INDAZOLE CONTAINING MACROCYCLES AND THEIR USE

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/350,309, filed June 8, 2022, U.S. Provisional Application No. 63/350,310, filed June 8, 2022, and U.S. Provisional Application No. 63/503,879, filed May 23, 2023, the entire disclosures of all of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present disclosure relates to indazole containing 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 necessary to invent kinase inhibitors that can target not only the kinase oncogenic drivers, overcome most frequent resistance mutations, but also tolerant persister cancer cells for overcoming resistance, achieving better efficacy and longer disease control.

[0004] Non-small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide (World Health Organisation. Cancer Fact Sheet 2017). Activating EGFR mutations have been reported in approximately 10% to 15% of cases of adenocarcinoma in white patients and 50% of cases in Asian patients (Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res* 2015; 4:36-54). The two most frequent *EGFR* alterations found in NSCLC tumors are short in-frame deletions in exon 19 (del19) of the *EGFR* gene and L858R, a single missense mutation in exon 21 (Konduri K. et al. EGFR Fusions as Novel Therapeutic Targets in Lung Cancer. *Cancer Discovery* 2016, 6:601-11).

[0005] The first-generation reversible EGFR inhibitors, erlotinib and gefitinib are superior to chemotherapy in patients with advanced *EGFR* mutation-positive (Del19 or L858R) NSCLC and have been used as first-line standard of care in this setting. However, most patients will develop resistance to gefitinib or erlotinib with 50% to 70% of tumors developing EGFR T790M gatekeeper mutation with time of treatment (Sequist LV, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011; 3:75ra26). The second generation of EGFR inhibitors afatinib and dacomitinib are covalent, irreversible EGFR inhibitors that also inhibit HER2 and ERB4 of the ERB family (Li D, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008; 27: 4702-11; Ou SH, Soo RA. Dacomitinib in lung cancer: a "lost generation" EGFR tyrosine-kinase inhibitor from a bygone era? *Drug Des Devel Ther* 2015; 9:5641-53).

[0006] Although afatinib and dacomitinib are more potent EGFR inhibitors approved as first-line therapy for advanced *EGFR* mutation-positive (Del19 or L858R) NSCLC with longer progression free survival time (PFS) in comparison with gefitinib and erlotinib, EGFR T790M has been developed with time of treatment with afatinib (Tanaka K, et al. Acquisition of the T790M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naive

patients with non-small cell lung cancer harboring EGFR mutations. *Onco-target* 2017; 8:68123-30). EGFR T790M confers resistance to dacomitinib *In vitro* studies (Kobayashi Y, et al. EGFR T790M and C797S mutations as mechanisms of acquired resistance to dacomitinib. *J Thorac Oncol* 2018; 13: 727-31). The third-generation EGFR inhibitor Osimertinib is also an irreversible inhibitor targeting both EGFR activating mutations (Del19 and L858R) and T790M resistant double mutations, with selectivity over the wild-type EGFR (Finlay MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem* 2014; 57:8249-67). Osimertinib was first approved for patients with metastatic EGFR T790M mutation-positive NSCLC after failure of first-line EGFR inhibitors, and later approved in the first-line setting for patients with EGFR mutation-positive NSCLC following the phase III FLAURA trial with head-to-head trials comparing with erlotinib or gefitinib (Soria JC, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; 378:113-25). The mutation C797S at the EGFR covalent binding residue with irreversible EGFR inhibitor Osimertinib has been detected in Osimertinib-resistant patients (Ramalingam SS, et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Presented at the ESMO 2018).

[0007] Therefore, it is necessary to develop a new generation reversible EGFR inhibitor that are potent against oncogenic driver EGFR mutations, such as L858R, Del19, Δ746-750, Δ746-750/T790M, Δ746-750/C979S, L858R/T790M, Del19/T790M, L858R/C979S, Del19/C979S, L858R/T790M/C979S, and Δ746-750/T790M/C979S, as well as other emerging and established resistance mutations, while maintaining good selectivity over wild-type EGFR.

[0008] 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).

[0009] 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.

[0010] 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).

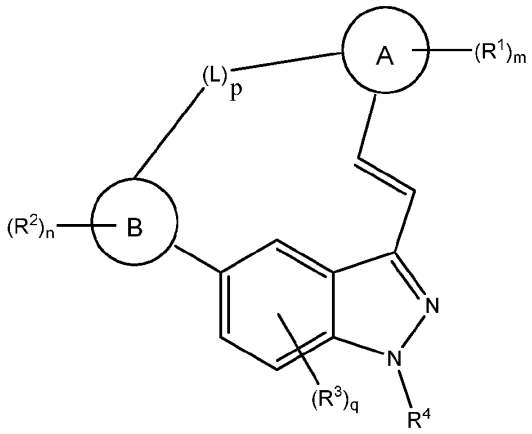
[0011] Cdc-like kinases (CLKs) are evolutionary conserved dual-specificity kinases that are able to phosphorylate serine, threonine, and tyrosine residues. CLKs catalyze the phosphorylation of SR proteins, serine, and arginine-rich splicing factors 1-12 (SRSF1-12),

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.

[0012] Therefore, it is necessary to develop a new generation of multitargeted EGFR inhibitors and multitargeted ALK inhibitors that are potent against oncogenic driver EGFR mutations, ALK fusions, and point mutations, other emerging and established EGFR and ALK resistance mutations, as well as emerging resistance targets for tolerant/persistent cancer cells, e.g. PIM kinases and CLK kinases.

SUMMARY

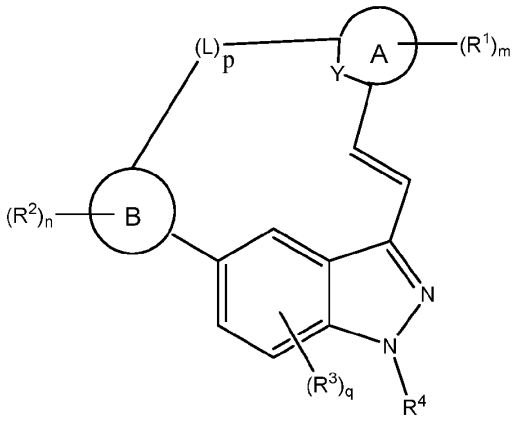
[0013] In one aspect, the disclosure provides a compound of the formula I, or a pharmaceutically acceptable salt thereof,



I

[0014] wherein R^1, R^2, R^3, R^4, A, B, L, m, n, p, and q are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

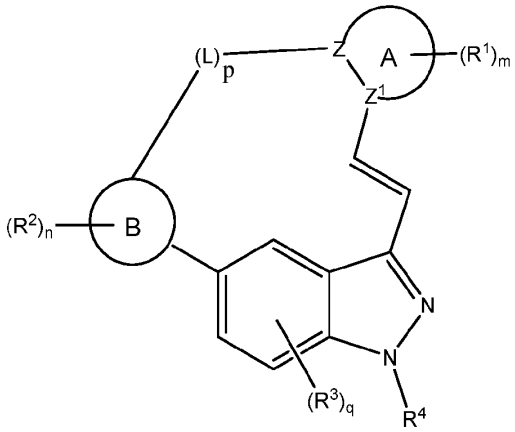
[0015] In some embodiments, the disclosure provides a compound of the formula II, or a pharmaceutically acceptable salt thereof,



II

[0016] wherein R^1, R^2, R^3, R^4, A, B, L, Y, m, n, p, and q, are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

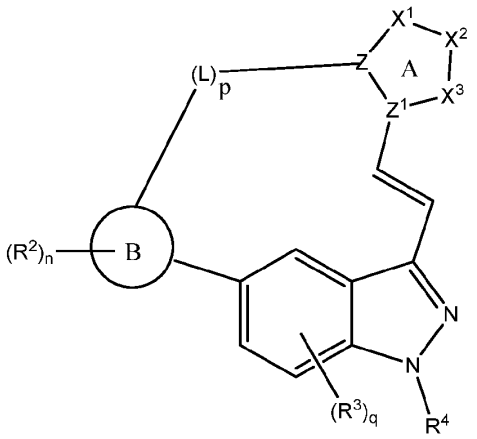
[0017] In some embodiments, the disclosure provides a compound of the formula III, or a pharmaceutically acceptable salt thereof,



III

[0018] wherein R^1, R^2, R^3, R^4, A, B, L, Z, Z^1, X^1, X^2, X^3, m, n, p, and q, are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

[0019] In some embodiments, the disclosure provides a compound of the formula IV, or a pharmaceutically acceptable salt thereof,



IV

[0020] wherein R^1, R^2, R^3, R^4, A, B, L, Z, Z^1, X^1, X^2, X^3, m, n, p, and q, are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

[0021] In further aspects, the disclosure relates to a pharmaceutical composition comprising at least one compound of Formula (I)-(XII) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the disclosure may further comprise a pharmaceutically acceptable excipient.

[0022] In further aspects, the disclosure relates to a compound of Formula (I)-(XII), or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0023] 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)-(XII), or a pharmaceutically acceptable salt thereof.

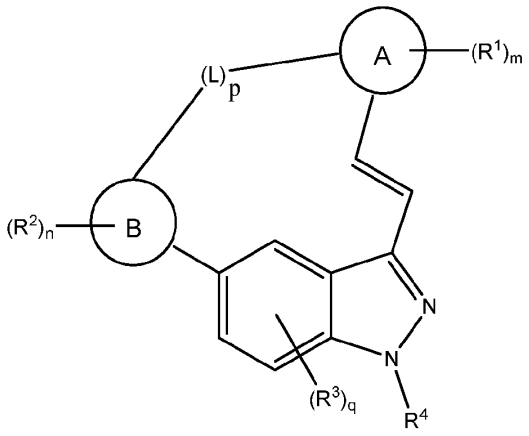
[0024] In further aspects, the disclosure relates to use of a compound of Formula (I)-(XII), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of disease, such as cancer, and the use of such compounds and salts for treatment of such diseases.

[0025] In further aspects, the disclosure relates to a method of inhibiting EGFR, including the certain mutations as described herein, PIM kinases, and/or CLK kinases, comprising contacting a cell comprising one or more of an aberrant EGFR, including the certain mutations as described herein, a PMI kinase, and/or CLK kinase, with an effective amount of at least one compound of Formula (I)-(XII), 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.*

[0026] 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.

[0027] 1. A compound of the formula I



I

[0028] wherein

[0029] ring A is a 5- to 10-membered heteroarylene or C_6-C_{10} arylene;

[0030] ring B is a 5-membered heteroarylene;

[0031] each L is independently –O-, -S-, -S(O)-, -$S(O)_2$-, -$N(R^5)C(O)$-, -$C(O)N(R^5)$-, -$N(R^5)$-, -$N(R^5)S(O)$-, -$S(O)N(R^5)$-, -$N(R^5)S(O)_2$-, -$S(O)_2N(R^5)$-, or –$C(R^6)(R^7)$-, provided that $(L)_p$ does not comprise an O-O, S-O, or N-N bond;

[0032] each R^1, R^2, and R^3 when present, 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, 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, R^c, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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;

[0033] or two R^1, two R^2, or two R^3, taken together with the atoms 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^1, R^2 and R^3 are taken together is independently optionally substituted by -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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;

[0034] R^4 is H, deuterium, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$P(O)_2R^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)_2OR^c$, or -$S(O)_2OR^c$;

[0035] each R^5, when present, is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, -$C(O)R^a$, 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, or 5- to 10-membered heteroaryl is independently optionally substituted by -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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^6 and R^7, 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, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -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^{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, 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^{e}R^f, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)NR^{e}R^f, -OS(O)$_2$NR^{e}R^f, -SR^e, -S(O)R^e, -S(O)$_2$R^e, -S(O)NR^{e}R^f, -S(O)$_2$NR^{e}R^f, -NR^{e}R^f, -NR^{e}C(O)R^f, -NR^{e}C(O)OR^f, -NR^{e}C(O)NR^{e}R^f, -NR^{e}S(O)R^f, -NR^{e}S(O)$_2$R^f, -NR^{e}S(O)NR^{e}R^f, -NR^{e}S(O)$_2$NR^{e}R^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^f, -PR^{e}R^f, -P(O)R^{e}R^f, -P(O)$_2$R^{e}R^f, -P(O)NR^{e}R^f, -P(O)$_2$NR^{e}R^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO$_2$;

[0037] or two of R^5, R^6 and R^7, taken together with the atom or atoms 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^5, R^6 and R^7 are taken together is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^{e}R^f, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)NR^{e}R^f, -OS(O)$_2$NR^{e}R^f, -SR^e, -S(O)R^e, -S(O)$_2$R^e, -S(O)NR^{e}R^f, -S(O)$_2$NR^{e}R^f, -NR^{e}R^f, -NR^{e}C(O)R^f, -NR^{e}C(O)OR^f, -NR^{e}C(O)NR^{e}R^f, -NR^{e}S(O)R^f, -NR^{e}S(O)$_2$R^f, -NR^{e}S(O)NR^{e}R^f, -NR^{e}S(O)$_2$NR^{e}R^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^f, -PR^{e}R^f, -P(O)R^{e}R^f, -P(O)$_2$R^{e}R^f, -P(O)NR^{e}R^f, -P(O)$_2$NR^{e}R^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO$_2$;

[0038] 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, or 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;

[0039] m is 0, 1, 2, 3, or 4;

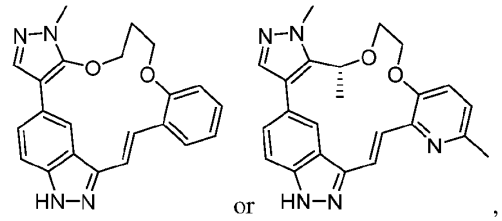
[0040] n is 0, 1, 2, or 3;

[0041] p is 4, 5, 6, 7, 8 or 9; and

[0042] q is 0, 1, or 2;

[0043] or a pharmaceutically acceptable salt thereof;

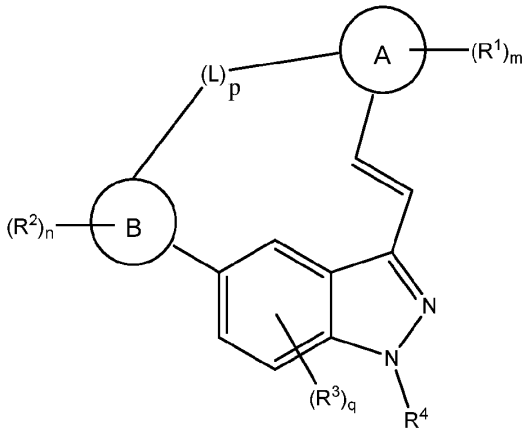
[0044] provided that the compound is not of the formula



,

[0045] or a pharmaceutically acceptable salt thereof.

[0046] 2. A compound of the formula I



I

[0047] wherein

[0048] ring A is a 5- to 10-membered heteroarylene or C_6-C_{10} arylene;

[0049] ring B is a 5-membered heteroarylene;

[0050] each L is independently –O-, -S-, -S(O)-, -$S(O)_2$-, -N(R^5)C(O)-, -C(O)N(R^5)-,

-$N(R^5)$-, -$N(R^5)S(O)$-, -$S(O)N(R^5)$-, -$N(R^5)S(O)_2$-, -$S(O)_2N(R^5)$-, or –$C(R^6)(R^7)$-, provided that $(L)_p$ does not comprise an O-O, S-O, or N-N bond;

[0051] each R^1, R^2, and R^3 when present, 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, 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, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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;

[0052] R^4 is H, deuterium, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$P(O)_2R^cR^d$, -$P(O)_2NR^cR^d$, -$P(O)_2OR^c$, or -$S(O)_2OR^c$;

[0053] each R^5, when present, is independently 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, 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, or 5- to 10-membered heteroaryl is independently optionally substituted by -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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;

[0054] each R^6 and R^7, 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, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -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 $-NO_2$, 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 $-NO_2$;

[0055] or two of R^5, R^6 and R^7, taken together with the atom or atoms 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^5, R^6 and R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$;

[0056] 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, or 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;

[0057] m is 0, 1, 2, 3, or 4;

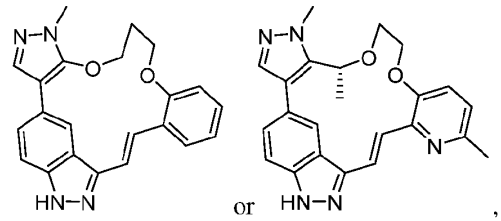
[0058] n is 0, 1, 2, or 3;

[0059] p is 4, 5, 6, 7, 8 or 9; and

[0060] q is 0, 1, or 2;

[0061] or a pharmaceutically acceptable salt thereof;

[0062] provided that the compound is not of the formula



,

[0063] or a pharmaceutically acceptable salt thereof.

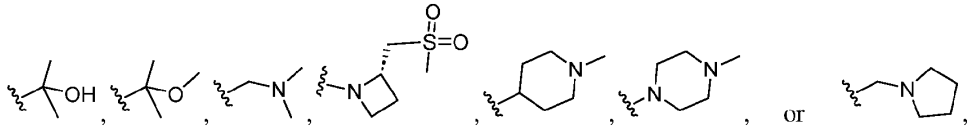
[0064] 3. The compound of clause 1 or 2, or a pharmaceutically acceptable salt thereof, wherein $(L)_p$ does not comprise a –$NR^5C(O)$- directly covalently attached to ring A.

[0065] 4. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a C_6-C_{10} arylene, and m is 0, 1, or 2.

[0066] 5. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, and m is 0, 1, or 2.

[0067] 6. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, and m is 0 or 1.

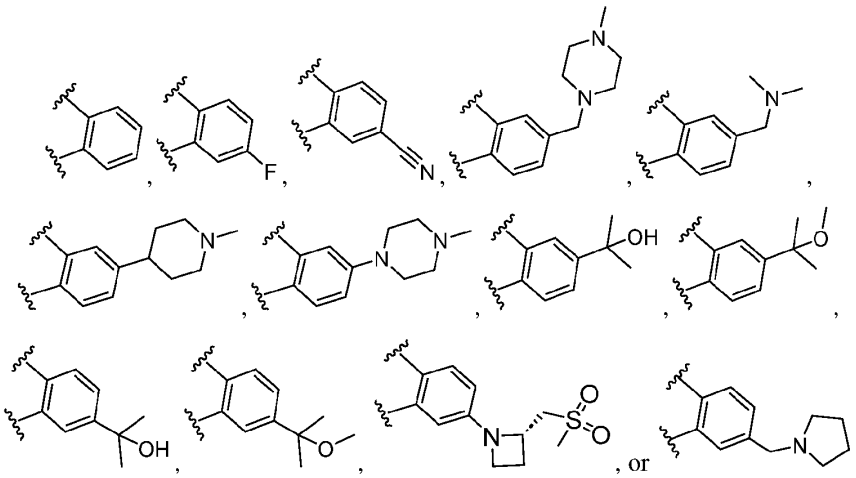
[0068] 7. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, m is 1, and R^1 is methyl, ethyl, F, Cl, Br, -CN,



,

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

[0069] 8. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is

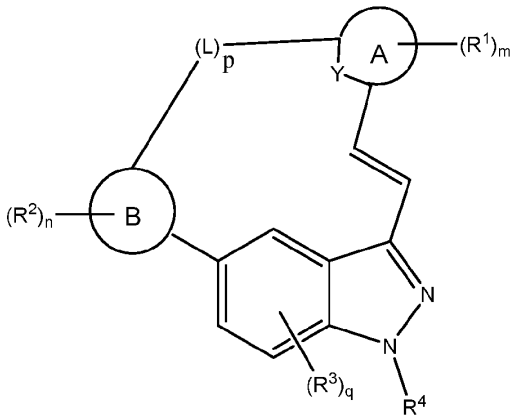


[0070] wherein each "〰" represents a point of covalent attachment.

[0071] 9. The compound of any one of clauses 1 to 4, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene, and m is 0, 1, 2, or 3.

[0072] 10. The compound of any one of clauses 1 to 4, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene, and m is 0, 1, or 2.

[0073] 11. The compound of any one of the clauses 1 to 4, or 10, or a pharmaceutically acceptable salt thereof, having the formula II

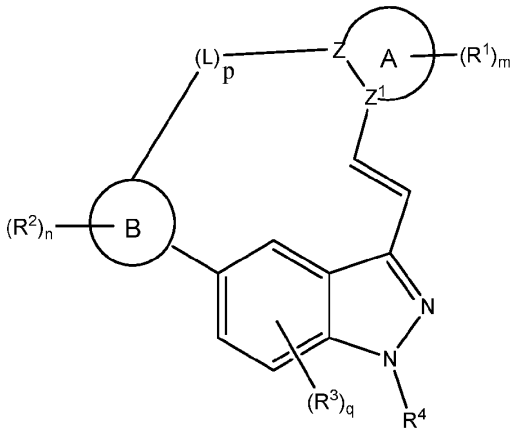


II

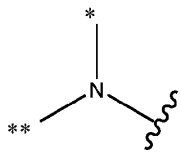
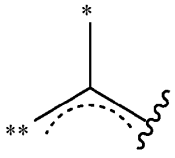
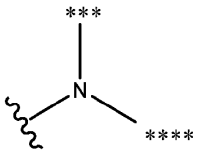
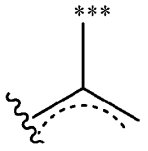
[0074] wherein Y is a single, a double bond, –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, and ring A is a 5- to 10-membered heteroarylene.

[0075] 12. The compound of any one of clauses 1 to 4, 10 or 11, or a pharmaceutically

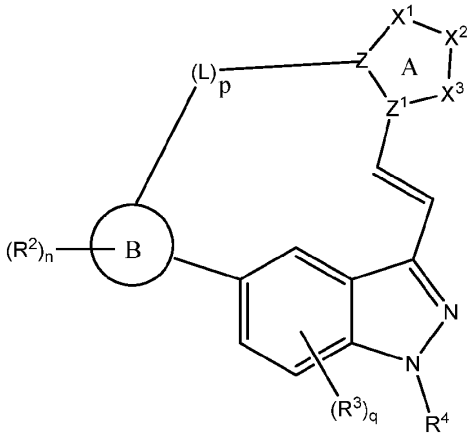
acceptable salt thereof, having the formula III



III

[0076] wherein Z is  or  , wherein * is a point of covalent attachment to $(L)_p$ provided that * is not an N-O or N-N bond, ** is a point of covalent attachment to Z^1, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⌒" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^1 is  or  wherein *** is a point of covalent attachment to "═", **** is a point of covalent attachment to Z, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⌒" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond, provided that both Z and Z^1 are not a nitrogen atom; and ring A is a 5- to 10-membered heteroarylene.

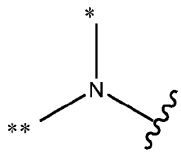
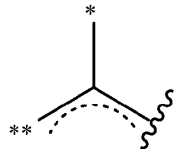
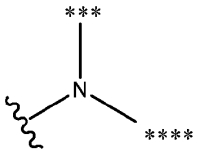
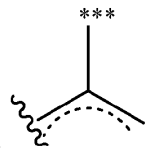
[0077] 13. The compound of any one of clauses 1 to 4, or 10 to 12, or a pharmaceutically acceptable salt thereof, having the formula IV



IV

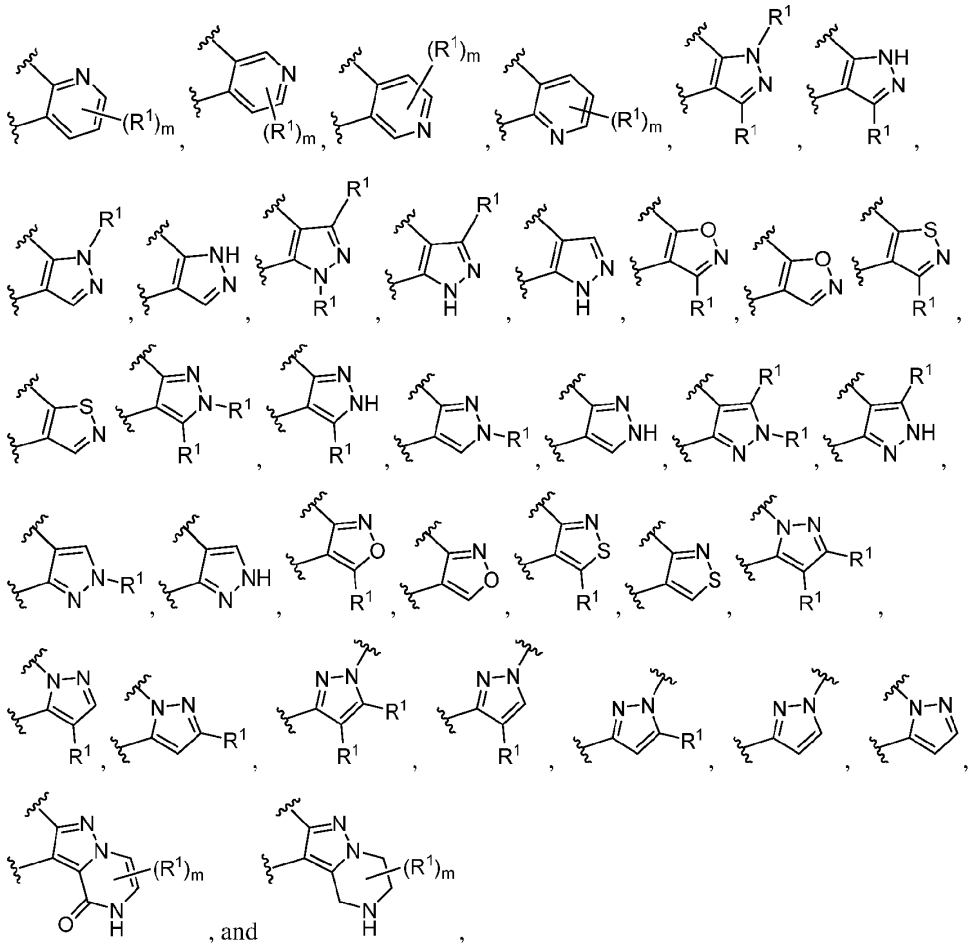
[0078] wherein

[0079] X^1, X^2, and X^3 are each independently –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-;

[0080] Z is  or  , wherein * is a point of covalent attachment to $(L)_p$ provided that * is not an N-O or N-N bond, ** is a point of covalent attachment to Z^1, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋱" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^1 is  or  wherein *** is a point of covalent attachment to "═", **** is a point of covalent attachment to Z, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋱" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond, provided that both Z and Z^1 are not a nitrogen atom; and

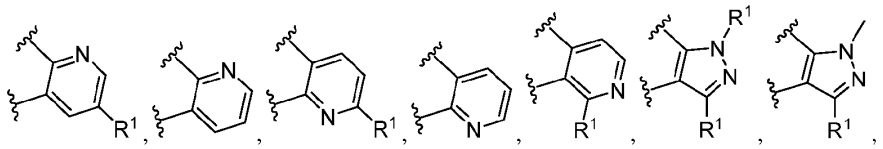
[0081] ring A is a 5- to 10-membered heteroarylene.

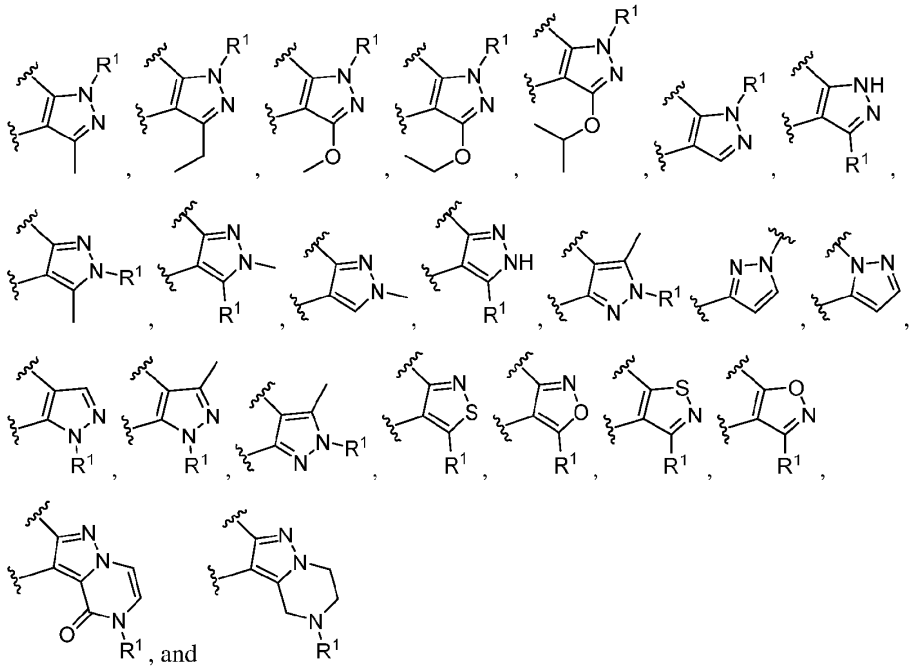
[0082] 14. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



[0083] wherein each "〰" represents a point of covalent attachment.

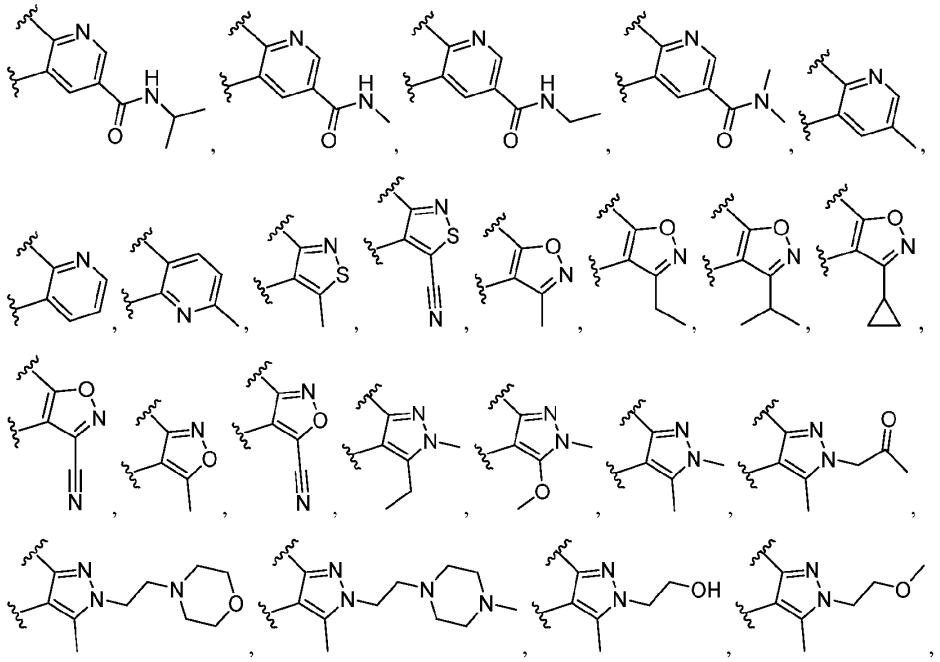
[0084] 15. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of

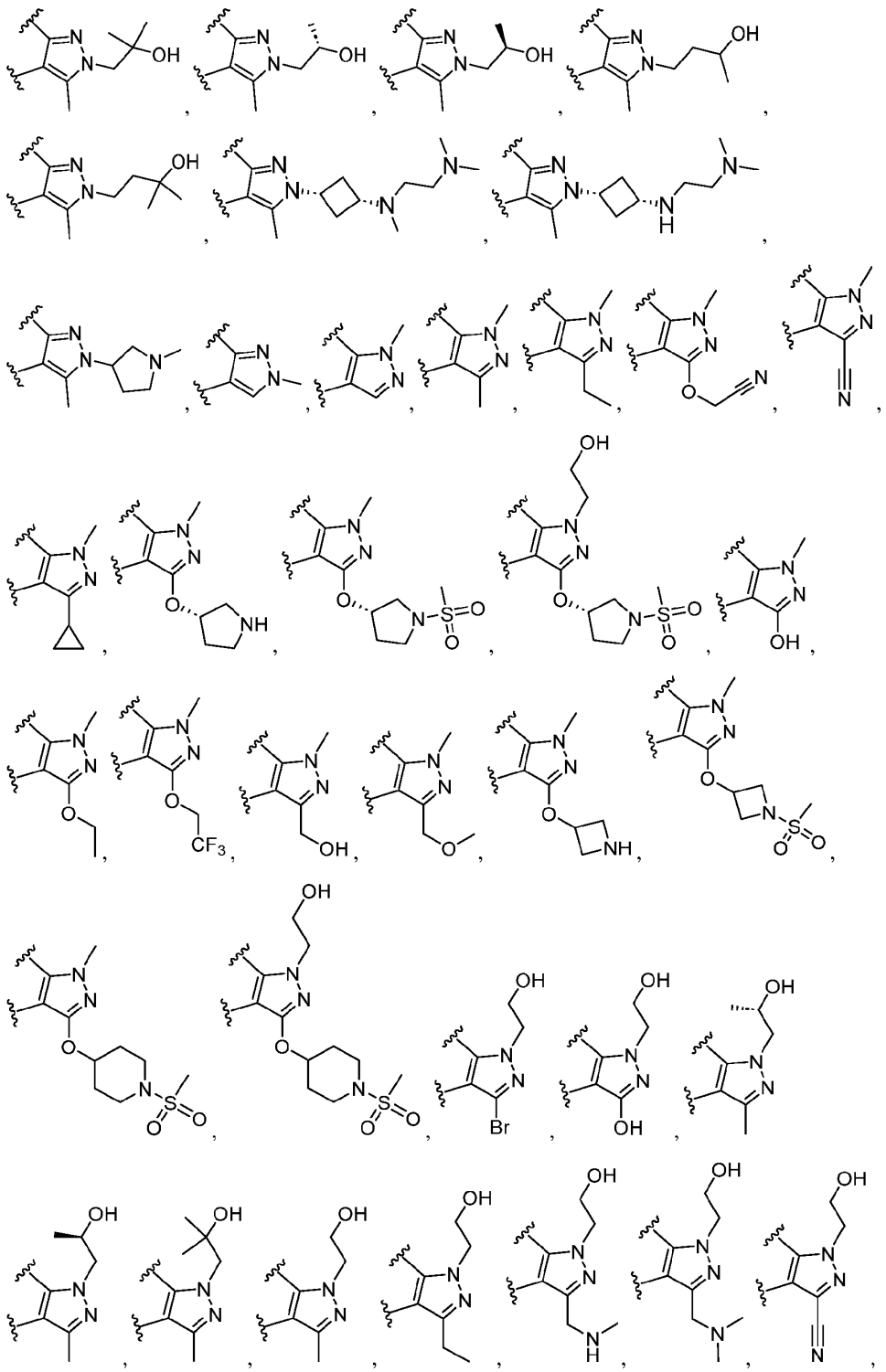


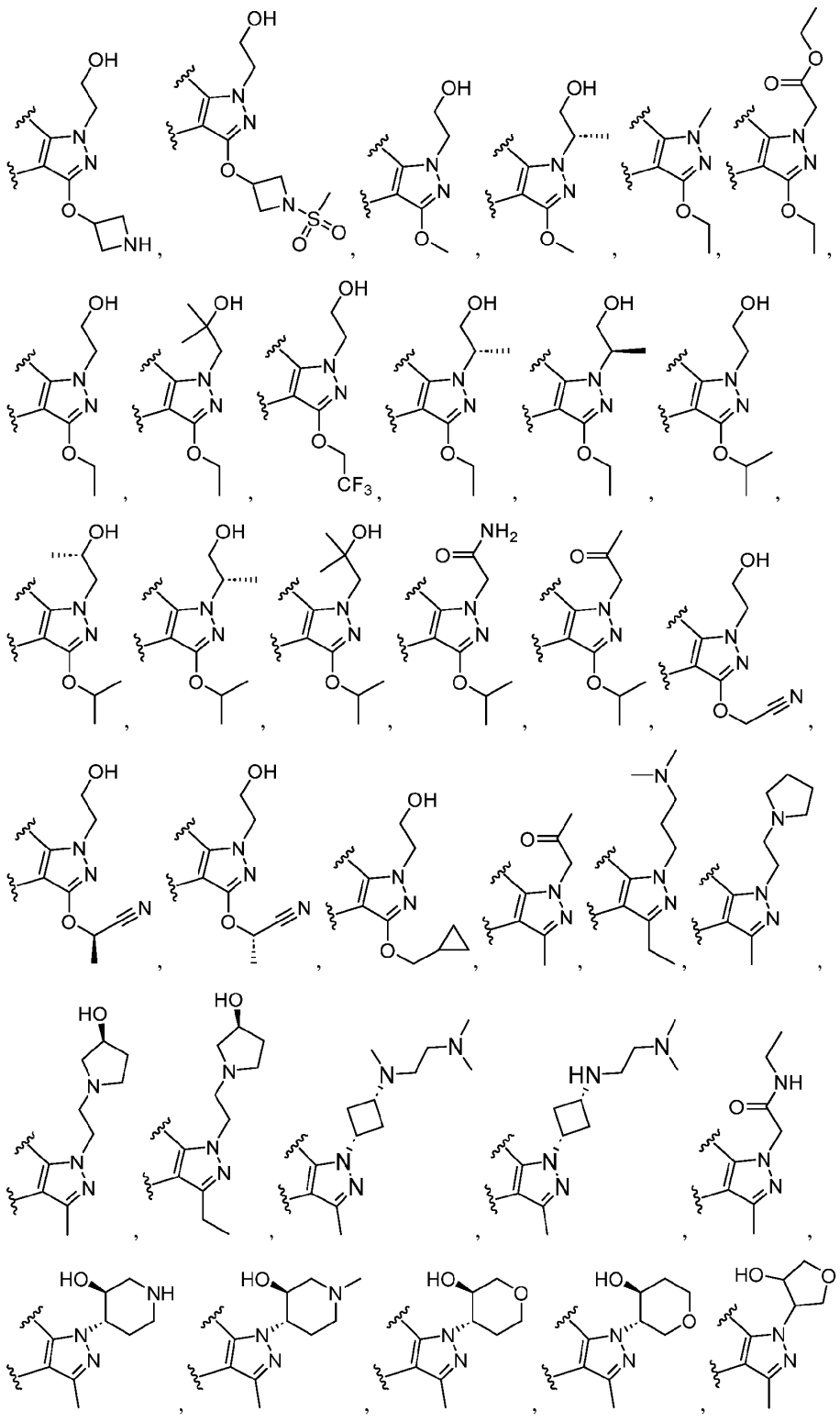


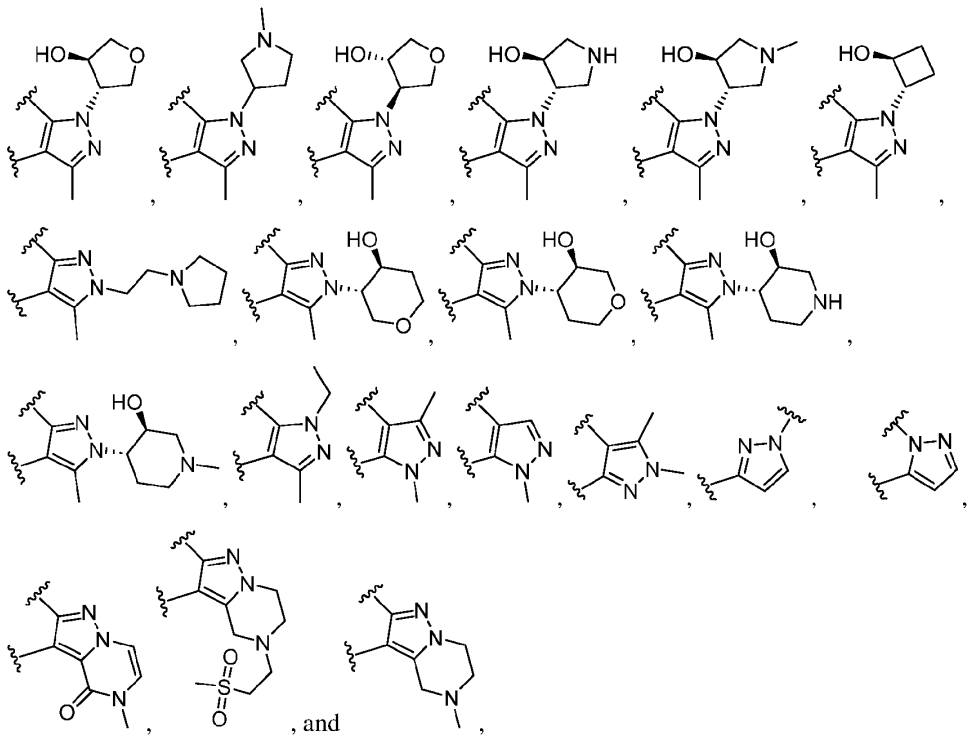
[0085] wherein each "〰" represents a point of covalent attachment.

