7-AZAINDAZOLE MACROCYCLES AND THEIR USE

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 63/766,726, filed March 4, 2025, 63/685,900, filed August 22, 2024, and 63/568,828, filed March 22, 2024, the entire disclosure of each of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] The present disclosure relates to ether linked macrocyclic compounds, pharmaceutical compositions containing macrocyclic compounds, and methods of using macrocyclic compounds to treat disease, such as cancer.

BACKGROUND

[0003] 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). Therefore, it is desirable 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.

[0004] The anaplastic lymphoma kinase (ALK) is a member of the family of insulin-like tyrosine kinase receptors involved in the oncogenesis of several tumor types. Approximately 5% of patients with non-small cell lung cancer (NSCLC) harbor rearrangement in the anaplastic lymphoma kinase *(ALK)* gene (Soda, M. et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007, 448, 561–566). ALK inhibitors have been approved by FDA as the standard of care in the first- and second-line treatment of ALK-rearranged NSCLC patients. However, as complete response to ALK inhibitors is rare, almost all patients with *ALK*-rearranged NSCLC inevitably acquire resistance to ALK inhibitors, resulting in tumor recurrence. Drug resistance mechanisms include ALK-independent and ALK-dependent processes. ALK-independent resistance mechanisms involve the activation of bypass pathways, such as EGFR, c-MET, KRAS, and AXL or transformation into small cell lung cancer (Gainor, J. F. et al. Molecular mechanisms of resistance to first- and second generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov.* 2016, 6, 1118–1133). Although five ALK inhibitors have been approved, they have a limited clinical ability to overcome ALK-independent resistance mechanisms. Therefore, it is necessary to develop next generation multitargeted ALK inhibitors with ability targeting not only primary ALK fusions and ALK secondary resistance mutations, but also targeting mechanisms associated with tolerant persister cancer cells for better efficacy and longer duration of response.

[0005] The proviral integration for the Moloney murine leukemia virus (PIM) kinases are oncogenic serine/threonine kinases that phosphorylate a wide range of substrates that regulate several of the hallmarks of cancer including tumor metabolism, survival, metastasis, immune evasion and inflammation (Toth RK, Warfel NA. Targeting PIM Kinases to Overcome Therapeutic Resistance in Cancer. *Mol Cancer Ther.* 2021, 20(1):3-10). PIM kinases interact with numerous major oncogenic players, including stabilization of p53, synergism with c-Myc, and notable parallel signaling with PI3K/Akt. The aberrant PIM kinase activity plays an

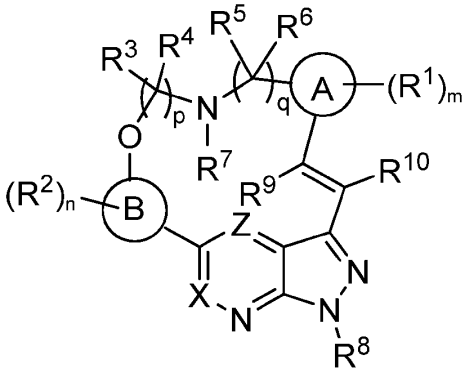
important role in resistance mechanisms of chemotherapy, radiotherapy, anti-angiogenic therapies and targeted therapies, providing a rationale for co-targeting treatment strategies for a more durable patient response (Malone T, et al. Current perspectives on targeting PIM kinases to overcome mechanisms of drug resistance and immune evasion in cancer. Pharmacol Ther 2020 Mar; 207).

[0006] 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. 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). 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). 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.

[0007] Therefore, it is desirable to develop a new generation multitargeted ALK inhibitors that are potent against oncogenic driver ALK fusions and point mutations, other emerging and established ALK resistance mutations, as well as emerging resistance targets for tolerant/persistent cancer cells, e.g., PIM kinases and CLK kinases.

SUMMARY

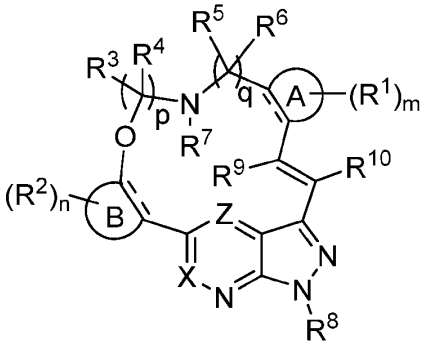
[0008] In one aspect, the disclosure provides a compound of the formula I, or a pharmaceutically acceptable salt thereof,



I

[0009] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, A, B, X, Z, m, n, p, and q are as described herein.

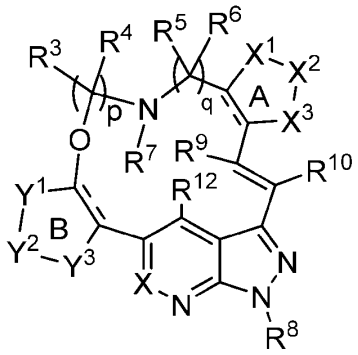
[0010] In some embodiments, the disclosure provides a compound of the formula II, or a pharmaceutically acceptable salt thereof,



II

[0011] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, A, B, X, Z, m, n, p, q, and "------" are as described herein.

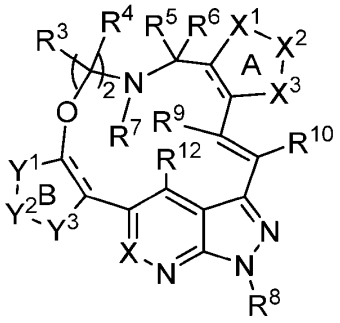
[0012] In some embodiments, the disclosure provides a compound of the formula III, or a pharmaceutically acceptable salt thereof,



III

[0013] wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, A, B, X, X^1, X^2, X^3, Y^1, Y^2, Y^3, p, q, and "======" are as described herein.

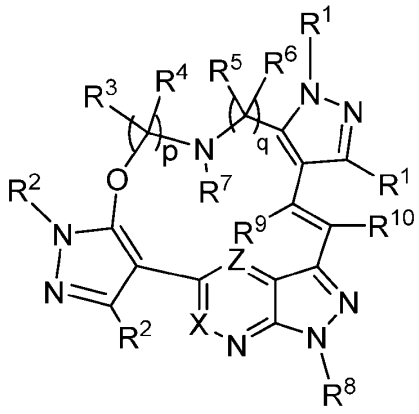
[0014] In some embodiments, the disclosure provides a compound of the formula IV, or a pharmaceutically acceptable salt thereof,



IV

[0015] wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, A, B, X, X^1, X^2, X^3, Y^1, Y^2, Y^3, and "======" are as described herein.

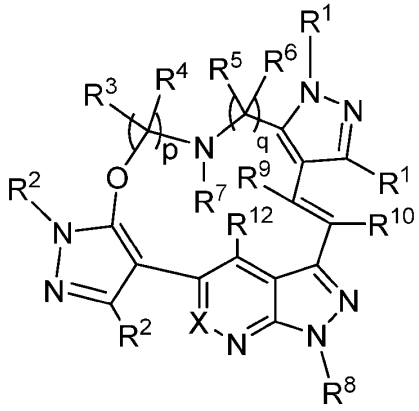
[0016] In some embodiments, the disclosure provides a compound of the formula V, or a pharmaceutically acceptable salt thereof,



V

[0017] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, p, and q are as described herein.

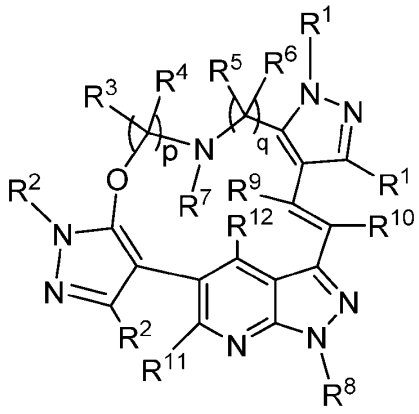
[0018] In some embodiments, the disclosure provides a compound of the formula VI, or a pharmaceutically acceptable salt thereof,



VI

[0019] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, X, p, and q are as described herein.

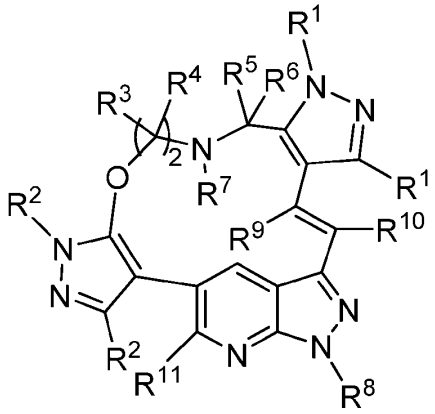
[0020] In some embodiments, the disclosure provides a compound of the formula VII, or a pharmaceutically acceptable salt thereof,



VII

[0021] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, p, and q are as described herein.

[0022] In some embodiments, the disclosure provides a compound of the formula VIII, or a pharmaceutically acceptable salt thereof,



VIII

[0023] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, are as described herein.

[0024] In further aspects, the disclosure relates to a pharmaceutical composition comprising at least one compound of Formula (I)-(VIII) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the disclosure may further comprise a pharmaceutically acceptable excipient.

[0025] In further aspects, the disclosure relates to a compound of Formula (I)-(VIII), or a pharmaceutically acceptable salt thereof, for use as a medicament.

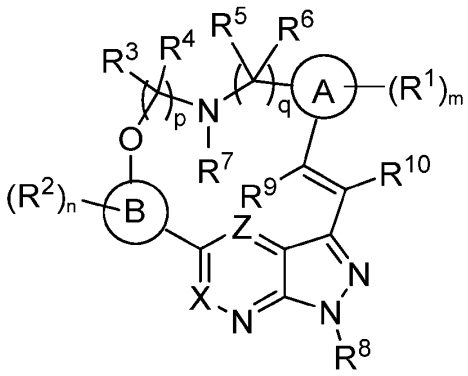
[0026] In further aspects, the disclosure relates to a method of treating disease, such as cancer comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (I)-(VIII), or a pharmaceutically acceptable salt thereof.

[0027] In further aspects, the disclosure relates to use of a compound of Formula (I)-(VIII), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of disease, such as cancer, and the use of such compounds and salts for treatment of such diseases.

[0028] In further aspects, the disclosure relates to a method of inhibiting a ALK, comprising contacting a cell comprising one or more of ALK with an effective amount of at least one compound of Formula (I)-(VIII), or a pharmaceutically acceptable salt thereof, and/or with at least one pharmaceutical composition of the disclosure, wherein the contacting is *in vitro, ex vivo,* or *in vivo.*

[0029] 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.

[0030] 1. A compound of the formula I



I

[0031] wherein

[0032] ring A and ring B are each independently a 5- or 6-membered heteroarylene;

[0033] X is N or C(R^{11});

[0034] Z is N or C(R^{12});

[0035] each R^1 and R^2, when present and bonded to a carbon atom, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$,

$-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or each R^1 and R^2, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

[0036] each R^3, R^4, R^5, and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or two of R^3, R^4, R^5, and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$;

[0037] R^7 is H, deuterium, $-C(O)R^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, or R^7 and one of R^3, R^4, R^5, or R^6, taken together with the atoms to which each is attached, combine to form a 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6

alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$,$-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, $-CN$, or $-NO_2$;

[0038] R^8 is H, $-S(O)_2R^c$, $-S(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-P(O)_2R^cR^d$, $-P(O)_2NR^cR^d$, or $-P(O)_2OR^c$;

[0039] each of R^9 and R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, $-CN$, or $-NO_2$;

[0040] R^{11}, when present, is H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, $-CN$, or $-NO_2$, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$,

-$P(O)NR^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)OR^c$, -$P(O)_2OR^c$, -CN, or -NO_2;

[0041] R^{12}, when present, is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -$C(=NR^b)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=NR^d)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=NR^d)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=NR^d)NR^cR^d$, -PR^cR^d, -$P(O)R^cR^d$, -$P(O)_2R^cR^d$, -$P(O)NR^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)OR^c$, -$P(O)_2OR^c$, -CN, or -NO_2;

[0042] each R^a, R^b, R^c, R^d, R^e, and R^f is independently selected from the group consisting of H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and C_1-C_6 alkylene-5- to 10-membered heteroaryl; or R^a and R^b or R^c and R^d or R^e and R^f, taken together with the atom to which they are attached, form a 3- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and C_1-C_6 alkylene-5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -OC_1-C_6 alkyl, -OC(O)-(H or C_1-C_6 alkyl), -OC(O)N(H or C_1-C_6 alkyl)$_2$, -OC(O)N(C_2-C_6 alkylene), -OS(O)-(H or C_1-C_6 alkyl), -$OS(O)_2$-(H or C_1-C_6 alkyl), -OS(O)N(H or C_1-C_6 alkyl)$_2$, -OS(O)N(C_2-C_6 alkylene), -$OS(O)_2$N(H or C_1-C_6 alkyl)$_2$, -$OS(O)_2$N(C_2-C_6 alkylene), -S(H or C_1-C_6 alkyl), -S(O)(H or C_1-C_6 alkyl), -$S(O)_2$(H or C_1-C_6 alkyl), -S(O)N(H or C_1-C_6 alkyl)$_2$, -S(O)N(C_2-C_6 alkylene), -$S(O)_2$N(H or C_1-C_6 alkyl)$_2$, -$S(O)_2$N(C_2-C_6 alkylene), -N(H or C_1-C_6 alkyl)$_2$, -N(C_2-C_6 alkylene), -N(H or C_1-C_6 alkyl)C(O)-(H or C_1-C_6 alkyl), -N(H or C_1-C_6 alkyl)C(O)O(H or C_1-C_6 alkyl), -N(H or C_1-C_6 alkyl)C(O)N(H or C_1-C_6 alkyl)$_2$, -N(H or C_1-C_6 alkyl)C(O)N(C_2-C_6 alkylene), -N(H or C_1-C_6 alkyl)S(O)-(H or C_1-C_6 alkyl), -N(H or C_1-C_6 alkyl)$S(O)_2$(H or C_1-C_6 alkyl), -N(H or C_1-C_6 alkyl)S(O)N(H or C_1-C_6 alkyl)$_2$, -N(H or C_1-C_6

alkyl)S(O)N(C_2-C_6 alkylene), -N(H or C_1-C_6 alkyl)S(O)$_2$N(H or C_1-C_6 alkyl)$_2$, -N(H or C_1-C_6 alkyl)S(O)$_2$N(C_2-C_6 alkylene), -C(O)-(H or C_1-C_6 alkyl), -C(O)O(H or C_1-C_6 alkyl), -C(O)N(C_2-C_6 alkylene), -P(H or C_1-C_6 alkyl)$_2$, -P(C_2-C_6 alkylene), -P(O)(H or C_1-C_6 alkyl)$_2$, -P(O)(C_2-C_6 alkylene), -P(O)$_2$(H or C_1-C_6 alkyl)$_2$, -P(O)$_2$(C_2-C_6 alkylene), -P(O)N(H or C_1-C_6 alkyl)$_2$, -P(O)N(C_2-C_6 alkylene), -P(O)$_2$N(H or C_1-C_6 alkyl)$_2$, -P(O)$_2$N(C_2-C_6 alkylene), -P(O)O(H or C_1-C_6 alkyl), -P(O)$_2$O(H or C_1-C_6 alkyl), -CN, or -NO_2;

[0043] m is 0, 1, 2, or 3;

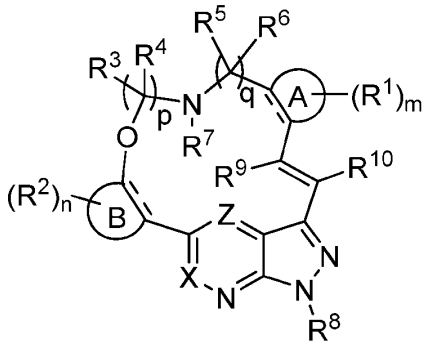
[0044] n is 0, 1, 2, or 3;

[0045] p is 1, 2, 3, or 4; and

[0046] q is 1, 2, or 3;

[0047] or a pharmaceutically acceptable salt thereof.

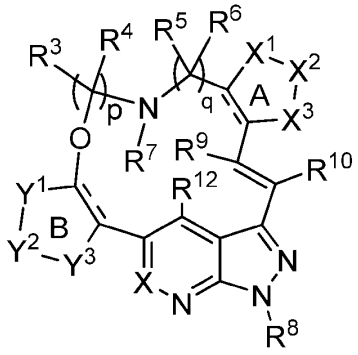
[0048] 2. The compound of clause 1, or a pharmaceutically acceptable salt thereof, having the formula II



II

[0049] wherein each "======" is independently a carbon-carbon single bond or a carbon-carbon double bond.

[0050] 3. The compound of clause 1 or 2, or a pharmaceutically acceptable salt thereof, having the formula III



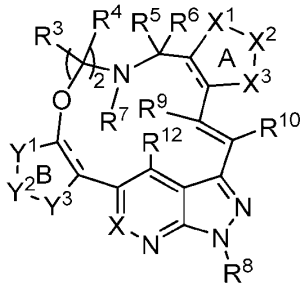
III

[0051] wherein each "======" is independently a carbon-carbon single bond or a carbon-carbon double bond;

[0052] X^1, X^2, and X^3 are each independently -O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N- and ring A is a 5-membered heteroarylene, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-; and

[0053] Y^1, Y^2, and Y^3 are each independently -O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, -N(R^2)- or =N- and ring B is a 5-membered heteroarylene, provided that at least one of Y^1, Y^2, and Y^3 is not =C(H)-, or =C(R^2)-.

[0054] 4. The compound of clause 3, having the formula IV



IV

[0055] or a pharmaceutically acceptable salt thereof.

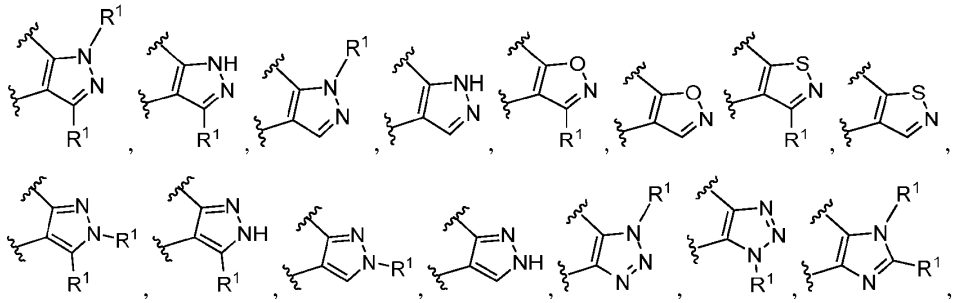
[0056] 5. The compound of clause 3 or 4, wherein

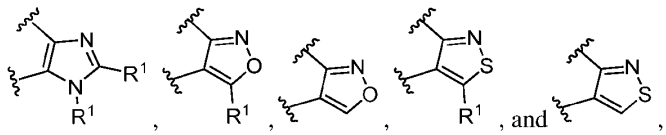
[0057] X^2 is =N- or -N(R^1)-, X^1 and X^3 are each independently -O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, or -N(R^1)-, and ring A is a 5-membered heteroarylene; or

[0058] Y^2 is =N-, Y^1 and Y^3 are each independently -O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, or -N(R^2)-, and ring B is a 5-membered heteroarylene.

[0059] 6. The compound of any one of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein:

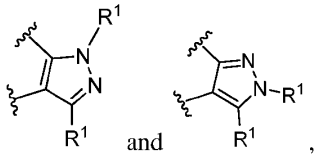
[0060] ring A is selected from the group consisting of





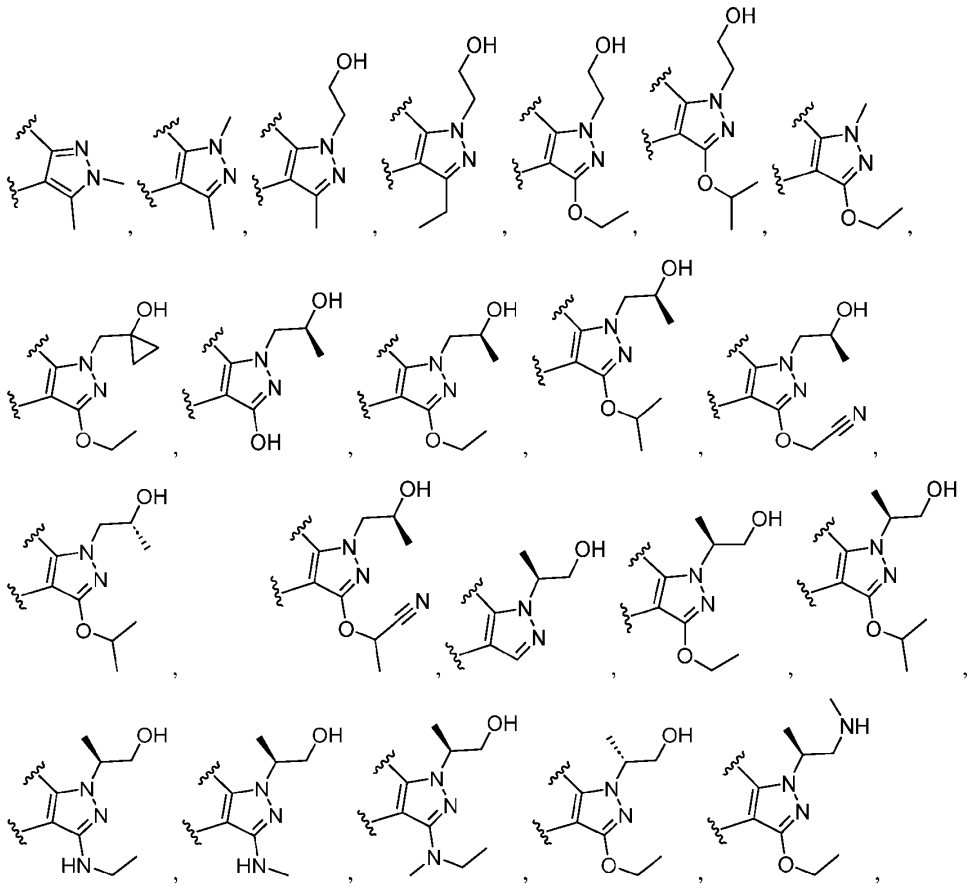
[0061] wherein each "〰" represents a point of covalent attachment.

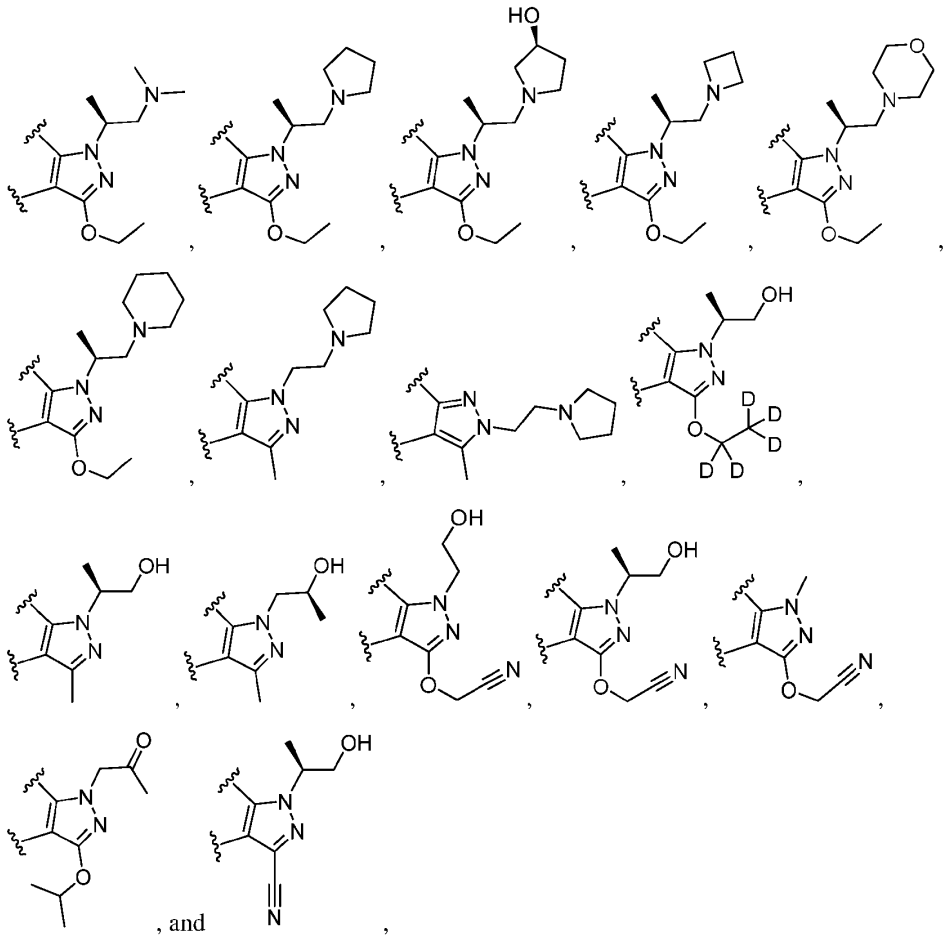
[0062] 7. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of



[0063] wherein each "〰" represents a point of covalent attachment.

[0064] 8. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of

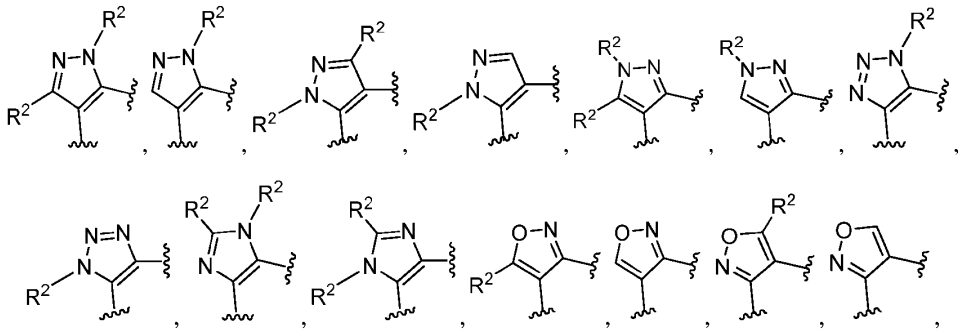


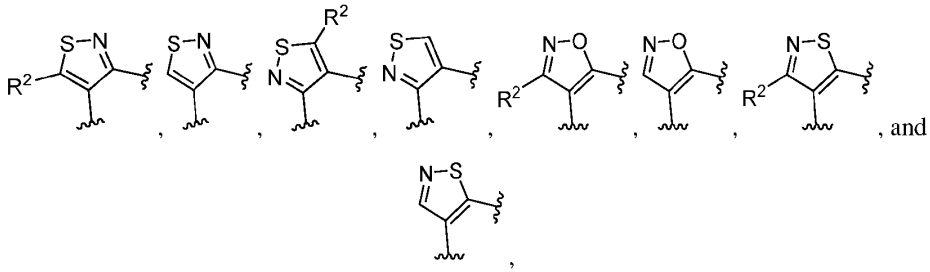


, and

[0065] wherein each "〰" represents a point of covalent attachment.

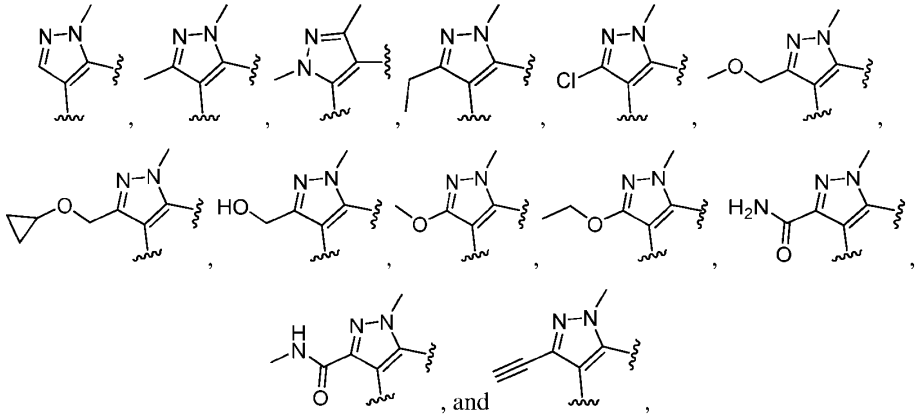
[0066] 9. The compound of any one of clauses 1 to 4 or 6, or a pharmaceutically acceptable salt thereof, wherein ring B is selected from the group consisting of





[0067] wherein each "〰" represents a point of covalent attachment.

[0068] 10. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring B is selected from the group consisting of



[0069] wherein each "〰" represents a point of covalent attachment.

[0070] 11. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein X is N.

[0071] 12. The compound of any one of clauses 1 to 10, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^{11})$.

[0072] 13. The compound of any one of the preceding clauses, wherein an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^e$, $-OS(O)NR^cR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, $-CN$, or $-NO_2$.

[0073] 14. The compound of any one of the preceding clauses, wherein R^7 and an R^3 or an R^4

, taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom in 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

[0074] 15. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein one or two of R^3 are each independently a C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

[0075] 16. The compound of any one of clauses 13 to 15, wherein any remaining R^3 and R^4 are H or deuterium.

[0076] 17. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein one or two of R^3 are each independently a C_1-C_6 alkyl; and any remaining R^3 and R^4 are H or deuterium.

[0077] 18. The compound of any one of the clauses 1 to 13, or a pharmaceutically acceptable salt thereof, wherein each R^3 and R^4 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$. , wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$,

$-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

[0078] 19. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each R^3 is methyl, and any remaining R^3 and R^4 are H or deuterium.

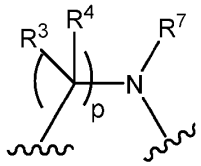
[0079] 20. The compound of any one of clauses 1 to 16, or a pharmaceutically acceptable salt thereof, wherein an R^3 is C_1-C_6 alkyl; and R^7 and an R^4, taken together with the atoms to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium.

[0080] 21. The compound of any one of clauses 1 to 16, or a pharmaceutically acceptable salt thereof, wherein an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium.

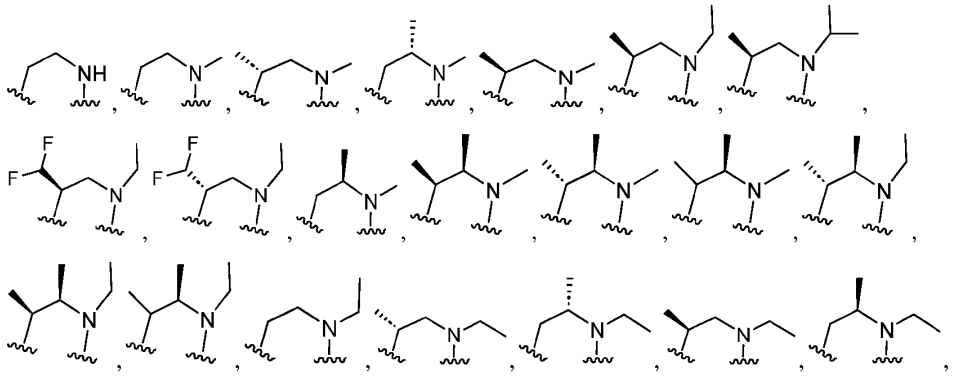
[0081] 22. The compound of any one of clause 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^7 is H, $-C(O)R^a$, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; or R^7 and one instance of R^3 or R^4, taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl.

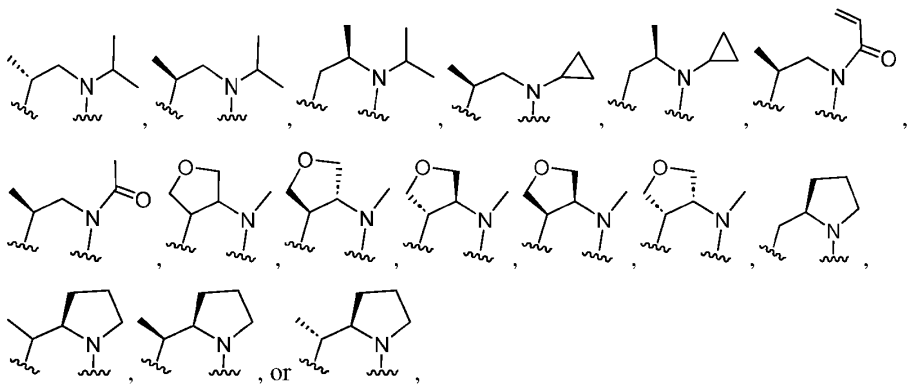
[0082] 23. The compound of any one of the preceding clauses, wherein p is 2 or 3.

[0083] 24. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein the portion



[0084] is of the formula

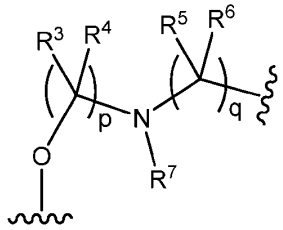




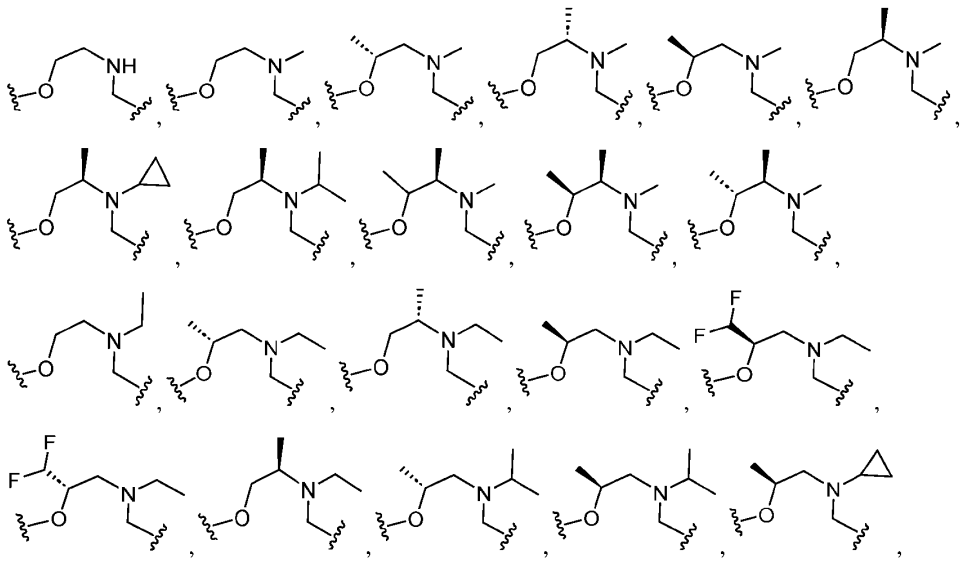
[0085] wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

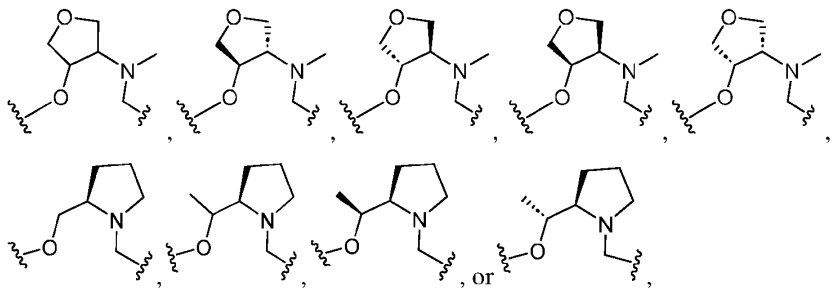
[0086] 25. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each H.

[0087] 26. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein the portion



[0088] is of the formula





[0089] wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

[0090] 27. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^8 is H or C_1-C_6 alkyl.

[0091] 28. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each of R^9 and R^{10} is independently H or deuterium.

[0092] 29. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each of R^9 and R^{10} is H.

[0093] 30. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^{11} is H, deuterium, halogen, -OH, $-OCH_3$, $-CH_3$, or $-CD_3$.

[0094] 31. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein Z is $C(R^{12})$.

[0095] 32. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^{12}, when present is H or deuterium.

[0096] 33. The compound of any one of clauses 1 to 30, or a pharmaceutically acceptable salt thereof, wherein Z is N.

[0097] 34. The compound of clause 1, selected from the group consisting of

[0098] (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0099] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0100] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0101] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0102] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0103] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0104] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0105] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0106] 2-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0107] 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0108] 2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0109] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0110] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0111] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0112] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10,19-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0113] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0114] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0115] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0116] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0117] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0118] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0119] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0120] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0121] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0122] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0123] {[(10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0124] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0125] (2*S*)-2-[(4a*R*,7a*S*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-

17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0126] (2*S*)-2-[(13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0127] (2*S*)-2-[(4a*S*,7a*R*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0128] (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0129] {[(10*S*,17*E*)-6,8,10,12,14-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0130] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0131] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0132] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0133] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol;

[0134] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0135] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0136] 2-{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0137] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0138] (2*S*)-1-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0139] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0140] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0141] {[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0142] {[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0143] (2*S*)-1-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0144] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0145] (2*S*)-1-[(11*R*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0146] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0147] (2*S*)-1-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0148] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,11,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0149] (2*S*)-2-[(11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0150] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0151] (2*R*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0152] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0153] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0154] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0155] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0156] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0157] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0158] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0159] (2*S*)-1-[(10*R*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0160] (2*S*)-1-[(10*S*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-

yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0161] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol; and

[0162] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0163] or a pharmaceutically acceptable salt thereof.

[0164] 35. A pharmaceutical composition comprising a compound of any one of the preceding clauses, and optionally one or more excipients.

[0165] 36. A method of treating disease in a subject comprising, administering a therapeutically effective amount of a compound of any one of clauses 1 to 34, or a pharmaceutical composition of clause 35.

[0166] 37. A compound according to any one of clauses 1 to 34, for use in a method of treating disease in a subject.

[0167] 38. Use of a compound according to any one of clauses 1 to 34, in the manufacture of a medicament for the treatment of disease in a subject.

DETAILED DESCRIPTION

[0168] 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.

[0169] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference. 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.

[0170] 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.

[0171] As used herein, the terms "including," "containing," and "comprising" are used in their open, non-limiting sense.

[0172] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about." It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

[0173] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0174] Except as otherwise noted, the methods and techniques of the present embodiments are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Loudon, Organic Chemistry, Fourth Edition, New York: Oxford University Press, 2002, pp. 360-361, 1084-1085; Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001.

[0175] Chemical nomenclature for compounds described herein has generally been derived using the commercially-available ACD/Labs 2022.2.3 (Advanced Chemistry Development, Inc.) or ChemDraw Professional 22.2.0.3300 (PerkinElmer Informatics, Inc.).

[0176] As used herein and in connection with chemical structures depicting the various embodiments described herein, "*", "**", and "", each represent a point of covalent attachment of the chemical group or chemical structure in which the identifier is shown to an

adjacent chemical group or chemical structure. For example, in a hypothetical chemical structure A-B, where A and B are joined by a covalent bond, in some embodiments, the portion of A-B defined by the group or chemical structure A can be represented by "A−*", "A−**", or "A—≋", where each of "-*", "-**", and "—≋" represents a bond to A and the point of covalent bond attachment to B. Alternatively, in some embodiments, the portion of A-B defined by the group or chemical structure B can be represented by "*—B", "**—B", or "≋B", where each of "-*", "-**", and "—≋" represents a bond to B and the point of covalent bond attachment to A.

[0177] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterized, and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

CHEMICAL DEFINITIONS

[0178] As described herein, a "macrocycle" is a compound comprising a continuous chain of at least 12 atoms connected to form a ring, in which the continuous chain of atoms includes but is not limited to C, N, O, and S. The continuous chain of at least 12 atoms that forms a macrocycle, as described herein, can be counted along the shortest path in the chain of atoms within the ring. For example, in compounds of the Formula I, as described herein, the continuous chain of at least 12 atoms in the macrocycle ring can be counted starting from the oxygen atom covalently attached to ring B, where the atoms counted in the macrocycle includes the shortest path through ring B, followed by the shortest path of atoms through the bicycloheteroarylene portion, followed by the atoms in the ethenylene portion, followed by the

shortest path of atoms through ring A, and finally the shortest path of atoms through the linker portion and terminating at the atom along the shortest chain that is attached to the oxygen that served as the starting point.

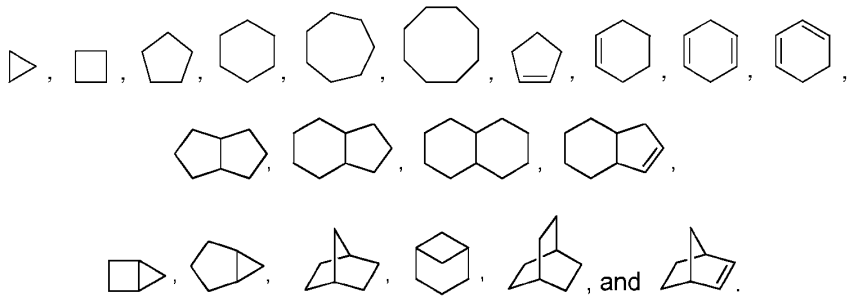
[0179] The term "alkyl" refers to a straight- or branched-chain monovalent hydrocarbon group. The term "alkylene" refers to a straight- or branched-chain divalent hydrocarbon group. In some embodiments, it can be advantageous to limit the number of atoms in an "alkyl" or "alkylene" to a specific range of atoms, such as C_1-C_{20} alkyl or C_1-C_{20} alkylene, C_1-C_{12} alkyl or C_1-C_{12} alkylene, or C_1-C_6 alkyl or C_1-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 (-CH_2-), ethylene ((-CH_2-)$_2$), n-propylene ((-CH_2-)$_3$), iso-propylene ((-C(H)(CH_3)CH_2-)), n-butylene ((-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.

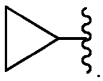
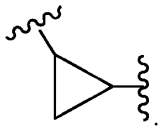
[0180] The term "alkenyl" refers to a straight- or branched-chain mono-valent hydrocarbon group having one or more double bonds. The term "alkenylene" refers to a straight- or branched-chain di-valent hydrocarbon group having one or more double bonds. In some embodiments, it can be advantageous to limit the number of atoms in an "alkenyl" or "alkenylene" to a specific range of atoms, such as C_2-C_{20} alkenyl or C_2-C_{20} alkenylene, C_2-C_{12} alkenyl or C_2-C_{12} alkenylene, or C_2-C_6 alkenyl or C_2-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) (-CH=CH-), n-propenylene (-CH=CHCH_2-), iso-propenylene (-CH=CH(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.

[0181] 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 C_2-C_{20} alkynyl or C_2-C_{20} alkynylene, C_2-C_{12} alkynyl or C_2-C_{12} alkynylene, or C_2-C_6 alkynyl or C_2-C_6 alkynylene. Examples of alkynyl groups include

acetylenyl (-C≡CH) and propargyl (-CH_2C≡CH), but-3-yn-1,4-diyl (-C≡C-CH_2CH_2-), 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.

[0182] 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.

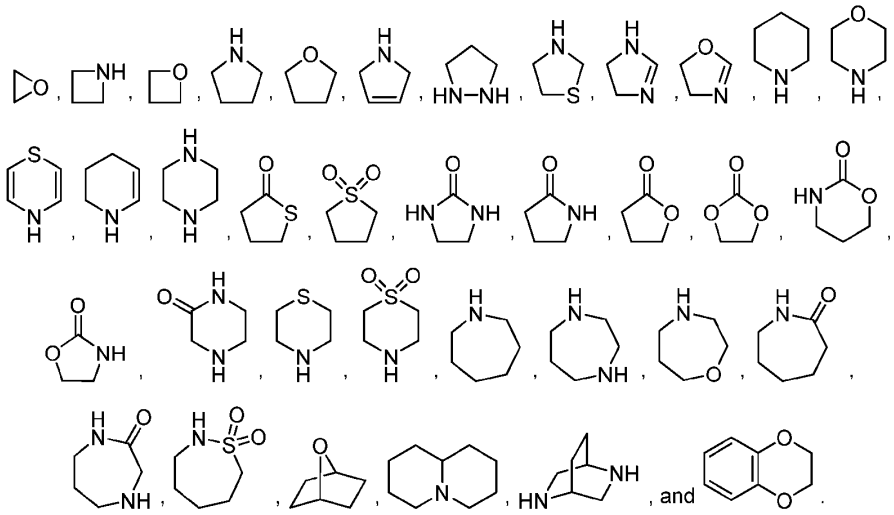
[0183] The term "halogen" or "halo" represents chlorine, fluorine, bromine, or iodine.

[0184] The term "haloalkyl" refers to an alkyl group with one or more halo substituents. Examples of haloalkyl groups include –CF_3, -$(CH_2)F$, -CHF_2, -CH_2Br, -CH_2CF_3, and -CH_2CH_2F. The term "haloalkylene" refers to an alkyl group with one or more halo

substituents. Examples of haloalkyl groups include -CF_2-, -C(H)(F)-, -C(H)(Br)-, -CH_2CF_2-, and -CH_2C(H)(F)-.

[0185] 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 (C_6-C_{14} aryl), monovalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 10 carbon atoms (C_6-C_{10} aryl), divalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 14 carbon atoms (C_6-C_{14} arylene), divalent all-carbon monocyclic or fused-ring polycyclic groups of 6 to 10 carbon atoms (C_6-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.

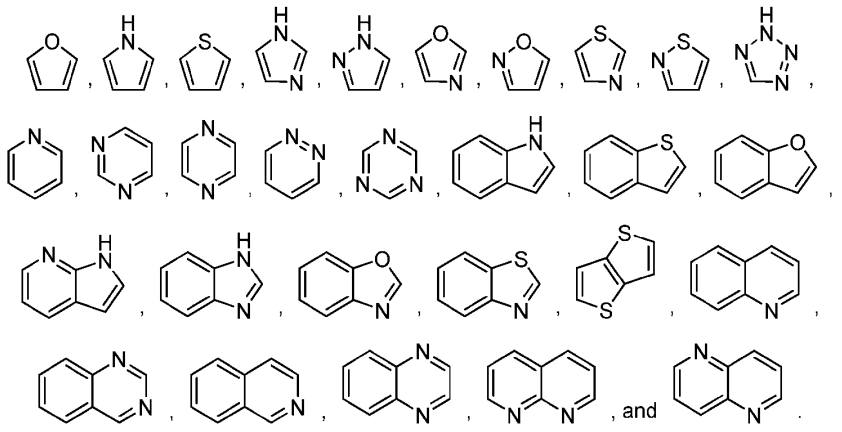
[0186] The term "heterocycloalkyl" refers to a mono-valent monocyclic or polycyclic ring structure that is saturated or partially saturated having one or more non-carbon ring atoms. The term "heterocycloalkylene" refers to a divalent monocyclic or polycyclic ring structure that is saturated or partially 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:



[0187] 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 thiirane. 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 azitidine, 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 heterocyle 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.

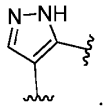
[0188] It will be appreciated that a heterocycloalkyl or heterocycloalkylene group can be unsubstituted or substituted as described herein. A heterocycloalkyl or heterocycloalkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0189] 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:



[0190] 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 mono-valent 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.

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 .

[0191] 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.

[0192] The term "oxo" represents a carbonyl oxygen. For example, a cyclopentyl substituted with oxo is cyclopentanone.

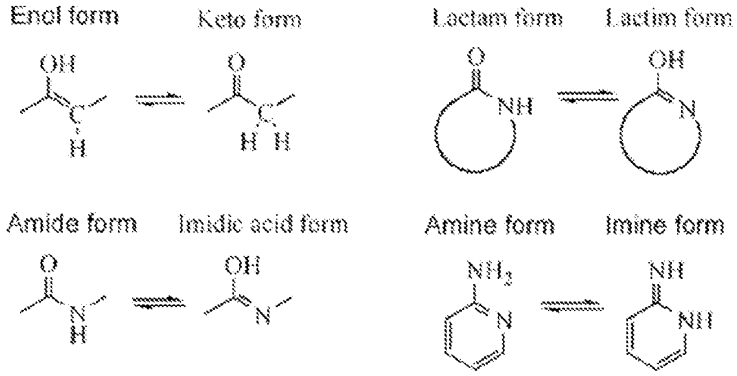
[0193] The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed 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.

[0194] 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.

[0195] 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 ^{2}H, ^{3}H, ^{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 ^{2}H or ^{3}H), 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., ^{2}H) 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.

[0196] Certain chemical entities of Formula (I)-(VIII) may be depicted in two or more tautomeric forms. Any and all alternative tautomers are included within the scope of these formulas, and no inference should be made as to whether the chemical entity exists as the tautomeric form in which it is drawn. It will be understood that certain chemical entities described herein can exist in different tautomeric forms. It will be readily appreciated by one

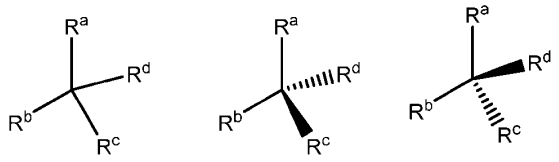
of skill in the art that because of rapid interconversion, tautomers can generally be considered to be the same chemical compound. Examples of tautomers include but are not limited to enol-keto tautomers, amine-imine tautomers, and the like.



[0197] The nomenclature "$(ATOM)_i$-$(ATOM)_j$" with j > i, when applied herein to a class of substituents, is meant to refer to embodiments of this disclosure for which each and every one of the number of atom members, from i to j including i and j, is independently realized. By way of example, the term C_1-C_3 refers independently to embodiments that have one carbon member (C_1), embodiments that have two carbon members (C_2), and embodiments that have three carbon members (C_3).

[0198] 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 ≠ 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.

[0199] 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



(S) (R)

where $R^a > R^b > R^c > R^d$ according to the Cahn-Ingold Prelog Rules.

[0200] The disclosure also includes pharmaceutically acceptable salts of the compounds represented by Formula (I)-(VIII), preferably of those described above and of the specific compounds exemplified herein, and pharmaceutical compositions comprising such salts, and methods of using such salts.

[0201] 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.

[0202] 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, isobutyrates, 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.

[0203] For a compound of Formula (I)-(VIII) 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,

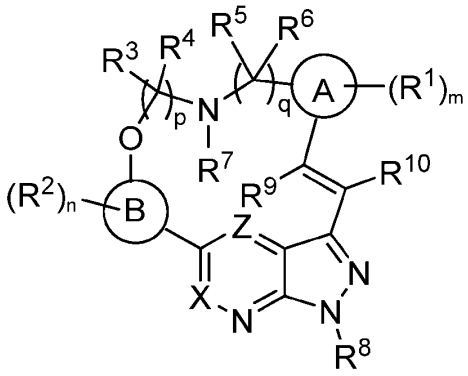
hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, 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.

[0204] The disclosure also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (I)-(VIII), 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 the compound of Formula (I)-(VIII)). 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.

[0205] The present disclosure also relates to pharmaceutically active metabolites of compounds of Formula (I)-(VIII), 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 of Formula (I)-(VIII) 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).

REPRESENTATIVE EMBODIMENTS

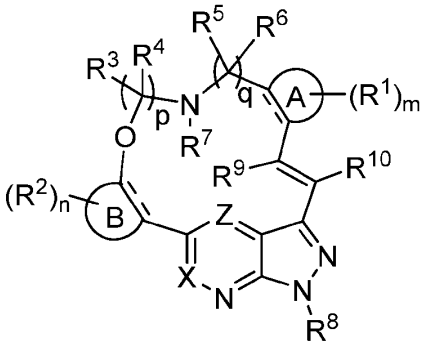
[0206] The present disclosure provides macrocyclic compounds that bind and/or modulate the activity of specific kinases. In some embodiments, the disclosure provides a compound of the formula I, or a pharmaceutically acceptable salt thereof,



I

[0207] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, A, B, X, Z, m, n, p, and q are as described herein.

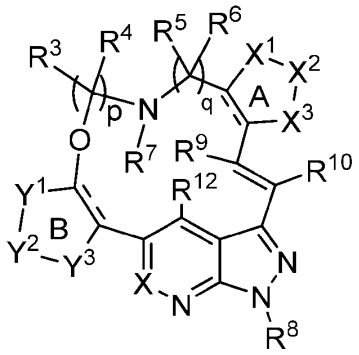
[0208] In some embodiments, the disclosure provides a compound of the formula II, or a pharmaceutically acceptable salt thereof,



II

[0209] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, A, B, X, Z, m, n, p, q, and "------" are as described herein.

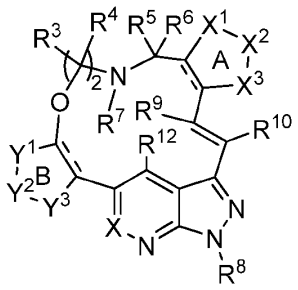
[0210] In some embodiments, the disclosure provides a compound of the formula III, or a pharmaceutically acceptable salt thereof,



III

[0211] wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, A, B, X, X^1, X^2, X^3, Y^1, Y^2, Y^3, p, q, and "------" are as described herein.

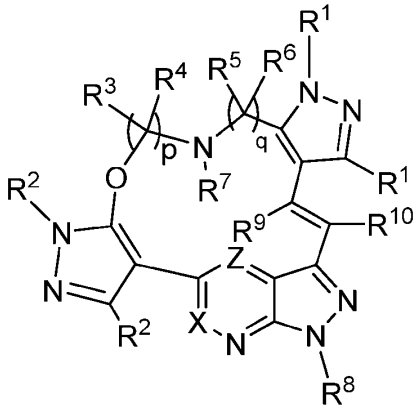
[0212] In some embodiments, the disclosure provides a compound of the formula IV, or a pharmaceutically acceptable salt thereof,



IV

[0213] wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, A, B, X, X^1, X^2, X^3, Y^1, Y^2, Y^3, and "------" are as described herein.

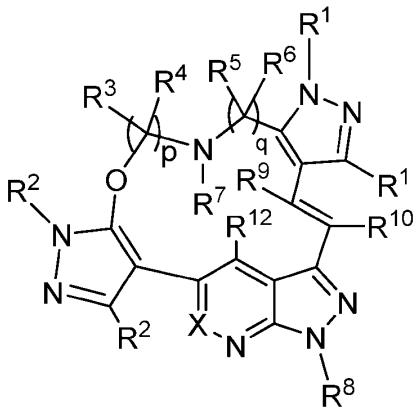
[0214] In some embodiments, the disclosure provides a compound of the formula V, or a pharmaceutically acceptable salt thereof,



V

[0215] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, p, and q are as described herein.

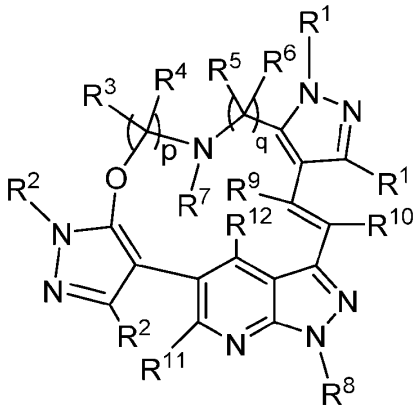
[0216] In some embodiments, the disclosure provides a compound of the formula VI, or a pharmaceutically acceptable salt thereof,



VI

[0217] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, X, p, and q are as described herein.

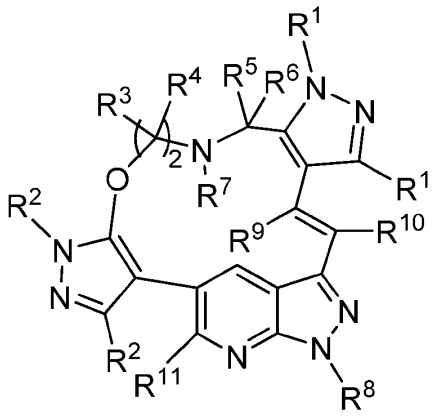
[0218] In some embodiments, the disclosure provides a compound of the formula VII, or a pharmaceutically acceptable salt thereof,



VII

[0219] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, p, and q are as described herein.

[0220] In some embodiments, the disclosure provides a compound of the formula VIII, or a pharmaceutically acceptable salt thereof,



VIII

[0221] wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, are as described herein.

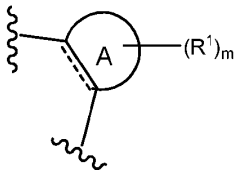
[0222] In some embodiments, ring A is a 5-membered heteroarylene.

[0223] In some embodiments, ring A is a 5-membered heteroarylene, wherein each R^1, when present and bonded to a carbon, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or each R^1, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

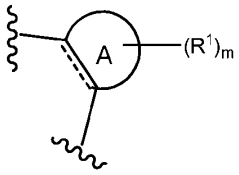
[0224] In some embodiments, ring A is pyrazolylene, isoxazolylene, isothiazolylene, imidazolylene wherein each is independently optionally substituted by 1, 2, or 3 R^1 (m of R^1), wherein each R^1, when present and bonded to a carbon, is independently deuterium, halogen,

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, or each R^1, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=NR^d)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=NR^d)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=NR^d)NR^cR^d$, -PR^cR^d, -$P(O)R^cR^d$, -$P(O)_2R^cR^d$, -$P(O)NR^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)OR^c$, -$P(O)_2OR^c$, -CN, or -NO_2.

[0225] In some embodiments, ring A is of the formula

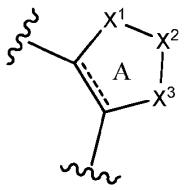


[0226] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "~~~" represents a point of covalent attachment, and R^1 and m are as described herein. In some embodiments, ring A is of the formula



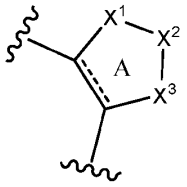
[0227] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "~~~" represents a point of covalent attachment, ring A is a 5-membered heteroarylene, and R^1 and m are as described herein.

[0228] In some embodiments, ring A is of the formula



[0229] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "~~~~" represents a point of covalent attachment, and X^1, X^2, and X^3 are each independently -O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N- and ring A is a 5-membered heteroarylene, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-.

