

INDAZOLE MACROCYCLE POLYMORPHS

RELATED APPLICATIONS

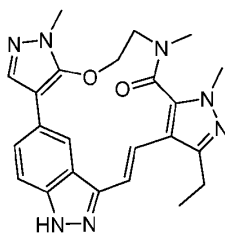
[001] This application claims the benefit of U.S. Provisional Application No. 63/725,441, filed November 26, 2024, and U.S. Provisional Application No. 63/607,349, filed December 7, 2023, the entire disclosures of all of which are incorporated herein by reference.

TECHNICAL FIELD

[002] This disclosure relates to polymorphs 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 that are useful in the treatment of disease, such as cancer, in mammals. This disclosure also relates to the preparation of such polymorphs. This disclosure also relates to compositions including such polymorphs, and to methods of using such compositions in the treatment of diseases, such as cancer, in mammals, especially in humans.

BACKGROUND

[003] The compound, (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 (also herein referred to as “Compound I”), represented by the formula I



I

is a potent small-molecule multi-kinase inhibitor showing activity against CLKs (Cdc2-like-kinases; CLK1, CLK2, CLK3, and CLK4), dual-specificity tyrosine-regulated kinases (DYRK1/2), proto-oncogene, serine/threonine kinase (PIM3), and fms-like tyrosine kinase (FLT3). Compound I has properties, including anti-tumor properties, that are pharmacologically mediated through, for example, suppressed tumor cell growth and induced apoptosis by modulating pre-mRNA splicing. Compound I is disclosed in International Patent Publication No. WO2023/240140, which is incorporated herein by reference in its entirety.

[004] 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 (Levitzki, 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).

[005] Alternative splicing plays a critical role in tumorigenesis, cancer progression, and treatment resistance *via* multiple mechanisms, including increased cell proliferation, decreased apoptosis, enhanced migration and metastatic potential, and induced resistance to chemotherapy and evasion of immune surveillance (Bradley 2023). Serine and arginine-rich splicing factors (SRSF) are RNA-binding proteins (RBPs) regulating both constitutive and alternative splicing. The Cdc2-like kinase (CLK) family and DYRK1A modulate the phosphorylation of SRSFs (SRSF1–12), leading to the regulation of spliceosome molecular machinery, exon recognition, and alternative splicing. Thus, targeting CLK/DYRK1A kinases may provide opportunities in modulating cancer-associated aberrant alternative splicing for cancer treatment.

[006] 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.

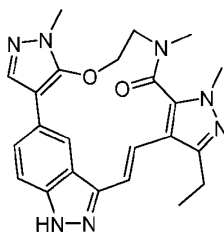
[007] While Compound I has found application in treating disease through inhibition of CLKs (CLK1, CLK2, CLK3, and CLK4), DYRK1/2, PIM3, and/or FLT3), it is advantageous to have polymorphic forms having improved properties, such as improved crystallinity, dissolution properties, and/or decreased hygroscopicity, while maintaining chemical and enantiomeric stability properties, and/or to provide enhanced efficacy through improved or modified PKPD properties (e.g., bioavailability), drug product dissolution properties, and the like.

SUMMARY

[008] In one aspect, the present disclosure provides a crystalline form 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).

[009] In another embodiment, the crystalline polymorph form 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 is anhydrous. In another embodiment, the crystalline polymorph form 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 is a solvate. In another embodiment, the crystalline polymorph form 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 is a hydrate, such as a pentahydrate, a tetrahydrate, a trihydrate, a dihydrate, or a monohydrate.

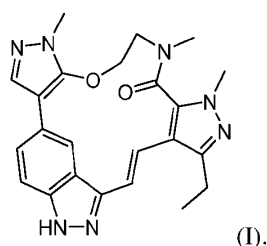
[010] In some embodiments, Compound I can be represented by the formula



I,

where the Compound I has been shown to exist as form A (a.k.a. crystalline polymorph form A), form B (a.k.a. pentahydrate crystalline polymorph form B), form C (a.k.a. crystalline polymorph form C), or form D (a.k.a. solvate crystalline polymorph form D) as described herein.

[011] The present disclosure further provides a pharmaceutical composition comprising a polymorph form (e.g., form A, B, C, or D) of Compound I of the formula



[012] The present disclosure further provides a capsule comprising pharmaceutical compositions as described herein.

[013] The present disclosure further provides a tablet comprising pharmaceutical compositions as described herein.

[014] In another aspect, the disclosure provides a method of treating disease, especially cancer, in a mammal, including a human, the method comprising administering to the mammal a therapeutically effective amount of a polymorph form (e.g., form A, B, C, or D) 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, as described herein, or a pharmaceutical composition comprising a polymorph form (e.g., form A, B, C, or D) 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, as described herein.

[015] In one embodiment, the present disclosure provides a method of treating abnormal cell growth in a mammal, including a human, in need of such treatment comprising, administering to said mammal a therapeutically effective amount of a free base polymorph form (e.g., form A, B, C, or D) of Compound I.

[016] 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.

[017] 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.

[018] 1. A crystalline polymorph form of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.

[019] 2. The crystalline polymorph form of clause 1, wherein the crystalline polymorph form is an anhydrous polymorph form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.

[020] 3. The crystalline polymorph form of clause 1, wherein the crystalline polymorph form is a hydrate or solvate polymorph form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.

[021] 4. The crystalline polymorph form of clause 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

[022] 5. The crystalline polymorph form of clause 1, 2, or 4, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2 θ) of 7.1 $\pm$ 0.1.

[023] 6. The crystalline polymorph form of clause 1, 2, 4, or 5, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1 and 21.1 $\pm$ 0.1.

[024] 7. The crystalline polymorph form of any one of clauses 1, 2, or 4-6, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 18.1 $\pm$ 0.1, and 21.1 $\pm$ 0.1.

[025] 8. The crystalline polymorph form of any one of clauses 1, 2, or 4-7, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 18.1 $\pm$ 0.1, 21.1 $\pm$ 0.1, and 25.1 $\pm$ 0.1.

[026] 9. The crystalline polymorph form of any one of claims 1, 2, or 4-8, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 17.6 $\pm$ 0.1, 18.1 $\pm$ 0.1, 21.1 $\pm$ 0.1, and 25.1 $\pm$ 0.1.

[027] 10. The crystalline polymorph form of any one of claims 1, 2, or 4-9, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 14.2 $\pm$ 0.1, 17.6 $\pm$ 0.1, 18.1 $\pm$ 0.1, 21.1 $\pm$ 0.1, and 25.1 $\pm$ 0.1.

[028] 11. The crystalline polymorph form of any one of clauses 1, 2 or 4-10, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising

peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

[029] 12. The crystalline polymorph form of clause 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 1A.

[030] 13. The crystalline polymorph form of any one of clauses 1, 2 or 4-12, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 0.6% to about 1.4% when heated from about 25° C. to about 320° C.

[031] 14. The crystalline polymorph form of any one of clauses 1, 2 or 4-12, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 5A.

[032] 15. The crystalline polymorph form of any one of clauses 1, 2 or 4-14, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 290 °C to about 295 °C.

[033] 16. The crystalline polymorph form of any one of clauses 1, 2 or 4-15, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 5B.

[034] 17. The crystalline polymorph form of clause 1 or 3, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 .

[035] 18. The crystalline polymorph form of clause 1, 3 or 17, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.8 ± 0.1 .

[036] 19. The crystalline polymorph form of any one of clauses 1, 3, 17, or 18, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8 ± 0.1 and 23.8 ± 0.1 .

[037] 20. The crystalline polymorph form of any one of clauses 1, 3, or 17-19, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

[038] 21. The crystalline polymorph form of any one of clauses 1, 3, or 17-20, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

[039] 22. The crystalline polymorph form of any one of clauses 1, 3 or 17-21, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

[040] 23. The crystalline polymorph form of any one of clauses 1, 3, or 17-22, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 .

[041] 24. The crystalline polymorph form of any one of clauses 1, 3, or 17-23, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern

comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 .

[042] 25. The crystalline polymorph form of clause 1 or 3, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 2.

[043] 26. The crystalline polymorph form of any one of clauses 1, 3 or 17-25, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 13% to about 18% when heated from about 25° C. to about 320° C.

[044] 27. The crystalline polymorph form of any one of clauses 1, 2 or 17-26, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 6A.

[045] 28. The crystalline polymorph form of any one of clauses 1, 2 or 17-27, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 88 °C to about 93 °C, an exotherm with an onset at about 215 °C to about 220 °C, and an endotherm with an onset at about 293 °C to about 298 °C.

[046] 29. The crystalline polymorph form of any one of clauses 1, 2 or 17-28, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 6B.

[047] 30. The crystalline polymorph form of clause 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising

one or more peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[048] 31. The crystalline polymorph form of clause 1, 2, or 30, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 25.0 ± 0.1 .

[049] 32. The crystalline polymorph form of clause 1, 2, 30, or 31, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 18.5 ± 0.1 and 25.0 ± 0.1 .

[050] 33. The crystalline polymorph form of any one of clauses 1, 2, or 30-32, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[051] 34. The crystalline polymorph form of any one of clauses 1, 2, or 30-33, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.9 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[052] 35. The crystalline polymorph form of any one of clauses 1, 2, or 30-34, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[053] 36. The crystalline polymorph form of any one of clauses 1, 2, or 30-35, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[054] 37. The crystalline polymorph form of any one of clauses 1, 2, or 30-36, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-

8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 9.5 $\pm$ 0.1, 12.9 $\pm$ 0.1, 13.4 $\pm$ 0.1, 15.8 $\pm$ 0.1, 17.5 $\pm$ 0.1, 18.5 $\pm$ 0.1, and 25.0 $\pm$ 0.1.

[055] 38. The crystalline polymorph form of clause 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 3.

[056] 39. The crystalline polymorph form of any one of clauses 1, 2 or 30-38, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of less than about 1% when heated from about 25° C. to about 320° C.

[057] 40. The crystalline polymorph form of any one of clauses 1, 2 or 30-39, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 7A.

[058] 41. The crystalline polymorph form of any one of clauses 1, 2 or 30-40, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 240 °C to about 245 °C, an exotherm with an onset at about 248 °C to about 253 °C, and an endotherm with an onset at about 293 °C to about 298 °C.

[059] 42. The crystalline polymorph form of any one of clauses 1, 2 or 30-41, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 7B.

[060] 43. A crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:

- [061] (a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 14.0 $\pm$ 0.1, 14.2 $\pm$ 0.1, 17.6 $\pm$ 0.1, 18.1 $\pm$ 0.1, 21.1 $\pm$ 0.1, and 25.1 $\pm$ 0.1;
- [062] (b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 1A;
- [063] (c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 0.6% to about 1.4% when heated from about 25 °C to about 320 °C;
- [064] (d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 5A;
- [065] (e) a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 290 °C to about 295 °C; and
- [066] (f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 5B.
- [067] 44. The crystalline polymorph form of clause 43, having at least two of characteristics (a)-(f).
- [068] 45. The crystalline polymorph form of clause 43, having at least three of characteristics (a)-(f).
- [069] 46. A pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:
- [070] (a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2 θ) of 7.3 $\pm$ 0.1, 7.9 $\pm$ 0.1, 13.7 $\pm$ 0.1, 15.8 $\pm$ 0.1, 17.1 $\pm$ 0.1, 23.0 $\pm$ 0.1, and 23.8 $\pm$ 0.1;
- [071] (b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 2;
- [072] (c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 13% to about 18% when heated from about 25 °C to about 320 °C;
- [073] (d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 6A;
- [074] (e) a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 88°C to about 93°C, an exotherm with an onset at about 215 °C to about 220 °C, and an endotherm with an onset at about 293 °C to about 298 °C; and
- [075] (f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 6B.
- [076] 47. The crystalline polymorph form of clause 46, having at least two of characteristics (a)-(f).
- [077] 48. The crystalline polymorph form of clause 46, having at least three of characteristics (a)-(f).

- [078] 49. A crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:
- [079] (a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2 θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 ;
- [080] (b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 3;
- [081] (c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of less than about 1% when heated from about 25 °C to about 320 °C;
- [082] (d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 7A;
- [083] (e) a differential scanning calorimetry (DSC) having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 240 °C to about 245 °C, an exotherm with an onset at about 248 °C to about 253 °C, and an endotherm with an onset at about 293 °C to about 298 °C; and
- [084] (f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 7B.
- [085] 50. The crystalline polymorph form of clause 49, having at least two of characteristics (a)-(f).
- [086] 51. The crystalline polymorph form of clause 49, having at least three of characteristics (a)-(f).
- [087] 52. A pharmaceutical composition comprising a crystalline polymorph according to any one of clauses 1-51 and at least one pharmaceutically acceptable excipient.
- [088] 53. The pharmaceutical composition of clause 52, comprising at least one of a filler, a disintegrant, a lubricant, and a wetting agent.
- [089] 54. The pharmaceutical composition of clause 52 or 53, wherein the composition is for oral administration.
- [090] 55. The pharmaceutical composition of any one of clauses 52-54, comprising about 1 mg to about 100 mg of the crystalline polymorph.
- [091] 56. The pharmaceutical composition of any one of clauses 52-54, comprising about 1 mg to about 50 mg of the crystalline polymorph.
- [092] 57. The pharmaceutical composition of any one of clauses 52-54, comprising about 5 mg to about 100 mg of the crystalline polymorph.
- [093] 58. The pharmaceutical composition of any one of clauses 52-54, comprising about 5 mg of the crystalline polymorph.

- [094] 59. The pharmaceutical composition of any one of clauses 52-54, comprising about 20 mg of the crystalline polymorph.
- [095] 60. The pharmaceutical composition of any one of clauses 52-54, comprising about 30 mg of the crystalline polymorph.
- [096] 61. The pharmaceutical composition of any one of clauses 52-54, wherein the composition comprises a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
- [097] 62. The pharmaceutical composition of clause 61, wherein the composition comprises at least two of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
- [098] 63. The pharmaceutical composition of clause 61, wherein the composition comprises at least three of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
- [099] 64. The pharmaceutical composition of clause 61, wherein the composition comprises a filler and at least two of a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
- [0100] 65. The pharmaceutical composition of clause 61, wherein the filler is present at about 50% to about 90% by weight of the formulation.
- [0101] 66. The pharmaceutical composition of clause 61 or 65, wherein the filler is a mixture of two or more fillers.
- [0102] 67. The pharmaceutical composition of any one of clauses 61, 65, or 66, wherein the binder is present at about 1% to about 10% by weight of the formulation.
- [0103] 68. The pharmaceutical composition of any one of clauses 61 or 65 to 67, wherein the disintegrant is about 1% to about 10 % by weight of the formulation.
- [0104] 69. The pharmaceutical composition of any one of clauses 61 or 65 to 68, wherein the disintegrant is a mixture of two or more disintegrants.
- [0105] 70. The pharmaceutical composition of any one of clauses 61 or 65 to 69, wherein the surfactant is about 3% to about 20 % by weight of the formulation.
- [0106] 71. The pharmaceutical composition of any one of clauses 61 or 65 to 70, wherein the glidant is about 0.1% to about 3% by weight of the formulation.
- [0107] 72. The pharmaceutical composition of any one of clauses 61 or 65 to 71, wherein the lubricant is about 0.1% to about 3% by weight of the formulation.
- [0108] 73. The pharmaceutical composition of clause 61, wherein the composition comprises [0109] about 3% to about 10% by weight a crystalline polymorph according to any one of clauses 1-51;

- [0110] about 50% to about 90% by weight of a filler or a mixture of fillers;
- [0111] optionally about 1% to about 10% by weight of a binder;
- [0112] optionally about 2% to about 10% of a disintegrant or a mixture of disintegrants;
- [0113] optionally about 3% to about 20% by weight of a surfactant;
- [0114] about 0.1% to about 3% by weight of a glidant; and
- [0115] about 0.1% to about 3% by weight of a lubricant.
- [0116] 74. The pharmaceutical formulation of clause 73, wherein the composition is in the form of a tablet.
- [0117] 75. The pharmaceutical composition of clause 74, wherein the composition comprises
- [0118] about 6% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0119] about 80% by weight of a filler or a mixture of fillers;
- [0120] about 5% of a disintegrant or a mixture of disintegrants;
- [0121] about 8% by weight of a surfactant;
- [0122] about 0.3% by weight of a glidant; and
- [0123] about 0.6% by weight of a lubricant.
- [0124] 76. The pharmaceutical composition of clause 74, wherein the composition comprises
- [0125] about 5% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0126] about 80% by weight of a filler or a mixture of fillers;
- [0127] about 2.5% by weight of a binder;
- [0128] about 5% of a disintegrant or a mixture of disintegrants;
- [0129] about 7% by weight of a surfactant;
- [0130] about 0.5% by weight of a glidant; and
- [0131] about 0.5% by weight of a lubricant.
- [0132] 77. The pharmaceutical composition of clause 74, wherein the composition comprises
- [0133] about 6% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0134] about 77% by weight of a filler or a mixture of fillers;
- [0135] about 3% by weight of a binder;
- [0136] about 5% of a disintegrant or a mixture of disintegrants;
- [0137] about 8% by weight of a surfactant;
- [0138] about 0.6% by weight of a glidant; and
- [0139] about 0.6% by weight of a lubricant.
- [0140] 78. The pharmaceutical formulation of clause 73, wherein the formulation is in the form of a capsule.
- [0141] 79. The pharmaceutical composition of clause 78, wherein the composition comprises

- [0142] about 7% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0143] about 73% by weight of a filler or a mixture of fillers;
- [0144] about 3% by weight of a binder;
- [0145] about 17% by weight of a surfactant;
- [0146] about 0.5% by weight of a glidant; and
- [0147] about 0.5% by weight of a lubricant.
- [0148] 80. The pharmaceutical composition of clause 78, wherein the composition comprises
- [0149] about 8% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0150] about 87% by weight of a filler or a mixture of fillers;
- [0151] about 4% by weight of a binder;
- [0152] about 0.4% by weight of a glidant; and
- [0153] about 0.6% by weight of a lubricant.
- [0154] 81. The pharmaceutical composition of clause 78, wherein the composition comprises
- [0155] about 7% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0156] about 80% by weight of a filler or a mixture of fillers;
- [0157] about 4% by weight of a binder;
- [0158] about 9% by weight of a surfactant;
- [0159] about 0.5% by weight of a glidant; and
- [0160] about 0.6% by weight of a lubricant.
- [0161] 82. The pharmaceutical composition of clause 78, wherein the composition comprises
- [0162] about 6% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0163] about 84% by weight of a filler or a mixture of fillers;
- [0164] about 3% by weight of a binder;
- [0165] about 7% by weight of a surfactant;
- [0166] about 0.6% by weight of a glidant; and
- [0167] about 0.6% by weight of a lubricant.
- [0168] 83. The pharmaceutical composition of clause 78, wherein the composition comprises
- [0169] about 6% by weight a crystalline polymorph according to any one of clauses 1-51;
- [0170] about 80% by weight of a filler or a mixture of fillers;
- [0171] about 3% by weight of a binder;
- [0172] about 4% of a disintegrant or a mixture of disintegrants;
- [0173] about 7% by weight of a surfactant;
- [0174] about 0.6% by weight of a glidant; and
- [0175] about 0.6% by weight of a lubricant.
- [0176] 84. The pharmaceutical composition of clause 61, wherein the composition comprises

- [0177] about 3 mg to about 40 mg of a crystalline polymorph according to any one of clauses 1-51;
- [0178] about 50 mg to about 500 mg of a filler or a mixture of fillers;
- [0179] optionally about 5 mg to about 20 mg of a binder;
- [0180] optionally about 1 mg to about 50 mg of a disintegrant or a mixture of disintegrants;
- [0181] optionally about 5 mg to about 75 mg by weight of a surfactant;
- [0182] about 0.1 mg to about 5 mg of a glidant; and
- [0183] about 0.1 mg to about 5 mg by weight of a lubricant.
- [0184] 85. The pharmaceutical composition of clause 61, wherein the composition comprises about 5% to about 10% by weight of the crystalline polymorph.
- [0185] 86. The pharmaceutical composition of clause 61, wherein the composition comprises about 6% by weight of the crystalline polymorph.
- [0186] 87. The pharmaceutical composition of clause 61, wherein the composition comprises about 8% by weight of the crystalline polymorph.
- [0187] 88. The pharmaceutical composition of clause 84, wherein the composition comprises about 5 mg of the crystalline polymorph.
- [0188] 89. The pharmaceutical composition of clause 84, wherein the composition comprises about 20 mg of the crystalline polymorph.
- [0189] 90. The pharmaceutical composition of clause 84, wherein the composition comprises about 30 mg of the crystalline polymorph.
- [0190] 91. The pharmaceutical composition of any one of clauses 61 to 90, wherein the filler or mixture of fillers is selected from microcrystalline cellulose, anhydrous lactose, mannitol, or a combination thereof.
- [0191] 92. The pharmaceutical composition of any one of clauses 61 to 91, wherein the binder is copovidone.
- [0192] 93. The pharmaceutical composition of any one of clauses 61 to 92, wherein the disintegrant or mixture of disintegrants is selected from croscopovidone, sodium starch glycolate, or a combination thereof.
- [0193] 94. The pharmaceutical composition of any one of clauses 61 to 93, wherein the surfactant is sodium lauryl sulfate.
- [0194] 95. The pharmaceutical composition of any one of clauses 61 to 94, wherein the glidant is silica.
- [0195] 96. The pharmaceutical composition of any one of clauses 61 to 95, wherein the lubricant is sodium stearyl fumarate.

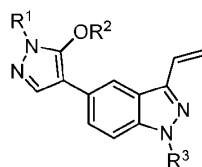
[0196] 97. A method of treating abnormal cell growth in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a crystalline polymorph according to any one of clauses 1-51 or a pharmaceutical composition according to any one of clauses 52-96.

[0197] 98. A method of treating cancer in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a crystalline polymorph according to any one of clauses 1-51 or a pharmaceutical composition according to any one of clauses 52-96.

[0198] 99. The method of clause 98, 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.

[0199] 100. The method of clause 98, wherein the cancer is acute myeloid leukemia (AML).

[0200] 101. A compound of the formula II



II

[0201] wherein R^1 is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and each of R^2 and R^3 is independently H or PG.

[0202] 102. The compound of clause 101, wherein R^1 is C₁-C₆ alkyl.

[0203] 103. The compound of clause 101 or 102, wherein R^1 is methyl.

[0204] 104. The compound of any one of clauses 101 to 103, wherein R^2 is H.

[0205] 105. The compound of any one of clauses 101 to 103, wherein R^2 is PG.

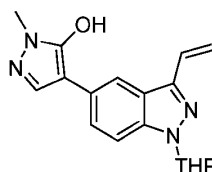
[0206] 106. The compound of any one of clauses 101 to 105, wherein R^3 is H.

[0207] 107. The compound of any one of clauses 101 to 105, wherein R^3 is PG.

[0208] 108. The compound of any one of clauses 101 to 107, wherein each PG, when present, is independently selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzyldiene, and Ts.

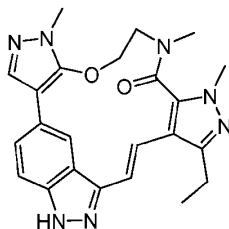
[0209] 109. The compound of any one of clauses 101 to 108, wherein each PG is THP.

[0210] 110. A compound of the formula I-2-3



I-2-3.

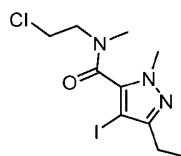
[0211] 111. A process for preparing a compound of the formula I



I

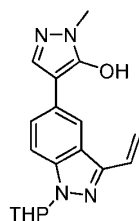
[0212] comprising

[0213] a. contacting a compound of the formula I-2-7



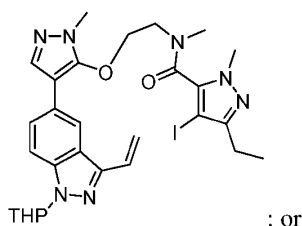
I-2-7

[0214] with a compound of the formula I-2-3



I-2-3

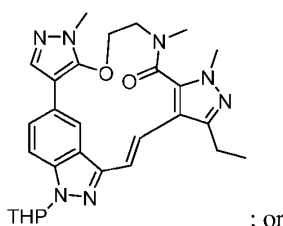
[0215] in the presence of a base to provide a compound of the formula I-2-8



; or

I-2-8

[0216] b. contacting a compound of the formula I-2-8 in the presence of a catalyst to provide a compound of the formula I-2-9



; or

I-2-9

[0217] c. contacting a compound of the formula I-2-9 with an acid to provide the compound of the formula I.

[0218] 112. The process of clause 111, wherein the base of step (a) is selected from the group consisting of Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , MgCO_3 , and CaCO_3 .

[0219] 113. The process of clause 111 or 112, wherein the base of step (a) is K_2CO_3 .