[0086] 16. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



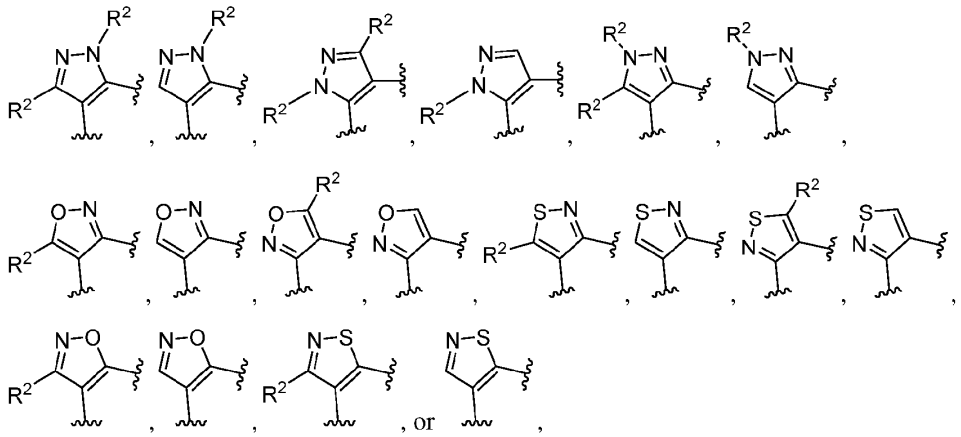






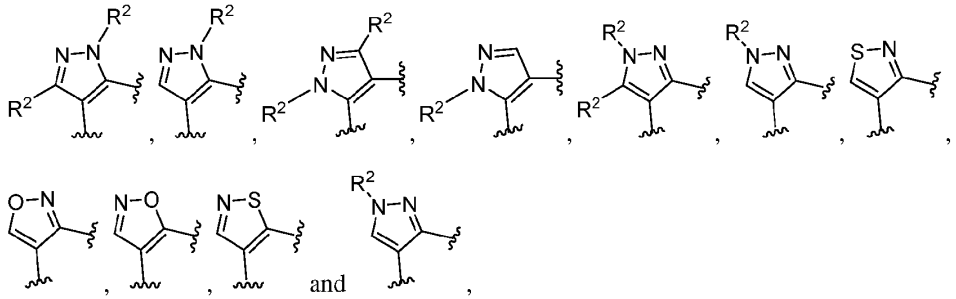
[0087] wherein each "〰" represents a point of covalent attachment.

[0088] 17. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



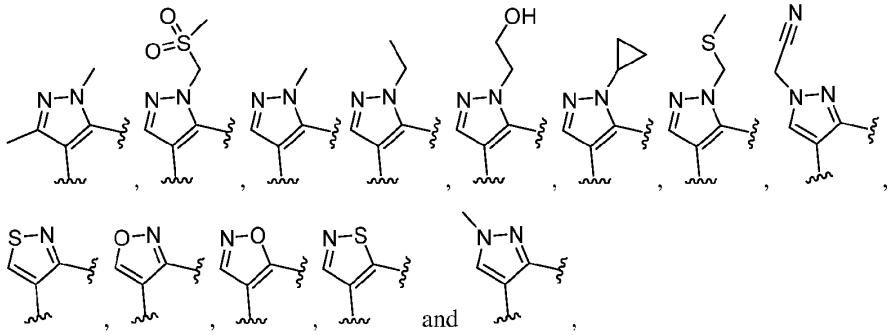
[0089] wherein each "〰" represents a point of covalent attachment.

[0090] 18. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



[0091] wherein each "〰" represents a point of covalent attachment.

[0092] 19. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



[0093] wherein each "〰" represents a point of covalent attachment.

[0094] 20. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, q is 0, 1, or 2.

[0095] 21. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, q is 0 or 1.

[0096] 22. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^3 is F.

[0097] 23. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein R^4 is H or methyl.

[0098] 24. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each L is independently $-C(R^6)(R^7)-$, $-C(O)-$, $-O-$, or $-N(R^5)-$, provided that $(L)_p$ does not comprise a $-O-O-$ or a $-O-N(R^5)-$ bond, and the point of covalent attachment of $(L)_p$ to ring A does not form a $-N-N-$ or a $-O-N-$ bond.

[0099] 25. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein $-(L)_p-$ is $-CR^6R^7-O(CR^6R^7)_2O-$, $-CR^6R^7-O(CR^6R^7)_3O-$, $-(CR^6R^7)C(O)N(R^5)-(CR^6R^7)_2-$, $-(CR^6R^7)N(R^5)C(O)-(CR^6R^7)_2-$,

$-O(CR^6R^7)_2N(R^5)C(O)-(CR^6R^7)O-$, $-N(R^5)-C(O)(CR^6R^7)_2O(CR^6R^7)_2-$, $-CR^6R^7O(CR^6R^7)_2O-(CR^6R^7)_2$, $-O(CR^6R^7)_2O(CR^6R^7)_2O-$, $-CR^6R^7O-CR^6R^7-C(O)N(R^5)-(CR^6R^7)_2-$, $-(CR^6R^7)_3O(CR^6R^7)_2-$, $-(CR^6R^7)_2O(CR^6R^7)_3-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_4O-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_3O-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_2O-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_2-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_3O-$, $-CR^6R^7-N(R^5)-(CR^6R^7)_3-$, $-O(CR^6R^7)_2O-CR^6R^7-$, $-O(CR^6R^7)_2O(CR^6R^7)_2-$, $-O(CR^6R^7)_2O(CR^6R^7)_3-$, $-(CR^6R^7)_2-N(R^5)-(CR^6R^7)_3-$, $-O(CR^6R^7)_2-N(R^5)-CR^6R^7-$, $-(CR^6R^7)_2-N(R^5)-(CR^6R^7)_2-$, $-O-(CR^6R^7)_2-$, $-O-(CR^6R^7)_3-$, $-O-(CR^6R^7)_4-$, $-O-(CR^6R^7)_5-$, $-O-(CR^6R^7)_2O-$, $-O-(CR^6R^7)_3O-$, $-O-(CR^6R^7)_4O-$, or $-O-(CR^6R^7)_5O-$.

[0100] 26. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently H, methyl, ethyl, $–C(O)CH_3$, or $–C(O)CH_2CH_3$; or R^5, when present, and an R^6 or R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^5 and an R^6 or R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

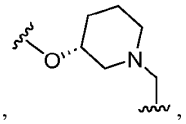
[0101] 27. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein an R^6 and R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^6 and R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

[0102] 28. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein each R^6, that is not taken together with R^5 or an R^7, is independently H or C_1C_6 alkyl.

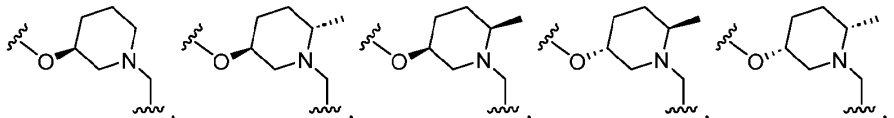
[0103] 29. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein one R^6, that is not taken together with R^5 or an R^7, is methyl, and the remaining R^6 and R^7 are H.

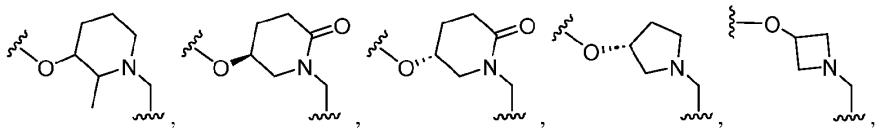
[0104]

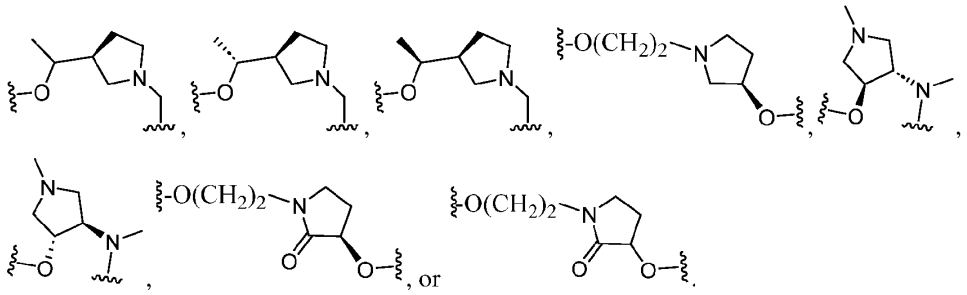
[0105] 30. The compound of any one of the preceding clauses, or a pharmaceutically acceptable salt thereof, wherein $-(L)_p-$ is $-O-(CH_2)_2O-CH_2-$, $-OC(H)(CH_3)-CH_2-O-CH_2-$, $-CH_2O-(CH_2)_2O-$, $-C(H)(CH_3)-O-(CH_2)_2O-$, $-CH_2N(H)-(CH_2)_2O-$, $-CH_2N(CH_3)-(CH_2)_2O-$, $-CH_2N(CH_2CH_3)-(CH_2)_2O-$, $-O(CH_2)_2N(H)CH_2-$, $-O(CH_2)_2N(CH_3)CH_2-$, $-OCH_2-C(H)(CH_3)-N(CH(CH_3)_2)CH_2-$, $-OCH_2-C(H)(CH_2F)-N(CH_3)CH_2-$, $-OCH_2-C(H)(CH_2CH_3)-N(CH_3)CH_2-$, $-O(CH_2)_2N(C(O)CH_3)CH_2-$, $-OC(H)(CH_3)CH_2N(H)CH_2-$, $-OC(H)(CH_3)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2CN)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2CH_3)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2F)CH_2N(CH_3)CH_2-$, $-OC(H)(CHF_2)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2OH)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_3)C(O)N(CH_3)CH_2-$, $-OC(H)(cyclobutyl)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_3)CH_2N(CH_2CH_3)CH_2-$, $-OC(H)(CH_3)CH_2N(CH(CH_3)_2)-CH_2-$, $-OC(H)(CH_3)CH_2N(CH_3)-C(H)(CH_3)-$, $-OC(H)(CH_3)CH_2N(CH(oxetan\text{-}3\text{-}yl)-CH_2-$, $-OC(H)(CH_3)CH_2N(cyclopropyl)-CH_2-$, $-OCH_2C(H)(CH_3)N(cyclopropyl)-CH_2-$, $-OC(H)(CH_3)CH_2N(C(O)CH_3)CH_2-$, $-O(C(H)(CH_3))CH_2N(C(O)CH_2CH_3)CH_2-$, $-CH_2N(H)-(CH_2)_2(C(H)CH_3)CH_2O-$, $-CH_2N(CH_3)-C(H)(CH_3)-CH_2O-$, $-CH_2N(CH_3)-(CH_2)_2(C(H)CH_3)CH_2O-$, $-CH_2N(CH_3)-(CH_2)-(C(H)CH_3)O-$, $-O(CH_2)_2-$, $-O(CH_2)_3-$, $-O(CH_2)_4-$, $-O(CH_2)_3O-$, $-O(CH_2)_4O-$, $-O(CH_2)_5O-$, $-O-(C(H)(CH_3)-(CH_2)_2O-$, $-O(CH_2)_2-C(H)(CH_3)-O-$, $-O(CH_2)_2C(H)(CH_3)CH_2O-$, $-O(CH_2)_3C(H)(CH_3)CH_2O-$, $-O(CH_2)_2N(H)C(O)-(CH_2)O-$, $-O(CH_2)_2N(CH_3)C(O)-(CH_2)O-$, $-O(CH_2)_2O(CH_2)_2O-$, $-OC(H)(CH_3)CH_2OCH_2-$,



$-O(CH_2)_2OCH_2C(H)(CH_3)O-$, $-O(CH_2)_2OC(H)(CH_3)-CH_2O-$,







[0106] 31. The compound of clause 1 or 2, selected from the group consisting of (11*E*)-1-methyl-1,18,19,21-tetrahydro-8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,4,12,13]benzodioxadiazacyclooctadecine;

[0107] (11*E*)-1-[(methanesulfonyl)methyl]-19,20-dihydro-1*H*,8*H*,18*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,5,12,13]benzodioxadiazacyclooctadecine;

[0108] (11*E*)-1-methyl-18,19,20,21-tetrahydro-1*H*,8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*g*][1,6,13,14]benzodioxadiazacyclononadecine;

[0109] (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0110] (10*R*,16*E*)-3-methyl-13-[(4-methylpiperazin-1-yl)methyl]-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0111] (10*R*,16*E*)-13-[(dimethylamino)methyl]-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0112] (10*R*,16*E*)-3-methyl-13-(1-methylpiperidin-4-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0113] (10*R*,16*E*)-13-(2-methoxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0114] (10*R*,16*E*)-3-methyl-13-(4-methylpiperazin-1-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0115] (10*R*,16*E*)-14-fluoro-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0116] (10*R*,16*E*)-14-(2-hydroxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0117] (10*R*,16*E*)-14-{(2*S*)-2-[(methanesulfonyl)methyl]azetidin-1-yl}-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0118] (10*R*,16*E*)-3-methyl-25-oxo-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine-14-carbonitrile; and

[0119] (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine;

[0120] or a pharmaceutically acceptable salt thereof.

[0121] 32. The compound of clause 1 or 2, selected from the group consisting of (18*E*)-8-methyl-*N*-(propan-2-yl)-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0122] (18*E*)-*N*,8-dimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0123] (18*E*)-*N*,*N*,8-trimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0124] (18*E*)-*N*-ethyl-8-methyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0125] (10*S*,18*E*)-8,10,16-trimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,5]dioxacyclopentadecino[7,6-*b*]pyridine;

[0126] (10*S*,18*E*)-17-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[4,3-*f*][1,4]oxazacyclopentadecine; and

[0127] (10*S*,18*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[3,2-*f*][1,4]oxazacyclopentadecine;

[0128] or a pharmaceutically acceptable salt thereof.

[0129] 33. The compound of clause 1 or 2, selected from the group consisting of (17*E*)-8,14,16-trimethyl-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0130] 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(2*H*)-yl]ethan-1-ol;

[0131] (17*E*)-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0132] (17*E*)-19-fluoro-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0133] (17*E*)-16-ethyl-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0134] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-2-methylpropan-2-ol;

[0135] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]propan-2-one;

[0136] 2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethan-1-ol;

[0137] (17*E*)-8,16-dimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0138] (3*S*)-1-{2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

[0139] (17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0140] (10*S*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0141] (10*R*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0142] (12*S*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0143] (12*R*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0144] (10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0145] (10*S*,17*E*)-16-cyclopropyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0146] (17*E*)-16-(methoxymethyl)-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0147] (17*E*)-8,14,16-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0148] 1-[(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0149] (17*E*)-8,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0150] (17*E*)-6,8,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0151] (17*E*)-16-ethyl-8,12,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0152] (17*E*)-7,14,16-trimethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0153] (17*E*)-7,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0154] 2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0155] (17*E*)-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0156] (17*E*)-8,10,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0157] 2-[(17*E*)-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0158] 2-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0159] 2-[(17*E*)-10-ethyl-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0160] (19*E*)-8,13,16,18-tetramethyl-2,11,12,13,14,16-hexahydro-8*H*,10*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0161] 2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,16*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-16-yl]ethan-1-ol;

[0162] (19*E*)-8,16,18-trimethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

[0163] (19*E*)-8,12,16,18-tetramethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

[0164] (13R,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

[0165] (13S,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

[0166] 2-[(19E)-8,13,18-trimethyl-2,8,10,11,13,14-hexahydro-16H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c']:8,9-c"]tripyrazol-16-yl]ethan-1-ol;

[0167] (19*E*)-8,13,18-trimethyl-16-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0168] (3*S*)-1-{2-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

[0169] (19*E*)-22-fluoro-8,16,18-trimethyl-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0170] 3-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-*N*,*N*-dimethylpropan-1-amine;

[0171] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]pyrrolidin-3-ol;

[0172] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpyrrolidin-3-ol;

[0173] (3*R*,4*S*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;

[0174] (3*S*,4*R*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;

[0175] (*rac*)-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutan-1-ol;

[0176] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol;

[0177] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol;

[0178] (*rac*)-1,5-anhydr-3o-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;

[0179] (*rac*)-1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;

[0180] (12*R*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0181] (12*S*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0182] (rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol;

[0183] (11*S*,17*E*)-8,11,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0184] (17*E*)-8,9,16-trimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0185] [(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-16-yl]methanol;

[0186] N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;

[0187] (11*S*,17*E*)-8,10,11,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0188] N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;

[0189] (10*R*,15*E*)-3,12,14-trimethyl-5,6,9,10,12,18-hexahydro-3*H*,8*H*-19,21-etheno-7,10-methanotripyrazolo[3,4-*i*:3',4'-*m*:4",3"-*q*][1,8,4]dioxazacyclooctadecin-24-one;

[0190] (17*E*)-16-ethyl-8,10,14-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0191] (17*E*)-10-ethyl-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0192] 2-[(10*S*,17*E*)-8,10,16-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0193] 2-[(10*S*,17*E*)-19-fluoro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0194] (17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0195] 2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0196] (10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0197] (10*R*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0198] (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0199] 2-[(10*S*,17*E*)-19-chloro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0200] (2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0201] 2-[(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0202] 2-[(10*S*,17*E*)-12-ethyl-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0203] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-[(piperidin-4-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0204] 2-[(10*R*,19*E*)-18-ethoxy-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0205] 2-[(10*S*,17*E*)-6,8,10,12,16-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0206] (10*S*,17*E*)-8,10,14,16-tetramethyl-12-(oxetan-3-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0207] 2-[(10*S*,17*E*)-16-ethoxy-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0208] (10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0209] (10*S*,13*R*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0210] (10*S*,13*S*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0211] 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0212] (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0213] (10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0214] (10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0215] 2-[(10*S*,17*E*)-16-ethoxy-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0216] 2-[(17*E*)-10-cyclobutyl-8,12,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0217] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-{[(3*S*)-pyrrolidin-3-yl]oxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0218] (10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0219] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0220] (10*S*,17*E*)-16-ethoxy-8,10,14-trimethyl-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0221] (10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno|1,5|dioxacyclopentadecino|10,11-*c*:15,14-*c'*:6,7-*c''*|tripyrazole-16-carbonitrile;

[0222] (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;

[0223] (10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0224] (10*S*,17*E*)-12-cyclopropyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0225] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-(2,2,2-trifluoroethoxy)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0226] {|(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0227] (10*S*,17*E*)-10,14,16-trimethyl-8-[(methylsulfanyl)methyl]-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0228] (10*S*,17*E*)-12-ethyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0229] 2-[(10*S*,17*E*)-16-ethoxy-8-ethyl-10,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0230] 2-{(10*S*,17*E*)-8-ethyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0231] (2*R*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0232] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0233] 2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0234] (10*S*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0235] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0236] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0237] 2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0238] 2-[(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0239] 2-[(10*S*,17*E*)-16-bromo-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0240] 2-{(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0241] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0242] (10*S*,17*E*)-16-{[3-(methanesulfonyl)cyclobutyl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0243] (10*S*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

[0244] (10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

[0245] 2-[(10*R*,19*E*)-18-ethoxy-22-fluoro-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0246] 2-{(11*S*,17*E*)-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0247] 2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0248] 2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0249] 2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0250] 2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0251] 2-|(10*R*,17*E*)-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0252] 2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0253] 2-[(10*R*,19*E*)-22-fluoro-8-methyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0254] (2*S*)-2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0255] 2-{(11*S*,17*E*)-6,8,11-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0256] 2-{(10*R*,17*E*)-6,8,10-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0257] {[(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0258] 2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0259] 2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,11-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0260] (10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0261] (2*S*)-2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0262] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;

[0263] (10*S*,17*E*)-12-ethyl-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0264] (10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0265] 2-[(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-(2,2,2-trifluoroethoxy)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0266] 2-{(10*R*,17*E*)-12-cyclopropyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0267] 2-{(11*S*,17*E*)-12-cyclopropyl-8,11-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0268] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0269] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0270] 2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0271] 1-[(10*R*,17*E*)-16-ethoxy-14-(2-hydroxyethyl)-8,10-dimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0272] ethyl [(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]acetate;

[0273] (2*S*)-2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0274] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,12,13,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-11(10*H*)-one;

[0275] 2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0276] 1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]-2-methylpropan-2-ol;

[0277] 2-{(10*S*,13*R*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0278] 2-{(10*S*,13*S*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0279] 2-{(17*E*)-10-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0280] 2-{(17*E*)-11-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0281] (2*S*)-1-{(10*R*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0282] (2*S*)-2-[(11*S*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0283] (2*S*)-2-[(10*R*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0284] (2*S*)-2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0285] (2*S*)-2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0286] 2-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}acetamide;

[0287] (10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0288] 2-[(8a*R*,19*E*)-1-(cyclopropylmethoxy)-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0289] (10*R*,18*E*)-17-ethoxy-8,15-dimethyl-2,8,11,12,14,15-hexahydro-10*H*-3,5-etheno-10,13-methanotripyrazolo[3,4-*g*:3',4'-*k*:4",3"-*o*][1,5]oxazacyclohexadecine;

[0290] {(17*E*)-14-(2-hydroxyethyl)-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-7-yl}acetonitrile;

[0291] (17*E*)-16-ethoxy-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno-10,12-methanotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0292] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0293] 2-[(8a*R*,9*R*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0294] 2-[(8a*R*,9*S*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0295] 2-[(19*E*)-18-ethoxy-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0296] 2-[(8a*R*,9*R*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0297] 2-[(8a*R*,9*S*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0298] 2-[(19*E*)-18-ethoxy-22-fluoro-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0299] 2-{(10*S*,17*E*)-8-cyclopropyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0300] (10*S*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0301] (10*R*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0302] (10*R*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0303] (10*S*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0304] 2-{(10*R*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0305] 2-[(8a*R*,9*S*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0306] 2-[(8a*R*,9*R*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0307] 2-[(19*E*)-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0308] 2-[(8a*R*,9*R*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0309] 2-[(8a*R*,9*S*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0310] 2-[(19*E*)-22-fluoro-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0311] 2-{(10*R*,17*E*)-10-(hydroxymethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0312] 2-[(11*S*,17*E*)-16-ethoxy-11-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0313] 2-[(10*S*,17*E*)-16-ethoxy-10-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0314] 2-[(10*S*,17*E*)-16-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0315] 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}-2-methylpropan-2-ol;

[0316] 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-one;

[0317] (10*R*,17*E*)-14-(2-hydroxyethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-10-carbonitrile;

[0318] 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0319] 2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol:

[0320] (2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0321] (2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0322] 2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

[0323] 2-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

[0324] {[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

[0325] {[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

[0326] 2-{(10*S*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0327] 2-{(10*R*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0328] 2-{(10*S*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0329] 2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0330] (4a*S*,7a*S*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

[0331] (4a*R*,7a*R*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

[0332] (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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0333] 2-{(11*R*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0334] 2-{(10*S*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0335] 2-[(11*R*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0336] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0337] {[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0338] 2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0339] (2*S*)-2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0340] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

[0342] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-(2-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile;

[0343] 2-[(10*S*,17*E*)-16-ethoxy-6-ethynyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0344] 2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0345] 2-[(10*S*,17*E*)-16-(ethylamino)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0346] (2*S*)-1-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0347] 2-[(10*S*,17*E*)-6-amino-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0348] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0349] 2,2'-[(10*S*,17*E*)-10,12-dimethyl-16-[(propan-2-yl)oxy]-10,11,12,13-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-8,14(2*H*)-diyl]di(ethan-1-ol);

[0350] (17*E*)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0351] 2-[(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno|1,4|dioxacyclopentadecino|10,11-*c*:15,14-*c'*:6,7-*c''*|tripyrazol-14(8*H*)-yl|-*N*-ethylacetamide;

[0352] (17*E*)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

[0353] (17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0354] (10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0355] (10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno|1,4|dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

[0356] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]oxazole-16-carbonitrile;

[0357] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]thiazole-16-carbonitrile;

[0358] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]oxazole-16-carbonitrile;

[0359] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]thiazole-16-carbonitrile; and

[0360] (10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0361] or a pharmaceutically acceptable salt thereof.

[0362] 34. The compound of clause 1 or 2, selected from the group consisting of (17*E*)-8,15,16-trimethyl-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0363] (17*E*)-8,15,16-trimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0364] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]propan-2-one;

[0365] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-2-methylpropan-2-ol;

[0366] 2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]ethan-1-ol;

[0367] (17*E*)-8,16-dimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0368] (10*S*,17*E*)-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0369] (17*E*)-8,15,16-trimethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0370] 1-[(17*E*)-8,15,16-trimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0371] (17*E*)-8,12,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0372] 1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0373] (10*S*,17*E*)-8,10,12,15,16-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0374] 2-[(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

[0375] 2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

[0376] (10*S*,17*E*)-12-ethyl-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0377] 1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]propan-1-one;

[0378] 2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,17*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-17-yl]ethan-1-ol;

[0379] (13*E*)-3-methyl-3,5,6,7,8,16-hexahydro-9,12-(azeno)-17,19-ethenodipyrazolo[3,4-*l*:4',3'-*p*][1,6]oxazacycloheptadecine;

[0380] (18*E*)-8-methyl-2,8,10,11,12,13-hexahydro-3,5-ethenotripyrazolo[1,5-*f*:3',4'-*j*:4",3"-*n*][1,6]oxazacyclopentadecine;

[0381] (17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0382] 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno|1,4|dioxacyclopentadecino|11,10-*c*:15,14-*c'*:6,7-*c''*|tripyrazol-15(2*H*)-yl|ethan-1-ol;

[0383] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]piperidin-3-ol;

[0384] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-1-methylpiperidin-3-ol;

[0385] (17*E*)-8,9,16-trimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0386] (*rac*)-1,5-anhydro-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;

[0387] 1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;

[0388] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0389] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(4-methylpiperazin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0390] (20*E*)-8,18-dimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3",4":10',11';4"',3"':14',15'][1,5]dioxacyclopentadecino[6',7':3,4]pyrazolo[1,5-*a*]pyrazin-19(18*H*)-one;

[0391] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(morpholin-4-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0392] 4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;

[0393] N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;

[0394] 2-methyl-4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;

[0395] 2-methyl-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0396] N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;

[0397] (17*E*)-8,10,16-trimethyl-15-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0398] (10*R*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0399] (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0400] (10*S*,17*E*)-8,10,12,14,15-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0401] (2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0402] (10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0403] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0404] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0405] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*][1,2]thiazolo[3,4-*f*][1,4]oxazacyclopentadecine;

[0406] (10*S*,20*E*)-18-[2-(methanesulfonyl)ethyl]-8,10,12-trimethyl-2,8,10,11,12,13,16,17,18,19-decahydro-3,5-ethenopyrazino[1',2':1,5]pyrazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0407] (10*S*,17*E*)-16-cyclopropyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0408] (10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0409] (10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0410] (10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0411] (10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0412] (10*R*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0413] (10*S*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0414] (10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole;

[0415] (10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole-16-carbonitrile;

[0416] (10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole;

[0417] (10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole-16-carbonitrile;

[0418] (10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;

[0419] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;

[0420] (10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;

[0421] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;

[0422] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole-16-carbonitrile;

[0423] (17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;

[0424] (17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole; and

[0425] (17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;

[0426] or a pharmaceutically acceptable salt thereof.

[0427] 35. A pharmaceutical composition comprising a compound of any one of the preceding clauses, and optionally one or more excipients.

[0428] 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.

[0429] 37. A compound according to any one of clauses 1 to 34, for use in a method of treating disease in a subject.

[0430] 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

[0431] 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.

[0432] 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.

[0433] 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.

[0434] As used herein, the terms "including," "containing," and "comprising" are used in their open, non-limiting sense.

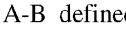
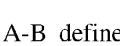
[0435] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about." It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant 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.

[0436] 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.

[0437] 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.

[0438] Chemical nomenclature for compounds described herein has generally been derived using the commercially-available ACD/Name 2014 (ACD/Labs) or ChemBioDraw Ultra 13.0 (Perkin Elmer).

[0439] 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  , , or , 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  , , or , where each of "-*", "-**", and "" represents a bond to B and the point of covalent bond attachment to A.

[0440] 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

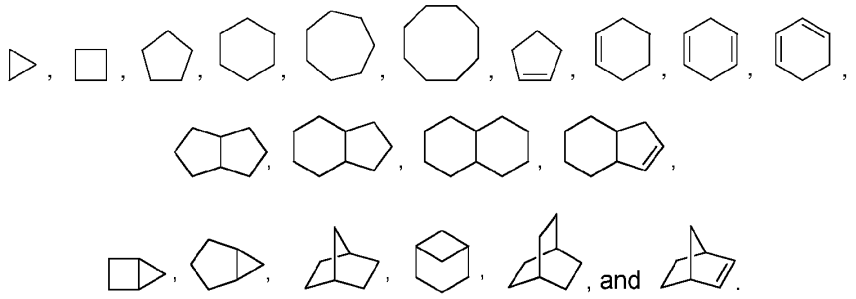
[0441] The term "alkyl" refers to a straight- or branched-chain monovalent hydrocarbon group. The term "alkylene" refers to a straight- or branched-chain divalent hydrocarbon group. In some embodiments, it can be advantageous to limit the number of atoms in an "alkyl" or "alkylene" to a specific range 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.

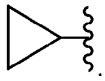
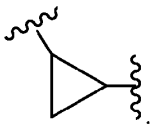
[0442] The term "alkenyl" refers to a straight- or branched-chain mono-valent hydrocarbon group having one or more double bonds. The term "alkenylene" refers to a straight- or branched-chain di-valent hydrocarbon group having one or more double bonds. In some embodiments, it can be advantageous to limit 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.

[0443] 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 ($-C\equiv CH$) and propargyl ($-CH_2C\equiv CH$), but-3-yn-1,4-diyl ($-C\equiv C-CH_2CH_2-$), 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.

[0444] 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  .

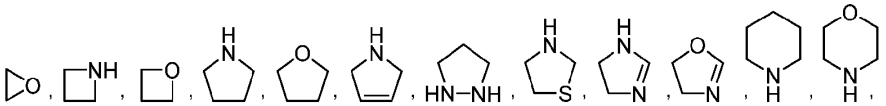
It will be appreciated that a cycloalkyl or cycloalkylene group can be unsubstituted or substituted as described herein. A cycloalkyl or cycloalkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

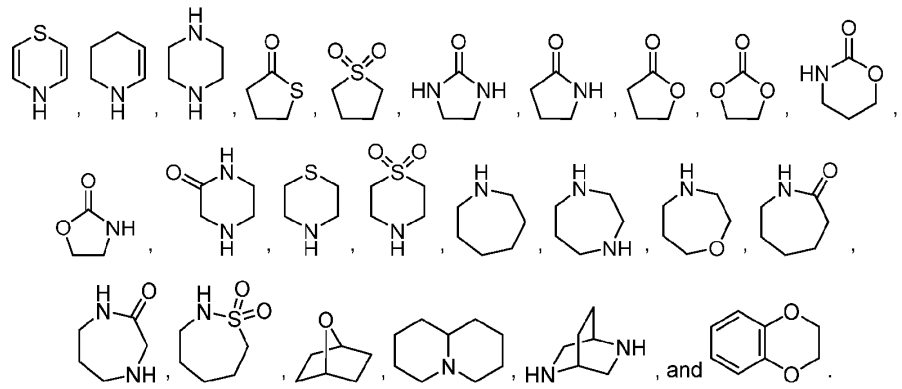
[0445] The term "halogen" or "halo" represents chlorine, fluorine, bromine, or iodine.

[0446] 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 $-CH_2C(H)(F)-$.

[0447] 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.

[0448] 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:

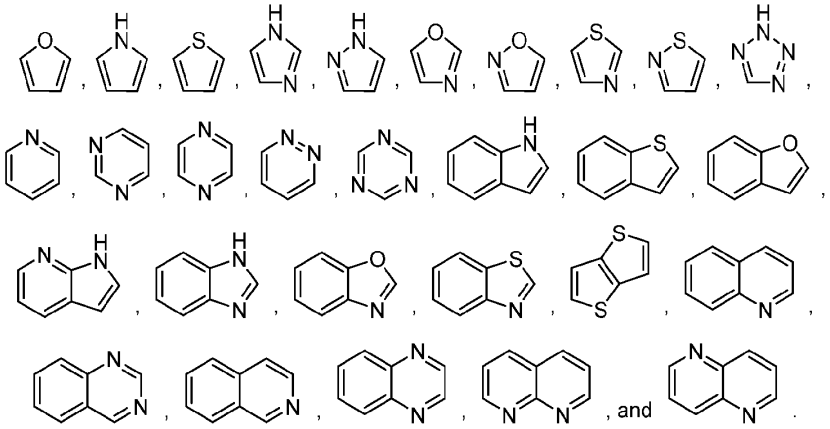




[0449] A three-membered heterocycle may contain at least one heteroatom ring atom, where the heteroatom ring atom is a sulfur, oxygen, or nitrogen. Non-limiting examples of three-membered heterocycle groups include monovalent and divalent radicals of oxirane, azetidine, and thiirane. A four-membered 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.

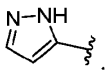
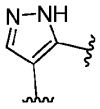
[0450] It will be appreciated that a heterocycloalkyl or heterocycloalkylene group can be unsubstituted or substituted as described herein. A heterocycloalkyl or heterocycloalkylene group can be substituted with any of the substituents in the various embodiments described herein, including one or more of such substituents.