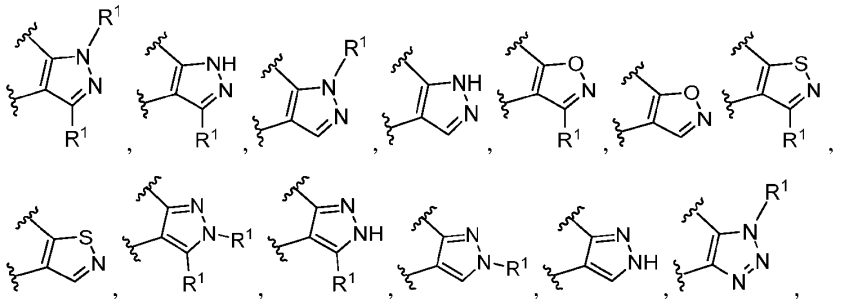
[0230] In some embodiments, ring A is of the formula

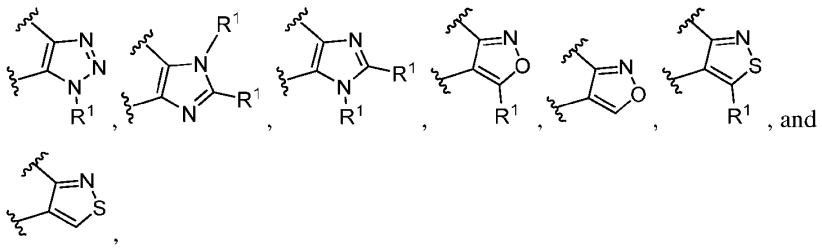


[0231] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "~~~~" represents a point of covalent attachment, X^2, is –O-, -S-, -N(H)-, -N(R^1)- or =N-, X^1 and X^3 are each independently –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, and ring A is a 5-membered heteroarylene, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-, ring A is a 5-membered heteroarylene, and R^1 and m are as described herein.

[0232] In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

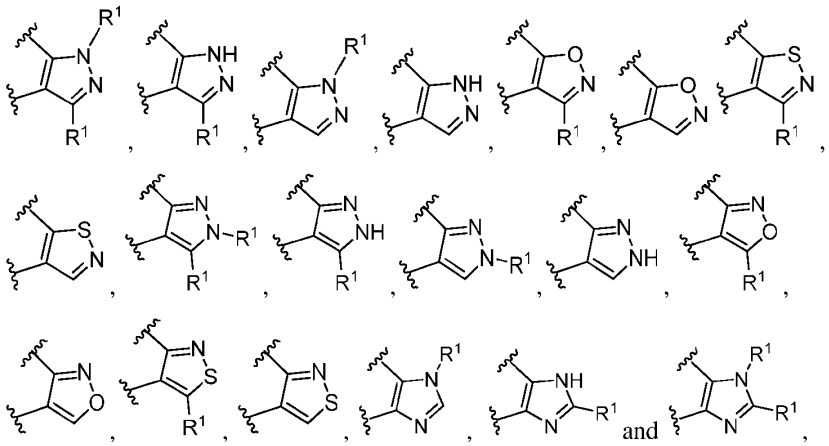
[0233] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of





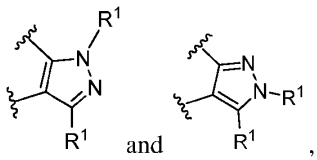
[0234] wherein each "〰" represents a point of covalent attachment, and each R^1 is independently as described herein.

[0235] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of



[0236] wherein each "〰" represents a point of covalent attachment, and each R^1 is independently as described herein.

[0237] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of



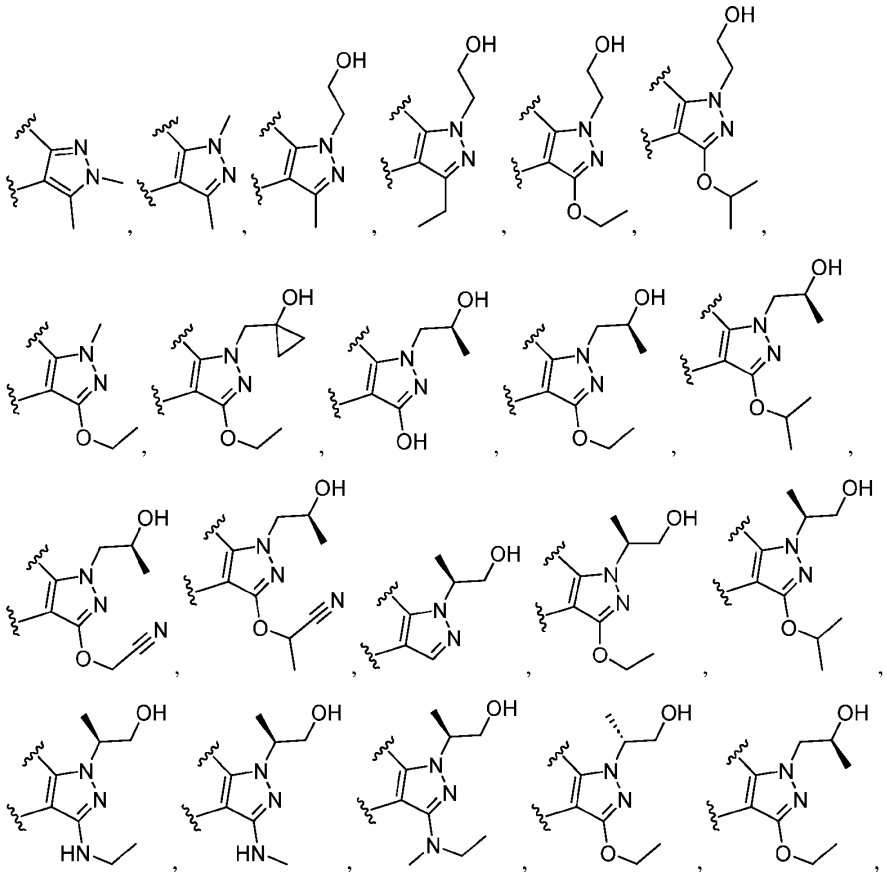
[0238] wherein each "〰" represents a point of covalent attachment, and R^1 is as described herein.

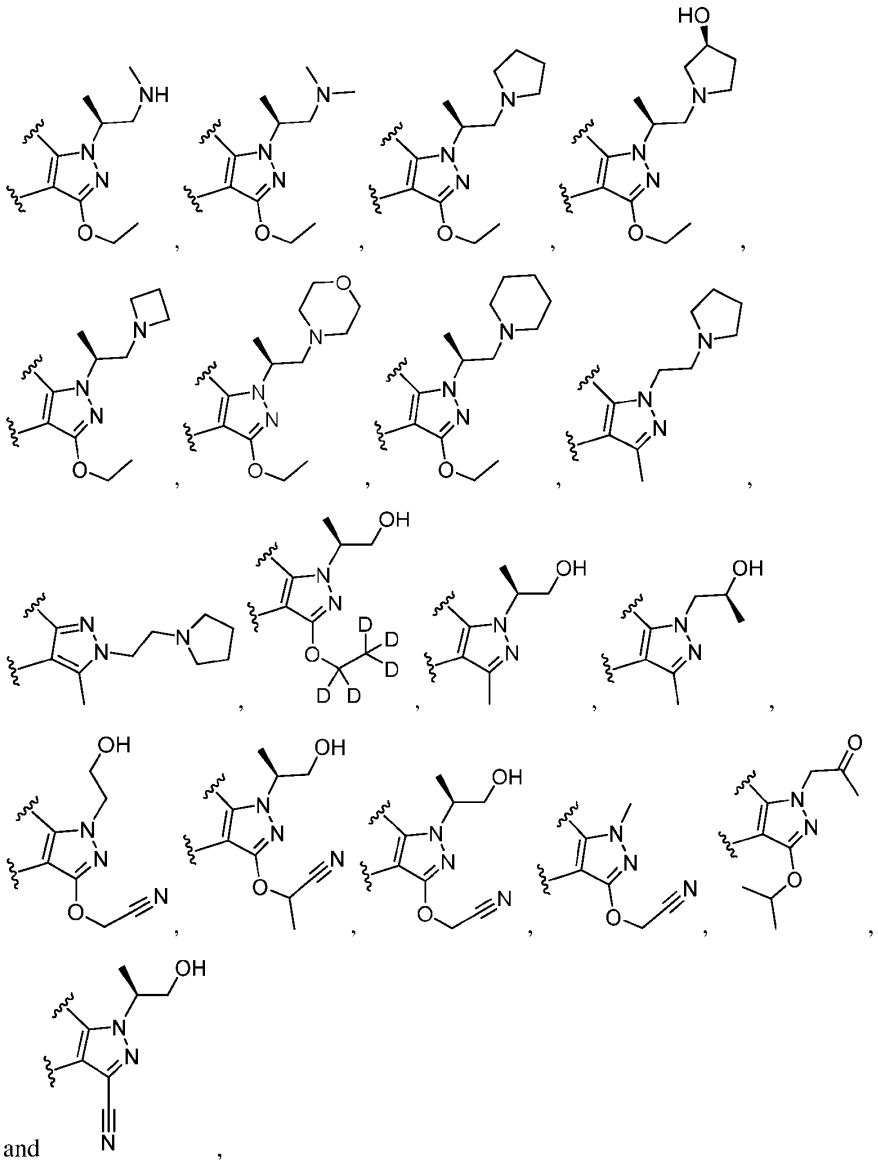
[0239] In some embodiments, each R^1, when present and bonded to a nitrogen atom, is independently a C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$,

-N(C(O)R^c)(C(O)R^d), -NR^{c}C(O)OR^d, -NR^{c}C(O)NR^{c}R^d, -NR^{c}C(=NR^d)NR^{c}R^d, -NR^{c}S(O)R^d, -NR^{c}S(O)$_2$R^d, -NR^{c}S(O)NR^{c}R^d, -NR^{c}S(O)$_2$NR^{c}R^d, -C(O)R^c, -C(O)OR^c, -C(O)NR^{c}R^d, -C(=NR^d)NR^{c}R^d, -PR^{c}R^d, -P(O)R^{c}R^d, -P(O)$_2$R^{c}R^d, -P(O)NR^{c}R^d, -P(O)$_2$NR^{c}R^d, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO$_2$.

[0240] In some embodiments, each R^1, when present and bonded to a carbon atom, is independently a C$_1$-C$_6$ alkyl, -OR^a, or -NR^{a}R^b, wherein each hydrogen atom in C$_1$-C$_6$ alkyl is independently optionally substituted by deuterium, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl, -OR^c, -OC(O)R^c, -OC(O)NR^{c}R^d, -OC(=NR^d)NR^{c}R^d, -OS(O)R^c, -OS(O)$_2$R^c, -OS(O)NR^{c}R^d, -OS(O)$_2$NR^{c}R^d, -SR^c, -S(O)R^c, -S(O)$_2$R^c, -S(O)NR^{c}R^d, -S(O)$_2$NR^{c}R^d, -NR^{c}R^d, -NR^{c}C(O)R^d, -N(C(O)R^c)(C(O)R^d), -NR^{c}C(O)OR^d, -NR^{c}C(O)NR^{c}R^d, -NR^{c}C(=NR^d)NR^{c}R^d, -NR^{c}S(O)R^d, -NR^{c}S(O)$_2$R^d, -NR^{c}S(O)NR^{c}R^d, -NR^{c}S(O)$_2$NR^{c}R^d, -C(O)R^c, -C(O)OR^c, -C(O)NR^{c}R^d, -C(=NR^d)NR^{c}R^d, -PR^{c}R^d, -P(O)R^{c}R^d, -P(O)$_2$R^{c}R^d, -P(O)NR^{c}R^d, -P(O)$_2$NR^{c}R^d, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO$_2$.

[0241] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of

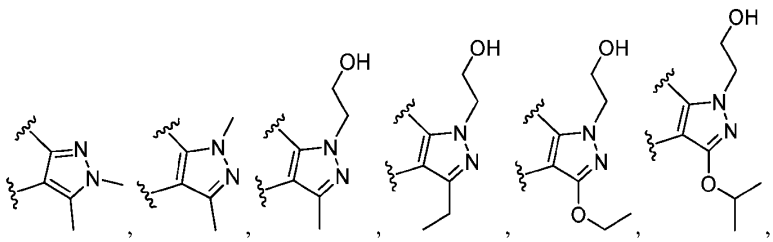


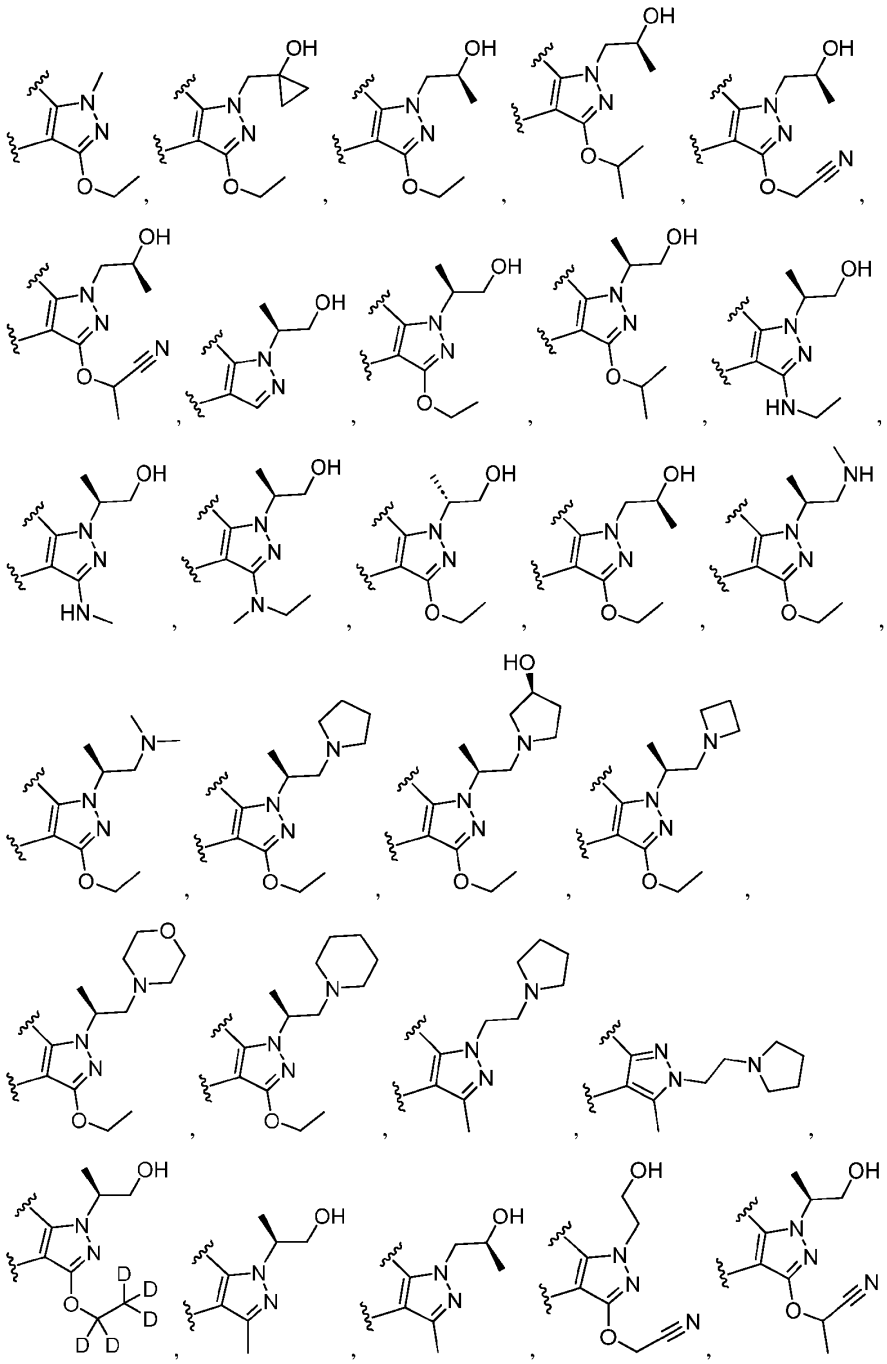


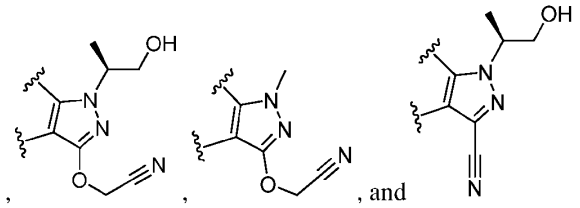
and ,

[0242] wherein each "〰" represents a point of covalent attachment.

[0243] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of

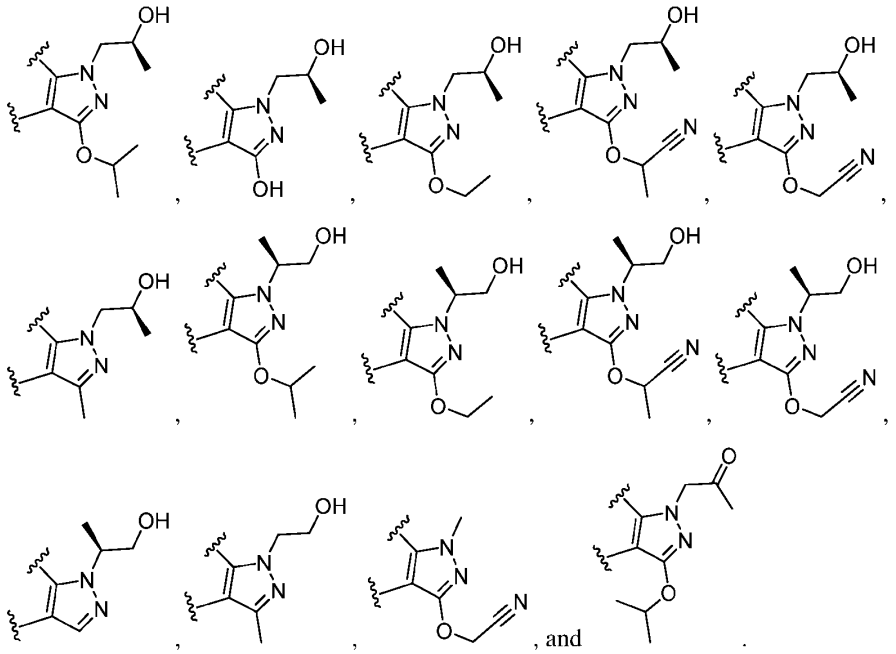




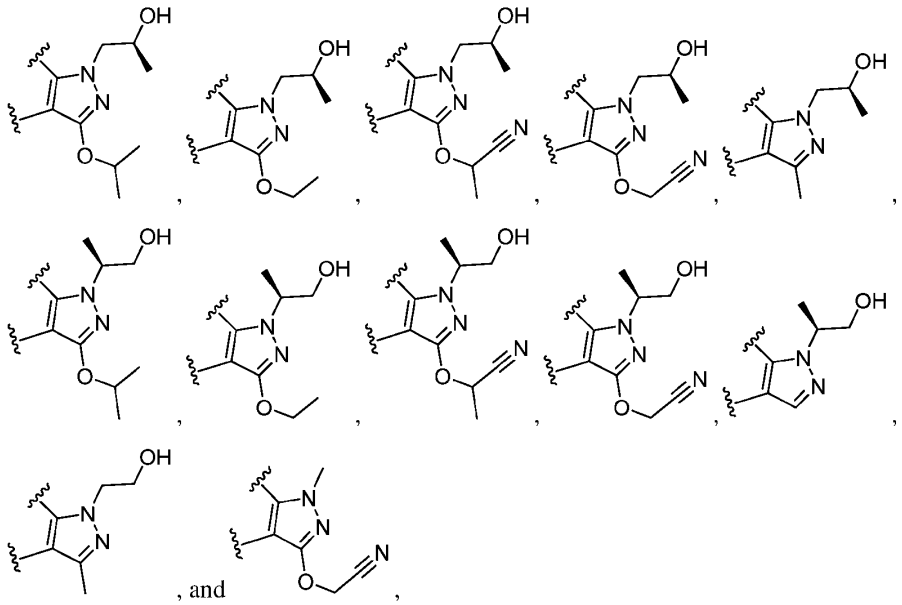


[0244] wherein each "〰" represents a point of covalent attachment.

[0245] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of

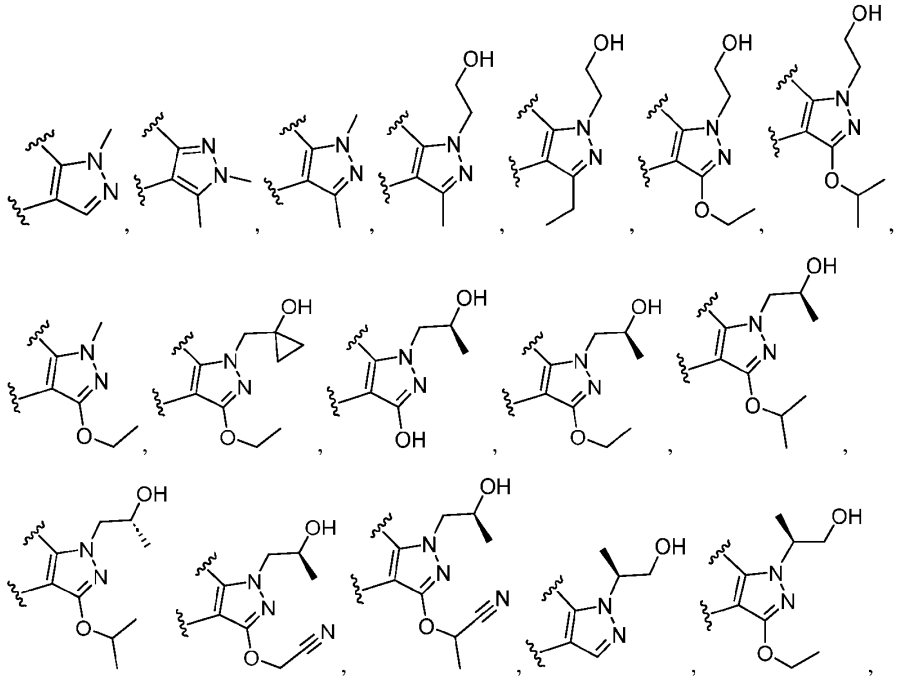


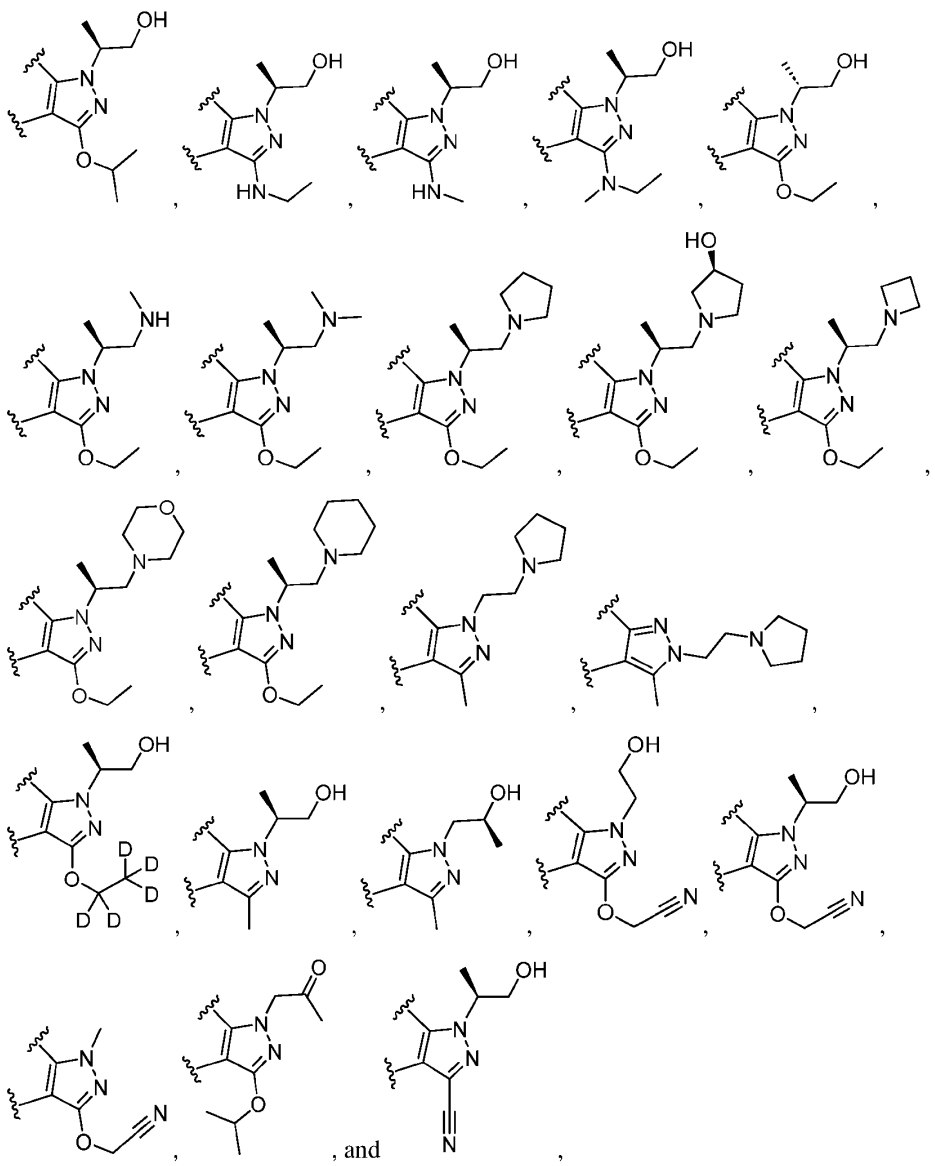
[0246] In some embodiments, ring A is a 5-membered heteroarylene selected from the group consisting of



[0247] wherein each "〰" represents a point of covalent attachment.

[0248] In some embodiments, ring A is selected from the group consisting of





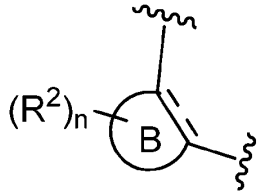
wherein each "〰" represents a point of covalent attachment.

[0249] In some embodiments, ring B is 5-membered heteroarylene.

[0250] In some embodiments, ring B is a 5-membered heteroarylene, wherein each R^2, when present and bonded to a carbon atom, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$,

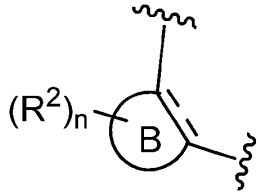
$-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or each R^2, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0251] In some embodiments, ring B is of the formula



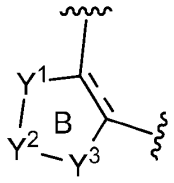
[0252] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "∿∿∿" represents a point of covalent attachment, and R^2 and n are as described herein.

[0253] In some embodiments, ring B is of the formula



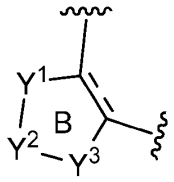
[0254] wherein "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "∿∿∿" represents a point of covalent attachment, ring B is a 5-membered heteroarylene, and R^2 and n are as described herein.

[0255] In some embodiments, ring B is of the formula



[0256] wherein each "〰" represents a point of covalent attachment, Y^1, Y^2, and Y^3 are each independently -O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, -N(R^2)-, or =N- and ring B is a 5-membered heteroarylene, provided that at least one of Y^1, Y^2, and Y^3 is not =C(H)-, or =C(R^2)-.

[0257] In some embodiments, ring B is of the formula



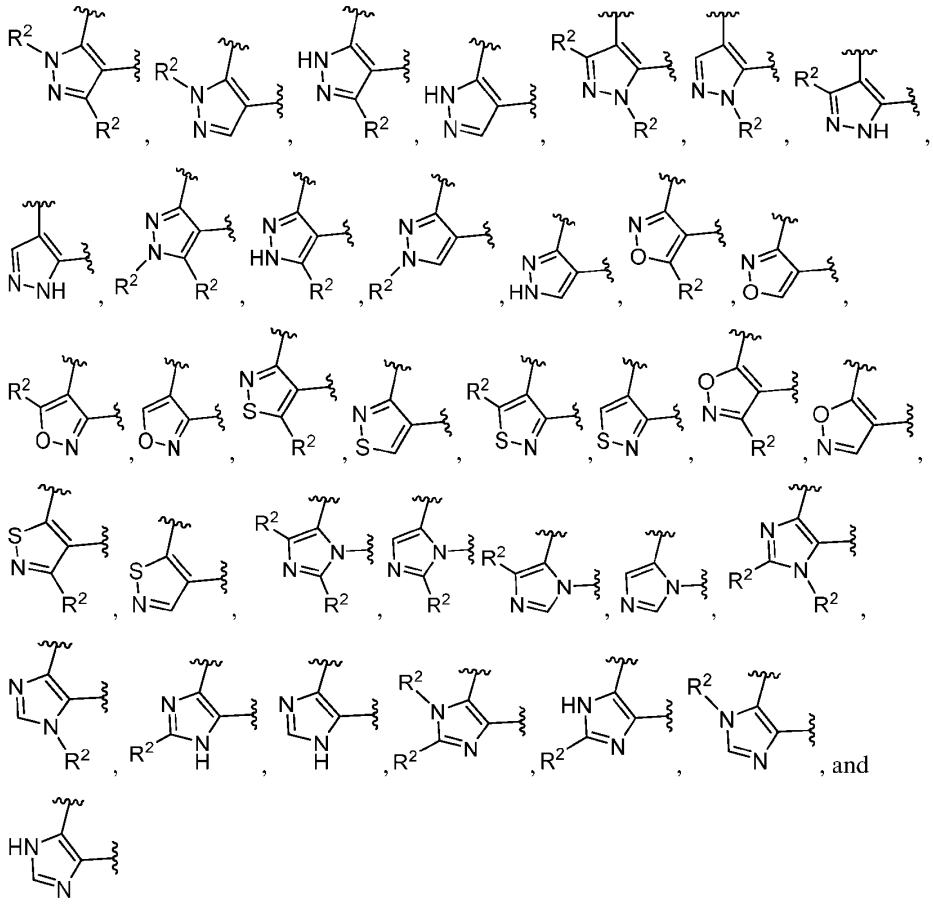
[0258] wherein each "〰" represents a point of covalent attachment, Y^2 is =N-, Y^1 and Y^3 are each independently -O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, or -N(R^2)-, and ring B is a 5-membered heteroarylene.

[0259] In some embodiments, ring B is pyrazolylene, isoxazolylene, isothiazolylene, imidazolylene wherein each is optionally substituted with 1, 2, or 3 R^2 (n of R^2), wherein each R^2, when present and bonded to a carbon atom, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -$C(=NR^b)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, or each R^2, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=NR^d)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=NR^d)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$,

-C(O)R^c, -C(O)OR^c, -C(O)N$R^c R^d$, -C(=NR^d)N$R^c R^d$, -P$R^c R^d$, -P(O)$R^c R^d$, -P(O)$_2$R^{c}R^d, -P(O)N$R^c R^d$, -P(O)$_2$N$R^c R^d$, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO$_2$.

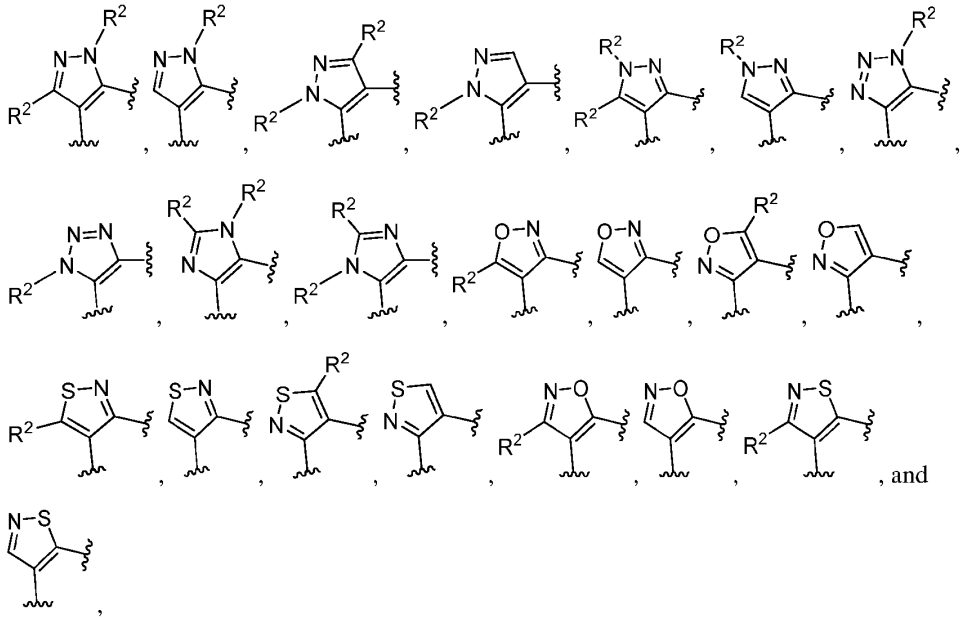
[0260] In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

[0261] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



[0262] wherein each "〰" represents a point of covalent attachment, and each R^2 is independently as described herein.

[0263] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



, and

,

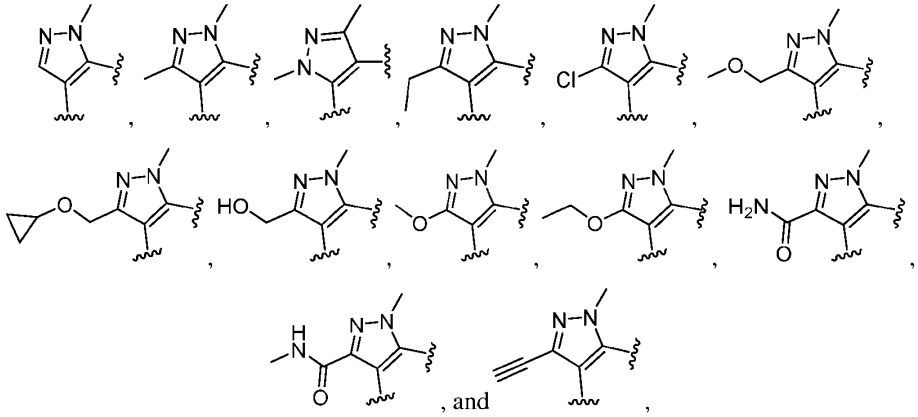
[0264] wherein each "〰" represents a point of covalent attachment.

[0265] In some embodiments, each R^2, when present and bonded to a carbon atom, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0266] In some embodiments, each R^2, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-

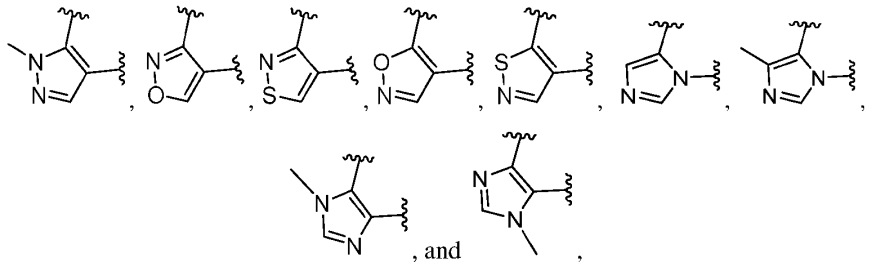
membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, $-CN$, or $-NO_2$.

[0267] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



[0268] wherein each "〰" represents a point of covalent attachment.

[0269] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



[0270] wherein each "〰" represents a point of covalent attachment.

[0271] In some embodiments, n is 1 and m is 2. In some embodiments, n is 2 and m is 2. In some embodiments, each of ring A and B is a 5-membered heteroarylene (e.g., pyrazolylene) and n is 1 and m is 2. In some embodiments, each of ring A and B is a 5-membered

heteroarylene (e.g., pyrazolylene), n is 2, and m is 2.

[0272] In some embodiments, each of ring A and B is a 5-membered heteroarylene (e.g., pyrazolylene) and n is 1 or 2, and each R^2 is optionally substituted C_1-C_6 alkyl (e.g., optionally substituted with $-OR^c$) or $-C(O)NR^aR^b$ (e.g., $-C(O)NH_2$ or $-C(O)NHC_1$-C_6 alkyl). In some embodiments, each of ring A and B is a 5-membered heteroarylene (e.g., pyrazolylene) and m is 2, and each R^2 is optionally substituted C_1-C_6 alkyl (e.g., optionally substituted with $-OR^c$) or $-OR^a$ (e.g., $-O-C_1$-C_6 alkyl which may be optionally substituted). In some embodiments, each of ring A and B is a 5-membered heteroarylene (e.g., pyrazolylene), n is 1 or 2, and each R^2 is optionally substituted C_1-C_6 alkyl (e.g., optionally substituted with $-OR^c$) or $-C(O)NR^aR^b$ (e.g., $-C(O)NH_2$ or $-C(O)NHC_1$-C_6 alkyl), and m is 2, and each R^2 is optionally substituted C_1-C_6 alkyl (e.g., optionally substituted with $-OR^c$) or $-OR^a$ (e.g., $-O-C_1$-C_6 alkyl which may be optionally substituted).

[0273] In some embodiments, R^7 is H, deuterium, $-C(O)R^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, or R^7 and one of R^3, R^4, R^5, or R^6, taken together with the atoms to which each is attached, combine to form a 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0274] In some embodiments, R^7 is $-C(O)R^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_6 cycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and C_3-C_6 cycloalkyl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0275] In some embodiments, R^7 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl and C_3-C_6 cycloalkyl is independently optionally substituted by $-OR^c$,

-OC(O)R^c, -OC(O)NR^cR^d, -OC(=NR^d)NR^cR^d, -OS(O)R^c, -OS(O)$_2R^c$, -OS(O)NR^cR^d, -OS(O)$_2NR^cR^d$, -SR^c, -S(O)R^c, -S(O)$_2R^c$, -S(O)NR^cR^d, -S(O)$_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -N(C(O)R^c)(C(O)R^d), -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=NR^d)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -C(=NR^d)NR^cR^d, -PR^cR^d, -P(O)R^cR^d, -P(O)$_2R^cR^d$, -P(O)NR^cR^d, -P(O)$_2NR^cR^d$, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO_2.

[0276] In some embodiments, R^7 is H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; or R^7 and one instance of R^3, R^4, R^5, or R^6, taken together with the atoms to which each is attached, combine to form 4- to 7-membered heterocycloalkyl. In some embodiments, R^7 is H or deuterium.

[0277] In some embodiments, R^8 is H, -S(O)$_2R^c$, -S(O)$_2NR^cR^d$, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -C(=NR^d)NR^cR^d, -P(O)$_2R^cR^d$, -P(O)$_2NR^cR^d$, or -P(O)$_2$OR^c.

[0278] In some embodiments, R^8 is H, deuterium, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -S(O)$_2NR^cR^d$, -P(O)$_2R^cR^d$, -P(O)$_2NR^cR^d$, or -P(O)$_2$OR^c.

[0279] In some embodiments, R^8 is H or deuterium.

[0280] In some embodiments, each of R^9 and R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2NR^eR^f$, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2NR^eR^f$, -NR^eR^f, -$NR^eC(O)R^f$, -$NR^eC(O)OR^f$, -$NR^eC(O)NR^eR^f$, -$NR^eS(O)R^f$, -$NR^eS(O)_2R^f$, -$NR^eS(O)NR^eR^f$, -$NR^eS(O)_2NR^eR^f$, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2NR^eR^f$, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2.

[0281] In some embodiments, each of R^9 and R^{10} is independently H, deuterium, or C_1-C_6 alkyl. In some embodiments, R^9 is H or deuterium. In some embodiments, R^{10} is H or deuterium. In some embodiments, R^9 and R^{10} are H.

[0282] In some embodiments, R^{11}, when present, is H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -OC(=NR^b)NR^aR^b, -OS(O)R^a, -OS(O)$_2R^a$, -SR^a, -S(O)R^a, -S(O)$_2R^a$, -S(O)NR^aR^b, -S(O)$_2NR^aR^b$, -OS(O)NR^aR^b, -OS(O)$_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -C(=NR^b)NR^aR^b, -PR^aR^b, -P(O)R^aR^b, -P(O)$_2R^aR^b$, -P(O)NR^aR^b, -P(O)$_2NR^aR^b$,

-P(O)OR^a, -P(O)$_2$OR^a, -CN, or -NO$_2$, wherein each hydrogen atom in C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl, -OR^c, -OC(O)R^c, -OC(O)NR^{c}R^d, -OC(=NR^d)NR^{c}R^d, -OS(O)R^c, -OS(O)$_2$R^c, -OS(O)NR^{c}R^d, -OS(O)$_2$NR^{c}R^d, -SR^c, -S(O)R^c, -S(O)$_2$R^c, -S(O)NR^{c}R^d, -S(O)$_2$NR^{c}R^d, -NR^{c}R^d, -NR^{c}C(O)R^d, -N(C(O)R^c)(C(O)R^d), -NR^{c}C(O)OR^d, -NR^{c}C(O)NR^{c}R^d, -NR^{c}C(=NR^d)NR^{c}R^d, -NR^{c}S(O)R^d, -NR^{c}S(O)$_2$R^d, -NR^{c}S(O)NR^{c}R^d, -NR^{c}S(O)$_2$NR^{c}R^d, -C(O)R^c, -C(O)OR^c, -C(O)NR^{c}R^d, -C(=NR^d)NR^{c}R^d, -PR^{c}R^d, -P(O)R^{c}R^d, -P(O)$_2$R^{c}R^d, -P(O)NR^{c}R^d, -P(O)$_2$NR^{c}R^d, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO$_2$.

[0283] In some embodiments, R^{11}, when present, is H, deuterium, halogen, C$_1$-C$_6$ alkyl, or -OR^a. In some embodiments, R^{11}, when present, is H, deuterium, halogen, -OH, -OCH$_3$, -CH$_3$, -CH$_2$CH$_3$, or -CD$_3$. In some embodiments, R^{11}, when present, is H, deuterium, halogen, -OH, -OCH$_3$, -CH$_3$, or -CD$_3$. In some embodiments, R^{11}, when present, is H, deuterium, -OH, -OCH$_3$, or -CH$_3$.

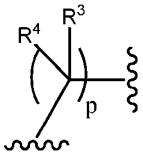
[0284] In some embodiments, Z is N. In some embodiments, Z is C(R^{12}).

[0285] In some embodiments, R^{12}, when present, is independently H, deuterium, halogen, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, 5- to 10-membered heteroaryl, -OR^a, -OC(O)R^a, -OC(O)NR^{a}R^b, -OC(=NR^b)NR^{a}R^b, -OS(O)R^a, -OS(O)$_2$R^a, -SR^a, -S(O)R^a, -S(O)$_2$R^a, -S(O)NR^{a}R^b, -S(O)$_2$NR^{a}R^b, -OS(O)NR^{a}R^b, -OS(O)$_2$NR^{a}R^b, -NR^{a}R^b, -NR^{a}C(O)R^b, -NR^{a}C(O)OR^b, -NR^{a}C(O)NR^{a}R^b, -NR^{a}C(=NR^b)NR^{a}R^b, -NR^{a}S(O)R^b, -NR^{a}S(O)$_2$R^b, -NR^{a}S(O)NR^{a}R^b, -NR^{a}S(O)$_2$NR^{a}R^b, -C(O)R^a, -C(O)OR^a, -C(O)NR^{a}R^b, -C(=NR^b)NR^{a}R^b, -PR^{a}R^b, -P(O)R^{a}R^b, -P(O)$_2$R^{a}R^b, -P(O)NR^{a}R^b, -P(O)$_2$NR^{a}R^b, -P(O)OR^a, -P(O)$_2$OR^a, -CN, or -NO$_2$, wherein each hydrogen atom in C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl, -OR^c, -OC(O)R^c, -OC(O)NR^{c}R^d, -OC(=NR^d)NR^{c}R^d, -OS(O)R^c, -OS(O)$_2$R^c, -OS(O)NR^{c}R^d, -OS(O)$_2$NR^{c}R^d, -SR^c, -S(O)R^c, -S(O)$_2$R^c, -S(O)NR^{c}R^d, -S(O)$_2$NR^{c}R^d, -NR^{c}R^d, -NR^{c}C(O)R^d, -N(C(O)R^c)(C(O)R^d), -NR^{c}C(O)OR^d, -NR^{c}C(O)NR^{c}R^d, -NR^{c}C(=NR^d)NR^{c}R^d, -NR^{c}S(O)R^d, -NR^{c}S(O)$_2$R^d, -NR^{c}S(O)NR^{c}R^d, -NR^{c}S(O)$_2$NR^{c}R^d, -C(O)R^c, -C(O)OR^c, -C(O)NR^{c}R^d, -C(=NR^d)NR^{c}R^d, -PR^{c}R^d, -P(O)R^{c}R^d, -P(O)$_2$R^{c}R^d, -P(O)NR^{c}R^d, -P(O)$_2$NR^{c}R^d, -P(O)OR^c, -P(O)$_2$OR^c, -CN, or -NO$_2$. In some embodiments, R^{12}, when present, is independently H, deuterium, halogen, or C$_1$-C$_6$ alkyl. In some embodiments, R^{12}, when present, is independently H, deuterium, halogen, or methyl. In some embodiments, R^{12}, when present, is independently H or deuterium.

[0286] In some embodiments, p is 2, 3, or 4. In some embodiments, p is 2 or 3. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4.

[0287] In some embodiments, each of R^3 and R^4 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or two of R^3 and R^4 taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

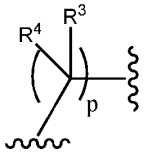
[0288] In some embodiments,



is an ethylene, propylene, or butylene, wherein each R^3 and R^4 is independently, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_3-C_6 cycloalkyl and 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$,

$-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$; or R^7 and an R^3 or an R^4 , taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in the 4- to 7-membered heterocycloalkyl formed is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$; and each "〰" represents a point of covalent attachment.

[0289] In some embodiments,



is an ethylene or propylene, wherein each R^3 and R^4 is independently, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$; or R^7 and an R^3 or an R^4 , taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in 4- to 7-membered heterocycloalkyl formed is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$,

-S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2; and each "〰" represents a point of covalent attachment.

[0290] In some embodiments, one or two of R^3 are each independently C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2, or two of R^3 and/or R^4, taken together with the carbon or carbons to which they are attached, optionally combine to form a C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, wherein each hydrogen atom in the C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl formed when two of R^3 and/or R^4 are taken together is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2; or R^7 and an R^3 or an R^4 and, taken together with the atoms to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in the 4- to 7-membered heterocycloalkyl is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2; and any remaining R^3 and R^4 are H or deuterium.

[0291] In some embodiments, one or two of R^3 are each independently a C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2; and/or R^7 and an R^3 or an R^4

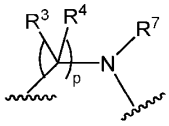
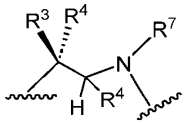
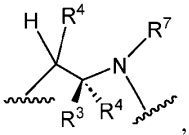
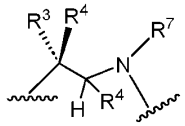
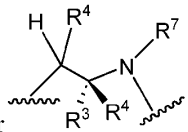
taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$; and any remaining R^3 and R^4 are H or deuterium.

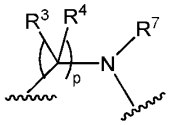
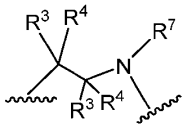
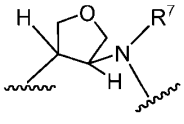
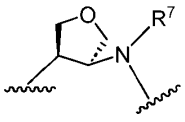
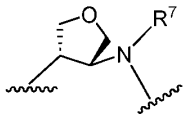
[0292] In some embodiments, one or two of R^3 are each independently a C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$; or two R^3 and R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in the C_3-C_6 cycloalkyl and 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

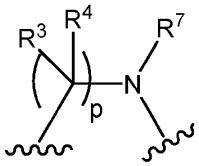
[0293] In some embodiments, one or two of R^3 is C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$, and any remaining R^3 and R^4 are H.

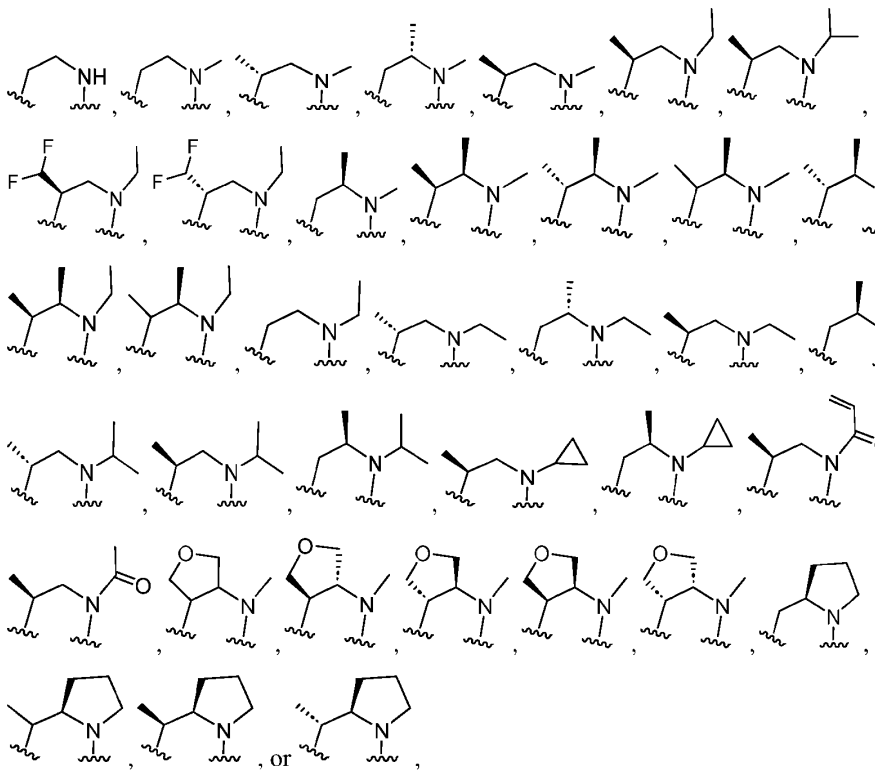
[0294] In some embodiments, one or two of R^3 are each independently C_1-C_6 alkyl; and any remaining R^3 and R^4 are H or deuterium. In some embodiments, each R^3 is methyl, and any remaining R^3 and R^4 are H or deuterium. In some embodiments, one R^3 is C_1-C_6 alkyl. In some embodiments, one R^3 is methyl, and any remaining R^3 and R^4 are H.

[0295] In some embodiments, one instance of R^3 is C_1-C_6 alkyl; R^7 and one instance of R^4, taken together with the atoms to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium. In some embodiments, two R^3 and R^4, taken together with the carbon or carbons to which they are attached, combine to form 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium.

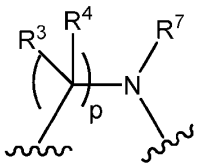
[0296] In some embodiments, the portion  is of the formula , , , or , wherein R^3 is C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is optionally substituted by halo (e.g., methyl or difluoromethyl) and each R^4 is independently H, deuterium, or C_1-C_6 alkyl (e.g., methyl).

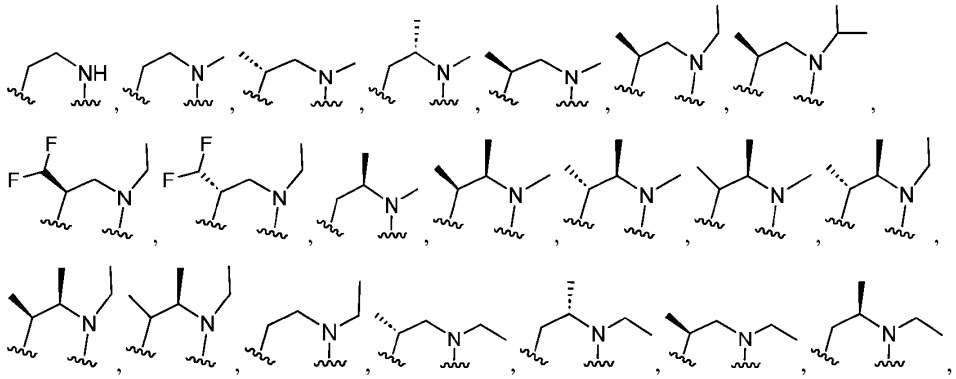
[0297] In some embodiments, the portion  is of the formula , wherein an R^3 or an R^4 on one carbon combines with an R^3 or an R^4 on the adjacent carbon to form a 3- to 7-membered heterocycloalkyl, for example a 5-membered heterocycloalkyl of the formula: , which may also be shown with stereochemistry as  or , for example.

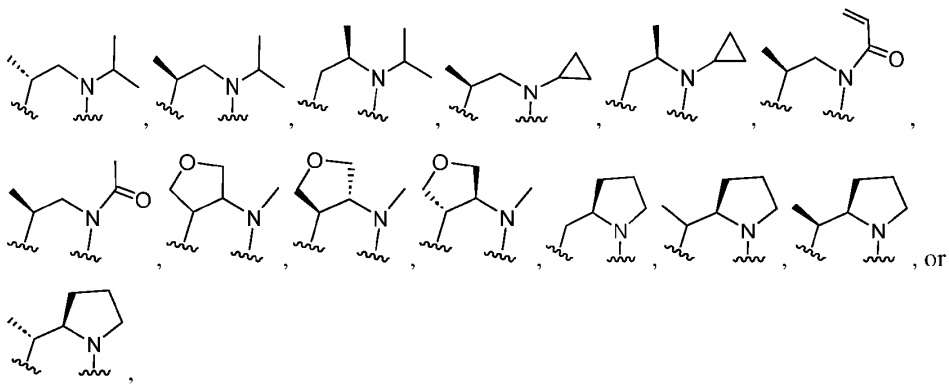
[0298] In some embodiments, the portion  is of the formula



[0299] wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

[0300] In some embodiments, the portion  is of the formula





[0301] wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

[0302] In some embodiments, q is 1 or 2. In some embodiments, q is 1. In some embodiments, q is 2.

[0303] In some embodiments, each R^5 and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or two of R^5 and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$. In some embodiments, R^5 and R^6 are H, deuterium, or C_1-C_6 alkyl. In some embodiments, R^5 and R^6 are H or deuterium. In some embodiments, R^5 and R^6 are H.

[0304] In some embodiments, each R^5 and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$,

-OS(O)R^a, -OS(O)$_2R^a$, -SR^a, -S(O)R^a, -S(O)$_2R^a$, -S(O)NR^aR^b, -S(O)$_2$NR^aR^b, -OS(O)NR^aR^b, -OS(O)$_2$NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -NR^aC(O)NR^aR^b, -NR^aC(=NR^b)NR^aR^b, -NR^aS(O)R^b, -NR^aS(O)$_2R^b$, -NR^aS(O)NR^aR^b, -NR^aS(O)$_2$NR^aR^b, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -C(=NR^b)NR^aR^b, -PR^aR^b, -P(O)R^aR^b, -P(O)$_2R^aR^b$, -P(O)NR^aR^b, -P(O)$_2$NR^aR^b, -P(O)OR^a, -P(O)$_2$OR^a, -CN, or -NO_2.

[0305] In some embodiments, two of R^5 and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2.

[0306] In some embodiments, an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OC(=NR^d)NR^cR^d, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^cC(=NR^d)NR^cR^d, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -C(=NR^d)NR^cR^d, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2. In some embodiments, any remaining R^3 and R^4 are H or deuterium.

[0307] In some embodiments, R^7 and an R^3 or an R^4 , taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom in 4- to 7-membered heterocycloalkyl is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^eR^f, -OC(=NR^d)NR^cR^d, -OS(O)R^e, -OS(O)$_2R^e$, -OS(O)NR^eR^f, -OS(O)$_2$NR^eR^f, -SR^e, -S(O)R^e, -S(O)$_2R^e$, -S(O)NR^eR^f, -S(O)$_2$NR^eR^f, -NR^eR^f, -NR^eC(O)R^f, -NR^eC(O)OR^f, -NR^eC(O)NR^eR^f, -NR^cC(=NR^d)NR^cR^d, -NR^eS(O)R^f, -NR^eS(O)$_2R^f$, -NR^eS(O)NR^eR^f, -NR^eS(O)$_2$NR^eR^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -C(=NR^d)NR^cR^d, -PR^eR^f, -P(O)R^eR^f, -P(O)$_2R^eR^f$, -P(O)NR^eR^f, -P(O)$_2$NR^eR^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO_2. In some embodiments, any remaining R^3 and R^4 are H or deuterium.

[0308] In some embodiments, one or two of R^3 are each independently a C_1-C_6 alkyl, wherein

each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, $-CN$, or $-NO_2$. In some embodiments, any remaining R^3 and R^4 are H or deuterium.

[0309] In some embodiments, one or two of R^3 are each independently a C_1-C_6 alkyl; and any remaining R^3 and R^4 are H or deuterium.

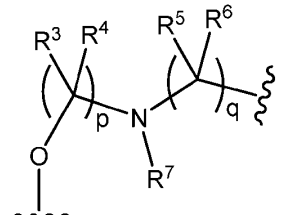
[0310] In some embodiments, each R^3 and R^4 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, $-CN$, or $-NO_2$, , wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, $-CN$, or $-NO_2$.

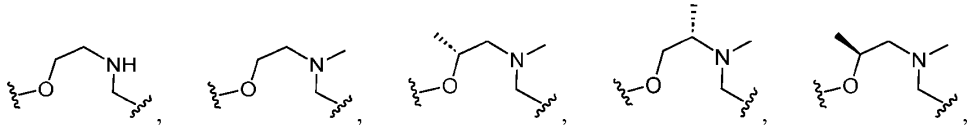
[0311] In some embodiments, each R^3, R^4, R^5, and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, $-CN$, or $-NO_2$.