[0220] 114. The process of any one of clauses 111 to 113, wherein step (a) is carried out in the presence of an inorganic salt selected from the group consisting of NaCl , KCl , CsCl , MgCl_2 , CaCl_2 , NaBr , KBr , CsBr , MgBr_2 , CaBr_2 , NaI , KI , CsI , MgI_2 , and CaI_2 .

[0221] 115. The process of clause 114, wherein the inorganic salt is KI .

[0222] 116. The process of any one of clauses 111 to 115, wherein the catalyst of step (b) is a palladium catalyst.

[0223] 117. The process of any one of clauses 111 to 116, wherein the catalyst of step (b) is selected from the group consisting of $\text{Pd}(\text{OAc})_2$, PdCl_2 , and $\text{Pd}(\text{PPh}_3)_4$.

[0224] 118. The process of any one of clauses 111 to 117, wherein the catalyst of step (b) is Pd(OAc)₂.

[0225] 119. The process of any one of clauses 111 to 118, wherein step (b) is carried out in the presence of a base selected from the group consisting of triethylamine, diisopropylamine, K₂CO₃, Na₂CO₃, KHCO₃, NaHCO₃, NaOAc, and KOAc.

[0226] 120. The process of clause 119, wherein the base is NaHCO₃.

[0227] 121. The process of any one of clauses 111 to 120, wherein step (b) is carried out in the presence of a phase transfer catalyst selected from tetrabutylammonium chloride (TBAC) and tetrabutylammonium bromide (TBAB).

[0228] 122. The process of clause 121, wherein the phase transfer catalyst is tetrabutylammonium chloride (TBAC).

[0229] 123. The process of any one of clauses 111 to 122, wherein the acid of step (c) is a strong inorganic acid.

[0230] 124. The process of any one of clauses 111 to 123, wherein the acid of step (c) is HCl.

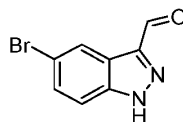
[0231] 125. The process of any one of clauses 111 to 124, comprising steps (a) and (b).

[0232] 126. The process of any one of clauses 111 to 125, comprising steps (b) and (c).

[0233] 127. The process of any one of clauses 111 to 126, comprising steps (a), (b), and (c).

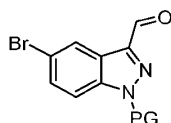
[0234] 128. A process for preparing a compound according to any one of clauses 101 to 109, the process comprising

[0235] a. contacting a compound of the formula II-1



II-1

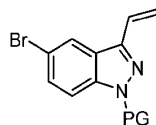
[0236] with a protecting group precursor to provide a compound of the formula II-2



II-2

[0237] wherein PG is selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzyldiene, and Ts; or

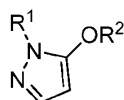
[0238] b. contacting a compound of the formula II-2 with methyltriphenylphosphonium bromide (MePPh₃Br) to provide a compound of the formula II-3



II-3

[0239] wherein PG is selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts; or

[0240] c. contacting a compound of the formula II-3 with a pyrazole of the formula II-4



II-4

[0241] in the presence of a catalyst, wherein R¹ is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and R² is H or PG, to provide the compound of the formula II.

[0242] 129. The process of clause 128, wherein the protecting group precursor of step (a) is selected from the group consisting of Fmoc-Cl, PMB-Cl, DHP, Boc₂O, Cbz-Cl, AcCl, BnBr, trityl-Cl, and TsCl.

[0243] 130. The process of clause 128 or 129, wherein the protecting group precursor of step (a) is DHP.

[0244] 131. The process of any one of clauses 128 to 130, wherein step (a) is carried out in the presence of a Lewis acid and/or a water scavenger selected from the group consisting of copper (II) sulfate, magnesium sulfate, tetraethoxytitanium, tetraisopropoxytitanium, boron trifluoride etherate, pyridinium p-toluenesulfonate (PPTS), TsOH, magnesium sulfate, sodium sulfate, tetraethoxytitanium, and tetraisopropoxytitanium.

[0245] 132. The process of clause 131, wherein the Lewis acid and/or a water scavenger is PPTS.

[0246] 133. The process of any one of clauses 128 to 132, wherein step (b) is carried out in the presence of a base selected from the group consisting of Na₂CO₃, K₂CO₃, Cs₂CO₃, MgCO₃, and CaCO₃.

[0247] 134. The process of clause 133, wherein the base is K₂CO₃.

[0248] 135. The process of any one of clauses 128 to 134, wherein the catalyst of step (c) is a palladium catalyst.

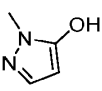
[0249] 136. The process of any one of clauses 128 to 135, wherein the catalyst of step (c) is selected from the group consisting of Pd(OAc)₂, PdCl₂, Pd(PPh₃)₄, and tBuBrettPhos Pd G3.

[0250] 137. The process of any one of clauses 128 to 136, wherein the catalyst of step (c) is tBuBrettPhos Pd G3.

[0251] 138. The process of any one of clauses 128 to 137, wherein step (c) is carried out in the presence of a base selected from the group consisting of Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , MgCO_3 , and CaCO_3 .

[0252] 139. The process of clause 138, wherein the base is K_2CO_3 .

[0253] 140. The process of any one of clauses 128 to 139, wherein the pyrazole is of the

formula , or a salt thereof.

[0254] 141. The process of any one of clauses 128 to 140, comprising steps (a) and (b).

[0255] 142. The process of any one of clauses 128 to 141, comprising steps (b) and (c).

[0256] 143. The process of any one of clauses 128 to 142, comprising steps (a), (b), and (c).

DEFINITIONS

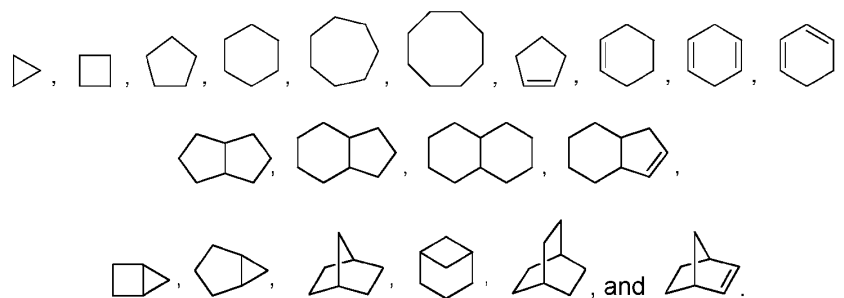
[0257] The term “alkyl” refers to a straight- or branched-chain monovalent hydrocarbon group. The term “alkylene” refers to a straight- or branched-chain divalent hydrocarbon group. In some embodiments, it can be advantageous to limit the number of atoms in an “alkyl” or “alkylene” to a specific range of atoms, such as $\text{C}_1\text{-C}_{20}$ alkyl or $\text{C}_1\text{-C}_{20}$ alkylene, $\text{C}_1\text{-C}_{12}$ alkyl or $\text{C}_1\text{-C}_{12}$ alkylene, or $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ alkylene. Examples of alkyl groups include methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples. Examples of alkylene groups include methylene ($-\text{CH}_2-$), ethylene ($(-\text{CH}_2)_2$), n-propylene ($(-\text{CH}_2)_3$), isopropylene ($(\text{C}(\text{H})(\text{CH}_3)\text{CH}_2-)$), n-butylene ($(-\text{CH}_2)_4$), and the like. It will be appreciated that an alkyl or alkylene group can be unsubstituted or substituted as described herein. An alkyl or alkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

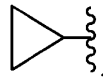
[0258] The term “alkenyl” refers to a straight- or branched-chain mono-valent hydrocarbon group having one or more double bonds. The term “alkenylene” refers to a straight- or branched-chain di-valent hydrocarbon group having one or more double bonds. In some embodiments, it can be advantageous to limit the number of atoms in an “alkenyl” or “alkenylene” to a specific range of atoms, such as $\text{C}_2\text{-C}_{20}$ alkenyl or $\text{C}_2\text{-C}_{20}$ alkenylene, $\text{C}_2\text{-C}_{12}$ alkenyl or $\text{C}_2\text{-C}_{12}$ alkenylene, or $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkenylene. Examples of alkenyl groups include ethenyl (or vinyl), allyl, and but-3-en-1-yl. Examples of alkenylene groups include ethenylene (or vinylene) ($-\text{CH}=\text{CH}-$), n-propenylene ($-\text{CH}=\text{CHCH}_2-$), iso-propenylene ($-\text{CH}=\text{CH}(\text{CH}_3)-$), and the like. Included within this term are cis and trans isomers and mixtures thereof. It will be appreciated

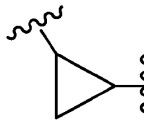
that an alkenyl or alkenylene group can be unsubstituted or substituted as described herein. An alkenyl or alkenylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0259] The term “alkynyl” refers to a straight- or branched-chain monovalent hydrocarbon group having one or more triple bonds. The term “alkynylene” refers to a straight- or branched-chain divalent hydrocarbon group having one or more triple bonds. In some embodiments, it can be advantageous to limit the number of atoms in an “alkynyl” or “alkynylene” to a specific range of atoms, such as C₂-C₂₀ alkynyl or C₂-C₂₀ alkynylene, C₂-C₁₂ alkynyl or C₂-C₁₂ alkynylene, or C₂-C₆ alkynyl or C₂-C₆ alkynylene. Examples of alkynyl groups include acetylenyl (-C≡CH) and propargyl (-CH₂C≡CH), but-3-yn-1,4-diyl (-C≡C-CH₂CH₂-), and the like. It will be appreciated that an alkynyl or alkynylene group can be unsubstituted or substituted as described herein. An alkynyl or alkynylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0260] The term “cycloalkyl” refers to a saturated or partially saturated, monocyclic or polycyclic mono-valent carbocycle. The term “cycloalkylene” refers to a saturated or partially saturated, monocyclic or polycyclic divalent carbocycle. In some embodiments, it can be advantageous to limit the number of atoms in a “cycloalkyl” or “cycloalkylene” to a specific range of atoms, such as having 3 to 12 ring atoms. Polycyclic carbocycles include fused, bridged, and spiro polycyclic systems. Illustrative examples of cycloalkyl groups include monovalent radicals of the following entities, while cycloalkylene groups include divalent radicals of the following entities, in the form of properly bonded moieties:



In particular, a cyclopropyl moiety can be depicted by the structural formula . In

particular, a cyclopropylene moiety can be depicted by the structural formula . It will be appreciated that a cycloalkyl or cycloalkylene group can be unsubstituted or substituted

as described herein. A cycloalkyl or cycloalkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

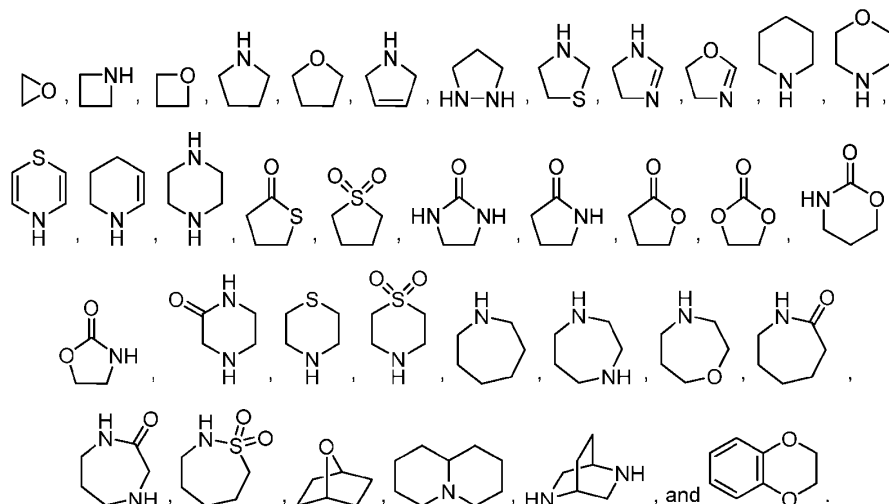
[0261] The term “halogen” or “halo” represents chlorine, fluorine, bromine, or iodine.

[0262] The term “haloalkyl” refers to an alkyl group with one or more halo substituents. Examples of haloalkyl groups include $-\text{CF}_3$, $-(\text{CH}_2)\text{F}$, $-\text{CHF}_2$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{CF}_3$, and $-\text{CH}_2\text{CH}_2\text{F}$. The term “haloalkylene” refers to an alkyl group with one or more halo substituents. Examples of haloalkyl groups include $-\text{CF}_2-$, $-\text{C}(\text{H})(\text{F})-$, $-\text{C}(\text{H})(\text{Br})-$, $-\text{CH}_2\text{CF}_2-$, and $-\text{CH}_2\text{C}(\text{H})(\text{F})-$.

[0263] The term “aryl” refers to a monovalent all-carbon monocyclic or fused-ring polycyclic group having a completely conjugated pi-electron system. The term “arylene” refers to a divalent all-carbon monocyclic or fused-ring polycyclic group having a completely conjugated pi-electron system. In some embodiments, it can be advantageous to limit the number of atoms in an “aryl” or “arylene” to a specific range of atoms, such as mono-valent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 14 carbon atoms ($\text{C}_6\text{-C}_{14}$ aryl), monovalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 10 carbon atoms ($\text{C}_6\text{-C}_{10}$ aryl), divalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 14 carbon atoms ($\text{C}_6\text{-C}_{14}$ arylene), divalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 10 carbon atoms ($\text{C}_6\text{-C}_{10}$ arylene). Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. Examples, without limitation, of arylene groups are phenylene, naphthalenylene and anthracenylene. It will be appreciated that an aryl or arylene group can be unsubstituted or substituted as described herein. An aryl or arylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0264] The term “heterocycloalkyl” refers to a mono-valent monocyclic or polycyclic ring structure that is saturated or partially saturated having one or more non-carbon ring atoms. The term “heterocycloalkylene” refers to a divalent monocyclic or polycyclic ring structure that is saturated or partially saturated having one or more non-carbon ring atoms. In some embodiments, it can be advantageous to limit the number of atoms in a “heterocycloalkyl” or “heterocycloalkylene” to a specific range of ring atoms, such as from 3 to 12 ring atoms (3- to 12-membered), or 3 to 7 ring atoms (3- to 7-membered), or 3 to 6 ring atoms (3- to 6-membered), or 4 to 6 ring atoms (4- to 6-membered), 5 to 7 ring atoms (5- to 7-membered), or 4 to 10 ring atoms (4- to 10-membered). In some embodiments, it can be advantageous to limit the number and type of ring heteroatoms in “heterocycloalkyl” or “heterocycloalkylene” to a specific range or type of heteroatoms, such as 1 to 5 ring heteroatoms selected from nitrogen, oxygen, and sulfur. Polycyclic ring systems include fused, bridged, and spiro systems. The ring structure may

optionally contain an oxo group or an imino group on a carbon ring member or up to two oxo groups on sulfur ring members. Illustrative examples of heterocycloalkyl groups include monovalent radicals of the following entities, while heterocycloalkylene groups include divalent radicals of the following entities, in the form of properly bonded moieties:

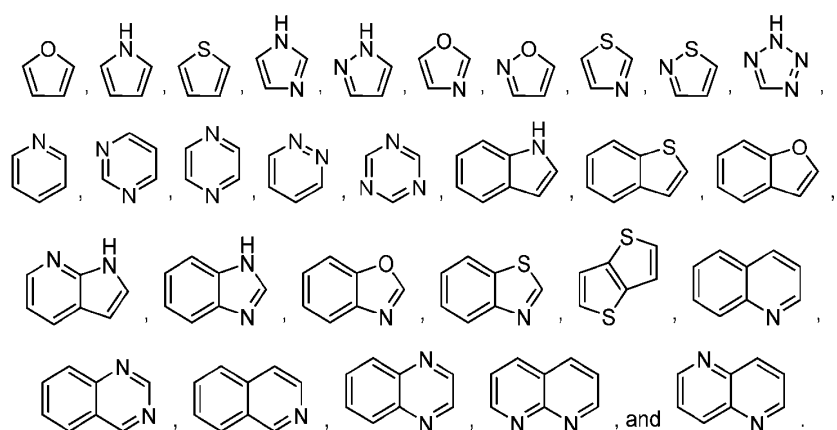


[0265] A three-membered heterocycle may contain at least one heteroatom ring atom, where the heteroatom ring atom is a sulfur, oxygen, or nitrogen. Non-limiting examples of three-membered heterocycle groups include monovalent and divalent radicals of oxirane, azetidine, and thirane. A four-membered heterocycle may contain at least one heteroatom ring atom, where the heteroatom ring atom is a sulfur, oxygen, or nitrogen. Non-limiting examples of four-membered heterocycle groups include monovalent and divalent radicals of azetidine, oxtenane, and thietane. A five-membered heterocycle can contain up to four heteroatom ring atoms, where (a) at least one ring atom is oxygen and sulfur and zero, one, two, or three ring atoms are nitrogen, or (b) zero ring atoms are oxygen or sulfur and up to four ring atoms are nitrogen. Non-limiting examples of five-membered heterocycle groups include mono-valent and divalent radicals of pyrrolidine, tetrahydrofuran, 2, 5-dihydro-1H- pyrrole, pyrazolidine, thiazolidine, 4,5-dihydro-1H-imidazole, dihydrothiophen-2(3H)-one, tetrahydrothiophene 1,1-dioxide, imidazolidin-2-one, pyrrolidin-2-one, dihydrofuran-2(3H)-one, 1,3-dioxolan-2-one, and oxazolidin-2-one. A six-membered heterocycle can contain up to four heteroatom ring atoms, where (a) at least one ring atom is oxygen and sulfur and zero, one, two, or three ring atoms are nitrogen, or (b) zero ring atoms are oxygen or sulfur and up to four ring atoms are nitrogen. Non-limiting examples of six-membered heterocycle groups include mono-valent or divalent radicals of piperidine, morpholine, 4H-1,4-thiazine, 1,2,3,4-tetrahydropyridine, piperazine, 1,3-oxazinan-2-one,

piperazin-2-one, thiomorpholine, and thiomorpholine 1,1-dioxide. A “heterobicycle” is a fused bicyclic system comprising one heterocycle ring fused to a cycloalkyl or another heterocycle ring.

[0266] It will be appreciated that a heterocycloalkyl or heterocycloalkylene group can be unsubstituted or substituted as described herein. A heterocycloalkyl or heterocycloalkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

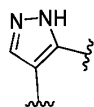
[0267] The term “heteroaryl” refers to a mono-valent monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms or members selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) that is fully unsaturated and having from 3 to 12 ring atoms per heterocycle. The term “heteroarylene” refers to a divalent monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms or members selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle. In some embodiments, it can be advantageous to limit the number of ring atoms in a “heteroaryl” or “heteroarylene” to a specific range of atom members, such as 5- to 10-membered heteroaryl or 5- to 10-membered heteroarylene. In some instances, a 5- to 10-membered heteroaryl can be a monocyclic ring or fused bicyclic rings having 5- to 10-ring atoms wherein at least one ring atom is a heteroatom, such as N, O, or S. In some instances, a 5- to 10-membered heteroarylene can be a monocyclic ring or fused bicyclic rings having 5- to 10-ring atoms wherein at least one ring atom is a heteroatom, such as N, O, or S. The ring structure may optionally contain an oxo group or an imino group on a carbon ring member or up to two oxo groups on sulfur ring members. Illustrative examples of 5- to 10-membered heteroaryl groups include monovalent radicals of the following entities, while examples of 5- to 10-membered heteroarylene groups include divalent radicals of the following entities, in the form of properly bonded moieties:



[0268] In some embodiments, a “monocyclic” heteroaryl can be an aromatic five- or six-membered heterocycle. A five-membered heteroaryl or heteroarylene can contain up to four heteroatom ring atoms, where (a) at least one ring atom is oxygen and sulfur and zero, one, two, or three ring atoms are nitrogen, or (b) zero ring atoms are oxygen or sulfur and up to four ring atoms are nitrogen. Non-limiting examples of five-membered heteroaryl groups include monovalent radicals of furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, oxadiazole, thiadiazole, triazole, or tetrazole. Non-limiting examples of five-membered heteroarylene groups include di-valent radicals of furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, oxadiazole, thiadiazole, triazole, or tetrazole. A six-membered heteroaryl or heteroarylene can contain up to four heteroatom ring atoms, where (a) at least one ring atom is oxygen and sulfur and zero, one, two, or three ring atoms are nitrogen, or (b) zero ring atoms are oxygen or sulfur and up to four ring atoms are nitrogen. Non-limiting examples of six-membered heteroaryl groups include monovalent radicals of pyridine, pyrazine, pyrimidine, pyridazine, or triazine. Non-limiting examples of six-membered heteroarylene groups include divalent radicals of pyridine, pyrazine, pyrimidine, pyridazine, or triazine. A “bicyclic heteroaryl” or “bicyclic heteroarylene” is a fused bicyclic system comprising one heteroaryl ring fused to a phenyl or another heteroaryl ring. Non-limiting examples of bicyclic heteroaryl groups include monovalent radicals of quinoline, isoquinoline, quinazoline, quinoxaline, 1,5-naphthyridine, 1,8-naphthyridine, isoquinolin-3(2H)-one, thieno[3,2-*b*]thiophene, 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzo[*d*]imidazole, benzo[*d*]oxazole, and benzo[*d*]thiazole. Non-limiting examples of bicyclic heteroarylene groups include divalent radicals of quinoline, isoquinoline, quinazoline, quinoxaline, 1,5-naphthyridine, 1,8-naphthyridine, isoquinolin-3(2H)-one, thieno[3,2-*b*]thiophene, 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzo[*d*]imidazole, benzo[*d*]oxazole, and benzo[*d*]thiazole.



[0269] In particular, a pyrazolyl moiety can be depicted by the structural formula . In particular, an example of a pyrazolylene moiety can be depicted by the structural formula



[0270] It will be appreciated that a heteroaryl or heteroarylene group can be unsubstituted or substituted as described herein. A heteroaryl or heteroarylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0271] The term “oxo” represents a carbonyl oxygen. For example, a cyclopentyl substituted with oxo is cyclopentanone.

[0272] The term “substituted” means that the specified group or moiety bears one or more substituents. The term “unsubstituted” means that the specified group bears no substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. In some embodiments, “substituted” means that the specified group or moiety bears one, two, or three substituents. In other embodiments, “substituted” means that the specified group or moiety bears one or two substituents. In still other embodiments, “substituted” means the specified group or moiety bears one substituent.

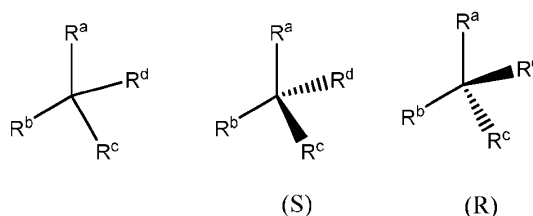
[0273] Any formula depicted herein is intended to represent a compound of that structural formula as well as certain variations or forms. For example, a formula given herein is intended to include a racemic form, or one or more enantiomeric, diastereomeric, or geometric isomers, or a mixture thereof. Additionally, any formula given herein is intended to refer also to a hydrate, solvate, or polymorph of such a compound, or a mixture thereof.

[0274] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0275] Any disubstituent referred to herein is meant to encompass the various attachment possibilities when more than one of such possibilities are allowed. For example, reference to disubstituent –J-K-, where $J \neq K$, refers herein to such disubstituent with J attached to a first substituted member and K attached to a second substituted member, and it also refers to such

disubstituent with J attached to the second substituted member and K attached to the first substituted member.

[0276] It will be appreciated that certain of the compounds described herein include one or more position that can exists as stereoisomers. For example, certain of the compounds described herein include one or more carbon atoms that can exist in one or more stereoisomeric arrangements. It will be appreciated that a carbon atom that can exist in stereoisomeric arrangements that is depicted without showing any stereoisomeric arrangement includes as a disclosure each of eh possible stereoisomeric arrangements. For example, a carbon atom having four groups that can be prioritized according to the Cahn-Ingold Prelog Rules known to one of skill in the art will be understood herein as describing no particular stereochemical definition as in the structure on the left below, and also as describing both possible stereoisomers (S) and (R) as shown below



where $\text{R}^a > \text{R}^b > \text{R}^c > \text{R}^d$ according to the Cahn-Ingold Prelog Rules. ‘

[0277] The disclosure also includes pharmaceutically acceptable salts of Compound I, preferably of those described above and of the specific compounds exemplified herein, and pharmaceutical compositions comprising such salts, and methods of using such salts.

[0278] A “pharmaceutically acceptable salt” is intended to mean a salt of a free acid or base of a compound represented herein that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. 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.

[0279] 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.

[0280] For Compound I that contains a basic nitrogen, a pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

[0281] The disclosure also relates to pharmaceutically acceptable prodrugs of the Compound I, and treatment methods employing such pharmaceutically acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to Compound I). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985.