[0451] 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:



[0452] 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.

[0453] 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  .

[0454] 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.

[0455] The term "oxo" represents a carbonyl oxygen. For example, a cyclopentyl substituted with oxo is cyclopentanone.

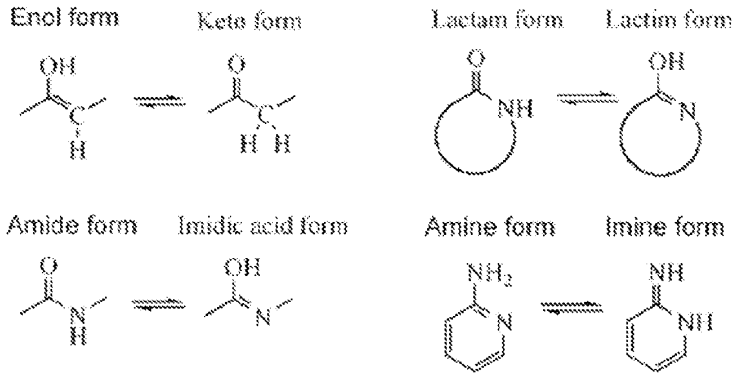
[0456] The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed 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.

[0457] 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.

[0458] 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.

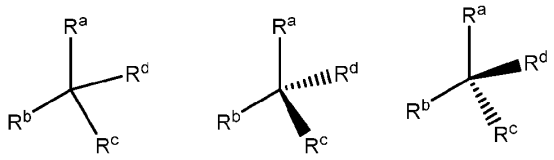
[0459] Certain chemical entities of Formula (I)-(XII) may be depicted in two or more tautomeric forms. Any and all alternative tautomers are included within the scope of these formulas, and no inference should be made as to whether the chemical entity exists as the tautomeric form in which it is drawn. 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.



[0460] 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).

[0461] 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.

[0462] 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.

[0463] The disclosure also includes pharmaceutically acceptable salts of the compounds represented by Formula (I)-(XII), preferably of those described above and of the specific compounds exemplified herein, and pharmaceutical compositions comprising such salts, and methods of using such salts.

[0464] 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.

[0465] 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.

[0466] For a compound of Formula (I)-(XII) 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

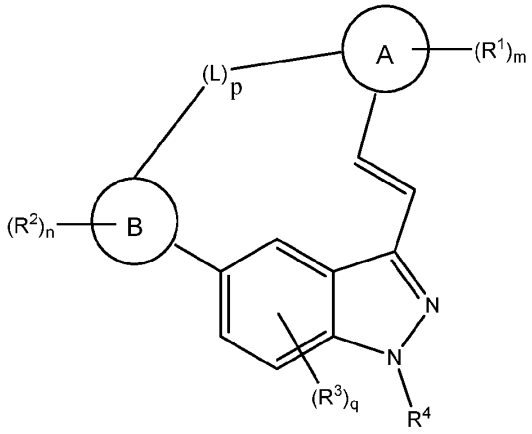
organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, 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.

[0467] The disclosure also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (I)-(XII), 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)-(XII)). 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.

[0468] The present disclosure also relates to pharmaceutically active metabolites of compounds of Formula (I)-(XII), 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)-(XII) 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

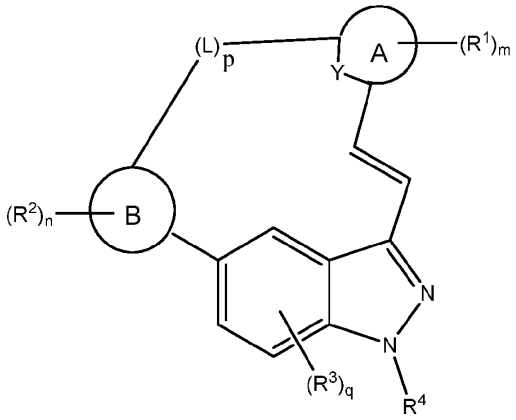
[0469] In some embodiments, the disclosure provides a compound of the formula I, or a pharmaceutically acceptable salt thereof,



I

[0470] wherein R^1, R^2, R^3, R^4, A, B, L, m, n, p, and q are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

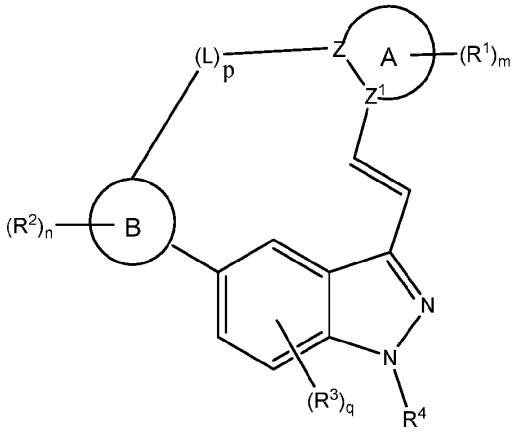
[0471] In some embodiments, the disclosure provides a compound of the formula II, or a pharmaceutically acceptable salt thereof,



II

[0472] wherein R^1, R^2, R^3, R^4, A, B, L, Y, m, n, p, and q are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

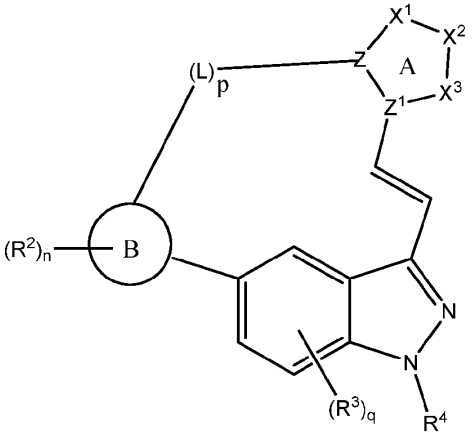
[0473] In some embodiments, the disclosure provides a compound of the formula III, or a pharmaceutically acceptable salt thereof,



III

[0474] wherein R^1, R^2, R^3, R^4, A, B, L, Z, Z^1, m, n, p, and q are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

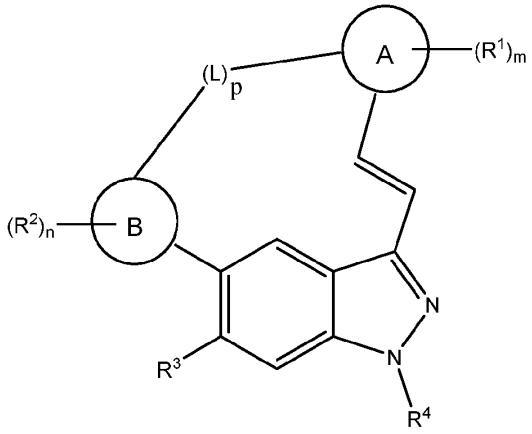
[0475] In some embodiments, the disclosure provides a compound of the formula IV, or a pharmaceutically acceptable salt thereof,



IV

[0476] wherein R^2, R^3, R^4, A, B, L, X^1, X^2, X^3, Z, Z^1, m, n, p, and q are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

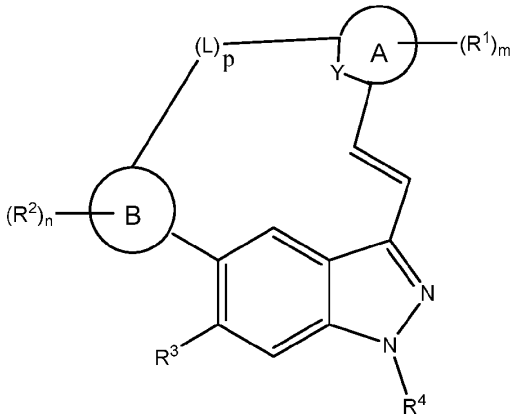
[0477] In some embodiments, the disclosure provides a compound of the formula V, or a pharmaceutically acceptable salt thereof,



V

[0478] wherein R^1, R^2, R^3, R^4, A, B, L, m, n, and p are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

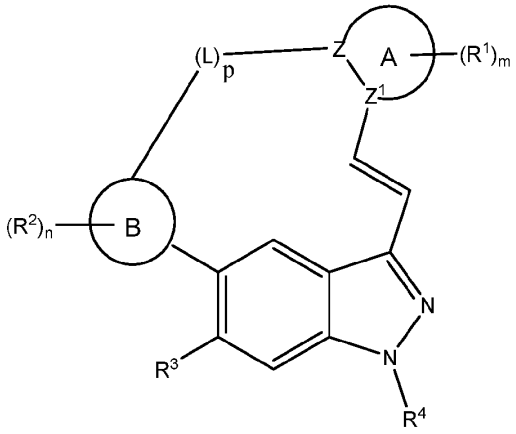
[0479] In some embodiments, the disclosure provides a compound of the formula VI, or a pharmaceutically acceptable salt thereof,



VI

[0480] wherein R^1, R^2, R^3, R^4, A, B, L, Y, m, n, and p are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

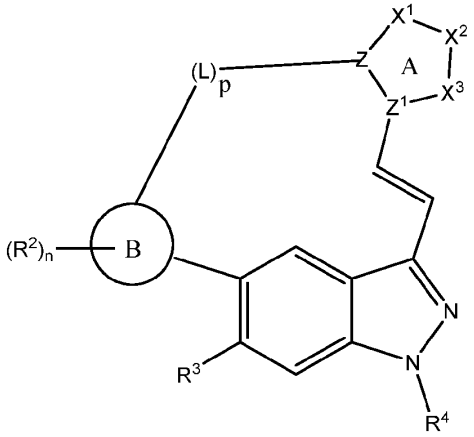
[0481] In some embodiments, the disclosure provides a compound of the formula VII, or a pharmaceutically acceptable salt thereof,



VII

[0482] wherein R^1, R^2, R^3, R^4, A, B, L, Z, Z^1, m, n, and p are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

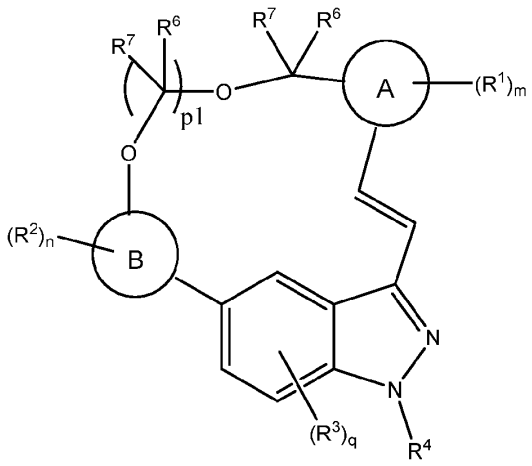
[0483] In some embodiments, the disclosure provides a compound of the formula VIII, or a pharmaceutically acceptable salt thereof,



VIII

[0484] wherein R^2, R^3, R^4, A, B, L, X^1, X^2, X^3, Z, Z^1, m, n, and p are as described herein. In some embodiments of this aspect, $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A. In some embodiments of this aspect, $(L)_p$ does not comprise a $-O-CR^6R^7-$ fragment directly covalently to ring A.

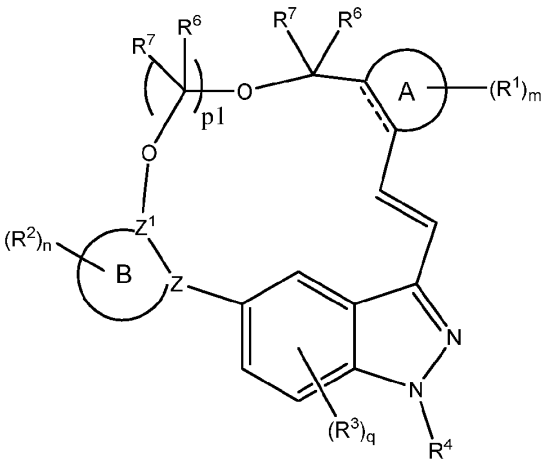
[0485] In some embodiments, the disclosure provides a compound of the formula IX, or a pharmaceutically acceptable salt thereof,



IX

[0486] wherein R^1, R^2, R^3, R^4, R^6, R^7, A, B, m, n, p1, and q are as described herein.

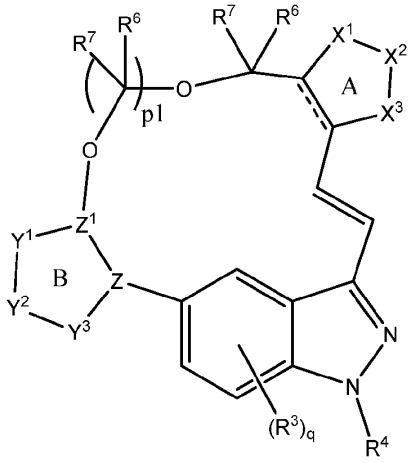
[0487] In some embodiments, the disclosure provides a compound of the formula X, or a pharmaceutically acceptable salt thereof,



X

[0488] wherein R^1, R^2, R^3, R^4, R^6, R^7, A, B, Z, Z^1, m, n, p1, and q are as described herein.

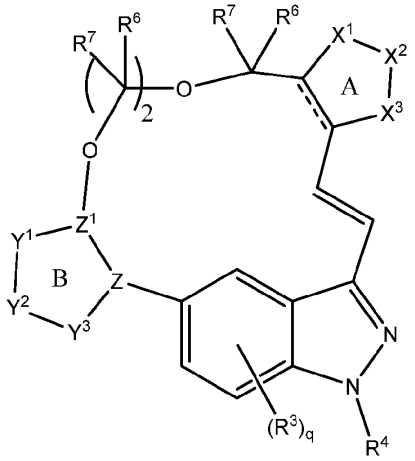
[0489] In In some embodiments, the disclosure provides a compound of the formula XI, or a pharmaceutically acceptable salt thereof,



XI

[0490] wherein R^1, R^2, R^3, R^4, R^6, R^7, A, B, X^1, X^2, X^3, Y^1, Y^2, Y^3, Z, Z^1, p1, and q are as described herein.

[0491] In some embodiments, the disclosure provides a compound of the formula XII, or a pharmaceutically acceptable salt thereof,



XII

[0492] wherein R^3, R^4, R^6, R^7, A, B, X^1, X^2, X^3, Y^1, Y^2, Y^3, Z, Z^1, and q are as described herein.

[0493] In some embodiments, ring B is a 5- to 10-membered heteroarylene or a C_6-C_{10} arylene. In some embodiments, Ring B is mono- or bi-cyclic C_6-C_{10} arylene or mono- or bi-cyclic 5- to 10-membered heteroarylene.

[0494] In some embodiments, ring A is a 5- to 10-membered heteroarylene. In some embodiments, ring A is a 5- or 6-membered heteroarylene. In some embodiments, ring A is a

5-membered heteroarylene. In some embodiments, ring A is a 6-membered heteroarylene. In some embodiments, ring A is a fused bicyclic 8- to 10-membered heteroarylene.

[0495] In some embodiments, ring A is a 5- to 10-membered heteroarylene, such as a monocyclic 5- or 6-membered heteroarylene or a bicyclic 8- to 10-membered heteroarylene, wherein each hydrogen atom in the 5- to 10-membered heteroarylene, as described herein, is independently optionally substituted by an R^1 that is 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0496] In some embodiments, ring A is pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, or imidazolylene, wherein each hydrogen atom in pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, and imidazolylene, is independently optionally substituted by an R^1 that is 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$,

$-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0497] In some embodiments, ring A is pyridinylene, pyrazinylene, pyrimidinylene, or pyridazineylene, wherein each hydrogen atom in pyridinylene, pyrazinylene, pyrimidinylene, or pyridazineylene, is independently optionally substituted by an R^1 that is 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0498] In some embodiments, ring A is a 5- to 10-membered heteroarylene, such as a monocyclic 5- or 6-membered heteroarylene or a bicyclic 8- to 10-membered heteroarylene, wherein the 5- to 10-membered heteroarylene, as described herein, is optionally substituted with 1, 2, 3, 4, or 5 of R^1 (m of R^1), each of which is independently selected from the group consisting of 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, and $-NO_2$, 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,

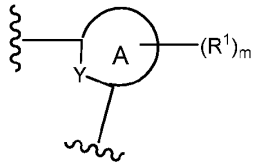
C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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. In some embodiments, two R^1 taken together with the atoms to which they are attached 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^1 are taken together is independently optionally substituted by -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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.

[0499] In some embodiments, ring A is pyridinylene, pyrazinylene, pyrimidinylene, or pyridazineylene, wherein each is optionally substituted with 1, 2, 3, 4, or 5 of R^1 (m of R^1), each of which is independently selected from the group consisting of 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, 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, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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. In some embodiments, ring A is pyridinylene, pyrazinylene, pyrimidinylene, or pyridazineylene, wherein two R^1 in pyridinylene, pyrazinylene, pyrimidinylene, or pyridazineylene, as described herein, taken together with the atoms to which they are attached 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^1 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

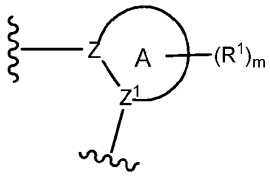
[0500] In some embodiments, ring A is pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, or imidazolylene, wherein each is optionally substituted with 1, 2, 3, 4, or 5 of R^1 (m of R^1), each of which is independently selected from the group consisting of deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 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, and $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$. In some embodiments, two R^1 in pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, or imidazolylene, as described herein, taken together with the atoms to which they are attached 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^1 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

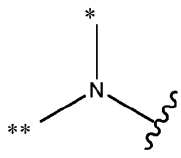
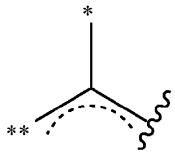
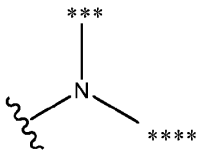
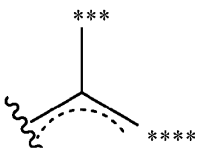
[0501] In some embodiments, ring A is of the formula



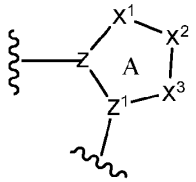
[0502] wherein Y is a single, a double bond, –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, each "〰" represents a point of covalent attachment, and R^1 and m are as described herein. In some embodiments, ring A is 5- to 10-membered heteroarylene. In some embodiments, ring A is a 5- or 6-membered heteroarylene.

[0503] In some embodiments, ring A is of the formula



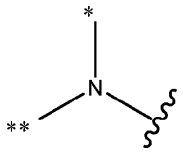
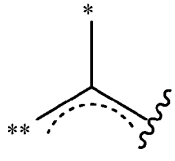
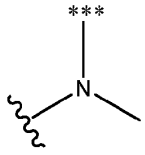
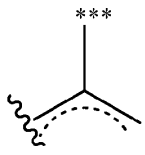
[0504] wherein Z is  or  , wherein * is a point of covalent attachment to $(L)_p$, ** is a point of covalent attachment to Z^1, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⌒" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^1 is  or  wherein *** is a point of covalent attachment to "═", **** is a point of covalent attachment to Z, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⌒" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond, and provided that both Z and Z^1 are not a nitrogen atom. In some embodiments, ring A is 5- to 10-membered heteroarylene. In some embodiments, ring A is a 5- or 6-membered heteroarylene.

[0505] In some embodiments, ring A is of the formula



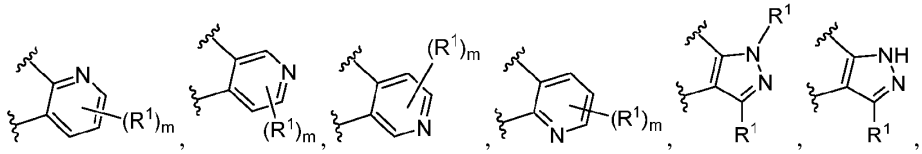
[0506] wherein

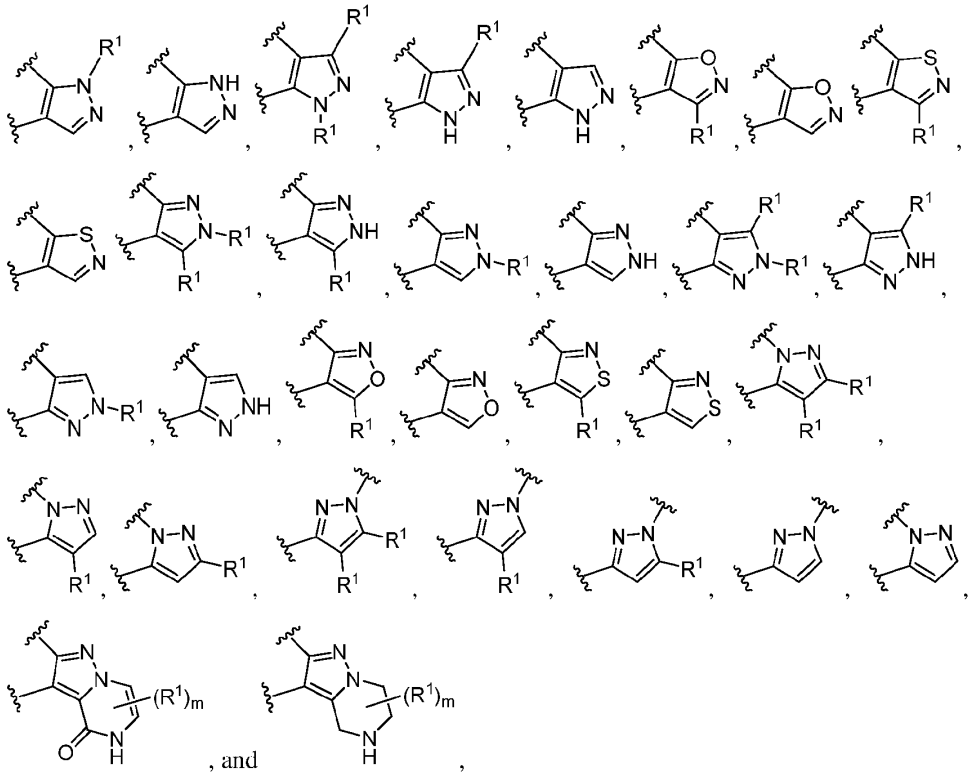
[0507] X^1, X^2, and X^3 are each independently –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-;

[0508] Z is  or  , wherein * is a point of covalent attachment to $(L)_p$, ** is a point of covalent attachment to Z^1, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^1 is  or  wherein *** is a point of covalent attachment to "═", **** is a point of covalent attachment to Z, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond, and provided that both Z and Z^1 are not a nitrogen atom. In some embodiments, ring A is 5- to 10-membered heteroarylene. In some embodiments, ring A is a 5- or 6-membered heteroarylene

[0509] In some embodiments, m is 0, 1, 2, 3, or 4. 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. In some embodiments, m is 4.

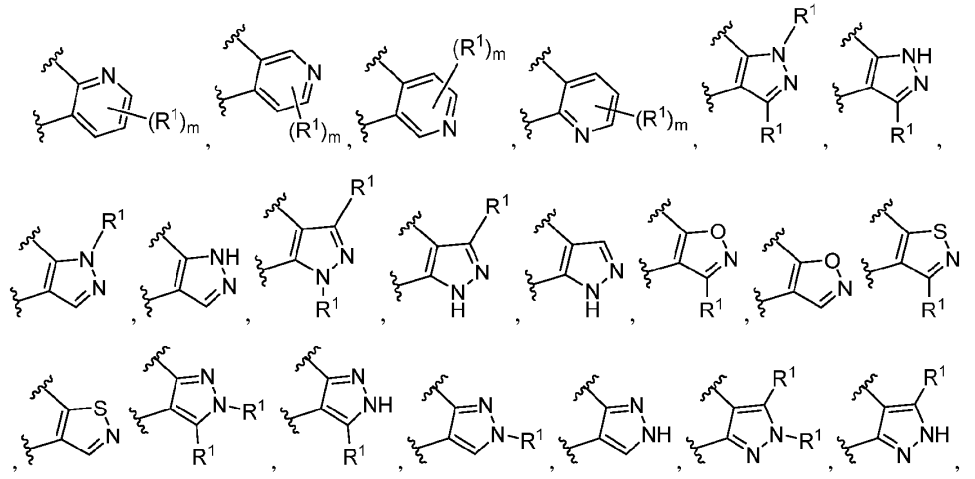
[0510] In some embodiments, ring A is a 5- to 10-membered heteroarylene selected from the group consisting of

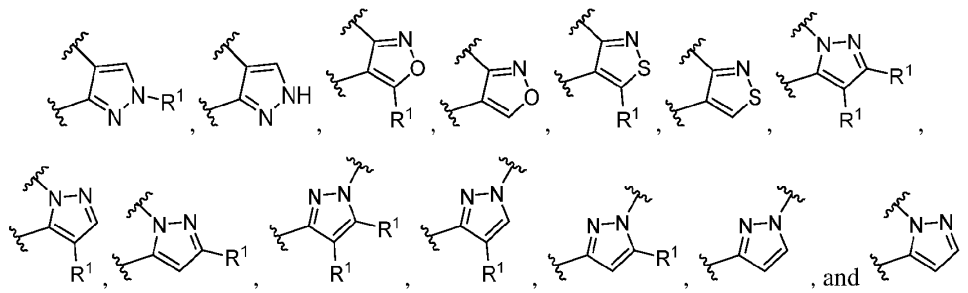




[0511] wherein each "〰" represents a point of covalent attachment.

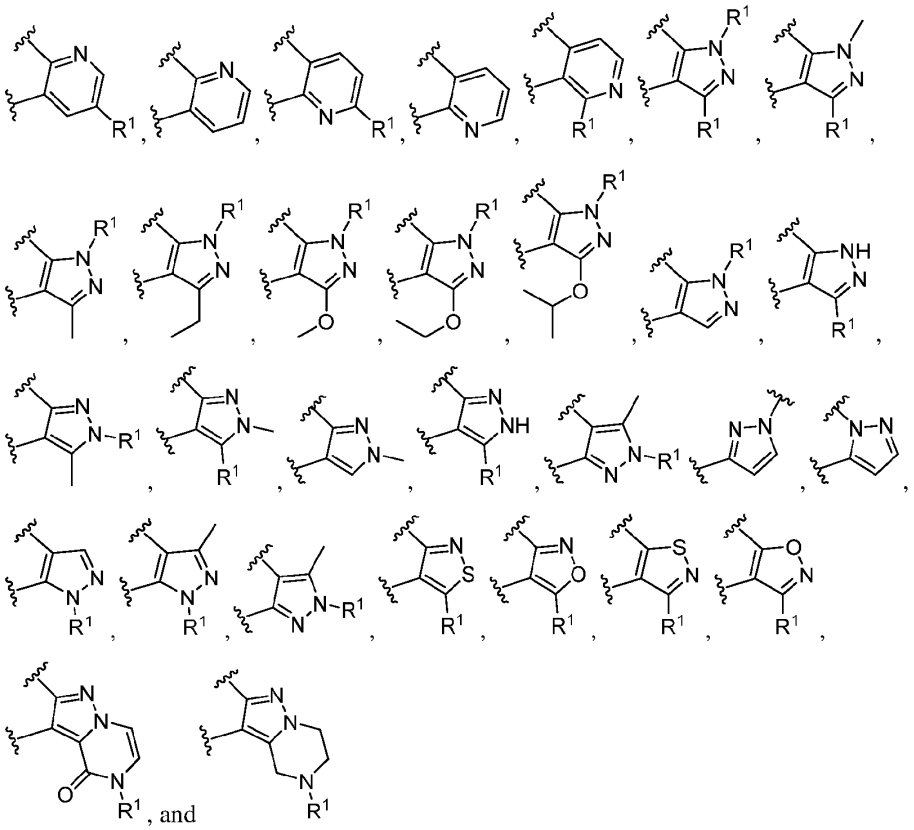
[0512] In some embodiments, ring A is a 5- or 6-membered heteroarylene selected from the group consisting of





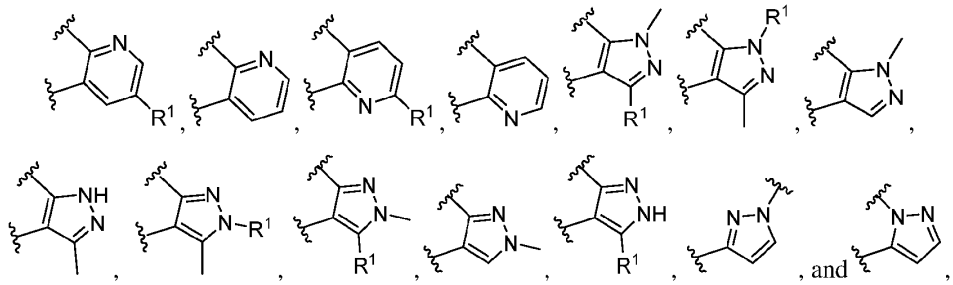
[0513] wherein each "〰" represents a point of covalent attachment, and each R^1 is independently as described herein.

[0514] In some embodiments, ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



[0515] wherein each "〰" represents a point of covalent attachment.

[0516] In some embodiments, ring A is a 5- or 6-membered heteroarylene selected from the group consisting of



[0517] wherein each "∿∿∿" represents a point of covalent attachment, and each R^1 is as described herein.

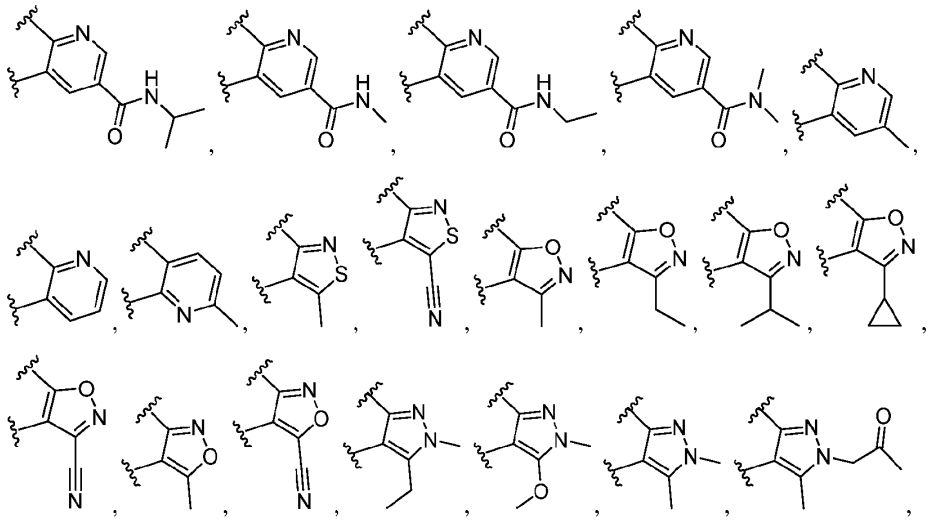
[0518] In some embodiments, each R^1 is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

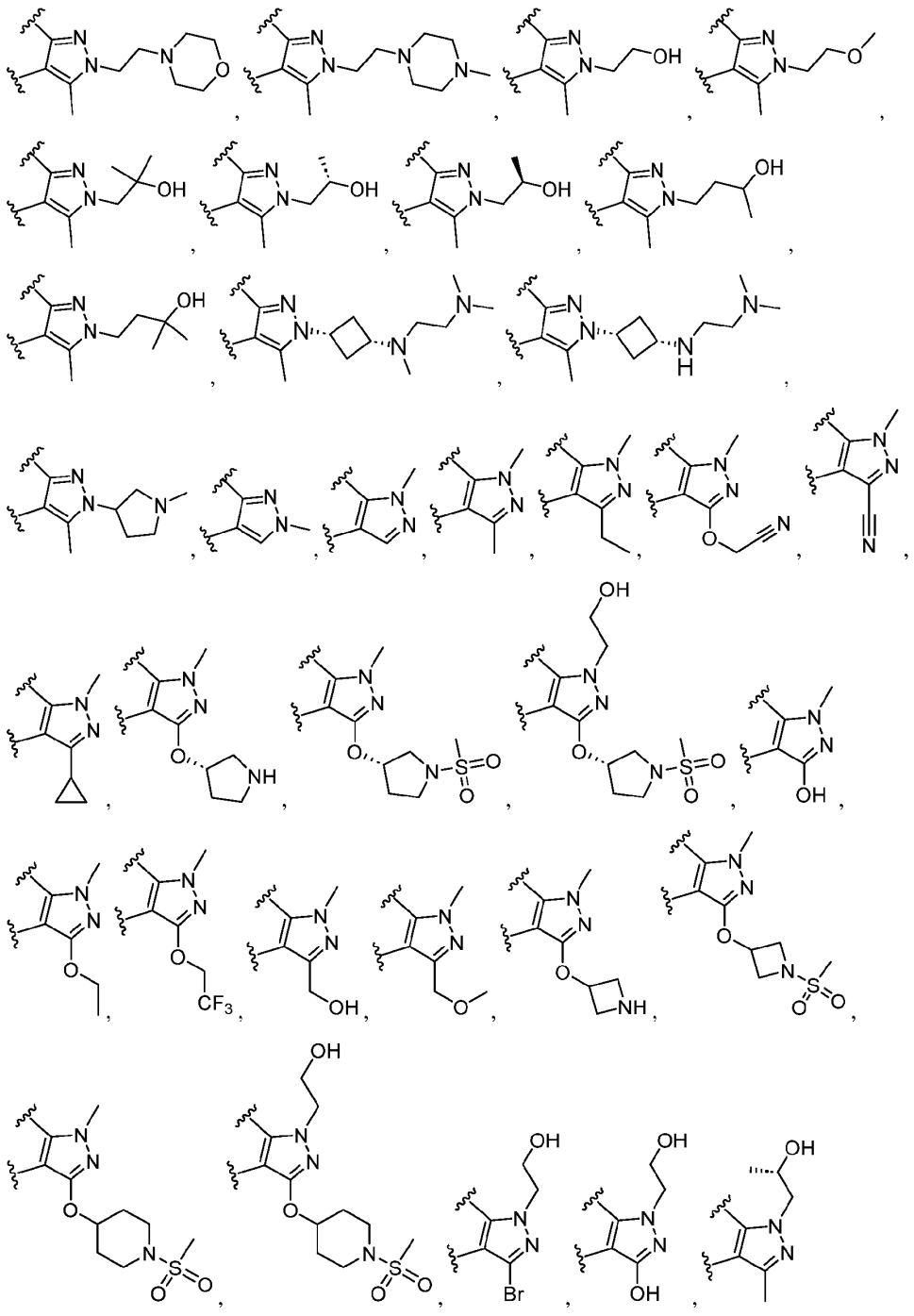
[0519] In some embodiments, each R^1 is independently deuterium, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, -CN, $-OR^a$, or $-C(O)NR^aR^b$, wherein each hydrogen atom in C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, is independently optionally substituted deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

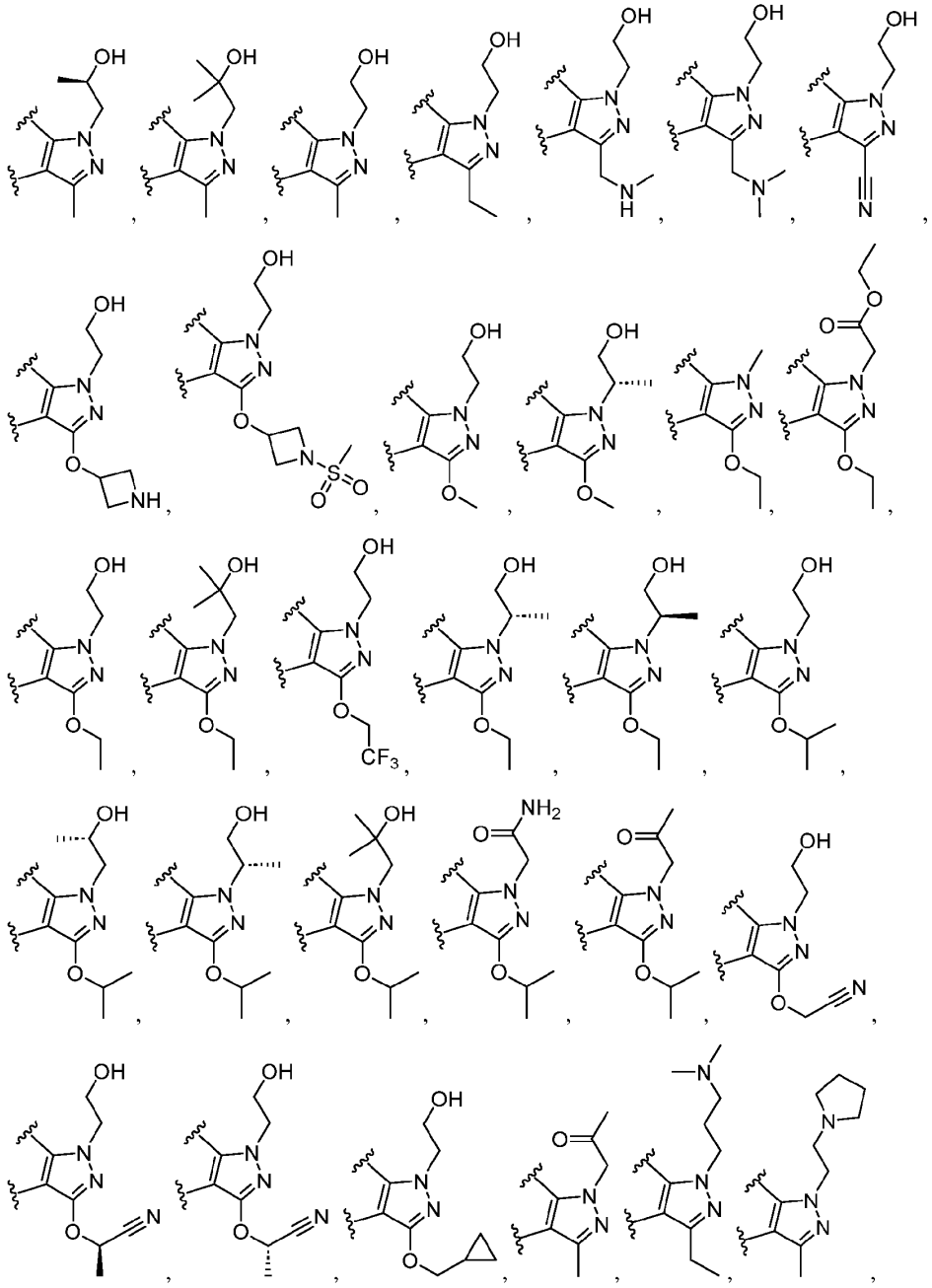
[0520] In some embodiments, each R^1 is independently deuterium, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, or $-C(O)NR^aR^b$, wherein each hydrogen atom in C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, is independently optionally substituted deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, $-CN$, or $-NO_2$.