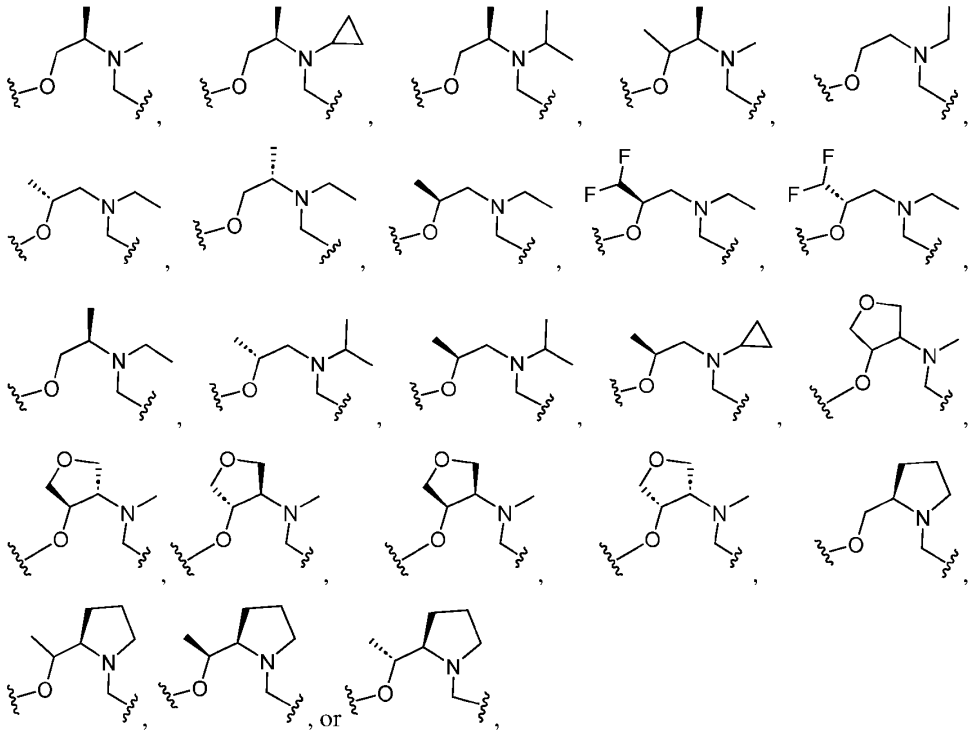
[0312] In some embodiments, two of R^3, R^4, R^5, and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_3-C_6 cycloalkyl and 3- to 7-membered

heterocycloalkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -SR^e, -$S(O)R^e$, -$S(O)_2R^e$, -$S(O)NR^eR^f$, -$S(O)_2NR^eR^f$, -NR^eR^f, -$NR^eC(O)R^f$, -$NR^eC(O)OR^f$, -$NR^eC(O)NR^eR^f$, -$NR^eS(O)R^f$, -$NR^eS(O)_2R^f$, -$NR^eS(O)NR^eR^f$, -$NR^eS(O)_2NR^eR^f$, $C(O)R^e$, -$C(O)OR^e$, -$C(O)NR^eR^f$, -PR^eR^f, -$P(O)R^eR^f$, -$P(O)_2R^eR^f$, -$P(O)NR^eR^f$, -$P(O)_2NR^eR^f$, -$P(O)OR^e$, -$P(O)_2OR^e$, -CN, or -NO_2.

[0313] In some embodiments, each R^3, R^4, R^5, and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -$C(=NR^b)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, or two of R^3, R^4, R^5, and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -SR^e, -$S(O)R^e$, -$S(O)_2R^e$, -$S(O)NR^eR^f$, -$S(O)_2NR^eR^f$, -NR^eR^f, -$NR^eC(O)R^f$, -$NR^eC(O)OR^f$, -$NR^eC(O)NR^eR^f$, -$NR^eS(O)R^f$, -$NR^eS(O)_2R^f$, -$NR^eS(O)NR^eR^f$, -$NR^eS(O)_2NR^eR^f$, -$C(O)R^e$, -$C(O)OR^e$, -$C(O)NR^eR^f$, -PR^eR^f, -$P(O)R^eR^f$, -$P(O)_2R^eR^f$, -$P(O)NR^eR^f$, -$P(O)_2NR^eR^f$, -$P(O)OR^e$, -$P(O)_2OR^e$, -CN, or -NO_2.

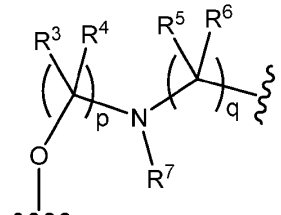
[0314] In some embodiments, the portion  is of the formula

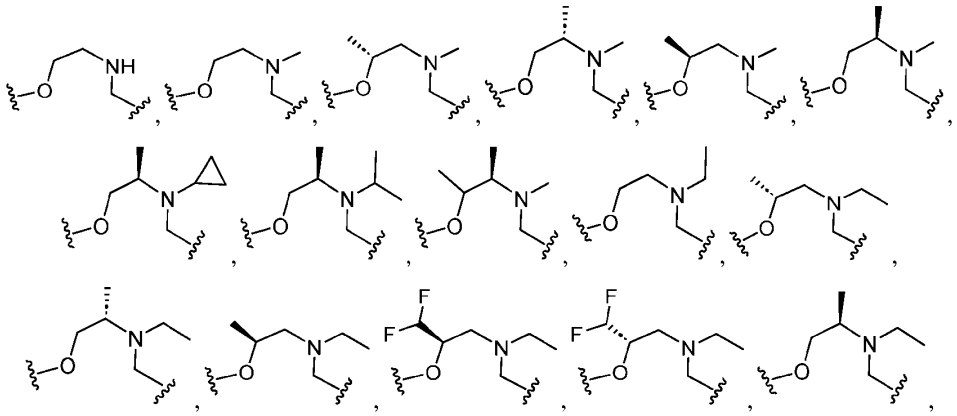


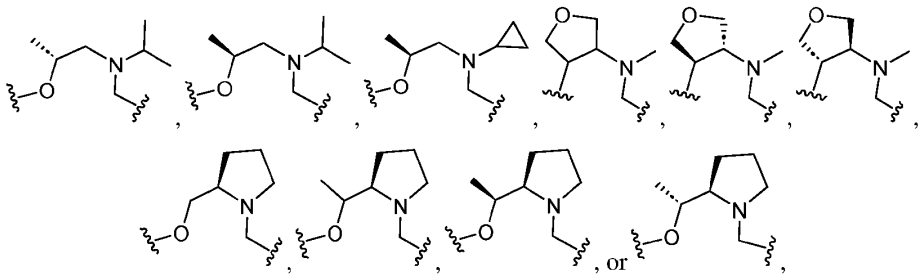


, or

[0315] wherein each "~~~" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

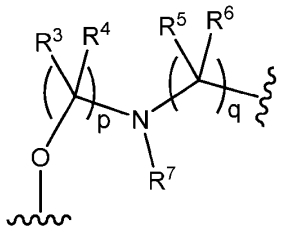
[0316] In some embodiments, the portion  is of the formula



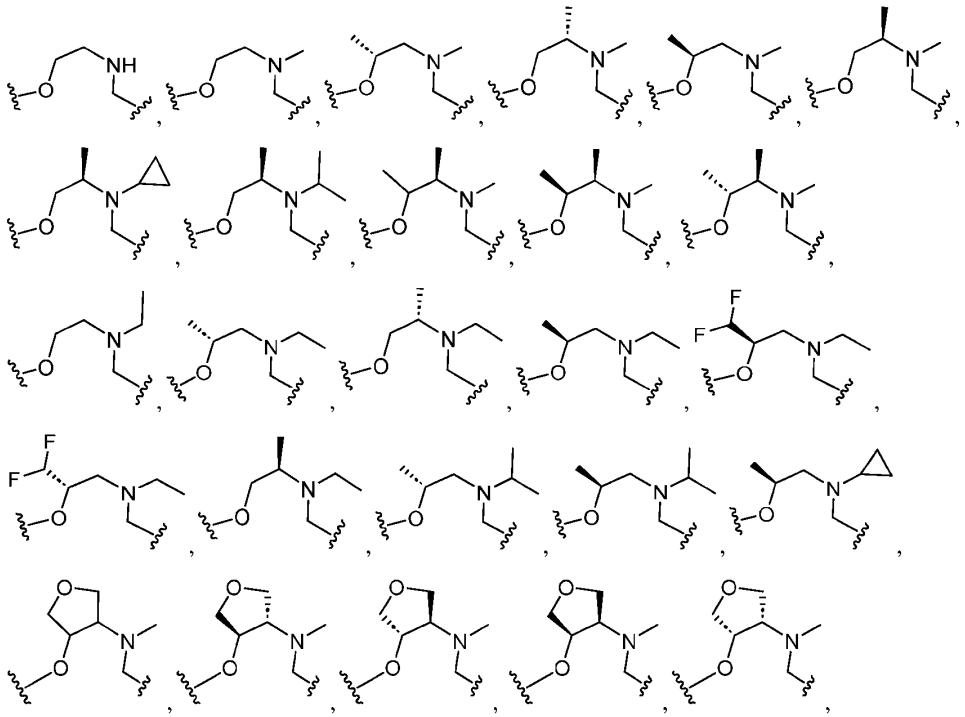


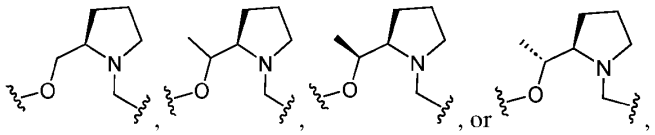
[0317] wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

[0318] In some embodiments, the portion



is of the formula





wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

[0319] In certain aspects, the compounds of the present disclosure are macrocycles. For example, in the compounds of Formula I, it will be appreciated that ring A and ring B are connected by a linker portion as described herein, wherein the linker portion comprises a chain of atoms, including but not limited to C, N, O, and S to provide a macrocycle.

[0320] In some embodiments, the disclosure provides a compound selected from the group consisting of (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0321] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0322] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0323] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0324] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0325] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0326] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0327] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0328] 2-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0329] 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0330] 2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0331] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0332] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0333] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0334] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10,19-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0335] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0336] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0337] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0338] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0339] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0340] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0341] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0342] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0343] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0344] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0345] {[(10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0346] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0347] (2*S*)-2-[(4a*R*,7a*S*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0348] (2*S*)-2-[(13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0349] (2*S*)-2-[(4a*S*,7a*R*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0350] (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0351] {[(10*S*,17*E*)-6,8,10,12,14-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0352] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0353] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0354] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0355] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol;

[0356] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0357] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0358] 2-{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0359] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0360] (2*S*)-1-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0361] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0362] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0363] {[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0364] {[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0365] (2*S*)-1-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0366] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0367] (2*S*)-1-[(11*R*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0368] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0369] (2*S*)-1-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0370] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,11,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0371] (2*S*)-2-[(11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0372] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0373] (2*R*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0374] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0375] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0376] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0377] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0378] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0379] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0380] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0381] (2*S*)-1-[(10*R*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0382] (2*S*)-1-[(10*S*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0383] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol; and

[0384] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0385] (2*S*)-1-[(4a*R*,7a*R*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

[0386] (2*S*)-1-[(4a*S*,7a*S*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

[0387] (2*S*)-1-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

[0388] (2*S*)-1-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

[0389] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol; and

[0390] 1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-one;

[0391] or a pharmaceutically acceptable salt thereof.

[0392] In some embodiments, the disclosure provides a compound selected from the group consisting of (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0393] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0394] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0395] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0396] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0397] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0398] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0399] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0400] 2-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0401] 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0402] 2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0403] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0404] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0405] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0406] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10,19-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0407] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0408] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0409] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0410] (2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0411] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0412] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0413] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0414] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0415] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0416] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0417] {[(10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0418] (2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0419] (2*S*)-2-[(4a*R*,7a*S*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0420] (2*S*)-2-[(13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0421] (2*S*)-2-[(4a*S*,7a*R*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;

[0422] (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0423] {[(10*S*,17*E*)-6,8,10,12,14-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0424] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0425] (2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0426] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0427] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol;

[0428] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0429] (2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0430] 2-{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0431] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0432] (2*S*)-1-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0433] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0434] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0435] {[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0436] {[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0437] (2*S*)-1-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0438] (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0439] (2*S*)-1-[(11*R*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0440] {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0441] (2*S*)-1-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0442] (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,11,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0443] (2*S*)-2-[(11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0444] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0445] (2*R*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0446] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0447] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0448] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0449] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0450] (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0451] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0452] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

[0453] (2*S*)-1-[(10*R*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0454] (2*S*)-1-[(10*S*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

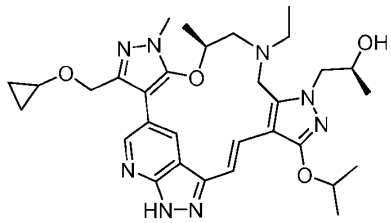
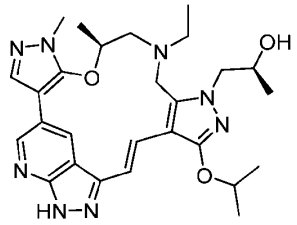
[0455] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

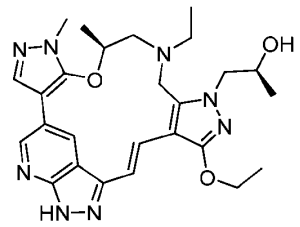
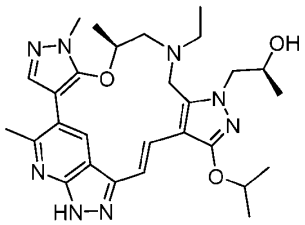
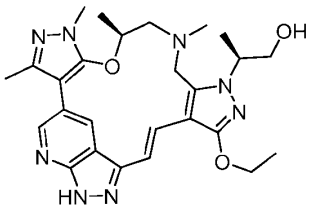
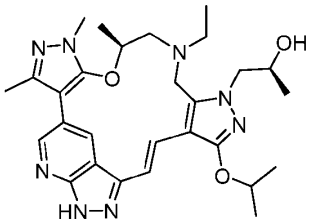
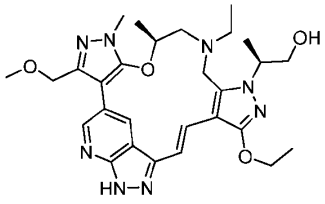
[0456] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol; and

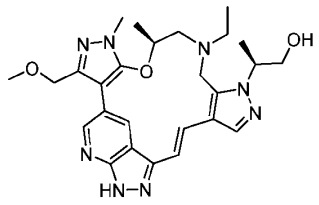
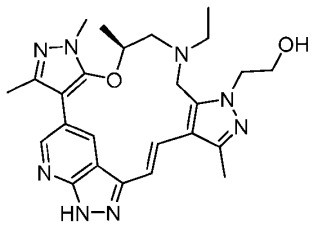
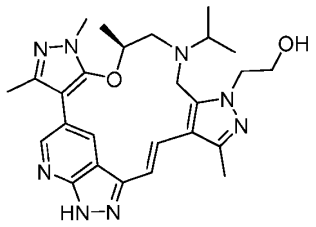
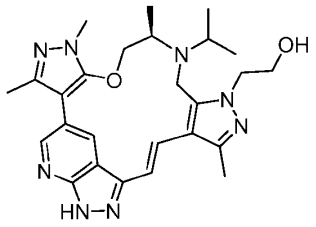
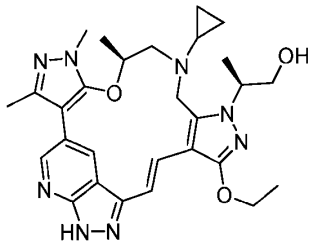
[0457] (11*R*,17*E*)-7,11,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-(azenometheno)dipyrazolo[3,4-*f*:3',4'-*j*][1,2,3]triazolo[4,5-*n*][1,4]oxazacyclopentadecine

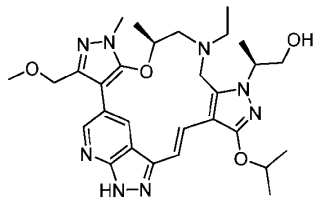
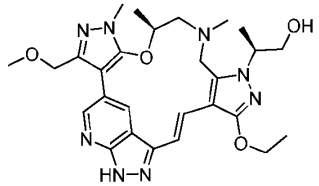
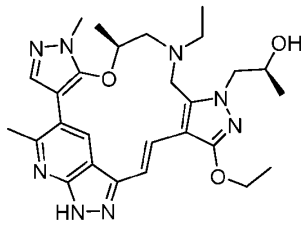
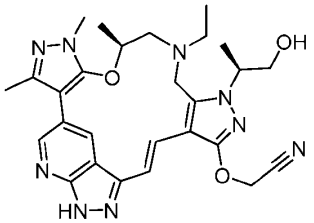
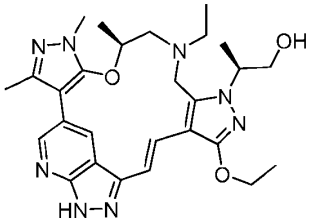
[0458] or a pharmaceutically acceptable salt thereof.

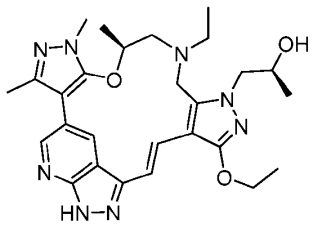
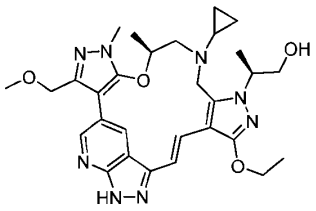
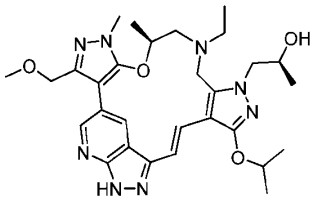
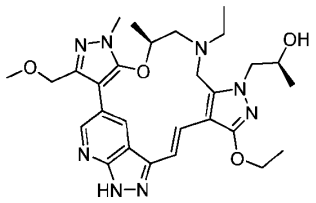
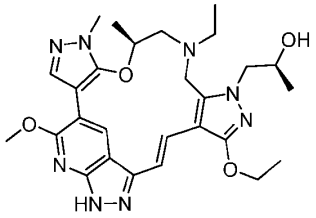
[0459] The following represent illustrative embodiments of compounds of Formula (I-VIII):

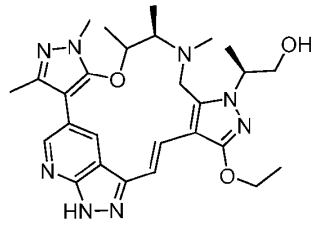
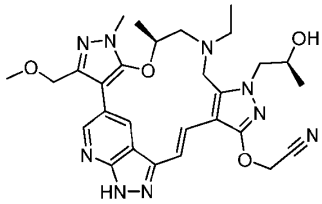
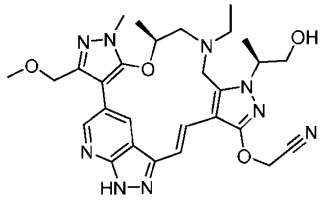
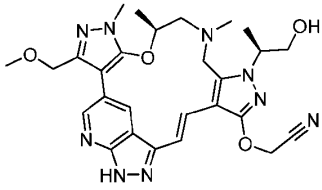
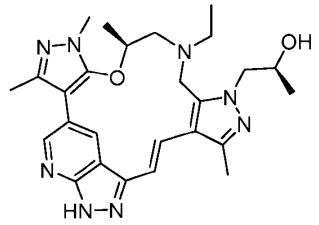
Ex.#	Structure (ChemDraw)	Name (ACD)
1		(2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
2		(2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol

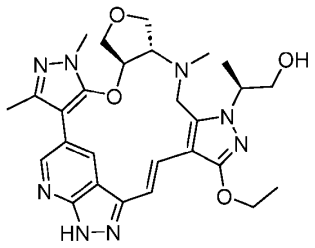
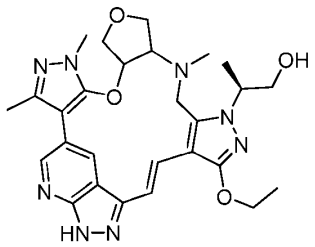
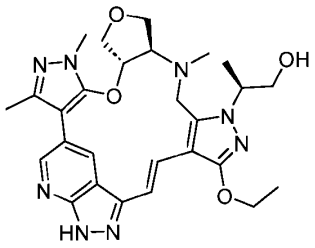
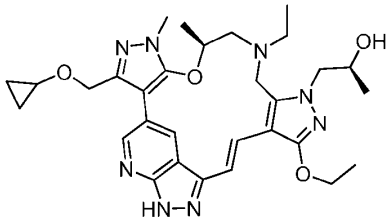
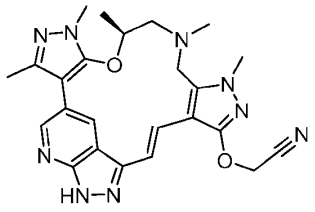
Ex.#	Structure (ChemDraw)	Name (ACD)
3		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
4		(2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
5		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
6		(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
7		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

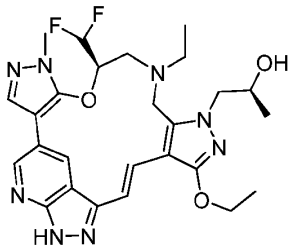
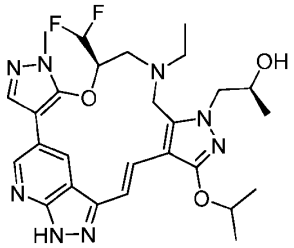
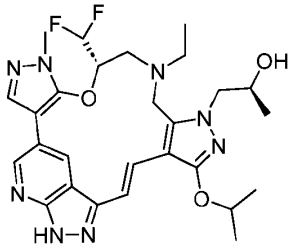
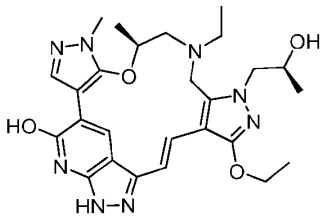
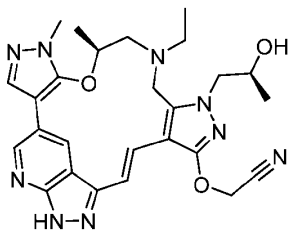
Ex.#	Structure (ChemDraw)	Name (ACD)
8		(2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
9		2-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
10		2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
11		2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
12		(2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

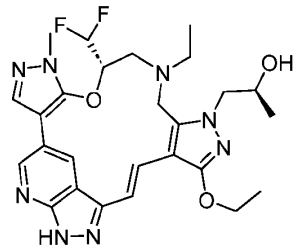
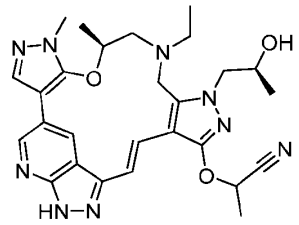
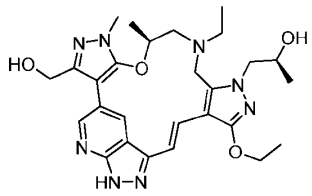
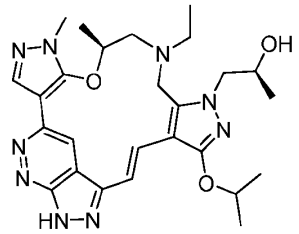
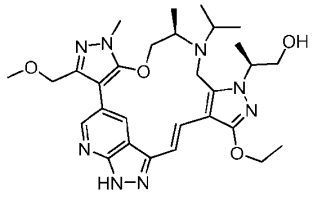
Ex.#	Structure (ChemDraw)	Name (ACD)
13		(2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
14		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
15		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10,19-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
16		{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
17		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

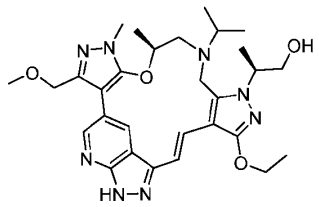
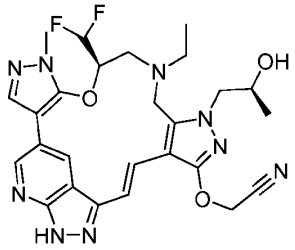
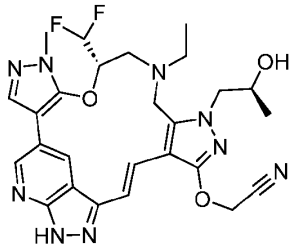
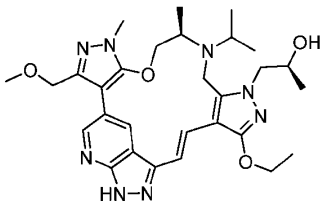
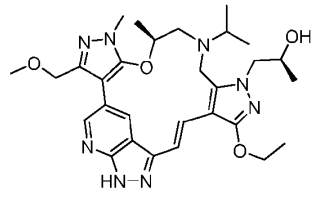
Ex.#	Structure (ChemDraw)	Name (ACD)
18		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
19		(2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
20		(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
21		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
22		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol

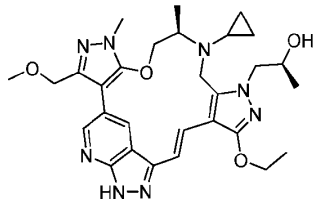
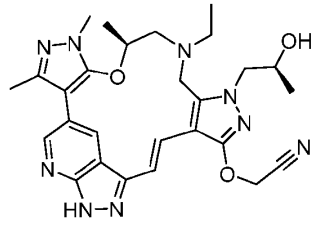
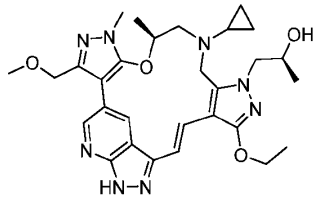
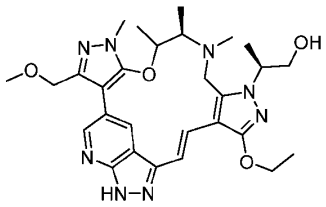
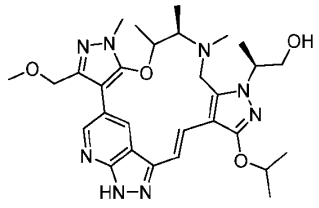
Ex.#	Structure (ChemDraw)	Name (ACD)
23		(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
24		{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
25		{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
26		{[(10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
27		(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol

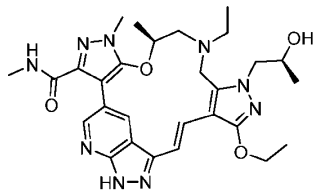
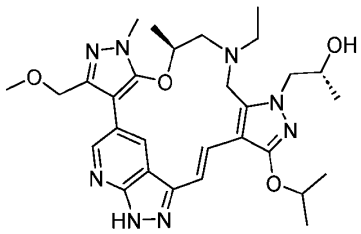
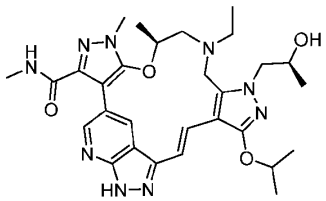
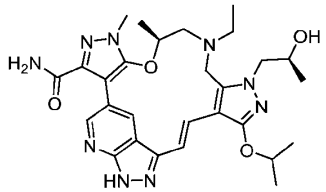
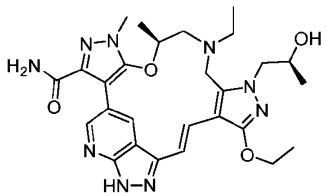
Ex.#	Structure (ChemDraw)	Name (ACD)
28		(2*S*)-2-[(4a*R*,7a*S*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol
29		(2*S*)-2-[(13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol
30		(2*S*)-2-[(4a*S*,7a*R*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol
31		(2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
32		{[(10*S*,17*E*)-6,8,10,12,14-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile

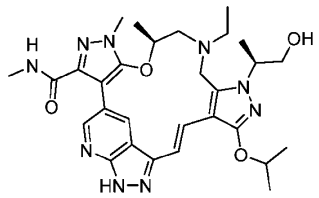
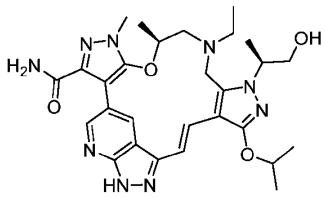
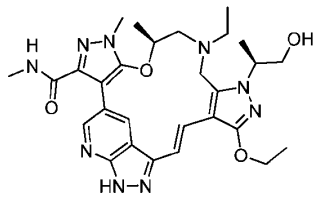
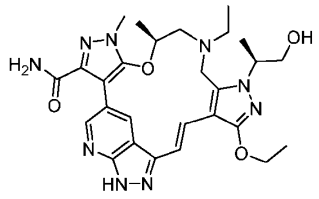
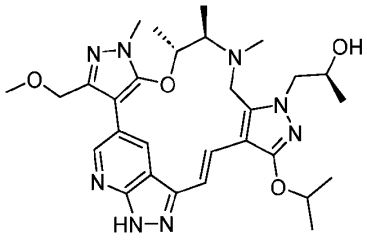
Ex.#	Structure (ChemDraw)	Name (ACD)
33		(2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
34		(2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
35		(2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
36		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol
37		{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile

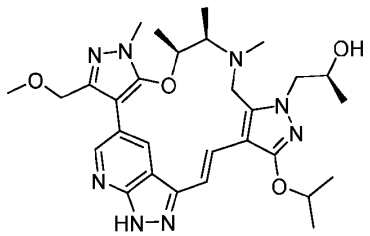
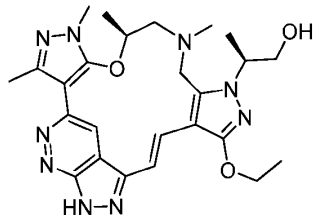
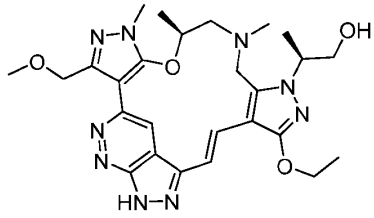
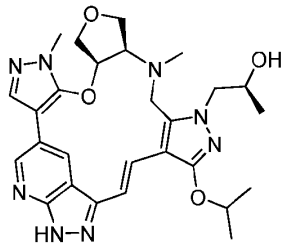
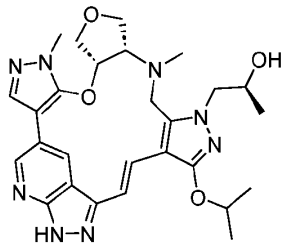
Ex.#	Structure (ChemDraw)	Name (ACD)
38		(2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
39		2-{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile
40		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
41		(2*S*)-1-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol
42		(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

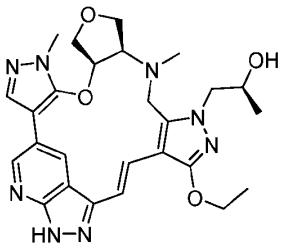
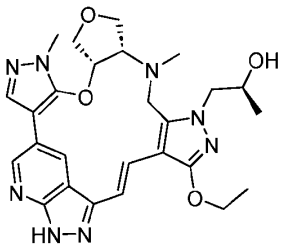
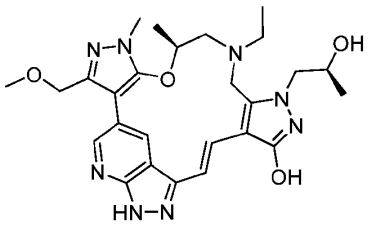
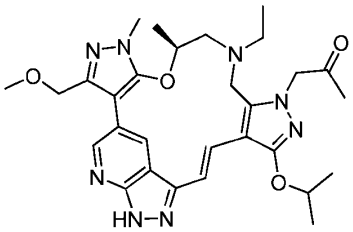
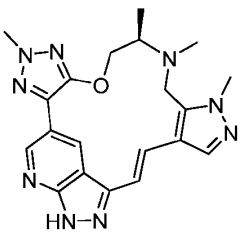
Ex.#	Structure (ChemDraw)	Name (ACD)
43		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
44		{[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
45		{[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
46		(2*S*)-1-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
47		(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol

Ex.#	Structure (ChemDraw)	Name (ACD)
48		(2*S*)-1-[(11*R*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
49		{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
50		(2*S*)-1-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
51		(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,11,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
52		(2*S*)-2-[(11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

Ex.#	Structure (ChemDraw)	Name (ACD)
53		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
54		(2*R*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
55		(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
56		(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
57		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide

Ex.#	Structure (ChemDraw)	Name (ACD)
58		(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
59		(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
60		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
61		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide
62		(2*S*)-1-[(10*R*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol

Ex.#	Structure (ChemDraw)	Name (ACD)
63		(2*S*)-1-[(10*S*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
64		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
65		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
66		(2S)-1-[(4aR,7aR,13E)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10H-17,19-(azenometheno)furo[3,4-b]tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-10-yl]propan-2-ol
67		(2S)-1-[(4aS,7aS,13E)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10H-17,19-(azenometheno)furo[3,4-b]tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-10-yl]propan-2-ol

Ex.#	Structure (ChemDraw)	Name (ACD)
68		(2S)-1-[(4aR,7aR,13E)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10H-17,19-(azenometheno)furo[3,4-b]tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-10-yl]propan-2-ol
69		(2S)-1-[(4aS,7aS,13E)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10H-17,19-(azenometheno)furo[3,4-b]tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-10-yl]propan-2-ol
70		(10S,17E)-12-ethyl-14-[(2S)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8H-3,5-(azenometheno)tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-16-ol
71		1-[(10S,17E)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14H-3,5-(azenometheno)tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecin-14-yl]propan-2-one
72		(11*R*,17*E*)-7,11,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-(azenometheno)dipyrazolo[3,4-*f*:3',4'-*j*][1,2,3]triazolo[4,5-*n*][1,4]oxazacyclopentadecine

and pharmaceutically acceptable salts thereof.

[0460] Those skilled in the art will recognize that the species listed or illustrated herein are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

PHARMACEUTICAL COMPOSITIONS

[0461] For treatment purposes, pharmaceutical compositions comprising the compounds described herein may further comprise one or more pharmaceutically-acceptable excipients. A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In preferred embodiments, pharmaceutical compositions according to the disclosure are sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art.

[0462] Sterile compositions are also contemplated by the disclosure, including compositions that are in accord with national and local regulations governing such compositions.

[0463] 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 disclosure may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. Preferably, the compositions are formulated for intravenous or oral administration.

[0464] For oral administration, the compounds the disclosure 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 disclosure may be formulated to yield a dosage of, *e.g.*, from about 0.1 mg to 1 g daily, or about 1 mg to 50 mg daily, or about 50 to 250 mg daily, or about 250 mg to 1 g daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and

calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0465] 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.

[0466] 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.

[0467] For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the agents of the disclosure 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 μg/kg/minute of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0468] 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.

[0469] For topical applications, the compounds of the present disclosure 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 disclosure may utilize a patch formulation to effect transdermal delivery.

[0470] As used herein, the terms "treat" or "treatment" encompass both "preventative" and "curative" treatment. "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. "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, 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.

[0471] The term "subject" refers to a mammalian patient in need of such treatment, such as a human.

[0472] Exemplary diseases include cancer, pain, neurological diseases, autoimmune diseases, and inflammation. As used herein, the term "cancer" includes, but is not limited to, ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER^+ breast cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia, acute myeloid leukemia (AML), congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, and serous and clear cell endometrial cancer. In some embodiments, cancer includes, lung cancer, colon cancer, breast cancer, prostate cancer, hepatocellular carcinoma,

renal cell carcinoma, gastric and esophago-gastric cancers, glioblastoma, head and neck cancers, inflammatory myofibroblastic tumors, and anaplastic large cell lymphoma.

[0473] In the inhibitory methods of the disclosure, an "effective amount" means an amount sufficient to inhibit the target protein. Measuring such target modulation may be performed by routine analytical methods such as those described below. Such modulation is useful in a variety of settings, including *in vitro* assays. In such methods, the cell is preferably a cancer cell with abnormal signaling due to a mutation of ALK, PIM, and/or CLK as described herein.

[0474] In treatment methods according to the disclosure, an "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic benefit in subjects needing such treatment, such as those described herein having a disease, such as cancer, including those associated with aberrant ALK, including oncogenic driver mutations such as those described herein, and ALK resistance mutations, such as those described herein, aberrant PIM kinases, and/or aberrant CLK kinases. Effective amounts or doses of the compounds of the disclosure 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 exemplary dose is in the range of about from about 0.1 mg to 1 g daily, or about 1 mg to 50 mg daily, or about 50 to 250 mg daily, or about 250 mg to 1 g daily. The total dosage may be given in single or divided dosage units (e.g., BID, TID, QID).

[0475] As used herein, "ALK" refers to anaplastic lymphoma kinase, which along with leukocyte tyrosine kinase (LTK), belongs to the insulin receptor (IR) superfamily of receptor tyrosine kinases. It will be appreciated that ALK refers to the *ALK* gene, the corresponding mRNA transcribed from the *ALK* gene, the protein product of translation of the corresponding mRNA, as well as each of the aforementioned involving the rearrangement or fusion of a portion of ALK with another gene or gene product, including but not limited to NPM, EML4, TPR, TFG, ATIC, CLTC1, TPM4, MSN, ALO17, MYH9, and the like. Furthermore, it will be appreciated that "ALK" refers to mutations in the *ALK* gene, or the ALK protein, that can be the result of acquired resistance mechanisms to treatment with ALK inhibitors, as described above. It will be appreciated that the ALK mutation is not necessarily dependent on the identity of the rearrangement or fusion partner, e.g., EML4, NPM, and the like, and that the mutation can be, for example a missense mutation, an insertion, or a deletion that occurs in the ALK portion of the ALK rearrangement or fusion protein. Examples of mutation sites include, but are not limited to L1196, L1198, G1202, D1203, S1206, T1151, L1152, E1210, F1174, C1156, I1171, V1180, F1245, G1269, R1275, and the like, and combinations thereof. Examples of

ALK mutations include but are not limited to L1196M, G1202R, C1156Y, D1203N, G1202 deletion, E1210K, S1206C, F1174C, F1174L, F1174S, F1174V, F1245C, G1269A, G1269S, I1171N, L1152P, L1152R, L1198F, R1275Q, S1206R, T1151-L1152insT, T1151M, V1180L, and the like, and combinations thereof. Examples of multiple ALK mutations include but are not limited to E1210K/D1203N, E1210K/S1206C, L1198F/C1156Y, L1198F/G1202R, L1198F/L1196M, L1196M/G1202R, and the like.

[0476] 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.

DRUG COMBINATIONS

[0477] 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 disclosure or may be included with a compound of the present disclosure 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 disclosure.

[0478] 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 disclosure, 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 ALK inhibitors (e.g., crizotinib), Raf inhibitors (e.g., vemurafenib), VEGFR inhibitors (e.g., sunitinib), 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 disclosure may additional 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.

CHEMICAL SYNTHESIS METHODS

[0479] The following examples are offered to illustrate but not to limit the disclosure. One of skill in the art will recognize that the following synthetic reactions and schemes may be modified by choice of suitable starting materials and reagents in order to access other compounds of Formula (I)-(VIII).

[0480] Abbreviations: 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
mL	milliliters
MHz	megahertz
ppm	parts per million
δ	chemical shift
s	singlet
d	doublet
t	triplet
q	quartet
quin	quintet
br	broad
m	multiplet
Hz	hertz
THF	tetrahydrofuran
°C	degrees Celsius
FA	Formic acid
PE	petroleum ether
EtOAc or EA	ethyl acetate
R_f	retardation factor
N	normal
J	coupling constant
DMSO-d_6	deuterated dimethyl sulfoxide

n-BuOH	n-butanol
t-BuOH	*Tert*-Butanol
AcOH	Acetic Acid
MeTHF	2-methyltetrahydrofuran
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
MeCN (ACN)	Acetonitrile
Hex	hexanes
DMAc	Dimethylacetamide
DIEA, DIPEA, or Hunig's base	N,N-diisopropylethylamine
TMS	trimethylsilyl
TBS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
min	minutes
hr	hours
Me	methyl
Et	ethyl
i-Pr	isopropyl
TLC	thin layer chromatography
M	molar
Compd#	compound number
MS	mass spectrum
m/z	mass-to-charge ratio
Ms	methanesulfonyl
Boc	tert-butyloxycarbonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Tos	toluenesulfonyl
DMAP	4-(dimethylamino)pyridine
mM	millimolar
µM or uM	micromolar
RT	Room Temperature
ATP	adenosine triphosphate
IC_{50}	half maximal inhibitory concentration
U/mL	units of activity per milliliter
KHMDS	potassium bis(trimethylsilyl)amide
DIAD	diisopropyl azodicarboxylate
DBAD	di-tert-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DPPA	diphenyl phosphoryl azide

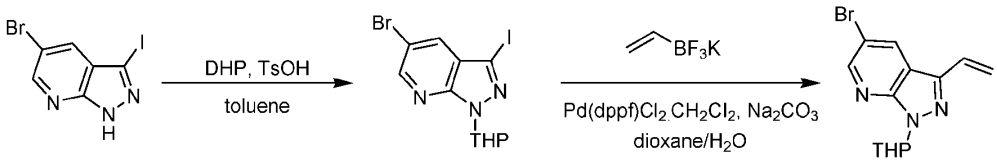
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
MOM	methoxymethyl
MTBE	Methy *tert*-Butyl Ether
SEM	[2-(Trimethylsilyl)ethoxy]methyl acetal
mCPBA	*Meta*-Chloroperoxy benzoic acid
oxone	Potassium peroxymonosulfate
PPTS	Pyridinium p-Toluenesulfonate
p-TSA	*Para*-Tolylsulfonic acid
PPh_3	Triphenyl phosphine
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(OAc)_2$	palladium(II) acetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dtbpf)Cl_2$	[1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)
$Pd(amphos)Cl_2$	Dichlorobis[di-tert-butyl(4-dimethylaminophenyl)phosphine]palladium(II)
tBuBrettphos Pd G3	tert-BuBrettPhos-Pd-G3; [(2-Di-tert-butylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
TBAF	Tetrabutylammonium fluoride
TBAC	Tetrabutylammonium chloride
TBAB	Tetrabutylammonium bromide
TBAHS	Tetrabutylammonium hydrogensulfate
BPD or B_2pin_2 or $(Bpin)_2$	Bis(pinacolato)diboron; 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane
DHP	3,4-dihydropyran
THP	tetrahydropyran
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
$LiBH_4$	Lithium borohydride
$LiAlH_4$ or LAH	Lithium aluminium hydride
DIBAL-H	Diisobutylaluminium hydride
Ms_2O	Methanesulfonic anhydride

[0481] The examples described herein are used to prepare the starting materials, intermediates and products of the disclosure. The materials, intermediates and products are either commercially available or prepared via conventional chemistry from commercially available materials. Examples of commercially available materials that can be used in the syntheses of the disclosure include 5-bromo-3-iodo-1H-pyrazolo[3,4-b]pyridine; 5-bromo-2-hydroxy-6-methylnicotinonitrile; 6-chloro-1*H*-pyrazolo[3,4-*b*]pyridine; 5-chloro-1*H*-pyrazolo[3,4-*c*]pyridazin-3-amine; methyl 4-methoxy-3-oxo-butanoate; ethyl 4-chloro-3-oxobutanoate; cyclopropanol; 5-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine;

(2*R*)-2-methyloxirane; (2S)-2-methyloxirane; methyl amine; ethanamine; isopropyl amine; tert-butyl (*R*)-(1-oxopropan-2-yl)carbamate; *tert*-butyl (*R*)-(2-hydroxypropyl)carbamate; ethyl 3-hydroxy-1H-pyrazole-5-carboxylate; 2-iodopropane; 2-iodoacetonitrile; iodoethane; ethyl (2*S*)-2-hydroxypropanoate; ethyl (2*R*)-2-hydroxypropanoate; dimethyl but-2-ynedioate; ethyl 3-hydroxy-1*H*-pyrazole-5-carboxylate; methyl 1H-pyrazole-5-carboxylate; methyl 3-methyl-1*H*-pyrazole-5-carboxylate; methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate; 4,5-dibromo-2-methyl-2H-1,2,3-triazole; tert-butyl (R)-(1-hydroxypropan-2-yl)carbamate; methyl 1-methyl-1H-pyrazole-5-carboxylate. Those skilled in the art will recognize that the commercially available materials listed or illustrated herein are not exhaustive, and that additional commercially available materials may also be selected.

[0482] Intermediate Synthesis:

[0483] Preparation of 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (I-1-1).

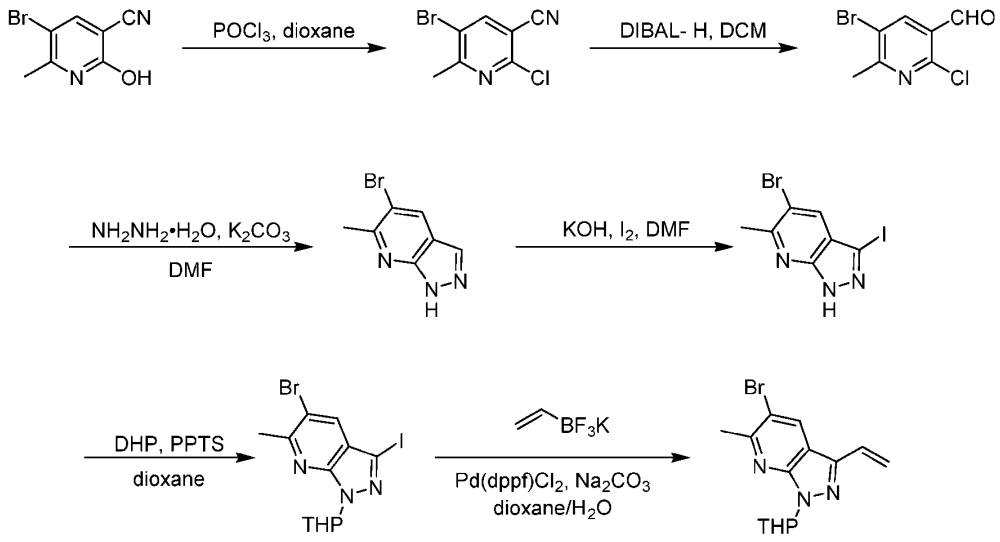


I-1-1

[0484] Step 1. To a solution of 5-bromo-3-iodo-1H-pyrazolo[3,4-b]pyridine (20.0 g, 61.7 mmol, 1 eq) and DHP (7.79 g, 92.6 mmol, 8.47 mL, 1.5 eq) in toluene (200 mL) was added 4-methylbenzenesulfonic acid (2.13 g, 12.4 mmol, 0.2 eq). The mixture was stirred at 90 °C for 16 h. On completion, the reaction was filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (220 g silica gel column, THF in PE 0-100%) to give 5-bromo-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (21.1 g, 51.8 mmol, 83.9% yield) as a yellow oil. LCMS: *m/z* 409.7 (M+1).

[0485] Step 2. To a solution of 5-bromo-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (21.1 g, 51.8 mmol, 1 eq), potassium vinyltrifluoroborate (7.63 g, 57 mmol, 1.1 eq) in dioxane (210 mL) and H_2O (42 mL) was added Na_2CO_3 (16.5 g, 155 mmol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (4.23 g, 5.18 mmol, 0.1 eq) under N_2. The mixture was stirred at 80 °C for 30 h under N_2. On completion, the mixture was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (80 g silica gel column, EA in PE 0-100 %) to give 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (8.10 g, 26.3 mmol, 50.7% yield) as a light yellow oil.

[0486] Preparation of 5-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (I-1-2).



I-1-2

[0487] Step 1. To a solution of 5-bromo-2-hydroxy-6-methylnicotinonitrile (5.00 g, 23.4 mmol, 1 eq) in dioxane (40 mL) was added $POCl_3$ (12.6 g, 82.1 mmol, 3.5 eq). The mixture was stirred at 100 °C for 16 h. On completion, the reaction mixture was concentrated in vacuo to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 20:1 ~ 4:1) to give 5-bromo-2-chloro-6-methylnicotinonitrile (2.00 g, 7.78 mmol, 33% yield) as a yellow solid.

[0488] Step 2. To a solution of 5-bromo-2-chloro-6-methylnicotinonitrile (2.00 g, 8.64 mmol, 1 *eq)* in DCM (100 mL) was added DIBAL-H (1 M, 10.5 mL, 1.2 *eq*) at -78 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched with water (100 mL), extracted with DCM (3 × 50 mL), and the combined organic layers were concentrated in *vacuo* to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 1:0 ~ 20:1) to give 5-bromo-2-chloro-6-methylnicotinaldehyde (2.00 g, 8.53 mmol, 98% yield) as a yellow solid.

[0489] Step 3. To a solution of 5-bromo-2-chloro-6-methylnicotinaldehyde (2.00 g, 8.53 mmol, 1 eq) in DMF (3 mL) was added $NH_2NH_2.H_2O$ (3.20 g, 63.9 mmol, 7.5 eq) and K_2CO_3 (2.36 g, 17.0 mmol, 2 eq). On completion, the mixture was quenched with water (20 mL), extracted with EA (15 mL × 3), and the combined organic layers were washed with brine (15 mL × 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 1:0 ~ 1:1) to give 5-bromo-6-methyl-1*H*-

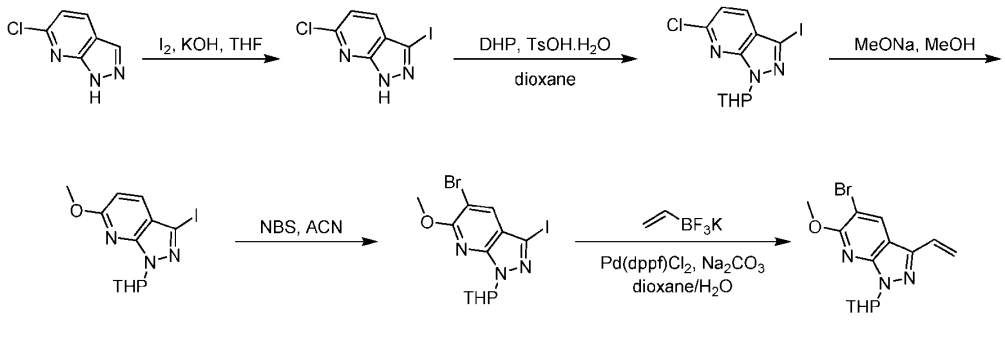
pyrazolo[3,4-*b*]pyridine (1.02 g, 4.33 mmol, 50% yield) as a yellow solid. LCMS: *m/z* 211.9 (M+1)

[0490] Step 4. To a solution of 5-bromo-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (1.02 g, 4.81 mmol, 1 eq) in DMF (10 mL) was added I_2 (1.59 g, 6.25 mmol, 1.3 eq) and KOH (809 mg, 14.4 mmol, 3 eq). The mixture was stirred at 25 °C for 2 h. On completion, the reaction was diluted with sat. $Na_2S_2O_3$ (10 mL), extracted with EA (3 × 10 mL), and concentrated in vacuo to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 10:1 ~ 2:1) to give 5-bromo-3-iodo-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (910 mg, 2.67 mmol, 55% yield) as a yellow solid. LCMS: *m/z* 337.8 (M+1).

[0491] Step 5. To a solution of 5-bromo-3-iodo-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (910 mg, 2.69 mmol, 1 eq) in dioxane (1 mL) was added DHP (453 mg, 5.39 mmol, 2 eq) and PPTS (102 mg, 0.538 mmol, 0.2 eq). The mixture was stirred at 80 °C for 1 h. On completion, the reaction was concentrated in vacuo to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 10:1 ~ 2:1) to give 5-bromo-3-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (1.00 g, 2.32 mmol, 86% yield) as a yellow solid. LCMS: *m/z* 421.8 (M+1).

[0492] Step 6. To a solution of 5-bromo-3-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (1.00 g, 2.37 mmol, 1 eq), potassium vinyltrifluoroborate (525 mg, 3.55 mmol, 1.5 eq) in dioxane (10 mL) and H_2O (2 mL) was added $Pd(dppf)Cl_2$ (173 mg, 0.236 mmol, 0.1 eq) and Na_2CO_3 (753 mg, 7.11 mmol, 3 eq). The mixture was stirred at 80 °C for 1 h under N_2 atmosphere. On completion, the reaction was concentrated in vacuo to give a residue. The residue was purified by SiO_2 column chromatography (PE: EA = 1:0 ~ 10:1) to give 5-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (600 mg, 1.84 mmol, 77% yield) as a yellow solid.

[0493] Preparation of 5-bromo-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-*b*]pyridine (I-1-3)



I-1-3

[0494] Step 1. To a solution of 6-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (10.0 g, 65.1 mmol, 1 eq) in THF (100 mL) was added KOH (10.9 g, 195 mmol, 3 eq) and I_2 (16.5 g, 65.1 mmol, 13.1 mL, 1 eq). The mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was quenched by addition sat. $Na_2S_2O_3$ (300 mL) at 0 °C, then diluted with H_2O (200 mL), and extracted with ethyl acetate (8 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 86/14) to give 6-chloro-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (6.00 g, 21.2 mmol, 32% yield, 99% purity) as a white solid. LCMS: *m/z* 279.8 (M+1)

[0495] Step 2. To a solution of 6-chloro-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (6.00 g, 21.4 mmol, 1 eq) in dioxane (60 mL) was added DHP (3.61 g, 42.9 mmol, 3.93 mL, 2 eq) and TsOH.H_2O (816 mg, 4.29 mmol, 0.2 eq). The mixture was stirred at 60 °C for 2 hrs. On completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 1/1) to give 6-chloro-3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine (6.70 g, 18.3 mmol, 85% yield, 99% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.02 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 5.99 - 5.83 (m, 1H), 3.93 (d, J = 11.2 Hz, 1H), 3.76 - 3.65 (m, 1H), 2.46 - 2.34 (m, 1H), 2.06 - 1.97 (m, 1H), 1.97 - 1.88 (m, 1H), 1.83 - 1.69 (m, 1H), 1.64 - 1.51 (m, 2H).

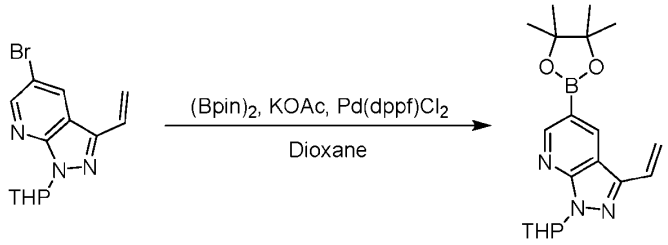
[0496] Step 3. To a solution of 6-chloro-3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine (6.70 g, 18.4 mmol, 1 eq) in MeOH (70 mL) was added NaOMe (5.4 M, 6.83 mL, 2 eq). The mixture was stirred at 80 °C for 2 hrs. On completion, the reaction mixture was concentrated in vacuo to give a residue. Then the residue was diluted with H_2O (100 mL) and extracted with Ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (3 × 100mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 100/1 to 10/1) to give 3-iodo-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (6.40 g, 17.4 mmol, 94% yield, 98%purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 7.75 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 5.91 - 5.78 (m, 1H), 3.97 (s, 3H), 3.92 (s, 1H), 3.71 - 3.58 (m, 1H), 2.48 - 2.39 (m, 1H), 2.02 (d, *J* = 12.8 Hz, 1H), 1.93 - 1.84 (m, 1H), 1.80 - 1.67 (m, 1H), 1.64 - 1.51 (m, 2H).

[0497] Step 4. To a solution of 3-iodo-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (5.80 g, 16.1 mmol, 1 eq) in ACN (60 mL) was added NBS (3.45 g,

19.3 mmol, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was concentrated in vacuo to give a residue. And then the crude product was triturated with ACN (50 mL) at 25 °C for 30 mins to give 5-bromo-3-iodo-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (6.57 g, 15.0 mmol, 92% yield) as a white solid. LCMS: *m/z* 439.8 (M+2).

[0498] Step 5 was conducted according to procedure described in the final step of the preparation of I-1-2 with stirring for 2 hours at 80 °C to afford 5-bromo-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-*b*]pyridine (I-1-3).

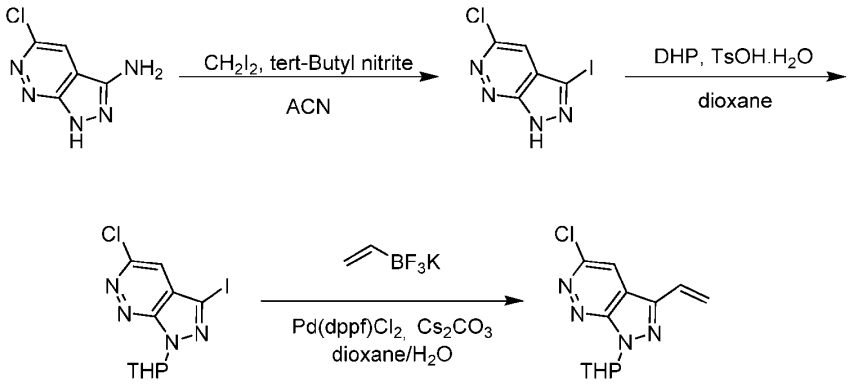
[0499] Preparation of 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (I-1-4)



I-1-1 I-1-4

[0500] Step 1. To a solution of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-b]pyridine (3.00 g, 9.73 mmol, 1 *eq*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.94 g, 19.4 mmol, 2 *eq*) in dioxane (30 mL) was added KOAc (1.91 g, 19.4 mmol, 2 *eq*) and Pd(dppf)Cl_2 (712 mg, 0.973 mmol, 0.1 *eq*). The mixture was stirred at 90 °C for 1 hr under N_2. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 1:0 to 1:1) to give 1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-pyrazolo[3,4-b]pyridine (3.20 g, 9.01 mmol, 92% yield) as a colorless oil.

[0501] Preparation of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-c]pyridazine (I-1-5)



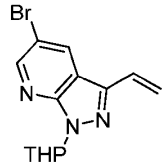
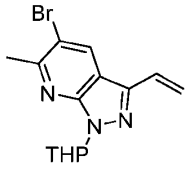
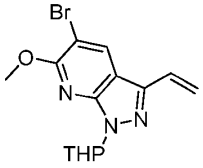
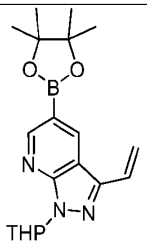
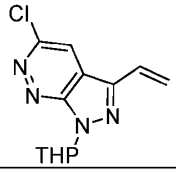
I-1-5

[0502] Step 1. To a solution of 5-chloro-1*H*-pyrazolo[3,4-*c*]pyridazin-3-amine (5.60 g, 33.0 mmol, 1 *eq*) in ACN (56 mL) was added tert-butyl nitrite (5.11 g, 49.0 mmol, 1.5 *eq*) and diiodomethane (17.7 g, 66.0 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH= 1/0 to 10/1) to give 5-chloro-3-iodo-1*H*-pyrazolo[3,4-*c*]pyridazine (4.50 g, 16.0 mmol, 48% yield) as a brown solid. LCMS: *m/z* 280.9 (M+1).

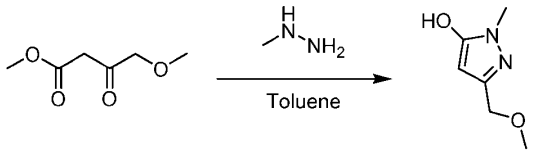
[0503] Step 2. To a solution of 5-chloro-3-iodo-1H-pyrazolo[3,4-c]pyridazine (4.1 g, 14.6 mmol, 1 *eq*) in dioxane (41 mL) was added DHP (2.46 g, 29.2 mmol, 2 *eq*) and $TsOH.H_2O$ (556 mg, 2.92 mmol, 0.2 *eq*). The mixture was stirred at 70 °C for 2 hours. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 5/1) to give 5-chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1*H*-pyrazolo[3,4-c]pyridazine (3.00 g, 8.00 mmol, 56% yield) as a yellow solid. LCMS: *m/z* 365.0 (M+1).