[0282] The present disclosure also relates to pharmaceutically active metabolites of Compound I, and uses of such metabolites in the methods of the disclosure. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a Compound I or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine

techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs*, *Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

[0283] As used herein, unless otherwise indicated, the term “abnormal cell growth” refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition).

[0284] A “patient,” “subject,” 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).

[0285] As used herein, unless otherwise indicated, the term “treating” means reversing, alleviating, inhibiting the progress of (i.e., curative treatment), or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” as defined immediately above. “Preventative” treatment is meant to indicate a postponement of development of a disease, a symptom of a disease, or medical condition, suppressing symptoms that may appear, or reducing the risk of developing or recurrence of a disease or symptom. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount. “Curative” treatment includes reducing the severity of or suppressing the worsening of an existing disease, symptom, or condition. Thus, treatment includes ameliorating or preventing the worsening of existing disease symptoms, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable, preventing additional symptoms from occurring, ameliorating or preventing the underlying systemic causes of symptoms, inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0286] “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.

[0287] 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.

[0288] As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

[0289] A “therapeutically effective amount” or a “therapeutically effective dose” of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject’s size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

[0290] As used herein, “ C_{max} ” is a pharmacokinetic term that may refer to the maximum (or peak) serum concentration that a drug or agent achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose.

[0291] As used herein, “AUC” or “area under the curve” is a pharmacokinetic term that may refer to the definite integral of the concentration of a drug or agent in blood plasma as a function of time. In pharmacology, the AUC may provide insight into the extent of exposure to a drug or agent and its clearance rate from the body.

[0292] As used herein, the term “essentially the same” with reference to X-ray diffraction peak positions means that typical peak position and intensity variability are taken into account. For example, one skilled in the art will appreciate that the peak positions (2θ) will show some inter-apparatus variability, such as 0.1° , or in some cases 0.2° . Further, one skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors known to those skilled in the art and should be taken as qualitative measures only.

[0293] As used herein, the term “protecting group” or “PG” refers to any group as commonly known to one of ordinary skill in the art that can be introduced into a molecule by chemical modification of a functional group, such as an amine or hydroxyl, to achieve chemoselectivity in a subsequent chemical reaction. It will be appreciated that such protecting groups can be subsequently removed from the functional group at a later point in a synthesis to provide further opportunity for reaction at such functional groups or, in the case of a final product, to unmask such functional group. Protecting groups have been described in, for example, Wuts, P. G. M., Greene, T. W., Greene, T. W., & John Wiley & Sons. (2006). *Greene's protective groups in organic synthesis*. Hoboken, N.J.: Wiley-Interscience. One of skill in the art will readily appreciate the chemical process conditions under which such protecting groups can be installed on a functional group. Suitable amine protecting groups useful in connection with the present disclosure include, but are not limited to, tetrahydropyran, (THP), 9-Fluorenylmethyl-carbonyl (FMOC), p-methoxybenzyl (PMB), *t*-butylcarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl (Ac), trifluoroacetyl, phthalimide, benzyl (Bn), triphenylmethyl (trityl, Tr), benzylidene, and *p*-toluenesulfonyl (tosylamide, Ts).

BRIEF DESCRIPTION OF THE DRAWINGS

[0294] FIG. 1A shows a powder X-ray diffraction pattern of the crystalline form of free base (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, anhydrous crystalline polymorph form A.

[0295] FIG. 1B shows a powder X-ray diffraction pattern of the crystalline form of free base (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, anhydrous crystalline polymorph form A. The pattern in FIG. 1B is an enlarged version of FIG. 1A to show greater detail.

[0296] FIG. 2 shows a powder X-ray diffraction pattern of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, pentahydrate crystalline polymorph form B.

[0297] FIG. 3 shows a powder X-ray diffraction pattern of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, anhydrous crystalline polymorph form C.

[0298] FIG. 4A shows a powder X-ray diffraction pattern of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, solvate crystalline polymorph form D (wet).

[0299] FIG. 4B shows a powder X-ray diffraction pattern of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, solvate crystalline polymorph form D (dry).

[0300] FIG. 5A shows a thermographic analysis (TGA) curve of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form A. The curve was generated from a sample size of crystalline polymorph form A of 6.51 mg with a step showing a loss of -0.9366 % (-60.9732e-03 mg).

[0301] FIG. 5B shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form A showing a transition event with an enthalpy (normalized) = 734.79 mJ, at an onset of 293.82 °C, and a peak temperature of 296.86 °C.

[0302] FIG. 6A shows a thermographic analysis (TGA) curve of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, pentahydrate crystalline polymorph form B. The curve was generated from a sample size of pentahydrate crystalline polymorph form B of 6.8400 mg with a step showing a loss of -15.9647 % (-1.0920 mg).

[0303] FIG. 6B shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, pentahydrate crystalline polymorph form B showing a transition events at with an enthalpy (normalized) = 1539.25 mJ, at an onset of 91.45 °C, and a peak temperature of 109.80 °C, -379.92 mJ, at an onset of 217.11 °C, and a peak temperature of 224.01 °C, and 712.60 mJ, at an onset of 296.26 °C, and a peak temperature of 300.77 °C.

[0304] FIG. 7A shows a thermographic analysis (TGA) curve of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form C. The curve was generated from a sample size of crystalline polymorph form C of 7.230 mg with a step showing mass loss of 0.0 up to ~320 °C.

[0305] FIG. 7B shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form C showing a transition events at with an enthalpy (normalized) = 340.29 mJ, at an onset of 243.90 °C, and a peak temperature of 247.68 °C, -190.41 mJ, at an onset of 250.03 °C, and a peak temperature of 251.77 °C, and 840.68 mJ, at an onset of 295.64 °C, and a peak temperature of 298.78 °C.

[0306] FIG. 8A shows a thermographic analysis (TGA) curve of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form D (wet). The curve was generated from a sample size of crystalline polymorph form D of 6.375 mg with a step showing mass loss of -19.2638% (-1.2281 mg) and a step showing mass loss of -11.5437% (-0.7359 mg).

[0307] FIG. 8B shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of free base (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one, crystalline polymorph form D (wet) showing a transition events at with an enthalpy (normalized) = 456.09 mJ, at an onset of 88.95 °C, and a peak temperature of 91.36 °C, and 571.51 mJ, at an onset of 291.43 °C, and a peak temperature of 297.65 °C.

[0308] FIG. 9 shows a comparison of the pharmacokinetics of crystalline polymorph form A of Compound I, pentahydrate crystalline polymorph form B of Compound I, and crystalline polymorph form C of Compound I as measured *in vivo* in female BALB/c mice by single dose, PO, at 25 mg/kg.

DETAILED DESCRIPTION

[0309] Before the present disclosure is further described, it is to be understood that this disclosure 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 disclosure will be limited only by the appended claims.

[0310] 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 disclosure 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.

[0311] 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.

[0312] A unique physical form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one (a.k.a. crystalline polymorph form A) has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of crystalline polymorph form A is shown in FIGS. 1A and 1B, with corresponding tabulated data shown in Table 1.

Table 1

Angle (°2θ)	d-Spacing (Å)	Relative intensity
7.09	12.47	100.0
8.80	10.04	4.2
11.59	7.63	1.8
12.54	7.05	2.3
12.81	6.91	0.1
13.17	6.72	3.0
13.66	6.48	2.0
14.00	6.32	5.5
14.17	6.25	5.7
14.56	6.08	1.0
16.40	5.40	0.4
16.77	5.28	0.9
17.31	5.12	3.2
17.64	5.02	6.0
17.76	4.99	4.2
18.13	4.89	13.1
19.27	4.60	0.4
19.69	4.51	0.6
19.80	4.48	2.9
20.66	4.30	0.5
20.80	4.27	0.6
21.07	4.21	14.4

Angle ($^{\circ}2\theta$)	d-Spacing ($\text{\AA}$)	Relative intensity
21.30	4.17	2.4
21.89	4.06	0.9
22.13	4.01	0.2
22.56	3.94	2.4
23.30	3.81	0.1
23.64	3.76	0.1
23.89	3.72	0.5
24.62	3.61	0.9
24.83	3.58	0.8
25.13	3.54	7.5
25.97	3.43	1.7
26.51	3.36	0.2
27.08	3.29	1.1
27.49	3.24	0.3
27.86	3.20	0.1
28.00	3.18	0.3
28.17	3.17	0.4
28.70	3.11	0.9
28.99	3.08	0.2
29.39	3.04	1.6
29.55	3.02	0.7
30.00	2.98	0.4
30.37	2.94	0.2
30.97	2.88	0.4
31.10	2.87	0.9
31.54	2.83	0.3
31.92	2.80	0.3
32.97	2.71	0.3
33.62	2.66	0.6
33.75	2.65	0.3
35.86	2.50	0.8
38.80	2.32	0.3
39.07	2.30	0.2

[0313] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) as shown in Table 1 and/or FIGS. 1A/1B.

[0314] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 8.8 ± 0.1 , 11.6 ± 0.1 , 12.5 ± 0.1 , 13.2 ± 0.1 , 13.7 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 14.6 ± 0.1 , 17.3 ± 0.1 , 17.6 ± 0.1 , 17.8 ± 0.1 , 18.1 ± 0.1 , 19.8 ± 0.1 ,

21.1±0.1, 21.3±0.1, 22.6±0.1, 25.1±0.1, 26.0±0.1, 27.1±0.1, and 29.4±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 11.6±0.1, 12.5±0.1, 13.2±0.1, 13.7±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, 25.1±0.1, 26.0±0.1, 27.1±0.1, and 29.4±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 11.6±0.1, 12.5±0.1, 13.2±0.1, 13.7±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, 25.1±0.1, 26.0±0.1, and 29.4±0.1.

[0315] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 11.6±0.1, 12.5±0.1, 13.2±0.1, 13.7±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, 25.1±0.1, and 26.0±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 11.6±0.1, 12.5±0.1, 13.2±0.1, 13.7±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 12.5±0.1, 13.2±0.1, 13.7±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, and 25.1±0.1.

[0316] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 12.5±0.1, 13.2±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, and

25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 13.2±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, 22.6±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 13.2±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, 21.3±0.1, and 25.1±0.1.

[0317] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 13.2±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 19.8±0.1, 21.1±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 13.2±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 21.1±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 14.0±0.1, 14.2±0.1, 17.3±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 21.1±0.1, and 25.1±0.1.

[0318] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 14.0±0.1, 14.2±0.1, 17.6±0.1, 17.8±0.1, 18.1±0.1, 21.1±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1±0.1, 8.8±0.1, 14.0±0.1, 14.2±0.1, 17.6±0.1, 18.1±0.1, 21.1±0.1, and 25.1±0.1. In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-

2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

[0319] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 7.1 ± 0.1 . In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 and 21.1 ± 0.1 . In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 18.1 ± 0.1 , and 21.1 ± 0.1 . In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

[0320] In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 . In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 . In some embodiments, the crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

[0321] In some embodiments, the crystalline polymorph form A of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern substantially the same as shown in FIGS. 1A and 1B.

[0322] In some embodiments, the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 0.6% to about 1.4% when heated from about 25 °C to about 320 °C. The TGA thermogram for pentahydrate crystalline polymorph form B is shown in FIG. 5A.

[0323] In some embodiments, the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 290 °C to about 295 °C. The DSC thermogram for crystalline polymorph form A is shown in FIG. 5B.

[0324] A unique physical hydrate form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one (a.k.a. pentahydrate crystalline polymorph form B) has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of pentahydrate crystalline polymorph form B is shown in FIG. 2, with corresponding tabulated data shown in Table 2.

Table 2

Angle (°2θ)	d-Spacing (Å)	Relative intensity
6.86	12.88	11
7.26	12.17	19
7.89	11.20	35
11.99	7.38	10
12.75	6.94	7
13.03	6.79	6
13.52	6.54	6
13.71	6.45	23
14.41	6.14	1
14.49	6.11	1
15.19	5.83	9
15.43	5.74	6
15.78	5.61	42
16.40	5.40	8
16.61	5.33	8
16.95	5.23	2
17.12	5.18	16

Angle (°2θ)	d-Spacing (Å)	Relative intensity
18.25	4.86	2
18.73	4.73	2
19.14	4.63	6
20.07	4.42	1
20.29	4.37	7
20.60	4.31	2
20.97	4.23	9
21.44	4.14	1
21.82	4.07	1
22.48	3.95	6
22.71	3.91	8
22.98	3.87	18
23.75	3.74	100
24.53	3.63	8
24.94	3.57	6
25.25	3.52	2
25.71	3.46	2
25.89	3.44	1
26.24	3.39	1
26.54	3.36	8
26.71	3.34	3
27.84	3.20	6
28.05	3.18	2
28.59	3.12	7
28.82	3.10	4
29.13	3.06	4
29.34	3.04	1
29.98	2.98	1
30.60	2.92	1
31.03	2.88	2
31.14	2.87	2
31.71	2.82	1
32.08	2.79	1
32.53	2.75	2
33.06	2.71	1
33.70	2.66	1
34.17	2.62	1
34.97	2.56	6
36.12	2.48	2
36.43	2.46	2
37.60	2.39	1

[0325] In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) as shown in Table 2 and/or FIG. 2.

[illegible]

one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 20.3 ± 0.1 , 21.0 ± 0.1 , 22.5 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , 26.5 ± 0.1 , 27.8 ± 0.1 , and 28.6 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 20.3 ± 0.1 , 21.0 ± 0.1 , 22.5 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , 26.5 ± 0.1 , 27.8 ± 0.1 , and 28.6 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 20.3 ± 0.1 , 21.0 ± 0.1 , 22.5 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , 26.5 ± 0.1 , and 28.6 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 20.3 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , 26.5 ± 0.1 , and 28.6 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 20.3 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , and 26.5 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 12.8 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , and 26.5 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3'''-

n[1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , 24.5 ± 0.1 , and 26.5 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-

13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , 23.8 ± 0.1 , and 24.5 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-

f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 22.7 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 16.6 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-

n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 16.4 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 21.0 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 . In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9 ± 0.1 , 7.3 ± 0.1 , 7.9 ± 0.1 , 12.0 ± 0.1 , 13.7 ± 0.1 , 15.2 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 23.0 ± 0.1 , and

23.8±0.1 In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9±0.1, 7.3±0.1, 7.9±0.1, 12.0±0.1, 13.7±0.1, 15.8±0.1, 17.1±0.1, 23.0±0.1, and 23.8±0.1 In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 6.9±0.1, 7.3±0.1, 7.9±0.1, 13.7±0.1, 15.8±0.1, 17.1±0.1, 23.0±0.1, and 23.8±0.1. In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.3±0.1, 7.9±0.1, 13.7±0.1, 15.8±0.1, 17.1±0.1, 23.0±0.1, and 23.8±0.1.

[0327] In some embodiments, the pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.8±0.1. In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8±0.1 and 23.8±0.1. In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9±0.1, 15.8±0.1, and 23.8±0.1. In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9±0.1, 13.7±0.1, 15.8±0.1, and 23.8±0.1. In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3±0.1, 7.9±0.1,

13.7±0.1, 15.8±0.1, and 23.8±0.1. In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3±0.1, 7.9±0.1, 13.7±0.1, 15.8±0.1, 23.0±0.1, and 23.8±0.1.

[0328] In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern substantially the same as shown in FIG. 2.

[0329] In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 13% to about 18% when heated from about 25 °C to about 320 °C. The TGA thermogram for pentahydrate crystalline polymorph form B is shown in FIG. 6A.

[0330] In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 293 °C to about 298 °C . In some embodiments, the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 88 °C to about 93 °C, an exotherm with an onset at about 215 °C to about 220 °C, and an endotherm with an onset at about 293 °C to about 298 °C. The DSC thermogram for pentahydrate crystalline polymorph form B is shown in FIG. 6B.

[0331] A unique physical hydrate form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one (a.k.a. crystalline polymorph form C or anhydrous polymorph form C) has been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of crystalline polymorph form C is shown in FIG. 3, with corresponding tabulated data shown in Table 3.

Table 3

Angle (°2 θ)	d-Spacing (Å)	Relative intensity
9.05	9.76	17
9.37	9.43	10
9.53	9.27	42
12.32	7.18	2
12.42	7.12	2
12.87	6.87	49
13.45	6.58	21
14.01	6.32	1
15.77	5.62	59
16.60	5.34	16
17.54	5.05	21
18.04	4.91	19
18.49	4.80	64
18.75	4.73	6
19.09	4.64	2
19.49	4.55	2
19.62	4.52	8
19.80	4.48	15
20.20	4.39	6
20.34	4.36	4
20.98	4.23	1
21.21	4.19	1
22.99	3.87	1
23.71	3.75	5
24.03	3.70	11
24.37	3.65	3
24.96	3.56	100
25.49	3.49	10
25.97	3.43	1
26.22	3.40	14
27.31	3.26	4
27.68	3.22	2
28.08	3.18	7
28.15	3.17	3
29.00	3.08	2
29.20	3.06	10
29.63	3.01	9
29.66	3.01	7
30.32	2.95	2
31.17	2.87	2
31.77	2.81	1
32.41	2.76	2
32.92	2.72	3
35.06	2.56	2
35.13	2.55	2
36.68	2.45	4
36.74	2.44	1
36.90	2.43	1

Angle (°2θ)	d-Spacing (Å)	Relative intensity
37.43	2.40	1
37.94	2.37	1

[0332] In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) as shown in Table 3 and/or FIG. 3.

[0333] In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 18.8±0.1, 19.6±0.1, 19.8±0.1, 20.2±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 28.1±0.1, 29.2±0.1, 29.6±0.1, and 29.7±0.1.

[0334] In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.6±0.1, 19.8±0.1, 20.2±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 28.1±0.1, 29.2±0.1, 29.6±0.1, and 29.7±0.1.

[0335] In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.6±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 28.1±0.1, 29.2±0.1, 29.6±0.1, and 29.7±0.1.

[0336] In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.6±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 28.1±0.1, 29.2±0.1, and 29.6±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of

9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.5±0.1, 18.8±0.1, 19.6±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 29.2±0.1, and 29.6±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, 29.2±0.1, and 29.6±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, 26.2±0.1, and 29.2±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, 25.5±0.1, and 26.2±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, and 26.2±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.4±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, and 26.2±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, 24.0±0.1, 25.0±0.1, and 26.2±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0±0.1, 9.5±0.1, 12.9±0.1, 13.4±0.1, 15.8±0.1, 16.6±0.1, 17.5±0.1, 18.0±0.1, 18.5±0.1, 19.8±0.1, and 25.0±0.1. In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-

13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0 ± 0.1 , 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 16.6 ± 0.1 , 17.5 ± 0.1 , 18.0 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.0 ± 0.1 , 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.0 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.0 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

[0337] In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 25.0 ± 0.1 .

[0338] In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 18.5 ± 0.1 and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.9 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 . In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-

13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 9.5 $\pm$ 0.1, 12.9 $\pm$ 0.1, 15.8 $\pm$ 0.1, 18.5 $\pm$ 0.1, and 25.0 $\pm$ 0.1. In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 9.5 $\pm$ 0.1, 12.9 $\pm$ 0.1, 13.4 $\pm$ 0.1, 15.8 $\pm$ 0.1, 18.5 $\pm$ 0.1, and 25.0 $\pm$ 0.1. In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 9.5 $\pm$ 0.1, 12.9 $\pm$ 0.1, 13.4 $\pm$ 0.1, 15.8 $\pm$ 0.1, 17.5 $\pm$ 0.1, 18.5 $\pm$ 0.1, and 25.0 $\pm$ 0.1.

[0339] In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern substantially the same as shown in FIG. 3.

[0340] In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of less than about 1% when heated from about 25 °C to about 320 °C. The TGA thermogram for crystalline polymorph form C is shown in FIG. 7A.

[0341] In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 293 °C to about 298 °C. In some embodiments, the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 240 °C to about 245 °C, an exotherm with an onset at about 248 °C to about 253 °C, and an endotherm with an onset at about 293 °C to about 298 °C. The DSC thermogram for anhydrous crystalline polymorph form C is shown in FIG. 7B.

[0342] A unique physical hydrate form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one (a.k.a. solvate crystalline polymorph form D) has

been prepared according to the methods described herein. The powder X-ray diffraction (PXRD) pattern of solvate crystalline polymorph form D is shown in FIG. 4A (wet) and 4B (dry), with corresponding tabulated data shown in Tables 4A (wet) and 4B (dry).

Table 4A

Angle (°2θ)	d-Spacing (Å)	Relative intensity
4.26	20.73	2
8.51	10.38	45
8.74	10.11	1
9.06	9.75	6
10.35	8.54	26
11.14	7.93	7
11.61	7.62	1
13.04	6.78	19
14.23	6.22	6
14.52	6.09	1
14.96	5.92	1
15.3	5.79	2
15.65	5.66	7
16.11	5.5	7
16.53	5.36	2
16.65	5.32	3
17.04	5.2	100
17.32	5.11	4
17.51	5.06	4
17.82	4.97	2
18.16	4.88	7
18.73	4.73	14
19.56	4.53	1
20.46	4.34	16
20.75	4.28	7
21.07	4.21	1
21.34	4.16	32
21.97	4.04	8
22.37	3.97	6
22.74	3.91	39
23.4	3.8	1
23.77	3.74	10
24.44	3.64	1
25.32	3.51	6
25.67	3.47	29
26.27	3.39	26

Angle (°2 θ)	d-Spacing (Å)	Relative intensity
26.85	3.32	1
27.18	3.28	1
27.44	3.25	1
28.14	3.17	1
28.71	3.11	3
28.98	3.08	1

Table 4B

Angle (°2 θ)	d-Spacing (Å)	Relative intensity
4.26	20.73	2
8.51	10.38	45
8.74	10.11	1
9.06	9.75	6
10.35	8.54	26
11.14	7.93	7
11.61	7.62	1
13.04	6.78	19
14.23	6.22	6
14.52	6.09	1
14.96	5.92	1
15.3	5.79	2
15.65	5.66	7
16.11	5.5	7
16.53	5.36	2
16.65	5.32	3
17.04	5.2	100
17.32	5.11	4
17.51	5.06	4
17.82	4.97	2
18.16	4.88	7
18.73	4.73	14
19.56	4.53	1
20.46	4.34	16
20.75	4.28	7
21.07	4.21	1
21.34	4.16	32
21.97	4.04	8
22.37	3.97	6
22.74	3.91	39
23.4	3.8	1
23.77	3.74	10

Angle ($^{\circ}2\theta$)	d-Spacing ($\text{\AA}$)	Relative intensity
24.44	3.64	1
25.32	3.51	6
25.67	3.47	29
26.27	3.39	26
26.85	3.32	1
27.18	3.28	1
27.44	3.25	1
28.14	3.17	1
28.71	3.11	3
28.98	3.08	1

[0343] The TGA thermogram for crystalline polymorph form D (wet) is shown in FIG. 8A. The DSC thermogram for crystalline polymorph form D (wet) is shown in FIG. 8B. NMR analysis showed 29.60 wt. % (1.85 eq.) NMP and 0.63 wt. % (0.04 eq.) of EtOAc, indicating that crystalline polymorph form D is a solvated form.

[0344] In some embodiments, the crystalline polymorph form D (wet) of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) as shown in Table 4A and/or FIG. 4A.

[0345] In some embodiments, the crystalline polymorph form D (dry) of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) as shown in Table 4B and/or FIG. 4B.

[0346] In some embodiments, crystalline polymorph form D (wet) of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern substantially the same as shown in FIG. 4A.

[0347] In some embodiments, the crystalline polymorph form D (dry) of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one has a powder X-ray diffraction pattern substantially the same as shown in FIG. 4B.

[0348] 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. 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.

[0349] 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.

[0350] 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.

[0351] 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.

[0352] An example of cancer, for example one 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.

[0353] 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).

[0354] 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.

[0355] In treatment methods according to the invention, an “effective amount” means an amount or dose sufficient to generally bring about the desired therapeutic benefit in subjects needing such treatment. Effective amounts or doses of the compounds of the invention may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the infection, the subject’s health status, condition, and weight, and the judgment of the treating physician. An example dose is in the range of about from about 0.1 mg to about 1 g daily, or about 1 mg to about 500 mg daily, or about 5 mg to about 250 mg daily, or about 10 mg to about 200 mg daily. The total dosage may be given in single or divided dosage units (e.g., QD, BID, or TID).

[0356] Once improvement of the patient’s disease has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms. Patients may also require chronic treatment on a long-term basis.