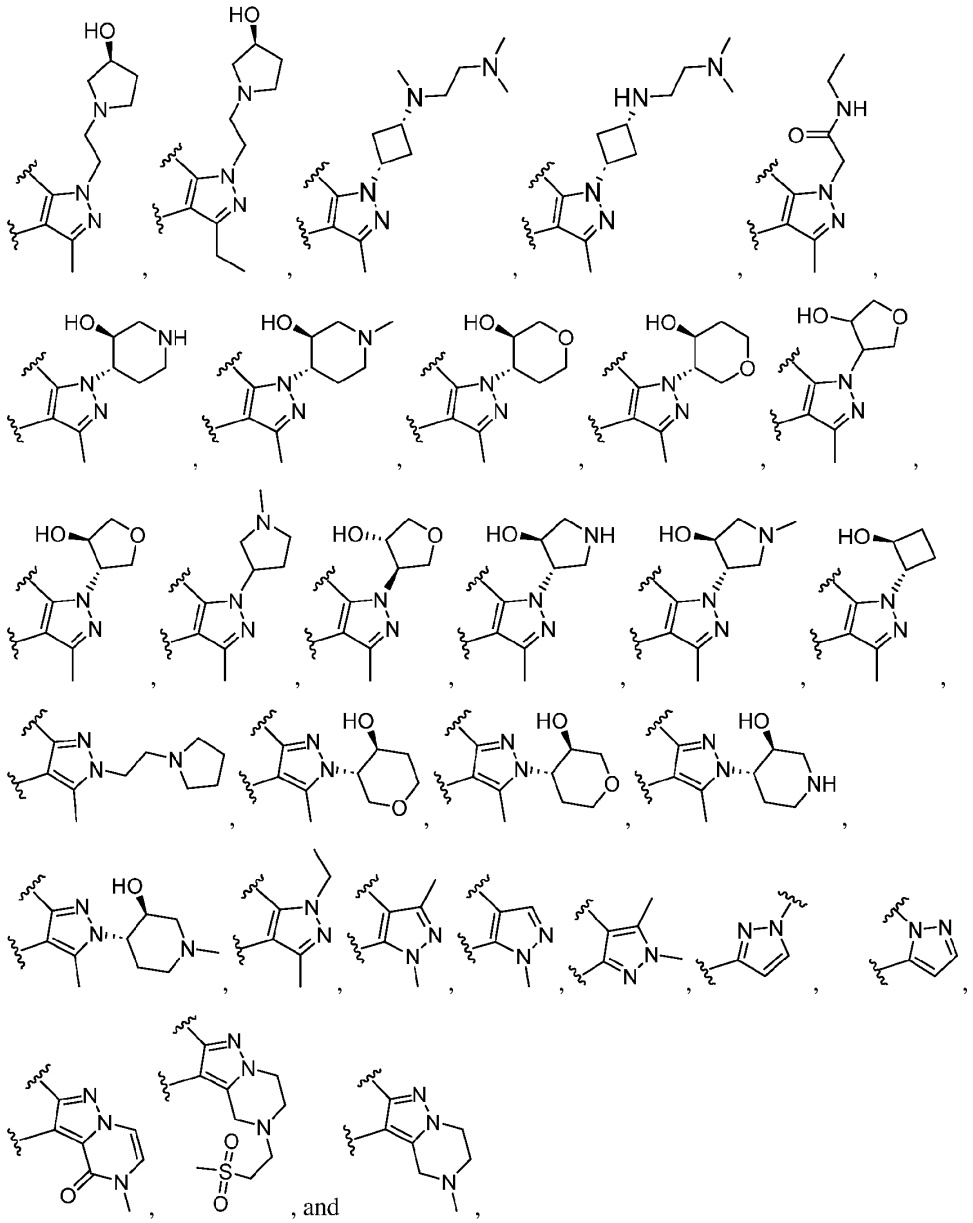
[0521] In some embodiments, two R^1 taken together with the atoms to which they are attached, optionally combine to form a C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, wherein each hydrogen atom in the C_3-C_6 cycloalkyl or 3- to 7-membered heterocycloalkyl formed when two of R^1 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, $-CN$, or $-NO_2$.

[0522] In some embodiments, ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



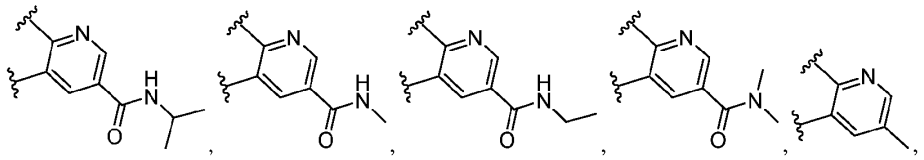


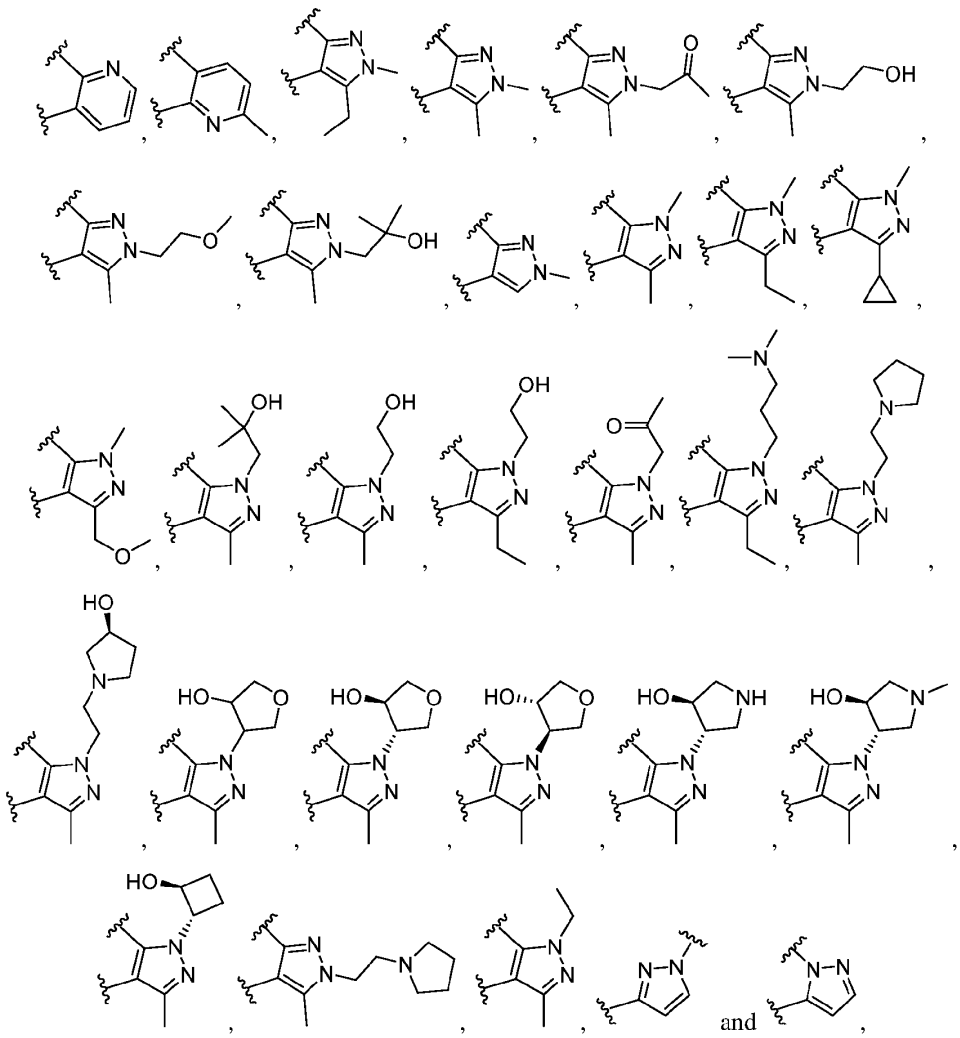




[0523] wherein each "〰" represents a point of covalent attachment.

[0524] In some embodiments, Ring A is a 5- or 6-membered heteroarylene selected from the group consisting of





and

[0525] wherein each "〰" represents a point of covalent attachment.

[0526] In some embodiments, Ring A is mono- or bi-cyclic C_6-C_{10} arylene. In some embodiments, Ring A is monocyclic C_6-C_{10} arylene. In some embodiments, Ring A is bicyclic C_6-C_{10} arylene.

[0527] In some embodiments, Ring A is a C_6-C_{10} mono-or bi-cyclic arylene, wherein each hydrogen atom in C_6-C_{10} mono- or bi-cyclic arylene is independently optionally substituted by an R^1 that is 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^{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(=N)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(=N)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(=N)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$_2$.

[0528] In some embodiments, Ring A is phenylene or naphthylene, wherein each hydrogen atom in phenylene or naphthylene is independently optionally substituted by an R^1 that is 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, -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}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, -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(=N)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(=N)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(=N)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$_2$.

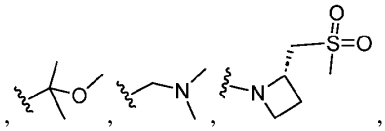
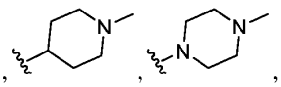
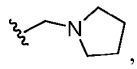
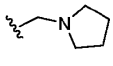
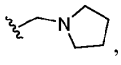
[0529] In some embodiments, Ring A is a C$_6$-C$_{10}$ mono-or bi-cyclic arylene, wherein each is optionally substituted with 1, 2, 3, 4, or 5 of R^1 (m of R^1), each of which is independently selected from the group consisting of deuterium, halogen, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ 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, -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}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, -PR^{a}R^b, -P(O)R^{a}R^b, -P(O)$_2$R^{a}R^b,

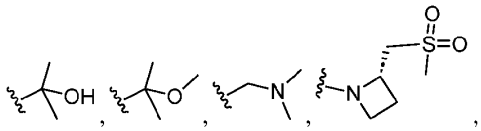
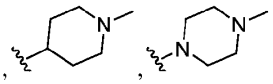
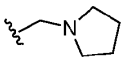
-P(O)NR^{a}R^b, -P(O)$_2$NR^{a}R^b, -P(O)OR^a, -P(O)$_2$OR^a, -CN, or -NO$_2$, wherein each hydrogen atom in C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or 5- to 10-membered heteroaryl, is independently optionally 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(=N)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(=N)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(=N)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, and -NO$_2$.

[0530] In some embodiments, Ring A is phenylene or naphthylene, wherein each is optionally substituted with 1, 2, 3, 4, or 5 of R^1 (m of R^1), each of which is independently selected from the group consisting of 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, -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}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, -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(=N)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(=N)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(=N)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$_2$.

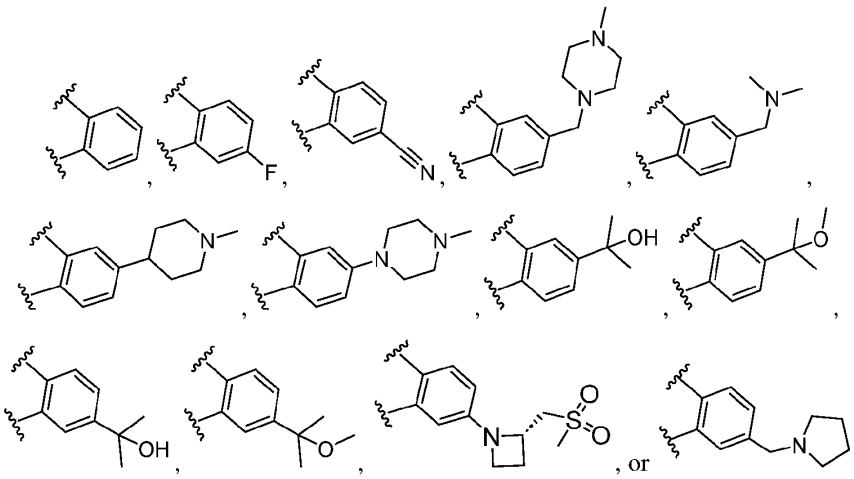
[0531] In some embodiments, ring A is a C$_6$-C$_{10}$ arylene, and m is as defined herein. In some embodiments, ring A is a phenylene, and m is as defined herein.

[0532] In some embodiments, m is 0, 1, 2, 3, or 4. 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. In some embodiments, m is 4.

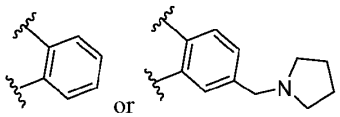
[0533] In some embodiments, each R^1 is independently methyl, ethyl, F, Cl, Br, -CN, 


, or  , wherein each "〰" represents a point of covalent attachment. In some embodiments, R^1 is methyl, ethyl, F, Cl, Br, or  , wherein "〰" represents a point of covalent attachment. In some embodiments, ring A is a phenylene, n is 1, and R^1 is methyl, ethyl, F, Cl, Br, or  , wherein "〰" represents a point of covalent attachment.

[0534] In some embodiments, ring A is a phenylene, m is 1, and R^1 is methyl, ethyl, F, Cl, Br, -CN, 

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

[0535] In some embodiments, ring A is of the formula



[0536] wherein each "〰" represents a point of covalent attachment. In some embodiments, ring A is ring A is of the formula



[0537] wherein each "〰" represents a point of covalent attachment.

[0538] In some embodiments, ring B is a 5- membered heteroarylene.

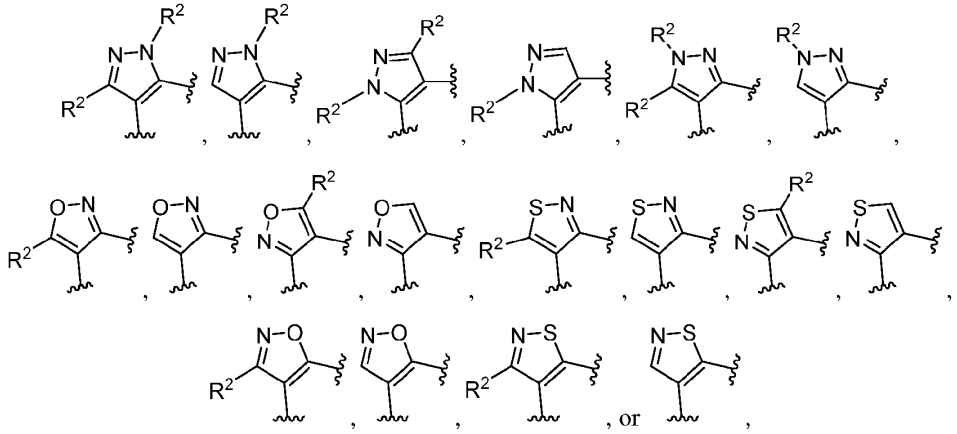
[0539] In some embodiments, ring B is pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, or imidazolylene, wherein each hydrogen atom in pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, and imidazolylene, is independently optionally substituted by an R^2 that is deuterium, halogen, 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, $-CN$, or $-NO_2$.

[0540] In some embodiments, ring B is pyrrolylene, isoxazolylene, isothiazolylene, pyrazolylene, or imidazolylene, wherein each is optionally substituted with 1, 2, 3, 4, or 5 of R^2 (n of R^2), each of which is independently selected from the group consisting of 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$,

$-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, and $-NO_2$.

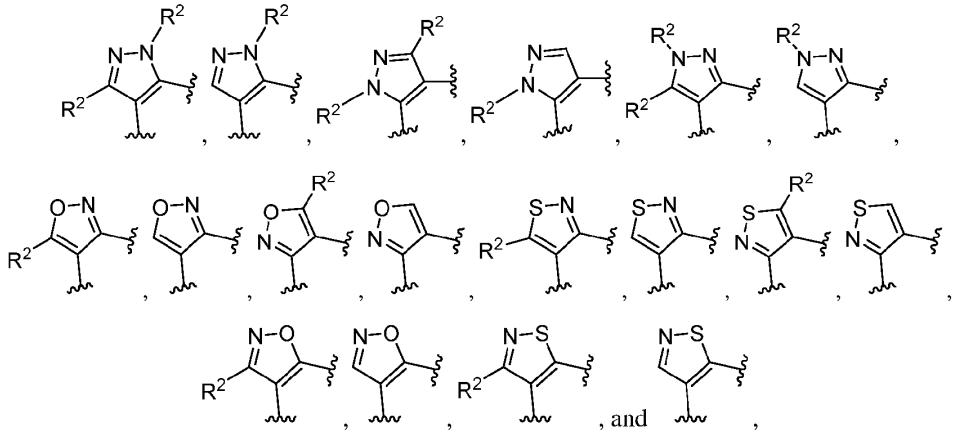
[0541] In some embodiments, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[0542] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



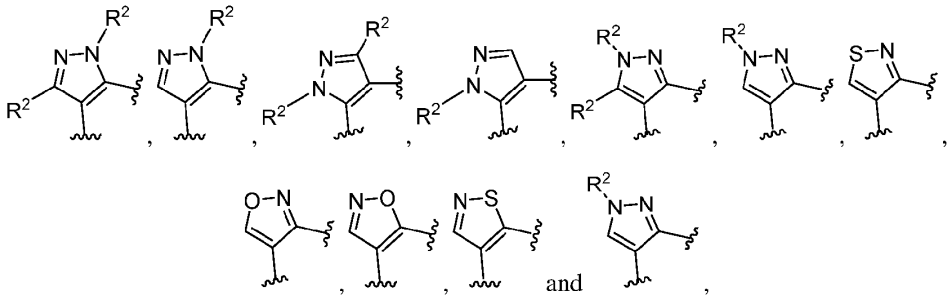
[0543] wherein each "∿∿∿" represents a point of covalent attachment.

[0544] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



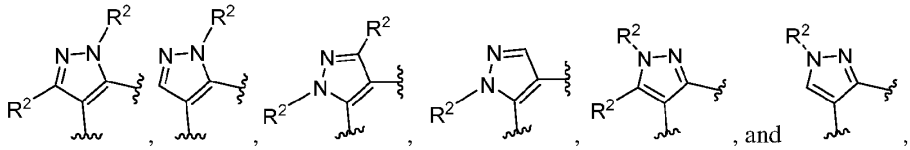
[0545] wherein each "∿∿∿" represents a point of covalent attachment, and each R^2 is independently as described herein.

[0546] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



[0547] wherein each "〰" represents a point of covalent attachment.

[0548] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of

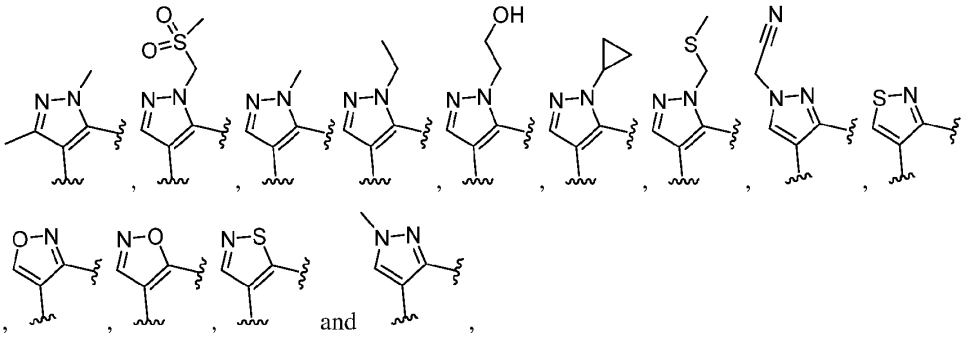


[0549] wherein each "〰" represents a point of covalent attachment, and each R^2 is independently as described herein.

[0550] In some embodiments, each R^2 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$. In some embodiments, each R^2 is independently deuterium or 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, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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. In some embodiments two R^2 taken together with the atoms 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^1 are taken together is independently optionally substituted by -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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.

[0551] In some embodiments, ring B is a 5-membered heteroarylene selected from the group consisting of



[0552] wherein each "∿∿∿" represents a point of covalent attachment.

[0553] In some embodiments, q is 0, 1, or 2. In some embodiments, q is 0 or 1. In some embodiments, q is 0. In some embodiments, q is 1.

[0554] In some embodiments, R^3 is 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, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$. In some embodiments, R^3 is halogen. In some embodiments, R^3 is fluoro, chloro, or bromo. In some embodiments, two R^3 taken together with the atoms 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^1 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

[0555] In some embodiments, R^4 is H, deuterium, C_1-C_6 alkyl, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-P(O)_2R^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)_2OR^c$, or $-S(O)_2OR^c$. In some embodiments, R^4 is H or deuterium. In some embodiments, R^4 is H. In some embodiments, R^4 is C_1-C_6 alkyl. In some embodiments, R^4 is methyl or ethyl.

[0556] In some embodiments, each R^5, when present, is independently 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, 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, or 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$. In some embodiments, each R^5 is independently H, methyl, ethyl, $-C(O)CH_3$, or $-C(O)CH_2CH_3$; or an R^5 combines with an R^6 to form a 3- to 7-membered heterocycloalkyl.

[0557] In some embodiments, each R^5, when present, is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, -C(O)R^a, 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, or 5- to 10-membered heteroaryl is independently optionally substituted by -OR^c, -OC(O)R^c, -OC(O)NR^cR^d, -OC(=N)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(=N)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(=N)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. In some embodiments, each R^5 is independently H, methyl, ethyl, –C(O)CH_3, or -C(O)CH_2CH_3; or an R^5 combines with an R^6 to form a 3- to 7-membered heterocycloalkyl.

[0558] In some embodiments, each L is independently -C(R^6)(R^7)-, -C(O)-, -O-, or -N(R^5)-, provided that $(L)_p$ does not comprise a –O-O- or a –O-N(R^5)- bond, and the point of covalent attachment of $(L)_p$ to ring A does not form a –N-N- or a –O-N- bond.

[0559] In some embodiments, p is 3, 4, 5, 6, 7, 8, or 9. In some embodiments, p is 4, 5, 6, 7, 8, or 9. In some embodiments, p is 4, 5, 6, 7, or 8. In some embodiments, p is 4, 5, 6, or 7. In some embodiments, p is 5, 6, 7, or 8. In some embodiments, p is 5, 6, or 7. In some embodiments, p is 3, 4, 5, 6, or 7. In some embodiments, p is 3, 4, 5, or 6. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6. In some embodiments, p is 7. In some embodiments, p is 8. In some embodiments, p is 9.

[0560] In some embodiments, p1 is 2, 3, or 4. In some embodiments, p1 is 2. In some embodiments, p1 is 3. In some embodiments, p1 is 4.

[0561] In some embodiments, -$(L)_p$- comprises -CR^6R^7-O(CR^6R^7)$_2$O-, -CR^6R^7-O(CR^6R^7)$_3$O-, -(CR^6R^7)C(O)N(R^5)-(CR^6R^7)$_2$-, -(CR^6R^7)N(R^5)C(O)-(CR^6R^7)$_2$-, -O(CR^6R^7)$_2$N(R^5)C(O)-(CR^6R^7)O-, -N(R^5)-C(O)(CR^6R^7)$_2$O(CR^6R^7)$_2$-, -CR^6R^7O(CR^6R^7)$_2$O-(CR^6R^7)$_2$, -O(CR^6R^7)$_2$O(CR^6R^7)$_2$-, -O(CR^6R^7)$_2$O(CR^6R^7)$_2$O-, -CR^6R^7O-CR^6R^7-C(O)N(R^5)-(CR^6R^7)$_2$-, -(CR^6R^7)$_3$O(CR^6R^7)$_2$-, -(CR^6R^7)$_2$O(CR^6R^7)$_3$-, -CR^6R^7-N(R^5)-(CR^6R^7)$_4$O-, -CR^6R^7-N(R^5)-(CR^6R^7)$_3$O-, -CR^6R^7-N(R^5)-(CR^6R^7)$_2$O-, -CR^6R^7-N(R^5)-(CR^6R^7)$_2$-, -CR^6R^7-N(R^5)-(CR^6R^7)$_3$O-, -CR^6R^7-N(R^5)-(CR^6R^7)$_3$-, -O(CR^6R^7)$_2$O(CR^6R^7)$_3$-, -(CR^6R^7)$_2$-N(R^5)-(CR^6R^7)$_3$-, -O(CR^6R^7)$_2$-N(R^5)-CR^6R^7-, -(CR^6R^7)$_2$-N(R^5)-(CR^6R^7)$_2$-, -O-(CR^6R^7)$_2$-, -O-(CR^6R^7)$_3$-, -O-(CR^6R^7)$_4$-, -O-(CR^6R^7)$_5$-, -O-(CR^6R^7)$_2$O-, -O-(CR^6R^7)$_3$O-, -O-(CR^6R^7)$_4$O-, or -O-(CR^6R^7)$_5$O-.

[0562] In some embodiments, -$(L)_p$- is -CR^6R^7-$O(CR^6R^7)_2O$-, -CR^6R^7-$O(CR^6R^7)_3O$-, -$(CR^6R^7)C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)N(R^5)C(O)$-$(CR^6R^7)_2$-, -$O(CR^6R^7)_2N(R^5)C(O)$-$(CR^6R^7)O$-, -$N(R^5)$-$C(O)(CR^6R^7)_2O(CR^6R^7)_2$-, -$CR^6R^7O(CR^6R^7)_2O$-$(CR^6R^7)_2$, -$O(CR^6R^7)_2O(CR^6R^7)_2$-, -$O(CR^6R^7)_2O(CR^6R^7)_2O$-, -$CR^6R^7O$-$CR^6R^7$-$C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)_3O(CR^6R^7)_2$-, -$(CR^6R^7)_2O(CR^6R^7)_3$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_4O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2O(CR^6R^7)_3$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2$-$N(R^5)$-$CR^6R^7$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_3$-, -O-$(CR^6R^7)_4$-, -O-$(CR^6R^7)_5$-, -O-$(CR^6R^7)_2O$-, -O-$(CR^6R^7)_3O$-, -O-$(CR^6R^7)_4O$-, or -O-$(CR^6R^7)_5O$-.

[0563] In some embodiments, -$(L)_p$- comprises -CR^6R^7-$O(CR^6R^7)_2O$-, -CR^6R^7-$O(CR^6R^7)_3O$-, -$(CR^6R^7)C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)N(R^5)C(O)$-$(CR^6R^7)_2$-, -$O(CR^6R^7)_2N(R^5)C(O)$-$(CR^6R^7)O$-, -$N(R^5)$-$C(O)(CR^6R^7)_2O(CR^6R^7)_2$-, -$CR^6R^7O(CR^6R^7)_2O$-$(CR^6R^7)_2$, -$O(CR^6R^7)_2O(CR^6R^7)_2O$-, -$CR^6R^7O$-$CR^6R^7$-$C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)_3O(CR^6R^7)_2$-, -$(CR^6R^7)_2O(CR^6R^7)_3$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_4O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2O$-$CR^6R^7$-, -$O(CR^6R^7)_2O(CR^6R^7)_2$-, -$O(CR^6R^7)_2O(CR^6R^7)_3$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2$-$N(R^5)$-$CR^6R^7$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_3$-, -O-$(CR^6R^7)_4$-, -O-$(CR^6R^7)_5$-, -O-$(CR^6R^7)_2O$-, -O-$(CR^6R^7)_3O$-, -O-$(CR^6R^7)_4O$-, or -O-$(CR^6R^7)_5O$-.

[0564] In some embodiments, -$(L)_p$- is -CR^6R^7-$O(CR^6R^7)_2O$-, -CR^6R^7-$O(CR^6R^7)_3O$-, -$(CR^6R^7)C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)N(R^5)C(O)$-$(CR^6R^7)_2$-, -$O(CR^6R^7)_2N(R^5)C(O)$-$(CR^6R^7)O$-, -$N(R^5)$-$C(O)(CR^6R^7)_2O(CR^6R^7)_2$-, -$CR^6R^7O(CR^6R^7)_2O$-$(CR^6R^7)_2$, -$O(CR^6R^7)_2O(CR^6R^7)_2O$-, -$CR^6R^7O$-$CR^6R^7$-$C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)_3O(CR^6R^7)_2$-, -$(CR^6R^7)_2O(CR^6R^7)_3$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_4O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2O$-$CR^6R^7$-, -$O(CR^6R^7)_2O(CR^6R^7)_2$-, -$O(CR^6R^7)_2O(CR^6R^7)_3$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2$-$N(R^5)$-$CR^6R^7$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_3$-, -O-$(CR^6R^7)_4$-, -O-$(CR^6R^7)_5$-, -O-$(CR^6R^7)_2O$-, -O-$(CR^6R^7)_3O$-, -O-$(CR^6R^7)_4O$-, or -O-$(CR^6R^7)_5O$-.

[0565] In some embodiments, each R^5 is H, methyl, ethyl, –$C(O)CH_3$, or –$C(O)CH_2CH_3$; or an R^5 combines with an R^6 to form a 3- to 7-membered heterocycloalkyl. In some embodiments, each R^6 is H or C_1-C_6 alkyl; or an R^6 combines with an R^5 to form a 3- to 7-

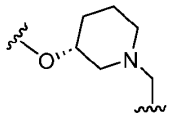
membered heterocycloalkyl. In some embodiments, one R^6 is methyl, and the remaining R^6 and R^7 are H.

[0566] In some embodiments, each R^5 is independently H, methyl, ethyl, –$C(O)CH_3$, or -$C(O)CH_2CH_3$; or R^5, when present, and an R^6 or R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^5 and an R^6 or R^7 are taken together is independently optionally substituted by -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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.

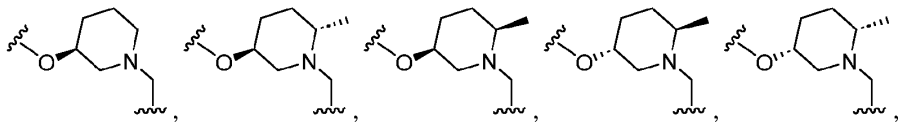
[0567] In some embodiments, an R^6 and R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^6 and R^7 are taken together is independently optionally substituted by -OR^e, -$OC(O)R^e$, -$OC(O)NR^eR^f$, -$OS(O)R^e$, -$OS(O)_2R^e$, -$OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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.

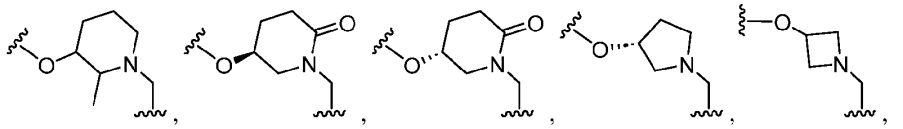
[0568] In some embodiments, -$(L)_p$- comprises -O-$(CH_2)_2O$-CH_2-, -$OC(H)(CH_3)$-CH_2-O-CH_2-, -CH_2O-$(CH_2)_2O$-, -$C(H)(CH_3)$-O-$(CH_2)_2O$-, -$CH_2N(H)$-$(CH_2)_2O$-, -$CH_2N(CH_3)$-$(CH_2)_2O$-, -$CH_2N(CH_2CH_3)$-$(CH_2)_2O$-, -$O(CH_2)_2N(H)CH_2$-, -$O(CH_2)_2N(CH_3)CH_2$-, -OCH_2-$C(H)(CH_3)$-$N(CH(CH_3)_2)CH_2$-, -OCH_2-$C(H)(CH_2F)$-$N(CH_3)CH_2$-, -OCH_2-$C(H)(CH_2CH_3)$-$N(CH_3)CH_2$-, -$O(CH_2)_2N(C(O)CH_3)CH_2$-, -$OC(H)(CH_3)CH_2N(H)CH_2$-, -$OC(H)(CH_3)CH_2N(CH_3)CH_2$-, -$OC(H)(CH_2CN)CH_2N(CH_3)CH_2$-, -$OC(H)(CH_2CH_3)CH_2N(CH_3)CH_2$-, -$OC(H)(CH_2F)CH_2N(CH_3)CH_2$-, -$OC(H)(CHF_2)CH_2N(CH_3)CH_2$-, -$OC(H)(CH_2OH)CH_2N(CH_3)CH_2$-, -$OC(H)(CH_3)C(O)N(CH_3)CH_2$-, -OC(H)(cyclobutyl)$CH_2N(CH_3)CH_2$-, -$OC(H)(CH_3)CH_2N(CH_2CH_3)CH_2$-, -$OC(H)(CH_3)CH_2N(CH(CH_3)_2)$-$CH_2$-, -$OC(H)(CH_3)CH_2N(CH_3)$-$C(H)(CH_3)$-, -OC(H)($CH_3$)$CH_2$N(CH(oxetan-3-yl)-$CH_2$-, -OC(H)($CH_3$)$CH_2$N(cyclopropyl)-$CH_2$-, -$OCH_2C(H)(CH_3)N$(cyclopropyl)-$CH_2$-, -$OC(H)(CH_3)CH_2N(C(O)CH_3)CH_2$-, -$O(C(H)(CH_3))CH_2N(C(O)CH_2CH_3)CH_2$-, -$CH_2N(H)$-$(CH_2)_2(C(H)CH_3)CH_2O$-,

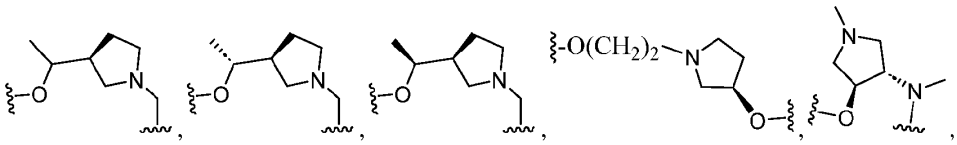
-$CH_2N(CH_3)$-C(H)(CH_3)-CH_2O-, -$CH_2N(CH_3)$-$(CH_2)_2$(C(H)CH_3)CH_2O-, -$CH_2N(CH_3)$-(CH_2)-(C(H)CH_3)O-, -O$(CH_2)_2$-, -O$(CH_2)_3$-, -O$(CH_2)_4$-, -O$(CH_2)_3O$-, -O$(CH_2)_4O$-, -O$(CH_2)_5O$-, -O-(C(H)(CH_3)-$(CH_2)_2O$-, -O$(CH_2)_2$-C(H)(CH_3)-O-, -O$(CH_2)_2$C(H)$(CH_3)CH_2O$-, -O$(CH_2)_3$C(H)$(CH_3)CH_2O$-, -O$(CH_2)_2$N(H)C(O)-(CH_2)O-, -O$(CH_2)_2$N(CH_3)C(O)-(CH_2)O-, -O$(CH_2)_2O(CH_2)_2$O-, -OC(H)$(CH_3)CH_2OCH_2$-,