[0504] Step 3. A mixture of 5-chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1*H*-pyrazolo[3,4-c]pyridazine (3.00 g, 8.00 mmol, 1 *eq*), potassium vinyltrifluoroborate (1.21 g, 9.00 mmol, 1.1 *eq*), Cs_2CO_3 (8.04 g, 24.0 mmol, 3 *eq*) and $Pd(dppf)Cl_2$ (602 mg, 0.822 mmol, 0.1 *eq*) in dioxane (30 mL) and H_2O (6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 1 hour under N_2 atmosphere. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 8/1) to give 5-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-c]pyridazine (1.50 g, 5.67 mmol, 69% yield) as a white solid.

[0505] Intermediate Table 1.

Int. #	Structure	*m/z*	^{1}H NMR
I-1-1		309.8	(400 MHz, CDCl3-d) δ = 8.57 (d, J = 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 7.95 - 7.81 (m, 2H), 7.42 - 7.36(m, 1H), 6.98 (dd, J = 11.2, 18.0 Hz, 1H), 6.17 - 5.98 (m, 2H), 5.65 - 5.55 (m, 1H), 4.14 - 4.10 (m, 1H), 3.82 (t, J = 2.4, 11.2 Hz, 1H), 2.70 - 2.54 (m, 1H), 2.22 - 2.10 (m, 1H), 2.01 - 1.92 (m, 1H), 1.88 - 1.72 (m, 3H), 1.69 - 1.59 (m, 1H)
I-1-2		237.9	
I-1-3		338.0	(400 MHz, DMSO-d6) δ = 8.74 (s, 1H), 6.96 - 6.83 (m, 1H), 6.17 (d, J = 18.0 Hz, 1H), 5.90 - 5.81 (m, 1H), 5.55 (d, J = 11.6 Hz, 1H), 4.05 (s, 3H), 3.95 (d, J = 12.0 Hz, 1H), 3.74 - 3.60 (m, 1H), 2.48 - 2.39 (m, 1H), 2.03 (d, J = 12.4 Hz, 1H), 1.93 - 1.83 (m, 1H), 1.81 - 1.67 (m, 1H), 1.64 - 1.51 (m, 2H).
I-1-4		356.1	
I-1-5		265.0	

[0506] Preparation of 3-(methoxymethyl)-1-methyl-1*H*-pyrazol-5-ol (I-2-3).

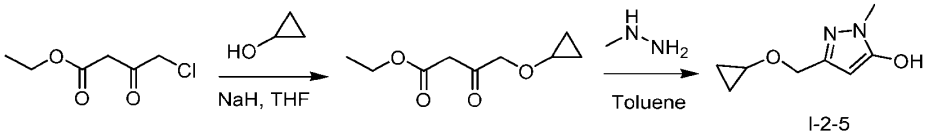


I-2-3

[0507] Step 1. To a solution of methyl 4-methoxy-3-oxo-butanoate (5.00 g, 34.2 mmol, 1 eq) in toluene (150 mL) was added dropwise methylhydrazine (3.94 g, 34.2 mmol, 4.5 mL, 40%

purity, 1 eq) at 0 °C over 0.5 h. The resulting mixture was stirred at 100 °C for 1.5 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF= 1:0 to 1:1) to give 3-(methoxymethyl)-1-methyl-1*H*-pyrazol-5-ol (3.90 g, 27.4 mmol, 80% yield) as a yellow solid.

[0508] Preparation of 3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-ol (I-2-5).

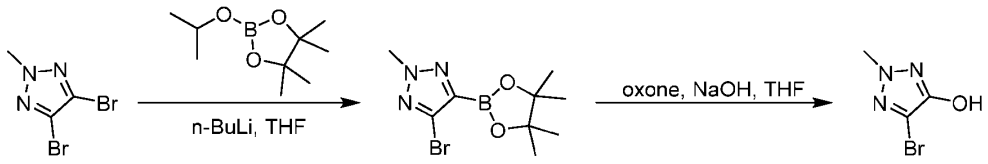


I-2-5

[0509] Step 1. To a solution of ethyl 4-chloro-3-oxobutanoate (21.2 g, 129 mmol, 17.5 mL, 1 *eq*) in THF (150 mL) was added NaH (15.5 g, 387 mmol, 60% purity, 3 *eq*) at 0 °C for 30 minutes. And then, cyclopropanol (15.0 g, 258 mmol, 2 *eq*) was added. The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (200 mL) and extracted with EA (300 mL ×3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 100/1 to 30/1) to give ethyl 4-cyclopropoxy-3-oxobutanoate (15.0 g, 80.5 mmol, 63% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 4.21$ (s, 2H), 4.12 - 4.05 (m, 2H), 3.55 (s, 2H), 3.46 - 3.38 (m, 1H), 1.21 - 1.17 (m, 3H), 0.55 - 0.48 (m, 2H), 0.47 - 0.40 (m, 2H).

[0510] Step 2. To a mixture of methylhydrazine (7.99 g, 69.3 mmol, 9.20 mL, 1.29 *eq*) in toluene (50 mL) at 0 °C under N_2 was added a solution ethyl 4-cyclopropoxy-3-oxobutanoate (10.0 g, 53.7 mmol, 1 *eq*) in toluene (50 mL) drop wise at 0 °C for 30 minutes. The mixture was stirred at 100 °C for 1.5 h. On completion, the reaction mixture was poured into ice-water (100 mL), stirred for 5 minutes, and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 5/1 to 1/1) to give 3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-ol (7.00 g, 41.6 mmol, 77% yield) as a white solid.

[0511] Preparation of 5-bromo-2-methyl-2H-1,2,3-triazol-4-ol (I-2-6)

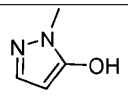
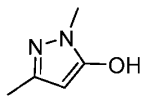
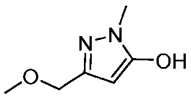
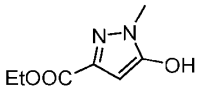
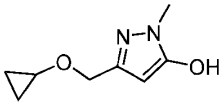
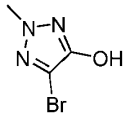


I-2-6

[0512] Step 1. To a solution of 4,5-dibromo-2-methyl-2H-1,2,3-triazole (2.00 g, 8.30 mmol, 1 *eq*) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.86 g, 20.7 mmol, 2.5 *eq*) in THF (20 mL) was added n-BuLi (2.5 M in n-hexane, 5.98 mL, 1.8 *eq*) dropwise at -78 °C under N_2. The resulting mixture was stirred at -78 °C for 1 h. On completion, the mixture was quenched with sat. NH_4Cl (30 mL) and extracted with DCM: MeOH (10:1) (20 mL × 8). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give 4-bromo-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-1,2,3-triazole (2.65 g, crude) as a colorless oil. LCMS: *m/z* 288.0 (M+1).

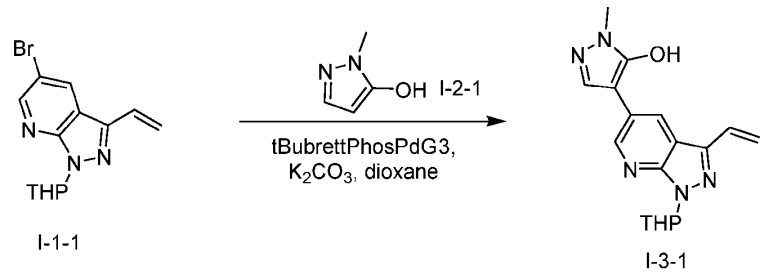
[0513] Step 2. To a solution of 4-bromo-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-1,2,3-triazole (2.55 g, 8.86 mmol, 1 *eq*) in THF (25.5 mL) was added NaOH (1 M in H_2O, 22.1 mL, 2.5 *eq*) and oxone (3.72 g, 22.1 mmol, 2.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with sat. Na_2SO_3 (20 mL), then adjusted pH to 3 with aq. citric acid (10 mL), and extracted with 2-MeTHF (20 mL × 3). The combined organic layers were washed with brine (30 mL× 2), dried over Na_2SO_4, filtered and concentrated to give 5-bromo-2-methyl-triazol-4-ol (1.90 g, crude) as a yellow oil.

[0514] Intermediate Table 2.

Int. #	Structure	*m/z*	^{1}H NMR
I-2-1			commercially available
I-2-2			commercially available
I-2-3			(400 MHz, CDCl3) δ = 4.18 (s, 2H), 3.40 (s, 3H), 3.32 (s, 3H), 3.29 (s, 2H)
I-2-4			commercially available
I-2-5			(400 MHz, DMSO-*d*$_6$) δ = 10.81 (s, 1H), 5.30 (s, 1H), 4.21 (s, 2H), 3.45 (s, 3H), 3.31 - 3.26 (m, 1H), 0.49 - 0.44 (m, 2H), 0.43 - 0.38 (m, 2H)
I-2-6			

[0515] Intermediate Method I-A.

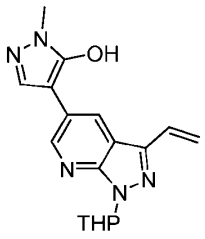
[0516] Preparation of 1-methyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrazol-5-ol (I-3-1).

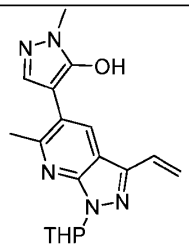
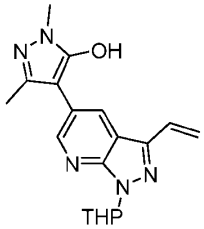
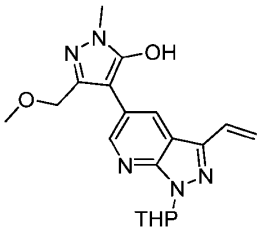
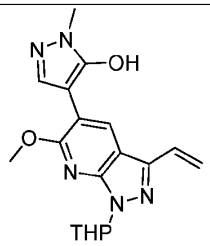
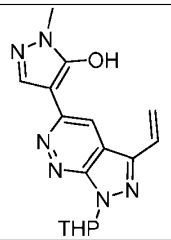


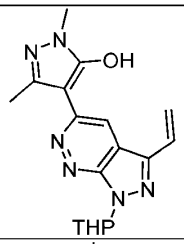
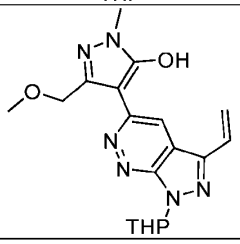
[0517] Step 1. A mixture of 5-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (4.00 g, 12.9 mmol, 1 eq), 1-methyl-1*H*-pyrazol-5-ol (1.53 g, 15.6 mmol, 1.2 eq), tBubrettphos Pd G3 (665 mg, 0.778 mmol, 0.06 eq), K_2CO_3 (5.38 g, 39.0 mmol, 3 eq) in dioxane (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 130 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 10:1) to give 1-methyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrazol-5-ol (635 mg, 1.72 mmol, 13% yield, 88% purity) as a brown solid.

[0518] I-3-2 through 1-3-8 were prepared according to steps described in Intermediate Method I-A using the appropriate intermediates from Intermediate Table 1 and Table 2 as starting materials.

[0519] Intermediate Table 3

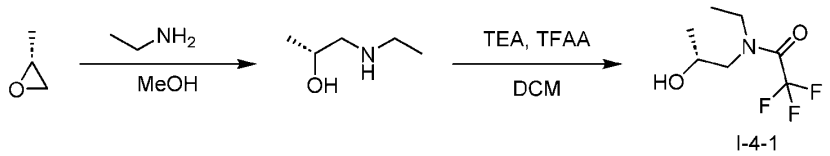
Int. #	SMs	Structure	*m/z*	^{1}H NMR
I-3-1	I-1-1 I-2-1		326.0	(400 MHz, DMSO-d6) δ = 8.93 (s, 1H), 8.66 (s, 1H), 7.94 (s, 1H), 7.02 - 6.93 (m, 1H), 6.17 (d, J = 18.0 Hz, 1H), 6.00 (d, J = 8.4 Hz, 1H), 5.59 (d, J = 11.6 Hz, 1H), 3.94 (d, J = 10.8 Hz, 1H), 3.75 - 3.63 (m, 2H), 3.54 (s, 3H), 2.04 (d, J = 12.8 Hz, 1H), 1.93 - 1.87 (m, 1H), 1.81 - 1.73 (m, 1H), 1.58 (s, 2H)

Int. #	SMs	Structure	*m/z*	^{1}H NMR
I-3-2	I-1-2 I-2-1		340.0	
I-3-3	I-1-1 I-2-2		340.0	1H NMR (400 MHz, CDCl3) δ = 8.44 (s, 1H), 8.15 (s, 1H), 6.97 - 6.83 (m, 1H), 6.10 (d, J = 10.0 Hz, 1H), 5.96 (d, J = 18.0 Hz, 1H), 5.50 (d, J = 11.6 Hz, 1H), 4.27 - 4.13 (m, 1H), 3.91 - 3.82 (m, 1H), 3.54 - 3.45 (m, 1H), 3.38 (d, J = 5.4 Hz, 3H), 2.78 - 2.67 (m, 1H), 2.23 - 2.14 (m, 2H), 2.10 (s, 3H), 2.02 (d, J = 12.8 Hz, 2H), 1.89 - 1.75 (m, 4H), 1.72 - 1.62 (m, 2H)
I-3-4	I-1-1 I-2-3		370.1	(400 MHz, DMSO-d6) δ = 8.74 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.02 - 6.92 (m, 1H), 6.10 (d, J = 18.0 Hz, 1H), 6.03 - 5.98 (m, 1H), 5.59 (d, J = 12.0 Hz, 1H), 4.25 (s, 2H), 3.94 (d, J = 10.8 Hz, 2H), 3.72 - 3.63 (m, 2H), 3.55 (s, 3H), 3.27 (s, 3H), 2.04 (d, J = 12.0 Hz, 2H), 1.92 - 1.87 (m, 1H), 1.83 - 1.71 (m, 2H)
I-3-5	I-1-3 I-2-1		356.0	
I-3-6	I-1-5 I-2-1		327.1	

Int. #	SMs	Structure	*m/z*	^{1}H NMR
I-3-7	I-1-5 I-2-2		341.2	
I-3-8	I-1-5 I-2-3		371.2	

[0520] Intermediate Method I-B.

[0521] Preparation of (*R*)-*N*-ethyl-2,2,2-trifluoro-*N*-(2-hydroxypropyl)acetamide (I-4-1)



I-4-1

[0522] Step 1. To a solution of (2*R*)-2-methyloxirane (10 g, 172.18 mmol, 1 eq) in MeOH (100 mL) was added ethanamine (2 M, 258 mL, 3 eq). The mixture was stirred at 25 °C for 12 h. On completion, the mixture was concentrated to give (*R*)-1-(ethylamino)propan-2-ol (8.13 g, 78.8 mmol, 46% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.84 - 3.70 (m, 1H), 2.74 - 2.55 (m, 3H), 2.45 - 2.34 (m, 2H), 1.16 - 1.05 (m, 6H).

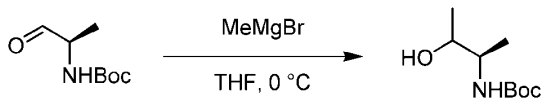
[0523] Step 2. To a solution of (*R*)-1-(ethylamino)propan-2-ol (8.13 g, 78.8 mmol, 1 eq) in DCM (80 mL) was added trifluoroacetic anhydride (24.8 g, 118 mmol, 16.4 mL, 1.5 eq) and TEA (39.9 g, 394 mmol, 5 eq) at 0 °C, then the mixture was stirred at 0 °C for 1 h. On completion, the reaction mixture was partitioned between DCM (100 mL × 3) and water (100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF=1:1) to give (*R*)-*N*-ethyl-2,2,2-trifluoro-*N*-(2-hydroxypropyl)acetamide (7.92 g, 39.8 mmol, 50% yield) as a white solid. LCMS: *m/z* 200.1 (M+1).

[0524] I-4-2 was prepared according to Method I-B using methyl amine in step 1.

[0525] I-4-3 was prepared according to Method I-B using (S)-2-methyloxirane and isopropyl amine in step 1.

[0526] I-4-4 was prepared according to Method I-B starting using cyclopropylamine and (S)-2-methyloxirane in step 1.

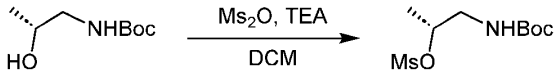
[0527] Preparation of tert-butyl ((2*R*)-3-hydroxybutan-2-yl)carbamate (I-4-5)



I-4-5

[0528] Step 1. A mixture of tert-butyl (*R*)-(1-oxopropan-2-yl)carbamate (2.00 g, 11.5 mmol, 1 *eq*) and MeMgBr (3 M, 7.70 mL, 2 eq) in THF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 0.5 hours under N_2 atmosphere. On completion, the mixture was quenched with saturated solution of NH_4Cl (40 mL) and extracted with THF (50 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 (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 4:1) to give tert-butyl ((2*R*)-3-hydroxybutan-2-yl)carbamate (0.650 g, 3.43 mmol, 30% yield) as colorless oil.

[0529] Preparation of (R)-1-((tert-butoxycarbonyl)amino)propan-2-yl methanesulfonate (I-4-8)



I-4-8

[0530] Step 1. To a solution of *tert*-butyl (*R*)-(2-hydroxypropyl)carbamate (5.00 g, 26.7 mmol, 1 *eq*) in DCM (50 mL) was added TEA (8.11 g, 80.1 mmol, 3 *eq*) and Ms_2O (6.98 g, 40.0 mmol, 1.5 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched with water (40 mL) and extracted with DCM (40 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (R)-1-((tert-butoxycarbonyl)amino)propan-2-yl methanesulfonate (6.30 g, 23.7 mmol, 89% yield) as a yellow oil.

[0531] Preparation of (R)-2-((tert-butoxycarbonyl)amino)propyl methanesulfonate (I-4-10)

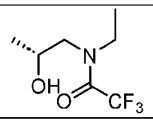
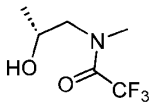
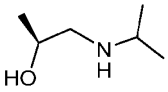
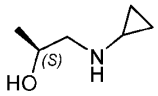
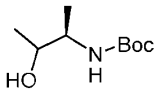
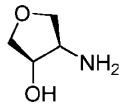
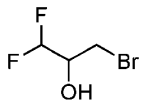
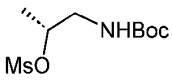


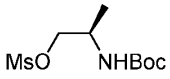
I-4-10

[0532] Step 1. To a solution of tert-butyl (R)-(1-hydroxypropan-2-yl)carbamate (10.0 g, 57.0 mmol, 1 *eq*) in DCM (100 mL) was added Ms_2O (24.8 g, 142 mmol, 2.5 *eq*) and TEA (17.3 g, 171 mmol, 3 *eq*). The mixture was stirred at 0 °C for 1 hour. On completion, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (50 mL × 3). The combined

organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (R)-2-((tert-butoxycarbonyl)amino)propyl methanesulfonate (14.2 g, 56.0 mmol, 98% yield) as yellow oil.

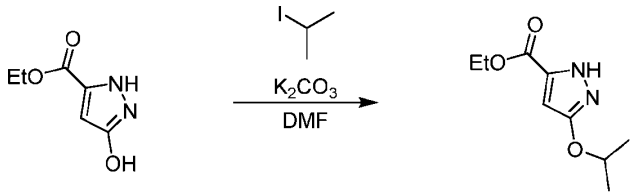
[0533] Intermediate Table 4

Intermediate. #	Structure	*m/z*	^{1}H NMR
I-4-1		200.1	
I-4-2			(400 MHz, CDCl3) δ = 4.05 - 3.96 (m, 1H), 3.38 (d, J = 3.6 Hz, 1H), 3.34 - 3.24 (m, 2H), 3.16 (d, J =1.6 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H).
I-4-3			(400 MHz, $CDCl_3$) δ = 3.78 - 3.65 (m, 1H), 2.83 - 2.65 (m, 2H), 2.39 - 2.28 (m, 1H), 1.17 - 1.09 (m, 3H), 1.08 - 0.99 (m, 6H)
I-4-4			(400 MHz, $CDCl_3$) δ 3.87 - 3.71 (m, 1H), 2.82 (*dd*, *J* = 2.0, 12.0 Hz, 1H), 2.61 - 2.44 (m, 2H), 2.15(d, *J* = 3.2 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.53 - 0.41 (m, 2H), 0.40 - 0.27 (m, 2H).
I-4-5			(400 MHz, DMSO-d6) δ = 4.51 - 4.41 (m, 1H), 3.57 - 3.48 (m, 1H), 3.48 - 3.36 (m, 1H), 1.37 (s, 9H), 1.02 - 0.93 (m, 6H).
I-4-6			Commercially available
I-4-7			Commercially available
I-4-8			
I-4-9			Commercially available

Intermediate. #	Structure	*m/z*	^{1}H NMR
I-4-10			

[0534] Intermediate Method I-C.

[0535] Preparation of ethyl 3-isopropoxy-1*H*-pyrazole-5-carboxylate (I-5-1a).

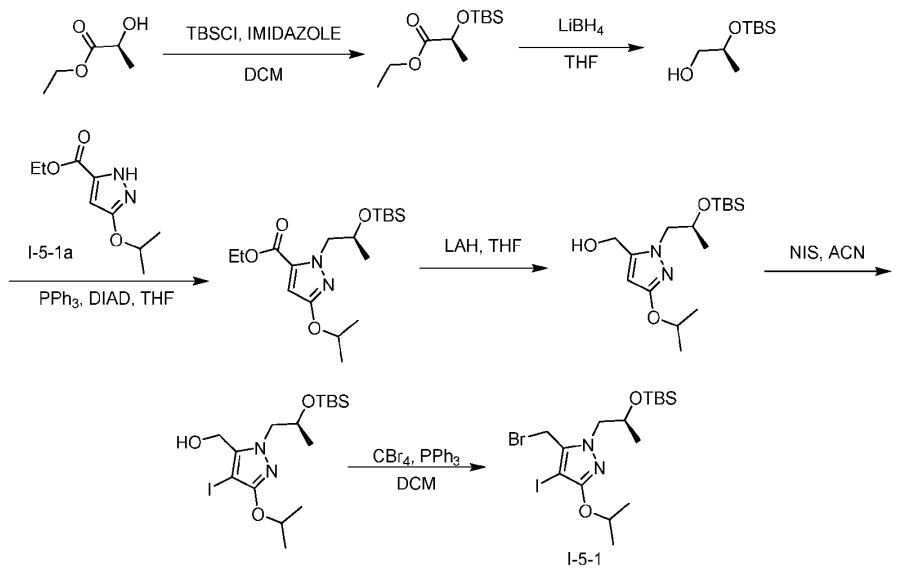


I-5-1a

[0536] Step 1. To a solution of ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (30.0 g, 192 mmol, 1 *eq*) in DMF (300 mL) was added K_2CO_3 (39.8 g, 288 mmol, 1.5 *eq*) and 2-iodopropane (34.2 g, 202 mmol, 20.1 mL, 1.05 *eq*). The mixture was stirred at 80 °C for 1 hr. On completion, the reaction mixture was diluted with H_2O (500 mL) and extracted with EA mL (200 mL × 5). The combined organic layers were washed with H_2O mL (200 mL × 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1) to give ethyl 3-isopropoxy-1*H*-pyrazole-5-carboxylate (23.0 g, 116 mmol, 60% yield) as yellow oil. LCMS: *m/z* 199.0 (M+1).

[0537] Intermediate Method I-D.

[0538] Preparation of (*S*)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1*H*-pyrazole (I-5-1).



[0539] Step 1. To a solution of ethyl (2*S*)-2-hydroxypropanoate (3.00 g, 25.4 mmol, 1 *eq*) in DCM (30 mL) was added imidazole (5.19 g, 76.2 mmol, 3 *eq*), then TBSCl (5.74 g, 38.1 mmol, 1.5 eq) was added at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with dilute citric acid (100 mL) and extracted with DCM (50mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: EA= 10:1) to give ethyl (*S*)-2-((tert-butyldimethylsilyl)oxy)propanoate (5.80 g, crude) as a white oil. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 4.32 (d, *J* = 6.8 Hz, 1H), 4.15 - 4.03 (m, 2H), 1.30 - 1.26 (m, 3H), 1.21 - 1.16 (m, 3H), 0.86 (s, 9H), 0.04 (d, *J* = 3.2 Hz, 6H).

[0540] Step 2. A mixture of ethyl (*S*)-2-((tert-butyldimethylsilyl)oxy)propanoate (20.0 g, 86.1 mmol, 1 *eq*) in THF (200 mL) was degassed and purged with N_2 for 3 times, and then $LiBH_4$ (2 M, 215 mL, 5 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 4 h under N_2 atmosphere. The reaction mixture was quenched by addition MeOH (100 mL) at 0 °C. On completion of methanol addition, the mixture was further quenched by addition of saturated NH_4Cl solution (100 mL) at 0 °C. The reaction mixture was diluted with H_2O (100 mL) and extracted with EA (50 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1) to give (*S*)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol (16.4 g, 81.9 mmol, 95% yield, 95% purity) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.87 - 3.76 (m, 1H), 3.64 - 3.56 (m, 1H), 3.38 - 3.34 (m, 1H), 2.48 (br s, 1H), 1.14 - 1.10 (m, 3H), 0.94 - 0.89 (m, 9H), 0.12 - 0.06 (m, 6H).

[0541] Step 3. A mixture of ethyl 3-isopropoxy-1*H*-pyrazole-5-carboxylate (9.30 g, 46.9 mmol, 1 *eq*), (*S*)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol (13.4 g, 70.4 mmol, 1.5 *eq*), PPh_3 (27.1 g, 103 mmol, 2.2 *eq*) in THF (100 mL) was degassed and purged with N_2 for 3 times, and the mixture was stirred at 25 °C for 0.5 h under N_2 atmosphere. DIAD (20.9 g, 103 mmol, 20.0 mL, 2.2 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 2 hr under N_2 atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1) to give ethyl (*S*)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-1*H*-pyrazole-5-carboxylate (12.5 g, 33.7 mmol, 72% yield, 100% purity) was obtained as a colorless oil. LCMS: *m/z* 371.2 (M+1).

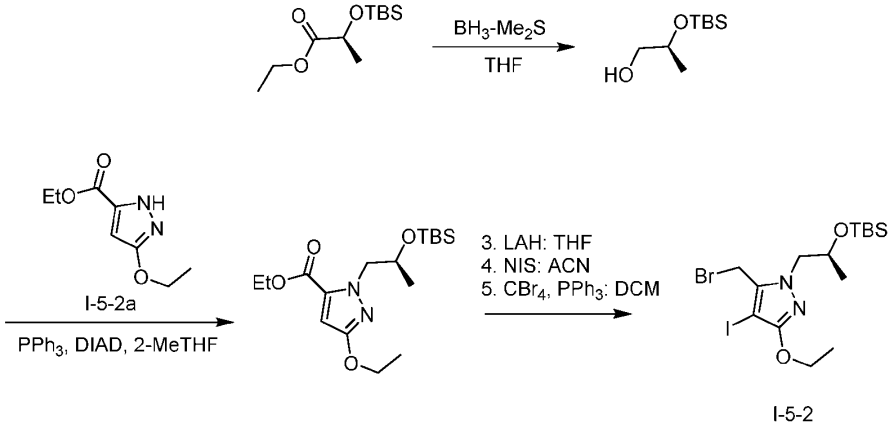
[0542] Step 4. To a solution of ethyl (*S*)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-1*H*-pyrazole-5-carboxylate (13.9 g, 37.5 mmol, 1 *eq*) in THF (140 mL) was added $LiAlH_4$ (2.5 M, 22.5 mL, 1.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was quenched sequentially with water (0.3 mL): NaOH (15%) (0.3 mL): water (0.9 mL). Then the mixture was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1). (*S*)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-isopropoxy-1*H*-pyrazol-5-yl)methanol (9.90 g, 30.1 mmol, 80% yield) was obtained as a yellow oil. LCMS: *m/z* 329.1 (M+1).

[0543] Step 5. To a solution of (*S*)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-isopropoxy-1*H*-pyrazol-5-yl)methanol (8.90 g, 27.1 mmol, 1 *eq*) in ACN (90 mL) was added NIS (6.70 g, 29.8 mmol, 1.1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the reaction mixture was quenched by addition Na_2SO_3 (50 mL) at 0 °C, and then diluted with H_2O (50 mL) and extracted with EA (50 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1). (*S*)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1*H*-pyrazol-5-yl)methanol (12.8 g, 25.4 mmol, 94% yield, 90% purity) was obtained as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.30 - 5.23 (m, 1H), 4.81 - 4.69 (m, 1H), 4.54 - 4.45 (m, 2H), 4.40 - 4.29 (m, 1H), 3.67 (s, 1H), 3.66 - 3.64 (m, 1H), 1.30 - 1.25 (m, 9H), 0.75 (s, 9H), -0.06 - -0.09 (m, 3H), -0.16 (s, 3H).

[0544] Step 6. A mixture of (*S*)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1*H*-pyrazol-5-yl)methanol (8.90 g, 19.6 mmol, 1 *eq*), PPh_3 (6.16 g, 23.5 mmol, 1.2 *eq*) in DCM (120 mL) was degassed and purged with N_2 for 3 times, an then CBr_4 (7.79 g, 23.5 mmol, 1.2 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 2 hr under N_2

atmosphere. On completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with DCM (50 mL × 4). The combined organic layers were washed dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1) to give [(1S)-2-[5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl]-1-methyl-ethoxy]-tert-butyl-dimethyl-silane (1.98 g, 3.64 mmol, 19% yield, 95% purity) as a yellow oil.

[0545] Preparation of (*S*)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazole (I-5-2)



I-5-2

[0546] Intermediate I-5-2a was prepared according to those described in the Method I-C with iodoethane.

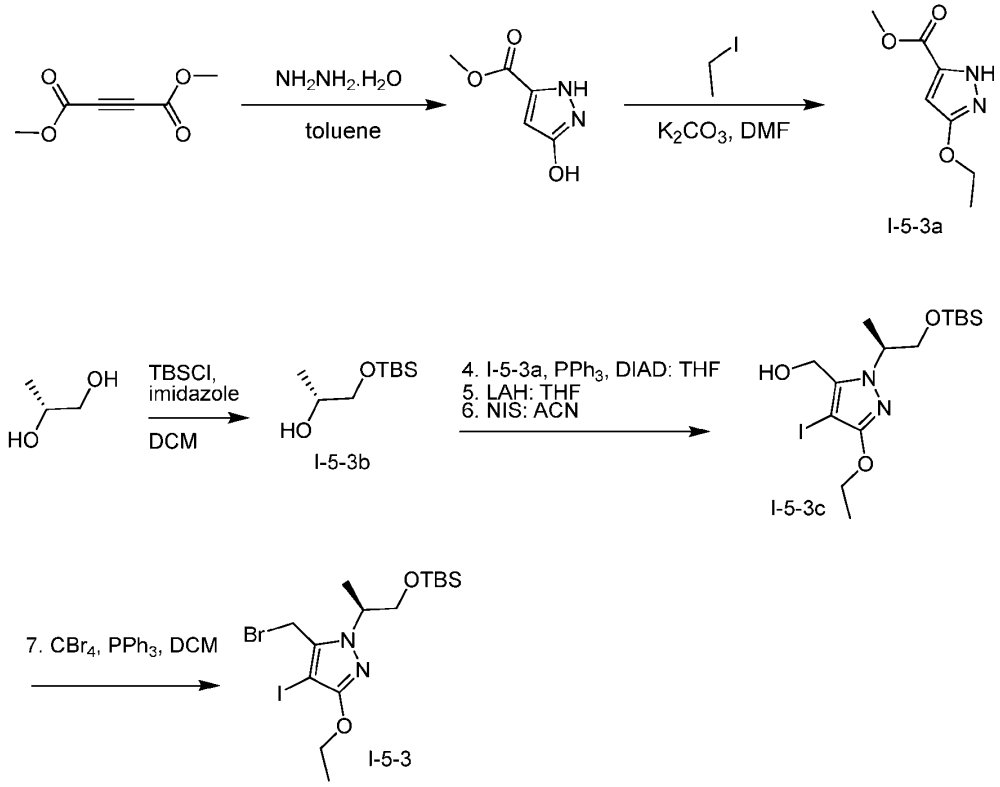
[0547] Step 1. To a solution of ethyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (3.00 g, 12.9 mmol, 1 *eq*) in THF (30 mL), under N_2 replacement, BH_3-Me_2S (10 M, 2.58 mL, 2 *eq*) was added at 0 °C, and the mixture was stirred at 25 °C for 0.5 h. Then, the mixture was stirred at 70 °C for 2 h. On completion, the mixture was quenched with MeOH (10 mL) and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: EA= 10:1) to give (*S*)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol (1.96 g, crude) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 4.54 (t, *J* = 5.6 Hz, 1H), 3.77 - 3.68 (m, 1H), 3.31 - 3.10 (m, 2H), 1.04 (d, *J* = 6.0 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H)

[0548] Step 2 was performed in a manner similar to those described in Step 3 of Method I-D using intermediate I-5-2a and substituting 2-MeTHF as a solvent instead.

[0549] Steps 3-5 were performed according to the methods described in steps 4-6 of Method I-D to give (*S*)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazole.

[0550] Intermediate Method I-E.

[0551] Preparation of methyl (*S*)-5-(bromomethyl)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1*H*-pyrazole (I-5-3)



[0552] Step 1. To a solution of dimethyl but-2-ynedioate (100 g, 703 mmol, 1 *eq*) in toluene (500 mL) was added hydrazine hydrate (46.7 g, 914 mmol, 45.2 mL, 98% purity, 1.3 *eq*). The mixture was stirred at 25 °C for 4 h. On completion, the mixture was concentrated in vacuo to give a residue. The crude product was triturated with EA (100 mL) at 25 °C for 30 min to give methyl 3-hydroxy-1*H*-pyrazole-5-carboxylate (92.0 g, 647 mmol, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.74 (s, 1H), 3.75 (s, 3H).

[0553] Step 2. To a solution of methyl 3-hydroxy-1*H*-pyrazole-5-carboxylate (30.0 g, 211 mmol, 1 *eq*) in DMF (300 mL) was added K_2CO_3 (43.7 g, 316 mmol, 1.5 *eq*) and iodoethane (32.9 g, 211 mmol, 1 *eq*). The mixture was stirred at 80 °C for 2 h. On completion, the mixture was poured into H_2O (1000 mL) and extracted with EA (300 mL × 4). The combined organic phase was washed with H_2O (300 mL × 3) and dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 10:1 to 5:1) to give methyl 3-ethoxy-1*H*-pyrazole-5-carboxylate (7.19 g, 42.2 mmol, 20% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.11 (s, 1H),

6.23 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.86 - 3.79 (m, 3H), 1.33 - 1.26 (m, 3H). LCMS: *m/z* 171.1 (M+1).

[0554] Step 3 used the procedure of step 1 in Method I-D. Steps 4-7 followed the procedures of steps 3-6 of Method I-D using I-5-3a in step 4 to give I-5-3.

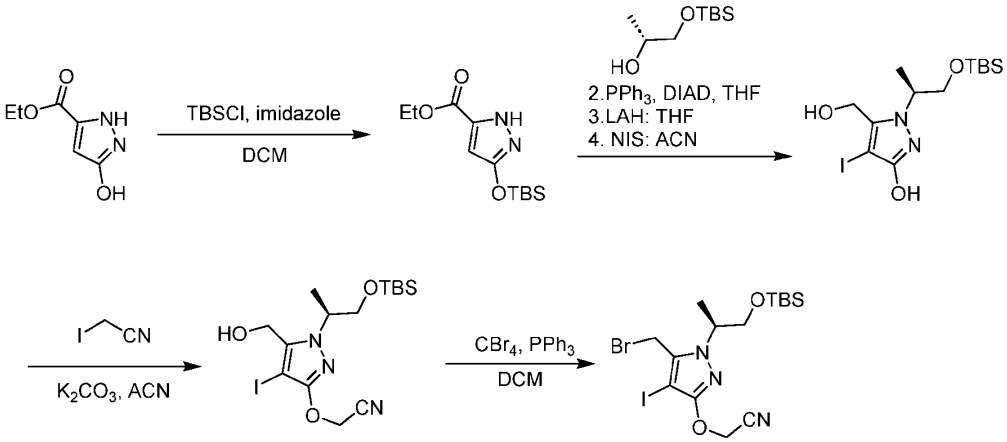
[0555] I-5-4 was prepared according to steps 3-6 described in synthesis of Method I-D starting with methyl 1H-pyrazole-5-carboxylate and I-5-3b.

[0556] I-5-5 was prepared according to methods described in synthesis of Method I-D steps 3-6 starting from methyl 3-methyl-1*H*-pyrazole-5-carboxylate and 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol.

[0557] I-5-6 was prepared according to methods described in Method I-E using 2-iodopropane in step 2.

[0558] Intermediate Method I-F.

[0559] Preparation of (*S*)-2-((5-(bromomethyl)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4-iodo-1*H*-pyrazol-3-yl)oxy)acetonitrile (I-5-7)



I-5-7

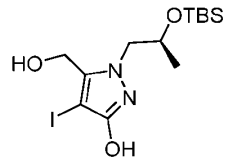
[0560] Step 1. To a solution of ethyl 3-hydroxy-1*H*-pyrazole-5-carboxylate (20.0 g, 128 mmol, 1 eq) in DCM (200 mL) was added TBSCl (28.9 g, 192 mmol, 23.6 mL, 1.5 eq) and imidazole (26.1 g, 384.2 mmol, 3eq). The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 20:1 to 1:1) to give ethyl 3-((*tert*-butyldimethylsilyl)oxy)-1*H*-pyrazole-5-carboxylate (35.7 g, 95.0 mmol, 74% yield, 72% purity) as a white solid. LCMS: *m/z* 271.0 (M+1).

[0561] Steps 2-4 were conducted according to those described in the Method I-D steps 3-5 to give (*S*)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-5-(hydroxymethyl)-4-iodo-1*H*-pyrazol-3-ol.

[0562] Step 5. To a solution of (*S*)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-5-(hydroxymethyl)-4-iodo-1*H*-pyrazol-3-ol (5.40 g, 13.1 mmol, 1 eq) and 2-iodoacetonitrile (3.28 g, 19.6 mmol, 1.5 eq) in ACN (54 mL) was added K_2CO_3 (5.43 g, 39.2 mmol, 3 eq). The mixture was stirred at 80 °C for 2 hr. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 10:1 to 1:1) to give (*S*)-2-((1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-(hydroxymethyl)-4-iodo-1*H*-pyrazol-3-yl)oxy)acetonitrile (2.30 g, 5.10 mmol, 38% yield, 100% purity) as a colorless oil. ^{1}H NMR (400 MHz, CDCl3) δ = 4.96 - 4.86 (m, 2H), 4.63 - 4.47 (m, 3H), 3.74 (br d, J = 6.4 Hz, 2H), 3.16 (br t, J = 4.4 Hz, 1H), 1.46 (br d, J = 6.4 Hz, 3H), 0.79 (s, 9H), -0.04 (d, J = 17.2 Hz, 6H). LCMS: *m/z* 451.9 (M+1).

[0563] Step 6 was conducted in manner similar to those described in the Method I-D step 6 to give (*S*)-2-((5-(bromomethyl)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4-iodo-1*H*-pyrazol-3-yl)oxy)acetonitrile.

[0564] I-5-8a was prepared according to methods described in the Method I-F steps 1-4 using commercially available (*S*)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol in step 2.

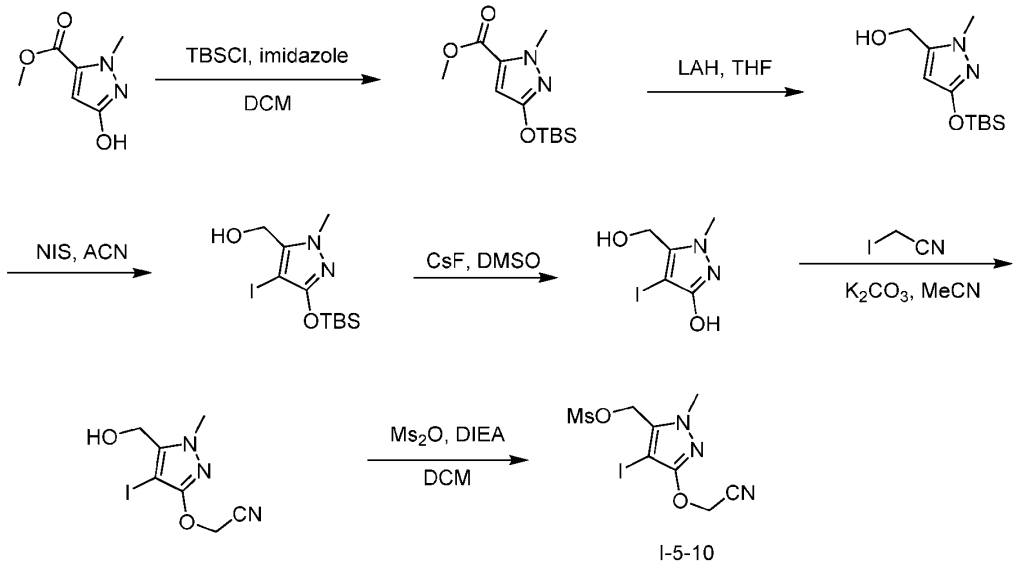


I-5-8a

[0565] I-5-8 was prepared according to methods described in the Method I-F steps 5-6 starting with I-5-8a.

[0566] I-5-9 was prepared according to methods described in steps 3-6 in the Method I-D with methyl 3-methyl-1H-pyrazole-5-carboxylate and (*S*)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol (both commercially available) as starting material.

[0567] Preparation of (3-(cyanomethoxy)-4-iodo-1-methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate (I-5-10)



I-5-10

[0568] Step 1. To a solution of methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate (5.00 g, 32.0 mmol, 1 eq) in DCM (50 mL) was added TBSCl (7.24 g, 48.0 mmol, 5.91 mL, 1.5 eq) and imidazole (6.54 g, 96.1 mmol, 3 eq). The mixture was stirred at 25 °C for 2 h. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 120 mL/min) to give methyl 3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-*1H*-pyrazole-5-carboxylate (6.40 g, 23.7 mmol, 74% yield, 100% purity) as a colorless oil. ^{1}H NMR (400 MHz, CDCl3-d) δ = 6.13 (s, 1H), 4.02 (s, 3H), 3.86 (s, 3H), 0.98 (s, 9H), 0.25 (s, 6H). LCMS: *m/z* 271.0 (M+1).

[0569] Step 2. To a solution of methyl 3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-*1H*-pyrazole-5-carboxylate (6.00 g, 22.2 mmol, 1 eq) in THF (60 mL) was added LAH (2.5 M, 9.76 mL, 1.1 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. On completion, the reaction mixture was quenched by the addition of 15% NaOH (5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-*1H*-pyrazol-5-yl)methanol (4.68 g, 19.3 mmol, 87% yield) was obtained as a light yellow oil and it was used into the next step without further purification. LCMS: *m/z* 243.2 (M+1).

[0570] Step 3. To a solution of (3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-*1H*-pyrazol-5-yl)methanol (4.58 g, 18.9 mmol, 1 eq) in ACN (45 mL) was added NIS (4.68 g, 20.8 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was poured into Na_2SO_3 (80 mL) aqueous solution, and the aqueous phase was extracted with ethyl acetate (60 mL × 2). The combined organic phase was washed with brine (40 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product (3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-methyl-*1H*-pyrazol-5-yl)methanol (5.8 g, crude) was obtained as a yellow liquid and it was used into the next step without further purification. LCMS: *m/z* 369.2.

[0571] Step 4. To a solution of (3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-methyl-*1H*-pyrazol-5-yl)methanol (5.80 g, 11.0 mmol, 1 eq) in DMSO (60 mL) was added CsF (8.37 g, 55.1 mmol, 5 eq). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was adjusted to pH~5 with citric acid. The mixture was extracted with ethyl acetate (50 mL × 5) and the combined organic phase was washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~56% THF/Petroleum ether gradient @ 100 mL/min) to give 5-(hydroxymethyl)-4-iodo-1-methyl-1*H*-pyrazol-3-ol (1.6 g, 6.30 mmol, 57% yield) as a yellow solid. LCMS: *m/z* 254.8 (M+1).

[0572] Step 5. To a solution of 5-(hydroxymethyl)-4-iodo-1-methyl-1*H*-pyrazol-3-ol (1.40 g, 5.51 mmol, 1 eq) and 2-iodoacetonitrile (1.38 g, 8.27 mmol, 1.5 eq) in ACN (15 mL) was added K_2CO_3 (2.29 g, 16.5 mmol, 3 eq). The mixture was stirred at 80 °C for 1 h. On completion, the mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~45% THF/Petroleum ether gradient @ 40 mL/min) to give 2-((5-(hydroxymethyl)-4-iodo-1-methyl-1*H*-pyrazol-3-yl)oxy)acetonitrile (1.13 g, 3.66 mmol, 66% yield, 95% purity) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3-d) δ = 4.91 (s, 2H), 4.63 (s, 2H), 3.93 - 3.85 (m, 3H). LCMS: *m/z* 293.9 (M+1).

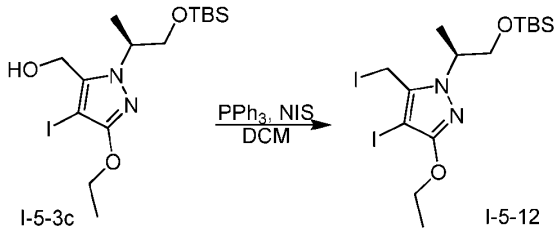
[0573] Step 6. To a solution of 2-((5-(hydroxymethyl)-4-iodo-1-methyl-1*H*-pyrazol-3-yl)oxy)acetonitrile (330 mg, 1.13 mmol, 1 *eq*) in DCM (3 mL) was added methylsulfonyl methanesulfonate (294 mg, 1.69 mmol, 1.5 *eq*) and DIEA (437 mg, 3.38 mmol, 0.588 mL, 3 *eq*). The mixture was stirred at 25 °C for 0.75 h. On completion, the reaction mixture was quenched by addition H_2O (10 mL) at 0 °C, and extracted with DCM (6 mL × 3). The combined organic layers were washed with H_2O (5 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (3-(cyanomethoxy)-4-iodo-1-

methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate (350 mg, 0.943 mmol, 84% yield) as a brown oil. LCMS: *m/z* 371.8 (M+1).

[0574] I-5-11 was prepared according to methods described in steps 5 and 6 of Method I-F (preparation of I-5-7) using 2-bromopropanenitrile and intermediate I-5-8a.

[0575] Intermediate Method I-G.

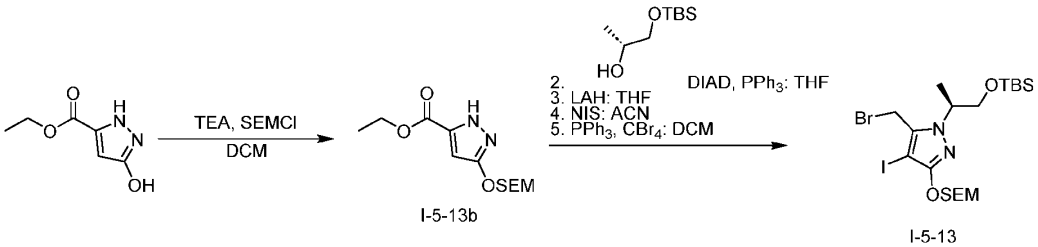
[0576] Preparation of (*S*)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-5-(iodomethyl)-1*H*-pyrazole (I-5-12)



I-5-3c I-5-12

[0577] Step 1. A solution of (*S*)-(1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1*H*-pyrazol-5-yl)methanol (1.00 kg, 2.27 mol, 1 *eq*), NIS (1.02 kg, 4.54 mol, 2 *eq*) in DCM (7 L) was degassed and purged with N_2 for 3 times, and then a solution of PPh_3 (893 g, 3.41 mol, 1.5 *eq*) in DCM (800 mL) was slowly added to the reaction solution at 0 °C. The mixture was stirred at 25 °C for 1 h under N_2 atmosphere. On completion, the mixture was poured into saturated sodium sulfite (7000 mL) aqueous solution. The aqueous phase was extracted with DCM (2000 mL × 3). The combined organic phase was washed with brine (2000 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate= 1/0, 10/1) to give (*S*)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-5-(iodomethyl)-1*H*-pyrazole (950 g, 1.62 mol, 71% yield, 94% purity) as a yellow oil.

[0578] Preparation of (*S*)-5-(bromomethyl)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4-iodo-3-((2-(trimethylsilyl)ethoxy)methoxy)-*1H*-pyrazole (I-5-13)



I-5-13b I-5-13

[0579] Step 1. A mixture of ethyl 3-hydroxy-*1H*-pyrazole-5-carboxylate (10.0 g, 64 mmol, 1 eq), SEM-Cl (42.7 g, 256 mmol, 4 eq), TEA (38.9 g, 384 mmol, 6 eq) in DCM (100 mL) at 0

°C was stirred at 25 °C for 1 h. On completion, the mixture was diluted with water (500 mL) and extracted with DCM (100 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography on silica gel (120 g silica gel, 0% to 100% EA in Petroleum ether) to give ethyl 3-((2-(trimethylsilyl)ethoxy)methoxy)-1*H*-pyrazole-5-carboxylate (10.6 g, 35.8 mmol, 56% yield, 97% purity) as a colorless oil. LCMS: *m/z* 259.0 (M+1-28).

[0580] Steps 2-5 were performed according to procedures described in steps 3-6 of Method I-D to give (*S*)-5-(bromomethyl)-1-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4-iodo-3-((2-(trimethylsilyl)ethoxy)methoxy)-*1H*-pyrazole.

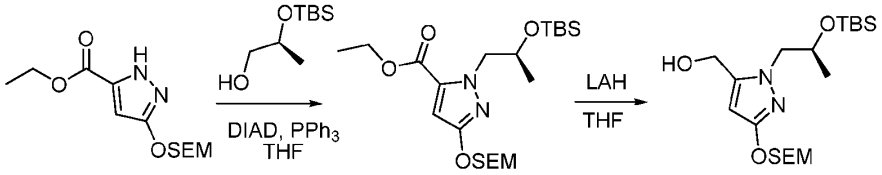
[0581] I-5-14 was prepared similar to those described in Method I-G (preparation of I-5-12) using appropriate intermediate ((R)-1-((tert-butyldimethylsilyl)oxy)propan-2-ol) from I-5-6.

[0582] I-5-15 was prepared similar to those described in Method I-G (preparation of I-5-12) using appropriate intermediate ((S)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol) from I-5-1.

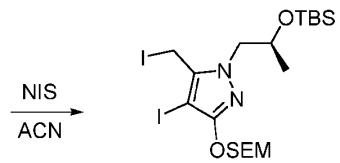
[0583] I-5-16 was prepared similar to those described in Method I-G (preparation of I-5-12) using appropriate intermediate (benzylic alcohol immediately prior to bromination) from I-5-2.

[0584] I-5-17 was prepared similar to those described in steps 1-5 in Method I-D starting with ethyl (2*R*)-2-hydroxypropanoate in step 1 and then Method I-G (preparation of I-5-12) for the final step.

[0585] Preparation of (S)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-5-(iodomethyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazole (I-5-18)



I-5-13b



I-5-18

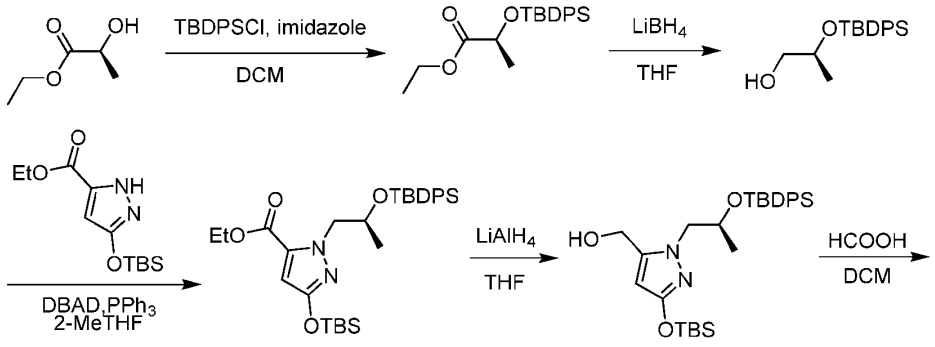
[0586] Step 1. To a solution of ethyl 3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazole-5-carboxylate (24.0 g, 83.8 mmol, 1 *eq*), (S)-2-((tert-butyldimethylsilyl)oxy)propan-1-ol (23.9 g, 125 mmol, 1.5 *eq*) in THF (200 mL) that was degassed and purged with N_2 for 3 times was added PPh_3 (43.9 g, 167 mmol, 2 *eq*) and DIAD (25.4 g, 125 mmol, 1.5 *eq*). The mixture was

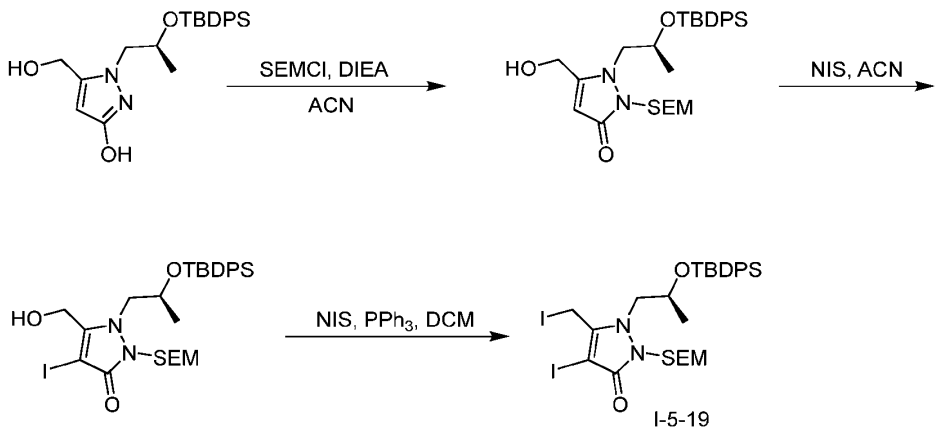
stirred at 25 °C for 2 hours. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10:1) to give ethyl (S)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazole-5-carboxylate (28.0 g, 61.0 mmol, 72% yield) as a colorless oil. LCMS: *m/z* 459.6 (M+1).

[0587] Step 2. To a solution of ethyl (S)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazole-5-carboxylate (28.0 g, 61.0 mmol, 1 *eq*) in THF (250 mL) was added LAH (2.5 M, 29.3 mL, 1.2 *eq*) into the mixture at 0 °C. The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was sequentially quenched by H_2O (3 mL), 15% NaOH (3 mL), H_2O (9 mL), dried over Na_2SO_4, and filtered and concentrated under reduced pressure to give (S)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazol-5-yl)methanol (20.2 g, 48.4 mmol, 79% yield) as a colorless oil. LCMS: *m/z* 417.3 (M+1).

[0588] Step 3. To a solution of (S)-(1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazol-5-yl)methanol (20.0 g, 48.0 mmol, 1 *eq*) in ACN (200 mL) was added NIS (14.0 g, 62.3 mmol, 1.3 *eq*), and the mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was quenched by addition Na_2SO_3 (100mL) at 0 °C and then diluted with H_2O (400 mL) and extracted with EA (100mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (S)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-5-(iodomethyl)-3-((2-(trimethylsilyl)ethoxy)methoxy)-1H-pyrazole (6.00 g, 9.20 mmol, 19% yield) as a yellow oil.

[0589] Preparation of (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-4-iodo-5-(iodomethyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one (I-5-19)





I-5-19

[0590] Step 1. To a solution of ethyl (*S*)-2-hydroxypropanoate (45.0 g, 381 mmol, 1 *eq*) in DCM (450 mL) was added TBDPSCl (110 g, 400 mmol, 1.05 *eq*) and imidazole (77.8 g, 1.14 mol, 3 *eq*), and the mixture was stirred at 0 °C for 5 hr. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-10% Ethyl acetate/Petroleum ether) to give Compound ethyl (S)-2-((tert-butyldiphenylsilyl)oxy)propanoate (120 g, 337 mmol, 88 % yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (t, *J* = 8.4 Hz, 5H), 7.36 - 7.28 (m, 5H), 4.23 - 4.17 (m, 1H), 4.00 - 3.91 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H); LCMS: *m/z* 279.0 (M+1).

[0591] Step 2. To a solution of ethyl (S)-2-((tert-butyldiphenylsilyl)oxy)propanoate (100 g, 280 mmol, 1 *eq*) in THF (1000 mL) was added $LiBH_4$ (2 M in THF, 701 mL, 5 *eq*) under N_2, then the mixture was stirred at 25 °C for 16 h under N_2. On completion, the reaction mixture was quenched by addition sat. NH_4Cl (2000 mL) at 0 °C, and extracted with EA (300 mL × 3). The combined organic layers were washed with brine (500 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound (S)-2-((tert-butyldiphenylsilyl)oxy)propan-1-ol (110 g, crude) was obtained as a yellow oil.

[0592] Step 3. A mixture of ethyl 3-((tert-butyldimethylsilyl)oxy)-1H-pyrazole-5-carboxylate, which was prepared according to step 1 described in Method I-F (67.0 g, 248 mmol, 1 *eq*), (S)-2-((tert-butyldiphenylsilyl)oxy)propan-1-ol (93.5 g, 297 mmol, 1.2 *eq*), DBAD (126 g, 545 mmol, 2.2 *eq*), and PPh_3 (130 g, 496 mmol, 2 *eq*) in 2-MeTHF (670 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-10% Ethyl acetate/Petroleum). Compound ethyl (S)-3-((tert-butyldimethylsilyl)oxy)-1-(2-((tert-

butyldiphenylsilyl)oxy)propyl)-1H-pyrazole-5-carboxylate (115 g, crude) was obtained as a yellow oil. LCMS: *m/z* 567.4 (M+1).