[0357] The polymorph forms of Compound I may be administered at certain concentrations. In some embodiments, a polymorph form of Compound I is administered at a dosage of about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.5 mg/kg, 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, or about 2 mg/kg. An example concentration for a polymorph form of Compound I may be administered in the range of about 0.05 mg/kg to about 2 mg/kg, about 0.1 mg/kg to about 2 mg/kg, about 0.2 mg/kg to about 2 mg/kg, about 0.3 mg/kg to about 2 mg/kg, about 0.4 mg/kg to about 2 mg/kg, about 0.5 mg/kg to about 2 mg/kg, about 0.5 mg/kg to about 1.7 mg/kg, or about 0.5 mg/kg to about 1.5 mg/kg.

[0358] The polymorph forms of Compound I may be administered at certain concentrations. In some embodiments, a polymorph form of Compound I is administered at a dosage of about 1

mg/kg, about 2.5 mg/kg, about 5 mg/kg, about 10 mg/kg, about 25 mg/kg, or about 50 mg/kg. An example concentration for a polymorph form of Compound I may be administered in the range of about 1 mg/kg to about 50 mg/kg, about 2.5 mg/kg to about 50 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 50 mg/kg, about 25 mg/kg to about 50 mg/kg, about 1 mg/kg to about 25 mg/kg, about 2.5 mg/kg to about 25 mg/kg, about 5 mg/kg to about 25 mg/kg, about 10 mg/kg to about 25 mg/kg, about 1 mg/kg to about 10 mg/kg, about 2.5 mg/kg to about 10 mg/kg, or about 5 mg/kg to about 10 mg/kg.

[0359] For kinase inhibitors, the plasma exposure of the inhibitor is often positively correlated with target and downstream signaling inhibition, with higher plasma concentration of the inhibitor leading to deeper target inhibition (Mori et al., *Invest New Drugs*. 2017 Oct;35(5):556-565. doi: 10.1007/s10637-017-0470-z. Epub 2017 May 17. PMID: 28516360; PMCID: PMC5613053; Yoda et al., *Blood* 2022; 140 (Supplement 1): 489–490. doi: <https://doi.org/10.1182/blood-2022-159338>; Zou et al., *Cancer Cell*. 2015 Jul 13;28(1):70-81. doi: 10.1016/j.ccell.2015.05.010. Epub 2015 Jul 2. PMID: 26144315; PMCID: PMC4504786; Yates et al., *Mol Cancer Ther*. 2016 Oct;15(10):2378-2387. doi: 10.1158/1535-7163.MCT-16-0142. Epub 2016 Jul 20. PMID: 27439477). The pharmacokinetic profiles of polymorph forms of Compound I at certain concentrations (e.g., 25 mg/kg) in plasma following dosing (e.g., a single oral dose in mouse) can be obtained.

[0360] In some embodiments, the C_{max} for a polymorph form of Compound I in plasma following dosing is greater than about 500 ng/mL, greater than about 750 ng/mL, greater than about 1000 ng/mL, greater than about 2000 ng/mL, greater than about 3000 ng/mL, or greater than about 4000 ng/mL. An example C_{max} for a polymorph form of Compound I may be in the range of about 500 ng/mL to about 10,000 ng/mL, about 1000 ng/mL to about 10,000 ng/mL, about 2000 ng/mL to about 10,000 ng/mL, about 3000 ng/mL to about 10,000 ng/mL, about 4000 ng/mL to about 10,000 ng/mL, about 500 ng/mL to about 5,000 ng/mL, about 1000 ng/mL to about 5,000 ng/mL, about 2000 ng/mL to about 5,000 ng/mL, about 3000 ng/mL to about 5,000 ng/mL, or about 4000 ng/mL to about 5,000 ng/mL.

[0361] In some embodiments, the AUC_{last} for a polymorph form of Compound I in plasma following dosing is greater than about 1000 ng*h/mL, greater than about 1500 ng*h/mL, greater than about 2000 ng*h/mL, greater than about 3000 ng*h/mL, greater than about 5000 ng*h/mL, or greater than about 8000 ng*h/mL. An example AUC_{last} for a polymorph form of Compound I may be in the range of about 1000 ng*h/mL to about 20,000 ng*h/mL, about 1500 ng*h/mL to about 20,000 ng*h/mL, about 2000 ng*h/mL to about 20,000 ng*h/mL, about 3000 ng*h/mL to about 20,000 ng*h/mL, about 5000 ng*h/mL to about 20,000 ng*h/mL, about 8000 ng*h/mL to about 20,000 ng*h/mL, about 1000 ng*h/mL to about 12,000 ng*h/mL, about 1500 ng*h/mL to

about 12,000 ng*h/mL, about 2000 ng*h/mL to about 12,000 ng*h/mL, about 3000 ng*h/mL to about 12,000 ng*h/mL, about 5000 ng*h/mL to about 12,000 ng*h/mL, or about 8000 ng*h/mL to about 12,000 ng*h/mL.

[0362] The present disclosure further provides a capsule comprising pharmaceutical compositions as described herein.

[0363] The present disclosure further provides a tablet comprising pharmaceutical compositions as described herein.

[0364] In another aspect, the disclosure provides a method of treating disease, especially cancer, in a mammal, including a human, the method comprising administering to the mammal a therapeutically effective amount of a polymorph form (e.g., form A, B, C, or D) 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, as described herein, or a pharmaceutical composition comprising a polymorph form (e.g., form A, B, C, or D) 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, as described herein.

Pharmaceutical Compositions

[0365] The present disclosure also relates to pharmaceutical compositions comprising (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), for example a polymorph form (e.g., form A, B, C, or D) of Compound I as described herein.

[0366] Pharmaceutical compositions of the present disclosure may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition may include conventional pharmaceutically-acceptable excipients. In addition, pharmaceutical compositions described herein may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[0367] 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, wetting agents, fillers, diluents, anti-oxidants, binders, disintegrants, coloring agents, bulking agents,

glidants, emulsifiers, or taste-modifying agents. In certain embodiments, pharmaceutical compositions according to the invention are sterile compositions. In certain embodiments, pharmaceutical compositions according to the invention are non-sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art. Suitable excipients may be used as intragranular excipients, extragranular excipients, or both.

[0368] Sterile compositions are also contemplated by the invention, including compositions that are in accord with national and local regulations governing such compositions.

[0369] 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. In some embodiments, the compositions are formulated for intravenous or oral administration.

[0370] 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 about 1 g daily, or about 1 mg to about 500 mg daily, or about 5 mg to about 250 mg daily, or about 10 mg to about 200 mg daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, wetting agents, flow-enhancing agents (glidants), sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include microcrystalline cellulose, sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Example liquid oral excipients include ethanol, glycerol, water, and the like. Starch, crospovidone, sodium starch glycolate, cross-linked sodium carboxymethylcellulose, microcrystalline cellulose, and alginic acid are example disintegrating agents. Binding agents may include methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gelatin. Wetting agents are typically surfactants including sodium lauryl sulfate (SLS), polysorbate 80, polyoxy 40 stearate, or poloxamer 188. The lubricating agent, if present, may be sodium stearyl fumarate, magnesium stearate, stearic acid, or talc. The glidant, if present, may be colloidal silicon dioxide/silica or talc. If desired, the tablets may be coated with a material such as Opadry for immediate-release or glyceryl

monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0371] 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.

[0372] Tablets are solid dosage forms that may be prepared by compacting the bulk blend of the formulations described above. In some embodiments, the tablets include a coating (e.g., a film coating) surrounding the final tablet. In some embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). In other embodiments, the tablets include one or more excipients.

[0373] In some embodiments, pharmaceutical compositions described herein include about 5 mg to about 100 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 3 mg to about 40 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 5 mg to about 50 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 5 mg to about 30 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 5 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 20 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, pharmaceutical compositions described herein include about 30 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof.

[0374] In some embodiments, a tablet formulation is prepared that includes about 5 to about 100 mg (e.g., about 5 mg to about 50 mg, about 5 mg, or about 30 mg) of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, 2, 3, 4, or 5 of the tablet formulations are administered daily. In some embodiments, 3 or 4 of the tablets are administered daily. In some embodiments, 3 of the tablets are administered once daily. In some embodiments, 4 of the tablets are administered once daily. In some embodiments, the tablets are administered once daily. In other embodiments, the tablets are administered multiple times a day.

[0375] In some embodiments, the disclosure provides for a tablet formulation comprising any of the polymorph forms of Compound I as described herein in a tablet formulated as described

herein. In some embodiments, the disclosure provides a tablet having a total weight of from about 50 mg to about 1 gram comprising any of the polymorph forms of Compound I as described herein. In some embodiments, the disclosure provides a tablet having a tablet strength in the range of from about 5 mg to about 60 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. In some embodiments, the disclosure provides a tablet having a tablet strength in the range of from about 3 mg to about 40 mg of Compound I, for example a polymorph form (e.g., form A, B, C, or D) thereof. It will be appreciated that further adjustments to the dose of any of the polymorph forms of Compound I as described herein can be achieved in a tablet having a total composition up to about 1 gram by adjusting the ratio of certain of the ingredients in a tablet formulation as described herein relative to the total amount of the polymorph form of Compound I. For example, for a tablet having a tablet strength in the range of from about 60 mg of Compound I to about 150 mg of Compound I and a total composition of about 1 gram, the amount of lactose can be decreased in the same ratio as the increase in Compound I in the formulation, while maintaining approximately the same proportion of other ingredients in the tablet formulation.

[0376] The pharmaceutical solid dosage forms described herein can include Compound I and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the formulation of Compound I.

[0377] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerin, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[0378] Suitable filling agents (sometimes referred to as fillers) for use in the solid dosage forms described herein include, but are not limited to, lactose (e.g., anhydrous lactose), calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrans, dextrans, starches, pregelatinized starch, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate,

hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like. In some embodiments provided herein, fillers include microcrystalline cellulose, lactose, mannitol, and any combination thereof. In some embodiments provided herein, the filler is a mixture of two or more fillers.

[0379] In general, filler levels of 30-90% may be used in powder-filled gelatin capsule formulations. Filler usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients. Formulators skilled in art can determine the filler level for the formulations, but filler usage level of up to 90% in tablet formulations is common. In some embodiments, a filler is present at about 50% to about 90% by weight of the formulation. For example, the filler may be present at about 60% to about 90%, about 70% to about 90%, or about 75% to about 90% by weight of the formulation.

[0380] In order to release the Compound I from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants (sometimes referred to as disintegrating agents) help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, microcrystalline cellulose (e.g., Avicel®, Avicel® PH101, Avicel®PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vitacel®, Ming Tai Comprecel®, and Solka-Floc®), methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like. In some embodiments provided herein, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some embodiments provided herein, the disintegrant includes crospovidone, sodium starch glycolate, or a

combination thereof. In some embodiments provided herein, the disintegrant is a mixture of two or more disintegrants. In some embodiments, a disintegrant is present at about 1% to about 10% by weight of the formulation. For example, the disintegrant may be present at about 2% to about 10%, about 2% to about 8%, about 3% to about 10%, or about 3% to about 8% by weight of the formulation.

[0381] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacoat-603, hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), copovidone, larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[0382] In some embodiments, suitable binders in the solid dosage forms described herein include, but are not limited to, microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), copovidone, larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like. In some embodiments provided herein, the binder includes copovidone.

[0383] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. Formulators skilled in art can determine the binder level for the formulations,

but binder usage level of up to 70% in tablet formulations is common. In some embodiments, a binder is present at about 1% to about 50% by weight of the formulation. For example, the binder may be present at about 1% to about 20%, about 1% to about 10%, or about 2% to about 8% by weight of the formulation.

[0384] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, colloidal silicon dioxide, sodium stearyl fumarate, magnesium or sodium lauryl sulfate (SLS), and the like. In some embodiments provided herein, the glidant is silica or colloidal silicon dioxide. In some embodiments, a glidant is present at about 0.1% to about 5% by weight of the formulation. For example, the glidant may be present at about 0.1% to about 3%, about 0.1% to about 2%, or about 0.1% to about 1% by weight of the formulation. In some embodiments provided herein, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some embodiments provided herein, the lubricant is magnesium stearate. In some embodiments provided herein, the lubricant is sodium stearyl fumarate, magnesium stearyl fumarate, or a combination thereof. In some embodiments, a lubricant is present at about 0.1% to about 5% by weight of the formulation. For example, the lubricant may be present at about 0.1% to about 3%, about 0.1% to about 2%, or about 0.1% to about 1% by weight of the formulation.

[0385] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like. In some embodiments provided herein, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrans, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some embodiments provided herein, the diluent is microcrystalline cellulose. In some embodiments provided herein, the diluent is microcrystalline cellulose, lactose, mannitol, or any combination thereof. In some embodiments, a diluent is present at about 50% to about 90% by weight of the formulation. For example, the diluent may be present at about 60% to about 90%, about 70% to about 90%, or about 75% to about 90% by weight of the formulation.

[0386] The term “non water-soluble diluent” represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm³, e.g., Avicel®, powdered cellulose), and talc.

[0387] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like. In some embodiments, a surfactant can be used as a wetting agent. In some embodiments provided herein, the wetting agent is sodium lauryl sulfate. In some embodiments, a wetting agent is present at about 3% to about 20% by weight of the formulation. For example, the wetting agent may be present at about 5% to about 20%, about 5% to about 15%, about 5% to about 10%, about 10% to about 20%, or about 15% to about 20% by weight of the formulation.

[0388] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. In some embodiments, a wetting agent can be used as a surfactant. In some embodiments provided herein, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some embodiments provided herein, the surfactant is sodium lauryl sulfate. In some embodiments, a surfactant is present at about 3% to about 20% by weight of the formulation. For example, the surfactant may be present at about 5% to about 20%, about 5% to about 15%, about 5% to about 10%, about 10% to about 20%, or about 15% to about 20% by weight of the formulation.

[0389] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose,

hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[0390] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[0391] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely examples, and not limiting, of the types of additives that can be included in solid dosage forms described herein.

[0392] 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.

[0393] 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.

[0394] 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.

[0395] 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.

[0396] Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., 15th Edition (1975).

[0397] In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and at least one of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and at least two of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and at least three of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.

[0398] In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, and at least one of: a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, and at least two of: a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.

[0399] In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, a binder, a surfactant, a disintegrant, a glidant, and a lubricant. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, a binder, a surfactant, a disintegrant, a glidant, and a lubricant. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, a binder, a surfactant, a glidant, and a lubricant. In some embodiments, the pharmaceutical composition may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I), a filler, a binder, a glidant, and a lubricant.

[0400] In some embodiments, the pharmaceutical composition comprises about 3% to about 10% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 50% to about 90% by weight of a filler or a mixture of fillers; optionally about 1% to about 10% by weight of a binder; optionally about 2% to about 10% of a disintegrant or a mixture of

disintegrants; optionally about 3% to about 20% by weight of a surfactant; about 0.1% to about 3% by weight of a glidant; and about 0.1% to about 3% by weight of a lubricant.

[0401] In some embodiments, the pharmaceutical composition comprises about 6% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 80% by weight of a filler or a mixture of fillers; about 5% of a disintegrant or a mixture of disintegrants; about 8% by weight of a surfactant; about 0.3% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0402] In some embodiments, the pharmaceutical composition comprises about 5% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 80% by weight of a filler or a mixture of fillers; about 2.5% by weight of a binder; about 5% of a disintegrant or a mixture of disintegrants; about 7% by weight of a surfactant; about 0.5% by weight of a glidant; and about 0.5% by weight of a lubricant.

[0403] In some embodiments, the pharmaceutical composition comprises about 6% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 77% by weight of a filler or a mixture of fillers; about 3% by weight of a binder; about 5% of a disintegrant or a mixture of disintegrants; about 8% by weight of a surfactant; about 0.6% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0404] In some embodiments, the pharmaceutical composition comprises about 7% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 73% by weight of a filler or a mixture of fillers; about 3% by weight of a binder; about 17% by weight of a surfactant; about 0.5% by weight of a glidant; and about 0.5% by weight of a lubricant.

[0405] In some embodiments, the pharmaceutical composition comprises about 8% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 87% by weight of a filler or a mixture of fillers; about 4% by weight of a binder; about 0.4% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0406] In some embodiments, the pharmaceutical composition comprises about 7% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 80% by weight of a filler or a mixture of fillers; about 4% by weight of a binder; about 9% by weight of a surfactant; about 0.5% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0407] In some embodiments, the pharmaceutical composition comprises about 6% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 84% by weight of a filler or a mixture of fillers; about 3% by weight of a binder; about 7% by weight of a surfactant; about 0.6% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0408] In some embodiments, the pharmaceutical composition comprises about 6% by weight Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 80% by

weight of a filler or a mixture of fillers; about 3% by weight of a binder; about 4% of a disintegrant or a mixture of disintegrants; about 7% by weight of a surfactant; about 0.6% by weight of a glidant; and about 0.6% by weight of a lubricant.

[0409] In some embodiments, the pharmaceutical composition comprises about 3 mg to about 40 mg of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 50 mg to about 500 mg of a filler or a mixture of fillers; optionally about 5 mg to about 15 mg of a binder; optionally about 1 mg to about 40 mg of a disintegrant or a mixture of disintegrants; optionally about 5 mg to about 50 mg by weight of a surfactant; about 0.1 mg to about 5 mg of a glidant; and about 0.1 mg to about 5 mg by weight of a lubricant.

[0410] In one example, the pharmaceutical composition comprising (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), for example a polymorph form (e.g., form A, B, C, or D) thereof, is in the form of a tablet. In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.

[0411] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and a filler or a mixture of fillers, an optional binder, a disintegrant or a mixture of disintegrants, a surfactant, a glidant, and a lubricant. In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 5 mg to about 30 mg of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 50 mg to about 400 mg of a filler or a mixture of fillers; optionally about 5 mg to about 15 mg of a binder; about 1 mg to about 25 mg of a disintegrant or a mixture of disintegrants; about 5 mg to about 40 mg by weight of a surfactant; about 0.1 mg to about 3 mg by weight of a glidant; and about 0.1 mg to about 4 mg by weight of a lubricant.

[0412] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, crospovidone, silica, and sodium stearyl fumarate.

[0413] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 44% by weight of microcrystalline cellulose; about 36% by weight of lactose anhydrous; about 5% by weight of crospovidone; about 0.3% by weight of

silica; about 8% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0414] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 6% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 44% by weight of microcrystalline cellulose; about 36% by weight of lactose anhydrous; about 5% by weight of crospovidone; about 0.6% by weight of silica; about 8% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0415] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 44% of microcrystalline cellulose; about 36% of by weight lactose anhydrous; about 5% of crospovidone; about 0.3% by weight of silica; about 8% of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0416] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 5 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 35 mg $\pm$ 10% of microcrystalline cellulose; about 29 mg $\pm$ 10% of lactose anhydrous; about 4 mg $\pm$ 10% of crospovidone; about 0.25 mg $\pm$ 10% of silica; about 6 mg $\pm$ 10% of sodium lauryl sulfate; and about 0.5 mg $\pm$ 10% of sodium stearyl fumarate.

[0417] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 140 mg $\pm$ 10% of microcrystalline cellulose; about 115 mg $\pm$ 10% of lactose anhydrous; about 16 mg $\pm$ 10% of crospovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0418] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 30 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 212 mg $\pm$ 10% of microcrystalline cellulose; about 173 mg $\pm$ 10% of lactose anhydrous; about 24 mg $\pm$ 10% of crospovidone; about 1.5 mg $\pm$ 10% of silica; about 38 mg $\pm$ 10% of sodium lauryl sulfate; and about 3 mg $\pm$ 10% of sodium stearyl fumarate.

[0419] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, copovidone, sodium starch glycolate, silica, and sodium stearyl fumarate.

[0420] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 5% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 51% by weight of microcrystalline cellulose; about 29% by weight of lactose anhydrous; about 2.6% by weight of copovidone; about 5% by weight of sodium

starch glycolate; about 0.5% by weight of silica; about 6.5% by weight of sodium lauryl sulfate; and about 0.5% by weight of sodium stearyl fumarate.

[0421] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 42% by weight of microcrystalline cellulose; about 34% by weight of lactose anhydrous; about 3% by weight of copovidone; about 2.5% by weight of sodium starch glycolate; about 0.6% by weight of silica; about 8% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0422] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 196 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 20 mg $\pm$ 10% of sodium starch glycolate; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0423] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 135 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 8 mg $\pm$ 10% of sodium starch glycolate; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0424] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, crospovidone, copovidone, silica, and sodium stearyl fumarate.

[0425] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 42% by weight of microcrystalline cellulose; about 34% by weight of lactose anhydrous; about 3% by weight of copovidone; about 5% by weight of crospovidone; about 0.6% by weight of silica; about 8% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0426] In some embodiments, the pharmaceutical composition, for example in the form of a tablet, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 135 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 16 mg $\pm$ 10% of

crospovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0427] In one example, the pharmaceutical composition comprising (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), for example a polymorph form (e.g., form A, B, C, or D) thereof, is in the form of a capsule. In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.

[0428] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and a filler or a mixture of fillers, an optional binder, an optional disintegrant or a mixture of disintegrants, an optional surfactant, a glidant, and a lubricant. In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 5 mg to about 30 mg of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 100 mg to about 400 mg of a filler or a mixture of fillers; about 5 mg to about 15 mg of a binder; optionally about 1 mg to about 40 mg of a disintegrant or a mixture of disintegrants; optionally about 5 mg to about 60 mg by weight of a surfactant; about 0.1 mg to about 5 mg of a glidant; and about 0.1 mg to about 5 mg by weight of a lubricant.

[0429] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, copovidone, silica, and sodium stearyl fumarate.

[0430] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 7% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 36% by weight of microcrystalline cellulose; about 37% by weight of lactose anhydrous; about 3% by weight of copovidone; about 0.5% by weight of silica; about 17% by weight of sodium lauryl sulfate; and about 0.5% by weight of sodium stearyl fumarate.

[0431] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 7% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 39% by weight of microcrystalline cellulose; about 40% by weight of lactose anhydrous; about 4% by weight of copovidone; about 0.5% by weight of silica; about 9% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0432] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 54% by weight of microcrystalline cellulose; about 30% by weight of lactose anhydrous; about 3% by weight of copovidone; about 0.6% by weight of silica; about 7% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0433] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 108 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 1 mg $\pm$ 10% of silica; about 50 mg $\pm$ 10% of sodium lauryl sulfate; and about 1.5 mg $\pm$ 10% of sodium stearyl fumarate.

[0434] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 108 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 1 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 1.5 mg $\pm$ 10% of sodium stearyl fumarate.

[0435] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 196 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0436] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, copovidone, silica, and sodium stearyl fumarate.

[0437] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 8% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 43% by weight of microcrystalline cellulose; about 44% by weight of lactose anhydrous; about 4% by weight of copovidone; about 0.4% by weight of silica; and about 0.6% by weight of sodium stearyl fumarate.

[0438] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 108 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 1 mg $\pm$ 10% of silica; and about 1.5 mg $\pm$ 10% of sodium stearyl fumarate.

[0439] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, mannitol, sodium lauryl sulfate, copovidone, silica, and sodium stearyl fumarate.

[0440] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 7% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 39% by weight of microcrystalline cellulose; about 40% by weight of mannitol; about 4% by weight of copovidone; about 0.5% by weight of silica; about 9% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0441] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 108 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of mannitol; about 10 mg $\pm$ 10% of copovidone; about 1 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 1.5 mg $\pm$ 10% of sodium stearyl fumarate.

[0442] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, copovidone, sodium starch glycolate, silica, and sodium stearyl fumarate.

[0443] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 50% by weight of microcrystalline cellulose; about 30% by weight of lactose anhydrous; about 3% by weight of copovidone; about 4% by weight of sodium starch glycolate; about 0.6% by weight of silica; about 7% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0444] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 181 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 15 mg $\pm$ 10% of sodium starch glycolate; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0445] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, crospovidone, copovidone, silica, and sodium stearyl fumarate.

[0446] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 50% by weight of microcrystalline cellulose; about 30% by weight of lactose anhydrous; about 3% by weight of copovidone; about 4% by weight of crospovidone; about 0.6% by weight of silica; about 7% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0447] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 18% by weight of microcrystalline cellulose; about 62% by weight of lactose anhydrous; about 3% by weight of copovidone; about 4% by weight of crospovidone; about 0.6% by weight of silica; about 7% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0448] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 181 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 15 mg $\pm$ 10% of crospovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0449] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 65 mg $\pm$ 10% of microcrystalline cellulose; about 226 mg $\pm$ 10% of lactose anhydrous; about 10 mg $\pm$ 10% of copovidone; about 15 mg $\pm$ 10% of crospovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

[0450] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I) and microcrystalline cellulose, lactose anhydrous, mannitol, sodium lauryl sulfate, crospovidone, copovidone, silica, and sodium stearyl fumarate.

[0451] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 6% by weight of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 18% by weight of microcrystalline cellulose; about 30% by weight of lactose anhydrous; about 32% by weight of mannitol; about 3% by weight of copovidone; about 4% by weight of crospovidone; about 0.6% by weight of silica; about 7% by weight of sodium lauryl sulfate; and about 0.6% by weight of sodium stearyl fumarate.