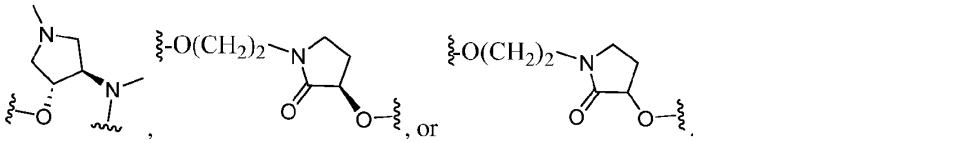


-O$(CH_2)_2OCH_2$C(H)(CH_3)O-, -O$(CH_2)_2$OC(H)(CH_3)-CH_2O-,



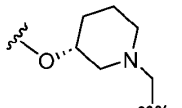




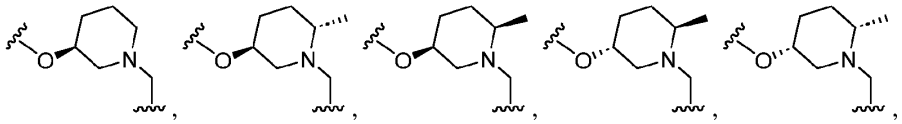


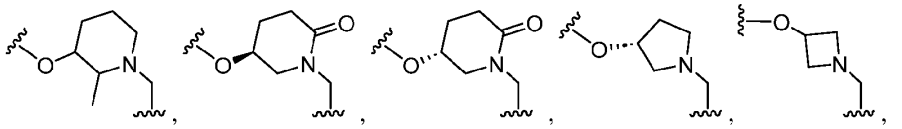
[0569] In some embodiments, -$(L)_p$- is -O-$(CH_2)_2O$-CH_2-, -OC(H)(CH_3)-CH_2-O-CH_2-, -CH_2O-$(CH_2)_2O$-, -C(H)(CH_3)-O-$(CH_2)_2O$-, -$CH_2N(H)$-$(CH_2)_2O$-, -$CH_2N(CH_3)$-$(CH_2)_2O$-, -$CH_2N(CH_2CH_3)$-$(CH_2)_2O$-, -O$(CH_2)_2N(H)CH_2$-, -O$(CH_2)_2N(CH_3)CH_2$-, -OCH_2-C(H)(CH_3)-N(CH$(CH_3)_2)CH_2$-, -OCH_2-C(H)(CH_2F)-N$(CH_3)CH_2$-, -OCH_2-C(H)(CH_2CH_3)-N$(CH_3)CH_2$-, -O$(CH_2)_2N(C(O)CH_3)CH_2$-, -OC(H)$(CH_3)CH_2N(H)CH_2$-, -OC(H)$(CH_3)CH_2N(CH_3)CH_2$-, -OC(H)$(CH_2CN)CH_2N(CH_3)CH_2$-, -OC(H)$(CH_2CH_3)CH_2N(CH_3)CH_2$-, -OC(H)$(CH_2F)CH_2N(CH_3)CH_2$-, -OC(H)$(CHF_2)CH_2N(CH_3)CH_2$-, -OC(H)$(CH_2OH)CH_2N(CH_3)CH_2$-, -OC(H)$(CH_3)C(O)N(CH_3)CH_2$-, -OC(H)(cyclobutyl)$CH_2N(CH_3)CH_2$-, -OC(H)$(CH_3)CH_2N(CH_2CH_3)CH_2$-, -OC(H)$(CH_3)CH_2N(CH(CH_3)_2)$-$CH_2$-, -OC(H)$(CH_3)CH_2N(CH_3)$-C(H)$(CH_3)$-, -OC(H)$(CH_3)CH_2N$(CH(oxetan-3-yl)-$CH_2$-, -OC(H)$(CH_3)CH_2N$(cyclopropyl)-$CH_2$-, -$OCH_2$C(H)$(CH_3)$N(cyclopropyl)-$CH_2$-, -OC(H)$(CH_3)CH_2N(C(O)CH_3)CH_2$-, -O(C(H)$(CH_3)$)$CH_2N(C(O)CH_2CH_3)CH_2$-, -$CH_2N(H)$-$(CH_2)_2$(C(H)$CH_3$)$CH_2O$-,

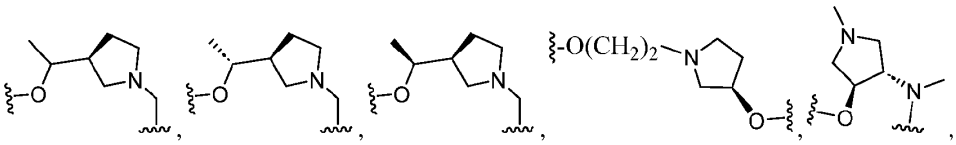
-$CH_2N(CH_3)$-C(H)(CH_3)-CH_2O-, -$CH_2N(CH_3)$-$(CH_2)_2$(C(H)CH_3)CH_2O-, -$CH_2N(CH_3)$-(CH_2)-(C(H)CH_3)O-, -O$(CH_2)_2$-, -O$(CH_2)_3$-, -O$(CH_2)_4$-, -O$(CH_2)_3O$-, -O$(CH_2)_4O$-, -O$(CH_2)_5O$-, -O-(C(H)(CH_3)-$(CH_2)_2O$-, -O$(CH_2)_2$-C(H)(CH_3)-O-, -O$(CH_2)_2$C(H)$(CH_3)CH_2O$-, -O$(CH_2)_3$C(H)$(CH_3)CH_2O$-, -O$(CH_2)_2$N(H)C(O)-(CH_2)O-, -O$(CH_2)_2$N(CH_3)C(O)-(CH_2)O-, -O$(CH_2)_2O(CH_2)_2$O-, -OC(H)$(CH_3)CH_2OCH_2$-,

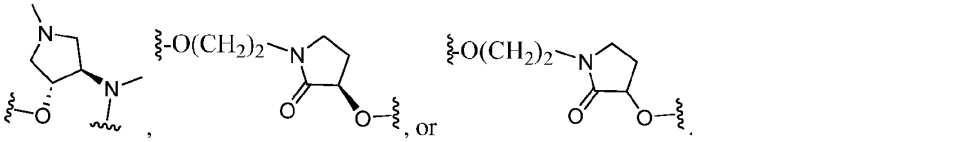


-O$(CH_2)_2OCH_2$C(H)(CH_3)O-, -O$(CH_2)_2$OC(H)(CH_3)-CH_2O-,

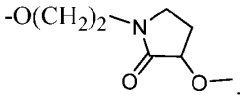




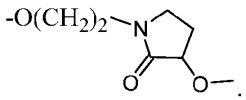




[0570] In some embodiments, -$(L)_p$- comprises -CH_2O-$(CH_2)_2O$-, -C(H)(CH_3)-O-$(CH_2)_2O$-, -CH_2N(H)-$(CH_2)_2O$-, -$CH_2N(CH_3)$-$(CH_2)_2O$-, -$CH_2N(CH_2CH_3)$-$(CH_2)_2O$-, -O$(CH_2)_2$N(H)CH_2-, -O$(CH_2)_2N(CH_3)CH_2$-, -O$(CH_2)_2$N(C(O)CH_3)CH_2-, -O(C(H)(CH_3))CH_2N(H)CH_2-, -O(C(H)(CH_3))$CH_2N(CH_3)CH_2$-, -O(C(H)(CH_3))$CH_2N(CH_2CH_3)CH_2$-, -O(C(H)(CH_3))CH_2N(C(O)CH_3)CH_2-, -O(C(H)(CH_3))CH_2N(C(O)CH_2CH_3)CH_2-, -CH_2N(H)-$(CH_2)_2$(C(H)CH_3)CH_2O-, -$CH_2N(CH_3)$-$(CH_2)_2$(C(H)CH_3)CH_2O-, -O$(CH_2)_2$-, -O$(CH_2)_3$-, -O$(CH_2)_4$-, -O$(CH_2)_3O$-, -O$(CH_2)_4O$-, -O$(CH_2)_5O$-, -O-(C(H)(CH_3)-$(CH_2)_2O$-, -O$(CH_2)_2$-(C(H)(CH_3)-O-, -O$(CH_2)_3$C(H)$(CH_3)CH_2O$-, -O$(CH_2)_2$N(H)C(O)-(CH_2)O-, -O$(CH_2)_2$N(CH_3)C(O)-(CH_2)O-, -O$(CH_2)_2O(CH_2)_2$O-, -O$(CH_2)_2OCH_2$C(H)(CH_3)O-, -O$(CH_2)_2$OC(H)(CH_3)-CH_2O-, or



[0571] In some embodiments, -$(L)_p$- is -CH_2O-$(CH_2)_2O$-, -C(H)(CH_3)-O-$(CH_2)_2O$-, -$CH_2N(H)$-$(CH_2)_2O$-, -$CH_2N(CH_3)$-$(CH_2)_2O$-, -$CH_2N(CH_2CH_3)$-$(CH_2)_2O$-, -$O(CH_2)_2N(H)CH_2$-, -$O(CH_2)_2N(CH_3)CH_2$-, -$O(CH_2)_2N(C(O)CH_3)CH_2$-, -O(C(H)(CH_3))$CH_2N(H)CH_2$-, -O(C(H)(CH_3))$CH_2N(CH_3)CH_2$-, -O(C(H)(CH_3))$CH_2N(CH_2CH_3)CH_2$-, -O(C(H)(CH_3))$CH_2N(C(O)CH_3)CH_2$-, -O(C(H)(CH_3))$CH_2N(C(O)CH_2CH_3)CH_2$-, -$CH_2N(H)$-$(CH_2)_2$(C(H)CH_3)CH_2O-, -$CH_2N(CH_3)$-$(CH_2)_2$(C(H)CH_3)CH_2O-, -$O(CH_2)_2$-, -$O(CH_2)_3$-, -$O(CH_2)_4$-, -$O(CH_2)_3O$-, -$O(CH_2)_4O$-, -$O(CH_2)_5O$-, -O-(C(H)(CH_3)-$(CH_2)_2O$-, -$O(CH_2)_2$-(C(H)(CH_3)-O-, -$O(CH_2)_3$C(H)$(CH_3)CH_2O$-, -$O(CH_2)_2N(H)C(O)$-$(CH_2)O$-, -$O(CH_2)_2N(CH_3)C(O)$-$(CH_2)O$-, -$O(CH_2)_2O(CH_2)_2O$-, -$O(CH_2)_2OCH_2C(H)(CH_3)O$-, -$O(CH_2)_2OC(H)(CH_3)$-$CH_2O$-, and



[0572] In connection with any of the embodiments described herein, $(L)_p$ does not comprise a $–NR^5C(O)$- directly covalently attached to ring A. In connection with any of the embodiments described herein, $(L)_p$ does not comprise a $–O-CR^6R^7$- fragment directly covalently to ring A. In connection with any of the embodiments described herein, $(L)_p$ does not comprise a $-NR^5C(O)$- directly covalently attached to ring A, and $(L)_p$ does not comprise a $–O-CR^6R^7$- fragment directly covalently to ring A.

[0573] In some embodiments, the disclosure provides a compound selected from the group consisting of (11*E*)-1-methyl-1,18,19,21-tetrahydro-8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,4,12,13]benzodioxadiazacyclooctadecine;

[0574] (11*E*)-1-[(methanesulfonyl)methyl]-19,20-dihydro-1*H*,8*H*,18*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,5,12,13]benzodioxadiazacyclooctadecine;

[0575] (11*E*)-1-methyl-18,19,20,21-tetrahydro-1*H*,8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*g*][1,6,13,14]benzodioxadiazacyclononadecine;

[0576] (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0577] (10*R*,16*E*)-3-methyl-13-[(4-methylpiperazin-1-yl)methyl]-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0578] (10*R*,16*E*)-13-[(dimethylamino)methyl]-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0579] (10*R*,16*E*)-3-methyl-13-(1-methylpiperidin-4-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0580] (10*R*,16*E*)-13-(2-methoxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0581] (10*R*,16*E*)-3-methyl-13-(4-methylpiperazin-1-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0582] (10*R*,16*E*)-14-fluoro-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0583] (10*R*,16*E*)-14-(2-hydroxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0584] (10*R*,16*E*)-14-{(2*S*)-2-[(methanesulfonyl)methyl]azetidin-1-yl}-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;

[0585] (10*R*,16*E*)-3-methyl-25-oxo-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine-14-carbonitrile; and

[0586] (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine;

[0587] or a pharmaceutically acceptable salt thereof.

[0588] 32. The compound of clause 1 or 2, selected from the group consisting of (18*E*)-8-methyl-*N*-(propan-2-yl)-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0589] (18*E*)-*N*,8-dimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0590] (18*E*)-*N*,*N*,8-trimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0591] (18*E*)-*N*-ethyl-8-methyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

[0592] (10*S*,18*E*)-8,10,16-trimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,5]dioxacyclopentadecino[7,6-*b*]pyridine;

[0593] (10*S*,18*E*)-17-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[4,3-*f*][1,4]oxazacyclopentadecine; and

[0594] (10*S*,18*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[3,2-*f*][1,4]oxazacyclopentadecine;

[0595] or a pharmaceutically acceptable salt thereof.

[0596]

[0597] 33. The compound of clause 1 or 2, selected from the group consisting of (17*E*)-8,14,16-trimethyl-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0598] 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(2*H*)-yl]ethan-1-ol;

[0599] (17*E*)-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0600] (17*E*)-19-fluoro-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0601] (17*E*)-16-ethyl-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0602] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-2-methylpropan-2-ol;

[0603] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]propan-2-one;

[0604] 2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethan-1-ol;

[0605] (17*E*)-8,16-dimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0606] (3*S*)-1-{2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

[0607] (17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0608] (10*S*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0609] (10*R*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0610] (12*S*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0611] (12*R*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0612] (10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0613] (10*S*,17*E*)-16-cyclopropyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0614] (17*E*)-16-(methoxymethyl)-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0615] (17*E*)-8,14,16-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0616] 1-[(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0617] (17*E*)-8,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0618] (17*E*)-6,8,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0619] (17*E*)-16-ethyl-8,12,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0620] (17*E*)-7,14,16-trimethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0621] (17*E*)-7,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0622] 2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0623] (17*E*)-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0624] (17*E*)-8,10,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0625] 2-[(17*E*)-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0626] 2-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0627] 2-[(17*E*)-10-ethyl-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0628] (19*E*)-8,13,16,18-tetramethyl-2,11,12,13,14,16-hexahydro-8*H*,10*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0629] 2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,16*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-16-yl]ethan-1-ol;

[0630] (19*E*)-8,16,18-trimethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

[0631] (19*E*)-8,12,16,18-tetramethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

[0632] (13R,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

[0633] (13S,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

[0634] 2-[(19E)-8,13,18-trimethyl-2,8,10,11,13,14-hexahydro-16H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazol-16-yl]ethan-1-ol;

[0635] (19*E*)-8,13,18-trimethyl-16-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0636] (3*S*)-1-{2-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

[0637] (19*E*)-22-fluoro-8,16,18-trimethyl-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

[0638] 3-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-*N*,*N*-dimethylpropan-1-amine;

[0639] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]pyrrolidin-3-ol;

[0640] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpyrrolidin-3-ol;

[0641] (3*R*,4*S*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;

[0642] (3*S*,4*R*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;

[0643] (*rac*)-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutan-1-ol;

[0644] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol;

[0645] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol;

[0646] (*rac*)-1,5-anhydr-3o-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;

[0647] (*rac*)-1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;

[0648] (12*R*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0649] (12*S*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0650] (rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol;

[0651] (11*S*,17*E*)-8,11,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0652] (17*E*)-8,9,16-trimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0653] |(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-16-yl]methanol;

[0654] N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;

[0655] (11*S*,17*E*)-8,10,11,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0656] N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;

[0657] (10*R*,15*E*)-3,12,14-trimethyl-5,6,9,10,12,18-hexahydro-3*H*,8*H*-19,21-etheno-7,10-methanotripyrazolo[3,4-*i*:3',4'-*m*:4",3"-*q*][1,8,4]dioxazacyclooctadecin-24-one;

[0658] (17*E*)-16-ethyl-8,10,14-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0659] (17*E*)-10-ethyl-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0660] 2-[(10*S*,17*E*)-8,10,16-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0661] 2-[(10*S*,17*E*)-19-fluoro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0662] (17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0663] 2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0664] (10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0665] (10*R*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0666] (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0667] 2-[(10*S*,17*E*)-19-chloro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0668] (2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol;

[0669] 2-[(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0670] 2-[(10*S*,17*E*)-12-ethyl-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0671] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-[(piperidin-4-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0672] 2-[(10*R*,19*E*)-18-ethoxy-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0673] 2-[(10*S*,17*E*)-6,8,10,12,16-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0674] (10*S*,17*E*)-8,10,14,16-tetramethyl-12-(oxetan-3-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0675] 2-[(10*S*,17*E*)-16-ethoxy-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0676] (10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0677] (10*S*,13*R*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0678] (10*S*,13*S*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0679] 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0680] (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0681] (10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0682] (10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0683] 2-[(10*S*,17*E*)-16-ethoxy-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0684] 2-[(17*E*)-10-cyclobutyl-8,12,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0685] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-{[(3*S*)-pyrrolidin-3-yl]oxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0686] (10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0687] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0688] (10*S*,17*E*)-16-ethoxy-8,10,14-trimethyl-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0689] (10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

[0690] (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;

[0691] (10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0692] (10*S*,17*E*)-12-cyclopropyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0693] (10*S*,17*E*)-8,10,12,14-tetramethyl-16-(2,2,2-trifluoroethoxy)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0694] {[(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0695] (10*S*,17*E*)-10,14,16-trimethyl-8-[(methylsulfanyl)methyl]-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0696] (10*S*,17*E*)-12-ethyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0697] 2-[(10*S*,17*E*)-16-ethoxy-8-ethyl-10,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0698] 2-{(10*S*,17*E*)-8-ethyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0699] (2*R*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0700] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0701] 2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0702] (10*S*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0703] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0704] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0705] 2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0706] 2-[(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0707] 2-[(10*S*,17*E*)-16-bromo-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0708] 2-{(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0709] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0710] (10*S*,17*E*)-16-{[3-(methanesulfonyl)cyclobutyl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0711] (10*S*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

[0712] (10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

[0713] 2-[(10*R*,19*E*)-18-ethoxy-22-fluoro-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0714] 2-{(11*S*,17*E*)-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0715] 2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0716] 2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0717] 2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0718] 2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0719] 2-[(10*R*,17*E*)-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0720] 2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0721] 2-[(10*R*,19*E*)-22-fluoro-8-methyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0722] (2*S*)-2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0723] 2-{(11*S*,17*E*)-6,8,11-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0724] 2-{(10*R*,17*E*)-6,8,10-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0725] {[(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0726] 2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0727] 2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,11-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0728] (10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0729] (2*S*)-2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0730] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;

[0731] (10*S*,17*E*)-12-ethyl-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0732] (10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0733] 2-[(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-(2,2,2-trifluoroethoxy)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0734] 2-{(10*R*,17*E*)-12-cyclopropyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0735] 2-{(11*S*,17*E*)-12-cyclopropyl-8,11-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0736] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0737] (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0738] 2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0739] 1-[(10*R*,17*E*)-16-ethoxy-14-(2-hydroxyethyl)-8,10-dimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0740] ethyl [(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]acetate;

[0741] (2*S*)-2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0742] (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,12,13,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-11(10*H*)-one;

[0743] 2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0744] 1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]-2-methylpropan-2-ol;

[0745] 2-{(10*S*,13*R*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0746] 2-{(10*S*,13*S*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0747] 2-{(17*E*)-10-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0748] 2-{(17*E*)-11-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0749] (2*S*)-1-{(10*R*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0750] (2*S*)-2-[(11*S*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0751] (2*S*)-2-[(10*R*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0752] (2*S*)-2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0753] (2*S*)-2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;

[0754] 2-{(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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}acetamide;

[0755] (10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

[0756] 2-[(8a*R*,19*E*)-1-(cyclopropylmethoxy)-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0757] (10*R*,18*E*)-17-ethoxy-8,15-dimethyl-2,8,11,12,14,15-hexahydro-10*H*-3,5-etheno-10,13-methanotripyrazolo[3,4-*g*:3',4'-*k*:4",3"-*o*][1,5]oxazacyclohexadecine;

[0758] {(17*E*)-14-(2-hydroxyethyl)-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-7-yl}acetonitrile;

[0759] (17*E*)-16-ethoxy-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno-10,12-methanotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0760] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0761] 2-[(8a*R*,9*R*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0762] 2-[(8a*R*,9*S*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0763] 2-[(19*E*)-18-ethoxy-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0764] 2-[(8a*R*,9*R*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0765] 2-[(8a*R*,9*S*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0766] 2-[(19*E*)-18-ethoxy-22-fluoro-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0767] 2-{(10*S*,17*E*)-8-cyclopropyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0768] (10*S*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0769] (10*R*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0770] (10*R*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0771] (10*S*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

[0772] 2-{(10*R*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0773] 2-[(8a*R*,9*S*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0774] 2-[(8a*R*,9*R*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0775] 2-[(19*E*)-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0776] 2-[(8a*R*,9*R*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0777] 2-[(8a*R*,9*S*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

[0778] 2-[(19*E*)-22-fluoro-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

[0779] 2-{(10*R*,17*E*)-10-(hydroxymethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0780] 2-[(11*S*,17*E*)-16-ethoxy-11-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0781] 2-[(10*S*,17*E*)-16-ethoxy-10-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0782] 2-[(10*S*,17*E*)-16-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0783] 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}-2-methylpropan-2-ol;

[0784] 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-one;

[0785] (10*R*,17*E*)-14-(2-hydroxyethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-10-carbonitrile;

[0786] 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0787] 2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol:

[0788] (2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0789] (2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

[0790] 2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

[0791] 2-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

[0792] {[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

[0793] {[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

[0794] 2-{(10*S*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0795] 2-{(10*R*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0796] 2-{(10*S*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0797] 2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0798] (4a*S*,7a*S*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

[0799] (4a*R*,7a*R*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

[0800] (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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0801] 2-{(11*R*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0802] 2-{(10*S*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

[0803] 2-[(11*R*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0804] 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0805] {[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

[0806] 2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0807] (2*S*)-2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0808] 2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0809] (2*S*)-2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0810] (10*S*,17*E*)-16-ethoxy-12-ethyl-14-(2-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile;

[0811] 2-[(10*S*,17*E*)-16-ethoxy-6-ethynyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0812] 2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0813] 2-[(10*S*,17*E*)-16-(ethylamino)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0814] (2*S*)-1-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

[0815] 2-[(10*S*,17*E*)-6-amino-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

[0816] (2*S*)-2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

[0817] 2,2'-[(10*S*,17*E*)-10,12-dimethyl-16-[(propan-2-yl)oxy]-10,11,12,13-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-8,14(2*H*)-diyl]di(ethan-1-ol);

[0818] (17*E*)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0819] 2-[(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(8*H*)-yl]-*N*-ethylacetamide;

[0820] (17*E*)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

[0821] (17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0822] (10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0823] (10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

[0824] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]oxazole-16-carbonitrile;

[0825] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]thiazole-16-carbonitrile;

[0826] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]oxazole-16-carbonitrile;

[0827] (10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]thiazole-16-carbonitrile; and

[0828] (10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno|1,4|dioxacyclopentadecino|10,11-*c*:15,14-*c'*:6,7-*c''*|tripyrazole;

[0829] or a pharmaceutically acceptable salt thereof.

[0830]

[0831] 34. The compound of clause 1 or 2, selected from the group consisting of (17*E*)-8,15,16-trimethyl-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0832] (17*E*)-8,15,16-trimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0833] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]propan-2-one;

[0834] 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-2-methylpropan-2-ol;

[0835] 2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]ethan-1-ol;

[0836] (17*E*)-8,16-dimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0837] (10*S*,17*E*)-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0838] (17*E*)-8,15,16-trimethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0839] 1-[(17*E*)-8,15,16-trimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0840] (17*E*)-8,12,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0841] 1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

[0842] (10*S*,17*E*)-8,10,12,15,16-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0843] 2-[(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

[0844] 2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

[0845] (10*S*,17*E*)-12-ethyl-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0846] 1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]propan-1-one;

[0847] 2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,17*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-17-yl]ethan-1-ol;

[0848] (13*E*)-3-methyl-3,5,6,7,8,16-hexahydro-9,12-(azeno)-17,19-ethenodipyrazolo[3,4-*l*:4',3'-*p*][1,6]oxazacycloheptadecine;

[0849] (18*E*)-8-methyl-2,8,10,11,12,13-hexahydro-3,5-ethenotripyrazolo[1,5-*f*:3',4'-*j*:4",3"-*n*][1,6]oxazacyclopentadecine;

[0850] (17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0851] 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15(2*H*)-yl]ethan-1-ol;

[0852] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]piperidin-3-ol;

[0853] (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-1-methylpiperidin-3-ol;

[0854] (17*E*)-8,9,16-trimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

[0855] (*rac*)-1,5-anhydro-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;

[0856] 1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;

[0857] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0858] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(4-methylpiperazin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0859] (20*E*)-8,18-dimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3",4":10',11';4"',3"':14',15'][1,5]dioxacyclopentadecino[6',7':3,4]pyrazolo[1,5-*a*]pyrazin-19(18*H*)-one;

[0860] (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(morpholin-4-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0861] 4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;

[0862] N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;

[0863] 2-methyl-4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;

[0864] 2-methyl-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0865] N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;

[0866] (17*E*)-8,10,16-trimethyl-15-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0867] (10*R*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0868] (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0869] (10*S*,17*E*)-8,10,12,14,15-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0870] (2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;

[0871] (10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0872] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0873] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0874] (10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*][1,2]thiazolo[3,4-*f*][1,4]oxazacyclopentadecine;

[0875] (10*S*,20*E*)-18-[2-(methanesulfonyl)ethyl]-8,10,12-trimethyl-2,8,10,11,12,13,16,17,18,19-decahydro-3,5-ethenopyrazino[1',2':1,5]pyrazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0876] (10*S*,17*E*)-16-cyclopropyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0877] (10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0878] (10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0879] (10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0880] (10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;

[0881] (10*R*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0882] (10*S*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

[0883] (10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole;

[0884] (10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole-16-carbonitrile;

[0885] (10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole;

[0886] (10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole-16-carbonitrile;

[0887] (10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;

[0888] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;

[0889] (10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;

[0890] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;

[0891] (10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole-16-carbonitrile;

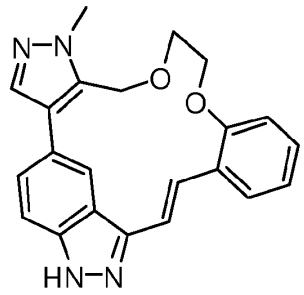
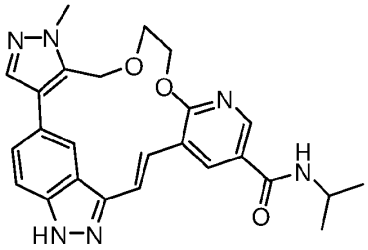
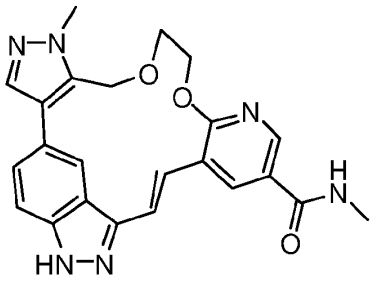
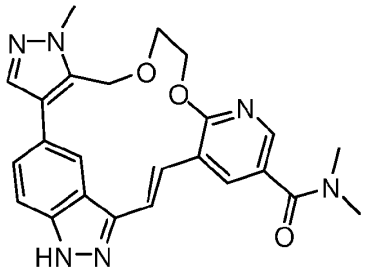
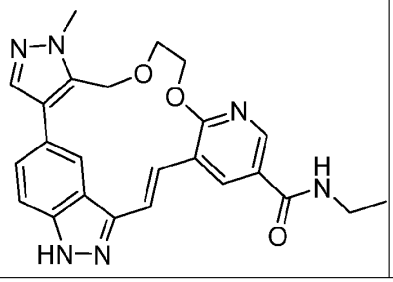
[0892] (17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;

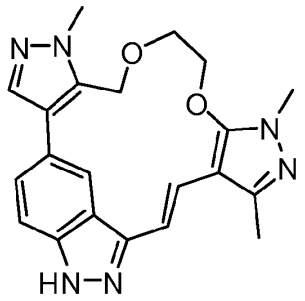
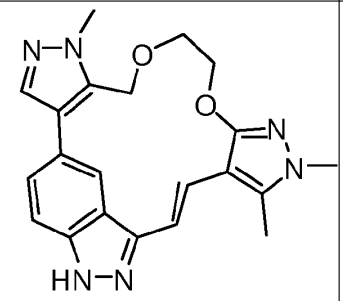
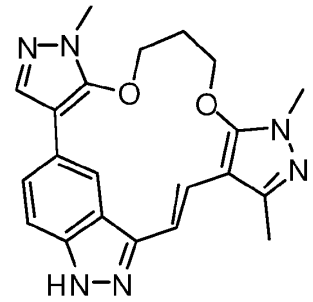
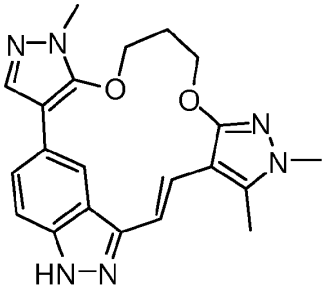
[0893] (17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole; and

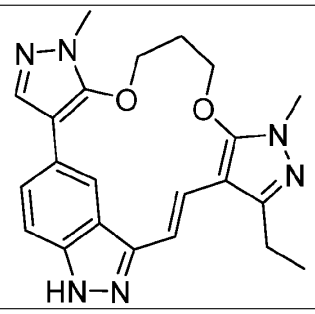
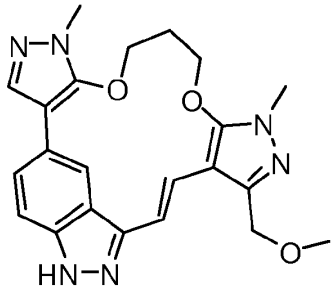
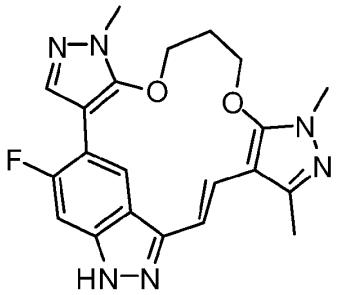
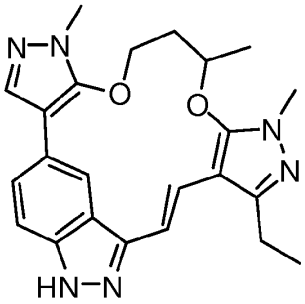
[0894] (17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;

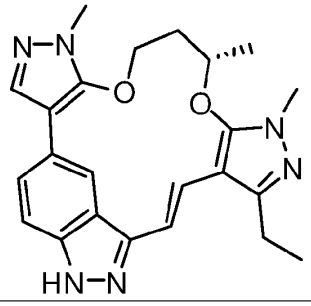
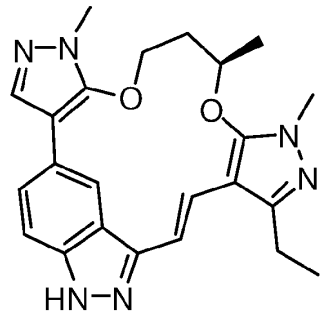
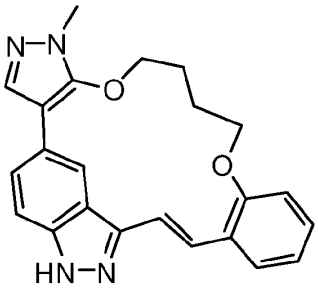
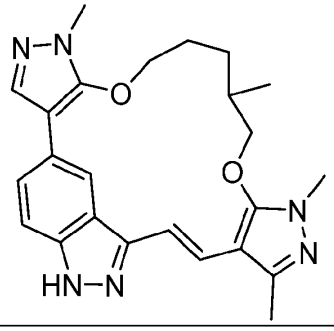
[0895] or a pharmaceutically acceptable salt thereof.

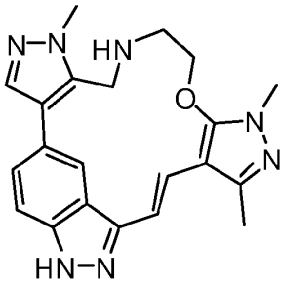
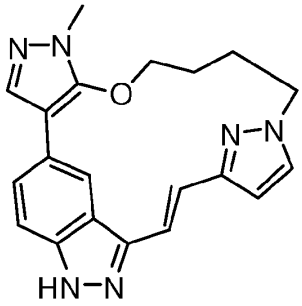
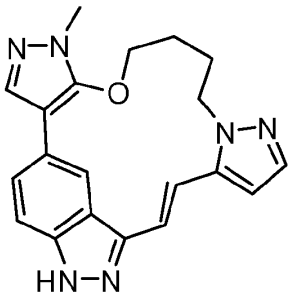
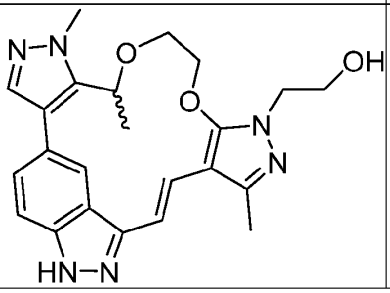
[0896] The following represent illustrative embodiments of compounds of Formula (I)-(XII):

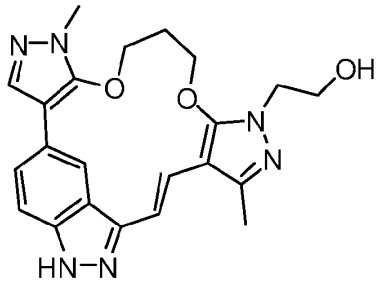
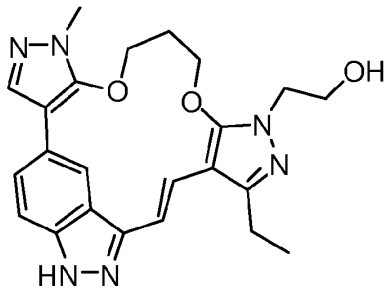
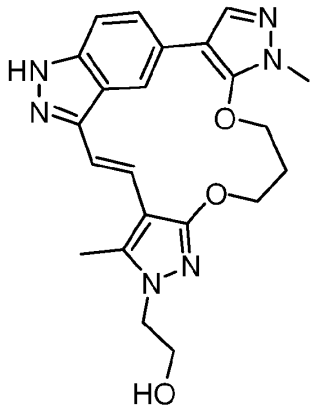
Ex #	Structure	Name
1		(11*E*)-1-methyl-1,18,19,21-tetrahydro-8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,4,12,13]benzodioxadiazacyclooctadecine
2		(18*E*)-8-methyl-*N*-(propan-2-yl)-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide
3		(18*E*)-*N*,8-dimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide
4		(18*E*)-*N*,*N*,8-trimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide
5		(18*E*)-*N*-ethyl-8-methyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide

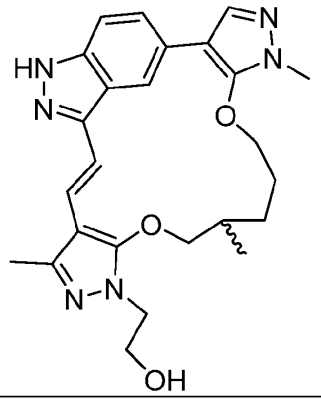
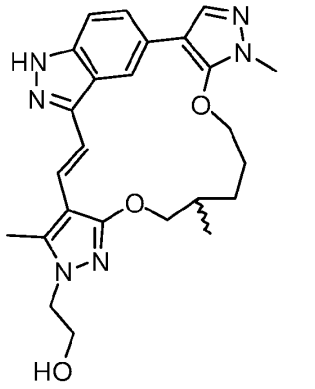
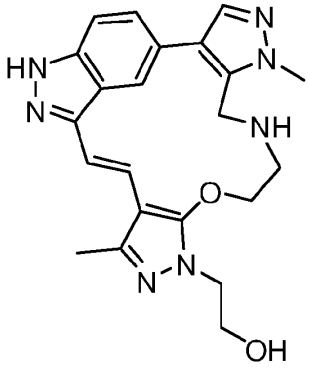
Ex #	Structure	Name
6		(17*E*)-8,14,16-trimethyl-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c*':6,7-*c*'']tripyrazole
7		(17*E*)-8,15,16-trimethyl-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c*':6,7-*c*'']tripyrazole
8		(17*E*)-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole
9		(17*E*)-8,15,16-trimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole

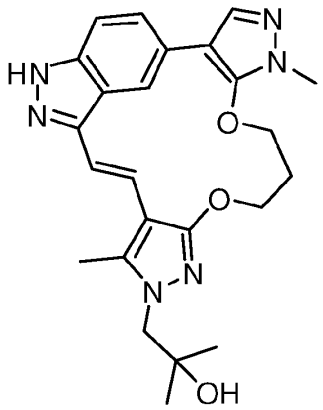
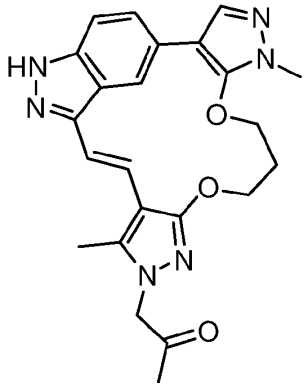
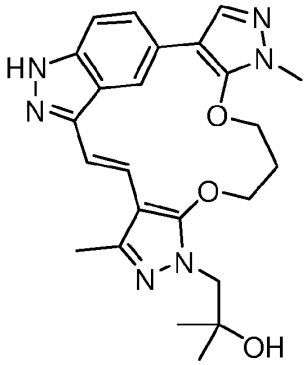
Ex #	Structure	Name
10		(17*E*)-16-ethyl-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
11		(17*E*)-16-(methoxymethyl)-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
12		(17*E*)-19-fluoro-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
13		(17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole

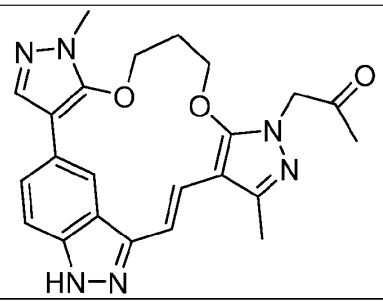
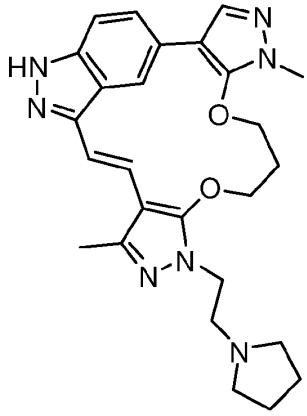
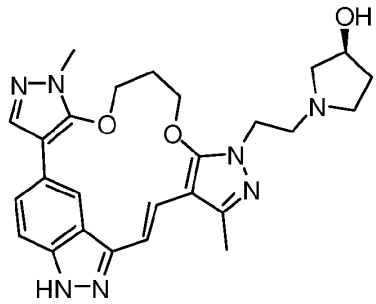
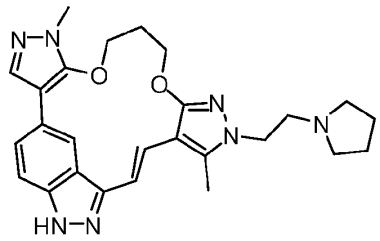
Ex #	Structure	Name
14		(12*S*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole
15		(12*R*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole
16		(11*E*)-1-methyl-18,19,20,21-tetrahydro-1*H*,8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*g*][1,6,13,14]benzodioxadiazacyclononadecine
17		(19*E*)-8,13,16,18-tetramethyl-2,11,12,13,14,16-hexahydro-8*H*,10*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c*':8,9-*c*'']tripyrazole

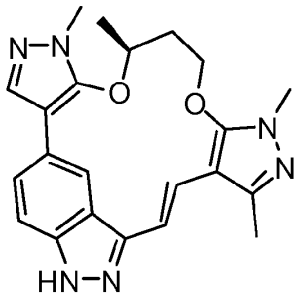
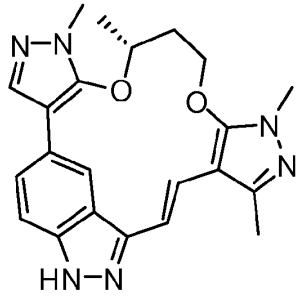
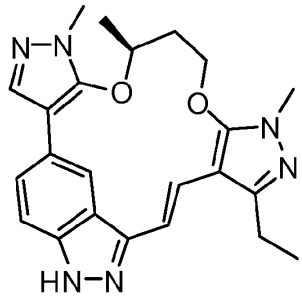
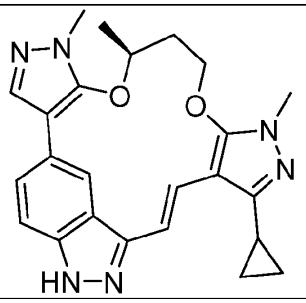
Ex #	Structure	Name
18		(17*E*)-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
19		(13*E*)-3-methyl-3,5,6,7,8,16-hexahydro-9,12-(azeno)-17,19-ethenodipyrazolo[3,4-*l*:4',3'-*p*][1,6]oxazacycloheptadecine
20		(18*E*)-8-methyl-2,8,10,11,12,13-hexahydro-3,5-ethenotripyrazolo[1,5-*f*:3',4'-*j*:4",3"-*n*][1,6]oxazacyclopentadecine
21		2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(2*H*)-yl]ethan-1-ol

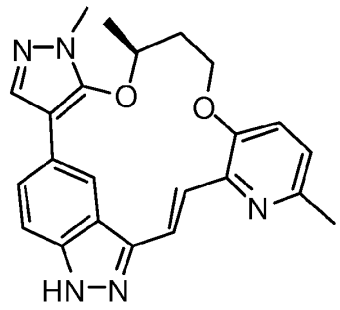
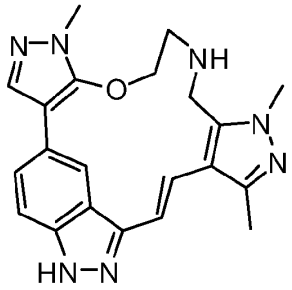
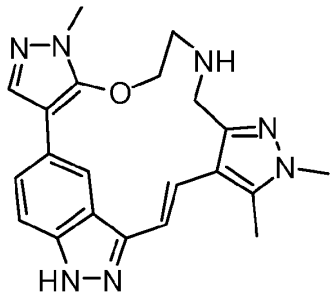
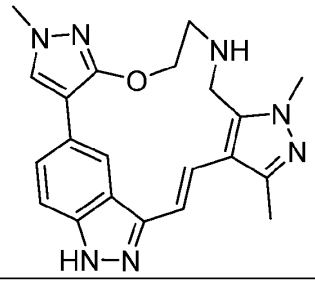
Ex #	Structure	Name
22		2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]ethan-1-ol
23		2-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]ethan-1-ol
24		2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-15-yl]ethan-1-ol

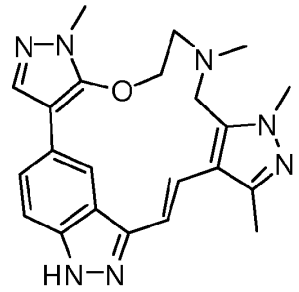
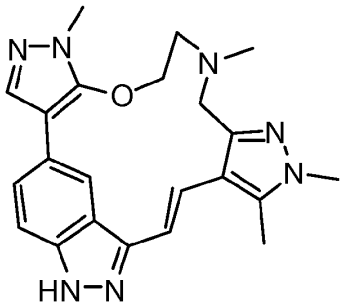
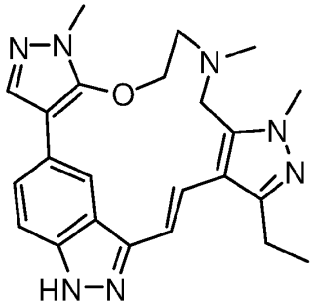
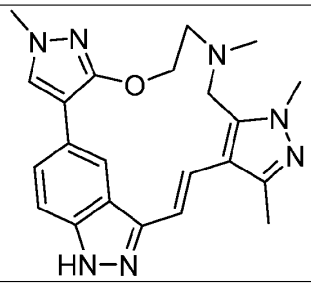
Ex #	Structure	Name
25		2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,16*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-16-yl]ethan-1-ol
26		2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,17*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-17-yl]ethan-1-ol
27		2-[(17*E*)-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

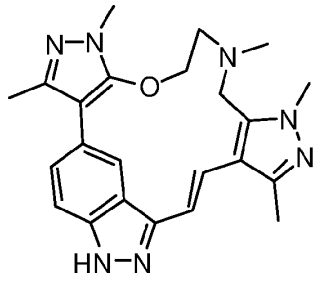
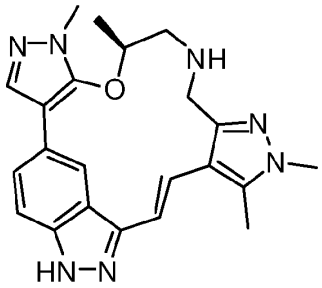
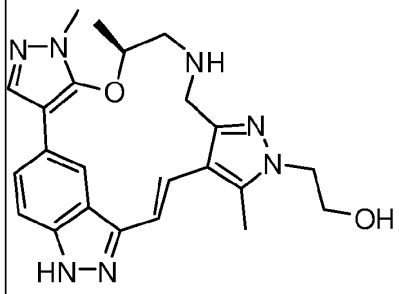
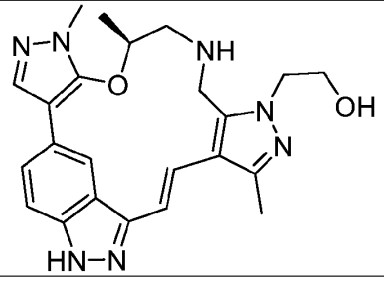
Ex #	Structure	Name
28		1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-2-methylpropan-2-ol
29		1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]propan-2-one
30		1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-2-methylpropan-2-ol

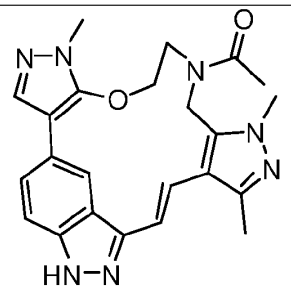
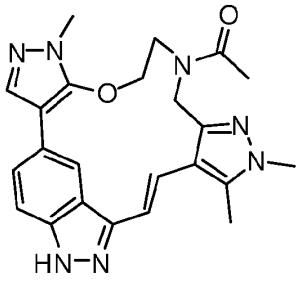
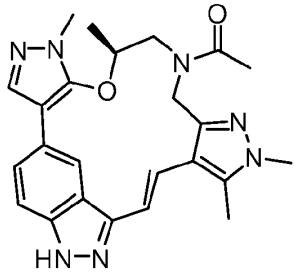
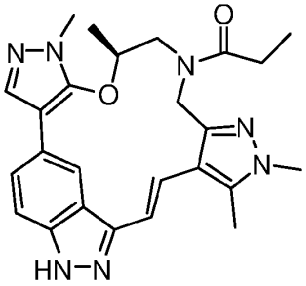
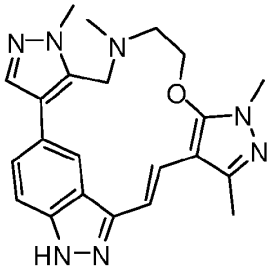
Ex #	Structure	Name
31		1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]propan-2-one
32		(17*E*)-8,16-dimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
33		(3*S*)-1-{2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol
34		(17*E*)-8,16-dimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole

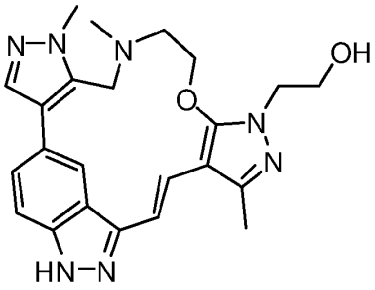
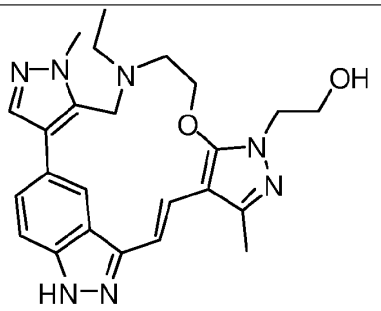
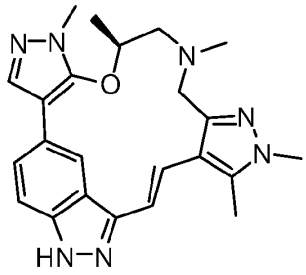
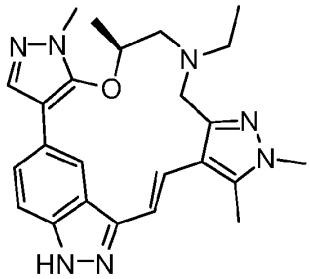
Ex #	Structure	Name
35		(10*S*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
36		(10*R*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
37		(10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
38		(10*S*,17*E*)-16-cyclopropyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole

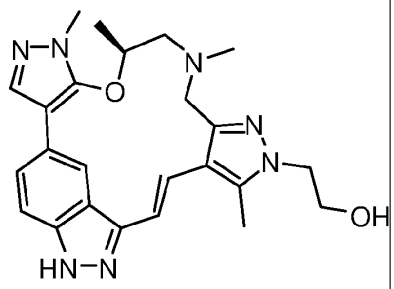
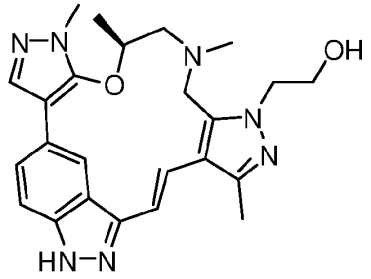
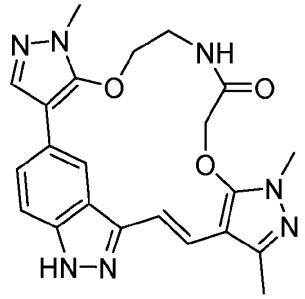
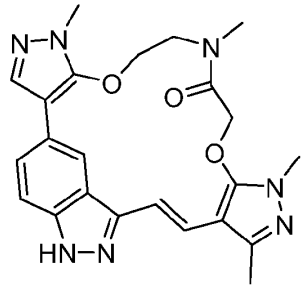
Ex #	Structure	Name
39		(10*S*,18*E*)-8,10,16-trimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,5]dioxacyclopentadecino[7,6-*b*]pyridine
40		(17*E*)-8,14,16-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
41		(17*E*)-8,15,16-trimethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
42		(17*E*)-7,14,16-trimethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

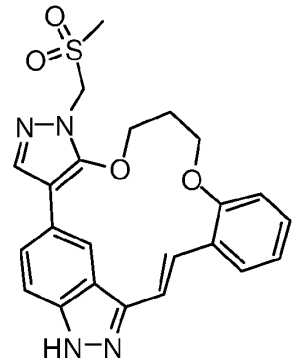
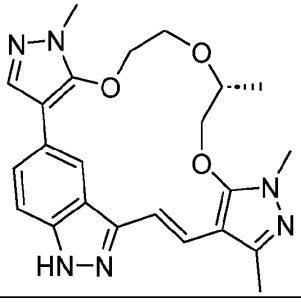
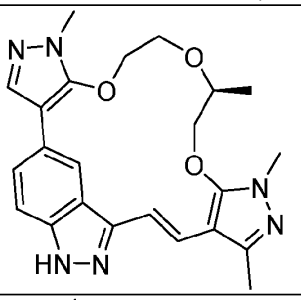
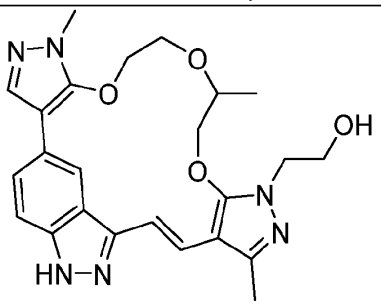
Ex #	Structure	Name
43		(17*E*)-8,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
44		(17*E*)-8,12,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
45		(17*E*)-16-ethyl-8,12,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
46		(17*E*)-7,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

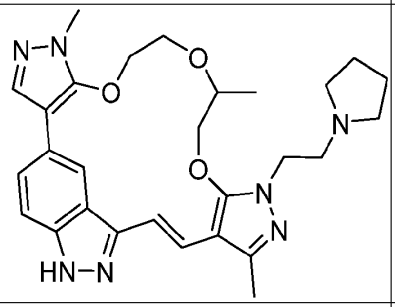
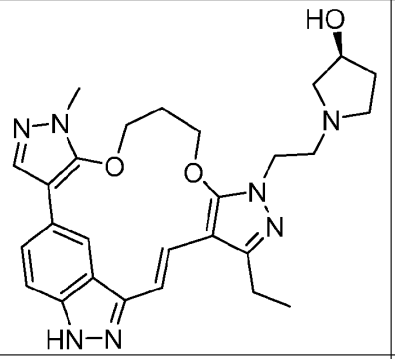
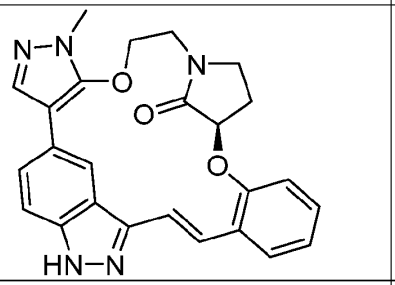
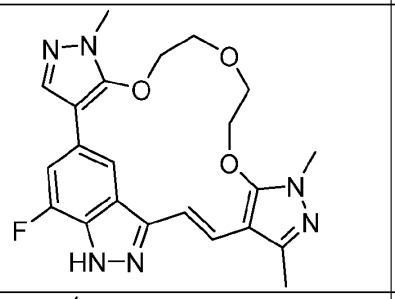
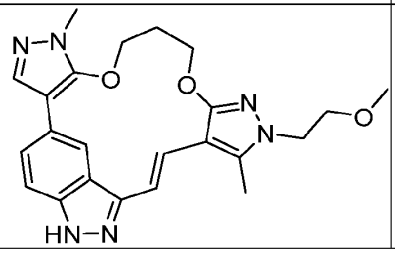
Ex #	Structure	Name
47		(17*E*)-6,8,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
48		(10*S*,17*E*)-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
49		2-[(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol
50		2-[(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

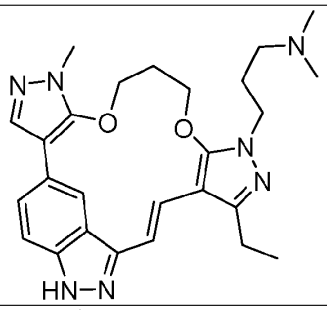
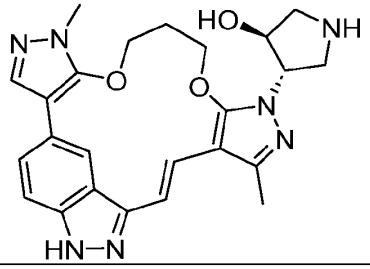
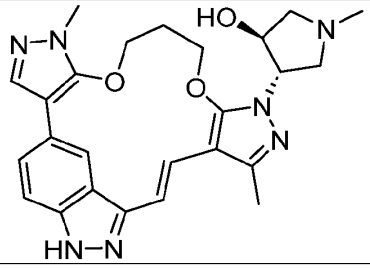
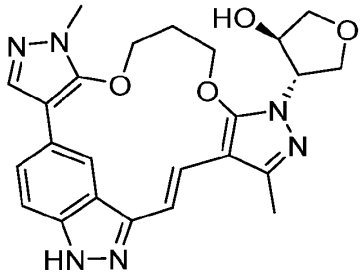
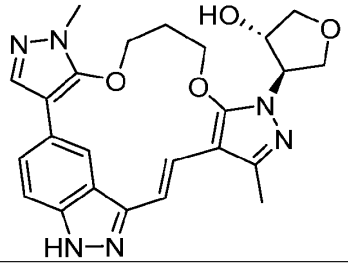
Ex #	Structure	Name
51		1-[(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one
52		1-[(17*E*)-8,15,16-trimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one
53		1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one
54		1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]propan-1-one
55		(17*E*)-8,10,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

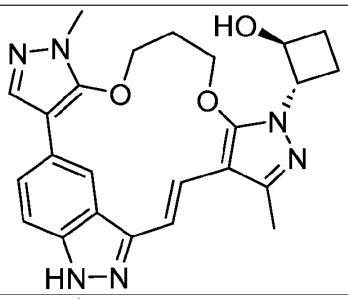
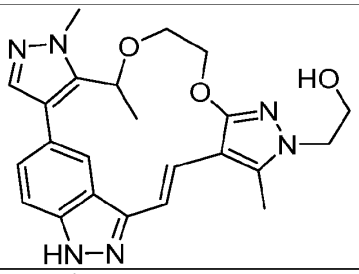
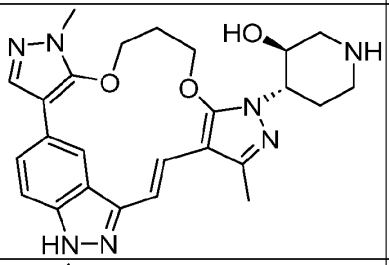
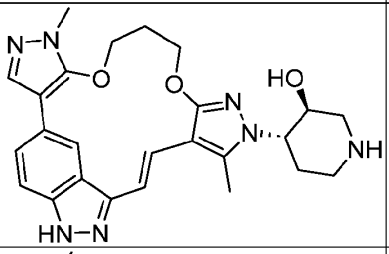
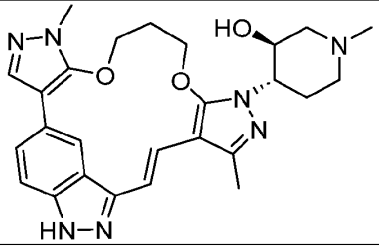
Ex #	Structure	Name
56		2-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
57		2-[(17*E*)-10-ethyl-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
58		(10*S*,17*E*)-8,10,12,15,16-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
59		(10*S*,17*E*)-12-ethyl-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

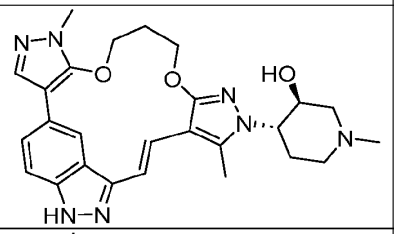
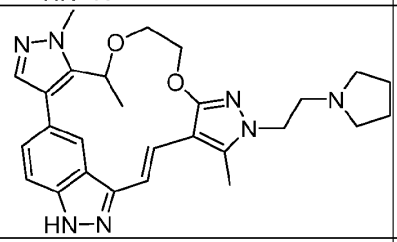
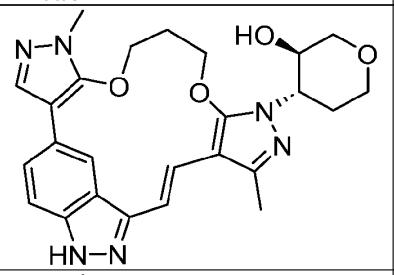
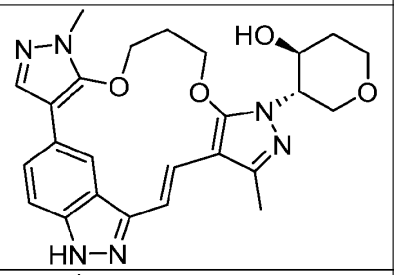
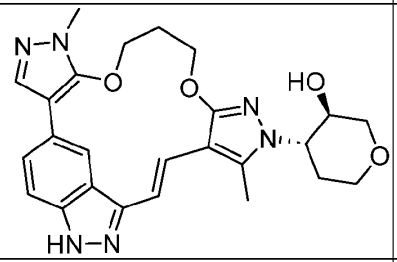
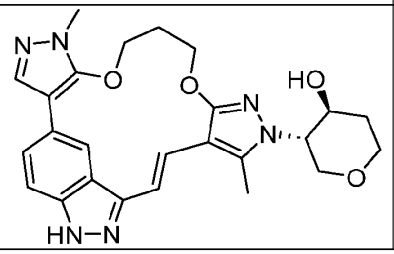
Ex #	Structure	Name
60		2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol
61		2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
62		(19*E*)-8,16,18-trimethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one
63		(19*E*)-8,12,16,18-tetramethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one

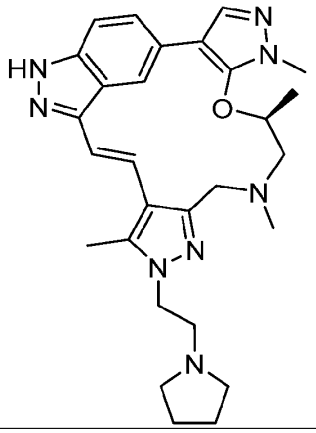
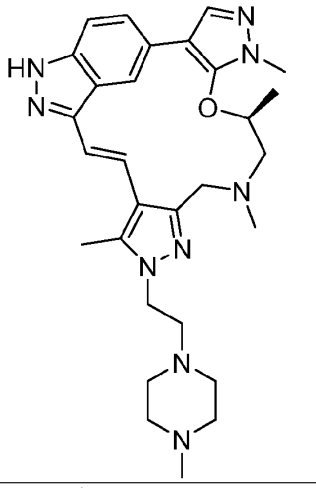
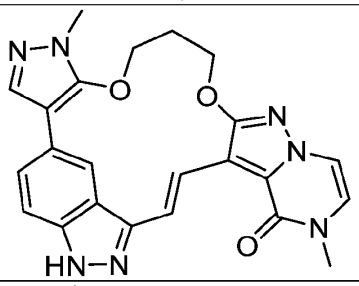
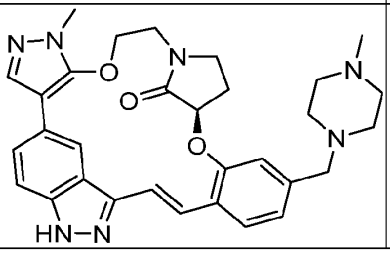
Ex #	Structure	Name
64		(11*E*)-1-[(methanesulfonyl)methyl]-19,20-dihydro-1*H*,8*H*,18*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,5,12,13]benzodioxadiazacyclooctadecine
65		(13R,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole
66		(13S,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole
67		2-[(19E)-8,13,18-trimethyl-2,8,10,11,13,14-hexahydro-16H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazol-16-yl]ethan-1-ol

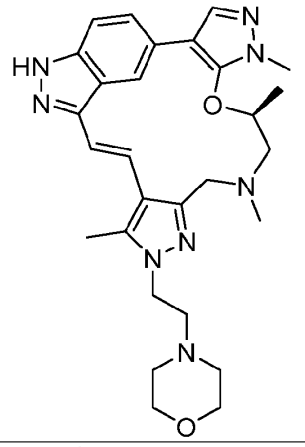
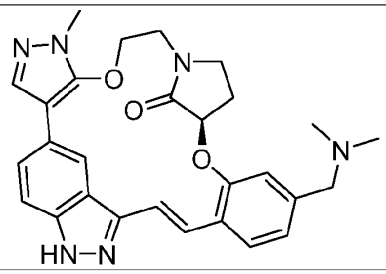
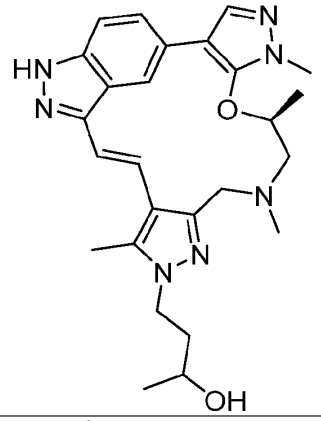
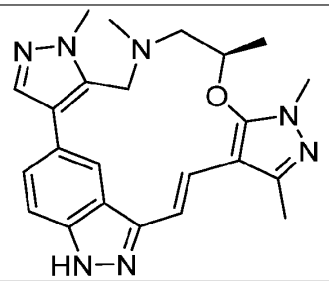
Ex #	Structure	Name
68		(19*E*)-8,13,18-trimethyl-16-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c*′:8,9-*c*″]tripyrazole
69		(3*S*)-1-{2-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol
70		(10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
71		(19*E*)-22-fluoro-8,16,18-trimethyl-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c*′:8,9-*c*″]tripyrazole
72		(17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole

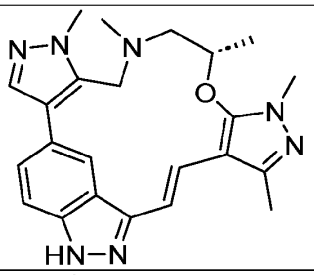
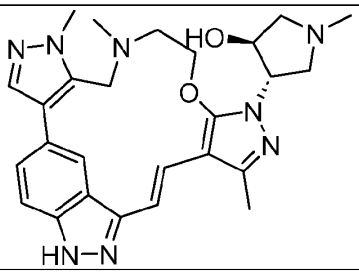
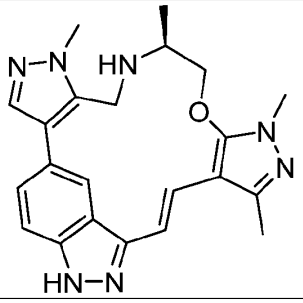
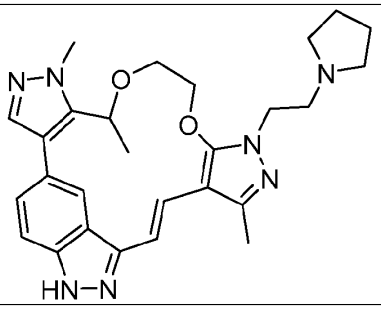
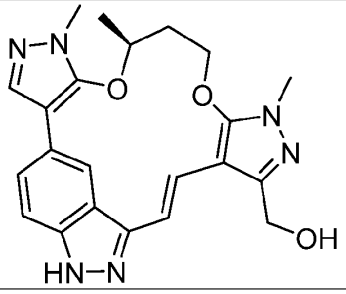
Ex #	Structure	Name
73		3-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]-*N*,*N*-dimethylpropan-1-amine
74		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]pyrrolidin-3-ol
75		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]-1-methylpyrrolidin-3-ol
76		(3*R*,4*S*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]oxolan-3-ol
77		(3*S*,4*R*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazol-14-yl]oxolan-3-ol

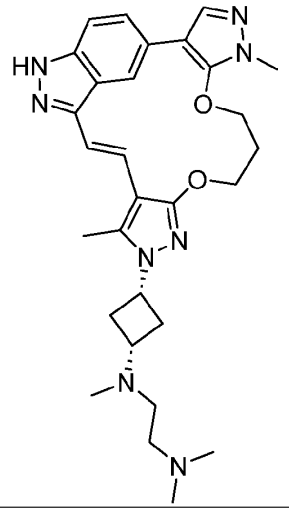
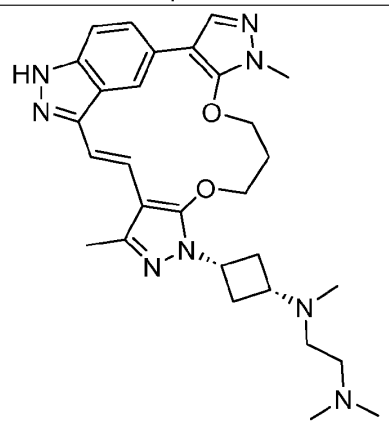
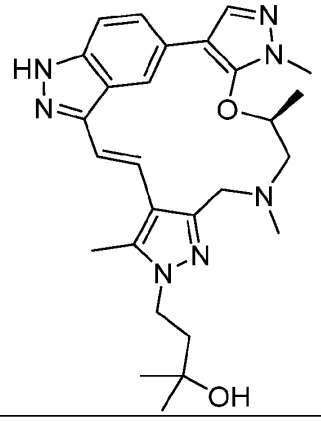
Ex #	Structure	Name
78		(*rac*)-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutan-1-ol
79		2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15(2*H*)-yl]ethan-1-ol
80		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol
81		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]piperidin-3-ol
82		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol

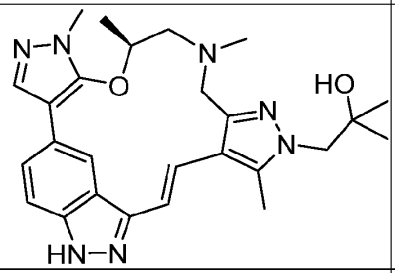
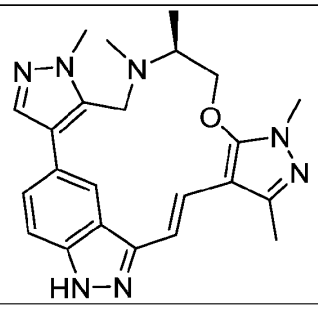
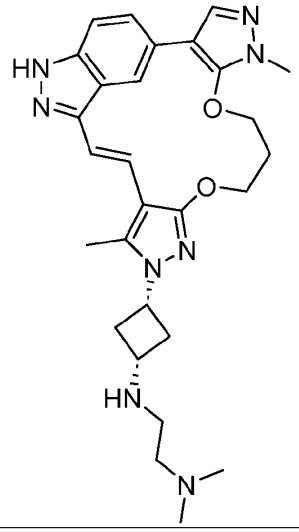
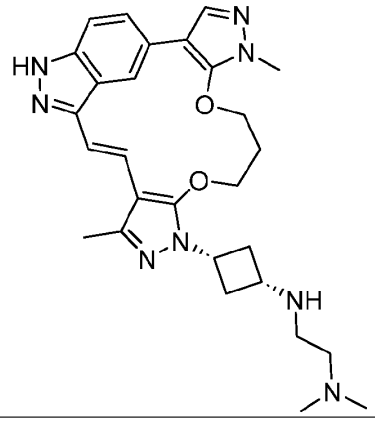
Ex #	Structure	Name
83		(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-1-methylpiperidin-3-ol
84		(17*E*)-8,9,16-trimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
85		(*rac*)-1,5-anhydr-3o-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol
86		(*rac*)-1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol
87		(*rac*)-1,5-anhydro-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol
88		1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol

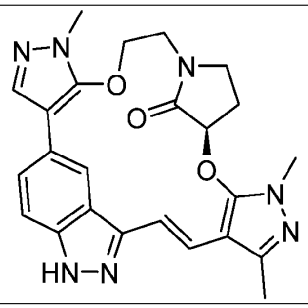
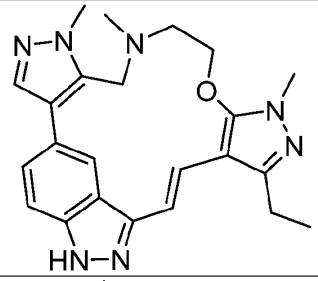
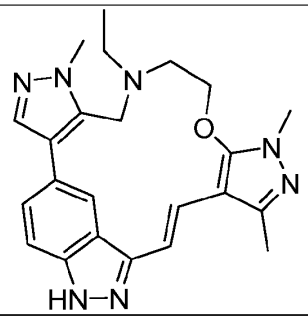
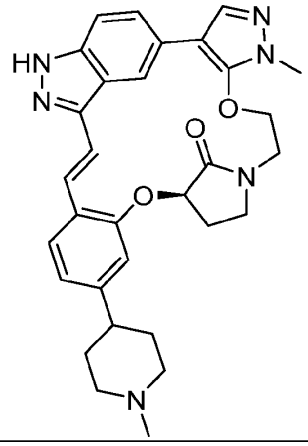
Ex #	Structure	Name
89		(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
90		(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(4-methylpiperazin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
91		(20*E*)-8,18-dimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3",4":10',11';4"',3"':14',15'][1,5]dioxacyclopentadecino[6',7':3,4]pyrazolo[1,5-*a*]pyrazin-19(18*H*)-one
92		(10*R*,16*E*)-3-methyl-13-[(4-methylpiperazin-1-yl)methyl]-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one

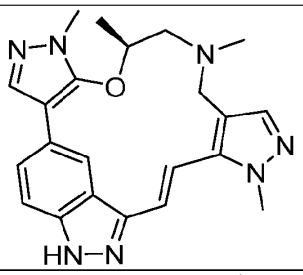
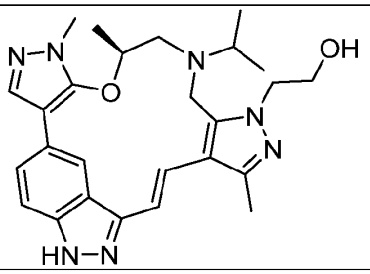
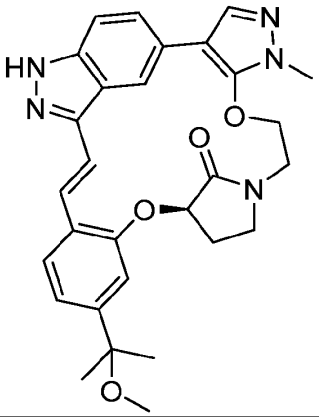
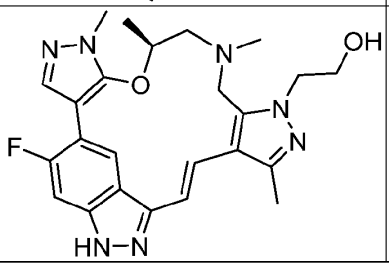
Ex #	Structure	Name
93		(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(morpholin-4-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
94		(10*R*,16*E*)-13-[(dimethylamino)methyl]-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
95		4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol
96		(12*R*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

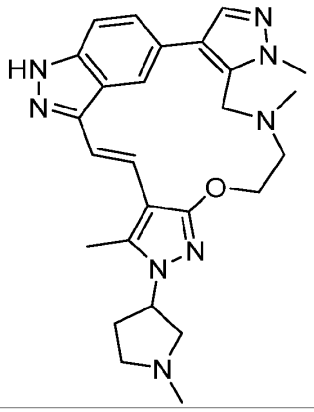
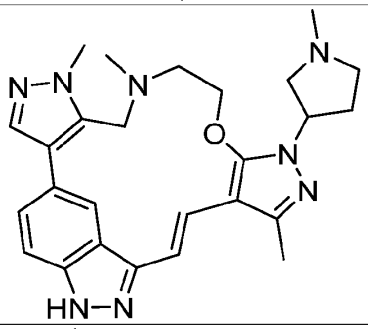
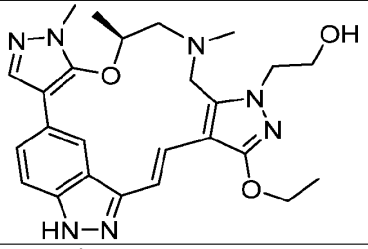
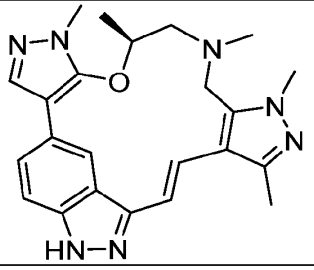
Ex #	Structure	Name
97		(12*S*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
98		(rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol
99		(11*S*,17*E*)-8,11,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
100		(17*E*)-8,9,16-trimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
101		[(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-16-yl]methanol

