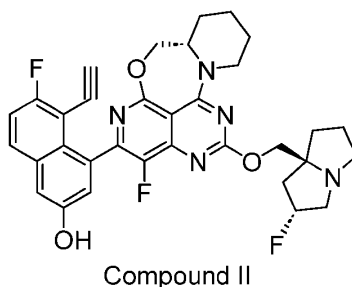
60. The use of any one of claims 51 to 59, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

61. The use of claim 60, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

62. The use of claim 60, wherein the additional anti-cancer agent is a FLT3 inhibitor.

63. The use of claim 60, wherein the additional anti-cancer agent is a KRAS inhibitor.

64. The use of claim 63, wherein the KRAS inhibitor is compound II having the formula

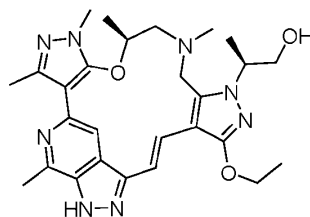


or a pharmaceutically acceptable salt thereof.

65. The use of claim 60, wherein the additional anti-cancer agent is an ALK inhibitor.

66. The use of claim 60, wherein the additional anti-cancer agent is an EGFR inhibitor.

67. The use of claim 66, wherein the EGFR inhibitor is compound III having the formula



Compound III

or a pharmaceutically acceptable salt thereof.

68. The use of claim 66, wherein the EGFR inhibitor is osimertinib.

69. The use of any one of claims 51 to 63, 65, or 66, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

70. The use of any one of claims 51 to 61, or 69, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

71. The use of any one of claims 51 to 60, 62, or 69, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

72. The use of any one of claims 51 to 60, 63, or 69, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

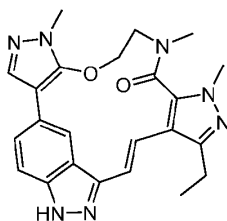
73. The use of any one of claims 51 to 60, 63, or 69, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

74. The use of any one of claims 51 to 73, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

75. The use of any one of claims 51 to 74, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

76. A composition comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

77. The composition of claim 76, wherein the CLK inhibitor is of the formula I



I

or a pharmaceutically acceptable salt thereof.

78. The composition of claim 76 or 77, wherein the cancer is a liquid tumor or a solid tumor.

79. The composition of any one of claims 76 to 78, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

80. The composition of any one of claims 76 to 79, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

81. The composition of any one of claims 76 to 80, wherein the cancer is acute myeloid leukemia (AML).

82. The composition of any one of claims 76 to 80, wherein the cancer is chronic

lymphocytic leukemia (CLL).

83. The composition of any one of claims 76 to 80, wherein the cancer is non-small cell lung cancer (NSCLC).

84. The composition of any one of claims 76 to 80, wherein the cancer is ovarian cancer.

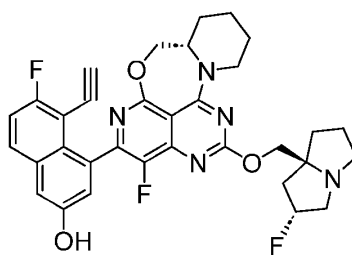
85. The composition of any one of claims 76 to 84, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

86. The composition of claim 85, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

87. The composition of claim 85, wherein the additional anti-cancer agent is a FLT3 inhibitor.

88. The composition of claim 85, wherein the additional anti-cancer agent is a KRAS inhibitor.

89. The composition of claim 88, wherein the KRAS inhibitor is compound II having the formula



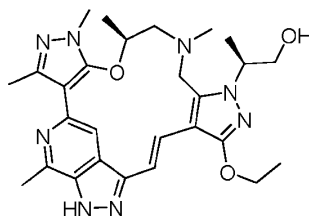
Compound II

or a pharmaceutically acceptable salt thereof.

90. The composition of claim 85, wherein the additional anti-cancer agent is an ALK inhibitor.

91. The composition of claim 85, wherein the additional anti-cancer agent is an EGFR inhibitor.

92. The composition of claim 91, wherein the EGFR inhibitor is compound III having the formula



Compound III

or a pharmaceutically acceptable salt thereof.

93. The composition of claim 91, wherein the EGFR inhibitor is osimertinib.

94. The composition of any one of claims 76 to 88, 90, or 91, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

95. The composition of any one of claims 76 to 86, or 94, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

96. The composition of any one of claims 76 to 85, 87, or 94, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

97. The composition of any one of claims 76 to 85, 88, or 94, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

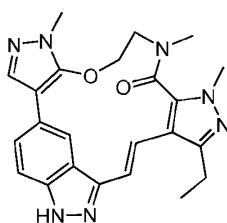
98. The composition of any one of claims 76 to 85, 88, or 94, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

99. The composition of any one of claims 76 to 98, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

100. The composition of any one of claims 76 to 99, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

101. A medicament comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, combined with at least one additional anti-cancer agent in fixed or free combination.

102. The medicament of claim 101, wherein the CLK inhibitor is of the formula I



I

or a pharmaceutically acceptable salt thereof.