[0452] In some embodiments, the pharmaceutical composition, for example in the form of a capsule, may comprise about 20 mg $\pm$ 10% of Compound I (e.g., a polymorph form (e.g., form A, B, C, or D) of Compound I); about 65 mg $\pm$ 10% of microcrystalline cellulose; about 110 mg $\pm$ 10% of lactose anhydrous; about 116 mg $\pm$ 10% of mannitol; about 10 mg $\pm$ 10% of copovidone; about 15 mg $\pm$ 10% of crospovidone; about 2 mg $\pm$ 10% of silica; about 25 mg $\pm$ 10% of sodium lauryl sulfate; and about 2 mg $\pm$ 10% of sodium stearyl fumarate.

Drug Combinations

[0453] The inventive compounds described herein may be used in pharmaceutical compositions or methods in combination with one or more additional active ingredients in the treatment of the diseases and disorders described herein. Further additional active ingredients include other therapeutics or agents that mitigate adverse effects of therapies for the intended disease targets. Such combinations may serve to increase efficacy, ameliorate other disease symptoms, decrease one or more side effects, or decrease the required dose of an inventive compound. The additional active ingredients may be administered in a separate pharmaceutical composition from a compound of the present invention or may be included with a compound of the present invention in a single pharmaceutical composition. The additional active ingredients may be administered simultaneously with, prior to, or after administration of a compound of the present invention.

[0454] Combination agents include additional active ingredients are those that are known or discovered to be effective in treating the diseases and disorders described herein, including those active against another target associated with the disease. For example, compositions and formulations of the invention, as well as methods of treatment, can further comprise other drugs or pharmaceuticals, e.g., other active agents useful for treating or palliative for the target diseases or related symptoms or conditions. For cancer indications, additional such agents include, but are not limited to, kinase inhibitors, such as EGFR inhibitors (e.g., erlotinib, gefitinib), Raf inhibitors (e.g., vemurafenib), VEGFR inhibitors (e.g., sunitinib), ALK inhibitors (e.g., crizotinib) standard chemotherapy agents such as alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, platinum drugs, mitotic inhibitors, antibodies, hormone therapies, or corticosteroids. For pain indications, suitable combination agents include anti-inflammatories such as NSAIDs. The pharmaceutical compositions of the invention may additionally comprise one or more of such active agents, and methods of treatment may additionally comprise administering an effective amount of one or more of such active agents.

[0455] In some embodiments, 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, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[0456] In some embodiments, a CLK inhibitor, or a pharmaceutically acceptable salt thereof, is 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, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[0457] In some embodiments, 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, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[0458] In some embodiments, 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.

[0459] In some embodiments, a medicament comprising a CLK inhibitor, or a pharmaceutically acceptable salt thereof, combined with a Bcl-2 inhibitor, a FLT3 inhibitor, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[0460] In some embodiments, a synergistic composition of a CLK inhibitor and a Bcl-2 inhibitor, a FLT3 inhibitor, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, where the two components come into contact with each other at a locus.

[0461] In some embodiments, a synergistic composition of a CLK inhibitor and a Bcl-2 inhibitor, a FLT3 inhibitor, KRAS inhibitor, ALK inhibitor, PARP inhibitor, or an EGFR inhibitor, where the two components come into contact with each other only in the human body.

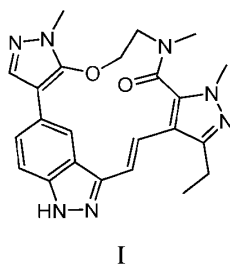
[0462] In some embodiments, the cancer is selected from the group consisting of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), small lymphocytic lymphoma (SLL), ALCL, non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumor, 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.

[0463] In certain embodiments, 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.

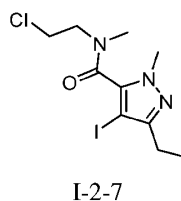
Synthesis Methods

[0464] In some embodiments, the disclosure provides a process for preparing a compound of the formula I

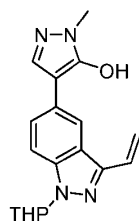


[0465] comprising

[0466] (a) contacting a compound of the formula I-2-7

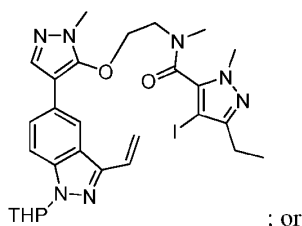


[0467] with a compound of the formula I-2-3



I-2-3

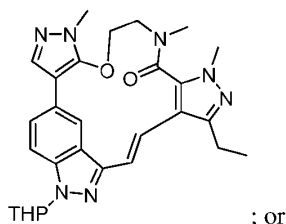
[0468] in the presence of a base to provide a compound of the formula I-2-8



; or

I-2-8

[0469] (b) contacting a compound of the formula I-2-8 in the presence of a catalyst to provide a compound of the formula I-2-9



; or

I-2-9

[0470] (c) contacting a compound of the formula I-2-9 with an acid to provide the compound of the formula I.

[0471] It will be appreciated that the present disclosure provides processes for preparing a compound of the formula I described in the paragraphs above, comprising more than one of the steps listed in the alternative. Accordingly, the present disclosure provides a process for preparing a compound of the formula I, comprising steps (a) and (b). Alternatively, the present disclosure provides a process for preparing a compound of the formula I, comprising steps (b) and (c). Alternatively, the present disclosure provides a process for preparing a compound of the formula I, comprising steps (a), (b) and (c).

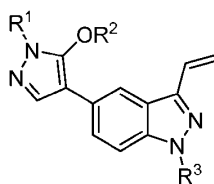
[0472] In the first step (a), the base can be any base, such as a carbonate base. Suitable bases include, but are not limited to, Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , MgCO_3 , CaCO_3 , and the like. In some embodiments, the base is K_2CO_3 . In some embodiments, step (a) can be carried out in the

presence of an inorganic salt. Suitable inorganic salts include, but are not limited to, NaCl, KCl, CsCl, MgCl₂, CaCl₂, NaBr, KBr, CsBr, MgBr₂, CaBr₂, NaI, KI, CsI, MgI₂, CaI₂, and the like. In some embodiments, the inorganic salt is KI. In some embodiments, step (a) can be carried out in the presence of a polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to, THF, 2-methyl-THF, Et₂O, DCM, DMAc, EtOAc, DMF, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is DMAc. In some embodiments, step (a) can be carried out at a temperature of from about 50 °C to about 150 °C. In some embodiments, the temperature is about 80 °C.

[0473] In step (b), the catalyst can be any catalyst, such as a palladium catalyst. Suitable palladium catalysts include, but are not limited to, Pd(OAc)₂, PdCl₂, Pd(PPh₃)₄, and the like. In some embodiments, the palladium catalyst is Pd(OAc)₂. In some embodiments, step (b) can be carried out in the presence of a base. Suitable bases include, but are not limited to, triethylamine, diisopropylamine, K₂CO₃, Na₂CO₃, KHCO₃, NaHCO₃, NaOAc, KOAc, and the like. In some embodiments, the base is NaHCO₃. In some embodiments, step (b) can be carried out in the presence of a phase transfer catalyst, such as quaternary ammonium salts. Suitable phase transfer catalysts include, but are not limited to, tetrabutylammonium chloride (TBAC), tetrabutylammonium bromide (TBAB), and the like. In some embodiments, the phase transfer catalyst is TBAC. In some embodiments, step (b) can be carried out in the presence of a polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to, THF, 2-methyl-THF, Et₂O, DCM, DMAc, EtOAc, DMF, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is DMF. In some embodiments, step (b) can be carried out at a temperature of from about 50 °C to about 150 °C. In some embodiments, the temperature is about 100 °C.

[0474] In step (c), the acid can be any reagent known in the art useful for deprotection of a THP protecting group. In step (c), the acid can be a strong inorganic acid, such as HCl, such as 4M HCl. In some embodiments, the acid can be a solution of a strong acid in a polar aprotic solvent, such as EtOAc. For example, a suitable acid for use in step (c) can include 4M HCl in EtOAc. In some embodiments, step (c) can be carried out in the presence of a further polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to THF, 2-methyl-THF, Et₂O, DCM, EtOAc, DMF, DMAc, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is EtOAc. In some embodiments, step (c) can be carried out at a temperature of from about 0 °C to about 50 °C. In some embodiments, the temperature is about 25 °C.

[0475] In some embodiments, the disclosure provides a process (Method A) for preparing a compound of the formula II



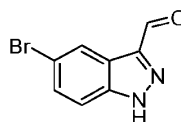
II

[0476] wherein

[0477] R^1 is H, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl, and each of R^2 and R^3 is independently H or PG; and each PG can be, for example, independently selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzylidene, and Ts;

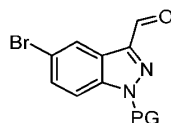
[0478] comprising

[0479] (a) contacting a compound of the formula II-1



II-1

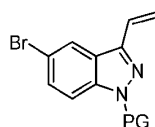
[0480] with a protecting group precursor to provide a compound of the formula II-2



II-2

[0481] wherein PG is as described herein; or

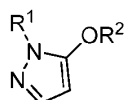
[0482] (b) contacting a compound of the formula II-2 with methyltriphenylphosphonium bromide (MePPh_3Br) to provide a compound of the formula II-3



II-3

wherein PG is as described herein; or

(c) contacting a compound of the formula II-3 with a pyrazole of the formula II-4



II-4

[0483] in the presence of a catalyst to provide the compound of the formula II,

wherein R¹ and R² are as described herein.

[0484] It will be appreciated that the present disclosure provides processes for preparing a compound of the formula II according to Method A as described in the paragraphs above, comprising more than one of the steps listed in the alternative. Accordingly, the present disclosure provides a process for preparing a compound of the formula II, comprising steps (a) and (b). Alternatively, the present disclosure provides a process for preparing a compound of the formula II, comprising steps (b) and (c). Alternatively, the present disclosure provides a process for preparing a compound of the formula II, comprising steps (a), (b) and (c).

[0485] In step (a) of Method A, the protecting group precursor can be any such reagent known in the art. Suitable protecting group precursors include, but are not limited to, FMOC-Cl, PMB-Cl, DHP, Boc₂O, Cbz-Cl, AcCl, BnBr, trityl-Cl, TsCl, and the like. In some embodiments, the protecting group precursor is DHP.

[0486] In some embodiments, step (a) of Method A can be carried out in the presence of a Lewis acid. In some embodiments, step (a) of Method A can be carried out in the presence of a water scavenger. In some embodiments, the Lewis acid and water scavenger can be the same reagent. In some embodiments, the Lewis acid and water scavenger can be different reagents. Suitable Lewis acids include, but are not limited to, copper (II) sulfate, magnesium sulfate, tetraethoxytitanium, tetraisopropoxytitanium, boron trifluoride etherate, and the like. Suitable water scavengers include, but are not limited to pyridinium p-toluenesulfonate (PPTS), TsOH, magnesium sulfate, sodium sulfate, tetraethoxytitanium, tetraisopropoxytitanium, and the like. In some embodiments, the Lewis acid and/or water scavenger is PPTS. In some embodiments, step (a) of Method A can be carried out in the presence of a polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to THF, 2-methyl-THF, Et₂O, DCM, EtOAc, DMF, DMAc, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is EtOAc. In some embodiments, step (a) of Method A can be carried out at a temperature of from about 25 °C to about 120 °C. In some embodiments, the temperature is about 65 °C to about 70 °C. In some embodiments, PG is THP.

[0487] In some embodiments, step (b) of Method A can be carried out directly after step (a) without purification. In some embodiments, step (b) of Method A can be carried out in the presence of a polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to THF, 2-methyl-THF, Et₂O, DCM, EtOAc, DMF, DMAc, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is EtOAc. In some embodiments, step (b) of Method A can be carried out in the presence of a base, such as a carbonate base. Suitable carbonate bases include, but are not limited to, Na₂CO₃, K₂CO₃, Cs₂CO₃, MgCO₃, CaCO₃, and the like. In some embodiments, the base is K₂CO₃. In some embodiments, step (b) of Method A

can be carried out at a temperature of from about 25 °C to about 120 °C. In some embodiments, the temperature is about 65 °C to about 70 °C. In some embodiments, PG is THP.

[0488] In step (c) of Method A, the catalyst can be any catalyst known in the art that can be used in a coupling reaction, such as a palladium catalyst. Suitable palladium catalysts include, but are not limited to, Pd(OAc)₂, PdCl₂, Pd(PPh₃)₄, tBuBrettPhos Pd G3, and the like. In some embodiments, the palladium catalyst is tBuBrettPhos Pd G3. In some embodiments, step (c) of Method A can be carried out in the presence of a base, such as a carbonate base. Suitable carbonate bases include, but are not limited to, Na₂CO₃, K₂CO₃, Cs₂CO₃, MgCO₃, CaCO₃, and the like. In some embodiments, the base is K₂CO₃. In some embodiments, step (c) of Method A can be carried out in the presence of a polar aprotic solvent. Suitable polar aprotic solvents include, but are not limited to THF, 2-methyl-THF, Et₂O, DCM, EtOAc, DMF, DMac, CH₃CN, acetone, HMPT, DMSO, and the like. In some embodiments, the polar aprotic solvent is 2-MeTHF. In some embodiments, step (c) of Method A can be carried out at a temperature of from about 25 °C to about 120 °C. In some embodiments, the temperature is about 77 °C to about 80 °C. In some embodiments, PG is THP.

[0489] In some embodiments, R¹ is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, R¹ is C₁-C₆ alkyl. In some embodiments, R¹ is methyl. In some embodiments, each of R² and R³ is independently H or PG. In some embodiments, R² is H or PG. In some embodiments, R² is H. In some embodiments, R³ is H or PG. In some embodiments, R³ is PG. In some embodiments, R¹ is methyl and R² is H.

EXAMPLES

[0490] The examples and preparations provided below further illustrate and exemplify particular aspects of embodiments of the disclosure. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples.

[0491] Abbreviations

[0492] The examples described herein use materials, including but not limited to, those described by the following abbreviations known to those skilled in the art:

g	grams
eq	equivalents
mmol	millimoles
umol or μmol	micromoles
mol	moles
mL	milliliters

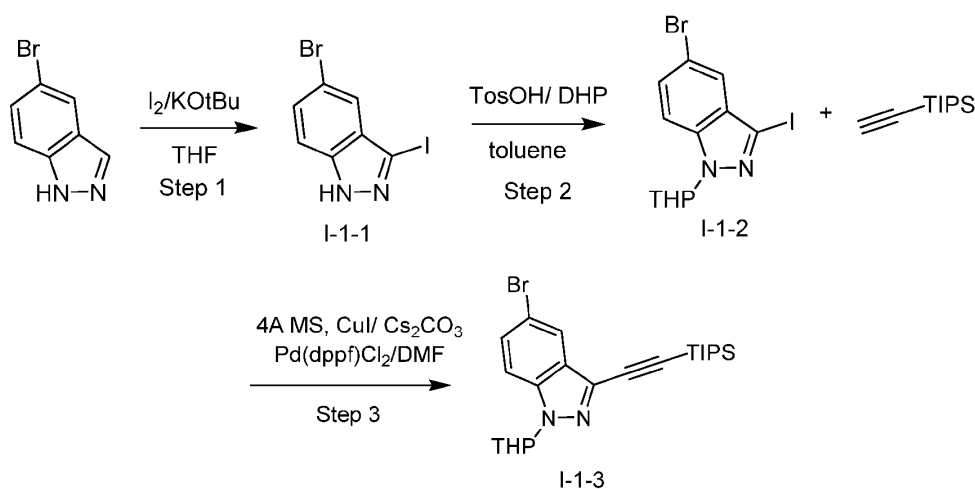
L	liters
psi	pounds per square inch
MHz	megahertz
δ	chemical shift
R _f	retardation factor
min or mins	minute or minutes
hrs, hr or h	hour or hours
M	molar
mM	millimolar
uM or μ M	micromolar
MS	mass spectrum
m/z	mass-to-charge ratio
IPC	ion-pair chromatography
LCMS	liquid chromatography mass spectrometry
TLC	thin layer chromatography
TGA	Thermogravimetric Analysis
DSC	Differential Scanning Calorimetry
C _{max}	maximum (or peak) serum concentration
AUC	area under the curve
PG	protecting group
DMSO- <i>d</i> ₆	deuterated dimethyl sulfoxide
CDCl ₃	deuterated chloroform
EtOAc or EA	ethyl acetate
MeCN or ACN	acetonitrile
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMAC or DMAc	dimethylacetamide
DMSO	dimethyl sulfoxide
DMF	N,N-dimethylformamide
MTBE or MtBE	methyl <i>tert</i> -butyl ether
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
THF	tetrahydrofuran
MeTHF or Me-THF or 2-MeTHF	2-methyltetrahydrofuran
PE	petroleum ether
NMP	N-methyl-2-pyrrolidone
n-BuOH	n-butanol
MeOH	methanol
EtOH	ethanol
IPA	isopropanol
DIEA or DIPEA or Hunig's Base	n,n-diisopropylethylamine
TEA	triethylamine
KHMDS	potassium bis(trimethylsilyl)amide
TMSCl	trimethylsilyl chloride
HMPT	hexamethylphosphoramide
TIPS	triisopropyl silane
Fmoc or Fmoc	fluorenylmethyloxycarbonyl
Ac	acetyl
Cbz	benzyloxycarbonyl
Boc	tert-butyloxycarbonyl

Bn	benzyl
Ts or Tos	toluenesulfonyl
TsOH or TosOH	tosylic acid or 4-methylbenzenesulfonic acid
PTSA	p-toluenesulfonic acid
DHP	3,4-dihydropyran
THP	tetrahydropyran
TBAC	tert-Butyl acetate
MS	molecular sieves
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
n-BuLi	n-butyllithium
T3P or T ₃ P	propanephosphonic acid anhydride
T4P or T ₄ P	butanephosphonic acid anhydride
B ₂ pin ₂	bis(pinacolato)diboron
TFA	Trifluoroacetic acid
PPTS	pyridinium p-toluenesulfonate
PMB	Para-methoxybenzyl
IPAc	isopropyl acetate
MEK	methyl ethyl ketone
MeOAc	methyl acetate
t-BuBrettPhos Pd G3	[(2-Di- <i>tert</i> -butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd(OAc) ₂	Palladium(II) acetate
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)

[0493] Example 1: Synthesis of Compound I

[0494] Compound I was prepared according to the following methods:

[0495] Part 1: Preparation of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-1-3)

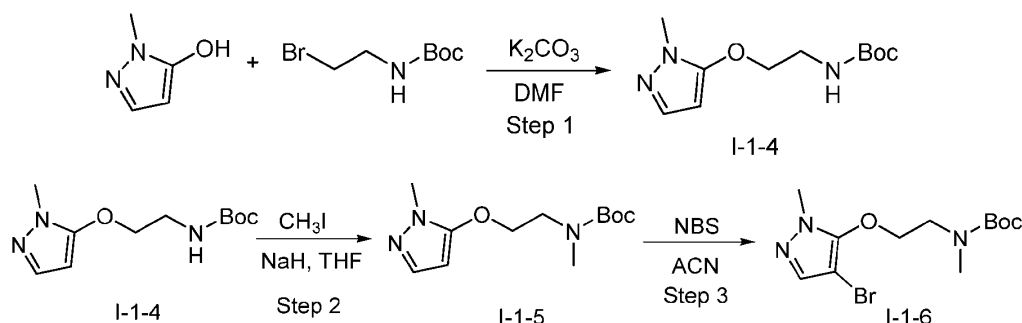


[0496] Step 1. A solution of commercially available 5-bromo-1H-indazole (21.0 g, 107 mmol, 1 eq) in THF (250 mL) was cooled down on an ice bath and KOtBu (35.9 g, 320 mmol, 3 eq) was added portion wise. The resulting slurry was stirred at 0 °C and a solution of I₂ (54.1 g, 213 mmol, 42.9 mL, 2 eq) in 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 (I-1-1, 120 g, 350 mmol, 82% yield, 94% purity) as a white solid. LCMS: 324.7 (M+1).

[0497] Step 2. To a mixture of 5-bromo-3-iodo-1H-indazole (I-1-1, 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 (I-1-2, 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).

[0498] Step 3. To a mixture of 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (I-1-2, 23.0 g, 56.5 mmol, 1 eq) and commercially available 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-1-3, 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).

[0499] Part 2: Preparation of tert-butyl N-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-N-methyl-carbamate (I-1-6)

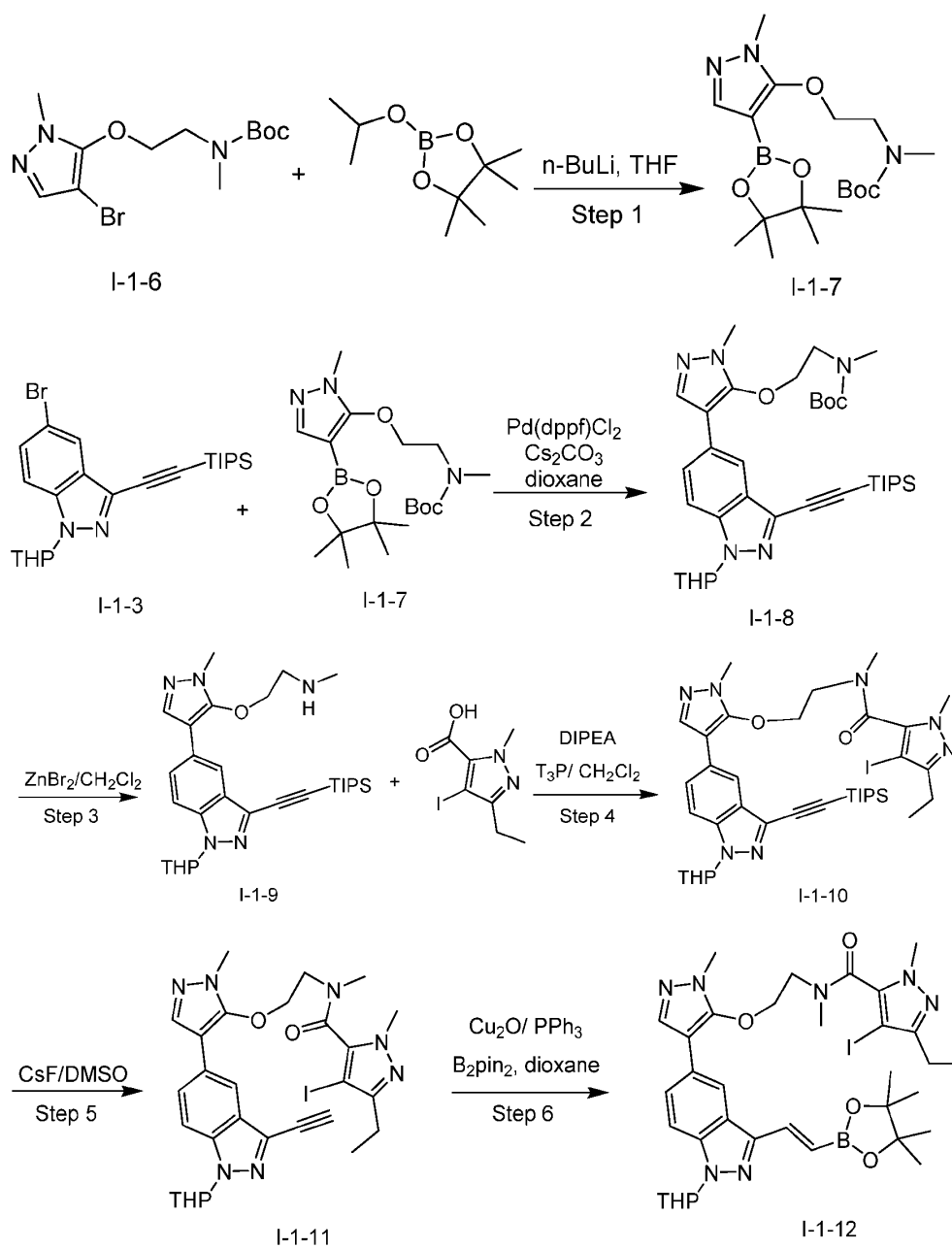


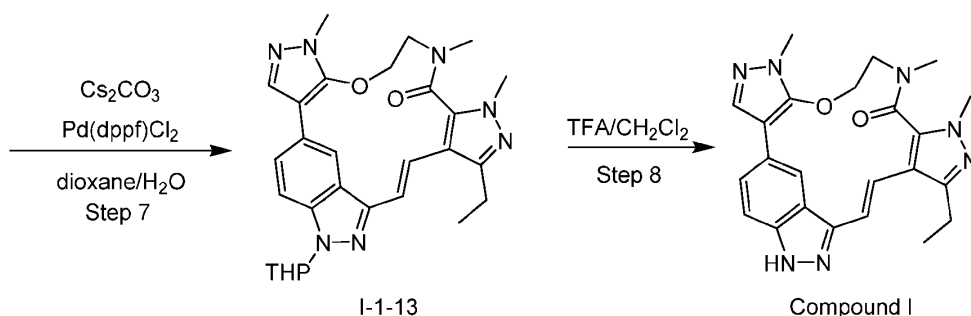
[0500] Step 1. To a mixture of commercially available 1-methyl-1H-pyrazol-5-ol (5 g, 50.9 mmol, 1 *eq*) and commercially available tert-butyl (2-bromoethyl)carbamate (13.7 g, 61.1 mmol, 1.2 *eq*) in DMF (50 mL) was added K_2CO_3 (21.1 g, 152 mmol, 3 *eq*). The mixture was stirred at 80 °C for 2 hours. 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 (2-((1-methyl-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-4, 11 g, 89.45% yield) as black oil. LCMS: (M+1:242.2).