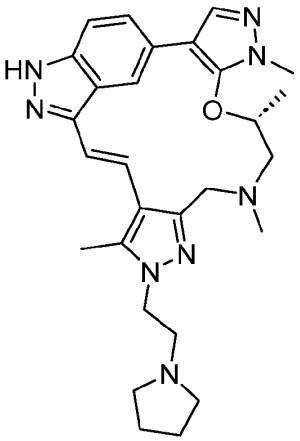
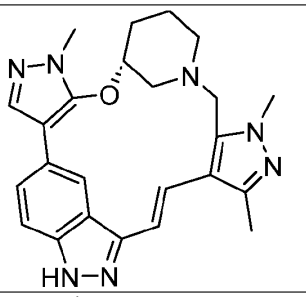
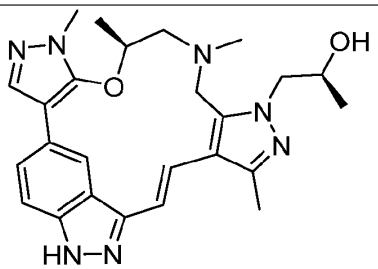
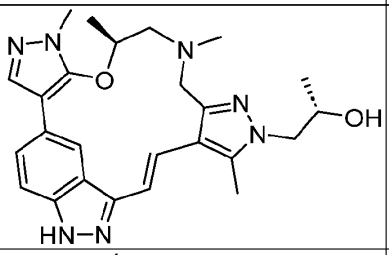
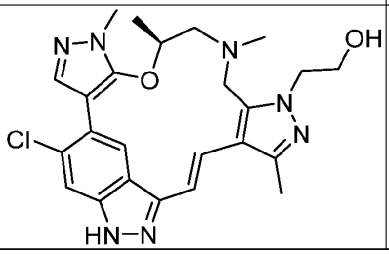
Ex #	Structure	Name
102		N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine
103		N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine
104		2-methyl-4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol

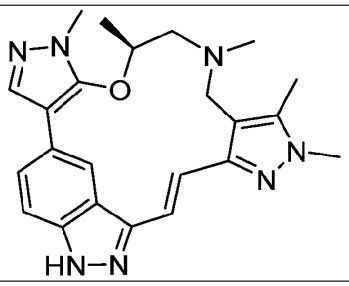
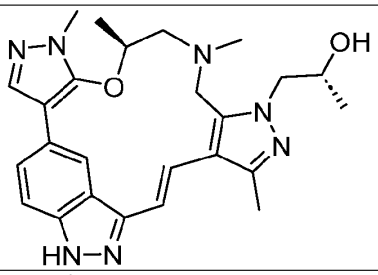
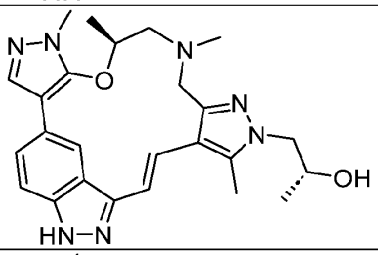
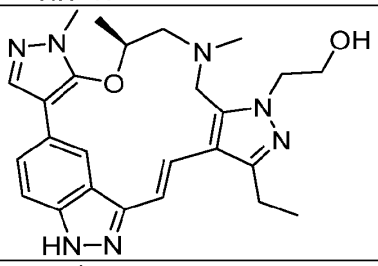
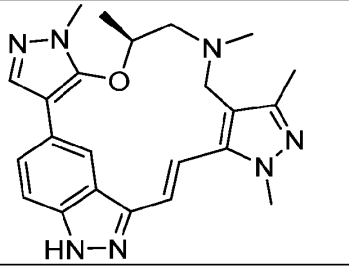
Ex #	Structure	Name
105		2-methyl-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol
106		(11*S*,17*E*)-8,10,11,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
107		N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine
108		N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine

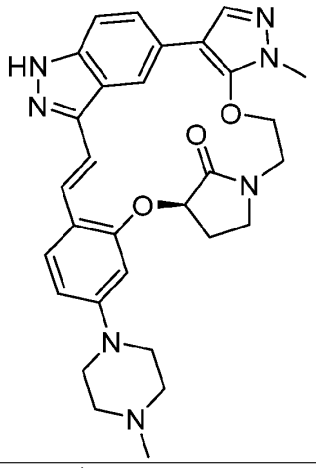
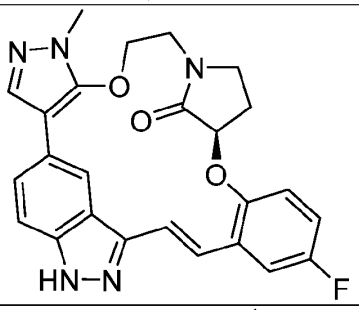
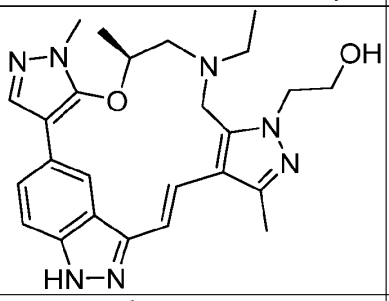
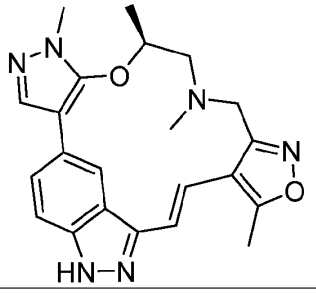
Ex #	Structure	Name
109		(10*R*,15*E*)-3,12,14-trimethyl-5,6,9,10,12,18-hexahydro-3*H*,8*H*-19,21-etheno-7,10-methanotripyrazolo[3,4-*i*:3',4'-*m*:4",3"-*q*][1,8,4]dioxazacyclooctadecin-24-one
110		(17*E*)-16-ethyl-8,10,14-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
111		(17*E*)-10-ethyl-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
112		(10*R*,16*E*)-3-methyl-13-(1-methylpiperidin-4-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one

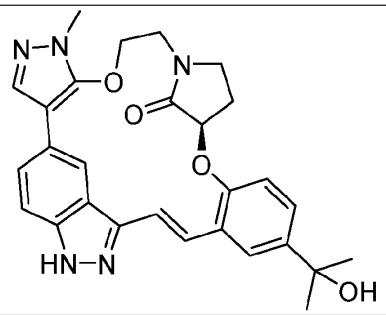
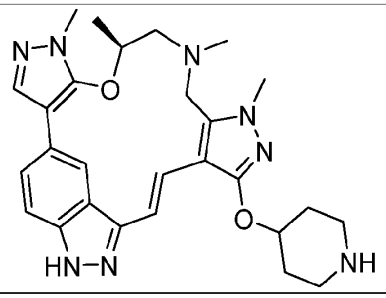
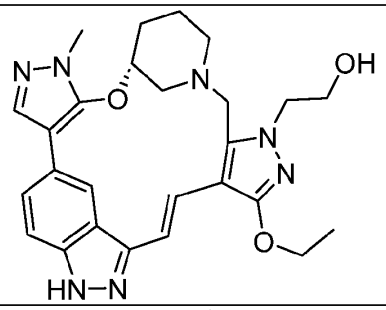
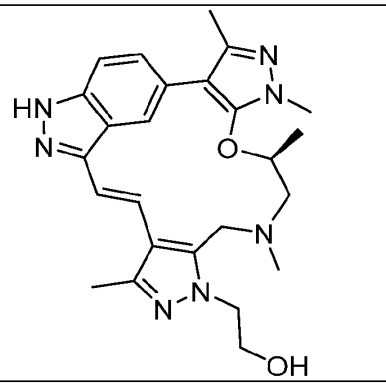
Ex #	Structure	Name
113		(10*S*,17*E*)-8,10,12,16-tetramethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
114		2-[(10*S*,17*E*)-8,10,16-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
115		(10*R*,16*E*)-13-(2-methoxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
116		2-[(10*S*,17*E*)-19-fluoro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

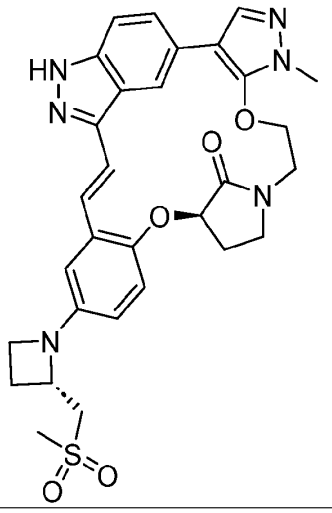
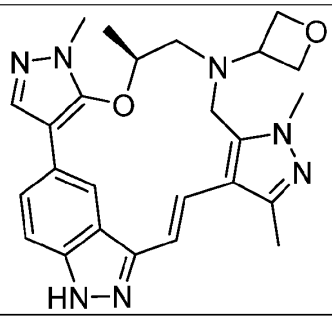
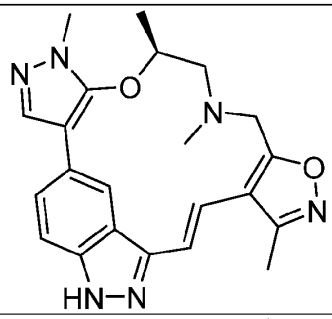
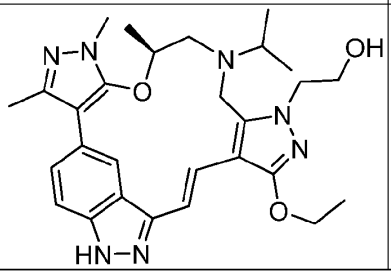
Ex #	Structure	Name
117		(17*E*)-8,10,16-trimethyl-15-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
118		(17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
119		2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
120		(10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

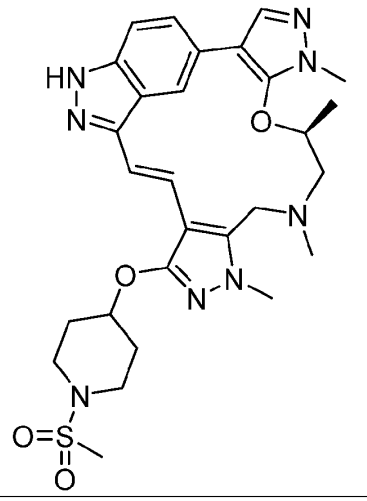
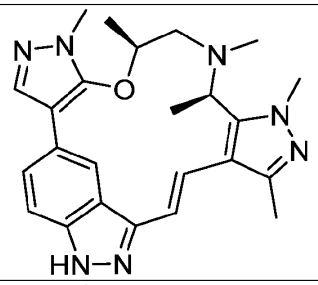
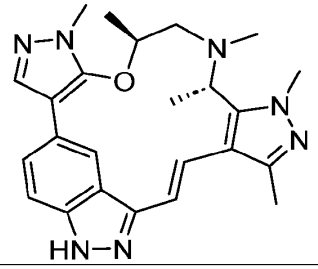
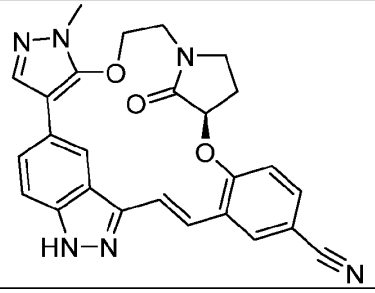
Ex #	Structure	Name
121		(10*R*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
122		(10*R*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine
123		(2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
124		(2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol
125		2-[(10*S*,17*E*)-19-chloro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

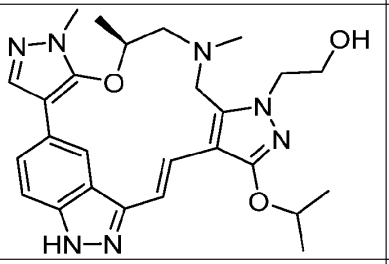
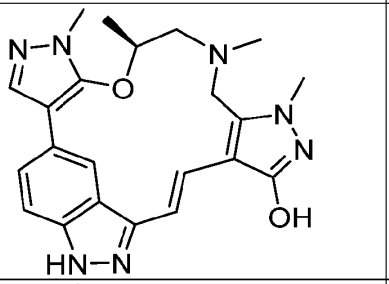
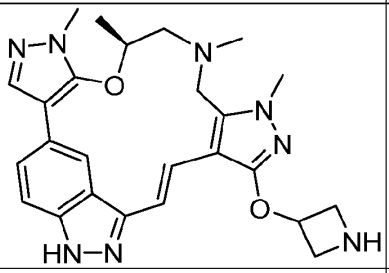
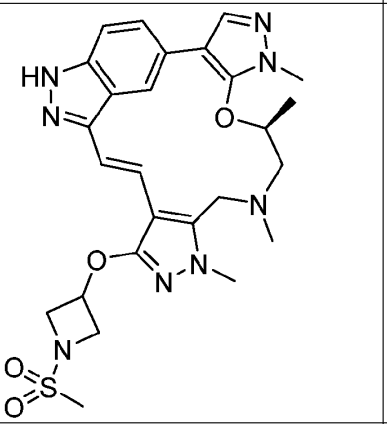
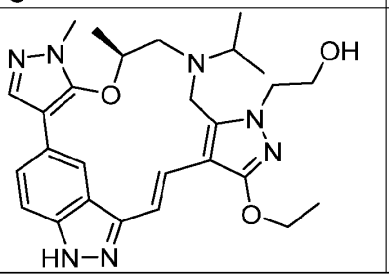
Ex #	Structure	Name
126		(10*S*,17*E*)-8,10,12,14,15-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
127		(2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol
128		(2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol
129		2-[(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
130		(10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

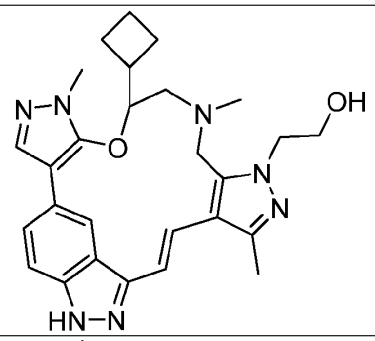
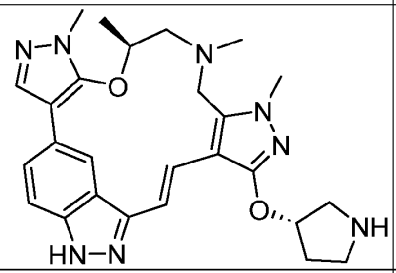
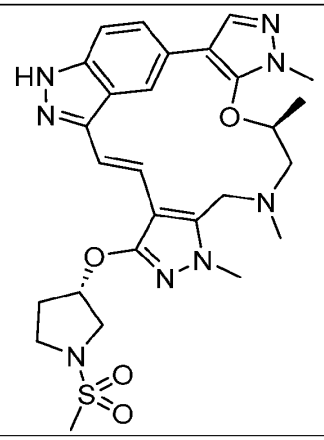
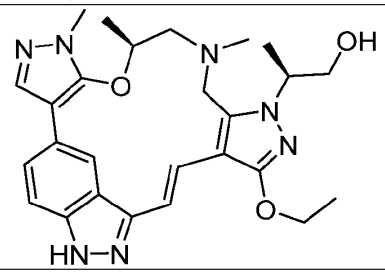
Ex #	Structure	Name
131		(10*R*,16*E*)-3-methyl-13-(4-methylpiperazin-1-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
132		(10*R*,16*E*)-14-fluoro-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
133		2-[(10*S*,17*E*)-12-ethyl-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
134		(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine

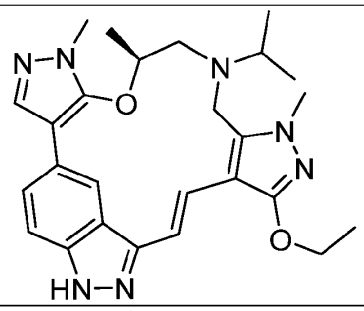
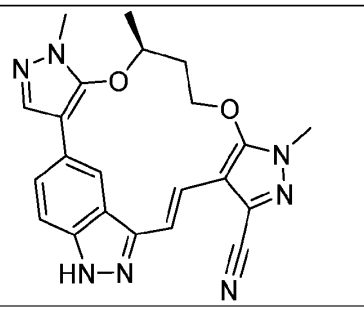
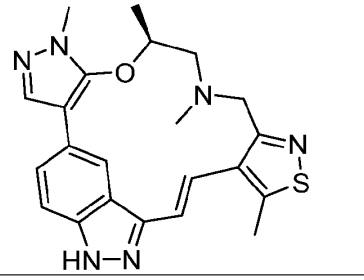
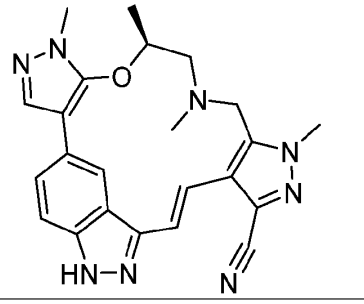
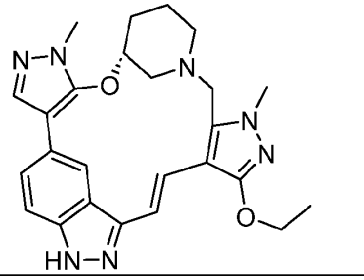
Ex #	Structure	Name
135		(10*R*,16*E*)-14-(2-hydroxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
136		(10*S*,17*E*)-8,10,12,14-tetramethyl-16-[(piperidin-4-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
137		2-[(10*R*,19*E*)-18-ethoxy-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
138		2-[(10*S*,17*E*)-6,8,10,12,16-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

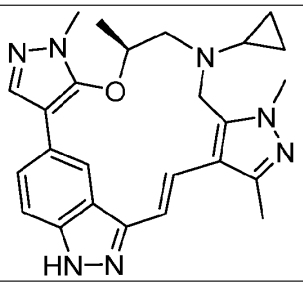
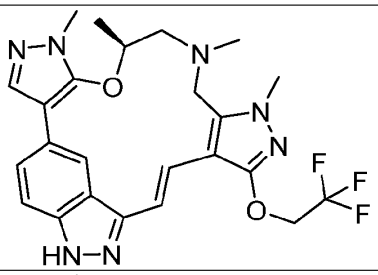
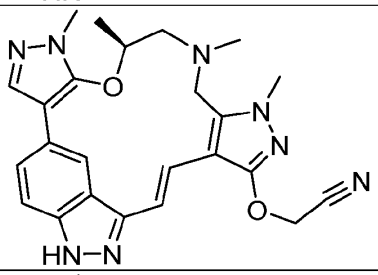
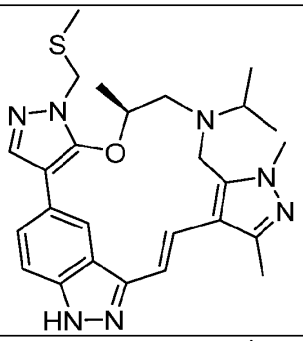
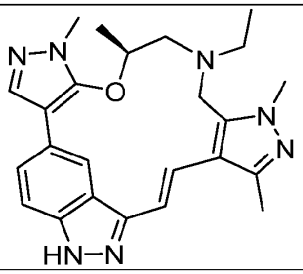
Ex #	Structure	Name
139		(10*R*,16*E*)-14-{(2*S*)-2-[(methanesulfonyl)methyl]azetidin-1-yl}-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one
140		(10*S*,17*E*)-8,10,14,16-tetramethyl-12-(oxetan-3-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
141		(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
142		2-[(10*S*,17*E*)-16-ethoxy-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

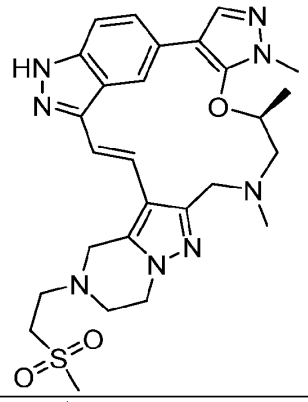
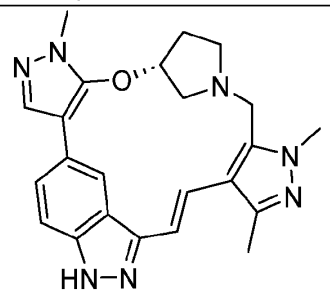
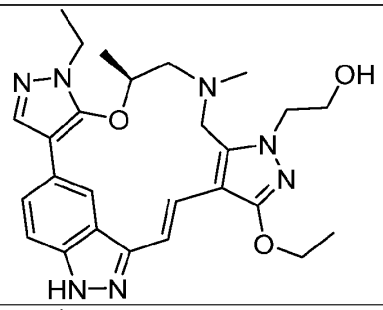
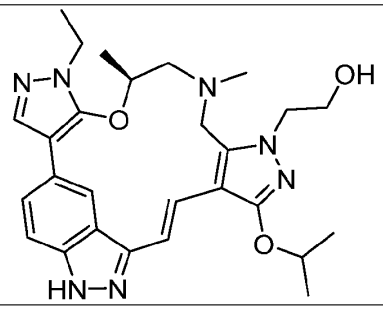
Ex #	Structure	Name
143		(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
144		(10*S*,13*R*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
145		(10*S*,13*S*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
146		(10*R*,16*E*)-3-methyl-25-oxo-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine-14-carbonitrile

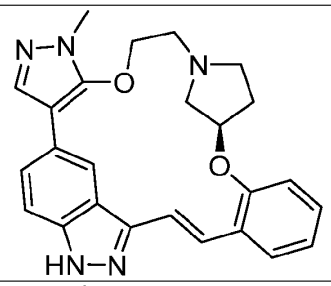
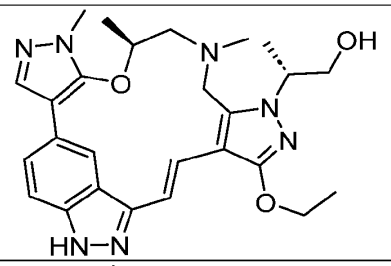
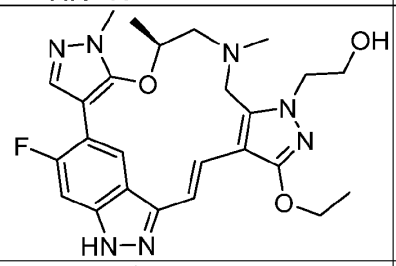
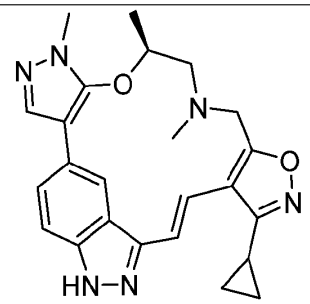
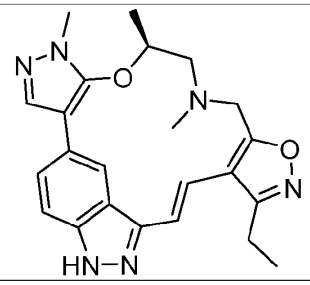
Ex #	Structure	Name
147		2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
148		(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol
149		(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
150		(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
151		2-[(10*S*,17*E*)-16-ethoxy-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

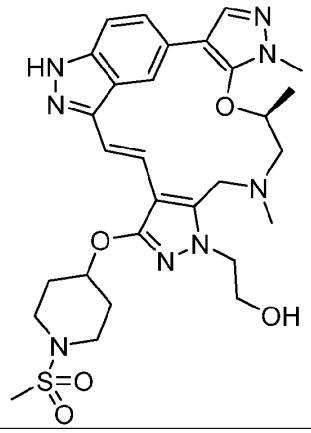
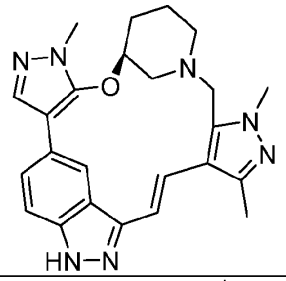
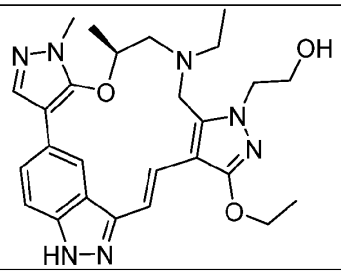
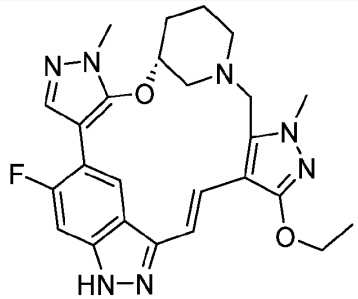
Ex #	Structure	Name
152		2-[(17*E*)-10-cyclobutyl-8,12,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
153		(10*S*,17*E*)-8,10,12,14-tetramethyl-16-{[(3*S*)-pyrrolidin-3-yl]oxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
154		(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
155		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol

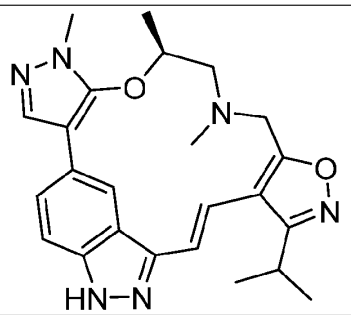
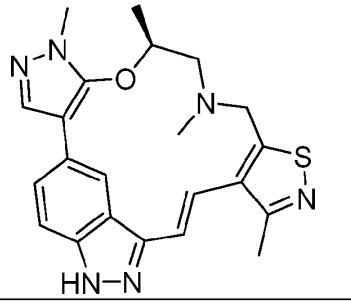
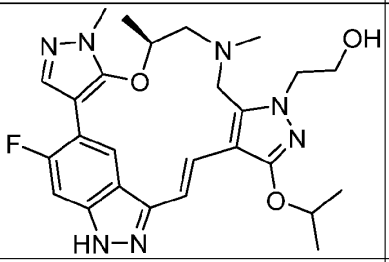
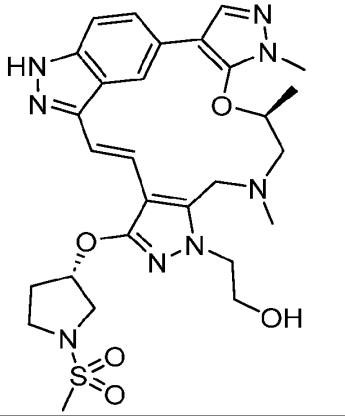
Ex #	Structure	Name
156		(10*S*,17*E*)-16-ethoxy-8,10,14-trimethyl-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
157		(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile
158		(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*][1,2]thiazolo[3,4-*f*][1,4]oxazacyclopentadecine
159		(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile
160		(10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine

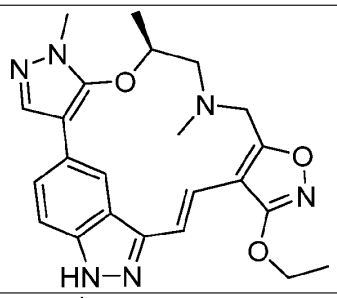
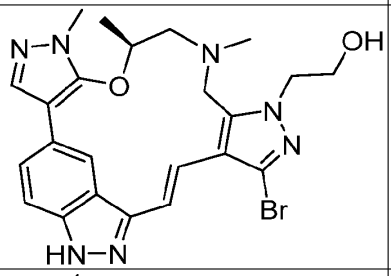
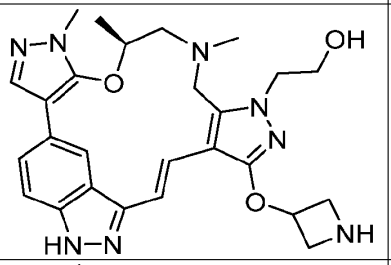
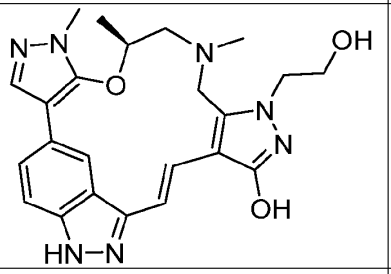
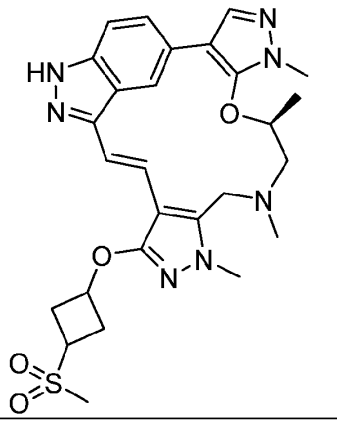
Ex #	Structure	Name
161		(10*S*,17*E*)-12-cyclopropyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
162		(10*S*,17*E*)-8,10,12,14-tetramethyl-16-(2,2,2-trifluoroethoxy)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
163		{[(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
164		(10*S*,17*E*)-10,14,16-trimethyl-8-[(methylsulfanyl)methyl]-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
165		(10*S*,17*E*)-12-ethyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

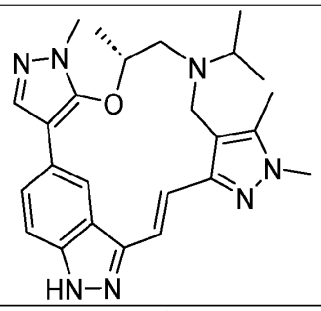
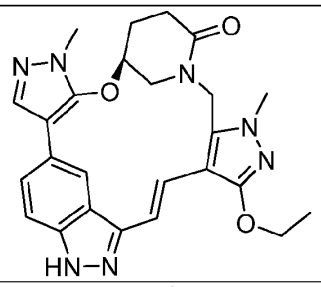
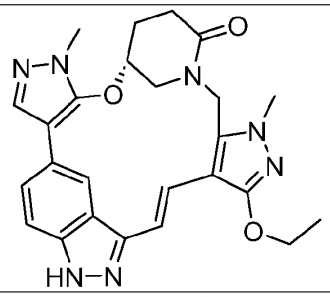
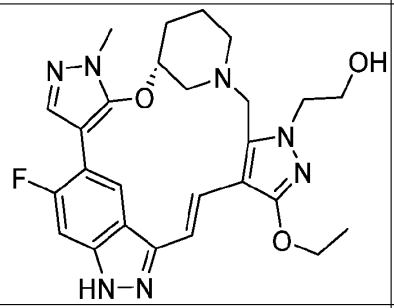
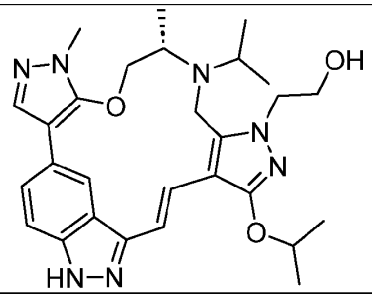
Ex #	Structure	Name
166		(10*S*,20*E*)-18-[2-(methanesulfonyl)ethyl]-8,10,12-trimethyl-2,8,10,11,12,13,16,17,18,19-decahydro-3,5-ethenopyrazino[1',2':1,5]pyrazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
167		(10*R*,18*E*)-8,15,17-trimethyl-2,8,11,12,14,15-hexahydro-10*H*-3,5-etheno-10,13-methanotripyrazolo[3,4-*g*:3',4'-*k*:4",3"-*o*][1,5]oxazacyclohexadecine
168		2-[(10*S*,17*E*)-16-ethoxy-8-ethyl-10,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
169		2-{(10*S*,17*E*)-8-ethyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

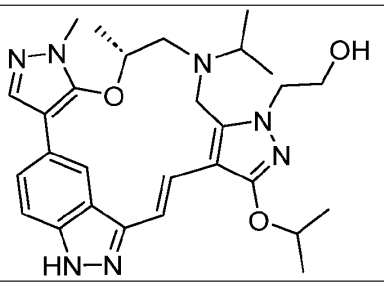
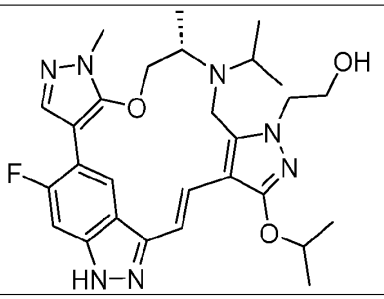
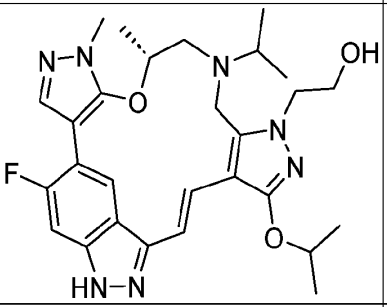
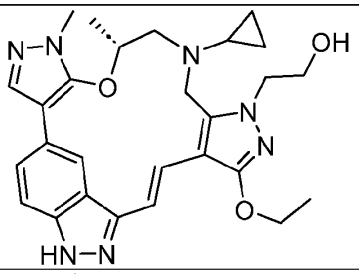
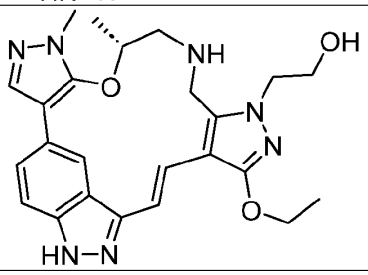
Ex #	Structure	Name
170		(10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine
171		(2*R*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
172		2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
173		(10*S*,17*E*)-16-cyclopropyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
174		(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine

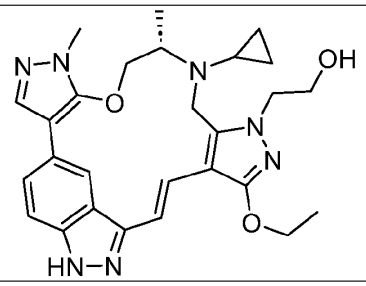
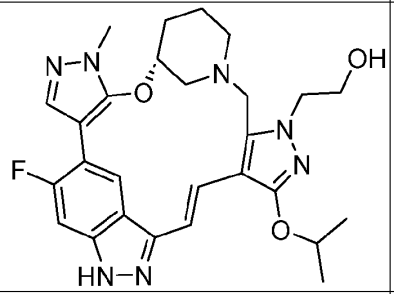
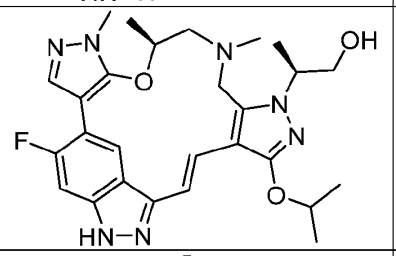
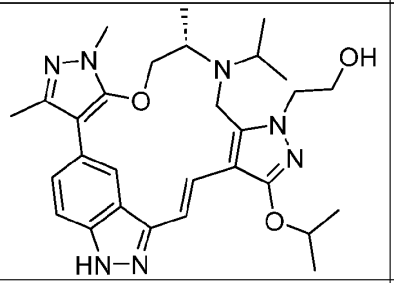
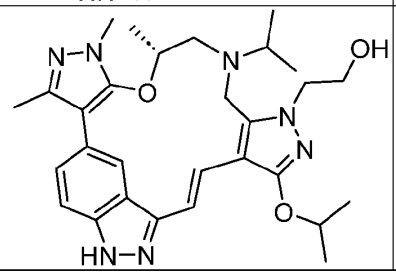
Ex #	Structure	Name
175		2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
176		(10*S*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine
177		2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
178		2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

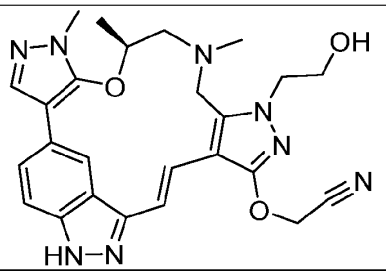
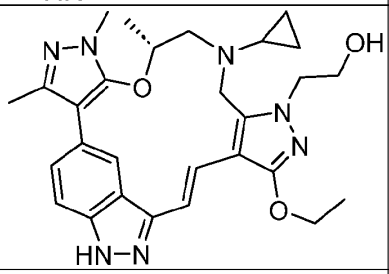
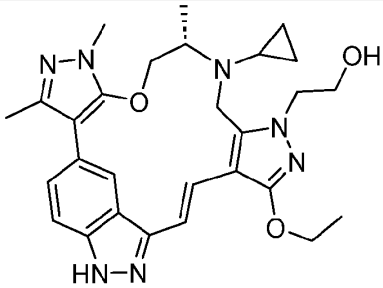
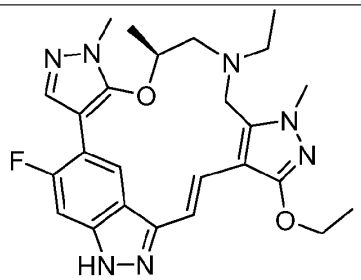
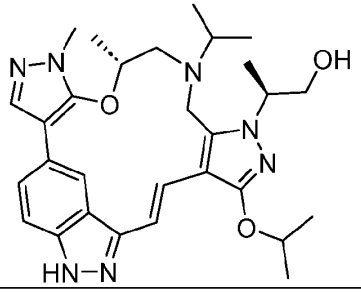
Ex #	Structure	Name
179		(10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
180		(10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
181		2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
182		2-[(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