103. The medicament of claim 101 or 102, wherein the cancer is a liquid tumor or a solid tumor.

104. The medicament of any one of claims 101 to 103, wherein the cancer is selected from

the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

105. The medicament of any one of claims 101 to 104, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

106. The medicament of any one of claims 101 to 105, wherein the cancer is acute myeloid leukemia (AML).

107. The medicament of any one of claims 101 to 105, wherein the cancer is chronic lymphocytic leukemia (CLL).

108. The medicament of any one of claims 101 to 105, wherein the cancer is non-small cell lung cancer (NSCLC).

109. The medicament of any one of claims 101 to 105, wherein the cancer is ovarian cancer.

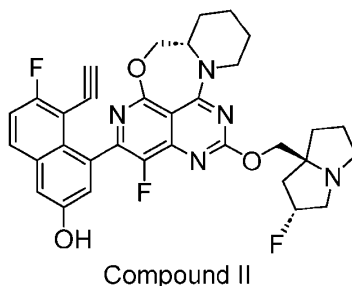
110. The medicament of any one of claims 101 to 109, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

111. The medicament of claim 110, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

112. The medicament of claim 110, wherein the additional anti-cancer agent is a FLT3 inhibitor.

113. The medicament of claim 110, wherein the additional anti-cancer agent is a KRAS inhibitor.

114. The medicament of claim 113, wherein the KRAS inhibitor is compound II having the formula

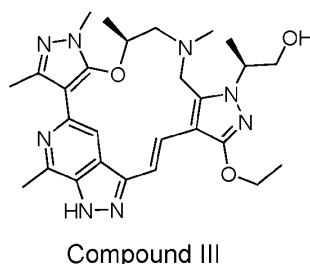


or a pharmaceutically acceptable salt thereof.

115. The medicament of claim 110, wherein the additional anti-cancer agent is an ALK inhibitor.

116. The medicament of claim 110, wherein the additional anti-cancer agent is an EGFR inhibitor.

117. The medicament of claim 116, wherein the EGFR inhibitor is compound III having the formula



or a pharmaceutically acceptable salt thereof.

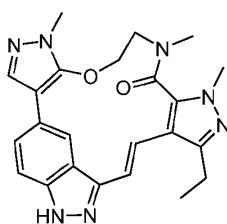
118. The medicament of claim 116, wherein the EGFR inhibitor is osimertinib.

119. The medicament of any one of claims 101 to 113, 115, or 116, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

120. The medicament of any one of claims 101 to 111, or 119, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

121. The medicament of any one of claims 101 to 110, 112, or 119, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

122. The medicament of any one of claims 101 to 110, 113, or 119, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.
123. The medicament of any one of claims 101 to 110, 113, or 119, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.
124. The medicament of any one of claims 101 to 123, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.
125. The medicament of any one of claims 101 to 124, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.
126. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other at a locus.
127. The synergistic composition of claim 126, wherein the CLK inhibitor is of the formula I



I

- or a pharmaceutically acceptable salt thereof.
128. The synergistic composition of claim 126 or 127, wherein the cancer is a liquid tumor or a solid tumor.
129. The synergistic composition of any one of claims 126 to 128, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid

carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

130. The synergistic composition of any one of claims 126 to 129, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

131. The synergistic composition of any one of claims 126 to 130, wherein the cancer is acute myeloid leukemia (AML).

132. The synergistic composition of any one of claims 126 to 130, wherein the cancer is chronic lymphocytic leukemia (CLL).

133. The synergistic composition of any one of claims 126 to 130, wherein the cancer is non-small cell lung cancer (NSCLC).

134. The synergistic composition of any one of claims 126 to 130, wherein the cancer is ovarian cancer.

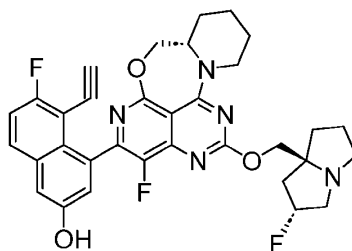
135. The synergistic composition of any one of claims 126 to 134, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

136. The synergistic composition of claim 135, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

137. The synergistic composition of claim 135, wherein the additional anti-cancer agent is a FLT3 inhibitor.

138. The synergistic composition of claim 135, wherein the additional anti-cancer agent is a KRAS inhibitor.

139. The synergistic composition of claim 138, wherein the KRAS inhibitor is compound II having the formula



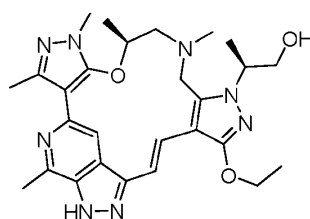
Compound II

or a pharmaceutically acceptable salt thereof.

140. The synergistic composition of claim 135, wherein the additional anti-cancer agent is an ALK inhibitor.

141. The synergistic composition of claim 135, wherein the additional anti-cancer agent is an EGFR inhibitor.

142. The synergistic composition of claim 141, wherein the EGFR inhibitor is compound III having the formula



Compound III

or a pharmaceutically acceptable salt thereof.