[0501] Step 2. To a solution of tert-butyl (2-((1-methyl-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-4, 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, and the mixture was stirred at 25 °C for 0.5 hours, and then CH_3I (1.41 g, 9.95 mmol, 1.2 *eq*) was 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 methyl(2-((1-methyl-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-5, 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).

[0502] Step 3. To a solution of tert-butyl methyl(2-((1-methyl-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-5, 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 and the residue was purified by silica gel column chromatography to provide Preparation of tert-butyl N-[2-(4-bromo-2-methyl-1H-pyrazol-3-yl)oxyethyl]-N-methyl-carbamate (I-1-6, 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).

[0503] Part 3. Preparation of (1*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





[0504] Step 1. To a solution of *tert*-butyl *N*-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-*N*-methyl-carbamate (I-1-6, 20.0 g, 59.8 mmol, 1 *eq*) 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 commercially available 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 × 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 *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-1-7, 21.2 g, 55.6 mmol, 92% yield) as a yellow oil. LCMS: *m/z* 381.9 (*M*+1).

[0505] Step 2. A mixture of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-1-3, 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-1-7, 4.96 g, 13.00 mmol, 1.2 *eq*), Pd(dppf)Cl₂ (1.59 g, 2.17 mmol, 0.2 *eq*), Cs₂CO₃ (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 *tert*-butyl methyl(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-8, 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).

[0506] Step 3. To a solution of *tert*-butyl methyl(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-

3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)carbamate (I-1-8, 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 N-methyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethan-1-amine (I-1-9, 800 mg, 1.49 mmol, 95.0% yield) as a yellow solid. LCMS: m/z 536.1 (M+1).

[0507] Step 4. To a solution of N-methyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethan-1-amine (I-1-9, 1.5 g, 2.80 mmol, 1 eq) and commercially available 5-ethyl-4-iodo-2-methyl-pyrazole-3-carboxylic acid (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 3-ethyl-4-iodo-N,1-dimethyl-N-(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)-1H-pyrazole-5-carboxamide (I-1-10, 1.15 g, 1.37 mmol, 49.0% yield, 95.1% purity) as a yellow gum. LCMS: (M+1: 798.4).

[0508] Step 5. To a solution of 3-ethyl-4-iodo-N,1-dimethyl-N-(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)-1H-pyrazole-5-carboxamide (I-1-10, 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 3-ethyl-N-(2-((4-(3-ethynyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1-methyl-1H-pyrazol-5-yl)oxy)ethyl)-4-iodo-N,1-dimethyl-1H-pyrazole-5-carboxamide (I-1-11, 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).

[0509] Step 6. A mixture of 3-ethyl-N-(2-((4-(3-ethynyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-1-methyl-1H-pyrazol-5-yl)oxy)ethyl)-4-iodo-N,1-dimethyl-1H-pyrazole-5-

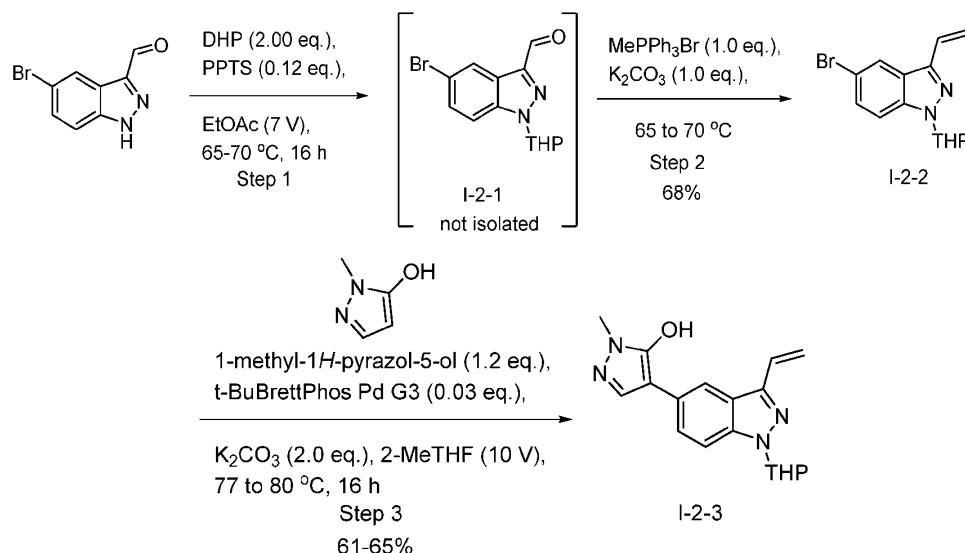
carboxamide (I-1-11, 650 mg, 1.01 mmol, 1 eq), Pin_2B_2 (257 mg, 1.01 mmol, 1 eq), PPh_3 (266 mg, 1.01 mmol, 1 eq) and Cu_2O (72.5 mg, 0.507 mmol, 0.5 eq) in dioxane (12 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was partitioned between H_2O (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 (E)-3-ethyl-4-iodo-N,1-dimethyl-N-(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)-1H-pyrazole-5-carboxamide (I-1-12, 750 mg, 0.974 mmol, 96.2% yield) as a yellow solid. LCMS: m/z 770.4 (M+1).

[0510] Step 7. A mixture of (E)-3-ethyl-4-iodo-N,1-dimethyl-N-(2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)ethyl)-1H-pyrazole-5-carboxamide (I-1-12, 700 mg, 0.91 mmol, 1 eq), Cs_2CO_3 (889 mg, 2.73 mmol, 3 eq) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (66.6 mg, 0.91 mmol, 0.1 eq) in dioxane (12 mL) and H_2O (1.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 hours under N_2 atmosphere. The reaction mixture was partitioned between H_2O (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 (17E)-16-ethyl-8,12,14-trimethyl-2-(oxan-2-yl)-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-13(10H)-one (I-1-13, 140 mg, 0.271 mmol, 29.7% yield) as a yellow oil. LCMS: m/z 516.3 (M+1).

[0511] Step 8. To a solution of (17E)-16-ethyl-8,12,14-trimethyl-2-(oxan-2-yl)-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-13(10H)-one (I-1-13, 140 mg, 0.271 mmol, 1 eq) in CH_2Cl_2 (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 NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (5 mL $\times$ 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. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 13.06 (s, 1H), 8.45 (s, 1H), 7.94 (s, 1H), 7.72 (dd, J = 1.2, 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 17.2 Hz, 1H), 7.08 (d, J = 17.2 Hz, 1H), 4.95 (dd, J = 4.0, 14.4 Hz, 1H), 4.36 - 4.22 (m, 2H), 3.78 (d, J = 3.6 Hz, 6H), 3.39 - 3.34 (m, 1H), 3.15 (s, 3H), 2.87 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H). LCMS: (M+1: 432.2).

[0512] Example 2: Large Scale Synthesis of Compound I

[0513] Part 1: Preparation of 1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-indazol-5-yl)-1H-pyrazol-5-ol (I-2-3).

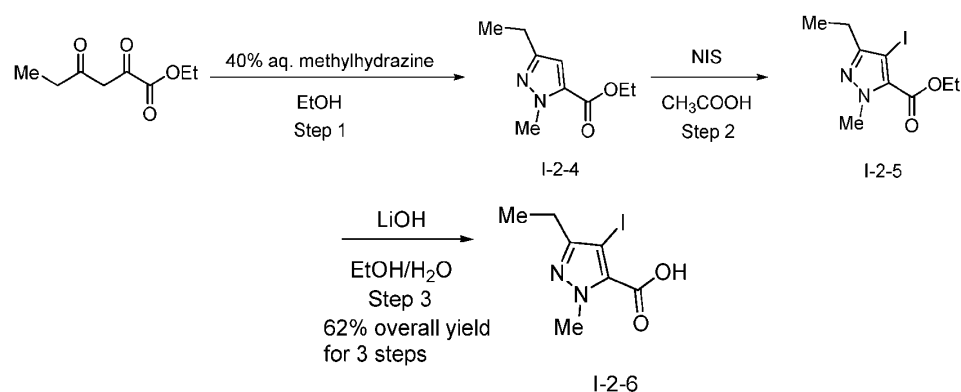


[0514] Step 1. A mixture of commercially available 5-bromo-1H-indazole-3-carbaldehyde (C, 1.0 eq, 1000 g, 4.44 mol), pyridinium p-toluenesulfonate (PPTS, 0.12 eq. 0.53 mol, 103.5 g), 3,4-dihydro-2H-pyran (DHP, 2.0 eq, 8.8 mol, 747.6 g) in EtOAc (7 L) was heated at 65-70 °C under N₂ for 16 h, at which time the mixture was cooled down to 20-25 °C, filtered, and the filter cake was washed with EtOAc (1 L). 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (I-2-1) in EtOAc solution was used directly without purification.

[0515] Step 2. To the filtrate from Step 1 was charged MePPh₃Br (1.0 eq., 4.44 mol, 1587.1 g), K₂CO₃ (1.0 eq., 4.44 mol, 614.0 g), and the mixture was heated at 65-70 °C under N₂ for 18 h, at which time celite (750 g) was added and the mixture was filtered, and the filter cake was washed with EtOAc (2 L). The filtrate was concentrated. To the residue was added heptane (18 L) and MgCl₂ (1.0 eq., 4.44 mol, 423.0 g), and the mixture was stirred at 45-50 °C for 4 h. The mixture was filtered and concentrated. A mixture of the residue, IPA (3 L) and water (1.4 L) was stirred at 65-70 °C overnight and then cooled to room temperature. The slurry was filtered, and the filter cake was washed with IPA/water = (2.5:1, 1 L x 2), the obtained cake was dried at 50 °C in a vacuum oven overnight to give 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-indazole (I-2-2, 928 g, 3.0 mol, 68% in 2 steps). ¹H NMR (400 MHz, CDCl₃) δ = 8.09 - 8.02 (m, 1H), 7.47 (d, J = 1.2 Hz, 2H), 6.99 (dd, J = 11.6, 18.0 Hz, 1H), 6.06 (dd, J = 1.2, 18.0 Hz, 1H), 5.67 (dd, J = 2.8, 9.2 Hz, 1H), 5.55 (dd, J = 0.8, 11.6 Hz, 1H), 4.10 - 3.99 (m, 1H), 3.81 - 3.68 (m, 1H), 2.62 - 2.47 (m, 1H), 2.22 - 2.02 (m, 2H), 1.82 - 1.63 (m, 3H). LCMS: (M+1:307.1/309.0).

[0516] Step 3. A mixture of 5-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-indazole (900 g, 2.93 mol, 1 eq), commercially available 2-methylpyrazol-3-ol (1.2 eq, 3.52 mol, 584.0 g), K₂CO₃ (2 eq, 5.86 mol, 809.9 g), and t-BuBrettPhos Pd G3 (0.03 eq, 0.09 mol, 75.1 g) in MeTHF (9 L) was heated at 80 °C under N₂ for 14 h, at which time H₂O (4.5 L) was added, and pH was adjusted to 3-4 by adding 2M HCl at 20-30 °C. 2-MeTHF (7.2 L) was added, and aqueous layer was discarded. The organic layer was washed with H₂O (1.8 L), and the resulting organic layer was treated with cysteine (135 g), activated carbon (135 g), and mercapto silica gel (135 g) followed by filtration. The filtrate was concentrated, and the residue was slurried with IPA (5.9 L)/heptane (9 L). 1-methyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-indazol-5-yl)-1*H*-pyrazol-5-ol (I-2-3, 580 g, 1.79 mol, 61%) was obtained from filtration and drying in vacuum oven at 40 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.098 (s, 1H), 7.44 (dd, *J* = 16.0, 8.0 Hz, 2H), 7.25 (s, 1H), 6.97 (dd, *J* = 20.0, 12.0 Hz, 1H), 6.07 (d, *J* = 20.0 Hz, 1H), 5.65 (d, *J* = 8.0 Hz, 1H), 5.47 (d, *J* = 12.0 Hz, 1H), 4.06 – 4.09 (m, 1H), 3.74 – 3.76 (m, 1H), 3.42 (s, 3H), 2.50 – 2.65 (m, 1H), 2.01 – 2.05 (m, 2H), 1.66 – 1.77 (m, 3H). LCMS: (M+1:325.1).

[0517] Part 2: Preparation of 3-ethyl-4-iodo-1-methyl-1*H*-pyrazole-5-carboxylic acid (I-2-6)

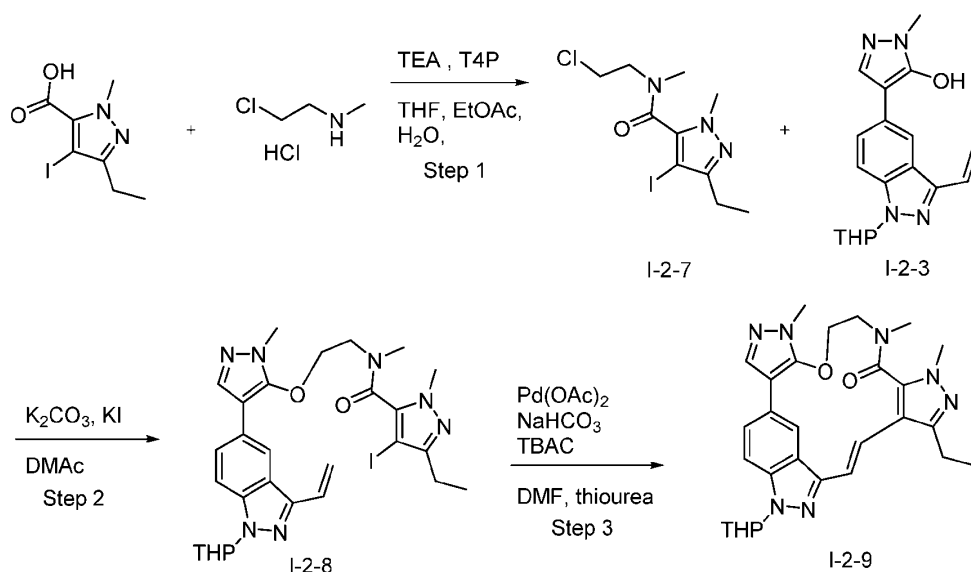


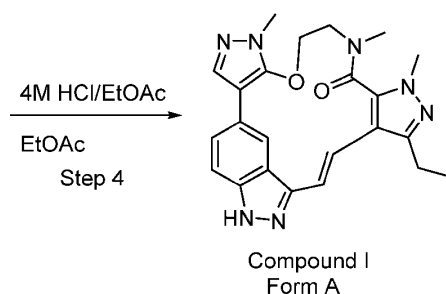
[0518] Step 1. To a solution of methylhydrazine (40% content, 1.0 eq., 669.0 g, 5.81 mol) in EtOAc (2.5 L) was added commercially available ethyl 2,4-dioxohexanoate (1.0 eq, 1000 g, 5.81 mol) in EtOH (2.5 L) at -10 °C under N₂. The reaction mixture was cooled at -10 °C until the reaction temperature was 0 °C. The mixture was then stirred at 0 °C for 4 h, at which time the mixture was warmed to 20 °C and concentrated. Water (2 L) was added to the residue and the mixture was extracted with EtOAc (5 L x 2). The combined organic layer was washed with 10% NaCl (5 L), dried over anhydrous MgSO₄ (250 g), and filtered. The filtrate, containing ethyl 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (I-2-4), was concentrated and the residue was used in the next step without further purification.

[0519] Step 2. A mixture of ethyl 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (I-2-4, 1.0 eq, 1058.0 g) and NIS (1.2 eq, 6.97 mol, 1568.1 g) in acetic acid (7 L) was heated at 60-65 °C for 4 h, at which time the mixture was cooled to 20 °C and added to a solution of 10% aq. Na₂SO₃ (5 L). The mixture was extracted with MTBE (5 L x 2). The combined organic layer was washed with H₂O (5 L), dried over anhydrous MgSO₄ (250 g), and filtered. The filtrate, containing ethyl 3-ethyl-4-iodo-1-methyl-1*H*-pyrazole-5-carboxylate (I-2-5), was concentrated and the residue was used in the next step without further purification.

[0520] Step 3. A mixture of ethyl 3-ethyl-4-iodo-1-methyl-1*H*-pyrazole-5-carboxylate (I-2-5, 1.0 eq, 1790.1 g, 5.81 mol) and LiOH·H₂O (5.0 eq, 29.04 mol, 1218.5 g) in EtOH/H₂O (4.2 L/2.1 L) was stirred at 20 °C for 4 h, at which time the mixture was poured into ice water (4.2 L) and stirred at 0 °C for 30 min. The pH was adjusted to a pH of 2-3 by adding 4 M HCl, and the mixture was stirred for 30 min at 20-25 °C, and then filtered. Trituration of the wet cake with 10% IPA/H₂O (10 L) from 60 °C to 20 °C followed by filtration gave a wet cake. The wet cake was dried in vacuum oven at 50-55 °C to give the 3-ethyl-4-iodo-1-methyl-1*H*-pyrazole-5-carboxylic acid (I-2-6, 1010 g, 3.61 mol, 62%). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.7 (s, 1H), 4.03 (s, 3H), 2.53 (q, *J* = 8.0 Hz, 2H), 1.14 (t, *J* = 8.0 Hz, 3H). LCMS: (M+1: 280.9).

[0521] Part 3. 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





[0522] Step 1: Commercially available 3-ethyl-4-iodo-1-methyl-1*H*-pyrazole-5-carboxylic acid (1.0 eq, 1000 g, 3.57 mol) was charged to a reactor and then THF (10 L) was added at 20-30 °C. The reaction mixture was cooled at -5 °C to 5 °C, and triethylamine (TEA, 4.5 eq) was added at -5 to 5 °C. The mixture was stirred at -5 to 5 °C for 0.5 h. Butanephosphonic acid anhydride (T4P, 50% EtOAc, 1.8 eq, 6.43 mol, 4758.8 g) was added dropwise at -5 to 5 °C and stirred for 30 min at this temperature. Then commercially available 2-chloro-*N*-methylethan-1-amine hydrochloride (1.8 eq, 6.43 mol, 835.7 g) was added at -5 to 5 °C in portions. The mixture was stirred at 45 °C for 7 h. On completion, water (0.2 L) was added at 0 to 10 °C. The mixture was concentrated to 2-3 L under vacuum below 45 °C. EtOAc (5 L) and H₂O (3 L) was added to the residue at 20-30 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (2 L x 3). The combined organic phase was washed with 7% aq. NaHCO₃ (4 L), 20% NH₄Cl aq. (1 L), and 5% Na₂SO₄ aq. (2 L). The organic phase was concentrated to remove EtOAc and switching with THF for three times (4 L x 3). *N*-(2-chloroethyl)-3-ethyl-4-iodo-*N*,1-dimethyl-1*H*-pyrazole-5-carboxamide (I-2-7) was obtained as light-brown viscous oil and was used in step 2 directly without further purification.

[0523] Step 2. A mixture of 1-methyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-indazol-5-yl)-1*H*-pyrazol-5-ol (I-2-3, 1.0 eq, 1000.0 g, 3.08 mol), K₂CO₃ (anhydrous powder, 3 eq, 10.71 mol, 1480.5 g), KI (0.2 eq, 0.71 mol, 118.6 g), and dimethylacetamide (DMAC, 3 L) was heated to 80 °C. A solution of *N*-(2-chloroethyl)-3-ethyl-4-iodo-*N*,1-dimethyl-1*H*-pyrazole-5-carboxamide (I-2-7) (1.6 eq, 5.71 mol, 2031.8 g) in DMAC (3 L) was added dropwise to the above mixture at 75-80 °C for 2 h. The reaction mixture was stirred at 80 °C for 2-3 h. The mixture was diluted with EtOAc (10 L) and water (5 L), then washed with 10% aq. K₂CO₃ solution (7 L), 1*N* HCl (3 L), 7% aq. NaHCO₃ solution (3 L), and 20% NaCl aq. solution (3 L). The organic phase was concentrated under vacuum to obtain crude product 3-ethyl-4-iodo-*N*,1-dimethyl-*N*-(2-((1-methyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-indazol-5-yl)-1*H*-pyrazol-5-yl)oxy)ethyl)-1*H*-pyrazole-5-carboxamide (I-2-8) which was used in step 3 directly without further purification.

[0524] Step 3. To a solution of 3-ethyl-4-iodo-*N*,1-dimethyl-*N*-(2-((1-methyl-4-(1-(tetrahydro-

2*H*-pyran-2-yl)-3-vinyl-1*H*-indazol-5-yl)-1*H*-pyrazol-5-yl)oxy)ethyl)-1*H*-pyrazole-5-carboxamide (I-2-8, 1.0 eq, 1000.0 g, 1.55 mol), tetrabutylammonium chloride (TBAC, 1.0 eq, 431.9 g) and NaHCO₃ (2.5 eq, 3.89 mol, 326.3 g) in dimethylformamide (DMF, 15 L) was added Pd(OAc)₂ (0.05 eq, 0.08 mol, 17.4 g) at 25 °C. The mixture was heated to 100 °C and stirred under N₂ for 21 h. On completion, the mixture was cooled to 20-30 °C, thiourea (1000.0 g) was added at 20-30 °C, and the mixture was stirred for 2 h, and then filtered through diatomite (0.3 kg). The filtrate was concentrated to 5-6 L under vacuum, and then the mixture was slowly added to saturated aq. NH₄Cl (20 L). The slurry was filtered, and the wet cake was treated with water (3 L) and DCM (6 L). The organic layer was collected, and the aqueous layer was extracted with DCM (3 L x 3). The combined organic layer was decolorized by CUNO and then concentrated. The residue was triturated with methanol (1.3 L) at 0-5 °C and stirred for 2 h. The slurry was filtered, and the wet cake was dried in vacuum oven at 50 °C until the constant weight was achieved to provide (17*E*)-16-ethyl-8,12,14-trimethyl-2-(oxan-2-yl)-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 (I-2-9, 440 g, 853.3 mmol, 24% yield in 3 steps). ¹H NMR (400 MHz, CDCl₃) δ = 8.41 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.32 (dd, *J* = 0.8, 17.2 Hz, 1H), 7.14 - 7.07 (m, 1H), 5.58 (ddd, *J* = 2.8, 4.0, 9.6 Hz, 1H), 5.13 (dd, *J* = 5.6, 14.8 Hz, 1H), 4.32 - 4.20 (m, 1H), 4.16 - 4.07 (m, 1H), 4.00 (d, *J* = 12.4 Hz, 1H), 3.81 - 3.72 (m, 6H), 3.70 - 3.62 (m, 1H), 3.18 (d, *J* = 5.6 Hz, 3H), 3.07 (dd, *J* = 8.0, 14.8 Hz, 1H), 2.85 (q, *J* = 7.6 Hz, 2H), 2.54 - 2.40 (m, 1H), 2.10 - 1.90 (m, 2H), 1.69 (t, *J* = 10.4 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). LCMS: (M+1:516.2).

[0525] Step 4. To a mixture of (17*E*)-16-ethyl-8,12,14-trimethyl-2-(oxan-2-yl)-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 (I-2-9, 1 eq, 1000 g, 1.94 mol) in EtOAc (5 L) was added 4M HCl/EtOAc (20 L, 41.2 eq) at 25 °C. Then the mixture was stirred at 25 °C for 16 h, at which time the reaction mixture was filtered, and the filter cake was washed with EtOAc (3 L). The wet cake was diluted with water (2 L), mixed solvents of DCM/MeOH (V:V = 10:1, 15 L) and MeOH (5 L). The pH was adjusted to pH of 8 by adding sat. NaHCO₃ at 20-30 °C. The organic phase was collected and the water layer was extracted with DCM/MeOH (V:V = 10:1, 5 L x 3). The combined organic phase was concentrated to remove DCM and MeOH under vacuum and switched with EtOAc (4 L x 3). Then EtOAc (2 L) was added. After stirring at 0-5 °C for 2 h, the mixture was filtered, and the filter cake was washed with EtOAc (0.5 L). The wet cake was dried at 50 °C under vacuum overnight to give (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) as polymorph form A as an off-white solid (780 g, 1.81 mol, 93%). The product identity was confirmed by ¹H NMR and MS, which matched the characterization data provided in Example 1,

and by PXRD as crystalline polymorph form A which was performed according to Example 12.