[0593] Step 4. To a solution of ethyl (S)-3-((tert-butyldimethylsilyl)oxy)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-1H-pyrazole-5-carboxylate (105 g, 185 mmol, 1 *eq*) in THF (1050 mL) was added dropwise $LiAlH_4$ (2.5 M in THF, 74.1 mL, 1 *eq*) at 0 °C under N_2 and stirred at 0 °C for 2 hr. On completion, the reaction mixture was quenched by addition of H_2O (**7** mL) at 0 °C, and then added into 15% NaOH (7 mL) and H_2O (21 mL). The mixture was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. (S)-(3-((tert-butyldimethylsilyl)oxy)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-1H-pyrazol-5-yl)methanol (90 g, crude) was obtained as a yellow oil. LCMS: *m/z* 525.2 (M+1).

[0594] Step 5. To a solution of (S)-(3-((tert-butyldimethylsilyl)oxy)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-1H-pyrazol-5-yl)methanol (90.0 g, 171 mmol, 1 *eq*) in DCM (1000 mL) was added HCOOH (171 mmol, 100 mL, 1 *eq*) and stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched by addition of aq. $NaHCO_3$ (200 mL) at 25 °C, and then diluted with H_2O (300 mL) and extracted with DCM (200 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-50% Ethyl acetate/Petroleum ether). Compound (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-1H-pyrazol-3-ol (41.0 g, 99.8 mmol, 58% yield) was obtained as a white solid. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.69 - 7.59 (m, 2H), 7.46 - 7.31 (m, 8H), 5.56 (d, *J* = 4.4 Hz, 1H), 4.71 - 4.40 (m, 3H), 4.36 - 4.22 (m, 1H), 4.11 - 4.00 (m, 1H), 3.84 - 3.67 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 1H), 1.00 - 0.87 (m, 12H); LCMS: *m/z* 411.2 (M+1).

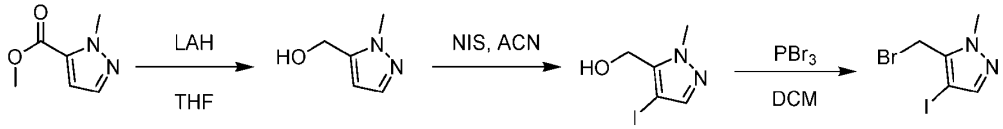
[0595] Step 6. To a solution of (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-1H-pyrazol-3-ol (15.0 g, 36.5 mmol, 1 *eq*) in ACN (150 mL) was added SEM-Cl (6.09 g, 36.5 mmol, 1 *eq*) and DIEA (5.67 g, 43.8 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF= 1:0 to 1:1) to give (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one (5.60 g, 10.3 mmol, 28% yield) as a yellow oil. LCMS: *m/z* 541.2 (M+1).

[0596] Step 7. To a solution of (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one (5.60 g, 10.3 mmol, 1 *eq*) in ACN (56 mL) was added NIS (2.33 g, 10.3 mmol, 1 *eq*). The mixture was stirred at 0 °C for 1 h. On completion, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (150 mL × 3). The combined organic phase was dried over

anhydrous sodium sulfate, filtered and the filtrated was concentrated to give (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-4-iodo-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one (6.50 g, 9.75 mmol, 94% yield) as a yellow oil. LCMS: *m/z* 667.2 (M+1).

[0597] Step 8. To a solution of (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-4-iodo-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one in DCM (64 mL) was added NIS (4.32 g, 19.2 mmol, 2 *eq*) and PPh_3 (3.78 g, 14.4 mmol, 1.5 *eq*). The mixture was stirred at 0 °C for 1 h. On completion, the mixture was quenched with water (100 mL), extracted with DCM (125 mL × 3), and the combined organic phase was dried over anhydrous sodium sulfate, filtered and the filtrated was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF= 5:1 to 1:1) to give (S)-1-(2-((tert-butyldiphenylsilyl)oxy)propyl)-4-iodo-5-(iodomethyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-3H-pyrazol-3-one (5.00 g, 6.44 mmol, 67%) yield as a yellow oil (I-5-19).

[0598] Preparation of 5-(bromomethyl)-4-iodo-1-methyl-1H-pyrazole (I-5-20)



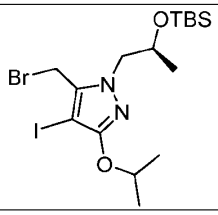
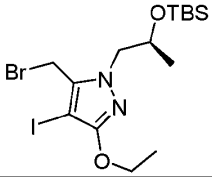
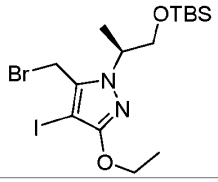
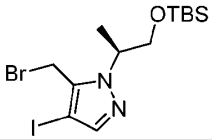
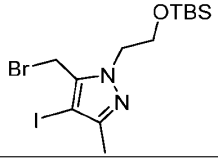
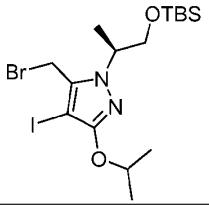
I-5-20

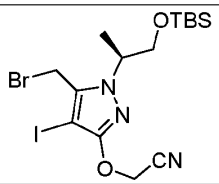
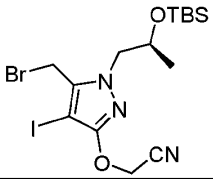
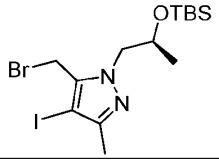
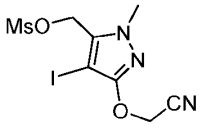
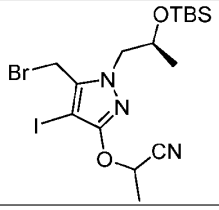
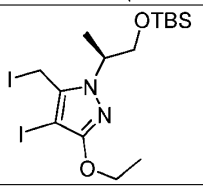
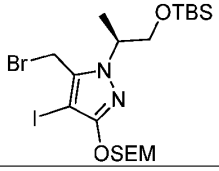
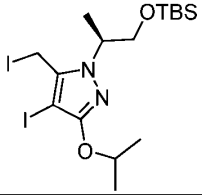
[0599] Step 1. To a solution of methyl 1-methyl-1H-pyrazole-5-carboxylate (10.0 g, 71.4 mmol, 1 *eq*) in THF (100 mL) was added LAH (2.5 M in THF, 42.8 mL, 1.5 *eq*) at 0 °C. The mixture was stirred at 0 °C for 6 hr. On completion, the reaction mixture was quenched with H_2O (4 mL) dropwise at 0 °C, followed by 15% NaOH (4 mL), H_2O (4 mL) and Na_2SO_4. The mixture was then stirred at 25 °C for 20 min and filtered. The filtrate was concentrated under reduced pressure to give (1-methyl-1H-pyrazol-5-yl)methanol (7.88 g, crude) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.31 (s, 1H), 6.17 (s, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.52 (d, *J* = 5.2 Hz, 2H), 3.79 (s, 3H).

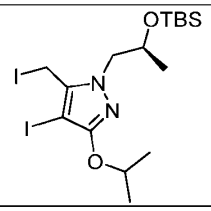
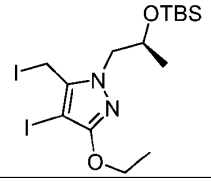
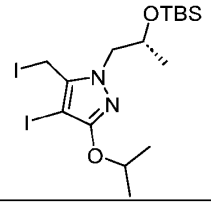
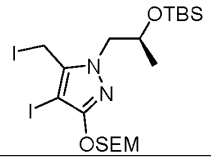
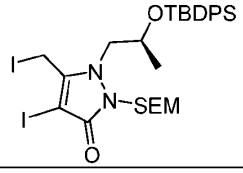
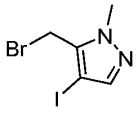
[0600] Step 2. To a solution of (2-(1-methyl-1H-pyrazol-5-yl)methanol (7.30 g, 65.1 mmol, 1 *eq*) in ACN (50 mL) was added NIS (17.6 g, 78.1 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was quenched with saturated solution of Na_2SO_3 (30 mL), partitioned between water (300 mL) and ethyl acetate (100 mL × 7), and the combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (4-iodo-1-methyl-1H-pyrazol-5-yl)methanol (13.0 g, 54.6 mmol, 84% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.43 (s, 1H), 5.32 (s, 1H), 4.48 (s, 2H), 3.87 (s, 3H); LCMS: *m/z* 238.9 (M+1)

Step 3. To a solution of (4-iodo-1-methyl-1H-pyrazol-5-yl)methanol (5.00 g, 21.0 mmol, 1 *eq*) in DCM (50 mL) was added tribromophosphane (6.82 g, 25.2 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 6 h. On completion, the mixture was quenched with sat. $NaHCO_3$ (100 mL) and extracted with DCM (100 mL). The organic layer was washed with water (100 mL), brine (2 × 200 mL), dried over sodium sulfate, and concentrated in vacuum to afford 5-(bromomethyl)-4-iodo-1-methyl-1H-pyrazole (4.50 g, 15.0 mmol, 71% yield) as a white solid.

[0601] Intermediate Table 5.

Int. #	Structure	*m/z*	^{1}H NMR
I-5-1		517.0	
I-5-2		503.0	
I-5-3		504.7	
I-5-4		460.9	
I-5-5		460.9	
I-5-6		504.8	

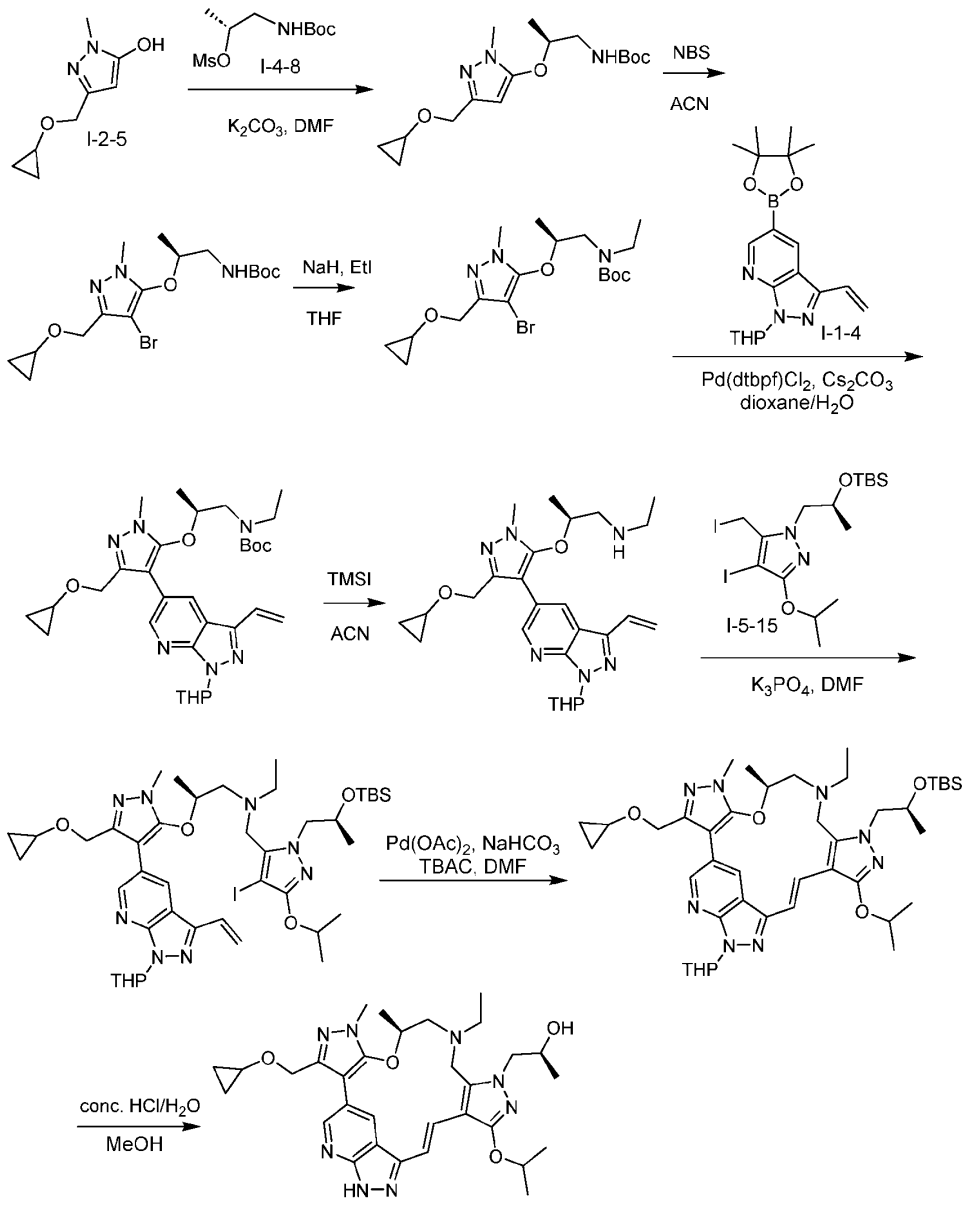
I-5-7		515.7	
I-5-8		515.9	
I-5-9		474.6	(400 MHz, DMSO-d6) δ = 4.75 - 4.55 (m, 2H), 4.21 - 3.96 (m, 3H), 2.10 (s, 3H), 1.14 (d, J = 6.0 Hz, 3H), 0.75 (s, 9H), -0.09 (s, 3H), -0.29 (s, 3H).
I-5-10		371.8	
I-5-11		530.0	
I-5-12		551.1	
I-5-13		607.0	
I-5-14		565.2	

I-5-15		565.2	
I-5-16		551.0	
I-5-17		565.1	
I-5-18		653.1	
I-5-19		777.0	
I-5-20		300.8	

[0602] Preparation of Final Macrocycles

[0603] General Method A-1:

[0604] Preparation of (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (Ex.1)



Ex. 1

[0605] Step 1. To a solution of 3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-ol (2.86 g, 17.0 mmol, 1 *eq*) in DMF (50 mL) was added K_2CO_3 (7.05 g, 51.0 mmol, 3 *eq*) and (R)-1-((tert-butoxycarbonyl)amino)propan-2-yl methanesulfonate (4.74 g, 18.7 mmol, 1.1 *eq*). The mixture was stirred at 80 °C for 12 h. On completion, the mixture was quenched with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (100 mL× 2), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (S)-(2-

((3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)carbamate (5.10 g, 15.7 mmol, 92% yield) as a red oil. LCMS: *m/z* 326.1 (M+1).

[0606] Step 2. To a solution of tert-butyl (S)-(2-((3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)carbamate (5.10 g, 15.7 mmol, 1 *eq*) in ACN (60 mL) was added NBS (3.07 g, 17.2 mmol, 1.1 *eq*). The mixture was stirred at 0 °C for 0.5 h. On completion, the mixture was quenched with sat. Na_2SO_3 (50 mL) and extracted with EA (20 mL × 2). The combined organic layers were washed with brine (15 mL× 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1:0 to 3:1) to give tert-butyl (S)-(2-((4-bromo-3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)carbamate (4.31 g, 10.7 mmol, 68% yield) as a yellow oil. LCMS: *m/z* 406.1 (M+1).

[0607] Step 3. To a solution of tert-butyl (S)-(2-((4-bromo-3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)carbamate (4.11 g, 10.2 mmol, 1 *eq*) and iodoethane (2.38 g, 15.2 mmol, 1.5 *eq*) in THF (41 mL) was added NaH (1.22 g, 30.5 mmol, 60% purity, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with sat. NH_4Cl (100 mL) and extracted with ethyl acetate (100 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 (SiO_2, PE:THF= 1:0 to 3:1) to give tert-butyl (S)-(2-((4-bromo-3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)(ethyl)carbamate (4.22 g, 9.77 mmol, 96 % yield) as a colorless oil. LCMS: *m/z* 434.1 (M+1).

[0608] Step 4. To a mixture of tert-butyl (S)-(2-((4-bromo-3-(cyclopropoxymethyl)-1-methyl-1H-pyrazol-5-yl)oxy)propyl)(ethyl)carbamate (4.02 g, 9.31 mmol, 1 *eq*) and 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (3.97 g, 11.2 mmol, 1.2 *eq*) in dioxane (40 mL) and H_2O (8 mL) was added Cs_2CO_3 (9.10 g, 27.93 mmol, 3 *eq*) and Pd(dtbpf)Cl_2 (607 mg, 931 μmol, 0.1 *eq*). The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 1 h under N_2 atmosphere. On completion, the mixture was dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane : Methanol= 1:0 to 20:1) to tert-butyl ((2S)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)(ethyl)carbamate (2.22 g, 3.82 mmol, 41% yield) as a brown oil. LCMS: *m/z* 603.3 (M+23).

[0609] Step 5. To a solution of tert-butyl ((2S)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-

yl)oxy)propyl)(ethyl)carbamate (2.20 g, 3.79 mmol, 1 *eq*) in ACN (22 mL) was added TMSI (758 mg, 3.79 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. On completion, the mixture was quenched with sat. $NaHCO_3$ (40 mL) and extracted with EA (40 mL × 3). The combined organic layers were washed with brine (30 mL× 2), dried over Na_2SO_4, filtered and concentrated to give (2S)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-ethylpropan-1-amine (1.40 g, 2.91 mmol, 77% yield) as a brown solid. LCMS: *m/z* 481.3 (M+1).

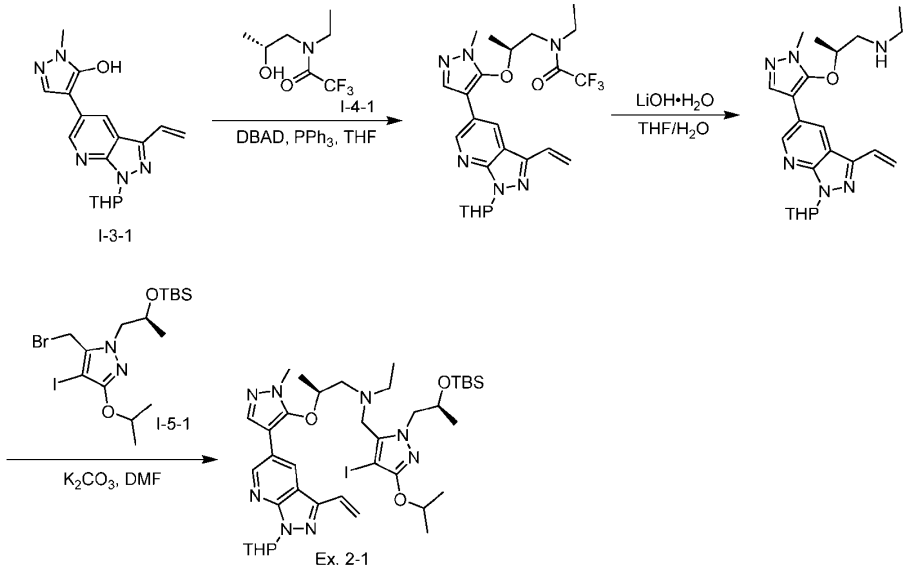
[0610] Step 6. To a solution of (2S)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-ethylpropan-1-amine (650 mg, 1.35 mmol, 1 *eq*) in DMF (6.5 mL) was added K_3PO_4 (574 mg, 2.70 mmol, 2 *eq*) and (S)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-5-(iodomethyl)-3-isopropoxy-1H-pyrazole (839 mg, 1.49 mmol, 1.1 *eq*). The mixture was stirred at 60 °C for 1 h. On completion, the mixture was quenched with water (20 mL) and extracted with EA (15 mL × 3). The combined organic layers were washed with brine (15 mL× 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF= 1:0 to 3:1) to give (2S)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-ethylpropan-1-amine (650 mg, 709 μmol, 52% yield) as a yellow solid. LCMS: *m/z* 917.5 (M+1).

[0611] Step 7. A mixture of (2S)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-2-((3-(cyclopropoxymethyl)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-ethylpropan-1-amine (600 mg, 654 μmol, 1 *eq*), $NaHCO_3$ (137 mg, 1.64 mmol, 2.5 *eq*), TBAC (182 mg, 654 μmol, 1 *eq*) and $Pd(OAc)_2$ (14.7 mg, 65.4 μmol, 0.1 *eq*) in DMF (12 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 130 °C for 1 h under N_2 atmosphere. On completion, the mixture was quenched with water (30 mL) and extracted with EA (25 mL × 3). The combined organic layers were washed with brine (15 mL× 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF= 1:0 to 2:1) to give (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (220 mg, 279 μmol, 43% yield) as a yellow solid. LCMS: *m/z* 789.9 (M+1).

[0612] Step 8. To a solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (190 mg, 241 μmol, 1 *eq*) in MeOH (2.1 mL) was added conc. HCl/H_2O (12 M, 0.7 mL, 34.9 *eq*). The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: CD01-Phenomenex luna C18 150*25*10um; mobile phase: [water(FA)-ACN]; gradient: 22%-52% B over 10 min) to give (2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (75.73 mg, 122.70 μmol, 50.96% yield, 95.71% purity) as a yellow solid.

[0613] General Method A:

[0614] Preparation of (2S)-N-[[2-[(2S)-2-[tert-butyl(dimethyl)silyl]oxypropyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl]-N-ethyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-pyrazolo[3,4-b]pyridin-5-yl)pyrazol-3-yl]oxy-propan-1-amine (Ex. 2-1)



[0615] Step 1. A mixture of 1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-ol (535 mg, 1.64 mmol, 1 *eq*), (R)-N-ethyl-2,2,2-trifluoro-N-(2-hydroxypropyl)acetamide (393.00 mg, 1.97 mmol, 1.2 *eq*) , DBAD (568 mg, 2.47 mmol, 1.5 *eq*) in THF (6 mL) was degassed and purged with N_2 for 3 times, and then PPh_3 (1.29 g, 4.93 mmol, 3 *eq*) was added. The mixture was stirred at 25 °C for 2 h under N_2

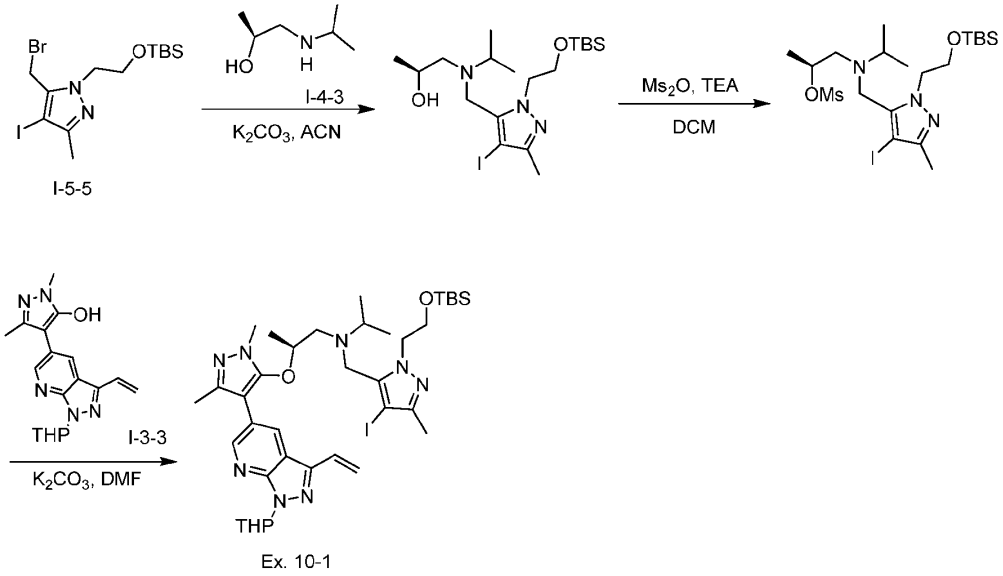
atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 100/1 to 0/1) to give N-ethyl-2,2,2-trifluoro-N-((2S)-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)acetamide (400 mg, 0.395 mmol, 24% yield, 50% purity) as a colorless oil. LCMS: *m/z* 507.2 (M+1).

[0616] Step 2. To a solution of N-ethyl-2,2,2-trifluoro-N-((2S)-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)acetamide (400 mg, 0.395 mmol, 1 *eq*) in THF (2 mL) and H_2O (2 mL) was added $LiOH·H_2O$ (24.9 mg, 0.592 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with EA (5 mL ×3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE: EA = 0:1) to give (2S)-N-ethyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (120 mg, 0.289 mmol, 73% yield, 99% purity) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.82 - 8.78 (m, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 7.84 (s, 1H), 7.06 - 6.95 (m, 1H), 6.23 (d, *J* =18.0 Hz, 1H), 6.02 (d, *J* = 10.4 Hz, 1H), 5.60 (d, *J* = 11.6 Hz, 1H), 4.20 - 4.12 (m, 1H), 4.06 - 4.00 (m, 1H), 3.95 (d, *J* =11.2 Hz, 1H), 3.71 (s, 3H), 2.79 - 2.73 (m, 1H), 2.66 - 2.60 (m, 1H), 2.04 (d, *J* = 13.2 Hz, 1H), 1.98 (s, 2H), 1.91 (d, *J* =12.8 Hz, 1H), 1.82 - 1.73 (m, 1H), 1.63 - 1.55 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 2H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.94 (t, *J* = 6.8Hz, 3H).

[0617] Step 3. To a solution of (2S)-N-ethyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (120 mg, 0.292 mmol, 1 *eq*) and (S)-5-(bromomethyl)-1-(2-(((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazole (181 mg, 0.351 mmol, 1.2 *eq)* in DMF (1.2 mL) was added K_2CO_3 (121 mg, 0.877 mmol, 3 *eq*). The mixture was stirred at 60 °C for 0.5 h. On completion, the reaction mixture was quenched with H_2O (6 mL) and extracted with EA (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE:EA= 5:1) to give (2S)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-N-ethyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (155 mg, 0.163 mmol, 56% yield, 89% purity) as a colorless oil. LCMS: *m/z* 847.2 (M+1).

[0618] General Method B:

[0619] Preparation of (2S)-N-((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1H-pyrazol-5-yl)methyl)-2-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-isopropylpropan-1-amine (Ex. 10-1)



Ex. 10-1

[0620] Step 1. To a solution of 5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1H-pyrazole (500 mg, 1.09 mmol, 1 eq) in ACN (10 mL) was added K_2CO_3 (451 mg, 3.27 mmol, 3 eq) and (S)-1-(isopropylamino)propan-2-ol (140 mg, 1.20 mmol, 1.1 eq). The mixture was stirred at 80 °C for 2 hours. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give (S)-1-(((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1H-pyrazol-5-yl)methyl)(isopropyl)amino)propan-2-ol (520 mg, 1.05 mmol, 96% yield) as a white oil. LCMS: *m/z* 496.5 (M+1).

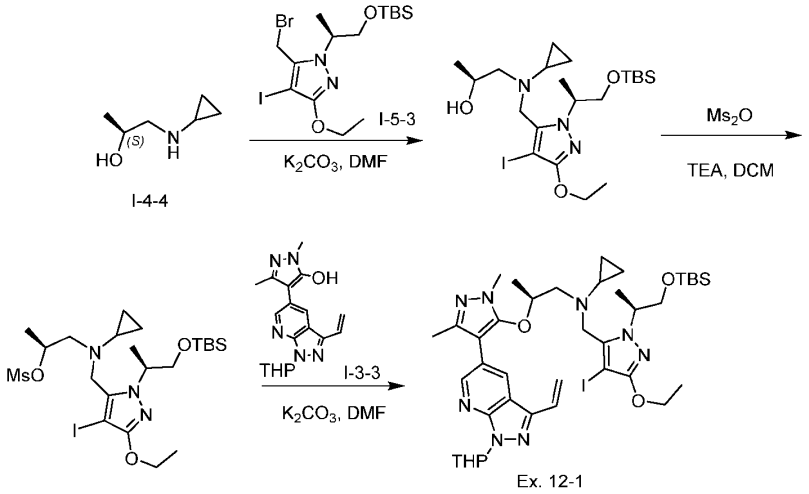
[0621] Step 2. To a solution of (S)-1-(((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1H-pyrazol-5-yl)methyl)(isopropyl)amino)propan-2-ol (500 mg, 1.01 mmol, 1 eq) in DCM (5 mL) was added TEA (306 mg, 3.03 mmol, 3 eq) and methylsulfonyl methanesulfonate (439 mg, 2.52 mmol, 2.5 eq). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was partitioned between DCM (10 mL × 3) and water (10 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (*R*)-1-(((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1*H*-pyrazol-5-yl)methyl)(isopropyl)amino)propan-2-yl methanesulfonate (570 mg, 0.993 mmol,

98% yield) as yellow oil. LCMS: *m/z* 574.3 (M+1).

[0622] Step 3. To a solution of *(R)*-1-(((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1*H*-pyrazol-5-yl)methyl)(isopropyl)amino)propan-2-yl methanesulfonate (570 mg, 0.993 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (412 mg, 2.98 mmol, 3 eq) and 1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-ol (269 mg, 0.794 mmol, 0.8 eq). The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was partitioned between ethyl acetate (15 mL × 3) and water (15 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give (2S)-N-((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-methyl-1H-pyrazol-5-yl)methyl)-2-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-isopropylpropan-1-amine (240 mg, 0.293 mmol, 29% yield) as a yellow oil.

[0623] General Method C:

[0624] Preparation of N-((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-N-((2S)-2-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)cyclopropanamine (Ex. 12-1)



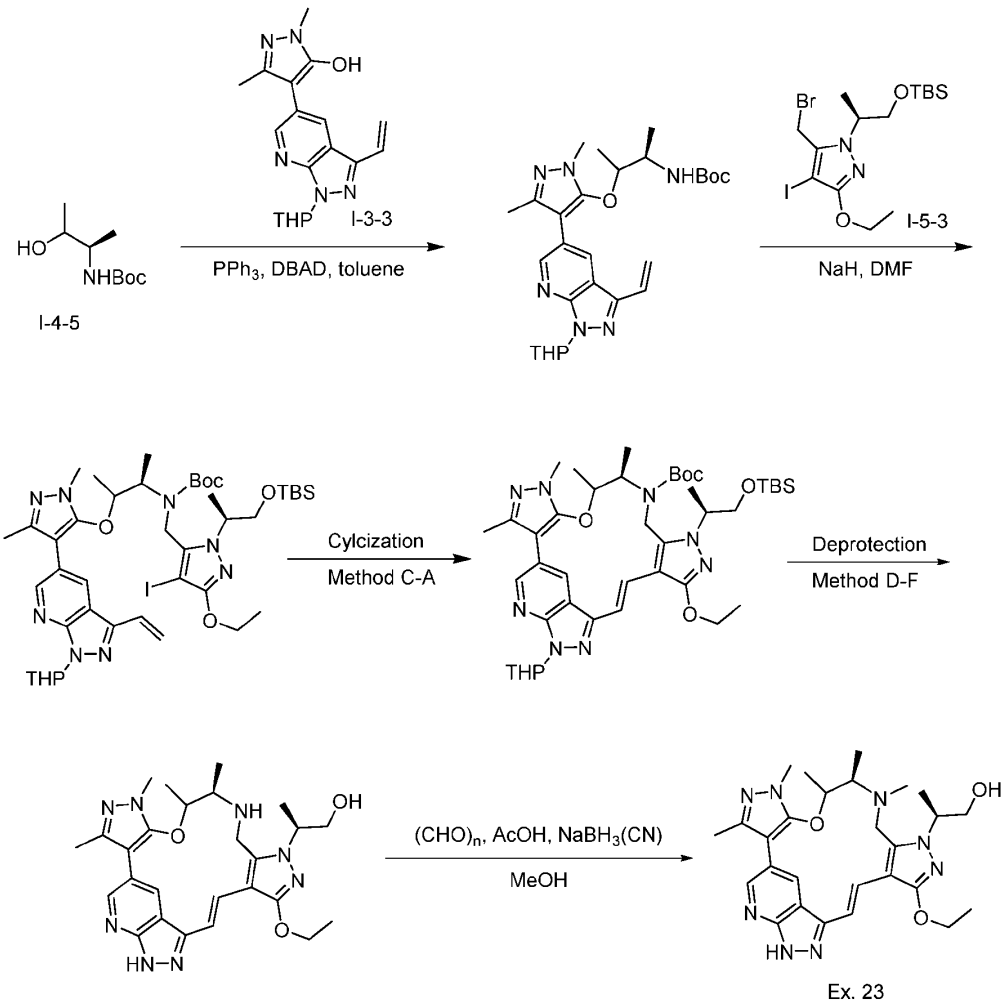
[0625] Step 1. To a solution of (2S)-1-(cyclopropylamino)propan-2-ol (1.03 g, 8.94 mmol, 1.5 eq), (S)-5-(bromomethyl)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazole (3.00 g, 5.96 mmol, 1 eq) in DMF (15 mL) was added K_2CO_3 (2.47 g, 17.8 mmol, 3 eq), and the mixture was stirred at 25 °C for 3 hours. On completion, the mixture was quenched with H_2O (200 mL) and extracted with ethyl acetate (100 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 (SiO_2, Petroleum ether/Ethyl acetate = 3:1) to give (S)-1-(((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(cyclopropyl)amino)propan-2-ol (3.00 g, 5.58 mmol, 93% yield) as a colorless oil. LCMS: m/z 538.4 (M+1).

[0626] Steps 2-3 were performed according to those described in General Method B to afford N-((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-N-((2S)-2-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)cyclopropanamine (400 mg, 0.465 mmol, 45% yield) as a white solid.

[0627] General Method D:

[0628] Preparation of (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Ex. 23)



[0629] Step 1. A mixture of 1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-pyrazol-5-ol (900 mg, 2.65 mmol, 1 *eq*), tert-butyl ((2R)-3-hydroxybutan-2-yl)carbamate (1.00 g, 5.30 mmol, 2 *eq*), PPh_3 (2.09 g, 7.96 mmol, 3 *eq*), DBAD (1.83 g, 7.96 mmol, 3 *eq*) in toluene (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was filtered and concentrated to give a residue. On completion, the reaction mixture was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 3:1) to give *tert*-butyl ((2*R*)-3-((1,3-dimethyl-4-(1-(tetrahydro-2*H*-pyran-2-yl)-3-vinyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)butan-2-yl)carbamate (800 mg, 1.57 mmol, 59% yield) as a white solid. LCMS: *m/z* 511.4 (M+1).

[0630] Step 2. To a solution of tert-butyl ((2R)-3-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)butan-2-yl)carbamate (750 mg, 1.47 mmol, 1 *eq*) in DMF (10 mL) was added NaH (117 mg, 2.94 mmol, 60% purity,

2 *eq*) and (S)-5-(bromomethyl)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazole (1.11 g, 2.20 mmol, 1.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was quenched with water (30 mL) and extracted with ethyl acetate (30 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 (SiO_2, Petroleum ether/THF = 1:0 to 1:1) to give tert-butyl ((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)((2R)-3-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)butan-2-yl)carbamate (1.00 g, 1.07 mmol, 73% yield) as a yellow solid. LCMS: *m/z* 933.3 (M+1).

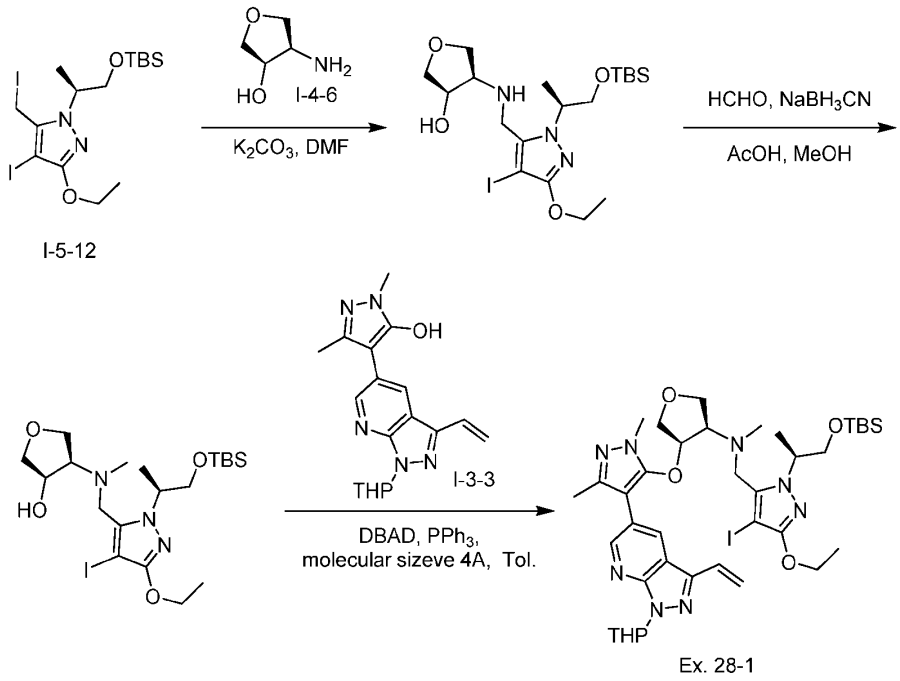
[0631] Step 3 was conducted in a manner described in Cyclization Method C-A.

[0632] Step 4 was conducted in a manner described in Deprotection Method D-F.

[0633] Step 5. To a solution of (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (40.0 mg, 0.0737 mmol, 1 *eq*, HCl) and Paraformaldehyde (40.0 mg, 0.0737 mmol, 1 *eq*) in MeOH (2 mL) was added AcOH (4.42 mg, 0.0737 mmol, 1 *eq*) and $NaBH_3CN$ (5.55 mg, 0.0884 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC purification (column: CD02-Waters Xbridge BEH C18 150 x 25 x 10um; mobile phase: [water(NH_3H_2O)-ACN]; gradient: 34%-54% B over 14 min) to give (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (1.27 mg, 0.00238 mmol, 3.23% yield, 97.61% purity) as a yellow solid.

[0634] General Method E:

[0635] Preparation of (3R,4R)-N-((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-4-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-methyltetrahydrofuran-3-amine (Ex. 28-1)



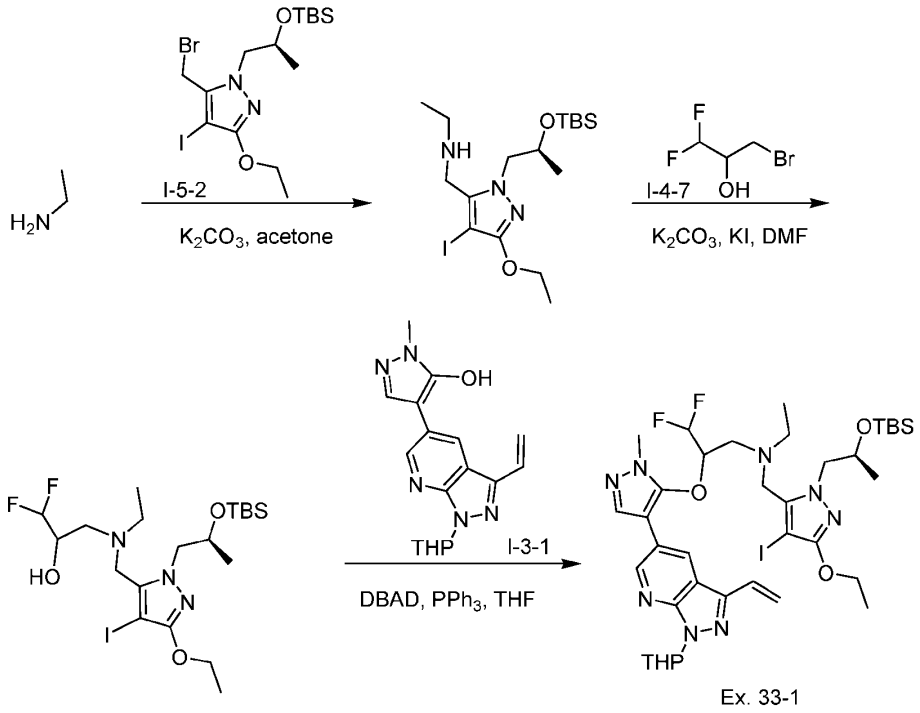
[0636] Step 1. To a solution of (S)-1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-5-(iodomethyl)-1H-pyrazole (3.10 g, 5.63 mmol, 1 *eq*) and (3R,4R)-4-aminotetrahydrofuran-3-ol (581 mg, 5.63 mmol, 1 *eq*) in DMF (20 mL) was added K_2CO_3 (1.56 g, 11.3 mmol, 2 *eq*). The mixture was stirred at 80 °C for 1 hr. On completion, the reaction mixture was partitioned between ethyl acetate (200 mL × 3) and water (200 mL). The combined organic phase was washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (3R,4R)-4-(((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)amino)tetrahydrofuran-3-ol (2.90 g, 4.69 mmol, 83% yield, 85% purity) as a colorless oil. LCMS: *m/z* 526.2 (M+1).

[0637] Step 2. To a solution of (3R,4R)-4-(((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)amino)tetrahydrofuran-3-ol (2.90 g, 5.52 mmol, 1 *eq*) in MeOH (250 mL) was added sodium cyanoborohydride (2.08 g, 33.1 mmol, 6 *eq*), acetic acid (1.33 g, 22.1 mmol, 1.26 mL, 4 *eq*) and formaldehyde (994 mg, 33.1 mmol, 6 *eq*). The mixture was stirred at 25 °C for 40 hr. On completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 1:0 to 1:1) to give (3R,4R)-4-(((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(methyl)amino)tetrahydrofuran-3-ol (2.56 g, 4.74 mmol, 86% yield) as a colorless oil. LCMS: *m/z* 540.3 (M+1).

[0638] Step 3. A mixture of (3R,4R)-4-(((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(methyl)amino)tetrahydrofuran-3-ol (1.10 g, 2.04 mmol, 1.8 *eq*), 1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-ol (384 mg, 1.13 mmol, 1 *eq*), PPh_3 (891 mg, 3.40 mmol, 3 *eq*) and molecular sieves 4A (1.10 g, 1.13 mmol, 1.00 *eq*) in toluene (10 mL) was degassed and purged with N_2 for 3 times, and then to the mixture was added DBAD (782.44 mg, 3.40 mmol, 3 *eq*) in toluene (3 mL) and stirred at 25 °C for 1 hr under N_2 atmosphere. On completion, the reaction mixture was filtered, and the filtrate was partitioned between ethyl acetate (50 mL × 3) and water (50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1:0 to 1:1) to give N-((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-4-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)-N-methyltetrahydrofuran-3-amine (700 mg, 0.813 mmol, 72% yield, mixture of racemate) as a yellow oil. LCMS: *m/z* 861.1 (M+1).

[0639] General Method F:

[0640] Preparation of N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-N-ethyl-3,3-difluoro-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (Ex. 33-1).



Ex. 33-1

[0641] Step 1. To a solution of ethanamine (2 M, 19.8 mL, 10 *eq*) in acetone (10 mL) was added K_2CO_3 (1.65 g, 11.9 mmol, 3 *eq*) and (S)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazole (2.00 g, 3.97 mmol, 1 *eq*). The mixture was stirred at 25 °C for 4 hours. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give (S)-N-((1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)ethanamine (1.60 g, 3.42 mmol, 86% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.31 (q, *J* = 6.8 Hz, 2H), 4.18 - 4.10 (m, 1H), 4.00 (d, *J* = 3.2 Hz, 1H), 3.98 - 3.94 (m, 1H),3.92 (s, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 2.73 (q, *J* = 7.2 Hz, 2H), 1.81 - 1.56 (m, 1H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.00 (s, 3H), -0.19 (s, 3H).

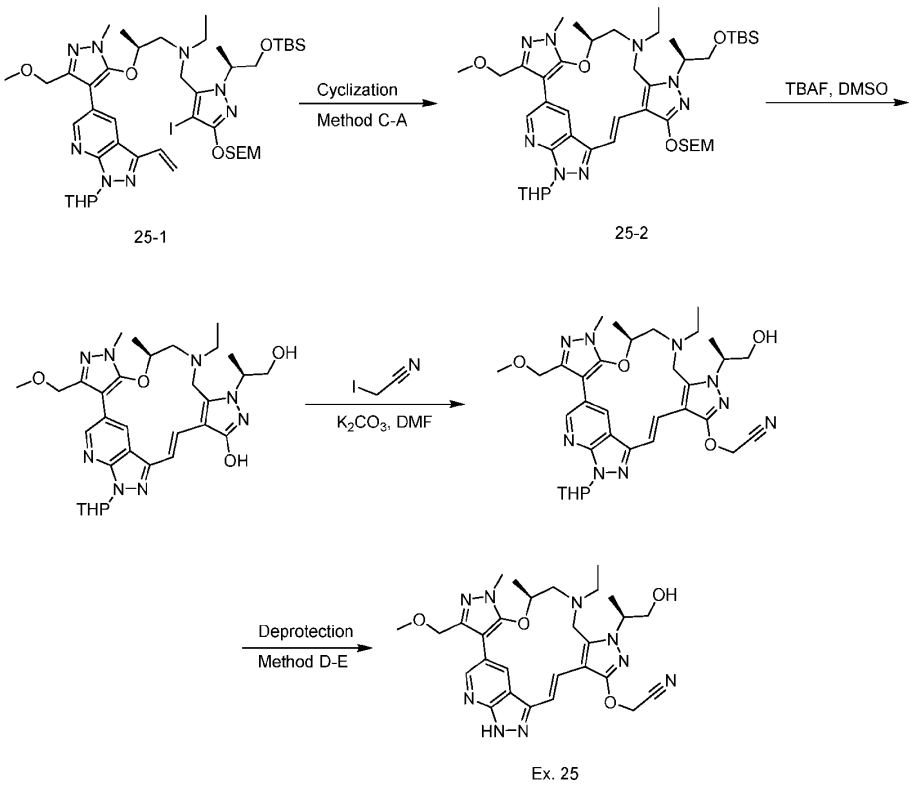
[0642] Step 2. To a solution of (S)-N-((1-(2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)ethanamine (1.50 g, 3.21 mmol, 1 *eq*) and 3-bromo-1,1-difluoro-propan-2-ol (1.12 g, 6.42 mmol, 2 *eq*) in DMF (20 mL) was added KI (532 mg, 3.21 mmol, 1 *eq*) and K_2CO_3 (1.33 g, 9.63 mmol, 3 *eq*). The mixture was stirred at 25 °C for 14 hours. On completion, the reaction mixture was partitioned between ethyl acetate (30 mL × 3) and water (30 mL), and the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2,

Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give 3-(((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(ethyl)amino)-1,1-difluoropropan-2-ol (840 mg, 1.50 mmol, 46% yield) as a yellow oil. LCMS: *m/z* 562.5 (M+1).

[0643] Step 3. A mixture of 1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-ol (380 mg, 1.17 mmol, 1 *eq*), 3-(((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(ethyl)amino)-1,1-difluoropropan-2-ol (721 mg, 1.28 mmol, 1.1 *eq*), DBAD (806 mg, 3.50 mmol, 3 *eq*), PPh_3 (918 mg, 3.50 mmol, 3 *eq*) in THF (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 1 hour under N_2 atmosphere. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-N-ethyl-3,3-difluoro-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (630 mg, 0.725 mmol, 62% yield) as a yellow solid. LCMS: *m/z* 869.3 (M+1).

[0644] General Method G:

[0645] Preparation of {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (Ex. 25)



[0646] Step 1. Compound 25-1 (prepared following the procedures described in General Method A from I-3-4, I-4-1, and I-5-13) was cyclized using Cyclization Method C-A to provide compound 25-2.

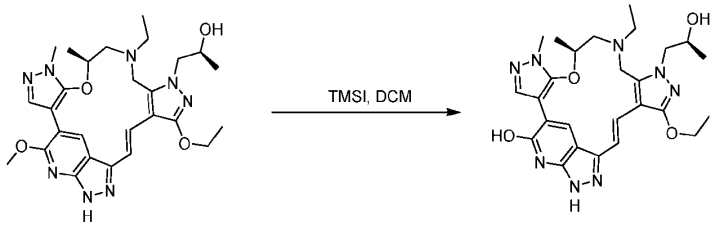
[0647] Step 2. To a solution of (10*S*,17*E*)-14-[(2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}propan-2-yl]-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-16-{[2-(trimethylsilyl)ethoxy]methoxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (250 mg, 0.297 mmol, 1 *eq*) in DMSO (2.5 mL) was added TBAF (1 M, 1.76 mL, 6 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the mixture was quenched with water (20 mL) and extracted with EA (15 mL × 3). The combined organic layers were washed with brine (15 mL× 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF (1% NH_3.MeOH)= 1:0 to 1:3) to give (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (120 mg, 0.198 mmol, 67% yield) as a yellow solid. LCMS: *m/z* 607.3 (M+1).

[0648] Step 3. To a solution of (10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-

(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (100 mg, 0.165 mmol, 1 *eq*) in DMF (2.5 mL) was added K_2CO_3 (68.3 mg, 0.494 mmol, 3 *eq*) and 2-iodoacetonitrile (33.0 mg, 0.198 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with water (20 mL) and extracted with EA (15 mL × 3). The combined organic layers were washed with brine (15 mL × 2), dried over Na_2SO_4, filtered and concentrated to give {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (140 mg, crude) as a brown oil. LCMS: *m/z* 646.3 (M+1).

[0649] Step 4 was conducted in a manner described in Deprotection Method D-E to afford Ex. 25.

[0650] Preparation of (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol (Ex. 36)

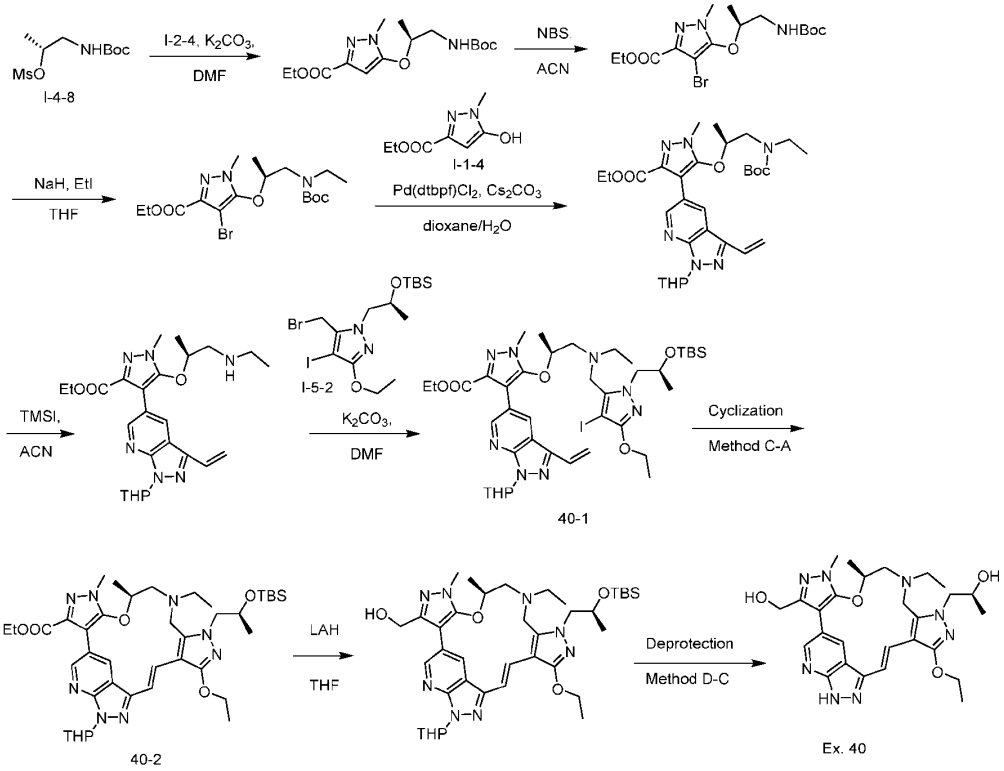


Ex. 22 Ex. 36

[0651] Step 1. To a solution of (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (25.0 mg, 0.0465 mmol, 1 eq) in DCM (1 mL) was added TMSI (0.0931 mmol, 12.6 μL, 2 eq). The mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was quenched by addition sat. $NaHCO_3$ (2 mL) at 25 °C, then diluted with H_2O (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. And then the residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase:[water(FA)-ACN]; gradient: 7%-37% B over 8 min) to give (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol (1.74 mg, 0.00326 mmol, 6% yield, 97% purity) as a yellow solid.

[0652] General Method H:

[0653] Preparation of (2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (Ex. 40)



[0654] Step 1. To a solution of (R)-1-((tert-butoxycarbonyl)amino)propan-2-yl methanesulfonate (4.91 g, 19.3 mmol, 1.1 *eq*) and ethyl 5-hydroxy-1-methyl-1*H*-pyrazole-3-carboxylate (3.00 g, 17.6 mmol, 1 *eq*) in DMF (40 mL) was added K_2CO_3 (7.31 g, 52.8 mmol, 3 *eq*), and the mixture was stirred at 80 °C for 12 h. On completion, the mixture was quenched with water (100 mL) and extracted with EA (150 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 4:1 to 3:1) to give ethyl (*S*)-5-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)-1-methyl-1*H*-pyrazole-3-carboxylate (5.00 g, 15.2 mmol, 86% yield) as a yellow oil. LCMS: *m/z* 328.2 (M+1).

[0655] Step 2. To a solution of ethyl (*S*)-5-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)-1-methyl-1*H*-pyrazole-3-carboxylate (5.00 g, 15.2 mmol, 1 *eq*) in ACN (50 mL) was added NBS (2.72 g, 15.2 mmol, 1 *eq*). The mixture was stirred at 0 °C for 1 h. On completion, the mixture was quenched with water (200 mL) and extracted with EA (250 mL × 3). The

combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give ethyl (S)-4-bromo-5-((1-((tert-butoxycarbonyl)amino)propan-2-yl)oxy)-1-methyl-1H-pyrazole-3-carboxylate (6.20 g, 15.2 mmol, 100% yield) as a yellow oil. LCMS: *m/z* 408.1 (M+1).

[0656] Step 3. To a solution of ethyl (S)-4-bromo-5-((1-((tert-butoxycarbonyl)amino)propan-2-yl)oxy)-1-methyl-1H-pyrazole-3-carboxylate (4.20 g, 10.3 mmol, 1 *eq*) in THF (62 mL) was added NaH (496 mg, 12.4 mmol, 60% purity, 1.2 *eq*) and iodoethane (3.22 g, 20.6 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched with water (100 mL) and extracted with EA (150 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 (SiO_2, PE/THF= 1:0 to 1:1) to give ethyl (S)-4-bromo-5-((1-((tert-butoxycarbonyl)(ethyl)amino)propan-2-yl)oxy)-1-methyl-1H-pyrazole-3-carboxylate (1.60 g, 3.68 mmol, 35% yield) as a yellow oil. LCMS: *m/z* 456.2 (M+23).

[0657] Step 4. To a solution of ethyl (S)-4-bromo-5-((1-((tert-butoxycarbonyl)(ethyl)amino)propan-2-yl)oxy)-1-methyl-1H-pyrazole-3-carboxylate (1.40 g, 3.22 mmol, 1 *eq*) and 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (1.37 g, 3.87 mmol, 1.2 *eq*) in dioxane (30 mL) and H_2O (6 mL) was added Cs_2CO_3 (3.15 g, 9.67 mmol, 3 *eq*) and $Pd(dtbpf)Cl_2$ (210 mg, 0.322 mmol, 0.1 *eq*). The mixture was stirred at 80 °C for 2 h. On completion, the mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the filtrated was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF= 1:0 to 1:1) to give ethyl 5-(((S)-1-((tert-butoxycarbonyl)(ethyl)amino)propan-2-yl)oxy)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazole-3-carboxylate (1.16 g, 1.99 mmol, 62% yield) as a yellow oil. LCMS: *m/z* 583.5 (M+1).

[0658] Step 5. To a solution of ethyl 5-(((S)-1-((tert-butoxycarbonyl)(ethyl)amino)propan-2-yl)oxy)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazole-3-carboxylate (1.06 g, 1.82 mmol, 1 *eq*) in ACN (10 mL) was added TMSI (364 mg, 1.82 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the filtrated was concentrated to give ethyl 5-(((S)-1-(ethylamino)propan-2-yl)oxy)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazole-3-carboxylate (520 mg, 1.08 mmol, 59% yield) as a yellow oil. LCMS: *m/z* 483.3 (M+1).

[0659] Step 6. To a solution of ethyl 5-(((S)-1-(ethylamino)propan-2-yl)oxy)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazole-3-carboxylate (482 mg, 0.998 mmol, 1 *eq*) and (S)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl) -3-ethoxy-4-iodo-1H-pyrazole (603 mg, 1.20 mmol, 1.2 *eq*) in DMF (5 mL) was added K_2CO_3 (276 mg, 2.00 mmol, 2 *eq*). The mixture was stirred at 60 °C for 2 h. On completion, the mixture was quenched with water (60 mL) and extracted with EA (60 mL × 3). The residue was purified by column chromatography (SiO_2, PE/THF= 1:0 to 2:1) to give ethyl 5-(((S)-1-(((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)(ethyl)amino)propan-2-yl)oxy)-1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazole-3-carboxylate (540 mg, 0.596 mmol, 60% yield) as a colorless oil. LCMS: *m/z* 905.5 (M+1).

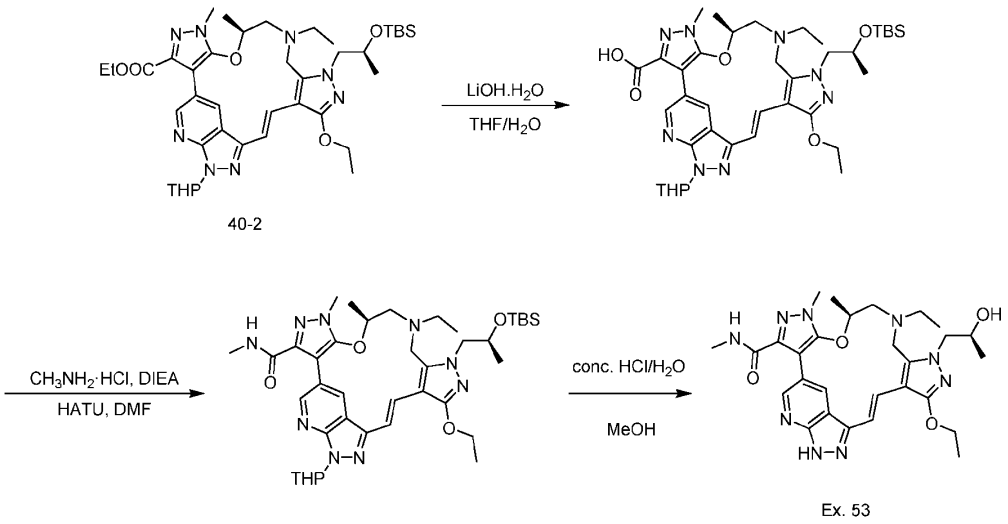
[0660] Step 7 was conducted as described in Cyclization Method C-A.