143. The synergistic composition of claim 141, wherein the EGFR inhibitor is osimertinib.

144. The synergistic composition of any one of claims 126 to 138, 140, or 141, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

145. The synergistic composition of any one of claims 126 to 136, or 144, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

146. The synergistic composition of any one of claims 126 to 135, 137, or 144, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

147. The synergistic composition of any one of claims 126 to 135, 138, or 144, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

148. The synergistic composition of any one of claims 126 to 135, 138, or 144, wherein the

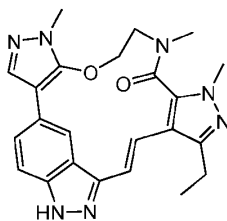
additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

149. The synergistic composition of any one of claims 126 to 148, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

150. The synergistic composition of any one of claims 126 to 149, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.

151. A synergistic composition of a CLK inhibitor and at least one additional anti-cancer agent, where the two components come into contact with each other only in the human body.

152. The synergistic composition of claim 151, wherein the CLK inhibitor is of the formula I



I

or a pharmaceutically acceptable salt thereof.

153. The synergistic composition of claim 151 or 152, wherein the cancer is a liquid tumor or a solid tumor.

154. The synergistic composition of any one of claims 151 to 153, wherein the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER⁺ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, chronic myelomonocytic leukemia (CML), pediatric glioma, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin

lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

155. The synergistic composition of any one of claims 151 to 154, wherein the cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), bladder cancer, ovarian cancer, prostate cancer, colon cancer, neuroblastoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer.

156. The synergistic composition of any one of claims 151 to 155, wherein the cancer is acute myeloid leukemia (AML).

157. The synergistic composition of any one of claims 151 to 155, wherein the cancer is chronic lymphocytic leukemia (CLL).

158. The synergistic composition of any one of claims 151 to 155, wherein the cancer is non-small cell lung cancer (NSCLC).

159. The synergistic composition of any one of claims 151 to 155, wherein the cancer is ovarian cancer.

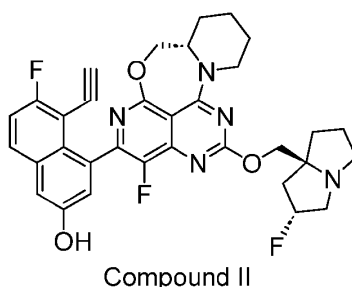
160. The synergistic composition of any one of claims 151 to 159, wherein the additional anti-cancer agent is a Bcl-2 inhibitor, a FLT3 inhibitor, a KRAS inhibitor, an ALK inhibitor, a PARP inhibitor, or an EGFR inhibitor.

161. The synergistic composition of claim 160, wherein the additional anti-cancer agent is a Bcl-2 inhibitor.

162. The synergistic composition of claim 160, wherein the additional anti-cancer agent is a FLT3 inhibitor.

163. The synergistic composition of claim 160, wherein the additional anti-cancer agent is a KRAS inhibitor.

164. The synergistic composition of claim 163, wherein the KRAS inhibitor is compound II having the formula

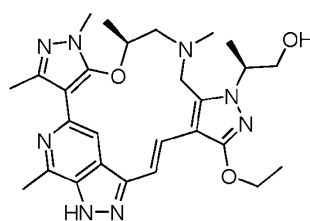


or a pharmaceutically acceptable salt thereof.

165. The synergistic composition of claim 160, wherein the additional anti-cancer agent is an ALK inhibitor.

166. The synergistic composition of claim 160, wherein the additional anti-cancer agent is an EGFR inhibitor.

167. The synergistic composition of claim 166, wherein the EGFR inhibitor is compound III having the formula



Compound III

or a pharmaceutically acceptable salt thereof.

168. The synergistic composition of claim 166, wherein the EGFR inhibitor is osimertinib.

169. The synergistic composition of any one of claims 151 to 163, 165, or 166, wherein the additional anti-cancer agent is venetoclax, gilteritinib, MRTX1133, adagrasib, sotorasib, crizotinib, lorlatinib, afatinib, gefitinib, osimertinib, azacitidine, carboplatin, cytarabine, or decitabine or pharmaceutically acceptable salts thereof.

170. The synergistic composition of any one of claims 151 to 161, or 169, wherein the additional anti-cancer agent is venetoclax, or a pharmaceutically acceptable salt thereof.

171. The synergistic composition of any one of claims 151 to 160, 162, or 169, wherein the additional anti-cancer agent is gilteritinib, or a pharmaceutically acceptable salt thereof.

172. The synergistic composition of any one of claims 151 to 160, 163, or 169, wherein the additional anti-cancer agent is MRTX1133, adagrasib, or sotorasib, or a pharmaceutically acceptable salt thereof.

173. The synergistic composition of any one of claims 151 to 160, 163, or 169, wherein the additional anti-cancer agent is adagrasib or sotorasib, or a pharmaceutically acceptable salt thereof.

174. The synergistic composition of any one of claims 151 to 173, wherein the CLK inhibitor in combination with a therapeutically effective amount of at least one additional anti-cancer agent provides an HSA synergy score of at least about 11 in a cancer cell line.

175. The synergistic composition of any one of claims 151 to 174, wherein the CLK inhibitor in combination with the at least one additional anti-cancer agent provides an HSA synergy score of at least about 15 in a cancer cell line.