[0526] Example 3: Formation of crystalline polymorph form A of Compound I.

[0527] Solid amorphous Compound I prepared according to the method described in Example 1 (2.37 g) was dissolved in DCM (~50 mL) and to this solution was added hexane (~50 mL). The mixture was concentrated under reduced pressure to remove about 30 mL DCM. The crystals that were formed were filtered and washed with hexane (1 mL) and dried under high vacuum to give anhydrous crystalline polymorph form A (1.46 g). The identity of the product as crystalline polymorph form A was confirmed by PXRD as described in Example 12.

[0528] Example 4: Formation of crystalline polymorph form B of Compound I.

[0529] Solid amorphous Compound I prepared according to the method described in Example 1 (125 mg) was dissolved in MeOH (1.4 mL) by heating the mixture. To this hot solution was added water (2.1 mL) followed by further heating then the mixture was cooled to ambient temperature and sonicated briefly. The mixture was then concentrated under reduced pressure to remove ~0.8 mL of solvent. A precipitate formed and more water was added (~3.8 mL). The mixture was shaken vigorously then transferred to a centrifuge tube and diluted with water (18 mL). Material was centrifuged and water decanted off. Then remaining crystals were air-dried over the weekend to give crystalline pentahydrate form B (78 mg). The identity of the product as crystalline polymorph form B was confirmed by PXRD as described in Example 12.

[0530] Example 5: Formation of crystalline polymorph form C of Compound I.

[0531] Approximately 20 mg of crystalline polymorph form A was added to a 2 mL vial followed by 0.75 mL of MeOH. The slurry was stirred at RT or at 50 °C for 2 days. After stirring for two days, the solids were centrifuged, then recovered for PXRD analysis according to Example 12. Both the RT and 50 °C slurries provided the crystalline polymorph form C of Compound I having PXRD patterns consistent with FIG. 3.

[0532] Example 6: Formation of crystalline polymorph form D of Compound I by direct antisolvent addition.

[0533] Approximately 20 mg of crystalline polymorph form A was added to 5 mL of NMP and dissolved with stirring at RT to dissolve the crystalline polymorph form A. To this stirred solution was added dropwise in four equal portions over 1 hour, 10 mL of EtOAc as an antisolvent. The solution was stirred at 5 °C for approximately 3 days, at which time the solution was cooled to -20 °C. The mixture was allowed to stand stagnant under cooling at -20 °C for 2 weeks, at which time the solids were recovered by filtration for PXRD analysis according to Example 12. The solid provided was crystalline solvate polymorph form D of Compound I having a PXRD pattern consistent with FIG. 4A.

[0534] Example 7: Formation of crystalline polymorph form D of Compound I by reverse antisolvent addition.

[0535] Approximately 20 mg of crystalline polymorph form A was added to 5 mL of NMP and dissolved with stirring at RT to dissolve the crystalline polymorph form A. The solution was transferred all at once to 10 mL of MTBE as an antisolvent with rapid stirring. The solution was stirred at 5 °C for approximately 3 days, at which time the solution was cooled to -20 °C. The mixture was allowed to stand stagnant under cooling at -20 °C for 2 weeks, at which time the solids were recovered by filtration for PXRD analysis according to Example 12. The solid provided was crystalline solvate polymorph form D of Compound I having a PXRD pattern consistent with FIG. 4A.

[0536] Example 8: Formation of crystalline polymorph forms by short-term slurry screen of crystalline polymorph form A of Compound I.

[0537] Following the procedure provided in Example 5, various solvents were screened and provided the crystalline polymorph forms as shown in Table 6. The identity of the crystalline polymorph form(s) obtained from each solvent system was confirmed by PXRD analysis according to Example 12. In Table 6, “-” means no data were collected.

Table 6

Solvent	PXRD pattern	
	RT	50 °C
MeOH	C	C
IPA	A	A
Acetone	A	A
MTBE	A	A
2-MeTHF	A	A
EtOAc	A	A
IPAc	A	A
ACN	A	A
MEK	A	A
Cyclohexane	A	A
Heptane	A	A
DMF	-	C
EtOH ^b	A	C
EtOH:water (98:2 vol.)	A	C + possibly trace A
EtOH:water (95:5 vol.)	A	C + possibly trace A
EtOH:water (9:1 vol.)	C + possibly trace A	C
EtOH:water (8:2 vol.)	C	C
EtOH:water (1:1 vol.)	B	B
EtOH:water (15:85 vol.)	A	A
ACN:water (8:2 vol.)	B	C
Acetone:water (9:1 vol.)	A	C
Water-saturated MeOAc	B	C

Solvent	PXRD pattern	
	RT	50 °C
DCM	A	-
Water	A	A

[0538] Example 9: Formation of crystalline polymorph forms by direct antisolvent addition screen of crystalline polymorph form A of Compound I.

[0539] Following the procedure provided in Example 6, various solvents were screened and provided the crystalline polymorph forms as shown in Table 7. The identity of the crystalline polymorph form(s) obtained from each solvent system was confirmed by PXRD analysis according to Example 12. In Table 7, “-” means no solids were collected, and L.C. means low crystalline.

Table 7

Mass of solid (mg)	Solvent (mL)	Antisolvent (mL)	PXRD pattern	Comments
21.7	DMF (8)	Acetone (16)	A (5 °C)	Yellow solution remained after final composition of DMF:acetone (1:2 vol.). Solution placed at 5 °C while stirring over the weekend. Slurry observed and sample filtered for XPRD.
18.4		2-MeTHF (16)	C (L.C.) (-20 °C)	Yellow solution remained after final composition of DMF:2-MeTHF (1:2 vol.). Solution placed at 5 °C while stirring over the weekend; solution remained. Placed at -20 °C for stagnant cooling for ~2 weeks.
18.0	NMP (5)	EtOAc (10)	D (-20 °C)	Yellow solution remained after final composition of NMP:EtOAc (1:2 vol.). Solution placed at 5 °C while stirring over the weekend; solution remained. Placed at -20 °C for stagnant cooling for ~2 weeks.
19.9		MtBE (10)	-	Yellow solution remained after final composition of NMP:MtBE (1:2 vol.). Solution placed at 5 °C while stirring over the weekend; solution remained. Placed at -20 °C for stagnant cooling for ~1 month, solution remained.
18.4		Water (10)	B	After the second addition of water, the solution became hazy. After the third addition of water, a thick slurry was observed.

Mass of solid (mg)	Solvent (mL)	Antisolvent (mL)	PXRD pattern	Comments
19.4	EtOH: water (8:2 vol.) (55)	Water (110)	B	After the third addition of water, a thick slurry was observed.
18.2		Acetone (110)	-	Yellow solution remained after final composition of EtOH:water:acetone (4:1:10 vol.). Solution placed at 5 °C while stirring over the weekend; solution remained. Placed at -20 °C for stagnant cooling for ~1 month; solution remained.
20.5		ACN (110)	-	Yellow solution remained after final composition of EtOH:water:ACN (4:1:10 vol.). Solution placed at 5 °C while stirring over the weekend; solution remained. Placed at -20 °C for stagnant cooling for ~1 month; solution remained.

[0540] Example 10: Formation of crystalline polymorph forms by reverse antisolvent addition screen of crystalline polymorph form A of Compound I.

[0541] Following the procedure provided in Example 7, various solvents were screened and provided the crystalline polymorph forms as shown in Table 8. The identity of the crystalline polymorph form(s) obtained from each solvent system was confirmed by PXRD analysis according to Example 12. In Table 8, “-” means no solids were collected, and L.C. means low crystalline.

Table 8

Mass of solid (mg)	Solvent (mL)	Antisolvent (mL)	PXRD pattern	Comments
17.2	DMF (8)	Acetone (16)	-	Hazy mixture. Left to stir at RT. Solution remained
18.4		2-MeTHF (16)	-	Yellow solution. Solution placed at 5 °C while stirring; solution remained. Placed at -20 °C for stagnant cooling for ~1 month; solution remained.
16.8	NMP (5)	EtOAc (10)	-	Yellow solution. Solution placed at 5 °C while stirring; solution remained. Placed at -20 °C for stagnant cooling for ~1 month; solution remained.
17.7		MtBE (10)	D (-20 °C)	Yellow solution. Solution placed at 5 °C while stirring; solution remained. Solution placed at -20 °C for stagnant cooling; solids observed.
19.5		Water (10)	B	Thick, off-white slurry observed.
17.3	EtOH:	Water	B	Thick, off-white slurry observed.

Mass of solid (mg)	Solvent (mL)	Antisolvent (mL)	PXRD pattern	Comments
	water	(110)		
16.9	(8:2 vol.) (55)	Acetone (110)	C	Yellow solution. Solution placed at 5 °C while stirring; solution remained. Solution placed at -20 °C for stagnant cooling; solids observed.
17.0		ACN (110)	A + C (-20 °C)	Yellow solution. Solution placed at 5 °C while stirring; solution remained. Solution placed at -20 °C for stagnant cooling; solids observed.

[0542] Example 11:

[0543] A small aliquot of the slurry was sampled for XRPD and determined to be Pattern D (Figure 4A). Pattern D was then filtered and dried under active vacuum at 50 °C for 3 h. TGA analysis showed a mass loss of 19.3 wt. % up to 190 °C, with an additional mass loss of 11.5 wt. % up to 305 °C (TGA/DSC Figure 8A/8B). The solids were also dried overnight under active vacuum at 50 °C and remained as pattern D (FIG 4B).

[0544] Example 12: Powder X-ray Diffraction (PXRD) of crystalline polymorph forms of Compound I.

[0545] PXRD data for all crystalline polymorph forms of Compound I were obtained using the following method.

[0546] XRPD was performed using a Bruker D8 Advance equipped with LYNXEYE detector in reflection mode (i.e., Bragg-Brentano geometry). Samples were prepared on Si zero-return wafers. The parameters for XRPD methods used are provided in Table 9.

Table 9

Parameter	Regular scan	High resolution scan
X-ray wavelength	Cu K α 1, 1.540598 Å	Cu K α 1, 1.540598 Å
X-ray tube setting	40 kV, 40 mA	40 kV, 40 mA
Slit condition	0.6 mm div. + 2.5° soller	0.6 mm div. + 2.5° soller
Scan mode	Step	Step
Scan range (°2 θ)	4–30	4–40
Step size (°2 θ)	0.03	0.02
Dwell time (s/step)	0.23	0.9
Spin	Yes (0.5 Hz)	Yes (0.5 Hz)

[0547] Results for each of the crystalline polymorph forms of Compound I are shown in: crystalline polymorph form A in FIGS. 1A and 1B; pentahydrate crystalline polymorph form B in FIG. 2; crystalline polymorph form C in FIG. 3; solvate crystalline polymorph form D in FIGS. 4A and 4B.

[0548] Example 13: Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) of crystalline polymorph forms of Compound I.

[0549] TGA and DSC were performed on the same sample simultaneously using a Mettler Toledo TGA/DSC³⁺. Protective and purge gas was nitrogen at a flowrate of 20–30 mL/min and 50–100 mL/min, respectively. The desired amount of sample (5–10 mg) was weighed directly in a hermetic aluminum pan with pinhole and analyzed according to the parameters shown in Table 10. Results for each of the crystalline polymorph forms of Compound I are shown in: crystalline polymorph form A in FIG. 5A and 5B; pentahydrate crystalline polymorph form B in FIG. 6A and 6B; crystalline polymorph form C in FIG. 7A and 7B; and crystalline polymorph form D (wet) in FIGS. 8A and 8B.

Table 10

Parameters	
Method	Ramp
Sample size	5–10 mg
Heating rate	10.0 °C/min
Temperature range	30 to 300 °C

Biological Examples

[0550] Example 14: Inhibition of CLK1, CLK2, CLK3 and CLK4 kinase activity

[0551] Kinase protein and substrate were pre-diluted in the HEPES assay buffer (100 mM HEPES, pH 7.5, 0.01% Triton X-100, 0.1% BSA, 5 mM MgCl₂, 1 mM DTT, 10 μM Sodium Orthovanadate, 10 μM Beta-Glycerophosphate) and dispensed into 384 well plate (5 μL per well). Control samples (0%-inhibition in the absence of inhibitor, DMSO only) and 100%-inhibition (in the absence of enzyme) were assembled in replicates of six and were used to calculate %-inhibition in the presence of compounds. Compound I was added to the protein samples by acoustic dispensing (Labcyte Echo550). Concentration of DMSO was equalized to 1% in all samples. Reactions were initiated by addition of ATP by acoustic dispensing (Labcyte Echo550) and incubated according to assay specific incubation time. After incubation, 5uL of Promega ADP-Glo reagent was added and incubated for 40 minutes. After 40 minutes, 10uL of Promega kinase detection reagent was added. After 10 min of incubation with Kinase detection reagent, the luminescence was read on microplate reader (Biotek Synergy).

[0552] Table 11. Inhibition of CLK1, CLK2, CLK3 and CLK4 kinase activity

Ex #	CLK1 IC ₅₀ (nM)	CLK2 IC ₅₀ (nM)	CLK3 IC ₅₀ (nM)	CLK4 IC ₅₀ (nM)
Compound I	0.134	0.165	5.87	0.446

[0553] Example 15: Tablet Formulations

[0554] The granulation and blending procedure for preparing tablet formulations of crystalline Form A of Compound I is follows:

[0555] Small scale batches (Formulations 1, 2, and 3 in Table 12) are described as follows:

1. Weigh and add the microcrystalline cellulose, lactose, SLS, and Copovidone (where used) into a glass vial. Pre-blend by mixing.
2. Pre-screen the jet milled Compound I through a #40 mesh screen. Weigh and add Compound I to the pre-blend. Blend by mixing.
3. Screen the pre-blend through a #40 mesh screen. Re-blend.
4. Compress the pre-blend powder into slugs on a manual single station press.

Tooling: 0.4724 in. round bi-concave

Compression force: ~2000 psi.

5. Crush the slugs into granules using a mortar and pestle.
6. Screen the granules through a #40 mesh screen. Weigh the intra-granular weight, adjusting the extra-granular amounts based on recovery.
7. Weigh and add the extra-granular microcrystalline cellulose, crospovidone, sodium starch glycolate (where used), silica, and sodium stearyl fumarate to the granules. Blend by mixing.
8. Screen the blend through a #40 mesh screen. Perform final blend.
9. Compress tablets on a manual single station press.

Tooling: 0.3740 in. round bi-concave

[0556] Large Scale process

[0557] Formulation 4 (Table 12) was scaled up to a batch size of 192.0 g following the composition as shown in Table 12. The granulation and blending procedure was substantially the same as the small-scale batches, except that the drug substance was not pre-screened before blending, a rotary press was used for both slugging and final compression, and a Turbula mixer was used for the powder blending steps.

[0558] Example process**[0559]** Procedure:

1. Tare mixing jar. Mixing jar: 32 oz. square plastic screw cap jar.
2. Weigh and add the microcrystalline cellulose, lactose, SLS, and intra-granular crospovidone into the mixing jar. Pre-blend 3 minutes by hand mixing.

3. Weigh and add the drug substance to the pre-blend. Blend by mixing 3 minutes in the Turbula blender.
4. Screen the pre-blend through a #40 mesh screen. Re-blend 10 minutes in the Turbula blender.
5. Compress the intra-granular blend powder into slugs on a 10-station rotary press fitted with a single tool and blanks in the remaining stations.

Tooling	12 mm (0.4724 in.) round bi-concave
Typical slug wt.	610-640 mg
Thickness	0.348-0.368 in.
Hardness	3-5 Kp

6. Crush the slugs into granules by hand using a mortar and pestle.
7. Screen the granules through a #40 mesh screen. Weigh the intra-granular weight, adjusting the extra-granular amounts based on recovery.

Intra-granular recovery: 99.31% of theoretical

8. Adjust the weight of extra-granular excipients based on the recovery of intra-granular phase. Weigh and add the extra-granular MCC, crospovidone, silica, and sodium stearyl fumarate to the granules. Blend by mixing 3 minutes in the Turbula blender.
9. Screen the blend through a #40 mesh screen. Blend by mixing 10 minutes in the Turbula blender.

Final blend yield: 99.2% of theoretical.

[0560] Example tablet formulations are provided in Table 12

[0561] Table 12

Phase	Component	4-2		6		1		2		3		4	
		mg/ tablet	Wt %	mg/ tablet	Wt %	mg/ tablet	Wt %	mg/ tablet	Wt %	mg/ tablet	Wt %	mg/ tablet	Wt %
Intra- granular	Compound I	5.0	6.3%	20.0	5.2%	20.0	6.3%	20.0	6.3%	20.0	6.3%	30.0	6.3%
	Microcrystalline cellulose	17.5	21.9%	65.0	16.9%	65.0	20.3%	65.0	20.3%	70.0	21.9%	105.0	21.9%
	Lactose anhydrous	28.8	35.9%	110.0	28.6%	110.0	34.4%	110.0	34.4%	115.0	35.9%	172.5	35.9%
	SLS	6.3	7.8%	25.0	6.5%	25.0	7.8%	25.0	7.8%	25.0	7.8%	37.5	7.8%
	Copovidone			10.0	2.6%	10.0	3.1%	10.0	3.1%				
	Crospovidone	2.0	2.5%			8.0	2.5%			8.0	2.5%	12.0	2.5%
Extra- granular	Sodium starch glycolate							8.0	2.5%				
	[subtotal]	[59.5]	[74.4%]	[230.0]	[59.7%]	[238.0]	[74.4%]	[238.0]	[74.4%]	[238.0]	[74.4%]	[357.0]	[74.4%]
	Microcrystalline cellulose	17.8	22.2%	131.0	34.0%	70.0	21.9%	70.0	21.9%	70.0	21.9%	106.5	22.2%
	Crospovidone	2.0	2.5%			8.0	2.5%			8.0	2.5%	12.0	2.5%
	Sodium starch glycolate			20.0	5.2%			8.0	2.5%				
	Silica	0.25	0.3%	2.0	0.5%	2.0	0.6%	2.0	0.6%	2.0	0.6%	1.5	0.3%
	Sodium stearyl fumarate	0.5	0.6%	2.0	0.5%	2.0	0.6%	2.0	0.6%	2.0	0.6%	3.0	0.6%
	TOTAL	80.0		385.0		320.0		320.0		320.0		480.0	

[0562] Example 16: Capsule Formulations

[0563] The granulation and blending procedure for preparing capsule formulations of crystalline Form A of Compound I is follows:

1. Weigh and add the microcrystalline cellulose, lactose, SLS, and copovidone into a glass vial. Pre- blend by mixing.
2. Weigh and add Compound I (jet milled) to the pre-blend. Blend by mixing.
3. Screen the pre-blend through a #40 mesh screen. Re-blend.
4. Compress the pre-blend powder into slugs on a single station manual press with a compression force of 2200 psi.
5. Crush the slugs into granules using a mortar and pestle.
6. Screen the granules through a #40 mesh screen. Weigh the intra-granular weight, adjusting the extra-granular amounts based on recovery.
7. Weigh and add the extra-granular microcrystalline cellulose, silica, and sodium stearyl fumarate to the granules. Blend by mixing.
8. Screen the blend through a #40 mesh screen. Perform final blend.
9. Fill the blend into size #0 capsule shells.

[0564] Example capsule formulations are provided in Tables 13 and 14

[0565] Table 13

Phase	Component	1		2		3		4		5	
		mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%
Intra-granular	Compound I	20.0	6.7%	20.0	8.0%	20.0	7.3%	20.0	7.3%	20.0	5.5%
	Microcrystalline cellulose	65.0	21.7%	65.0	26.0%	65.0	23.6%	65.0	23.6%	65.0	17.8%
	Lactose anhydrous	110.0	36.7%	110.0	44.0%	110.0	40.0%			110.0	30.1%
	Mannito 1 100SD							110.0	40.0%		
	SLS	50.0	16.7%			25.0	9.1%	25.0	9.1%	25.0	6.9%
	copovidone	10.0	3.3%	10.0	4.0%	10.0	3.6%	10.0	3.6%	10.0	2.7%
	Sodium starch glycolate										
	Sodium stearyl fumarate										
	Silica										
	[subtotal]	[255.0]	[85.0%]	[205.0]	[82.0%]	[230.0]	[83.6%]	[230.0]	[83.6%]	[230.0]	[63.0%]
	Microcrystalline cellulose	42.5	14.2%	42.5	17.0%	42.5	15.5%	42.5	15.5%	131.0	35.9%
	Lactose anhydrous										

Phase	Component	1		2		3		4		5	
		mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%
Extra-granular	Mannito 1 200SD										
	Silica	1.0	0.5%	1.0	0.4%	1.0	0.5%	1.0	0.5%	2.0	0.6%
	Sodium stearyl fumarate	1.5	0.5%	1.5	0.6%	1.5	0.6%	1.5	0.6%	2.0	0.6%
	Sodium starch glycolate										
	crospovidone										
	TOTAL	300.0		250.0		275.0		275.0		365.0	
Capsule		Size #0, Swedish orange									

[0566] Table 14

Phase	Component	6		7		8		9	
		mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%	mg/cap	Wt%
Intra-granular	Compound I	20.0	5.5%	20.0	5.5%	20.0	5.5%	20.0	5.5%
	Microcrystalline cellulose	65.0	17.8%	65.0	17.8%	65.0	17.8%	65.0	17.8%
	Lactose anhydrous	110.0	30.1%	110.0	30.1%	110.0	30.1%	110.0	30.1%
	Mannitol 100SD								
	SLS	25.0	6.9%	25.0	6.9%	25.0	6.9%	25.0	6.9%
	copovidone	10.0	2.7%	10.0	2.7%	10.0	2.7%	10.0	2.7%
	Sodium starch glycolate	15.0	4.1%						
	Sodium stearyl fumarate	1.0	0.3%						
	Silica	1.0	0.3%						
	[subtotal]	[247.0]	[67.7%]	[230.0]	[63.0%]	[230.0]	[63.0%]	[230.0]	[63.0%]
Extra-granular	Microcrystalline cellulose	116.0	31.8%	116.0	31.8%				
	Lactose anhydrous					116.0	31.8%		
	Mannitol 200SD							116.0	31.8%
	Silica	1.0	0.3%	2.0	0.6%	2.0	0.6%	2.0	0.6%
	Sodium stearyl fumarate	1.0	0.3%	2.0	0.6%	2.0	0.6%	2.0	0.6%
	Sodium starch glycolate								
	crospovidone			15.0	4.1%	15.0	4.1%	15.0	4.1%
	TOTAL	365.0		365.0		365.0		365.0	
Capsule		Size #0, Swedish orange							

[0567] Pharmacokinetic analysis of multiple solid forms of Compound I in mouse

[0568] Crystalline polymorph form A (Solid Form A), pentahydrate crystalline polymorph form B (Solid Form B), and crystalline polymorph form C (Solid Form C) were formulated at 2.5 mg/mL in vehicle solution (0.5% methylcellulose and 0.1% Tween-80 in water) as a uniform suspension. For crystalline polymorph form A and crystalline polymorph form C, formulations were prepared by weighing out the solid form A or C into the vehicle solution followed by sonication and vortexing immediately before dose administration. Formulation of crystalline polymorph form B was prepared by stirring formulation of crystalline polymorph form A for one week before dose administration to solid form A to pentahydrate crystalline solid form B. The PXRD of pentahydrate crystalline solid form B is consistent with the PXRD data described herein and shown in FIG. 2. For each formulation, 10 mL/kg of uniform suspension was administered to each female BALB/c mouse via oral gavage. The resulting dosage was 25 mg/kg for all three formulations. Blood samples were collected into tubes containing K₂-EDTA at predose or at 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours postdose. Plasma samples were prepared by centrifuge blood samples 4 °C for 10 minutes at 5,000 rpm and were stored at -80 °C until bioanalysis by LC/MS/MS.

[0569] The pharmacokinetic profiles of crystalline polymorph form A, pentahydrate crystalline polymorph form B, and crystalline polymorph form C of Compound I at 25 mg/kg in plasma following a single oral dose in mice were obtained as illustrated in FIG. 9. The C_{max} for crystalline polymorph form A, pentahydrate crystalline polymorph form B, and crystalline polymorph form C were 4430, 1240, and 784 ng/mL, respectively (Table 15) and the AUC_{last} for crystalline polymorph form A, pentahydrate crystalline polymorph form B, and crystalline polymorph form C were 10900, 2290, and 3670 ng*h/mL, respectively (Table 15). The results show a statistically significant difference in C_{max} and AUC_{last} between crystalline polymorph form A when compared to each of pentahydrate crystalline polymorph form B and crystalline polymorph form C. Crystalline polymorph form A of Compound I had the highest plasma exposure among the three solid forms tested. And accordingly, crystalline polymorph form A may show a deeper target

inhibition and greater efficacy than pentahydrate crystalline polymorph form B and crystalline polymorph form C.