[0661] Step 8. To a solution of ethyl (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxylate (380 mg, 0.332 mmol, 1 *eq*) in THF (5 mL) was added LAH (2.5 M, 159 μL, 1.2 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, the mixture was filtered and concentrated to give [(10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-6-yl]methanol (244 mg, 0.331 mmol, 100% yield) as a yellow oil. LCMS: *m/z* 735.5 (M+1).

[0662] Step 9 was performed as described in Deprotection Method D-C to afford Ex. 40 (67.08 mg, 0.125.00 mmol, 39.95% yield) as a yellow solid.

[0663] General Method I:

[0664] Preparation of (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide (Ex. 53)



40-2

Ex. 53

[0665] Step 1. To a solution of ethyl (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxylate (225 mg, 0.290 mmol, 1 eq) in THF (3 mL) and H_2O (1 mL) was added LiOH.H_2O (36.5 mg, 0.869 mmol, 3 eq). The mixture was stirred at 40 °C for 4 h. On completion, the mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 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 (SiO_2, DCM/MeOH= 1:0 to 1:1) to give (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxylic acid (200 mg, 0.267 mmol, 92% yield) as a yellow solid. LCMS: *m/z* 749.4 (M+1).

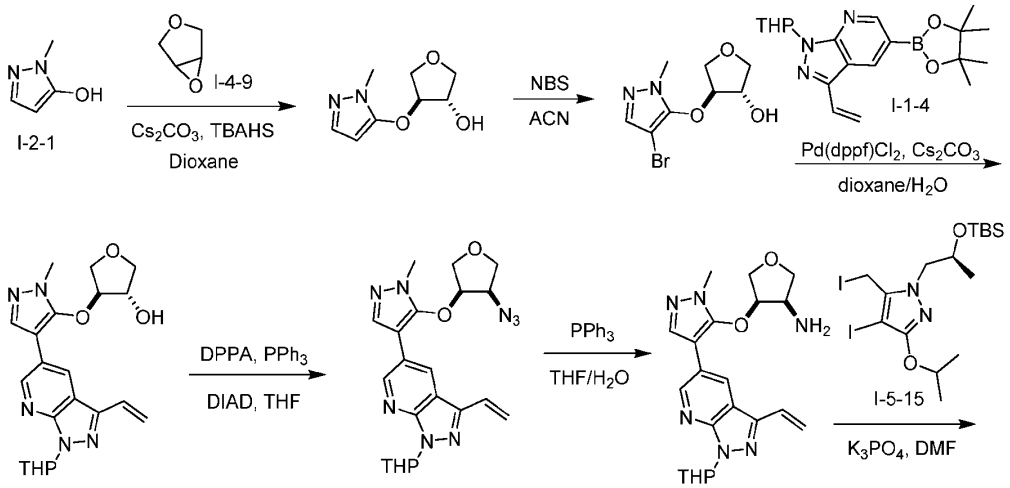
[0666] Step 2. To a solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxylic acid (70.0 mg, 0.0935 mmol, 1 *eq*) in DMF (1 mL) was added DIEA (36.2 mg, 0.280 mmol, 3 *eq*), methanamine hydrochloride (12.6 mg, 0.187 mmol, 2 *eq*) and stirred at 25 °C for 30 mins. Then, HATU (71.1 mg, 0.187 mmol, 2 *eq*) was added into the mixture and stirred at 25 °C for 1 h. On completion, the mixture was quenched with water (4 mL) and extracted with EA (5 mL×3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-*N*,8,10-trimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-

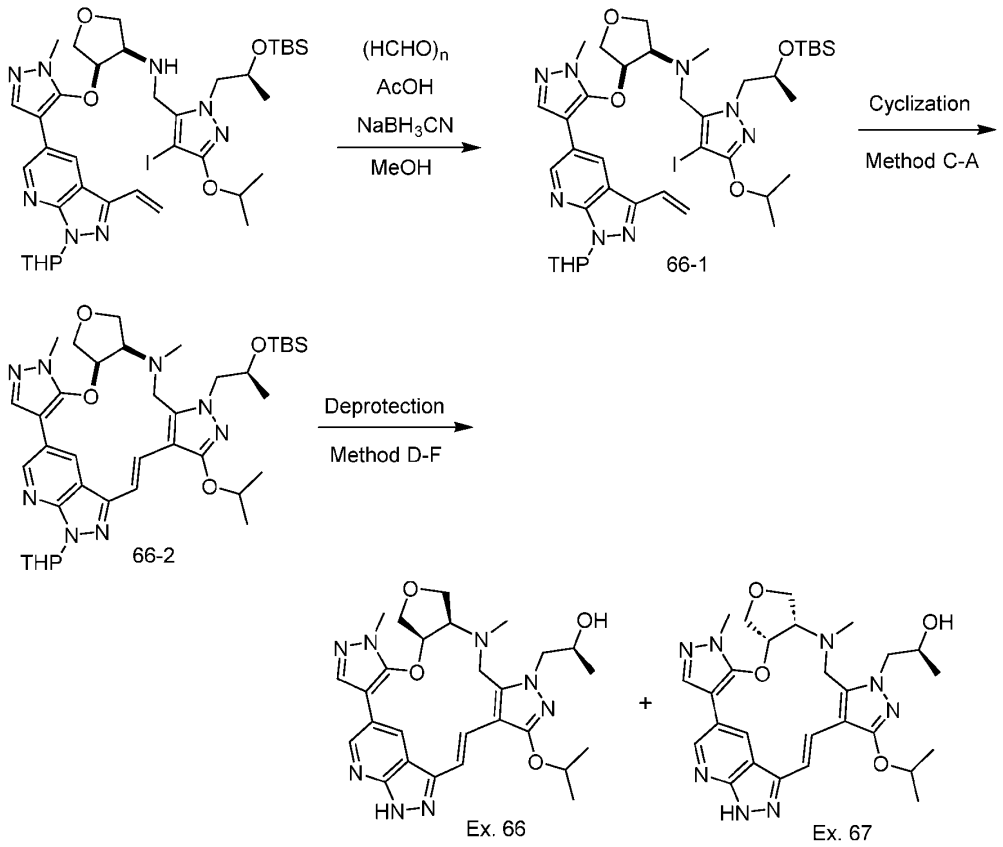
(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide (100 mg, 0.0919 mmol, 98% yield, 70% purity) as a yellow solid. LCMS: *m/z* 762.4 (M+1).

[0667] Step 3. To a solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-16-ethoxy-12-ethyl-*N*,8,10-trimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide (40.0 mg, 0.0525 mmol, 1 *eq*) in MeOH (0.6 mL) was added conc. HCl/H_2O (12 M, 0.2 mL). The mixture was stirred at 25 °C for 30 mins. On completion, the mixture was concentrated to give a residue, and the residue was purified by prep-HPLC (column: CD02-Waters Xbridge BEH C18 150*25*10um; mobile phase: [water(NH_3H_2O)-ACN]; gradient: 26%-46% B over 10 min) to give (10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide (3.00 mg, 0.00532 mmol, 10.14% yield) as an off-white solid.

[0668] General Method J:

[0669] Preparation of (2*S*)-1-[(4a*R*,7a*R*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol (Ex. 66) and (2*S*)-1-[(4a*S*,7a*S*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol (Ex. 67)





[0670] Step 1. To a solution of 1-methyl-1H-pyrazol-5-ol (10.0 g, 101 mmol, 1 *eq*), 3,6-dioxabicyclo[3.1.0]hexane (13.1 g, 152 mmol, 1.5 *eq*) in dioxane (100 mL) was added Cs_2CO_3 (66.4 g, 203 mmol, 2 *eq*) and tetrabutylammonium hydrogensulfate (3.46 g, 10.1 mmol, 0.1 *eq*). The mixture was stirred at 120 °C for 12 hours. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 1:0 to 0:1) to give (3S,4S)-4-((1-methyl-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-ol (6.00 g, 32.5 mmol, 31% yield) as a yellow oil. LCMS: *m/z* (M+1: 185.2).

[0671] Step 2. To a solution of (3S,4S)-4-((1-methyl-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-ol (3.30 g, 17.9 mmol, 1 *eq*) in ACN (33 mL) was added NBS (3.19 g, 17.9 mmol, 1 *eq*). The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was quenched with saturated solution of Na_2SO_3 (20 mL) and extracted with ethyl acetate (25 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 (SiO_2, Petroleum ether/THF = 1:0 to 4:1) to give (3S,4S)-4-((4-bromo-1-methyl-1H-pyrazol-5-

yl)oxy)tetrahydrofuran-3-ol (4.70 g, 17.8 mmol, 99% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (s, 1H), 5.10 - 5.07 (m, 1H), 4.54 - 4.50 (m, 1H), 4.21 - 4.16 (m, 1H), 4.12 -4.07 (m, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.86 - 3.81 (m, 1H), 3.65 (s, 3H), 2.75 (s, 1H).

[0672] Step 3. A mixture of (3S,4S)-4-((4-bromo-1-methyl-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-ol (2.00 g, 7.60 mmol, 1 *eq*), 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (2.70 g, 7.60 mmol, 1 *eq*), Cs_2CO_3 (7.43 g, 22.8 mmol, 3 *eq*), $Pd(dppf)Cl_2$ (278 mg, 380 μmol, 0.05 *eq*) in H_2O (8 mL) and dioxane (40 mL) was degassed and purged with N_2 3 times, and then, the mixture was stirred at 80 °C for 0.5 hours under N_2 atmosphere. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 0:1) to give (3S,4S)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-ol (1.10 g, 2.67 mmol, 35% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.69 - 8.63 (m, 1H), 8.31 - 8.21 (m, 1H), 7.55 (d, *J* = 4.0 Hz, 1H), 7.07 - 6.96 (m, 1H), 6.14 - 6.05 (m, 2H), 5.61 (d, *J* = 11.6 Hz, 1H), 4.47 - 4.37 (m, 2H), 4.24 - 4.02 (m, 3H), 3.91 - 3.85 (m, 2H), 3.77 - 3.75 (m, 1H), 3.75 - 3.72 (m, 3H), 2.70 - 2.58 (m, 1H), 2.21 - 2.08 (m, 1H), 2.01 - 1.92 (m, 1H), 1.84 - 1.74 (m, 2H), 1.68 - 1.55 (m, 1H).

[0673] Step 4. To a mixture of (3S,4S)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-ol (1.00 g, 2.43 mmol, 1 *eq*) in THF (10.0 mL), was added PPh_3 (764 mg, 2.92 mmol, 1.2 *eq*), and DIAD (589 mg, 2.92 mmol, 1.2 *eq*) at 0 °C, and the mixture was degassed and purged with N_2 for 3 times. To the mixture was added the DPPA (802 mg, 2.92 mmol, 1.2 *eq*), and then the mixture was stirred at 0 °C for 4 hours under N_2 atmosphere. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1:0 to 1:1) to give 5-(5-(((3R,4R)-4-azidotetrahydrofuran-3-yl)oxy)-1-methyl-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (600 mg, 1.37 mmol, 56% yield) as a yellow solid. LCMS: *m/z* (M+1: 437.2)

[0674] Step 5. To a solution of 5-(5-(((3R,4R)-4-azidotetrahydrofuran-3-yl)oxy)-1-methyl-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (500 mg, 1.15 mmol, 1 *eq*) in THF (5 mL) was added PPh_3 (360 mg, 1.37 mmol, 1.2 *eq*) and H_2O (1.5 mL). The mixture was stirred at 25 °C for 14 hours. On completion, the reaction mixture was partitioned between 2-MeTHF (10 mL × 3) and water (5 mL), and the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MEOH = 1:0 to 0:1) to give (3R,4R)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-

yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-amine (250 mg, 0.609 mmol, 53% yield) as a yellow oil. LCMS: *m/z* (M+1: 411.2).

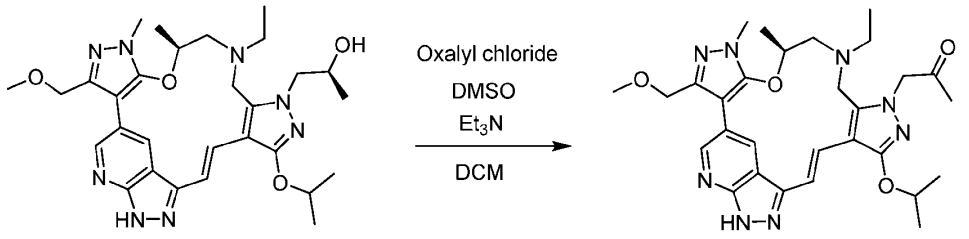
[0675] Step 6. To a solution of (3R,4R)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-amine (200 mg, 0.487 mmol, 1 *eq*) in DMF (5 mL) was added K_3PO_4 (206 mg, 0.974 mmol, 2 *eq*) and tert-butyl-[(1S)-2-[4-iodo-5-(iodomethyl)-3-isopropoxy-pyrazol-1-yl]-1-methyl-ethoxy]-dimethyl-silane (302 mg, 0.535 mmol, 1.1 *eq*), and the mixture was stirred at 60 °C for 3 hours. On completion, the reaction mixture was partitioned between ethyl acetate (10 mL × 3) and water (15 mL), and the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF = 1:0 to 2:1) to give (3R,4R)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-amine (220 mg, 0.259 mmol, 53% yield) as a yellow oil. LCMS: *m/z* (M+1: 847.2).

[0676] Step 7. To a solution of (3R,4R)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-amine (200 mg, 0.236 mmol, 1 *eq*) in MeOH (2 mL) was added $(HCHO)_n$ (200 mg, 2.36 mmol, 10 *eq*) and AcOH (21.2 mg, 0.354 mmol, 1.5 *eq*) at 0 °C for 0.5 hours. $NaBH_3CN$ (37.1 mg, 0.590 mmol, 2.5 *eq*) was added, and the mixture was stirred at 0 °C for 13.5 hours. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF = 1:0 to 0:1) to give (3R,4R)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-N-methyl-4-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)tetrahydrofuran-3-amine (90.0 mg, 0.104 mmol, 44% yield) as a yellow oil. LCMS: *m/z* (M+1: 861.3).

[0677] Step 8 was conducted as described in Cyclization Method C-A.

[0678] Step 9 was performed as described in Deprotection Method D-F to afford Ex. 66 (8.00 mg, 0.013 mmol, 68.80% yield, 86% purity) as a yellow solid and Ex. 67 (3.11 mg, 0.0052 mmol, 10.13% yield, 98% purity, FA salt) as a white solid.

[0679] Preparation of 1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-one (Ex. 71)

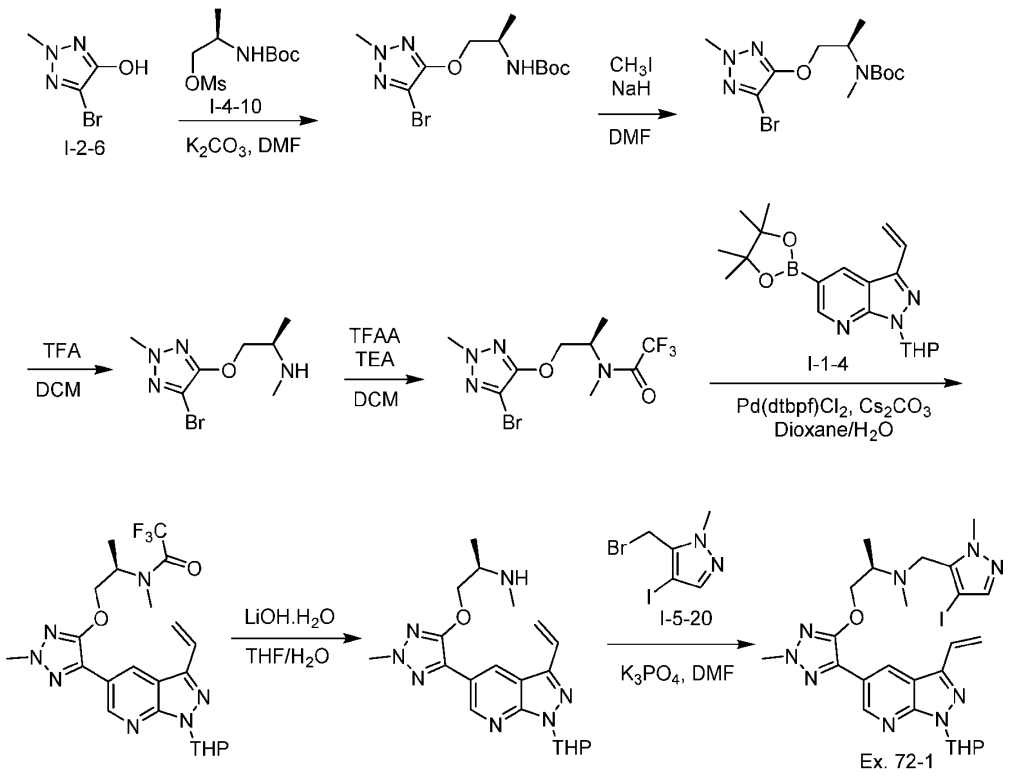


Ex. 20 Ex. 71

[0680] Step 1. A solution of oxalyl chloride (56.19 mg, 0.443 mmol, 0.039 mL) in CH_2Cl_2 (0.16 mL) was cooled to -78 °C, and a solution of DMSO (69.18 mg, 0.885 mmol, 0.063 mL) in CH_2Cl_2 (0.16 mL) was added dropwise. After stirring for 15 minutes at -78 °C, a solution of (2S)-1-[(11E,26S)-36-ethyl-24-isopropoxy-21-(methoxymethyl)-26,34-dimethyl-38-oxa-29,30,31,32,33,34,35,36-octazapentacyclohexacosa-7(16),8(30),11,17(23),18,20(31),21(32),22(25),24(33)-nonaen-35-yl]propan-2-ol (Ex. 20, 50 mg, 0.089 mmol) in DCM (0.3 mL) was slowly added dropwise. After stirring for 30 min at -78 °C, triethylamine (134.40 mg, 1.33 mmol, 0.185 mL) was added dropwise. The reaction was stirred for an additional 30 min at -78 °C, and then slowly allowed to warm to room temperature. The mixture was diluted with water (0.2 mL), extracted with DCM (2 x 1 mL), washed with brine, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give 1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-one (8.98 mg, 0.0132 mmol, 15% yield, 99.4% purity, TFA salt) as a yellow solid (Ex. 71).

[0681] General Method K:

[0682] Preparation of (2R)-N-((4-iodo-1-methyl-1H-pyrazol-5-yl)methyl)-N-methyl-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-amine (Ex. 72-1)



[0683] Step 1. To a solution of 5-bromo-2-methyl-2H-1,2,3-triazol-4-ol (1.80 g, 10.1 mmol, 1 *eq*) in DMF (18 mL) was added K_2CO_3 (4.19 g, 30.3 mmol, 3 *eq*) and (R)-2-((tert-butoxycarbonyl)amino)propyl methanesulfonate (2.56 g, 10.1 mmol, 1 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the mixture was quenched with water (50 mL) and extracted with EA (50 mL × 3). The combined organic layers were washed with brine (50 mL× 2), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF= 1:0 to 5:1) to give tert-butyl (R)-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)carbamate (350 mg, 1.04 mmol, 10% yield) as a colorless oil. LCMS: *m/z* (M+23: 357.0).

[0684] Step 2. To a solution of tert-butyl (R)-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)carbamate (300 mg, 895 μmol, 1 *eq*) in DMF (3 mL) was added NaH (71.6 mg, 1.79 mmol, 60% purity, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then CH_3I (190 mg, 1.34 mmol, 1.5 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was quenched with sat. NH_4Cl (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl (R)-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)(methyl)carbamate (400 mg, crude) as a yellow oil. LCMS: *m/z*

(M+1-100: 249.0).

[0685] Step 3. To a solution of tert-butyl (R)-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)(methyl)carbamate (7.20 g, 20.6 mmol, 1 *eq*) in DCM (75 mL) was added TFA (194 mmol, 14.4 mL, 9.40 *eq*), and the solution was stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to give (R)-1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)-N-methylpropan-2-amine (5.2 g, crude) as a yellow oil. LCMS: *m/z* (M+1: 250.9)

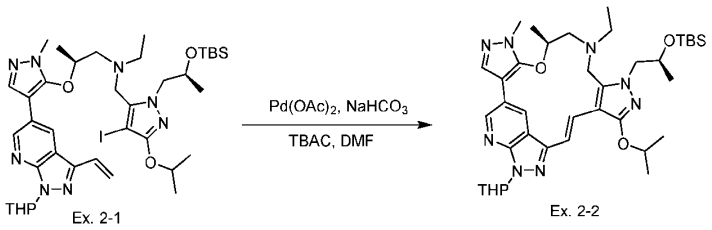
[0686] Step 4. To a solution of (R)-1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)-N-methylpropan-2-amine (5.20 g, 20.9 mmol, 1 *eq*) in DCM (50 mL) was added TEA (6.34 g, 62.6 mmol, 8.72 mL, 3 *eq*) and TFAA (6.58 g, 31.3 mmol, 4.35 mL, 1.5 *eq*), and the solution was stirred at 0 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to give (R)-N-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)-2,2,2-trifluoro-N-methylacetamide (7.20 g, crude) as a yellow oil. LCMS: *m/z* (M+1: 347.0)

[0687] Step 5. To a solution of 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridine (500 mg, 1.41 mmol, 1 *eq*) in dioxane (5 mL) and H_2O (1 mL) was added (R)-N-(1-((5-bromo-2-methyl-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)-2,2,2-trifluoro-N-methylacetamide (534 mg, 1.55 mmol, 1.1 *eq*), Pd(dtbpf)Cl_2 (91.7 mg, 0.141 mmol, 0.1 *eq*) and Cs_2CO_3 (1.38 g, 4.22 mmol, 3 *eq*), and the mixture was stirred at 80 °C for 1 h under N_2. On completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with EA (3 mL × 3). The combined organic layers were washed with brine (5 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-25% Ethyl acetate/Petroleum ether) to give 2,2,2-trifluoro-N-methyl-N-((2R)-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)acetamide (480 mg, 0.973 mmol, 69% yield) as a yellow oil. LCMS: *m/z* (M+1: 494.3)

[0688] Step 6. To a solution of 2,2,2-trifluoro-N-methyl-N-((2R)-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-yl)acetamide (380 mg, 0.770 mmol, 1 *eq*) in THF (3 mL) and H_2O (1.5 mL) was added LiOH.H_2O (96.9 mg, 2.31 mmol, 3 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with EA (2 mL × 3). The combined organic layers were washed with brine (5 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (2R)-N-methyl-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-amine (330 mg, crude) as a yellow oil. LCMS: *m/z* (M+1: 398.3)

[0689] Step 7. To a solution of (2R)-N-methyl-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-amine (280 mg, 0.704 mmol, 1 *eq*) in DMF (5 mL) was added 5-(bromomethyl)-4-iodo-1-methyl-1H-pyrazole (233 mg, 0.775 mmol, 1.1 *eq*), K_3PO_4 (449 mg, 2.11 mmol, 3 *eq*) and stirred at 80 °C for 1 h. On completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with EA (5 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Ethyl acetate/Petroleum ether) to afford (2R)-N-((4-iodo-1-methyl-1H-pyrazol-5-yl)methyl)-N-methyl-1-((2-methyl-5-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2H-1,2,3-triazol-4-yl)oxy)propan-2-amine (390 mg, 0.632 mmol, 90% yield) as a yellow oil. LCMS: *m/z* (M+1: 618.2)

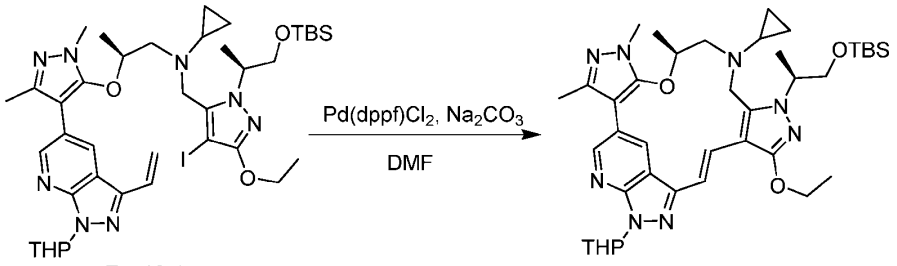
[0690] Cyclization Method C-A



Ex. 2-1 Ex. 2-2

[0691] Step 1. A mixture of (2S)-N-((1-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-N-ethyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (44.0 mg, 0.0519 mmol, 1 *eq*), $Pd(OAc)_2$ (2.33 mg, 0.0104 mmol, 0.2 *eq*), $NaHCO_3$ (10.9 mg, 0.130 mmol, 2.5 *eq*) and TBAC (14.4 mg, 0.052 mmol, 1 *eq*) in DMF (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 0.5 h under N_2 atmosphere. On completion, the reaction mixture was quenched with H_2O (5 mL) and extracted with EA (2 mL ×3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (30.0 mg, 0.0417 mmol, 81% yield) as a brown oil. LCMS: *m/z* 719.3 (M+1).

[0692] Cyclization Method C-B

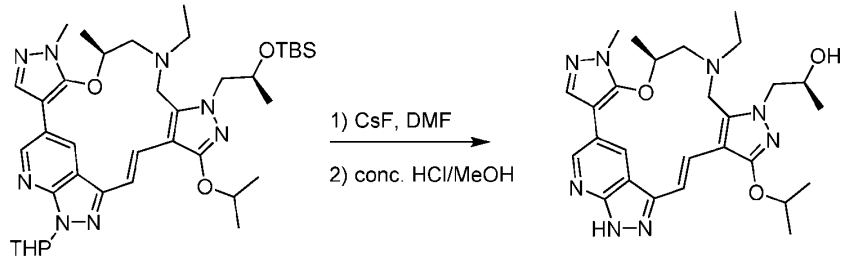


Ex. 12-1 12-2

[0693] Step 1. To a solution of N-((1-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methyl)-N-((2S)-2-((1,3-dimethyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrazol-5-yl)oxy)propyl)cyclopropanamine (180 mg, 0.202 mmol, 1 eq) in DMF (2 mL) was added Na_2CO_3 (64.3 mg, 0.607 mmol, 3 eq) and Pd(dppf)Cl_2 (14.8 mg, 0.0202 mmol, 0.1 eq). The mixture was stirred at 80 °C for 12 hours. On completion, the mixture was filtered and concentrated to give a residue, and the residue was purified by column chromatography (SiO_2, Petroleum ether/THF = 3:1) to give 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (30.0 mg, 0.0394 mmol, 19% yield) as yellow oil. LCMS: *m/z* 761.5 (M+1).

[0694] Deprotection Method D-A

[0695] Preparation of (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (Ex. 2)



Ex. 2-2 Ex. 2

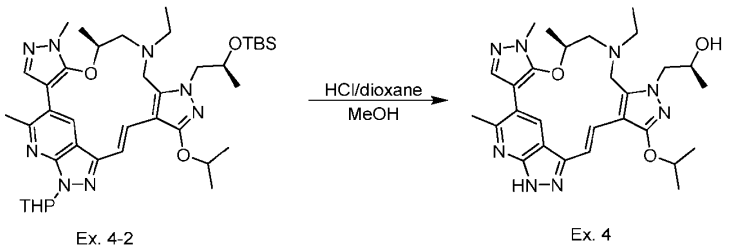
[0696] Step 1. To a solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (30.0 mg, 0.0417 mmol, 1 *eq*) in DMF (0.5 mL) was added CsF (25.4 mg, 0.167 mmol, 4 *eq*). The mixture was stirred at 80 °C for 16 h. On completion, the reaction mixture was quenched with H_2O (5

mL) and extracted with EA (2 mL × 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 35%-65% B over 8 min) to give (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (17.0 mg, 0.0253 mmol, 61% yield, 90% purity) as a white solid. LCMS: *m/z* 605.4 (M+1).

[0697] Step 2. To a solution of (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (17.0 mg, 0.0281 mmol, 1 *eq*) in MeOH (0.5 mL) was added conc. HCl (12 M, 33.9 μL, 14.5 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched by addition sat. $NaHCO_3$ (0.2 mL) at 25 °C, and then diluted with H_2O (3 mL) and extracted with DCM/MeOH= 10/1 (9 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 15%-45% B over 8 min) to give (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (13.18 mg, 0.0228 mmol, 81.09% yield, 98% purity, FA) as a brown gum.

[0698] Deprotection Method D-B

[0699] Preparation of (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (Ex. 4)



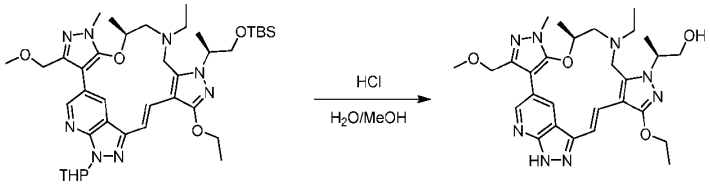
Ex. 4-2 Ex. 4

[0700] Step 1. To a solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}propyl]-12-ethyl-8,10,19-trimethyl-2-(oxan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine, which was prepared according to the method indicated in the

table below from compound 4-1 (35.0 mg, 0.0477 mmol, 1 eq), in MeOH (0.9 mL) was added HCl/dioxane (4 M, 300 μL, 25 eq). The mixture was stirred at 25 °C for 1 h. On completion, the reaction was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water (FA)-ACN]; gradient: 10%-40% B over 8 min) to give (2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (10.15 mg, 0.0183 mmol, 38% yield) as a yellow solid.

[0701] Deprotection Method D-C

[0702] Preparation of (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Ex. 7)

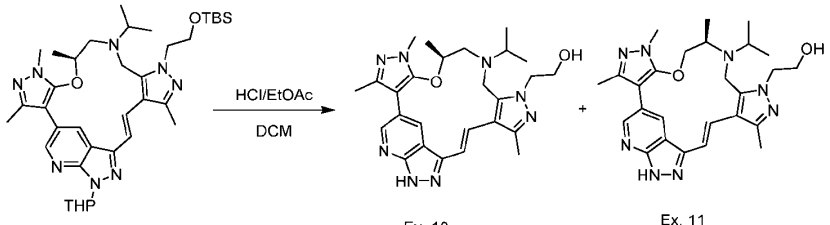


7-2 Ex. 7

[0703] Step 1. A solution of (10S,17E)-14-[(2S)-1-{[tert-butyl(dimethyl)silyl]oxy}propan-2-yl]-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8H-3,5-(azenometheno)tripyrazolo[3,4-f:3',4'-j:4",3"-n][1,4]oxazacyclopentadecine, which was prepared according to the method indicated in the table below from compound 7-1 (50.0 mg, 0.0667 mmol, 1 eq), in MeOH (0.6 mL) and HCl (0.2 mL, aq. concentrated) was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched by addition sat. $NaHCO_3$ (10 mL) at 25 °C, then diluted with H_2O (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over by anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. And then the residue was purified by prep-HPLC (column: CD02-Waters Xbridge BEH C18 150 x 25 x 10um; mobile phase: [water(NH_4HCO_3)-ACN];gradient: 32%-52% B over 10 min) to give (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (8.01 mg, 0.01398 mmol, 20.94% yield, 96.10% purity) as a yellow solid.

[0704] Deprotection Method D-D

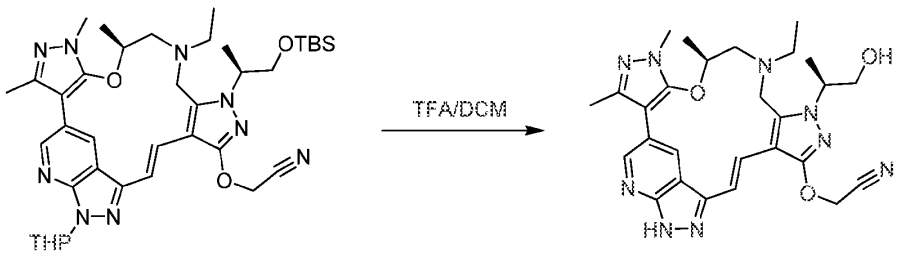
[0705] Preparation of 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 10) and 2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 11)



[0706] Step 1. To a solution of (10*S*,17*E*)-14-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-6,8,10,16-tetramethyl-2-(oxan-2-yl)-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine, which was prepared according to the method indicated in the table below from compound 10-1 (38.0 mg, 0.0551 mmol, 1 eq) in DCM (1 mL) was added HCl/EtOAc (2 M, 0.5 mL, 1 eq). The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: CD01-Phenomenex luna C18 150 x 25 x 10um; mobile phase: [water(FA)-ACN]; gradient: 0%-30% B over 10 min) to give 2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (6.39 mg, 0.0121 mmol, 22% yield, 93% purity) and 2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (840 µg, .00156 mmol, 2.8% yield, 91% purity) as a yellow solid.

[0707] General Deprotection D-E.

[0708] Preparation of {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (Ex. 16)

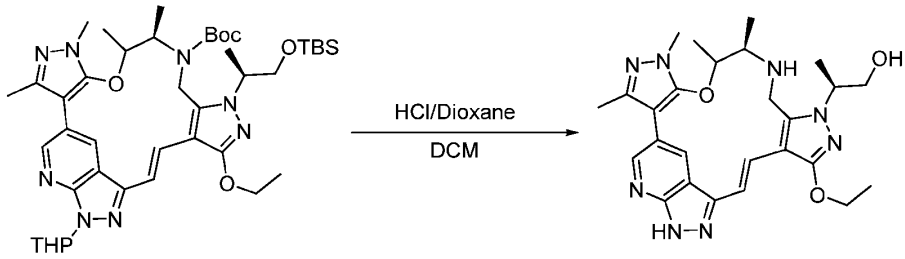


16-2 Ex. 16

[0709] Step 1. To a solution of {[(10*S*,17*E*)-14-[(2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}propan-2-yl]-12-ethyl-6,8,10-trimethyl-2-(oxan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile, which was prepared according to the method indicated in the table below from compound 16-1 (50.0 mg, 0.058 mmol, 1 eq), in DCM (0.9 mL) was added TFA (4.04 mmol, 0.3 mL). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched by addition sat. $NaHCO_3$ (0.2 mL) at 0 °C, then diluted with H_2O (2 mL) and extracted with DCM/MeOH= 10/1 (2 mL ×3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN];gradient: 12%-42% B over 8 min) to give {[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (11.63 mg, 0.0212 mmol, 30.92% yield, 96.8% purity) as a yellow solid.

[0710] Deprotection Method D-F.

[0711] Preparation of (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Ex. 23)

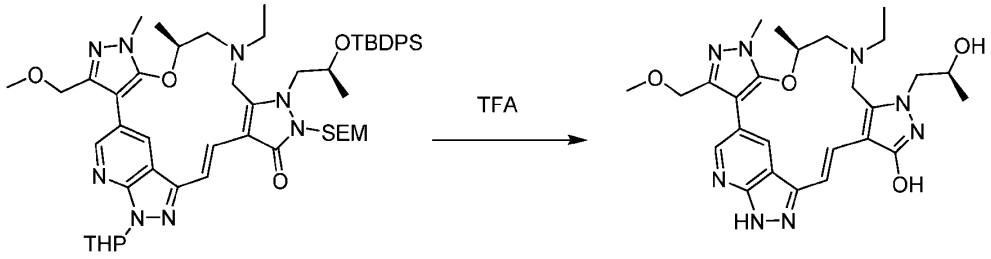


Ex. 23-2 Ex. 23

[0712] Step 1. To a solution of *tert*-butyl (11*R*,17*E*)-14-[(2*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}propan-2-yl]-16-ethoxy-6,8,10,11-tetramethyl-2-(oxan-2-yl)-2,8,10,11,13,14-hexahydro-12*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-12-carboxylate (90.0 mg, 0.112 mmol, 1 *eq*) in DCM (1 mL) was added HCl/dioxane (2 M, 2.00 mL, 36 *eq*). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated to give (2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (50.0 mg, 0.0921 mmol, 82% yield, HCl) as an orange solid.

[0713] Deprotection method D-G.

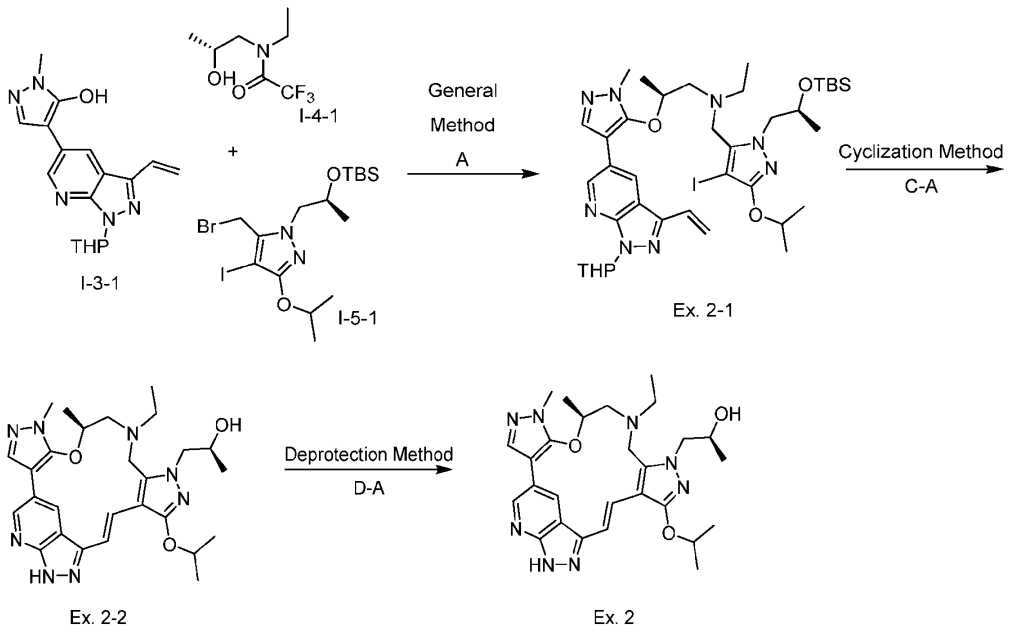
[0714] Preparation of (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (Ex. 70)



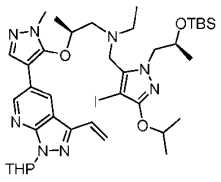
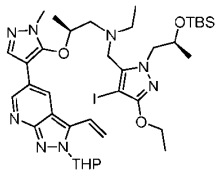
Ex. 70-2 Ex. 70

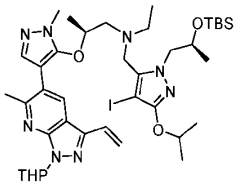
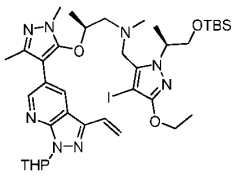
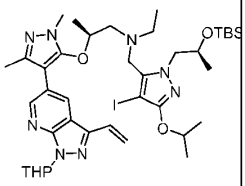
[0715] Step 1. A solution of (10*S*,17*E*)-14-[(2*S*)-2-{[*tert*-butyl(diphenyl)silyl]oxy}propyl]-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2-(oxan-2-yl)-15-{[2-(trimethylsilyl)ethoxy]methyl}-2,8,10,11,12,13,14,15-octahydro-16*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-one, which was prepared according to the method indicated in the table below from compound 70-1 (800 mg, 0.820 mmol, 1 *eq*) in TFA (8 mL) was stirred at 60 °C for 0.1 h. On completion, the mixture was filtered and concentrated to give a residue. The crude product was purified by prep-HPLC to give (10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (133.93 mg, 0.256 mmol, 31% yield) as an orange solid.

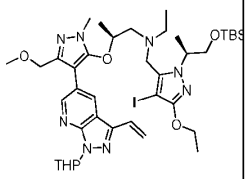
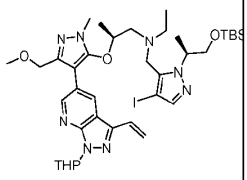
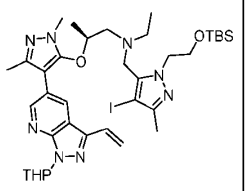
[0716] Example Macrocycle Synthesis Scheme

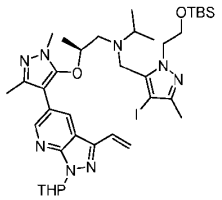
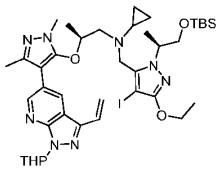
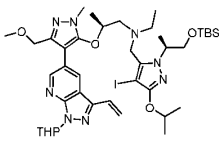


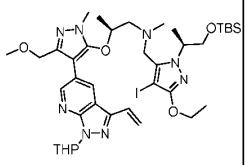
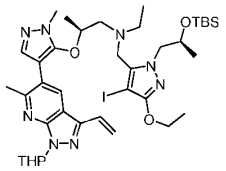
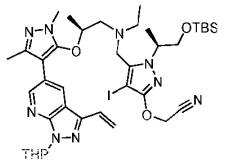
[0717] Table of Macrocycle Synthetic Methods

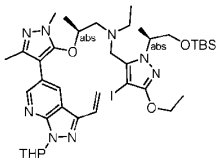
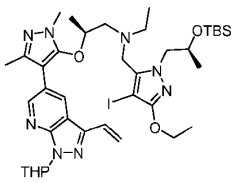
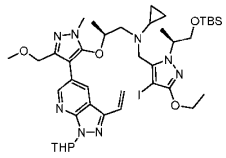
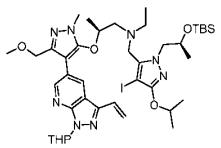
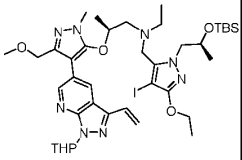
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
2	I-3-1, I-4-1, I-5-1	A	 2-1	(M+1) 847.2		C-A	D-A
3	I-3-1, I-4-1, I-5-2	A	 3-1	(M+1) 833.8	(400 MHz, $CDCl_3$) δ = 8.71 (s, 1H), 8.31 (s, 1H), 7.61 (s, 1H), 7.08 - 6.98 (m, 1H), 6.16 - 6.04 (m, 2H), 5.63 - 5.54 (m, 1H), 4.27 - 4.21 (m, 2H), 4.20 - 4.13 (m, 2H), 3.98 (s, 1H), 3.85 (d, *J* = 13.2Hz, 2H), 3.73 (s, 3H), 2.71 - 2.63 (m, 1H), 2.62 - 2.55 (m, 1H), 2.52 - 2.43 (m, 1H), 2.43 - 2.36 (m, 1H), 2.33 - 2.25 (m, 1H), 2.16 (s, 1H), 2.02 (s, 3H), 1.82 (s, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.30 - 1.19 (m,	C-A	D-A

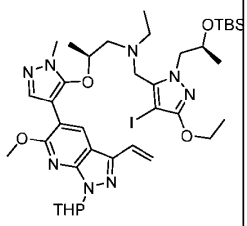
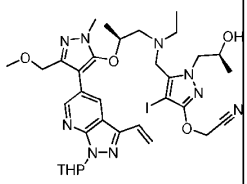
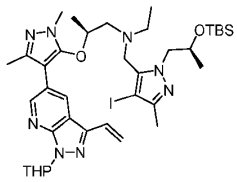
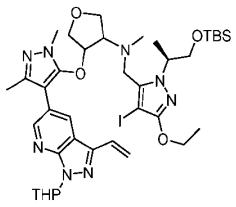
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
					1H), 1.08 - 0.98 (m, 6H), 0.96 - 0.87 (m, 4H), 0.74 (s, 9H), -0.11 (s, 3H), -0.35 (s, 3H).		
4	I-3-2, I-4-1, I-5-1	A*	 4-1	(M+1) 861.4		C-A	D-B
5	I-3-3, I-4-2, I-5-3	A	 5-1	(M+1) 833.4		C-A	D-A
6	I-3-3, I-4-1, I-5-1	A	 6-1	(M+1) 861.4	(400 MHz, $CDCl_3$) δ = 8.62 - 8.54 (m, 1H), 8.23 - 8.15 (m, 1H), 7.11 - 6.97 (m, 1H), 6.18 - 6.11 (m, 1H), 6.06 (d, *J* =18.0 Hz, 1H), 5.58 (d, *J* = 11.6 Hz, 1H), 4.85 - 4.73 (m, 1H), 4.25 - 4.07 (m, 3H), 3.90 - 3.71 (m, 4H), 3.66 (s, 3H), 3.25 - 3.18 (m, 1H), 2.75 - 2.60 (m, 1H), 2.53 - 2.34 (m, 2H), 2.26 (s, 3H), 2.26 - 2.11 (m, 3H), 1.99 (d, *J* = 12.8 Hz, 1H), 1.91 - 1.75 (m, 2H), 1.66 - 1.63 (m, 1H), 1.37 - 1.32 (m, 6H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.94 - 0.89 (m, 3H), 0.89 - 0.83 (m, 3H), 0.74 (s, 9H),-0.10 (s, 3H), -0.33 (s, 3H)	C-A	D-A

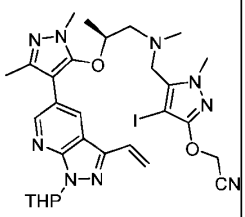
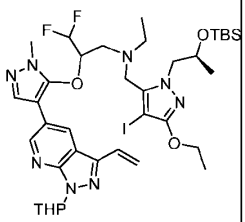
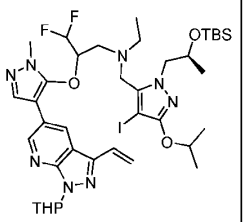
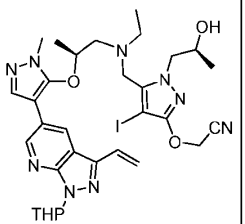
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
7	I-3-4, I-4-1, I-5-3	A	 7-1	(M+1) 877.7		C-A	D-C
8	I-3-4, I-4-1, I-5-4	A	 8-1	(M+1) 833.1	(400 MHz, $CDCl_3$) δ = 8.74 (s, 1H), 8.46 (s, 1H), 7.47 (s, 1H), 7.12 - 7.00 (m, 1H), 6.20 - 6.03 (m, 2H), 5.60 (d, *J* = 11.6 Hz, 1H), 5.31 (s, 3H), 4.81 - 4.70 (m, 1H), 4.32 (s, 2H), 4.17 (d, *J* = 11.2 Hz, 1H), 4.04 - 3.96 (m, 1H), 3.89 - 3.84 (m, 1H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.73 (s, 3H), 3.45 (s, 3H), 2.72 - 2.63 (m, 1H), 2.61 - 2.55 (m, 1H), 2.45 - 2.38 (m, 1H), 2.37 - 2.30 (m, 1H), 2.29 - 2.21 (m, 1H), 2.19 - 2.13 (m, 1H), 2.02 - 1.96 (m, 1H), 1.87 - 1.78 (m, 2H), 1.64 (d, *J* = 8.8 Hz, 1H), 1.36 (t, *J* = 5.6 Hz, 3H), 0.99 - 0.95 (m, 3H), 0.92 - 0.86 (m, 3H), 0.73 (s, 9H), -0.12 (s, 3H), -0.24 (s, 3H)	C-A	D-C
9	I-3-3, I-4-1, I-5-5	A	 9-1		(400 MHz, DMSO-d6) δ = 8.62 - 8.31 (m, 2H), 7.09 - 6.94 (m, 1H), 6.17 (d, J = 18.0 Hz, 1H), 6.02 (d, J = 10.0 Hz, 1H), 5.58 (d, J = 11.6 Hz, 1H), 4.10 - 4.07 (m, 1H), 3.98 - 3.92 (m, 1H), 3.85 - 3.80 (m, 1H), 3.74 (t, J = 5.6 Hz, 2H), 3.71 - 3.66 (m, 1H), 3.55 (s, 3H), 3.52 - 3.43 (m, 2H), 2.37 - 2.26 (m, 3H), 2.14 (s, 3H), 2.06 (s, 4H), 1.99 (s, 1H), 1.94 - 1.85 (m, 1H), 1.81 - 1.71 (m, 1H), 1.65 - 1.53 (m, 2H), 1.23 (s, 1H), 1.17 (t,	C-A	D-A

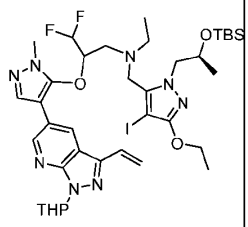
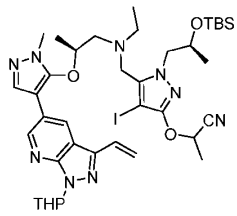
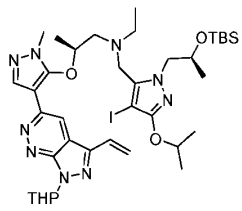
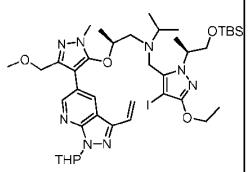
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
					J = 7.2 Hz, 1H), 0.90 (d, J = 4.8 Hz, 3H), 0.81 (t, J = 6.8 Hz, 3H), 0.71 (s, 9H), -0.18 (s, 6H).		
10/ 11	I-5-5, I-4-3, I-3-3	B	 10-1	(M+1) 817.6		C-A	D-D
12	I-3-3, I-4-4, I-5-3	C	 12-1	(M+1) 859.7		C-B	D-D
13	I-3-4, I-4-1, I-5-6	A	 13-1	(M+1) 891.4	(400 MHz, CDCl3) δ = 8.74 (s, 1H), 8.46 (s, 1H), 7.12 - 6.99 (m, 1H), 6.18 - 6.07 (m, 2H), 5.59 (d, J = 11.6 Hz, 1H), 4.86 - 4.75 (m, 1H), 4.62 - 4.53 (m, 1H), 4.33 (s, 2H), 4.22 - 4.13 (m, 1H), 4.04 - 3.95 (m, 1H), 3.89 - 3.81 (m, 1H), 3.73 (s, 3H), 3.68 - 3.62 (m, 1H), 3.62 - 3.58 (m, 1H), 3.44 (s, 3H), 3.29 (d, J = 13.6 Hz, 1H), 2.72 - 2.62 (m, 1H), 2.61 - 2.55 (m, 1H), 2.49 - 2.43 (m, 1H), 2.39 - 2.31 (m, 1H), 2.28 - 2.20 (m, 1H), 2.20 - 2.13 (m, 1H), 2.03 - 1.96 (m, 1H), 1.88 - 1.79 (m, 2H), 1.67 - 1.62 (m, 1H), 1.36 - 1.32 (m, 6H), 1.29 - 1.26 (m, 3H), 0.99 (t, J = 5.2 Hz, 3H), 0.90 - 0.85 (m, 3H), 0.81 - 0.76 (m, 1H), 0.74 (s, 9H), -0.11 (s, 3H), -0.20 (s, 3H)	C-A	D-C

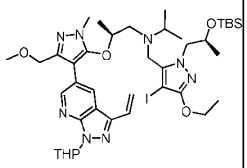
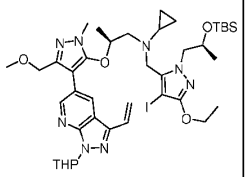
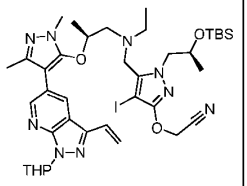
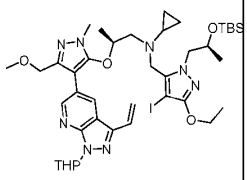
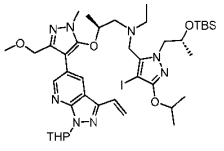
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
14	I-3-4, I-4-2, I-5-12	A	 14-1	(M+1) 863.5		C-A	D-C
15	I-3-2, I-4-1, I-5-2	A	 15-1		(400 MHz, DMSO-d_6) δ = 8.24 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 6.98 - 6.90 (m, 1H), 6.11 (d, *J* = 18.0 Hz, 1H), 6.03 - 5.98 (m, 1H), 5.53 (d, *J* = 11.2 Hz, 1H), 4.18 - 4.13 (m, 1H), 4.12 - 4.10 (m, 1H), 4.09 - 4.07 (m, 1H), 4.05 (d, *J* = 4.0 Hz, 1H), 3.98 - 3.91 (m, 2H), 3.66 (s, 3H), 3.63 - 3.58 (m, 1H), 2.56 (s, 3H), 2.55 (d, *J* = 2.4 Hz, 1H), 2.39 (d, *J* =5.6 Hz, 1H), 2.33 - 2.28 (m, 1H), 2.22 - 2.17 (m, 1H), 2.13 - 2.07 (m, 1H), 2.07 - 2.00 (m, 2H), 1.89 - 1.84 (m, 1H), 1.82 - 1.75 (m, 1H), 1.58 (s, 2H), 1.12 - 1.05 (m, 2H), 1.00 (d, *J* = 5.2 Hz, 3H), 0.89 - 0.82 (m, 6H), 0.72 (d, *J* = 2.0 Hz, 3H), 0.69 (s, 9H), -0.13 - -0.16 (m, 3H), -0.39 (d, *J* = 1.2 Hz, 3H).	C-A	D-C
16	I-3-3, I-4-1, I-5-7	A	 16-1	(M+1) 858.3		C-A	D-E

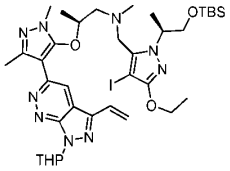
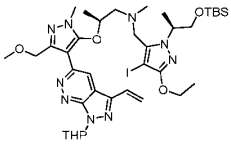
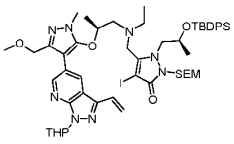
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
17	I-3-3, I-4-1, I-5-3	A	 17-1	(M+1) 847.4		C-A	D-D
18	I-3-3, I-4-1, I-5-2	A	 18-1	(M+1) 847.4		C-A	D-C
19	I-3-4, I-4-4, I-5-3	C	 19-1	(M+1) 889.4		C-B	D-D
20	I-3-4, I-4-1, I-5-1	A**	 20-1	(M+1) 891.4		C-A	D-D
21	I-3-4, I-4-1, I-5-2	A***	 21-1	(M+1) 877.3		C-A	D-C

Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
22	I-3-5, I-4-1, I-5-2	A	 22-1	(M+1) 863.3		C-A	D-C
24	I-3-4, I-4-1, I-5-8	A^{i}**	 24-1	(M+1) 774.2		C-A	D-E
27	I-3-3, I-4-1, I-5-9	A	 27-1	(M+1) 817.7		C-A	D-C
28-30	I-3-3, I-4-6, I-5-12	D-C	 28-1	(M+1) 861.1		C-A	D-C

Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
32	I-3-3, I-4-2, I-5-10	A***	 32-1	(M+1) 686.2		C-A	D-E
33	I-3-1, I-4-7, I-5-2	F	 33-1	(M+1) 869.3		C-A	D-F
34-35	I-5-1, I-3-1, I-4-7	F	 34-1	(M+1) 883.4		C-A	D-D
37	I-3-1, I-4-1, I-5-8	A[ii]***	 37-1	(M+1) 730.1		C-A	D-E

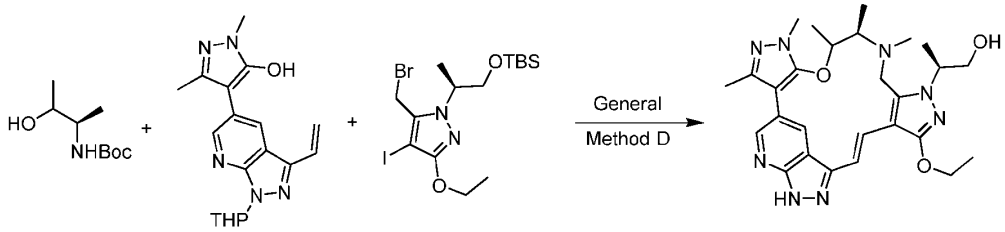
Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
38	I-3-1, I-4-7, I-5-2	F	 33-1	(M+1) 869.3		C-A	D-F
39	I-3-1, I-4-1, I-5-11	A	 39-1	(M+1) 858.5		C-A	D-E
41	I-3-6, I-4-1, I-5-1	A	 41-1	(M+1) 848.5		C-A	D-C
42-43	I-3-4, I-4-3, I-5-12	B	 42-1	(M+1) 891.5		C-A	D-C

Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
46-47	I-4-3, I-5-2, I-3-4	B	 46-1	(M+1) 891.5		C-A	D-C
48	I-5-2, I-4-4, I-3-4	B	 48-1	(M+1) 889.6		C-B	D-E
49	I-3-3, I-4-1, I-5-8	A	 49-1	(M+1) 858.5		C-A	D-E
50	I-5-2, I-4-4, I-3-4	B	 48-1	(M+1) 889.6		C-B	D-E
54	I-3-4, I-4-1, I-5-17	A[iii]	 54-1	(M+1) 891.5		C-A	D-C

Ex #	SMs	Gen. Meth.	Intermediate	LCMS : *m/z*	^{1}H NMR	Cycl. Meth.	Deprot. Meth.
64	I-3-7, I-4-2, I-5-12	A**	 64-1	(M+1) 834.3		C-A	D-C
65	I-3-8, I-4-2, I-5-3	A	 65-1	(M+1) 864.3		C-A	D-C
70	I-3-4, I-4-1, I-5-19	A^{iv}	 70-1	(M+1) 1103.4		C-A	D-G

Notes. A* use of Me-THF in place of THF in step 1 of General Method A
D-A* switches DMF for DMSO in step 1 of Deprotection Method D-A.
A** uses MeCN in place of DMF, 60 C-80 C for 2-16h, in step 3 of General Method A
A*** use of 1,4-Dioxane in place of THF in step 1 of General Method A.
A^{i} use of 1,4-Dioxane in place of THF in step 1 of General Method A., TBS group fell off during step 3.
A^{ii} uses MeCN in place of DMF, 60 C-80 C for 2-16h, in step 3 of General Method A, TBS group fell off during step 3.
A^{iii} use of Me-THF in place of THF in step 1 and use of MeCN instead of DMF in step 3 of General Method A.
A^{iv} uses K_3PO_4 instead of K_2CO_3 in step 3 of General Method A

[0718] Example Scheme



I-4-5 I-3-3 I-5-3 Ex. 23

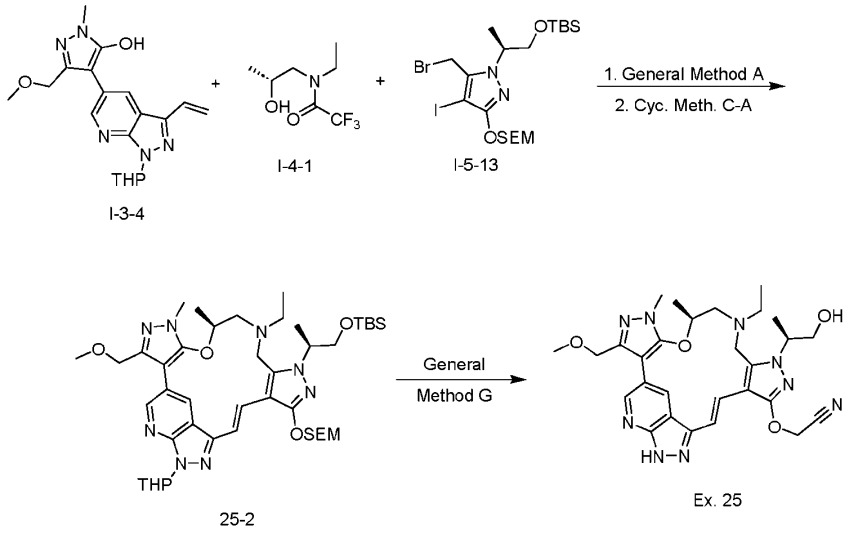
[0719] Table of SMs and General Methods used in the synthesis of Examples.