[0570] Table 15

Formulation	Dose Level (mg/kg)	C _{max} (ng/mL)	AUC _{last} (ng*h/mL)
Solid Form A	25	4430	10900
Solid Form B	25	784	2290
Solid Form C	25	1240	3670

WHAT IS CLAIMED IS:

1. A crystalline polymorph form of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.
2. The crystalline polymorph form of claim 1, wherein the crystalline polymorph form is an anhydrous polymorph form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.
3. The crystalline polymorph form of claim 1, wherein the crystalline polymorph form is a hydrate or solvate polymorph form of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one.
4. The crystalline polymorph form of claim 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1, 14.0 $\pm$ 0.1, 14.2 $\pm$ 0.1, 17.6 $\pm$ 0.1, 18.1 $\pm$ 0.1, 21.1 $\pm$ 0.1, and 25.1 $\pm$ 0.1.
5. The crystalline polymorph form of claim 1, 2, or 4, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2 θ) of 7.1 $\pm$ 0.1.
6. The crystalline polymorph form of claim 1, 2, 4, or 5, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2 θ) of 7.1 $\pm$ 0.1 and 21.1 $\pm$ 0.1.
7. The crystalline polymorph form of any one of claims 1, 2, or 4-6, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-

trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 18.1 ± 0.1 , and 21.1 ± 0.1 .

8. The crystalline polymorph form of any one of claims 1, 2, or 4-7, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

9. The crystalline polymorph form of any one of claims 1, 2, or 4-8, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

10. The crystalline polymorph form of any one of claims 1, 2, or 4-9, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

11. The crystalline polymorph form of any one of claims 1, 2 or 4-10, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 .

12. The crystalline polymorph form of claim 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 1A.

13. The crystalline polymorph form of any one of claims 1, 2 or 4-12, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 0.6% to about 1.4% when heated from about 25° C to about 320° C.

14. The crystalline polymorph form of any one of claims 1, 2 or 4-12, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 5A.

15. The crystalline polymorph form of any one of claims 1, 2 or 4-14, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 290 °C to about 295 °C.

16. The crystalline polymorph form of any one of claims 1, 2 or 4-15, wherein the crystalline polymorph form is a crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 5B.

17. The crystalline polymorph form of claim 1 or 3, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.3±0.1, 7.9±0.1, 13.7±0.1, 15.8±0.1, 17.1±0.1, 23.0±0.1, and 23.8±0.1.

18. The crystalline polymorph form of claim 1, 3 or 17, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 23.8±0.1.

19. The crystalline polymorph form of any one of claims 1, 3, 17, or 18, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8 ± 0.1 and 23.8 ± 0.1 .

20. The crystalline polymorph form of any one of claims 1, 3, or 17-19, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

21. The crystalline polymorph form of any one of claims 1, 3, or 17-20, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

22. The crystalline polymorph form of any one of claims 1, 3 or 17-21, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , and 23.8 ± 0.1 .

23. The crystalline polymorph form of any one of claims 1, 3, or 17-22, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 .

24. The crystalline polymorph form of any one of claims 1, 3, or 17-23, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern

comprising peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 .

25. The crystalline polymorph form of claim 1 or 3, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 2.

26. The crystalline polymorph form of any one of claims 1, 3 or 17-25, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 13% to about 18% when heated from about 25° C to about 320° C.

27. The crystalline polymorph form of any one of claims 1, 2 or 17-26, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 6A.

28. The crystalline polymorph form of any one of claims 1, 2 or 17-27, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 88°C to about 93°C, an exotherm with an onset at about 215 °C to about 220 °C, and an endotherm with an onset at about 293 °C to about 298 °C.

29. The crystalline polymorph form of any one of claims 1, 2 or 17-28, wherein the crystalline polymorph form is a pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 6B.

30. The crystalline polymorph form of claim 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

31. The crystalline polymorph form of claim 1, 2, or 30, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 25.0 ± 0.1 .

32. The crystalline polymorph form of claim 1, 2, 30, or 31, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 18.5 ± 0.1 and 25.0 ± 0.1 .

33. The crystalline polymorph form of any one of claims 1, 2, or 30-32, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

34. The crystalline polymorph form of any one of claims 1, 2, or 30-33, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.9 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

35. The crystalline polymorph form of any one of claims 1, 2, or 30-34, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .

36. The crystalline polymorph form of any one of claims 1, 2, or 30-35, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .
37. The crystalline polymorph form of any one of claims 1, 2, or 30-36, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.5 ± 0.1 , 12.9 ± 0.1 , 13.4 ± 0.1 , 15.8 ± 0.1 , 17.5 ± 0.1 , 18.5 ± 0.1 , and 25.0 ± 0.1 .
38. The crystalline polymorph form of claim 1 or 2, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 3.
39. The crystalline polymorph form of any one of claims 1, 2 or 30-38, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram comprising a weight loss of less than about 1% when heated from about 25° C. to about 320° C.
40. The crystalline polymorph form of any one of claims 1, 2 or 30-39, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 7A.
41. The crystalline polymorph form of any one of claims 1, 2 or 30-40, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC)

curve having an endotherm with an onset at about 240 °C to about 245 °C, an exotherm with an onset at about 248 °C to about 253 °C, and an endotherm with an onset at about 293 °C to about 298 °C.

42. The crystalline polymorph form of any one of claims 1, 2 or 30-41, wherein the crystalline polymorph form is a crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 7B.

43. A crystalline polymorph form A of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:

- (a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.1 ± 0.1 , 14.0 ± 0.1 , 14.2 ± 0.1 , 17.6 ± 0.1 , 18.1 ± 0.1 , 21.1 ± 0.1 , and 25.1 ± 0.1 ;
- (b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 1A;
- (c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 0.6% to about 1.4% when heated from about 25 °C to about 320 °C;
- (d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 5A;
- (e) a differential scanning calorimetry (DSC) curve that comprises an endotherm with an onset at about 290 °C to about 295 °C; and
- (f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 5B.

44. The crystalline polymorph form of claim 43, having at least two of characteristics (a)-(f).

45. The crystalline polymorph form of claim 43, having at least three of characteristics (a)-(f).

46. A pentahydrate crystalline polymorph form B of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:

- (a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 7.3 ± 0.1 , 7.9 ± 0.1 , 13.7 ± 0.1 , 15.8 ± 0.1 , 17.1 ± 0.1 , 23.0 ± 0.1 , and 23.8 ± 0.1 ;
- (b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 2;

(c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 13% to about 18% when heated from about 25 °C to about 320 °C;

(d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 6A;

(e) a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 88°C to about 93°C, an exotherm with an onset at about 215 °C to about 220 °C, and an endotherm with an onset at about 293 °C to about 298 °C; and

(f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 6B.

47. The crystalline polymorph form of claim 46, having at least two of characteristics (a)-(f).

48. The crystalline polymorph form of claim 46, having at least three of characteristics (a)-(f).

49. A crystalline polymorph form C of the free base of (17E)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8H-3,5-ethenotripyrazolo[3,4-f:3',4'-j:4'',3''-n][1,4]oxazacyclopentadecin-13(10H)-one having at least one of the following characteristics:

(a) a powder X-ray diffraction pattern comprising one or more peaks at diffraction angles (2θ) of 9.5 ±0.1, 12.9 ±0.1, 13.4 ±0.1, 15.8 ±0.1, 17.5 ±0.1, 18.5 ±0.1, and 25.0 ±0.1;

(b) a powder X-ray diffraction pattern substantially the same as shown in FIG. 3;

(c) a thermogravimetric analysis (TGA) thermogram comprising a weight loss of less than about 1% when heated from about 25 °C to about 320 °C;

(d) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in Fig. 7A;

(e) a differential scanning calorimetry (DSC) having a differential scanning calorimetry (DSC) curve having an endotherm with an onset at about 240 °C to about 245 °C, an exotherm with an onset at about 248 °C to about 253 °C, and an endotherm with an onset at about 293 °C to about 298 °C; and

(f) a differential scanning calorimetry (DSC) curve substantially the same as shown in Fig. 7B.

50. The crystalline polymorph form of claim 49, having at least two of characteristics (a)-(f).

51. The crystalline polymorph form of claim 49, having at least three of characteristics (a)-(f).
52. A pharmaceutical composition comprising a crystalline polymorph according to any one of claims 1-51 and at least one pharmaceutically acceptable excipient.
53. The pharmaceutical composition of claim 52, comprising at least one of a filler, a disintegrant, a lubricant, and a surfactant.
54. The pharmaceutical composition of claim 52 or 53, wherein the composition is for oral administration.
55. The pharmaceutical composition of any one of claims 52-54, comprising about 1 mg to about 100 mg of the crystalline polymorph.
56. The pharmaceutical composition of any one of claims 52-54, comprising about 1 mg to about 50 mg of the crystalline polymorph.
57. The pharmaceutical composition of any one of claims 52-54, comprising about 5 mg to about 100 mg of the crystalline polymorph.
58. The pharmaceutical composition of any one of claims 52-54, comprising about 5 mg of the crystalline polymorph.
59. The pharmaceutical composition of any one of claims 52-54, comprising about 20 mg of the crystalline polymorph.
60. The pharmaceutical composition of any one of claims 52-54, comprising about 30 mg of the crystalline polymorph.
61. The pharmaceutical composition of any one of claims 52-54, wherein the composition comprises a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
62. The pharmaceutical composition of claim 61, wherein the composition comprises at least two of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.

63. The pharmaceutical composition of claim 61, wherein the composition comprises at least three of a filler, a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
64. The pharmaceutical composition of claim 61, wherein the composition comprises a filler and at least two of a binder, a surfactant, a disintegrant, a wetting agent, a glidant, a lubricant, or a combination thereof.
65. The pharmaceutical composition of claim 61, wherein the filler is present at about 50% to about 90% by weight of the formulation.
66. The pharmaceutical composition of claim 61 or 65, wherein the filler is a mixture of two or more fillers.
67. The pharmaceutical composition of any one of claims 61, 65, or 66, wherein the binder is present at about 1% to about 10% by weight of the formulation.
68. The pharmaceutical composition of any one of claims 61 or 65 to 67, wherein the disintegrant is about 1% to about 10 % by weight of the formulation.
69. The pharmaceutical composition of any one of claims 61 or 65 to 68, wherein the disintegrant is a mixture of two or more disintegrants.
70. The pharmaceutical composition of any one of claims 61 or 65 to 69, wherein the surfactant is about 3% to about 20% by weight of the formulation.
71. The pharmaceutical composition of any one of claims 61 or 65 to 70, wherein the glidant is about 0.1% to about 3% by weight of the formulation.
72. The pharmaceutical composition of any one of claims 61 or 65 to 71, wherein the lubricant is about 0.1% to about 3% by weight of the formulation.
73. The pharmaceutical composition of claim 61, wherein the composition comprises about 3% to about 10% by weight a crystalline polymorph according to any one of claims 1-51;
about 50% to about 90% by weight of a filler or a mixture of fillers;
optionally about 1% to about 10% by weight of a binder;
optionally about 2% to about 10% of a disintegrant or a mixture of disintegrants;
optionally about 3% to about 20% by weight of a surfactant;

about 0.1% to about 3% by weight of a glidant; and
about 0.1% to about 3% by weight of a lubricant.

74. The pharmaceutical formulation of claim 73, wherein the composition is in the form of a tablet.
75. The pharmaceutical composition of claim 74, wherein the composition comprises
about 6% by weight a crystalline polymorph according to any one of claims 1-51;
about 80% by weight of a filler or a mixture of fillers;
about 5% of a disintegrant or a mixture of disintegrants;
about 8% by weight of a surfactant;
about 0.3% by weight of a glidant; and
about 0.6% by weight of a lubricant.
76. The pharmaceutical composition of claim 74, wherein the composition comprises
about 5% by weight a crystalline polymorph according to any one of claims 1-51;
about 80% by weight of a filler or a mixture of fillers;
about 2.5% by weight of a binder;
about 5% of a disintegrant or a mixture of disintegrants;
about 7% by weight of a surfactant;
about 0.5% by weight of a glidant; and
about 0.5% by weight of a lubricant.
77. The pharmaceutical composition of claim 74, wherein the composition comprises
about 6% by weight a crystalline polymorph according to any one of claims 1-51;
about 77% by weight of a filler or a mixture of fillers;
about 3% by weight of a binder;
about 5% of a disintegrant or a mixture of disintegrants;
about 8% by weight of a surfactant;
about 0.6% by weight of a glidant; and
about 0.6% by weight of a lubricant.
78. The pharmaceutical formulation of claim 73, wherein the formulation is in the form of a capsule.
79. The pharmaceutical composition of claim 78, wherein the composition comprises
about 7% by weight a crystalline polymorph according to any one of claims 1-51;

about 73% by weight of a filler or a mixture of fillers;
about 3% by weight of a binder;
about 17% by weight of a surfactant;
about 0.5% by weight of a glidant; and
about 0.5% by weight of a lubricant.

80. The pharmaceutical composition of claim 78, wherein the composition comprises
about 8% by weight a crystalline polymorph according to any one of claims 1-51;
about 87% by weight of a filler or a mixture of fillers;
about 4% by weight of a binder;
about 0.4% by weight of a glidant; and
about 0.6% by weight of a lubricant.
81. The pharmaceutical composition of claim 78, wherein the composition comprises
about 7% by weight a crystalline polymorph according to any one of claims 1-51;
about 80% by weight of a filler or a mixture of fillers;
about 4% by weight of a binder;
about 9% by weight of a surfactant;
about 0.5% by weight of a glidant; and
about 0.6% by weight of a lubricant.
82. The pharmaceutical composition of claim 78, wherein the composition comprises
about 6% by weight a crystalline polymorph according to any one of claims 1-51;
about 84% by weight of a filler or a mixture of fillers;
about 3% by weight of a binder;
about 7% by weight of a surfactant;
about 0.6% by weight of a glidant; and
about 0.6% by weight of a lubricant.
83. The pharmaceutical composition of claim 78, wherein the composition comprises
about 6% by weight a crystalline polymorph according to any one of claims 1-51;
about 80% by weight of a filler or a mixture of fillers;
about 3% by weight of a binder;
about 4% of a disintegrant or a mixture of disintegrants;
about 7% by weight of a surfactant;
about 0.6% by weight of a glidant; and

about 0.6% by weight of a lubricant.

84. The pharmaceutical composition of claim 61, wherein the composition comprises about 3 mg to about 40 mg of a crystalline polymorph according to any one of claims 1-51;
about 50 mg to about 500 mg of a filler or a mixture of fillers;
optionally about 5 mg to about 20 mg of a binder;
optionally about 1 mg to about 50 mg of a disintegrant or a mixture of disintegrants;
optionally about 5 mg to about 75 mg by weight of a surfactant;
about 0.1 mg to about 5 mg of a glidant; and
about 0.1 mg to about 5 mg by weight of a lubricant.
85. The pharmaceutical composition of claim 61, wherein the composition comprises about 5% to about 10% by weight of the crystalline polymorph.
86. The pharmaceutical composition of claim 61, wherein the composition comprises about 6% by weight of the crystalline polymorph.
87. The pharmaceutical composition of claim 61, wherein the composition comprises about 8% by weight of the crystalline polymorph.
88. The pharmaceutical composition of claim 84, wherein the composition comprises about 5 mg of the crystalline polymorph.
89. The pharmaceutical composition of claim 84, wherein the composition comprises about 20 mg of the crystalline polymorph.
90. The pharmaceutical composition of claim 84, wherein the composition comprises about 30 mg of the crystalline polymorph.
91. The pharmaceutical composition of any one of claims 61 to 90, wherein the filler or mixture of fillers is selected from microcrystalline cellulose, anhydrous lactose, mannitol, or a combination thereof.
92. The pharmaceutical composition of any one of claims 61 to 91, wherein the binder is copovidone.

93. The pharmaceutical composition of any one of claims 61 to 92, wherein the disintegrant or mixture of disintegrants is selected from crospovidone, sodium starch glycolate, or a combination thereof.

94. The pharmaceutical composition of any one of claims 61 to 93, wherein the surfactant is sodium lauryl sulfate.

95. The pharmaceutical composition of any one of claims 61 to 94, wherein the glidant is silica.

96. The pharmaceutical composition of any one of claims 61 to 95, wherein the lubricant is sodium stearyl fumarate.

97. A method of treating abnormal cell growth in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a crystalline polymorph according to any one of claims 1-51 or a pharmaceutical composition according to any one of claims 52-96.

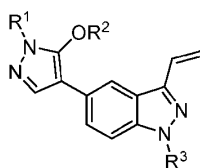
98. A method of treating cancer in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a crystalline polymorph according to any one of claims 1-51 or a pharmaceutical composition according to any one of claims 52-96.

99. The method of claim 98, 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.

100. The method of claim 98, wherein the cancer is acute myeloid leukemia (AML).

101. A compound of the formula II



II

wherein R¹ is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and each of R² and R³ is independently H or PG.

102. The compound of claim 101, wherein R¹ is C₁-C₆ alkyl.

103. The compound of claim 101 or 102, wherein R¹ is methyl.

104. The compound of any one of claims 101 to 103, wherein R² is H.

105. The compound of any one of claims 101 to 103, wherein R² is PG.

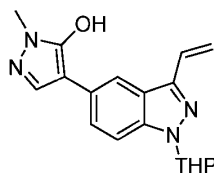
106. The compound of any one of claims 101 to 105, wherein R³ is H.

107. The compound of any one of claims 101 to 105, wherein R³ is PG.

108. The compound of any one of claims 101 to 107, wherein each PG, when present, is independently selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzyldiene, and Ts.

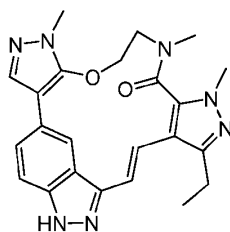
109. The compound of any one of claims 101 to 108, wherein each PG is THP.

110. A compound of the formula I-2-3



I-2-3.

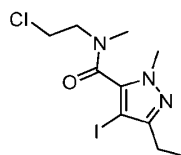
111. A process for preparing a compound of the formula I



I

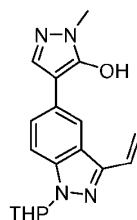
comprising

a. contacting a compound of the formula I-2-7



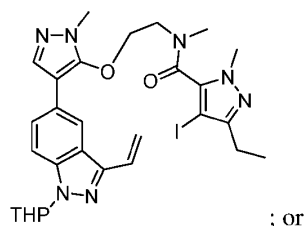
I-2-7

with a compound of the formula I-2-3



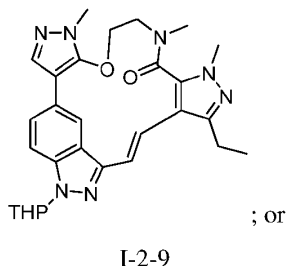
I-2-3

in the presence of a base to provide a compound of the formula I-2-8



I-2-8

b. contacting a compound of the formula I-2-8 in the presence of a catalyst to provide a compound of the formula I-2-9



c. contacting a compound of the formula I-2-9 with an acid to provide the compound of the formula I.

112. The process of claim 111, wherein the base of step (a) is selected from the group consisting of Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , MgCO_3 , and CaCO_3 .

113. The process of claim 111 or 112, wherein the base of step (a) is K_2CO_3 .

114. The process of any one of claims 111 to 113, wherein step (a) is carried out in the presence of an inorganic salt selected from the group consisting of NaCl , KCl , CsCl , MgCl_2 , CaCl_2 , NaBr , KBr , CsBr , MgBr_2 , CaBr_2 , NaI , KI , CsI , MgI_2 , and CaI_2 .

115. The process of claim 114, wherein the inorganic salt is KI .

116. The process of any one of claims 111 to 115, wherein the catalyst of step (b) is a palladium catalyst.

117. The process of any one of claims 111 to 116, wherein the catalyst of step (b) is selected from the group consisting of $\text{Pd}(\text{OAc})_2$, PdCl_2 , and $\text{Pd}(\text{PPh}_3)_4$.

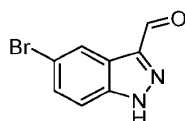
118. The process of any one of claims 111 to 117, wherein the catalyst of step (b) is $\text{Pd}(\text{OAc})_2$.

119. The process of any one of claims 111 to 118, wherein step (b) is carried out in the presence of a base selected from the group consisting of triethylamine, diisopropylamine, K_2CO_3 , Na_2CO_3 , KHCO_3 , NaHCO_3 , NaOAc , and KOAc .

120. The process of claim 119, wherein the base is NaHCO_3 .

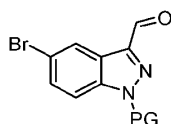
121. The process of any one of claims 111 to 120, wherein step (b) is carried out in the presence of a phase transfer catalyst selected from tetrabutylammonium chloride (TBAC) and tetrabutylammonium bromide (TBAB).

122. The process of claim 121, wherein the phase transfer catalyst is tetrabutylammonium chloride (TBAC).
123. The process of any one of claims 111 to 122, wherein the acid of step (c) is a strong inorganic acid.
124. The process of any one of claims 111 to 123, wherein the acid of step (c) is HCl.
125. The process of any one of claims 111 to 124, comprising steps (a) and (b).
126. The process of any one of claims 111 to 125, comprising steps (b) and (c).
127. The process of any one of claims 111 to 126, comprising steps (a), (b), and (c).
128. A process for preparing a compound according to any one of claims 101 to 109, the process comprising
- a. contacting a compound of the formula II-1



II-1

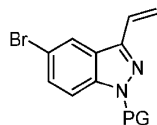
with a protecting group precursor to provide a compound of the formula II-2



II-2

wherein PG is selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzyldiene, and Ts; or

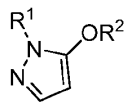
b. contacting a compound of the formula II-2 with methyltriphenylphosphonium bromide (MePPh₃Br) to provide a compound of the formula II-3



II-3

wherein PG is selected from the group consisting of Fmoc, PMB, THP, Boc, Cbz, Ac, trifluoroacetyl, phthalimide, Bn, trityl, benzyldiene, and Ts; or

c. contacting a compound of the formula II-3 with a pyrazole of the formula II-4



II-4

in the presence of a catalyst, wherein R¹ is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, and R² is H or PG, to provide the compound of the formula II.

129. The process of claim 128, wherein the protecting group precursor of step (a) is selected from the group consisting of FMOC-Cl, PMB-Cl, DHP, Boc₂O, Cbz-Cl, AcCl, BnBr, trityl-Cl, and TsCl.

130. The process of claim 128 or 129, wherein the protecting group precursor of step (a) is DHP.

131. The process of any one of claims 128 to 130, wherein step (a) is carried out in the presence of a Lewis acid and/or a water scavenger selected from the group consisting of copper (II) sulfate, magnesium sulfate, tetraethoxytitanium, tetraisopropoxytitanium, boron trifluoride etherate, pyridinium p-toluenesulfonate (PPTS), TsOH, magnesium sulfate, sodium sulfate, tetraethoxytitanium, and tetraisopropoxytitanium.

132. The process of claim 131, wherein the Lewis acid and/or a water scavenger is PPTS.

133. The process of any one of claims 128 to 132, wherein step (b) is carried out in the presence of a base selected from the group consisting of Na₂CO₃, K₂CO₃, Cs₂CO₃, MgCO₃, and CaCO₃.

134. The process of claim 133, wherein the base is K₂CO₃.

135. The process of any one of claims 128 to 134, wherein the catalyst of step (c) is a palladium catalyst.

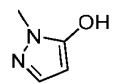
136. The process of any one of claims 128 to 135, wherein the catalyst of step (c) is selected from the group consisting of Pd(OAc)₂, PdCl₂, Pd(PPh₃)₄, and tBuBrettPhos Pd G3.

137. The process of any one of claims 128 to 136, wherein the catalyst of step (c) is tBuBrettPhos Pd G3.

138. The process of any one of claims 128 to 137, wherein step (c) is carried out in the presence of a base selected from the group consisting of Na₂CO₃, K₂CO₃, Cs₂CO₃, MgCO₃, and CaCO₃.

139. The process of claim 138, wherein the base is K_2CO_3 .

140. The process of any one of claims 128 to 139, wherein the pyrazole is of the formula



, or a salt thereof.

141. The process of any one of claims 128 to 140, comprising steps (a) and (b).

142. The process of any one of claims 128 to 141, comprising steps (b) and (c).

143. The process of any one of claims 128 to 142, comprising steps (a), (b), and (c).