Ex	SMs	Synthetic Method
23	I-3-3, I-4-5, I-5-3	General Method D
40	I-4-8, I-2-4, I-1-4, I-5-2	General Method H
51	I-3-4, I-4-5, I-5-12	General Method D
52	I-3-1, I-4-5, I-5-14	General Method D
62-63*	I-3-4, I-4-5, I-5-1	General Method D**

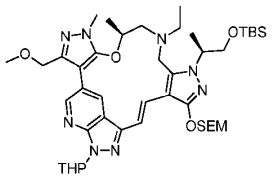
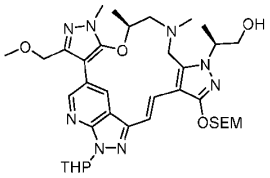
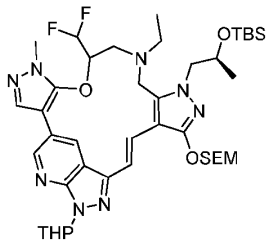
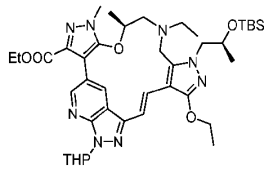
Notes. * Final isomers separated by HPLC, configuration at methyl adjacent to oxygen assigned arbitrarily.

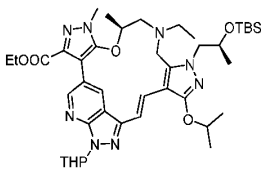
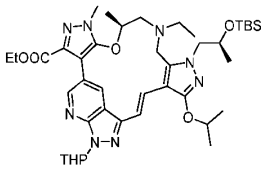
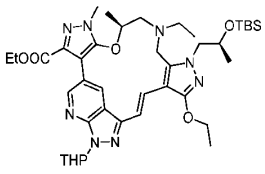
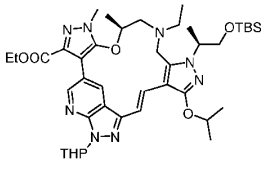
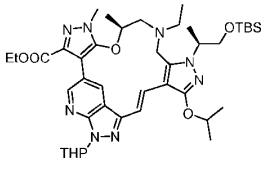
** Deprotection method D-D used in step 4 of General Method D.

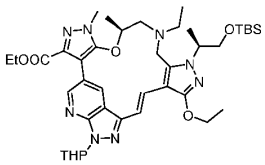
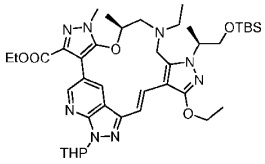
[0720] Example Scheme



[0721] Table of SMs, Key Intermediates and General Methods Employed in the synthesis of Example Compounds.

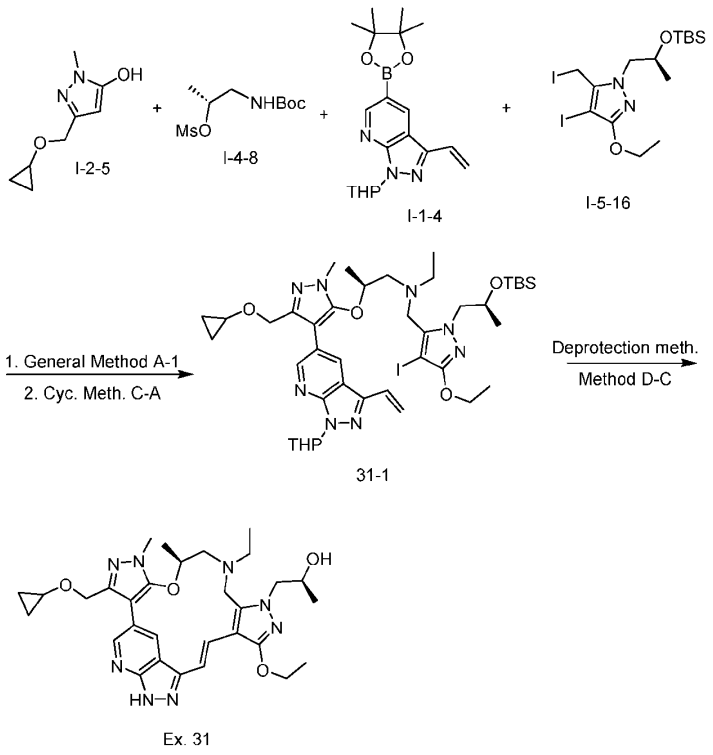
Ex.	SMs	Method(s) to Intermediate	Intermediate	LCMS: *m/z*	Method to Example Cmpd
25	I-3-4, I-4-1, I-5-13	General Method A + Cyclization Method C-A	 25-2	(M+1) 851.4	General Method G
26	I-3-4, I-4-2, I-5-13	General Method A + Cyclization Method C-A*	 26-2	(M+1) 723.5	General Method G
44-45	I-4-7, I-3-1, I-5-18	General Method F + Cyclization Method C-A	 44-2	(M+1) 843.4	General Method G.
53	I-4-8, I-2-4, I-1-4, I-5-2	General Method H	 40-2	(M+1) 777.6	General Method I

Ex.	SMs	Method(s) to Intermediate	Intermediate	LCMS: *m/z*	Method to Example Cmpd
55	I-4-8, I-2-4, I-1-4, I-5-1	General Method H	 55-2		General Method I
56	I-4-8, I-2-4, I-1-4, I-5-1	General Method H	 55-2		General Method I
57	I-4-8, I-2-4, I-1-4, I-5-2	General Method H	 40-2	(M+1) 777.6	General Method I
58	I-4-8, I-2-4, I-1-4, I-5-6	General Method H	 58-2		General Method I
59	I-4-8, I-2-4, I-1-4, I-5-6	General Method H			General Method I

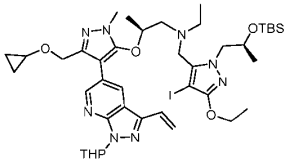
Ex.	SMs	Method(s) to Intermediate	Intermediate	LCMS: *m/z*	Method to Example Cmpd
			58-2		
60	I-4-8, I-2-4, I-1-4, I-5-3	General Method H	 60-2		General Method I
61	I-4-8, I-2-4, I-1-4, I-5-3	General Method H	 60-2		General Method I

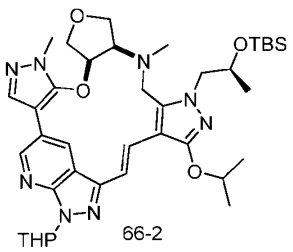
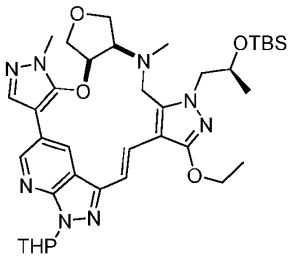
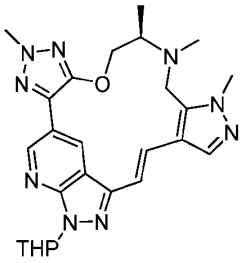
Notes. * Cyclization run at 130 °C for 1 h and TBS group fell off under these conditions.

[0722] Example Scheme

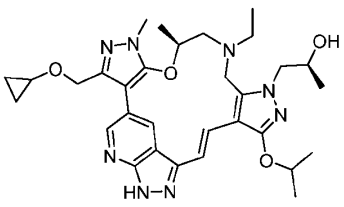


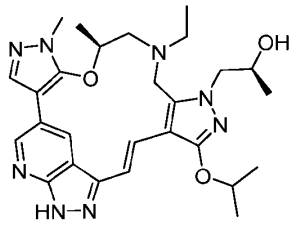
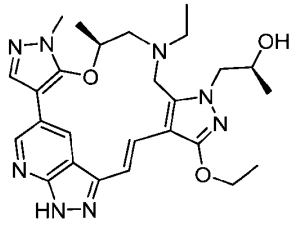
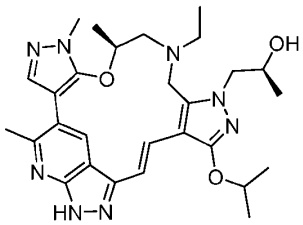
[0723] Table of SMs, Key Intermediates and General Methods Employed in the synthesis of Example Compounds.

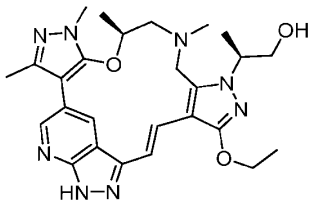
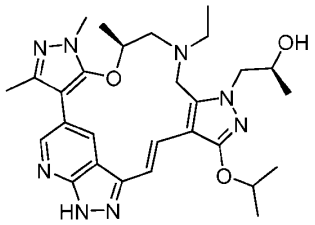
Ex.	SMs	Method(s) to Intermediate	Intermediate	LCMS: *m/z*	Deprotection Method
31	I-2-5, I-4-8, I-1-4, I-5-16	General Method A-1 + Cyclization Method C-A	 31-1	(M+1) 903.4	D-C

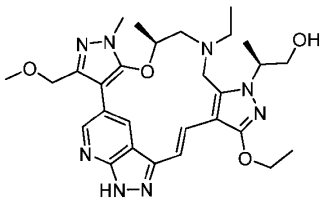
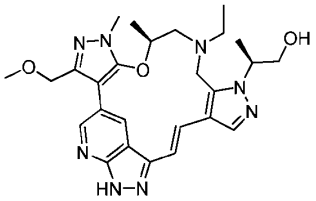
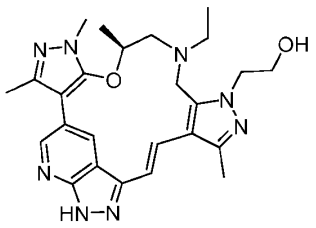
Ex.	SMs	Method(s) to Intermediate	Intermediate	LCMS: *m/z*	Deprotection Method
66-67	I-1-4, I-2-1, I-4-9, I-5-15	General Method J (includes Cyclization Method C-A)	 66-2	(M+1) 733.4	D-F
68-69	I-1-4, I-2-1, I-4-9, I-5-16	General Method J (includes Cyclization Method C-A)		(M+1) 719.4	D-F
72	I-2-6, I-4-10, I-1-4, I-5-20	General Method K + Cyclization Method C-A		(M+1) 490.3	D-E

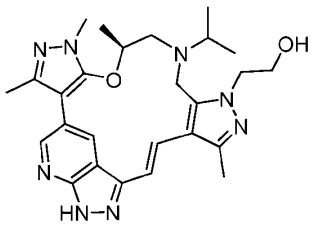
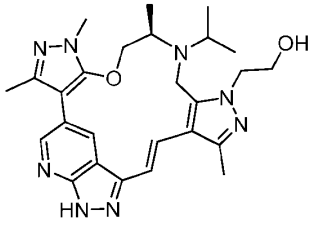
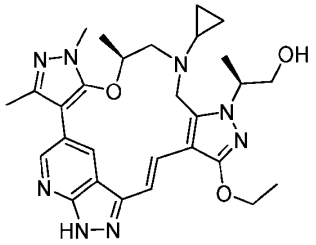
[0724] Characterization Table of Examples

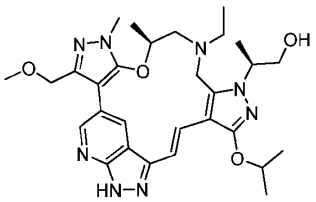
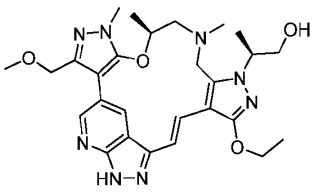
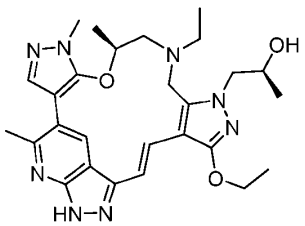
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
1		591.2	(400 MHz, MeOD-*d*$_4$) δ = 8.93 (s, 1H), 8.90 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 16.8 Hz, 1H), 7.19 (d, *J* = 16.8 Hz, 1H), 5.01 - 4.94 (m, 1H), 4.68 (s, 1H), 4.63 - 4.52 (m, 2H), 4.11 - 4.05 (m, 1H), 4.04 - 3.91 (m, 4H), 3.75 (s, 3H),

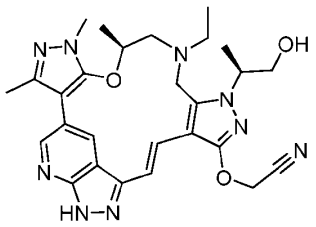
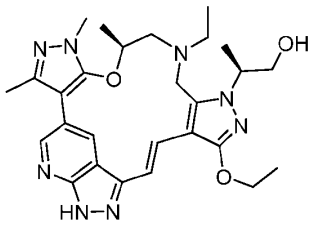
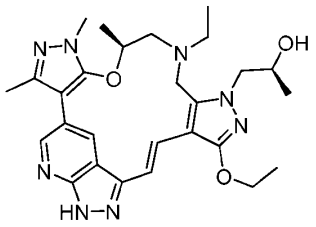
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
			3.51 - 3.45 (m, 1H), 3.07 - 2.99 (m, 1H), 2.86 (d, *J* = 14.8 Hz, 1H), 2.73 - 2.59 (m, 2H), 1.45 (t, *J* = 6.0 Hz, 6H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.72 - 0.65 (m, 2H), 0.59 - 0.52 (m, 2H)
2		521.2	(400 MHz, DMSO-d6) δ = 13.31 (s, 1H), 8.88 (br s, 2H), 8.13 - 7.96 (m, 2H), 7.08 (d, J = 17.2Hz, 1H), 4.95 - 4.82 (m, 2H), 4.78 - 4.61 (m, 1H), 3.98 - 3.87 (m, 4H), 3.87 - 3.81 (m, 1H), 3.69 (s, 3H), 3.03 - 2.94 (m, 1H), 2.91 - 2.83 (m, 1H), 2.75 - 2.65 (m, 1H), 2.64 - 2.54 (m, 1H), 1.43 - 1.36 (m, 6H), 1.13 - 1.03 (m, 6H), 0.94 (br t, J = 7.2 Hz, 3H)
3		507	(400 MHz, DMSO-d6) δ = 13.33 (s, 1H), 8.91 - 8.84 (m, 2H), 8.11 - 8.03 (m, 2H), 7.07 (d, J = 17.2 Hz, 1H), 4.84 (d, J = 4.4 Hz, 1H), 4.75 - 4.64 (m, 1H), 4.31 - 4.23 (m, 2H), 3.93 (d, J = 3.6 Hz, 2H), 3.91 - 3.87 (m, 2H), 3.84 (d, J = 9.2 Hz, 1H), 3.69 (s, 3H), 3.03 - 2.95 (m, 1H), 2.90 - 2.83 (m, 1H), 2.74 - 2.65 (m, 1H), 2.64 - 2.55 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.12 - 1.05 (m, 6H), 0.94 (t, J = 7.2 Hz, 3H)
4		535.3	(400 MHz, DMSO-d6) δ = 13.25 - 12.95 (m, 1H), 8.89 - 8.56 (m, 1H), 7.94 - 7.84 (m, 1H), 7.83 - 7.76 (m, 1H), 7.00 (d, J = 16.9 Hz, 1H), 4.97 (s, 2H), 4.57 - 4.37 (m, 1H), 4.03 - 3.80 (m, 5H), 3.77 - 3.66 (m, 3H), 2.96 - 2.84 (m, 2H), 2.81 - 2.71 (m, 3H), 1.39 (t, J = 6.3 Hz, 6H), 1.15 - 1.04 (m, 3H), 1.02 -

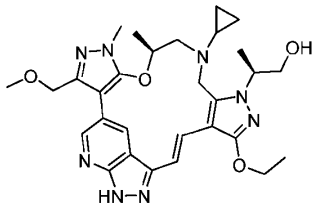
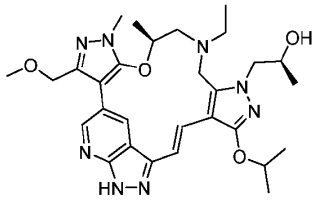
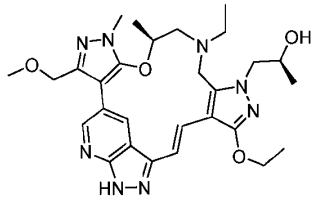
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
			0.90 (m, 3H), 0.89 - 0.76 (m, 3H)
5		507.3	(400 MHz, DMSO-d6) δ = 13.32 (br s, 1H), 8.70 (s, 2H), 8.05 (br d, J = 17.2 Hz, 1H), 7.02 (d, J = 17.2 Hz, 1H), 4.80 (br t, J = 5.4 Hz, 1H), 4.69 - 4.59 (m, 1H), 4.43 - 4.35 (m, 1H), 4.32 - 4.24 (m, 2H), 3.93 - 3.75 (m, 2H), 3.62 (s, 3H), 3.58 - 3.50 (m, 2H), 2.92 (br d, J = 14.0 Hz, 1H), 2.79 - 2.70 (m, 1H), 2.40 - 2.29 (m, 6H), 1.41 (t, J = 7.2 Hz, 3H), 1.31 (br d, J = 6.4 Hz, 3H), 0.99 (br d, J = 6.0 Hz, 3H)
6		535.4	(400 MHz, DMSO-d6) δ = 13.33 (s, 1H), 8.79 (s, 1H), 8.70 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 16.8 Hz, 1H), 7.04 (d, J =17.2 Hz, 1H), 4.94 - 4.87 (m, 1H), 4.84 (d, J = 4.4 Hz, 1H), 4.62 - 4.52 (m, 1H), 3.96 - 3.90 (m, 3H), 3.90 - 3.81 (m, 2H), 3.63 (s, 3H), 2.97 - 2.81 (m, 2H), 2.64 - 2.57 (m, 1H), 2.54 (d, J = 7.2 Hz, 1H), 2.40 (s, 3H), 1.41 - 1.37 (m, 6H), 1.09 (d, J = 5.6 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H)

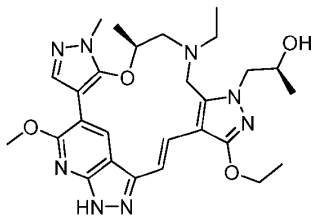
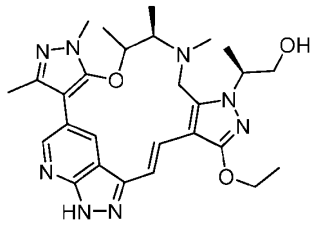
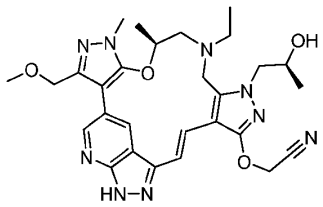
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
7		551.5	(400 MHz, DMSO-d6) δ = 13.33 (br s, 1H), 8.83 (d, J = 3.6 Hz, 2H), 7.93 (d, J = 16.8 Hz, 1H), 7.03 (d, J = 16.8 Hz, 1H), 4.79 (t, J = 5.6 Hz, 1H), 4.65 (t, J = 6.0 Hz, 1H), 4.49 - 4.43 (m, 2H), 4.42 - 4.38 (m, 1H), 4.32 - 4.24 (m, 2H), 3.99 - 3.85 (m, 2H), 3.70 (s, 3H), 3.57 - 3.49 (m, 2H), 3.33 (br s, 3H), 2.99 - 2.81 (m, 2H), 2.67 - 2.53 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H)
8		507.3	(400 MHz, DMSO-d6) δ = 13.39 (s, 1H), 8.89 (s, 1H), 8.84 (d, J = 1.6 Hz, 1H), 8.10 - 7.96 (m, 2H), 7.03 (d, J = 17.2 Hz, 1H), 4.84 (t, J = 5.6 Hz, 1H), 4.67 (br t, J = 6.0 Hz, 1H), 4.48 (br d, J = 5.2 Hz, 1H), 4.45 (d, J = 4.8 Hz, 2H), 3.99 (d, J = 2.8 Hz, 2H), 3.70 (s, 3H), 3.60 - 3.55 (m, 2H), 3.37 (s, 3H), 3.01 - 2.86 (m, 2H), 2.67 - 2.52 (m, 2H), 1.37 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.1 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H)
9		477.2	(400 MHz, DMSO-d6) δ = 13.41 (br s, 1H), 8.86 - 8.65 (m, 2H), 8.14 (d, J = 17.4 Hz, 1H), 6.84 (d, J = 17.4 Hz, 1H), 4.86 (t, J = 5.4 Hz, 1H), 4.56 (br t, J = 5.5 Hz, 1H), 4.16 - 4.06 (m, 2H), 3.95 (s, 2H), 3.72 - 3.64 (m, 2H), 3.63 (s, 3H), 2.96 - 2.80 (m, 2H), 2.54 (br d, J = 6.5 Hz, 1H), 2.48 - 2.44 (m, 1H), 2.40 (s, 6H), 0.99 (d, J = 6.3 Hz, 3H), 0.85 (t, J = 7.1 Hz, 3H)

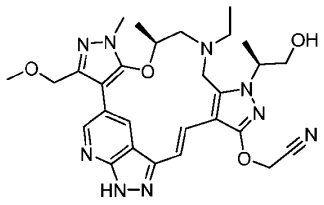
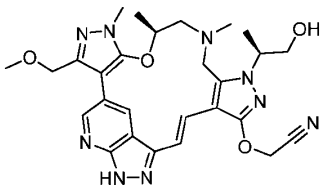
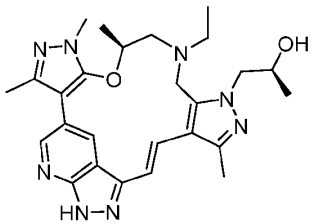
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
10		491.4	(400 MHz, DMSO-d6) δ = 13.42 (br s, 1H), 8.88 (s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.05 (br d, J = 17.6 Hz, 1H), 6.86 (d, J = 17.6 Hz, 1H), 4.88 (t, J = 5.2 Hz, 1H), 4.55 - 4.43 (m, 1H), 4.12 (t, J = 5.6 Hz, 2H), 4.06 - 3.95 (m, 2H), 3.69 (br d, J = 5.2 Hz, 2H), 3.65 (s, 3H), 2.86 - 2.74 (m, 2H), 2.71 - 2.64 (m, 1H), 2.41 (s, 6H), 0.99 (br d, J = 6.4 Hz, 3H), 0.87 (br dd, J = 6.8, 11.2 Hz, 6H)
11		491.3	(400 MHz, DMSO-d6) δ = 13.43 (br s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.73 (d, J = 2.0 Hz, 1H), 7.77 (br d, J = 17.6 Hz, 1H), 6.89 (d, J = 17.2 Hz, 1H), 4.97 - 4.84 (m, 1H), 4.54 - 4.39 (m, 1H), 4.28 - 4.07 (m, 2H), 4.05 - 3.78 (m, 4H), 3.73 (br s, 2H), 3.69 (s, 3H), 3.01 - 2.86 (m, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.13 - 1.02 (m, 3H), 0.94 - 0.85 (m, 3H)
12		533.2	(400 MHz, DMSO-d6) δ = 13.41 - 13.25 (m, 1H), 8.61 - 8.46 (m, 2H), 7.25 (d, J = 16.8 Hz, 1H), 7.01 (d, J = 16.8 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 4.47 - 4.35 (m, 2H), 4.26 - 4.19 (m, 2H), 4.15 (br dd, J = 7.2, 9.2 Hz, 1H), 4.07 - 3.98 (m, 1H), 3.72 (br d, J = 14.8 Hz, 1H), 3.64 (s, 3H), 3.54 - 3.48 (m, 3H), 2.31 (s, 3H), 2.06 - 2.00 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 6.8 Hz, 6H), 0.36 - 0.24 (m, 2H), 0.23 - 0.13 (m, 1H), 0.06 - -0.07 (m, 1H)

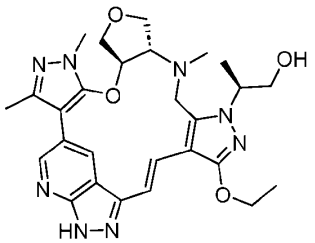
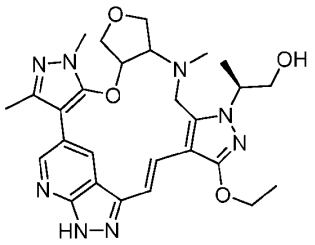
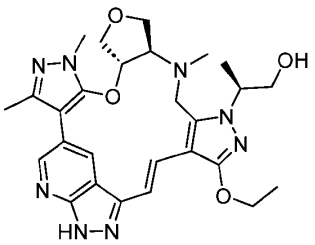
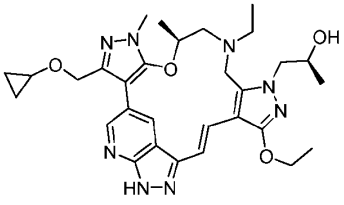
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
13		565.4	(400 MHz, DMSO-d6) δ = 13.27 (s, 1H), 8.81 (br d, J = 7.4 Hz, 2H), 7.94 - 7.81 (m, 1H), 7.04 (d, J = 16.9 Hz, 1H), 4.95 - 4.87 (m, 1H), 4.69 - 4.62 (m, 1H), 4.44 (d, J = 4.5 Hz, 1H), 3.95 - 3.87 (m, 2H), 3.69 (s, 3H), 3.58 - 3.51 (m, 2H), 3.33 (s, 3H), 3.19 - 3.13 (m, 2H), 2.98 - 2.91 (m, 1H), 2.87 - 2.80 (m, 1H), 2.66 - 2.59 (m, 1H), 1.62 - 1.52 (m, 2H), 1.39 (t, J = 6.6 Hz, 6H), 1.32 (br d, J = 6.5 Hz, 3H), 1.00 - 0.95 (m, 3H), 0.93 (d, J = 7.3 Hz, 3H)
14		537.2	(400 MHz, DMSO-d6) δ = 13.33 (s, 1H), 8.84 (d, J = 1.6 Hz, 1H), 8.75 (s, 1H), 8.06 (d, J = 17.2 Hz, 1H), 7.02 (d, J = 16.8 Hz, 1H), 4.79 (br t, J = 5.2 Hz, 1H), 4.69 (br t, J = 6.4 Hz, 1H), 4.48 - 4.35 (m, 3H), 4.32 - 4.22 (m, 2H), 3.96 - 3.87 (m, 1H), 3.80 (br d, J = 14.0 Hz, 1H), 3.69 (s, 3H), 3.60 - 3.47 (m, 2H), 3.34 - 3.33 (m, 3H), 2.94 (br d, J = 13.2 Hz, 1H), 2.81 - 2.71 (m, 1H), 2.31 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H)
15		521.3	(400 MHz, DMSO-d6) δ = 13.12 (s, 1H), 8.71 (s, 1H), 7.90 (d, J = 16.9 Hz, 1H), 7.79 (s, 1H), 6.99 (d, J = 16.9 Hz, 1H), 5.32 (t, J = 4.6 Hz, 1H), 4.84 (d, J = 4.5 Hz, 1H), 4.56 - 4.43 (m, 1H), 4.33 - 4.22 (m, 2H), 3.94 (s, 2H), 3.90 (br d, J = 5.6 Hz, 1H), 3.72 (s, 3H), 2.88 (br d, J = 4.0 Hz, 2H), 2.76 (s, 3H), 2.03 - 1.99 (m, 3H), 1.09 (br d, J = 5.5 Hz, 3H), 0.94 (br d, J = 6.3 Hz, 3H), 0.87 - 0.82 (m, 6H)

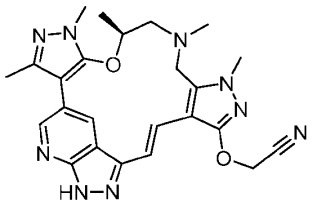
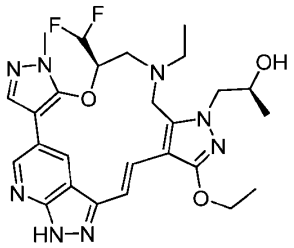
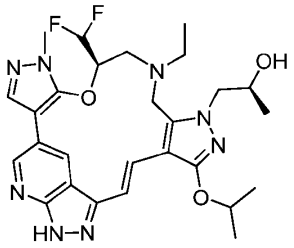
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
16		532.4	(400 MHz, DMSO-d6) δ = 13.41 (br s, 1H), 8.81 (s, 1H), 8.72 (s, 1H), 7.95 (d, J = 17.2 Hz, 1H), 6.99 (d, J = 17.2 Hz, 1H), 5.23 (s, 2H), 4.85 (t, J = 5.2 Hz, 1H), 4.62 (br t, J = 6.4 Hz, 1H), 4.54 - 4.39 (m, 1H), 3.97 (s, 2H), 3.64 (s, 3H), 3.56 (br t, J = 5.6 Hz, 2H), 3.04 - 2.80 (m, 2H), 2.70 - 2.55 (m, 2H), 2.42 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.00 (br d, J = 6.0 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H)
17		521.3	(400 MHz, DMSO-d6) δ = 13.34 (s, 1H), 8.80 (s, 1H), 8.71 (s, 1H), 7.93 (d, J = 16.8 Hz, 1H), 7.03 (d, J = 16.8 Hz, 1H), 4.81 (t, J = 5.6 Hz, 1H), 4.65 - 4.53 (m, 1H), 4.47 - 4.37 (m, 1H), 4.29 (dq, J = 3.2, 6.8 Hz, 2H), 3.93 (s, 2H), 3.64 (s, 3H), 3.58 - 3.48 (m, 2H), 2.99 - 2.78 (m, 2H), 2.61 (br d, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 1.33 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H)
18		521.2	(400 MHz, DMSO-d6) δ = 13.34 (s, 1H), 8.80 (s, 1H), 8.70 (s, 1H), 7.99 (d, J = 16.8 Hz, 1H), 7.03 (d, J = 16.8 Hz, 1H), 4.84 (d, J = 3.6 Hz, 1H), 4.63 - 4.51 (m, 1H), 4.32 - 4.22 (m, 2H), 3.93 (s, 2H), 3.91 - 3.81 (m, 3H), 3.63 (s, 3H), 2.96 - 2.83 (m, 2H), 2.63 - 2.53 (m, 2H), 2.40 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 5.6 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H)

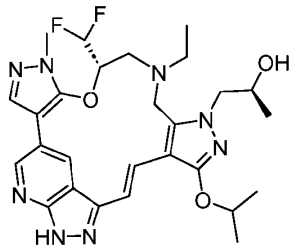
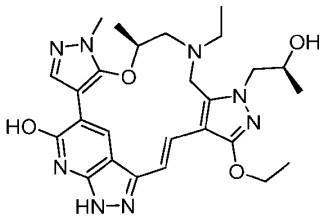
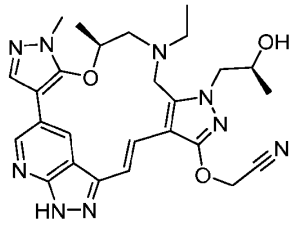
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
19		563.4	(400 MHz, DMSO-d6) δ = 13.38 - 13.24 (m, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.53 (s, 1H), 7.23 (d, J = 16.8 Hz, 1H), 6.98 (d, J = 16.8 Hz, 1H), 4.73 (t, J = 5.6 Hz, 1H), 4.40 (br d, J = 4.4 Hz, 2H), 4.36 (s, 1H), 4.34 - 4.29 (m, 1H), 4.22 - 4.17 (m, 2H), 4.16 - 4.10 (m, 1H), 4.01 (br d, J = 14.4 Hz, 1H), 3.71 (s, 1H), 3.68 (s, 3H), 3.55 - 3.43 (m, 3H), 3.36 (br s, 3H), 2.05 - 1.96 (m, 1H), 1.33 - 1.29 (m, 3H), 1.26 (br d, J = 6.4 Hz, 6H), 0.26 (br d, J = 6.4 Hz, 2H), 0.20 - 0.13 (m, 1H), -0.01 (br dd, J = 2.4, 9.6 Hz, 1H)
20		565.4	(400 MHz, METHANOL-d4) δ = 9.04 - 8.87 (m, 2H), 8.14 (d, J = 17.2 Hz, 1H), 7.21 (d, J = 16.8 Hz, 1H), 5.01 - 4.96 (m, 1H), 4.79 - 4.65 (m, 1H), 4.49 (s, 2H), 4.12 - 3.91 (m, 5H), 3.77 (s, 3H), 3.47 (s, 3H), 3.11 - 3.00 (m, 1H), 2.96 - 2.82 (m, 1H), 2.77 - 2.61 (m, 2H), 1.45 (t, J = 6.4 Hz, 6H), 1.21 (d, J = 6.4 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H)
21		551.4	(400 MHz, METHANOL-d4) δ = 8.95 (br d, J = 19.6 Hz, 2H), 8.14 (br d, J = 16.8 Hz, 1H), 7.18 (d, J = 16.8 Hz, 1H), 4.75 - 4.64 (m, 1H), 4.49 (s, 2H), 4.40 - 4.28 (m, 2H), 4.13 - 3.87 (m, 5H), 3.76 (s, 3H), 3.47 (s, 3H), 3.11 - 2.98 (m, 1H), 2.89 (br s, 1H), 2.76 - 2.58 (m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.24 - 1.18 (m, 3H), 1.08 (br d, J = 6.4 Hz, 3H), 0.95 (br t, J = 7.2 Hz, 3H)

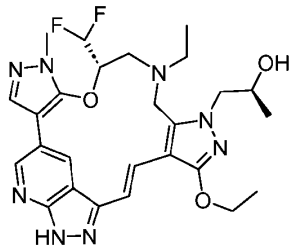
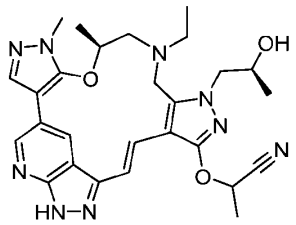
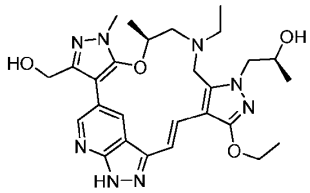
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
22		537.7	(400 MHz, DMSO-d6) δ = 13.07 (s, 1H), 8.91 (br s, 1H), 7.97 (s, 1H), 7.01 (d, J = 17.2 Hz, 1H), 4.84 (d, J = 4.4 Hz, 1H), 4.62 (d, J = 1.2 Hz, 1H), 4.32 - 4.20 (m, 2H), 4.05 (s, 3H), 3.95 - 3.84 (m, 5H), 3.69 (s, 3H), 2.93 (s, 2H), 2.63 - 2.54 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.30 - 1.19 (m, 1H), 1.09 (d, J = 5.6 Hz, 3H), 1.04 (d, J = 6.0 Hz, 3H), 0.94 - 0.89 (m, 3H)
23		521.2	(400 MHz, DMSO-d6) δ = 9.06 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 16.4 Hz, 1H), 7.18 (d, J = 17.2 Hz, 1H), 4.45 - 4.37 (m, 1H), 4.36 - 4.24 (m, 3H), 4.07 - 4.00 (m, 1H), 3.86 (d, J = 15.2 Hz, 1H), 3.68 (s, 3H), 3.62 - 3.49 (m, 3H), 2.92 (q, J = 6.4 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H), 1.44 -1.38 (m, 6H), 1.31 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H)
24		562.4	(400 MHz, METHANOL-d4) δ = 8.98 (s, 1H), 8.93 (s, 1H), 8.16 (br d, J = 16.8 Hz, 1H), 7.10 (d, J = 17.2 Hz, 1H), 5.16 (s, 2H), 4.76 - 4.67 (m, 1H), 4.50 (s, 2H), 4.19 - 4.06 (m, 2H), 4.06 - 4.00 (m, 2H), 3.77 (s, 3H), 3.47 (s, 3H), 3.12 -2.99 (m, 1H), 2.96 - 2.84 (m, 1H), 2.76 - 2.61 (m, 2H), 1.23 (d, J = 6.4 Hz, 3H), 1.09 (br d, J = 6.4 Hz, 3H), 0.99 - 0.93 (m, 3H)

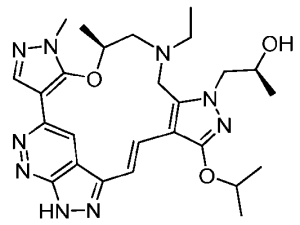
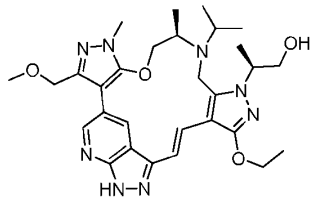
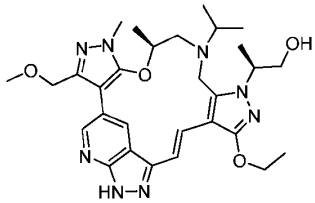
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
25		562.7	(400 MHz, METHANOL-d4) δ = 8.95 (br d, J = 14.4 Hz, 2H), 8.09 (br d, J = 16.8 Hz, 1H), 7.09 (d, J = 16.8 Hz, 1H), 5.17 (s, 2H), 4.72 (br d, J = 4.0 Hz, 1H), 4.57 - 4.51 (m, 1H), 4.49 (s, 2H), 4.09 - 3.96 (m, 2H), 3.86 - 3.79 (m, 1H), 3.76 (s, 3H), 3.73 - 3.68 (m, 1H), 3.47 (s, 3H), 3.12 - 3.01 (m, 1H), 2.87 (br d, J = 15.2 Hz, 1H), 2.78 - 2.62 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H), 1.08 (br d, J = 6.4 Hz, 3H), 0.98 (br t, J = 7.2 Hz, 3H)
26		548.3	(400 MHz, METHANOL-d4) δ = 8.93 (s, 1H), 8.87 (d, J = 1.2 Hz, 1H), 8.22 (d, J = 17.2 Hz, 1H), 7.08 (d, J = 17.2Hz, 1H), 5.17 (s, 2H), 4.60 (br s, 1H), 4.54 - 4.48 (m, 1H), 4.47 - 4.40 (m, 2H), 4.02 - 3.94 (m, 1H), 3.87 (d, J = 14.8 Hz, 1H), 3.84 - 3.79 (m, 1H), 3.75 (s, 3H), 3.73 - 3.67 (m, 1H), 3.47 (s, 3H), 2.98 - 2.90 (m, 1H), 2.89 - 2.79 (m, 1H), 2.42 (s, 3H), 1.43 (d, J = 6.4 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H)
27		491.3	(400 MHz, DMSO-d6) δ = 13.41 (s, 1H), 8.89 - 8.63 (m, 2H), 8.13 (d, J = 17.2 Hz, 1H), 6.84 (d, J = 17.2 Hz, 1H), 4.86 (d, J = 5.2 Hz, 1H), 4.57 (t, J = 6.0 Hz, 1H), 4.03 - 3.88 (m, 5H), 3.63 (s, 3H), 2.96 - 2.88 (m, 1H), 2.88 - 2.78 (m, 1H), 2.59 - 2.53 (m, 1H), 2.48 - 2.44 (m, 1H), 2.40 (s, 6H), 1.09 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H)

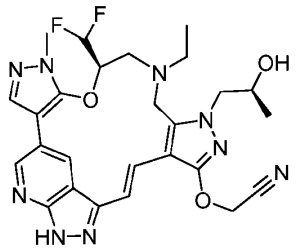
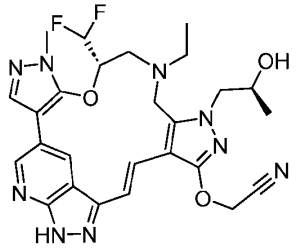
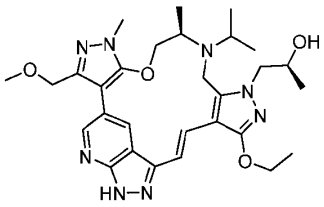
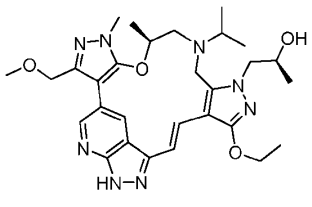
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
28		535.4	(400 MHz, METHANOL-d4) δ = 8.55 (br s, 1H), 8.43 (s, 1H), 7.59 - 7.50 (m, 1H), 7.38 (br d, J = 16.8 Hz, 1H), 4.49 - 4.37 (m, 2H), 4.31 - 4.20 (m, 1H), 3.99 - 3.90 (m, 1H), 3.83 - 3.70 (m, 2H), 3.67 - 3.46 (m, 3H), 3.39 - 3.33 (m, 1H), 3.29 (br s, 3H), 3.15 (s, 3H), 2.03 (br d, J = 4.4 Hz, 6H), 1.54 (t, J = 7.2 Hz, 3H), 1.21 (br d, J = 6.8 Hz, 3H)
29		535.2	(400 MHz, METHANOL-d4) δ = 8.69 - 8.60 (m, 2H), 7.93 (br dd, J = 5.4, 17.2 Hz, 1H), 7.21 (dd, J = 2.4, 16.8 Hz, 1H), 5.09 (br s, 1H), 4.47 - 4.30 (m, 3H), 4.18 - 4.07 (m, 2H), 3.88 - 3.77 (m, 5H), 3.71 (s, 4H), 3.64 - 3.52 (m, 2H), 2.41 (d, J = 2.0 Hz, 3H), 2.14 (d, J = 2.4 Hz, 3H), 1.47 (t, J = 7.2 Hz, 3H), 1.38 (d, J = 6.4 Hz, 3H)
30		535.2	(400 MHz, METHANOL-d4) δ = 8.60 (s, 1H), 8.50 (d, J = 1.6 Hz, 1H), 7.82 (d, J = 16.8 Hz, 1H), 7.16 (d, J = 16.8 Hz, 1H), 4.97 (br s, 1H), 4.46 - 4.27 (m, 3H), 4.14 - 4.01 (m, 2H), 3.90 - 3.66 (m, 9H), 3.53 (br s, 1H), 2.37 (s, 3H), 2.08 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H)
31		577.2	(400 MHz, MeOD-d_4) δ = 8.92 (s, 1H), 8.89 (d, *J* = 1.2 Hz, 1H), 8.11 (d, *J* = 16.8 Hz, 1H), 7.16 (d, *J* = 16.8 Hz, 1H), 4.68 (d, *J* = 5.2 Hz, 1H), 4.63 - 4.52 (m, 2H), 4.39 - 4.30 (m, 2H), 4.12 - 4.05 (m, 1H), 4.04 - 3.90 (m, 4H), 3.75 (s, 3H), 3.52 - 3.46 (m, 1H), 3.08 - 2.98 (m, 1H), 2.86 (d, *J* = 14.8 Hz, 1H), 2.72 - 2.59 (m, 2H), 1.49 (t, *J* = 7.2 Hz, 3H),

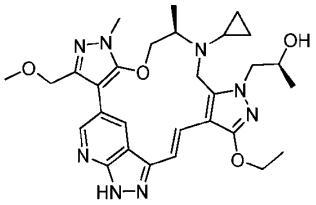
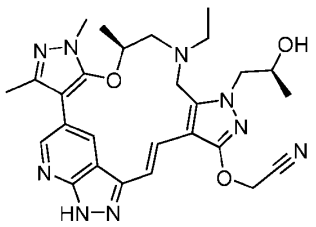
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
			1.21 (d, *J* = 6.0 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.73 - 0.64 (m, 2H), 0.58 - 0.52 (m, 2H)
32		474.1	(400 MHz, METHANOL-d4) δ = 8.82 (s, 1H), 8.71 (s, 1H), 8.56 - 8.43 (m, 1H), 8.14 (d, J = 17.0 Hz, 1H), 7.06 (d, J = 17.0 Hz, 1H), 5.14 (s, 2H), 4.78 - 4.63 (m, 1H), 3.95 - 3.89 (m, 1H), 3.84 - 3.78 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.98 - 2.77 (m, 2H), 2.45 (s, 3H), 2.37 (s, 3H), 1.03 - 0.99 (m, 3H)
33		543.3	(400 MHz, DMSO-d6) δ = 13.39 (s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.65 (br s, 1H), 8.11 - 7.96 (m, 2H), 7.05 (d, J = 17.2 Hz, 1H), 6.18 (t, J = 54.4 Hz, 1H), 4.96 - 4.79 (m, 2H), 4.34 - 4.22 (m, 2H), 4.01 - 3.93 (m, 2H), 3.93 - 3.79 (m, 3H), 3.73 (s, 3H), 3.18 - 2.99 (m, 2H), 2.82 - 2.58 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 5.6 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H)
34		557.3	(400 MHz, DMSO-d6) δ = 13.38 (s, 1H), 8.87 (d, J = 1.6 Hz, 1H), 8.65 (s, 1H), 8.18 - 7.89 (m, 2H), 7.06 (d, J = 17.2 Hz, 1H), 6.36 - 5.94 (m, 1H), 5.02 - 4.79 (m, 3H), 3.97 (s, 2H), 3.94 - 3.81 (m, 3H), 3.73 (s, 3H), 3.17 - 2.99 (m, 2H), 2.80 - 2.70 (m, 1H), 2.68 - 2.58 (m, 1H), 1.44 - 1.35 (m, 6H), 1.13 - 1.06 (m, 3H), 0.97 - 0.89 (m, 3H)

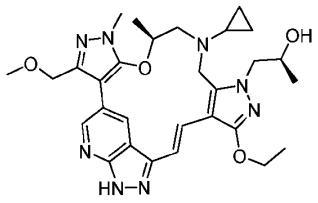
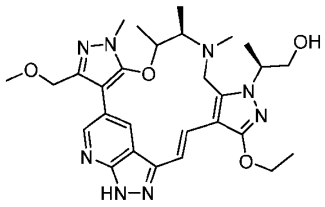
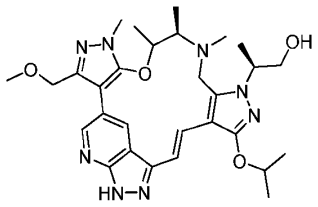
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
35		557.3	(400 MHz, DMSO-d6) δ = 13.37 (s, 1H), 8.87 (d, J = 1.6 Hz, 1H), 8.71 (s, 1H), 8.06 (d, J = 17.2 Hz, 1H), 8.01 (s, 1H), 7.08 (d, J = 17.2 Hz, 1H), 6.44 - 5.92 (m, 1H), 5.03 - 4.78 (m, 3H), 3.97 (s, 2H), 3.96 - 3.84 (m, 3H), 3.74 (s, 3H), 3.10 (s, 2H), 2.78 - 2.58 (m, 2H), 1.42 - 1.36 (m, 6H), 1.06 (d, J = 5.6 Hz, 3H), 0.95 - 0.88 (m, 3H)
36		523.4	(400 MHz, DMSO-d6) δ = 12.85 (s, 1H), 11.75 (s, 1H), 8.57 - 8.45 (m, 1H), 8.24 (s, 1H), 7.92 (d, J = 16.8 Hz, 1H), 6.89 (d, J = 16.8 Hz, 1H), 4.84 (d, J = 3.2 Hz, 1H), 4.63 (d, J = 8.8 Hz, 1H), 4.31 - 4.23 (m, 2H), 3.94 - 3.82 (m, 5H), 3.66 (s, 3H), 2.91 (s, 2H), 2.63 -2.53 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 5.2 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H)
37		518.1	(400 MHz, METHANOL-d4) δ = 8.98 (br s, 1H), 8.81 (s, 1H), 8.18 (br d, J = 16.8 Hz, 1H), 7.97 (s, 1H), 7.11 (br d, J = 17.2 Hz, 1H), 5.16 (s, 2H), 4.80 - 4.74 (m, 1H), 4.18 - 4.08 (m, 1H), 4.06 - 3.94 (m, 4H), 3.75 (s, 3H), 3.14 - 3.02 (m, 1H), 2.93 - 2.75 (m, 2H), 2.74 - 2.64 (m, 1H), 1.24 (br d, J = 6.4 Hz, 3H), 1.15 (br d, J = 6.4 Hz, 3H), 1.00 (br t, J = 7.2 Hz, 3H)

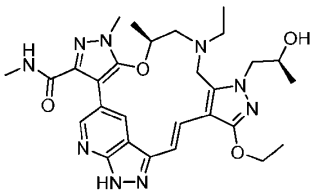
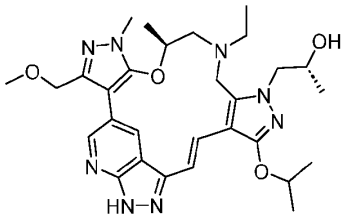
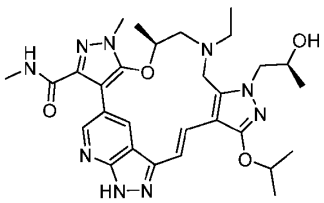
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
38		543.2	(400 MHz, DMSO-d6) δ = 13.38 (br s, 1H), 8.88 (s, 1H), 8.72 (br s, 1H), 8.08 (d, J = 17.2 Hz, 1H), 8.03 (s, 1H), 7.07(d, J = 17.2 Hz, 1H), 6.38 - 6.01 (m, 1H), 4.95 - 4.75 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.99 (s, 2H), 3.96 - 3.82 (m, 3H), 3.74 (s, 3H), 3.11 (br s, 2H), 2.79 - 2.59 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.12 - 1.02 (m, 3H), 0.92 (t, J = 6.8 Hz, 3H)
39		352.3	(400 MHz, METHANOL-d4) δ = 8.96 (s, 1H), 8.80 (d, J = 1.2 Hz, 1H), 8.15 (d, J = 17.2 Hz, 1H), 7.96 (s, 1H), 7.10 (d, J = 17.2 Hz, 1H), 5.59 - 5.47 (m, 1H), 4.78 - 4.68 (m, 1H), 4.21 - 4.08 (m, 1H), 4.06 - 3.98 (m, 3H), 3.97 - 3.87 (m, 1H), 3.74 (s, 3H), 3.13 - 3.04 (m, 1H), 2.87 (br d, J = 15.2 Hz, 1H), 2.82 - 2.73 (m, 1H), 2.72 - 2.62 (m, 1H), 1.86 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H)
40		537.1	(400 MHz, METHANOL-d4) δ = 9.09 (d, J = 1.6 Hz, 1H), 8.97 (d, J = 1.2 Hz, 1H), 8.13 (d, J = 16.0 Hz, 1H), 7.17 (d, J = 16.0 Hz, 1H), 4.74 - 4.65 (m, 2H), 4.62 (s, 1H), 4.40 - 4.29 (m, 2H), 4.15 - 4.05 (m, 1H), 4.04 - 3.89 (m, 4H), 3.75 (s, 3H), 3.03 (dd, J = 8.0, 16.0 Hz, 1H), 2.93 - 2.83 (m, 1H), 2.65 (tt, J = 6.4, 12.0 Hz, 2H), 1.49 (t, J = 8.0 Hz, 3H), 1.21 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H)

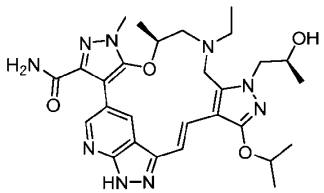
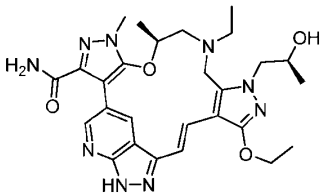
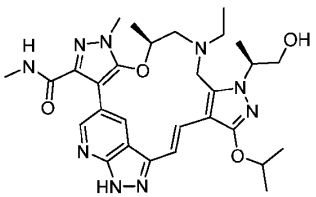
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
41		522.4	(400 MHz, DMSO-d6) δ = 14.05 (s, 1H), 8.67 (s, 1H), 8.19 (s, 1H), 8.15 (d, J = 17.6 Hz, 1H), 7.10 (d, J = 17.6 Hz, 1H), 4.94 - 4.87 (m, 1H), 4.85 (d, J = 4.4 Hz, 1H), 4.75 - 4.68 (m, 1H), 3.99 - 3.93 (m, 2H), 3.92 - 3.83 (m, 3H), 3.73 (s, 3H), 3.08 - 2.98 (m, 1H), 2.87 (d, J = 13.2 Hz, 1H), 2.77 - 2.69 (m, 1H), 2.64 - 2.58 (m, 1H), 1.40 (d, J = 4.4 Hz, 3H), 1.38 (d, J = 4.4 Hz, 3H), 1.13 (d, J = 4.4 Hz, 3H), 1.09 (d, J = 4.4 Hz, 3H), 0.95 (t, J = 8.8 Hz, 3H)
42		565.2	(400 MHz, METHANOL-d4) δ = 9.00 (br s, 1H), 8.87 (br s, 1H), 8.09 - 7.94 (m, 1H), 7.16 - 7.05 (m, 1H), 4.57 - 4.44 (m, 4H), 4.39 - 4.32 (m, 2H), 4.04 (br d, J = 1.2 Hz, 1H), 3.99 - 3.87 (m, 2H), 3.78 (s, 3H), 3.75 - 3.71 (m, 1H), 3.46 (s, 3H), 2.88 (br s, 2H), 2.83 - 2.75 (m, 1H), 1.47 (t, J = 6.8 Hz, 3H), 1.38 (d, J = 6.8 Hz, 3H), 1.10 (br d, J = 6.4 Hz, 3H), 0.94 (br d, J = 6.4 Hz, 3H), 0.89 (br d, J = 6.0 Hz, 3H)
43		565.2	(400 MHz, METHANOL-d4) δ = 9.03 (s, 1H), 8.87 (s, 1H), 7.69 (br d, J = 16.8 Hz, 1H), 7.22 (d, J = 16.4 Hz, 1H), 4.61 - 4.54 (m, 1H), 4.52 (s, 2H), 4.41 - 4.33 (m, 3H), 4.02 - 3.90 (m, 3H), 3.88 - 3.82 (m, 1H), 3.79 (s, 3H), 3.73 - 3.67 (m, 1H), 3.44 (s, 3H), 3.42 - 3.37 (m, 1H), 3.03 - 2.92 (m, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 6.0 Hz, 6H), 1.11 (br d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H)

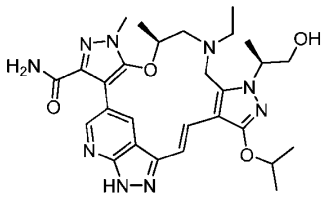
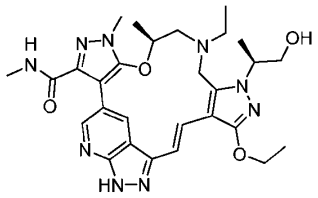
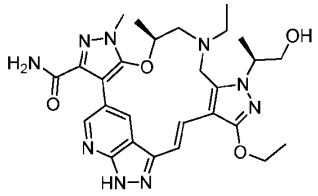
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
44		554.4	(400 MHz, DMSO-d6) δ = 13.45 (s, 1H), 8.89 (d, J = 1.6 Hz, 1H), 8.66 (br s, 1H), 8.07 (d, J = 17.2 Hz, 1H), 8.02 (s, 1H), 7.01 (d, J = 17.2 Hz, 1H), 6.41 - 6.00 (m, 1H), 5.24 (s, 2H), 5.00 - 4.77 (m, 2H), 4.02 (s, 2H), 3.99 - 3.87 (m, 3H), 3.73 (s, 3H), 3.20 - 3.00 (m, 2H), 2.70 - 2.60 (m, 2H), 1.12 (d, J = 5.6 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H)
45		554.2	(400 MHz, DMSO-d6) δ = 13.45 (s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.72 (br s, 1H), 8.10 (d, J = 17.2 Hz, 1H), 8.04 (s, 1H), 7.02 (d, J = 17.2 Hz, 1H), 6.43 - 6.01 (m, 1H), 5.24 (s, 2H), 4.98 - 4.74 (m, 2H), 4.02 (s, 2H), 4.00 - 3.91 (m, 3H), 3.74 (s, 3H), 3.12 (br s, 2H), 2.71 - 2.64 (m, 2H), 1.10 - 1.06 (m, 3H), 0.93 (t, J = 7.2 Hz, 3H)
46		565.2	(400 MHz, METHANOL-d4) δ = 9.15 - 8.80 (m, 2H), 8.22 - 7.97 (m, 1H), 7.34 - 6.97 (m, 1H), 4.61 - 4.44 (m, 3H), 4.39 - 4.31 (m, 2H), 4.15 - 4.07 (m, 2H), 4.06 - 3.93 (m, 3H), 3.77 (s, 3H), 3.46 (s, 3H), 3.02 - 2.70 (m, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H), 1.10 (br d, J = 6.4 Hz, 3H), 0.93 (br d, J = 6.4 Hz, 3H), 0.91 - 0.85 (m, 3H)
47		565.2	(400 MHz, METHANOL-d4) δ = 9.12 - 8.84 (m, 2H), 7.77 (s, 1H), 7.24 (d, J = 16.8 Hz, 1H), 4.53 (s, 2H), 4.41 - 4.28 (m, 3H), 4.18 - 4.04 (m, 2H), 4.03 - 3.90 (m, 4H), 3.81 (s, 3H), 3.47 - 3.37 (m, 4H), 3.00 - 2.86 (m, 1H), 1.50 (t, J = 7.2 Hz, 3H),1.43 (d, J = 7.2 Hz, 3H), 1.24 (d, J = 6.0

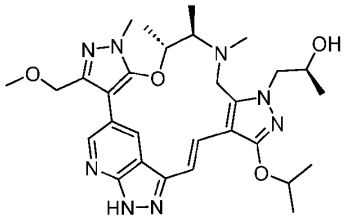
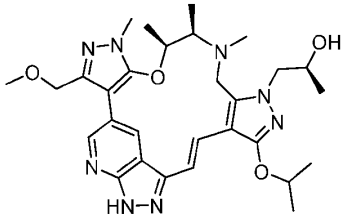
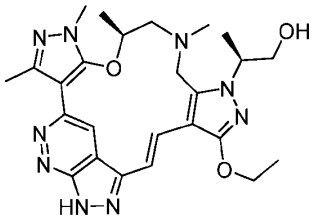
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
			Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H)
48		563.4	(400 MHz, METHANOL-d4) δ = 8.87 (s, 1H), 8.82 (s, 1H), 7.43 (br d, J = 16.8 Hz, 1H), 7.22 (d, J = 16.8 Hz, 1H), 4.49 (s, 2H), 4.48 - 4.44 (m, 1H), 4.39 - 4.29 (m, 2H), 4.28 - 4.21 (m, 1H), 4.11 (br d, J = 14.4 Hz, 2H), 4.05 (br d, J = 5.6 Hz, 2H), 3.88 (s, 1H), 3.83 (s, 3H), 3.57 - 3.49 (m, 1H), 3.44 (s, 3H), 2.16 - 2.08 (m, 1H), 1.49 (br t, J = 7.2 Hz, 3H), 1.44 (br d, J =6.8 Hz, 3H), 1.22 (br d, J = 6.4 Hz, 3H), 0.40 (br d, J = 5.6 Hz, 2H), 0.33 - 0.24 (m, 1H), 0.23 - 0.12 (m, 1H)
49		531.27	(400 MHz, METHANOL-d4) δ = 8.95 - 8.61 (m, 2H), 8.10 (br d, J = 17.2 Hz, 1H), 7.06 (d, J = 17.2 Hz, 1H), 5.16 (s, 2H), 4.67 - 4.55 (m, 1H), 4.14 (br d, J = 4.8 Hz, 1H), 4.07 - 3.91 (m, 4H), 3.69 (s, 3H), 3.07 - 2.95 (m, 1H), 2.91 - 2.80 (m, 1H),2.73 - 2.55 (m, 2H), 2.46 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H), 1.04 (br d, J = 6.4 Hz, 3H), 0.92 (br t, J = 7.2 Hz, 3H)

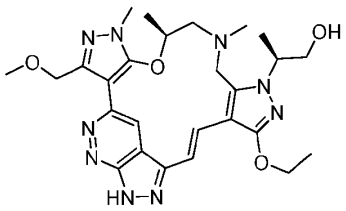
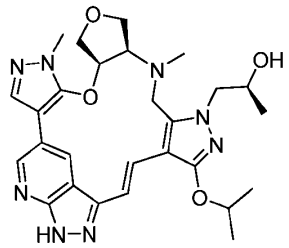
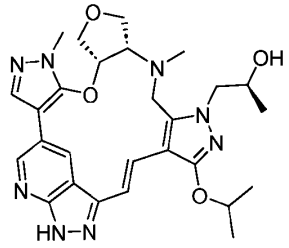
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
50		563.3	(400 MHz, METHANOL-d4) δ = 8.93 (s, 2H), 7.56 (d, J = 16.4 Hz, 1H), 7.17 (d, J = 16.8 Hz, 1H), 4.52 (s, 2H), 4.39 - 4.32 (m, 2H), 4.25 - 4.17 (m, 1H), 4.16 - 4.11 (m, 1H), 4.10 - 3.91 (m, 4H), 3.78 (s, 3H), 3.47 (s, 3H), 3.23 - 3.16 (m, 1H), 3.14(br d, J = 3.2 Hz, 1H), 2.02 (br s, 1H), 1.51 - 1.47 (m, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.49 - 0.23 (m, 3H), 0.13 - 0.03 (m, 1H)
51		551.3	(400 MHz, METHANOL-d4) δ = 9.25 (br s, 1H), 8.93 (s, 1H), 8.31 - 8.21 (m, 1H), 7.32 (d, J = 16.8 Hz, 1H), 4.59 -4.50 (m, 2H), 4.49 - 4.40 (m, 2H), 4.40 - 4.34 (m, 2H), 4.12 - 4.06 (m, 1H), 3.93 (br d, J = 14.4 Hz, 1H), 3.86 (br d, J = 11.2 Hz, 1H), 3.81 (s, 3H), 3.73 - 3.68 (m, 1H), 3.47 (s, 3H), 2.99 (br d, J = 6.4 Hz, 1H), 2.41 (s, 3H), 1.51 - 1.46 (m, 6H), 1.40 (d, J = 6.4 Hz, 3H), 1.22 (br d, J = 6.0 Hz, 3H)
52		565.3	(400 MHz, METHANOL-d4) δ = 9.23 (br s, 1H), 8.92 (d, J = 1.6 Hz, 1H), 8.23 (br d, J = 16.0 Hz, 1H), 7.33 (d, J = 16.8 Hz, 1H), 5.07 - 4.98 (m, 1H), 4.58 - 4.49 (m, 2H), 4.47 - 4.37 (m, 2H), 4.08 (d, J = 14.4 Hz, 1H), 3.92 (br d, J = 14.4 Hz, 1H), 3.87 - 3.83 (m, 1H), 3.81 (s, 3H), 3.74 - 3.67 (m, 1H), 3.47 (s, 3H), 3.04 - 2.92 (m, 1H), 2.41 (s, 3H), 1.49 - 1.43 (m, 9H),1.40 (d, J = 6.8 Hz, 3H), 1.21 (br d, J = 6.4 Hz, 3H

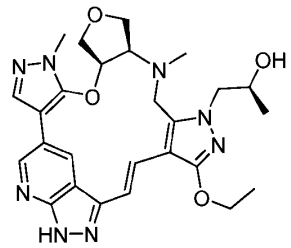
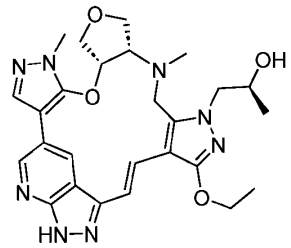
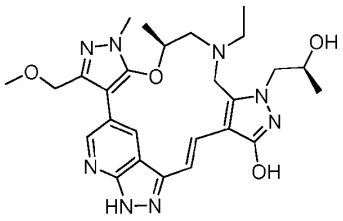
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
53		564.2	(400 MHz, METHANOL-d4) δ = 8.96 (d, J = 1.6 Hz, 1H), 8.92 (s, 1H), 8.10 (d, J = 16.8 Hz, 1H), 7.16 (d, J = 16.8 Hz, 1H), 4.67 - 4.56 (m, 1H), 4.39 - 4.30 (m, 2H), 4.13 - 4.05 (m, 1H), 4.04 - 3.92 (m, 4H), 3.90 - 3.66 (m, 4H), 3.05 - 2.96 (m, 1H), 2.91 (s, 3H), 2.69 - 2.51 (m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H)
54		565.2	(400 MHz, MeOD-d_4) δ = 9.01 (d, *J* = 1.6 Hz, 1H), 8.95 - 8.88 (m, 1H), 8.22 (s, 1H), 7.20 (d, *J* = 16.8 Hz, 1H), 5.02 - 4.93 (m, 1H), 4.70 - 4.64 (m, 1H), 4.49 (d, *J* = 1.2 Hz, 2H), 4.14 - 4.03 (m, 2H), 4.00 - 3.90 (m, 3H), 3.77 (s, 3H), 3.46 (s, 3H), 3.06 - 2.87 (m, 2H), 2.65 (q, *J* = 6.8 Hz, 2H), 1.45 (t, *J* = 5.6 Hz, 6H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H)
55		578.4	(400 MHz, METHANOL-d4) δ = 8.96 (d, J = 1.6 Hz, 1H), 8.91 (d, J = 1.6 Hz, 1H), 8.08 (d, J = 16.8 Hz, 1H), 7.17 (d, J = 16.8 Hz, 1H), 5.01 - 4.94 (m, 1H), 4.65 - 4.56 (m, 1H), 4.15 - 4.02 (m, 2H), 4.02 - 3.98 (m, 2H), 3.97 - 3.90 (m, 1H), 3.81 (s, 3H), 3.03 - 2.94 (m, 1H), 2.91 (s, 4H), 2.67 - 2.53 (m, 2H), 1.48 - 1.42 (m, 6H), 1.24 - 1.17 (m, 3H), 1.06 - 0.99 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H)

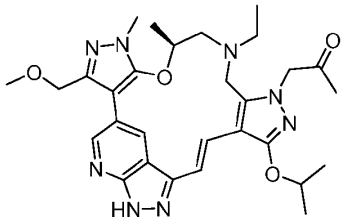
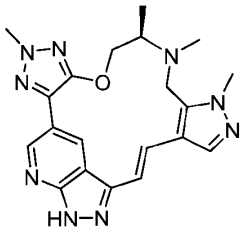
Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
56		564.3	(400 MHz, METHANOL-d4) δ = 9.03 (d, J = 1.6 Hz, 1H), 8.92 (s, 1H), 8.09 (d, J = 16.4 Hz, 1H), 7.18 (d, J = 16.8 Hz, 1H), 4.97 (br s, 1H), 4.61 (br s, 3H), 4.10 - 4.04 (m, 1H), 4.02 (br d, J = 3.6 Hz, 2H), 3.96 (br d, J = 4.0 Hz, 1H), 3.86 - 3.81 (m, 3H), 3.05 - 2.94 (m, 1H), 2.94 - 2.85 (m, 1H), 2.68 - 2.54 (m, 2H), 1.47 - 1.43 (m, 6H), 1.24 - 1.18 (m, 3H), 1.03 (br d, J = 6.4Hz, 3H), 0.92 (br t, J = 7.2 Hz, 3H
57		550.3	(400 MHz, METHANOL-d4) δ = 9.03 (s, 1H), 8.91 (d, J = 1.2 Hz, 1H), 8.09 (d, J = 16.8 Hz, 1H), 7.15 (d, J = 16.8 Hz, 1H), 4.66 - 4.55 (m, 1H), 4.41 - 4.28 (m, 2H), 4.12 - 4.05 (m, 1H), 4.04 - 3.91 (m, 4H), 3.83 (s, 3H), 3.05 - 2.86 (m, 2H), 2.69 -2.52 (m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H)
58		578.4	(400 MHz, METHANOL-d4) δ = 8.96 (s, 1H), 8.92 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 16.8 Hz, 1H), 7.17 (d, J = 16.8 Hz, 1H), 5.07 - 4.97 (m, 1H), 4.65 (br s, 1H), 4.55 - 4.43 (m, 1H), 4.00 (s, 2H), 3.82 (s, 3H), 3.81 - 3.76 (m, 1H), 3.71 - 3.66 (m, 1H), 3.05 - 2.97 (m, 1H), 2.91 (s, 4H), 2.71 - 2.55 (m, 2H), 1.48 - 1.39 (m, 9H), 1.02 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H)

Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
59		563.30	(400 MHz, METHANOL-d4) δ = 9.03 (br s, 1H), 8.91 (br s, 1H), 8.03 (br d, J = 17.2 Hz, 1H), 7.16 (br d, J = 16.4 Hz, 1H), 5.08 - 4.96 (m, 1H), 4.63 (br d, J = 1.6 Hz, 1H), 4.54 - 4.43 (m, 1H), 4.00 (br s, 2H), 3.83 (s, 3H), 3.79 (br d, J = 8.4 Hz, 1H), 3.74 - 3.64 (m, 1H), 3.06 - 2.84 (m, 2H), 2.73 - 2.51 (m, 2H), 1.50 - 1.38 (m, 9H), 1.02 (br d, J = 5.6 Hz, 3H), 0.94 (br t, J= 6.4 Hz, 3H)
60		563.3	(400 MHz, METHANOL-d4) δ = 8.96 (d, J = 2.0 Hz, 1H), 8.91 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 16.8 Hz, 1H), 7.15 (d, J = 16.8 Hz, 1H), 4.69 - 4.57 (m, 1H), 4.56 - 4.44 (m, 1H), 4.43 - 4.31 (m, 2H), 4.00 (s, 2H), 3.89 - 3.77 (m, 5H), 3.72 - 3.6 (m , 1H), 3.05 - 2.96 (m, 1H), 2.91 (s, 3H), 2.90 - 2.85 (m, 1H), 2.71 - 2.54 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.41 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H)
61		550.3	(400 MHz, METHANOL-d4) δ = 9.03 (d, J = 1.6 Hz, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 16.8 Hz, 1H), 7.14 (d, J = 16.8 Hz, 1H), 4.66 - 4.56 (m, 1H), 4.54 - 4.45 (m, 1H), 4.40 - 4.33 (m, 2H), 4.00 (s, 2H), 3.82 (s, 3H), 3.79 (s, 1H), 3.71 -3.64 (m, 1H), 3.02 - 2.94 (m, 1H), 2.92 - 2.85 (m, 1H), 2.69 - 2.51 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.41 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H)

Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
62		565.3	(400 MHz, METHANOL-d4) δ = 9.25 (br s, 1H), 8.93 (s, 1H), 8.49 (br s, 1H), 8.38 - 8.21 (m, 1H), 7.43 - 7.30 (m, 1H), 4.99 (br d, J = 6.0 Hz, 1H), 4.66 - 4.47 (m, 3H), 4.40 (br d, J = 5.6 Hz, 1H), 4.15 - 4.05 (m, 2H), 4.02 - 3.90 (m, 3H), 3.81 (s, 3H), 3.47 (s, 3H), 2.98 (br d, J = 9.6 Hz, 1H), 2.41 (br s, 3H), 1.51 - 1.42 (m, 9H), 1.26 - 1.15 (m, 6H)
63		565.2	(400 MHz, METHANOL-d4) δ = 8.96 (s, 1H), 8.79 - 8.67 (m, 1H), 8.55 - 8.48 (m, 1H), 8.43 - 8.31 (m, 1H), 7.32 - 7.15 (m, 1H), 5.23 - 5.12 (m, 1H), 5.02 - 4.98 (m, 2H), 4.52 - 4.42 (m, 2H), 4.11 - 4.00 (m, 3H), 3.99 - 3.89 (m, 2H), 3.79 (s, 3H), 3.49 (s, 3H), 3.10 - 2.98 (m, 1H), 2.45 (br s, 3H), 1.46 (dd, J = 6.0, 9.2 Hz, 6H), 1.38 (br d, J = 6.8 Hz, 3H), 1.23 (br d, J = 5.6 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H)
64		508.2	(400 MHz, MeOD-*d4*) δ = 8.72 (s, 1H), 8.32 (d, *J* = 16.8 Hz, 1H), 7.19 (d, *J* = 16.8 Hz, 1H), 4.74 - 4.70 (m, 1H), 4.59 (s, 1H), 4.49 - 4.42 (m, 1H), 4.39 - 4.32 (m, 2H), 4.02 - 3.95 (m, 1H), 3.87 - 3.78 (m, 2H), 3.71 (s, 3H), 3.00 - 2.83 (m, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.48 (t, *J* = 6.8 Hz, 3H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H)

Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
65		538.3	(400 MHz, DMSO-d_6) δ = 14.26 - 13.85 (m, 1H), 8.60 (s, 1H), 8.23 (d, *J* = 17.2 Hz, 1H), 7.07 (d, *J* = 17.2 Hz, 1H),4.97 (d, *J* = 11.6 Hz, 1H), 4.82 (t, *J* = 4.8 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 2H), 4.46 - 4.34 (m, 1H), 4.33 - 4.23 (m, 2H), 3.99 - 3.92 (m, 1H), 3.87 - 3.79 (m, 1H), 3.71 (s, 3H), 3.59 - 3.51 (m, 2H), 3.27 (s, 3H), 2.99 - 2.91 (m, 1H), 2.87 - 2.77 (m, 1H), 2.34(s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H)
66		535.4	(400 MHz, DMSO-d6) δ = 13.36 (d, J = 2.4 Hz, 1H), 8.94 - 8.75 (m, 2H), 8.18 - 7.97 (m, 2H), 7.03 (d, J = 17.2 Hz, 1H), 5.16 - 4.98 (m, 1H), 4.95 - 4.81 (m, 2H), 4.08 (d, J = 6.8 Hz, 2H), 3.99 - 3.82 (m, 5H), 3.74 (s, 3H), 3.72 - 3.66 (m, 1H),3.65 - 3.53 (m, 2H), 2.47 (s, 3H), 1.39 (d, J = 5.2 Hz, 6H), 1.07 (d, J = 5.2 Hz, 3H)
67		535.2	(400 MHz, DMSO-d6) δ = 13.53 - 13.23 (m, 1H), 9.00 - 8.70 (m, 2H), 8.26 - 7.97 (m, 2H), 7.03 (d, J = 17.2 Hz, 1H),4.96 (d, J = 4.4 Hz, 1H), 4.92 - 4.86 (m, 1H), 4.17 - 4.03 (m, 2H), 4.02 - 3.86 (m, 4H), 3.85 - 3.79 (m, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 3.58 (d, J = 11.2 Hz, 2H), 2.46 (s, 3H), 1.38 (dd, J = 6.0, 10.0 Hz, 6H), 1.08 (d, J = 6.0 Hz, 3H)

Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
68		521.2	(400 MHz, DMSO- d6) δ = 13.37 (br s, 1H), 8.87 (d, J = 1.2 Hz, 1H), 8.80 (d, J = 2.8 Hz, 1H), 8.17 - 8.07 (m, 1H), 8.04 (s, 1H), 7.04 (d, J = 17.2 Hz, 1H), 5.09 - 4.89 (m, 1H), 4.85 (d, J = 4.4 Hz, 1H), 4.33 - 4.23 (m, 2H), 4.21 - 4.11 (m, 1H), 4.06 (t, J = 7.6 Hz, 1H), 4.00 - 3.88 (m, 4H), 3.84 (d, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.71 - 3.62 (m, 2H), 3.61 - 3.55 (m, 1H), 2.46 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 5.6 Hz, 3H)
69		521.3	(400 MHz, DMSO- d6) δ = 13.36 (br s, 1H), 8.86 (s, 1H), 8.85 - 8.79 (m, 1H), 8.10 (dd, J = 3.6, 13.2 Hz, 1H), 8.04 (s, 1H), 7.03 (d, J = 16.8 Hz, 1H), 5.22 - 4.95 (m, 1H), 4.86 (d, J = 4.4 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.08 (d, J = 7.2 Hz, 2H), 4.01 - 3.83 (m, 6H), 3.74 (s, 3H), 3.72 - 3.66 (m, 1H), 3.60 (d, J = 11.6 Hz, 1H), 2.47 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 5.6 Hz, 3H)
70		523.2	(400 MHz, METHANOL- d4) δ = 8.98 (s, 1H), 8.92 (d, J = 4.0 Hz, 1H), 8.15 (d, J = 16.0 Hz, 1H), 7.22 (d, J = 16.0 Hz, 1H), 4.75 - 4.68 (m, 1H), 4.49 (s, 2H), 4.09 - 4.03 (m, 1H), 4.00 - 3.95 (m, 2H), 3.94 - 3.86 (m, 2H), 3.77 (s, 3H), 3.47 (s, 3H), 3.05 (br dd, J = 8.0, 16.0 Hz, 1H), 2.87 (br d, J = 16.0 Hz, 1H), 2.74 - 2.62 (m, 2H), 1.20 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 0.96 (t, J = 6.0 Hz, 3H)

Ex.#	Structure (ChemDraw)	LCMS *m/z*	^{1}H NMR
71		563.4	(499 MHz, DMSO- d6) δ = 13.36 (s, 1H), 8.87 (s, 1H), 8.83 (d, J = 1.9 Hz, 1H), 8.04 (d, J = 17.0 Hz, 1H), 7.07 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 3.0 Hz, 3H), 4.86 (td, J = 6.1, 12.3 Hz, 1H), 4.60 (br s, 1H), 4.49 - 4.40 (m, 2H), 3.88 - 3.79 (m, 1H), 3.78 - 3.72 (m, 1H), 3.69 (s, 3H), 3.35 - 3.33 (m, 3H), 2.94 - 2.82 (m, 2H), 2.65 - 2.52 (m, 2H), 2.15 (s, 3H), 1.37 (t, J = 6.3 Hz, 6H), 1.02 (d, J = 6.3 Hz, 4H), 0.87 (t, J = 7.1 Hz, 3H)
72		406.0	(400 MHz, MeOD-d_4) δ = 9.53 (br s, 1H), 8.97 (s, 1H), 8.01 (br d, *J* = 17.2 Hz, 1H), 7.89 (s, 1H), 7.05 (d, *J* = 17.2 Hz, 1H), 4.41 - 4.32 (m, 1H), 4.26 - 4.17 (m, 1H), 4.08 (s, 3H), 4.01 (br d, *J* = 14.0 Hz, 1H), 3.91 - 3.85 (m, 4H), 3.46 - 3.39 (m, 1H), 2.13 (s, 3H), 1.15 (br d, *J* = 6.4 Hz, 3H)

[0725] BIOLOGICAL ASSAYS

[0726] Cell line and cell culture.

[0727] Ba/F3 cell line was purchased from DSMZ (ACC 300). H2122 cell line was licensed from NIH. H3122 cells was cultured using standard cell culture techniques in RPMI-1640 medium (Corning, Inc.) with 10% fetal bovine serum (Thermo Fisher Scientific, Inc.), 100 U/mL of penicillin/streptomycin (Corning, Inc.) at 37 °C in a humidified atmosphere with 5% CO_2. Ba/F3 cells was cultured using standard cell culture techniques in RPMI-1640 medium (Corning, Inc.) with 10% fetal bovine serum (Thermo Fisher Scientific, Inc.), 100 U/mL of penicillin/streptomycin (Corning, Inc.) plus 1 ng/mL mouse IL3 ((Thermo Fisher Scientific, Inc.) at 37 °C in a humidified atmosphere with 5% CO_2.

[0728] Generation of Ba/F3 engineered cell line.

[0729] The EML4-ALK gene was synthesized at GenScript and cloned into pCDH-CMV-MCS-EF1-Puro plasmid (System Biosciences, Inc). Ba/F3 EML4-ALK cell line was generated by infecting Ba/F3 cells with lentivirus containing EML4-ALK plasmid. Stable cell lines were selected by puromycin treatment at 2 ug/mL, followed by IL-3 withdrawal.

[0730] 3-day cell proliferation assay.

[0731] Two thousand per well of stable Ba/F3 EML4-ALK cells were seeded in 384 well white plates, and treated with compounds for 72 hours (37 °C, 5% CO_2). Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega) following the manufactures' protocol. IC_{50} determinations were performed using GraphPad Prism software (GraphPad, Inc., San Diego, CA). Results for cell proliferation inhibitory activity (IC_{50}, nM) of compounds in Ba/F3 EML4-ALK cells are shown in Assay Table 1.

Assay Table 1

Ex. #	Ba/F3 (EML4-ALK) IC_{50}, nM
1	12.29
2	<1
3	<0.2
4	28.39
5	58.77
6	1
7	<1
8	106.4
9	230.8
10	182.1
11	1117
12	677.2
13	<1
14	<1
15	157.6
16	202.5
17	42.35
18	36.88
19	245.72
20	<1
21	<1
22	2
23	90.34
24	9.84
25	3.71
26	47.44
27	68.83
28	>10000
29	3646
30	3513
31	34.76
32	379.8
33	<1

Ex. #	Ba/F3 (EML4-ALK) IC_{50}, nM
34	<1
35	<1
36	>10000
37	<1
38	4.67
39	1
40	22.79
41	<1
42	63.85
43	114.8
44	<1
45	3.768
46	90.14
47	228.9
48	437.27
49	183.8
50	<1
51	<1
52	<1
53	3524
54	<1
55	1269
56	1484
57	3036
58	1153
59	1856
60	1231
61	1527
62	<1
63	<1
64	1.386
65	12.77
66	69
67	9.0
68	51
69	1055
70	1121
71	<1
72	1685

[0732] H3122 engineered cell line generation.

[0733] The EML4-ALK gene was synthesized at GenScript and cloned into pCDH-CMV-MCS-EF1-Puro plasmid (System Biosciences, Inc). EML4-ALK G1202R, G1202R/L1196M,

G1202R/G1269A/L1198F, G1202R/L1198F, G1269S, I1171N, I1171S cDNA clones were made at GenScript by site directed mutagenesis and confirmed by sequencing. H2122 EML4-ALK mutations cell lines were generated by infecting H3122 cells with lentivirus containing EML4-ALK mutations plasmids. Stable cell lines were selected by puromycin treatment at 2 μg/mL.

[0734] 5-day cell proliferation assay.

[0735] Cell proliferation assay was carried out in H3122 parental (licensed from NIH) and H3122 engineered cell lines over-expressing different EMLK-ALK mutations. 1000 cells/100 μL per well were seeded in 96 well black plate with clear bottom (Corning #3904). Compounds were added using Tecan D300e Digital Dispenser, starting at 1 μM, 1:3 titration, 9 doses. Plates were incubated for 5 days at 37 °C and 5% CO_2. Cell proliferation was measured using CellTiter-Glo 2.0 luciferase-based ATP detection assay (Promega, Madison, WI) at 50 μL per well following the manufacturer's protocol. Plates were then read on a TECAN Sparks multimode microplate reader. IC_{50} values were determined using Prism software (GraphPad Software, San Diego, CA). Results for the cell proliferation inhibitory activity (IC_{50}, nM) of compounds in H2122 and ALK mutations cells are shown in Assay Table 2.

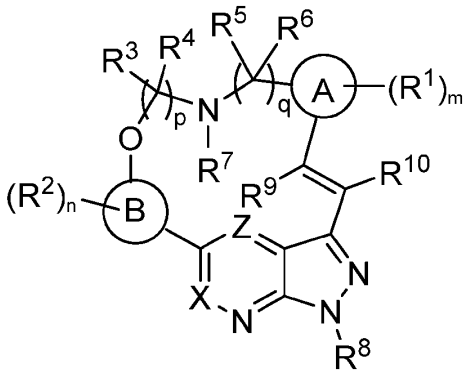
Assay Table 2

Ex. #	H3122 IC_{50}, nM	H3122 (EML4-ALK G1202R/L1196M) IC_{50}, nM	H3122 (EML4-ALK G1269S) IC_{50}, nM	H3122 (EML4-ALK G1202R) IC_{50}, nM	H3122 (EML4-ALK G1202R/G1269A/L1198F) IC_{50}, nM	H3122 (EML4-ALK G1202R/L1198F) IC_{50}, nM	H3122 (EML4-ALK I1171N) IC_{50}, nM	(H3122 EML4-ALK I1171S) IC_{50}, nM
2	0.41	26.32	0.79	21.01	41.19	18.53	3.41	0.99
3	0.86	16.98	1.15	5.12				
4	8.94	439.50	68.60	100.00				
5	17.51	698.69	38.84	347.30				
6	6.86	238.60	11.86	969.60				
7	0.60	18.32	0.73	2.36	2.44	9.78	1.00	6.79
13	0.44	60.50	0.65	2.15	9.48			
15	53.07	586.90	340.10	258.10	1000.00			
20	0.25	9.70	0.55	3.47	7.10	13.07	1.56	3.41
21	0.41	16.08	0.57	1.04	1.42	9.78	1.01	6.79
22	2.28							
34	0.54		2.87	9.32	55.36	161.00	3.00	1.85
35	3.87		55.39	130.70	411.10	429.50	51.16	19.98
50	1.22		2.24	5.75	4.59	15.65	2.27	23.49
51	0.97			4.63				
52	0.78			9.82				

Ex. #	H3122 IC$_{50}$, nM	H3122 (EML4-ALK G1202R/L1196M) IC$_{50}$, nM	H3122 (EML4-ALK G1269S) IC$_{50}$, nM	H3122 (EML4-ALK G1202R) IC$_{50}$, nM	H3122 (EML4-ALK G1202R/G1269A/L1198F) IC$_{50}$, nM	H3122 (EML4-ALK G1202R/L1198F) IC$_{50}$, nM	H3122 (EML4-ALK I1171N) IC$_{50}$, nM	(H3122 EML4-ALK I1171S) IC$_{50}$, nM
54	0.62	8.19	2.15	22.39	20.50		5.53	8.39
62	0.68	6.95	1.27	17.98	17.21		5.17	8.53
63	0.39	1.41	0.52	6.02	7.59		2.14	2.35

WHAT IS CLAIMED IS:

1. A compound of the formula I



I

wherein

ring A and ring B are each independently a 5- or 6-membered heteroarylene;

X is N or $C(R^{11})$;

Z is N or $C(R^{12})$;

each R^1 and R^2, when present and bonded to a carbon atom, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or each R^1 and R^2, when present and bonded to a nitrogen atom, is independently deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

each R^3, R^4, R^5, and R^6 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, or two of R^3, R^4, R^5, and R^6, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$;

R^7 is H, deuterium, $-C(O)R^a$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, or R^7 and one of R^3, R^4, R^5, or R^6, taken together with the atoms to which each is attached, combine to form a 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$,$-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

R^8 is H, $-S(O)_2R^c$, $-S(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-P(O)_2R^cR^d$, $-P(O)_2NR^cR^d$, or $-P(O)_2OR^c$;

each of R^9 and R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-

membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -SR^e, -$S(O)R^e$, -$S(O)_2R^e$, -$S(O)NR^eR^f$, -$S(O)_2NR^eR^f$, -NR^eR^f, -$NR^eC(O)R^f$, -$NR^eC(O)OR^f$, -$NR^eC(O)NR^eR^f$, -$NR^eS(O)R^f$, -$NR^eS(O)_2R^f$, -$NR^eS(O)NR^eR^f$, -$NR^eS(O)_2NR^eR^f$, -$C(O)R^e$, -$C(O)OR^e$, -$C(O)NR^eR^f$, -PR^eR^f, -$P(O)R^eR^f$, -$P(O)_2R^eR^f$, -$P(O)NR^eR^f$, -$P(O)_2NR^eR^f$, -$P(O)OR^e$, -$P(O)_2OR^e$, -CN, or -NO_2;

R^{11}, when present, is H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -$C(=NR^b)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=NR^d)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=NR^d)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=NR^d)NR^cR^d$, -PR^cR^d, -$P(O)R^cR^d$, -$P(O)_2R^cR^d$, -$P(O)NR^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)OR^c$, -$P(O)_2OR^c$, -CN, or -NO_2;

R^{12}, when present, is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OC(=NR^b)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, -$S(O)NR^aR^b$, -$S(O)_2NR^aR^b$, -$OS(O)NR^aR^b$, -$OS(O)_2NR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$NR^aC(O)OR^b$, -$NR^aC(O)NR^aR^b$, -$NR^aC(=NR^b)NR^aR^b$, -$NR^aS(O)R^b$, -$NR^aS(O)_2R^b$, -$NR^aS(O)NR^aR^b$, -$NR^aS(O)_2NR^aR^b$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)NR^aR^b$, -$C(=NR^b)NR^aR^b$, -PR^aR^b, -$P(O)R^aR^b$, -$P(O)_2R^aR^b$, -$P(O)NR^aR^b$, -$P(O)_2NR^aR^b$, -$P(O)OR^a$, -$P(O)_2OR^a$, -CN, or -NO_2, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=NR^d)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$,

$-NR^cC(=NR^d)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=NR^d)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

each R^a, R^b, R^c, R^d, R^e, and R^f is independently selected from the group consisting of H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and C_1-C_6 alkylene-5- to 10-membered heteroaryl; or R^a and R^b or R^c and R^d or R^e and R^f, taken together with the atom to which they are attached, form a 3- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, C_1-C_6 alkylene-C_6-C_{10} aryl, 5- to 10-membered heteroaryl, and C_1-C_6 alkylene-5- to 10-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, $-OC_1$-C_6 alkyl, $-OC(O)$-(H or C_1-C_6 alkyl), $-OC(O)N$(H or C_1-C_6 alkyl)$_2$, $-OC(O)N$(C_2-C_6 alkylene), $-OS(O)$-(H or C_1-C_6 alkyl), $-OS(O)_2$-(H or C_1-C_6 alkyl), $-OS(O)N$(H or C_1-C_6 alkyl)$_2$, $-OS(O)N$(C_2-C_6 alkylene), $-OS(O)_2N$(H or C_1-C_6 alkyl)$_2$, $-OS(O)_2N$(C_2-C_6 alkylene), -S(H or C_1-C_6 alkyl), $-S(O)$(H or C_1-C_6 alkyl), $-S(O)_2$(H or C_1-C_6 alkyl), $-S(O)N$(H or C_1-C_6 alkyl)$_2$, $-S(O)N$(C_2-C_6 alkylene), $-S(O)_2N$(H or C_1-C_6 alkyl)$_2$, $-S(O)_2N$(C_2-C_6 alkylene), -N(H or C_1-C_6 alkyl)$_2$, $-N$(C_2-C_6 alkylene), $-N$(H or C_1-C_6 alkyl)$C(O)$-(H or C_1-C_6 alkyl), $-N$(H or C_1-C_6 alkyl)$C(O)O$(H or C_1-C_6 alkyl), $-N$(H or C_1-C_6 alkyl)$C(O)N$(H or C_1-C_6 alkyl)$_2$, $-N$(H or C_1-C_6 alkyl)$C(O)N$(C_2-C_6 alkylene), $-N$(H or C_1-C_6 alkyl)$S(O)$-(H or C_1-C_6 alkyl), $-N$(H or C_1-C_6 alkyl)$S(O)_2$(H or C_1-C_6 alkyl), $-N$(H or C_1-C_6 alkyl)$S(O)N$(H or C_1-C_6 alkyl)$_2$, $-N$(H or C_1-C_6 alkyl)$S(O)N$(C_2-C_6 alkylene), $-N$(H or C_1-C_6 alkyl)$S(O)_2N$(H or C_1-C_6 alkyl)$_2$, $-N$(H or C_1-C_6 alkyl)$S(O)_2N$(C_2-C_6 alkylene), $-C(O)$-(H or C_1-C_6 alkyl), $-C(O)O$(H or C_1-C_6 alkyl), $-C(O)N$(C_2-C_6 alkylene), $-P$(H or C_1-C_6 alkyl)$_2$, $-P$(C_2-C_6 alkylene), $-P(O)$(H or C_1-C_6 alkyl)$_2$, $-P(O)$(C_2-C_6 alkylene), $-P(O)_2$(H or C_1-C_6 alkyl)$_2$, $-P(O)_2$(C_2-C_6 alkylene), $-P(O)N$(H or C_1-C_6 alkyl)$_2$, $-P(O)N$(C_2-C_6 alkylene), $-P(O)_2N$(H or C_1-C_6 alkyl)$_2$, $-P(O)_2N$(C_2-C_6 alkylene), $-P(O)O$(H or C_1-C_6 alkyl), $-P(O)_2O$(H or C_1-C_6 alkyl), -CN, or $-NO_2$;

m is 0, 1, 2, or 3;

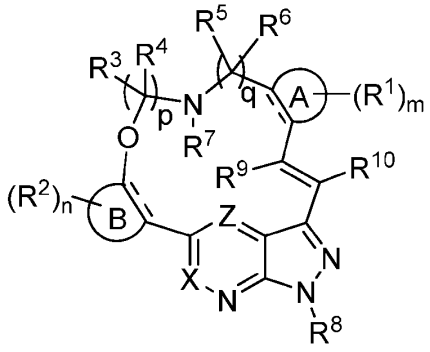
n is 0, 1, 2, or 3;

p is 1, 2, 3, or 4; and

q is 1, 2, or 3;

or a pharmaceutically acceptable salt thereof..

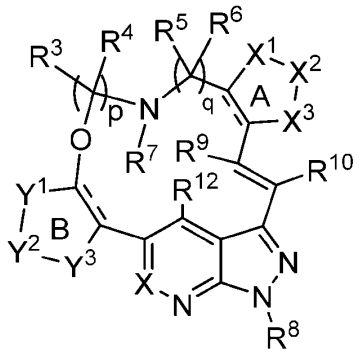
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula II



II

wherein each "------" is independently a carbon-carbon single bond or a carbon-carbon double bond.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, having the formula III



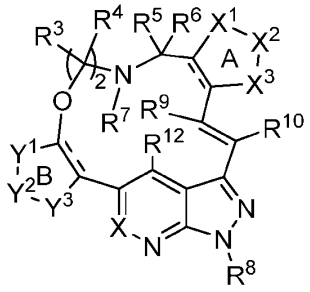
III

wherein each "------" is independently a carbon-carbon single bond or a carbon-carbon double bond;

X^1, X^2, and X^3 are each independently -O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N- and ring A is a 5-membered heteroarylene, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-; and

Y^1, Y^2, and Y^3 are each independently -O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, -N(R^2)- or =N- and ring B is a 5-membered heteroarylene, provided that at least one of Y^1, Y^2, and Y^3 is not =C(H)-, or =C(R^2)-.

4. The compound of claim 3, having the formula IV



IV

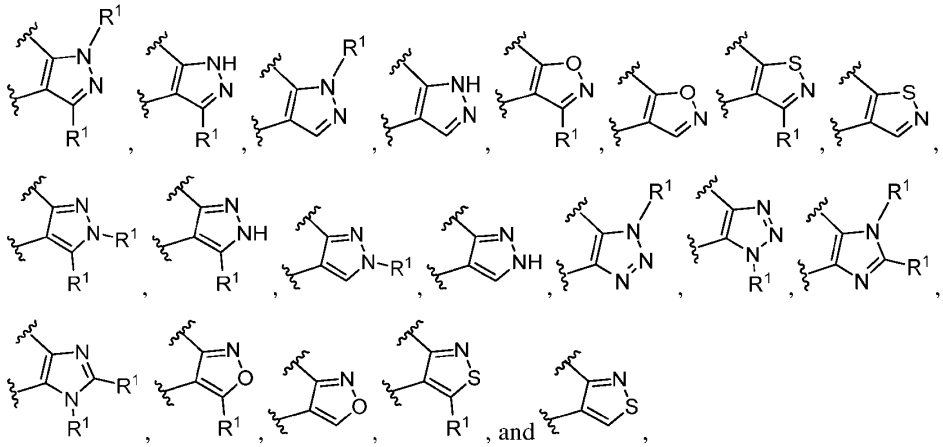
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 3 or 4, wherein

X^2 is =N- or N(R^1)-, X^1 and X^3 are each independently -O-, -S-, =C(H)-, =C(R^1)-, N(H), or N(R^1)-, and ring A is a 5-membered heteroarylene; and/or

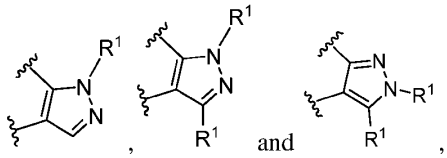
Y^2 is =N-, Y^1 and Y^3 are each independently O-, -S-, =C(H)-, =C(R^2)-, -N(H)-, or -N(R^2)-, and ring B is a 5-membered heteroarylene.

6. The compound of any one of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of



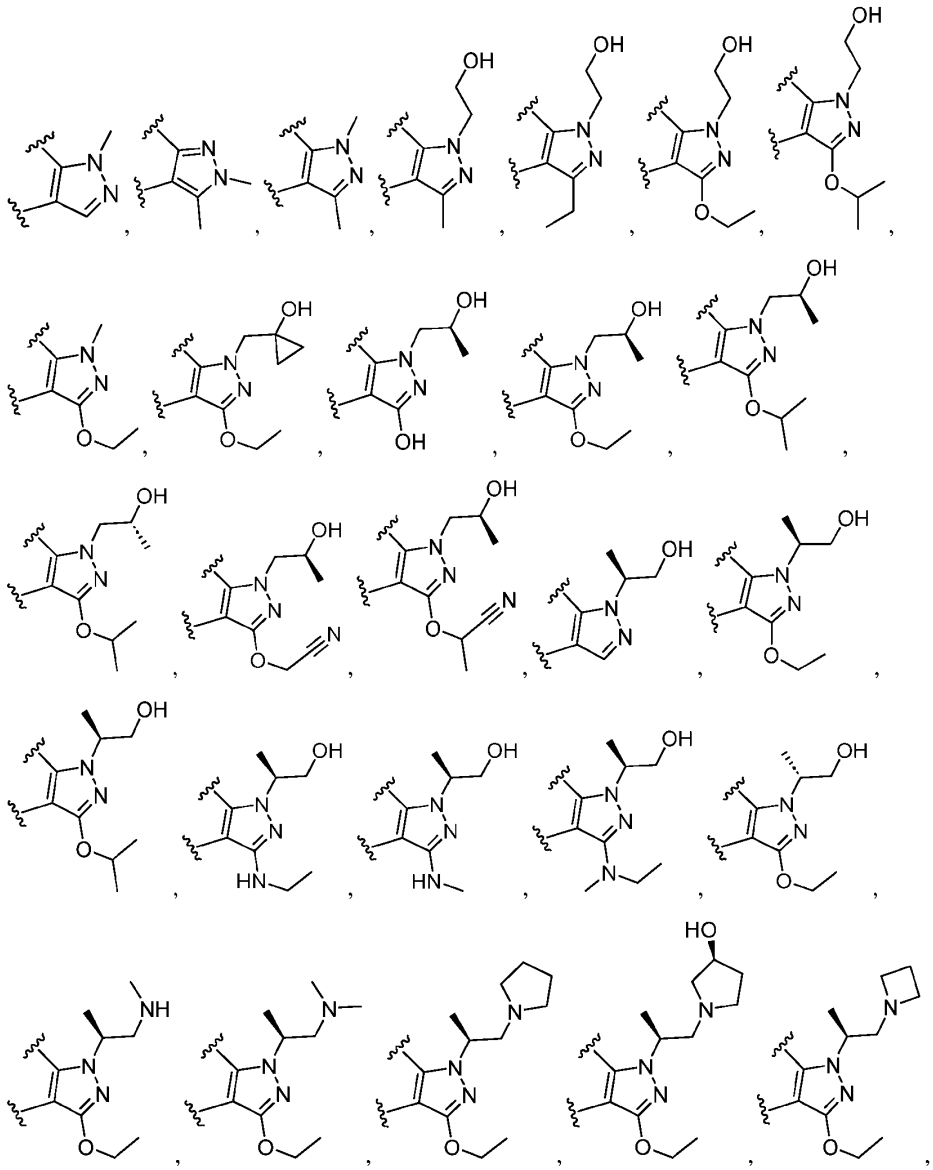
wherein each "〰" represents a point of covalent attachment.

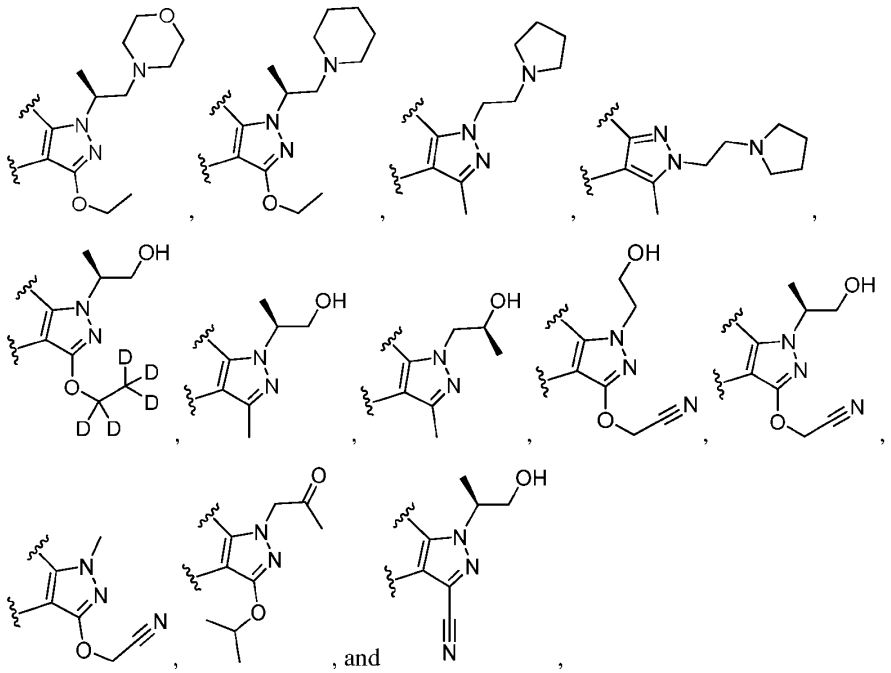
7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of



wherein each "〰" represents a point of covalent attachment.

8. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of

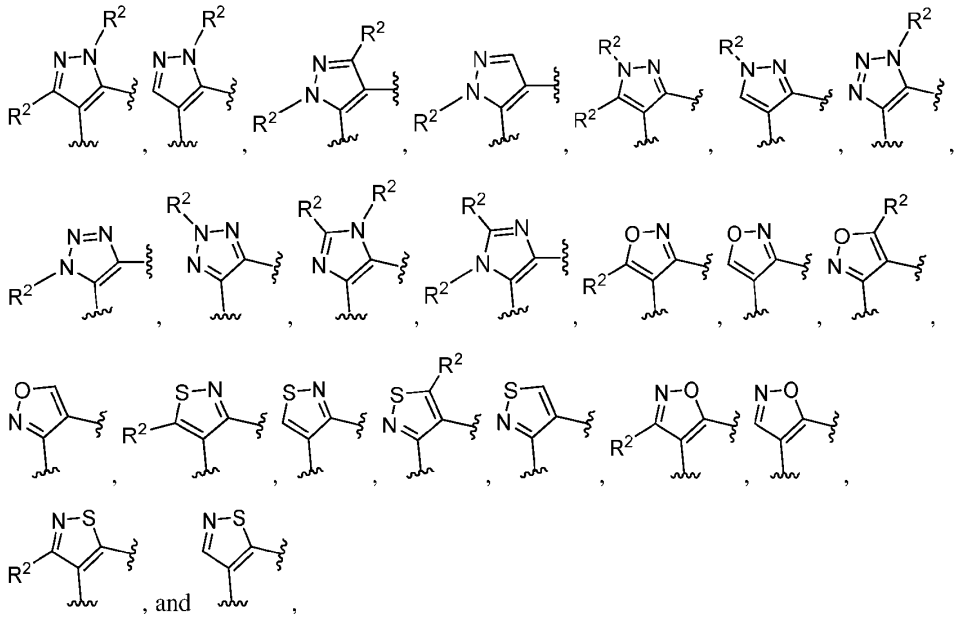




, and

wherein each "〰" represents a point of covalent attachment.

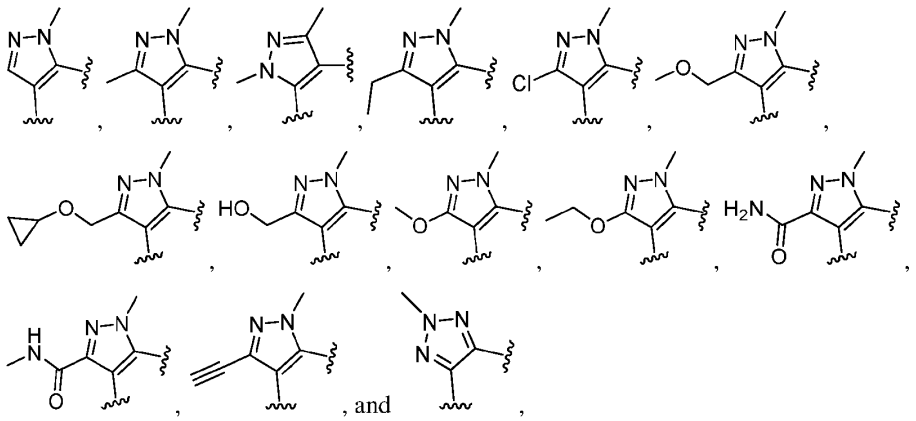
9. The compound of any one of claims 1 to 4 or 6, or a pharmaceutically acceptable salt thereof, wherein ring B is selected from the group consisting of



, and

wherein each "〰" represents a point of covalent attachment.

10. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring B is selected from the group consisting of



wherein each "〰" represents a point of covalent attachment.

11. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein X is N.

12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^{11})$.

13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_3-C_6 cycloalkyl or 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

14. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^7 and an R^3 or an R^4 , taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl; wherein each hydrogen atom

in 4- to 7-membered heterocycloalkyl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OC(=NR^d)NR^eR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eC(=NR^d)NR^eR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^eR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

15. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein one or two of R^3 are each independently a C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

16. The compound of any one of claims 13 to 15, or a pharmaceutically acceptable salt thereof, wherein any remaining R^3 and R^4 are H or deuterium.

17. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein one or two of R^3 are each independently a C_1-C_6 alkyl; and any remaining R^3 and R^4 are H or deuterium.

18. The compound of any one of the claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein each R^3 and R^4 is independently H, deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OC(=NR^b)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aC(=NR^b)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(=NR^b)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, , wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^e$, $-OC(O)R^e$,

$-OC(O)NR^eR^f$, $-OC(=NR^d)NR^cR^d$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^cC(=NR^d)NR^cR^d$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-C(=NR^d)NR^cR^d$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

19. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each R^3 is methyl, and any remaining R^3 and R^4 are H or deuterium.

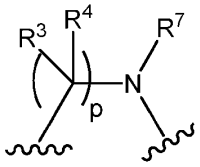
20. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein an R^3 is C_1-C_6 alkyl; and R^7 and an R^4, taken together with the atoms to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium.

21. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein an R^3 and an R^4, taken together with the carbon or carbons to which they are attached, combine to form a 4- to 7-membered heterocycloalkyl; and any remaining R^3 and R^4 are H or deuterium.

22. The compound of any one of claim 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^7 is H, $C(O)R^a$, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl; or R^7 and one instance of R^3 or R^4, taken together with the atoms to which they are attached, combine to form 4- to 7-membered heterocycloalkyl.

23. The compound of any one of the preceding claims, wherein p is 2 or 3.

24. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the portion



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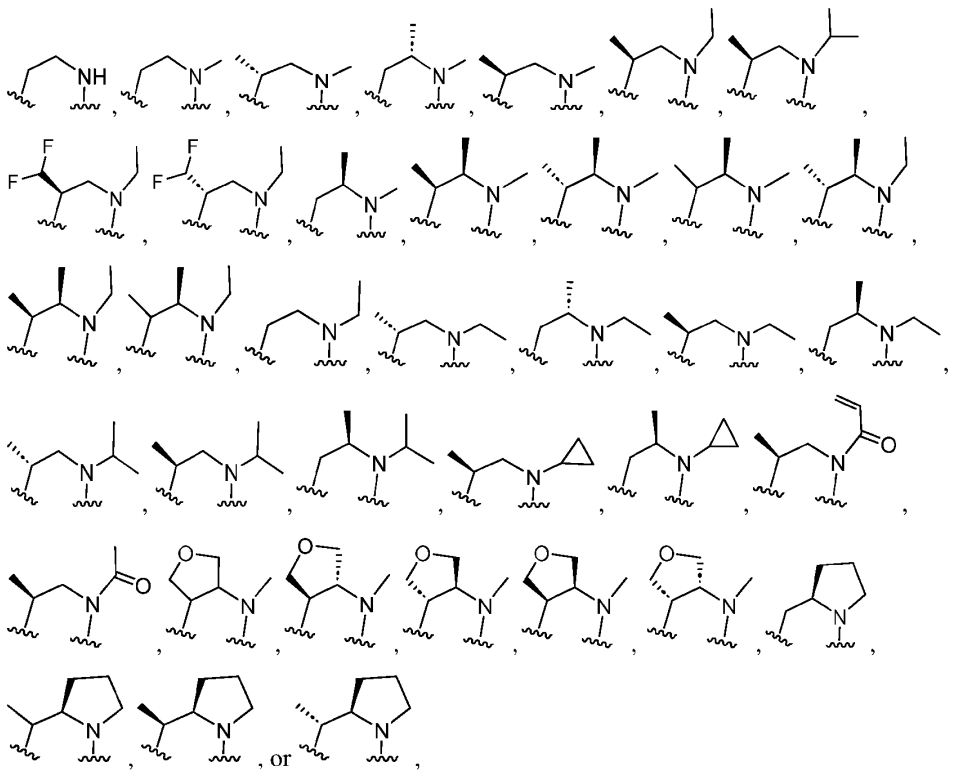
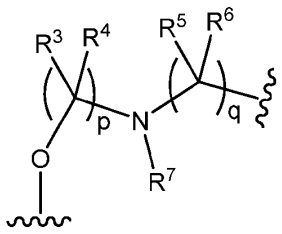


wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

25. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are each H.

26. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the portion



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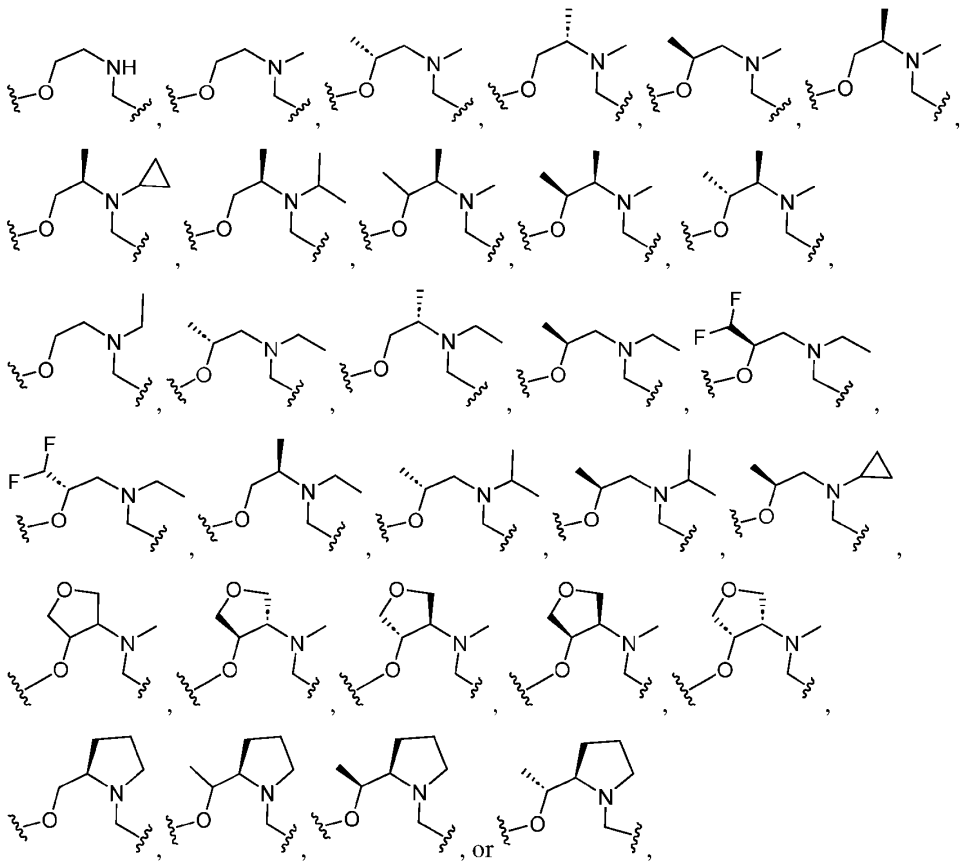

wherein each "〰" represents a point of covalent attachment, and each hydrogen is independently optionally substituted by deuterium.

27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^8 is H or C_1-C_6 alkyl.

28. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each of R^9 and R^{10} is independently H or deuterium.

29. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each of R^9 and R^{10} is H.

30. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^{11} is H, deuterium, halogen, -OH, OCH_3, CH_3, or CD_3.

31. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is $C(R^{12})$.

32. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^{12}, when present is H or deuterium.

33. The compound of any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein Z is N.

34. The compound of claim 1, selected from the group consisting of
(2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-12-ethyl-8,10,19-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
2-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(10*S*,17*E*)-6,8,10,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-

(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(11*R*,17*E*)-6,8,11,16-tetramethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10,19-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-2-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6,8,10,11,12-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-

(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
{[(10*S*,17*E*)-14-[(2*S*)-1-hydroxypropan-2-yl]-6-(methoxymethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(2*S*)-1-[(10*S*,17*E*)-12-ethyl-6,8,10,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-2-[(4a*R*,7a*S*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;
(2*S*)-2-[(13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;
(2*S*)-2-[(4a*S*,7a*R*,13*E*)-12-ethoxy-1,3,8-trimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-1-ol;
(2*S*)-1-[(10*S*,17*E*)-6-[(cyclopropyloxy)methyl]-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
{[(10*S*,17*E*)-6,8,10,12,14-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-8-methyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-19-ol;
{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(2*S*)-1-[(10*S*,17*E*)-10-(difluoromethyl)-16-ethoxy-12-ethyl-8-methyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
2-{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-6-(hydroxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;
(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
{[(10*R*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
{[(10*S*,17*E*)-10-(difluoromethyl)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8-methyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(2*S*)-1-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;
(2*S*)-1-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-12-(propan-2-yl)-

2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

(2*S*)-1-[(11*R*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

{[(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

(2*S*)-1-[(10*S*,17*E*)-12-cyclopropyl-16-ethoxy-6-(methoxymethyl)-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

(2*S*)-2-[(11*R*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,11,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

(2*S*)-2-[(11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(2*R*)-1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-*N*,8,10-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(10*S*,17*E*)-16-ethoxy-12-ethyl-14-[(2*S*)-1-hydroxypropan-2-yl]-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carboxamide;

(2*S*)-1-[(10*R*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

(2*S*)-1-[(10*S*,11*R*,17*E*)-6-(methoxymethyl)-8,10,11,12-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6,8,10,12-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-6-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-diazenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

(2*S*)-1-[(4a*R*,7a*R*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

(2*S*)-1-[(4a*S*,7a*S*,13*E*)-3,8-dimethyl-12-[(propan-2-yl)oxy]-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

(2*S*)-1-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

(2*S*)-1-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,8-dimethyl-3,4a,5,7,7a,8,9,16-octahydro-10*H*-17,19-(azenometheno)furo[3,4-*b*]tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-10-yl]propan-2-ol;

(10*S*,17*E*)-12-ethyl-14-[(2*S*)-2-hydroxypropyl]-6-(methoxymethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

1-[(10*S*,17*E*)-12-ethyl-6-(methoxymethyl)-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-(azenometheno)tripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-one; and
(11*R*,17*E*)-7,11,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-(azenometheno)dipyrazolo[3,4-*f*:3',4'-*j*][1,2,3]triazolo[4,5-*n*][1,4]oxazacyclopentadecine; or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising a compound of any one of the preceding claims, and optionally one or more excipients.

36. A method of treating disease in a subject comprising, administering a therapeutically effective amount of a compound of any one of claims 1 to 34, or a pharmaceutical composition of claim 35.

37. A compound according to any one of claims 1 to 34, for use in a method of treating disease in a subject.

38. Use of a compound according to any one of claims 1 to 34, in the manufacture of a medicament for the treatment of disease in a subject.