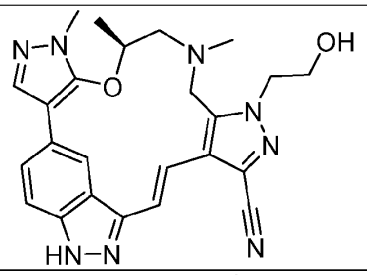
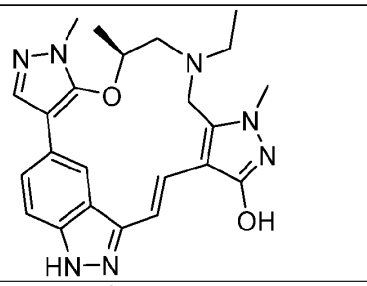
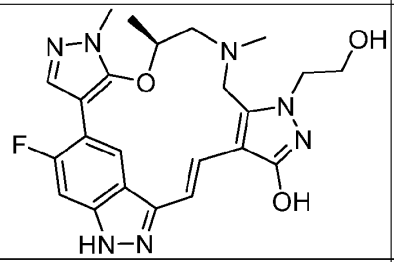
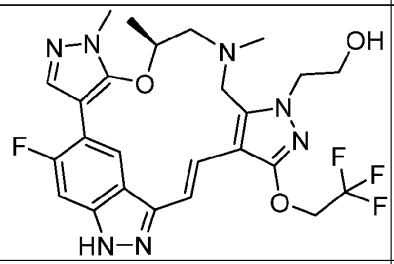
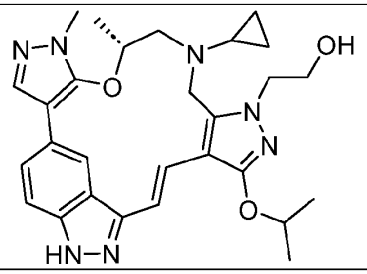
Ex #	Structure	Name
183		(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine
184		2-[(10*S*,17*E*)-16-bromo-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
185		2-{(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
186		(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol
187		(10*S*,17*E*)-16-{[3-(methanesulfonyl)cyclobutyl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine

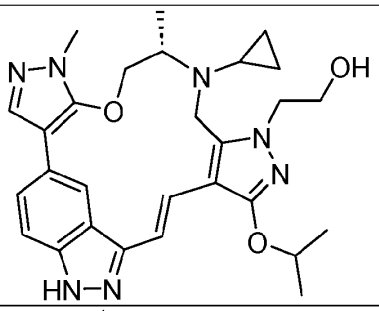
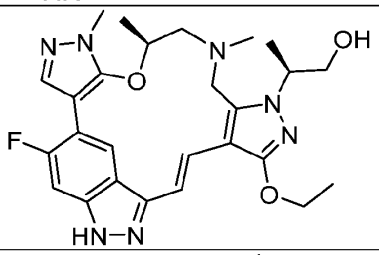
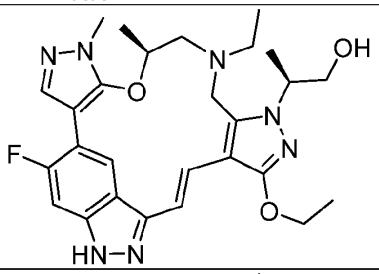
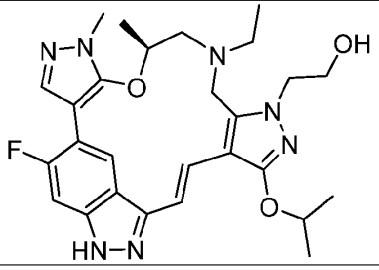
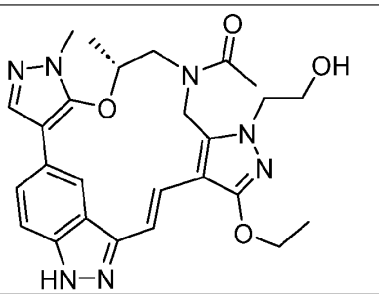
Ex #	Structure	Name
188		(10*R*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
189		(10*S*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one
190		(10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one
191		2-[(10*R*,19*E*)-18-ethoxy-22-fluoro-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
192		2-{(11*S*,17*E*)-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

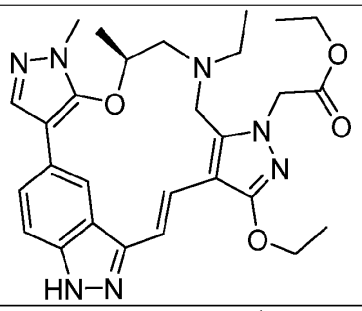
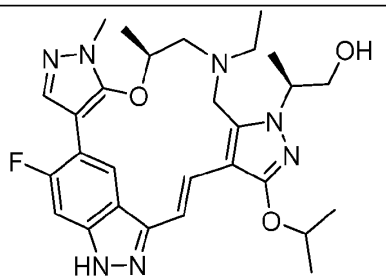
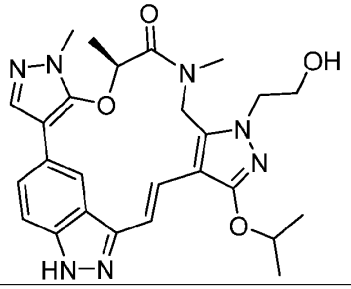
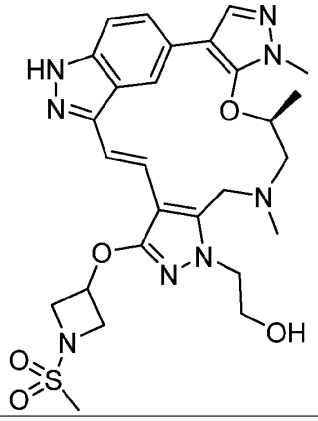
Ex #	Structure	Name
193		2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
194		2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
195		2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
196		2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
197		2-[(10*R*,17*E*)-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

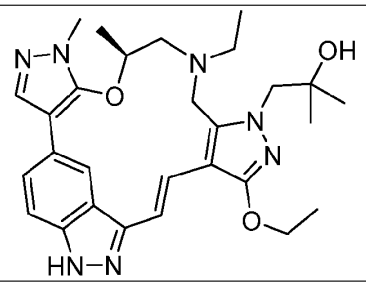
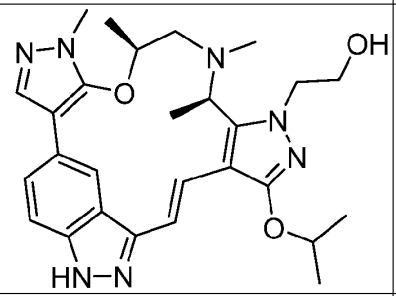
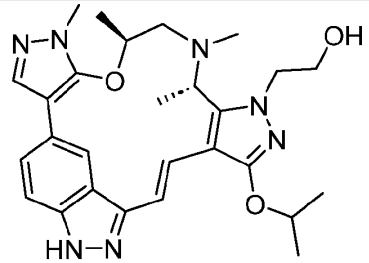
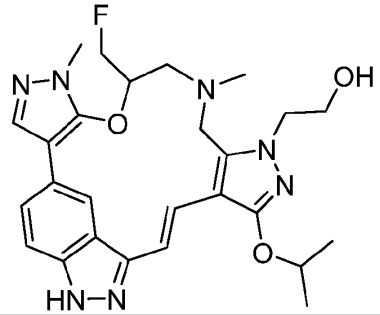
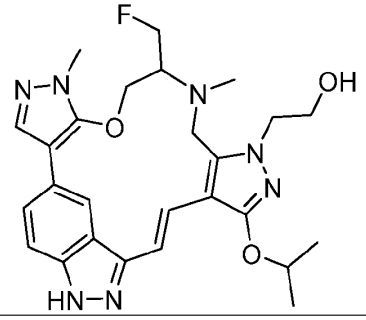
Ex #	Structure	Name
198		2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
199		2-[(10*R*,19*E*)-22-fluoro-8-methyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
200		(2*S*)-2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol
201		2-{(11*S*,17*E*)-6,8,11-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
202		2-{(10*R*,17*E*)-6,8,10-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

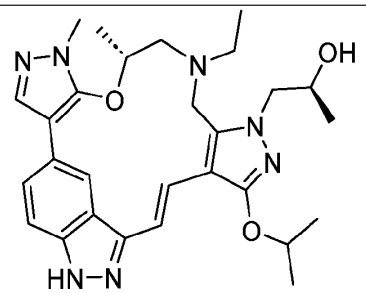
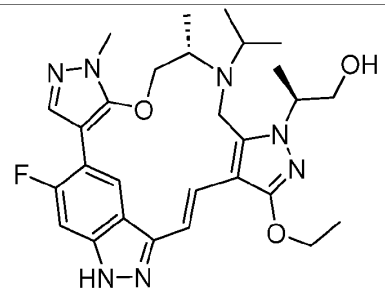
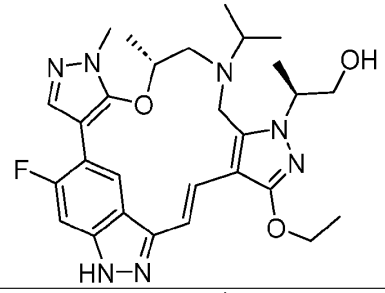
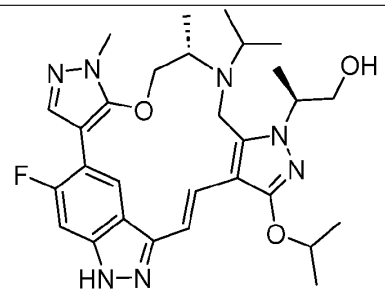
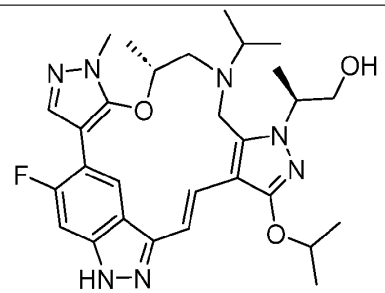
Ex #	Structure	Name
203		{[(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
204		2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
205		2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,11-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
206		(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
207		(2*S*)-2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol

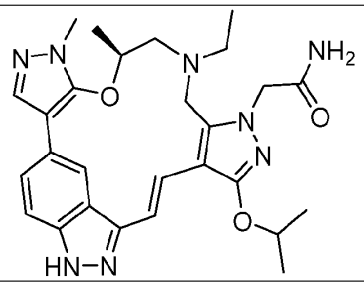
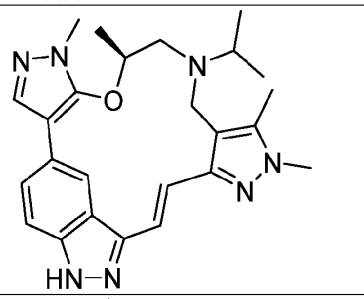
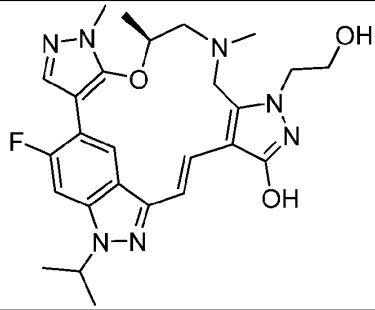
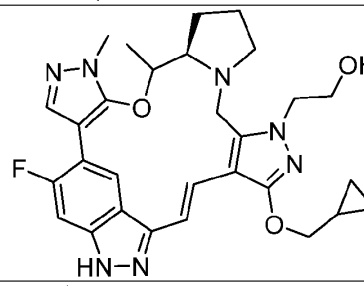
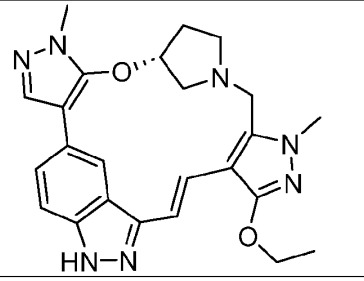
Ex #	Structure	Name
208		(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile
209		(10*S*,17*E*)-12-ethyl-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol
210		(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol
211		2-[(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-(2,2,2-trifluoroethoxy)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
212		2-{(10*R*,17*E*)-12-cyclopropyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

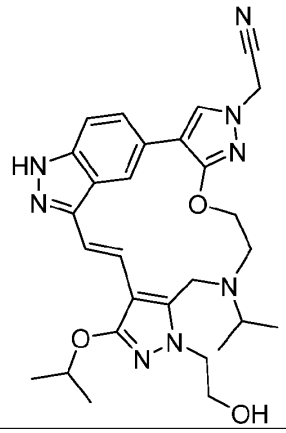
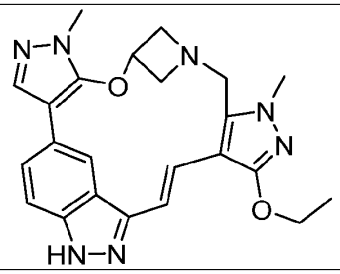
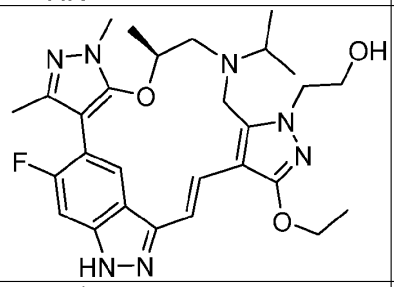
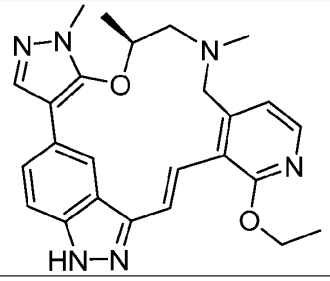
Ex #	Structure	Name
213		2-{(11*S*,17*E*)-12-cyclopropyl-8,11-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
214		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
215		(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
216		2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
217		1-[(10*R*,17*E*)-16-ethoxy-14-(2-hydroxyethyl)-8,10-dimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one

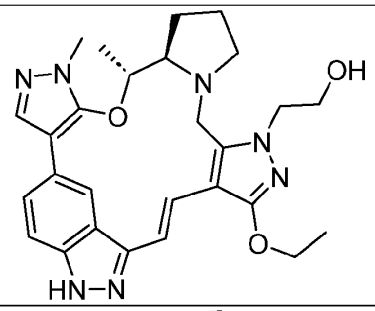
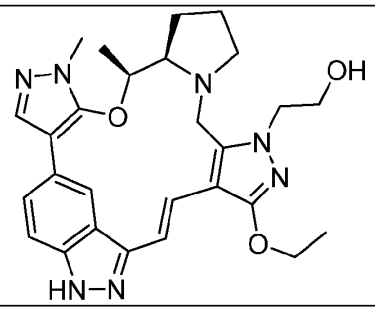
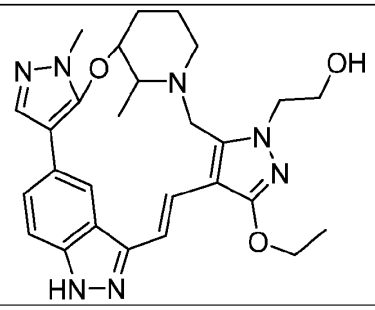
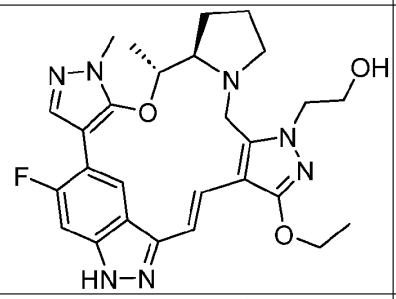
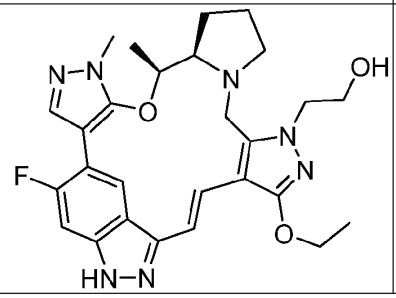
Ex #	Structure	Name
218		ethyl [(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]acetate
219		(2*S*)-2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol
220		(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,12,13,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-11(10*H*)-one
221		2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

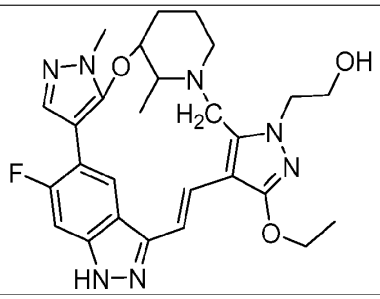
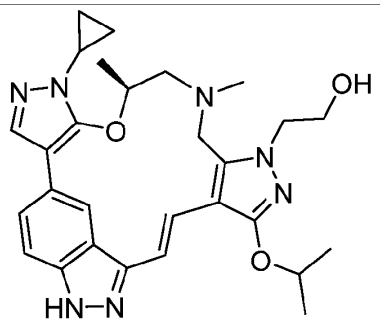
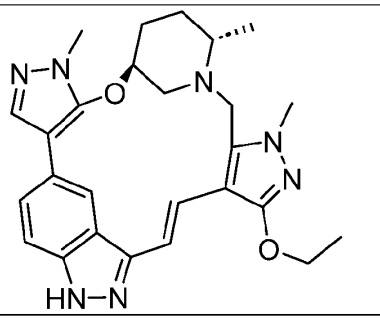
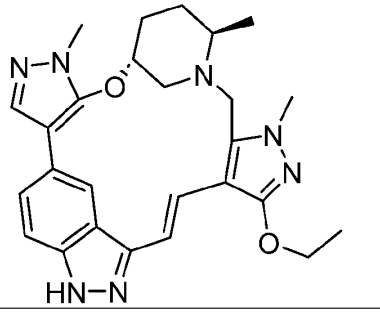
Ex #	Structure	Name
222		1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]-2-methylpropan-2-ol
223		2-{(10*S*,13*R*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
224		2-{(10*S*,13*S*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
225		2-{(17*E*)-10-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
226		2-{(17*E*)-11-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

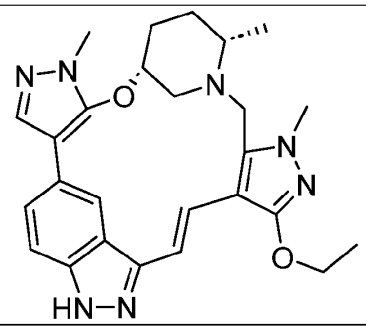
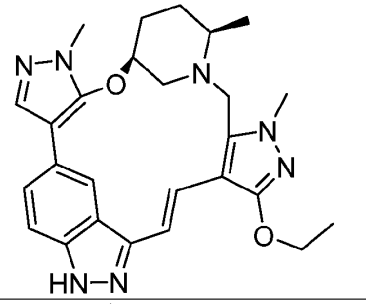
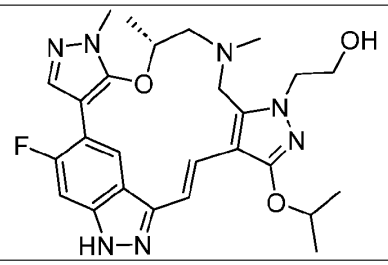
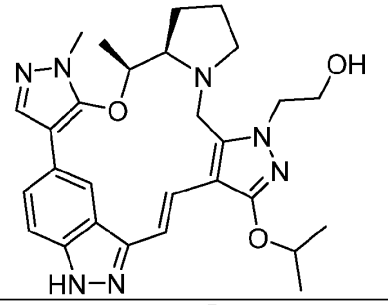
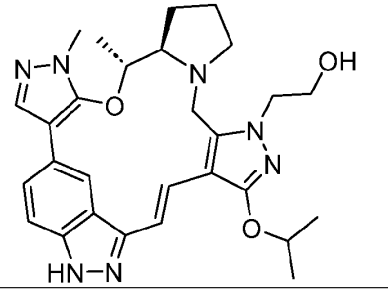
Ex #	Structure	Name
227		(2*S*)-1-{(10*R*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol
228		(2*S*)-2-[(11*S*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
229		(2*S*)-2-[(10*R*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
230		(2*S*)-2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol
231		(2*S*)-2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol

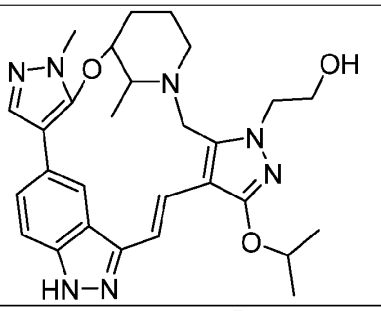
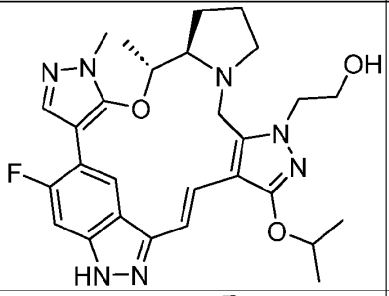
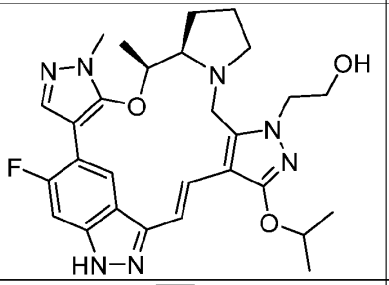
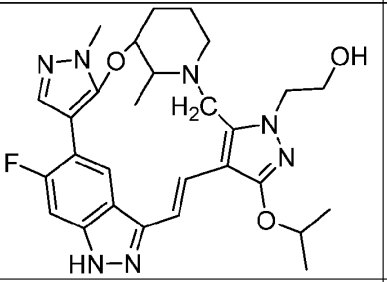
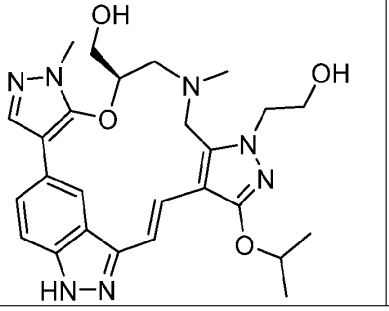
Ex #	Structure	Name
232		2-{(10*S*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}acetamide
233		(10*S*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
234		(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol
235		2-[(8a*R*,19*E*)-1-(cyclopropylmethoxy)-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
236		(10*R*,18*E*)-17-ethoxy-8,15-dimethyl-2,8,11,12,14,15-hexahydro-10*H*-3,5-etheno-10,13-methanotripyrazolo[3,4-*g*:3',4'-*k*:4",3"-*o*][1,5]oxazacyclohexadecine

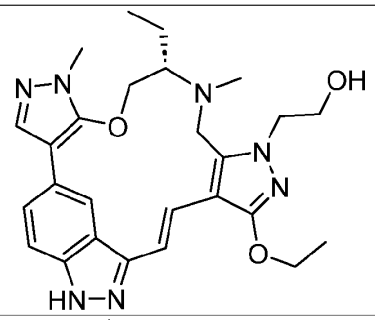
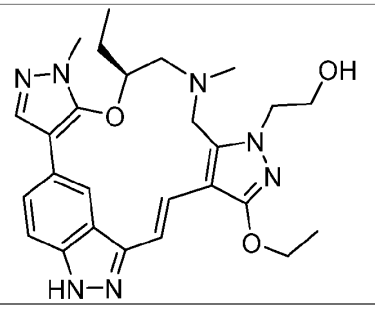
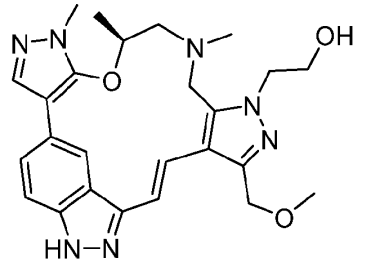
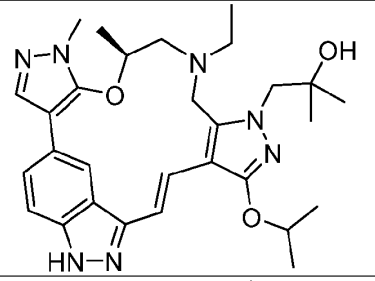
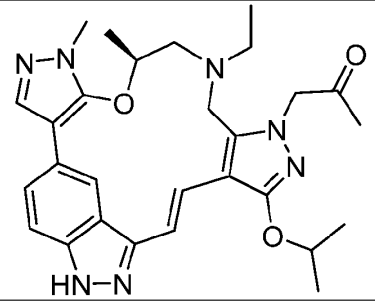
Ex #	Structure	Name
237		{(17*E*)-14-(2-hydroxyethyl)-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-7-yl}acetonitrile
238		(17*E*)-16-ethoxy-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno-10,12-methanotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine
239		2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
240		(10*S*,18*E*)-17-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[4,3-*f*][1,4]oxazacyclopentadecine

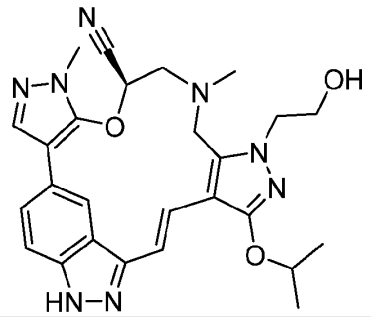
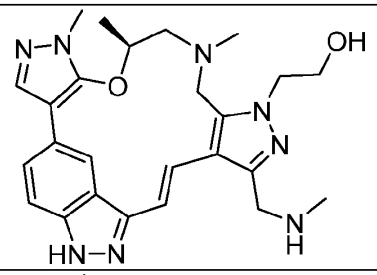
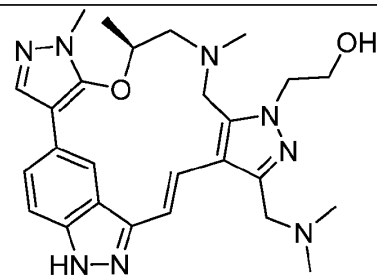
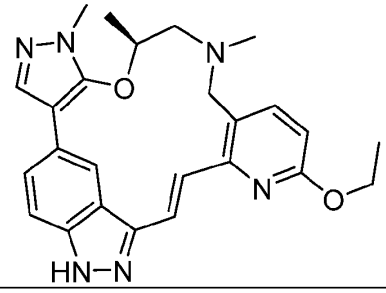
Ex #	Structure	Name
241		2-[(8a*R*,9*R*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
241		2-[(8a*R*,9*S*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
242		2-[(19*E*)-18-ethoxy-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
243		2-[(8a*R*,9*R*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
244		2-[(8a*R*,9*S*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol

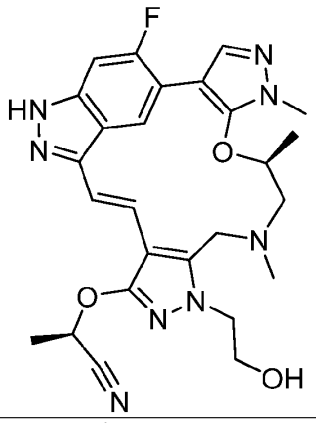
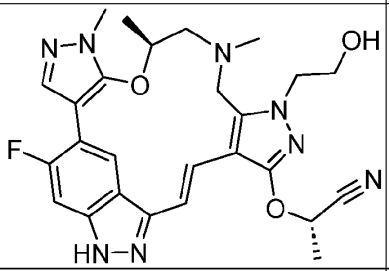
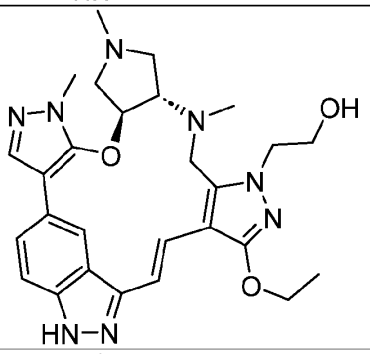
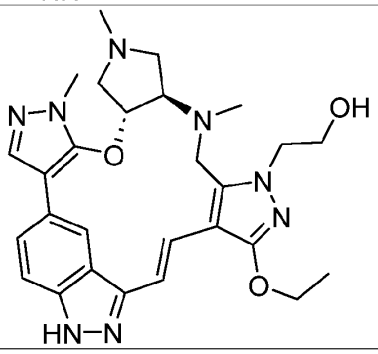
Ex #	Structure	Name
245		2-[(19*E*)-18-ethoxy-22-fluoro-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
246		2-{(10*S*,17*E*)-8-cyclopropyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
247		(10*S*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine
248		(10*R*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine

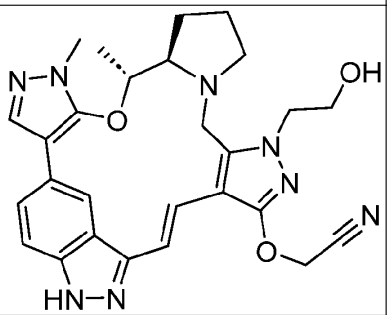
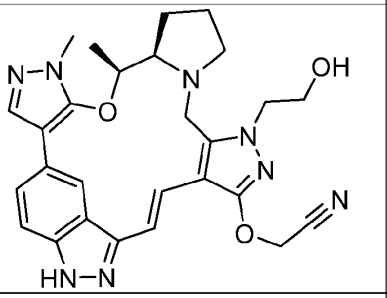
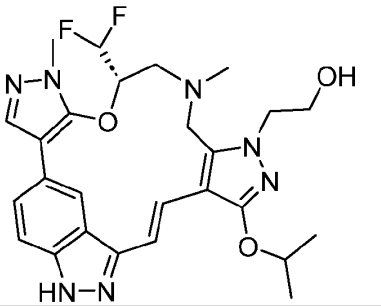
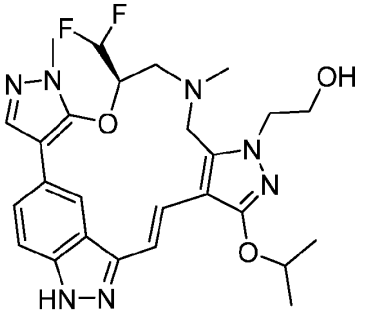
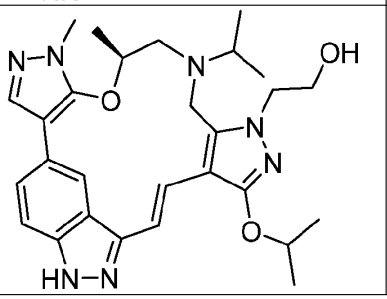
Ex #	Structure	Name
249		(10*R*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine
250		(10*S*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine
251		2-{(10*R*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
252		2-[(8a*R*,9*S*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
253		2-[(8a*R*,9*R*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol

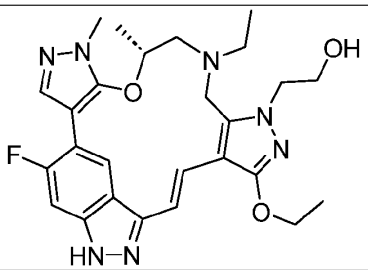
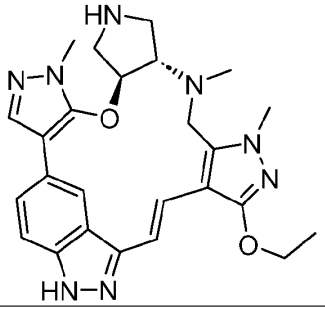
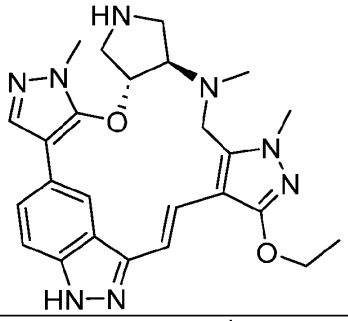
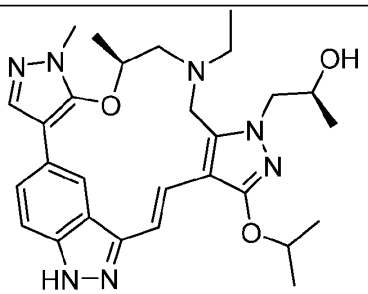
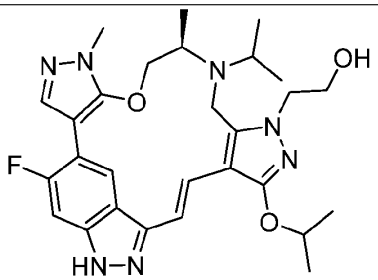
Ex #	Structure	Name
254		2-[(19*E*)-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
255		2-[(8a*R*,9*R*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
256		2-[(8a*R*,9*S*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol
257		2-[(19*E*)-22-fluoro-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol
258		2-{(10*R*,17*E*)-10-(hydroxymethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

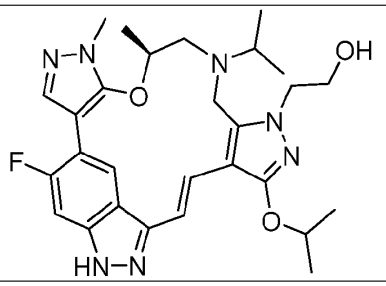
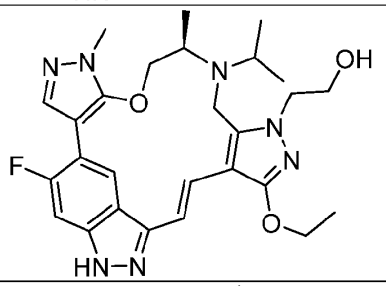
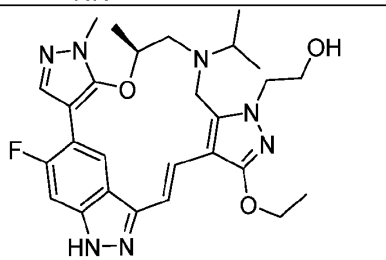
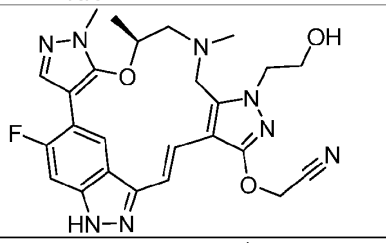
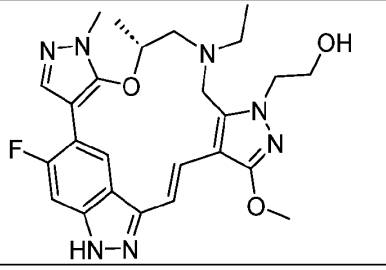
Ex #	Structure	Name
259		2-[(11*S*,17*E*)-16-ethoxy-11-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
260		2-[(10*S*,17*E*)-16-ethoxy-10-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
261		2-[(10*S*,17*E*)-16-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
262		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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}-2-methylpropan-2-ol
263		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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-one

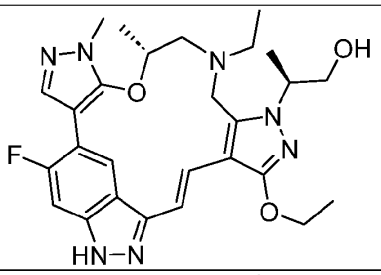
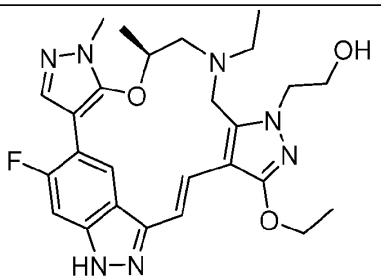
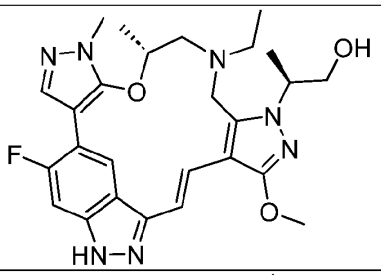
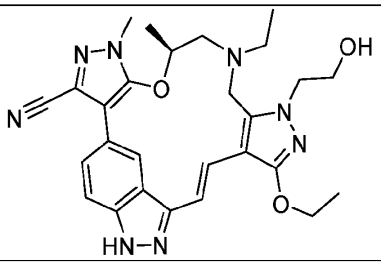
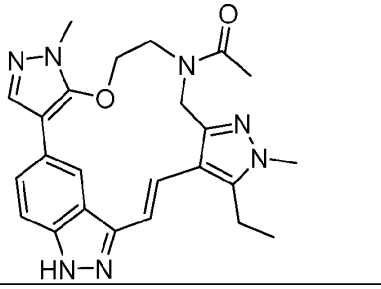
Ex #	Structure	Name
264		(10*R*,17*E*)-14-(2-hydroxyethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-10-carbonitrile
265		2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
266		2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
267		(10*S*,18*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[3,2-*f*][1,4]oxazacyclopentadecine

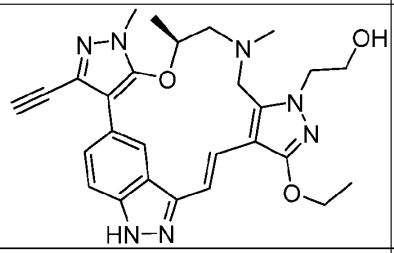
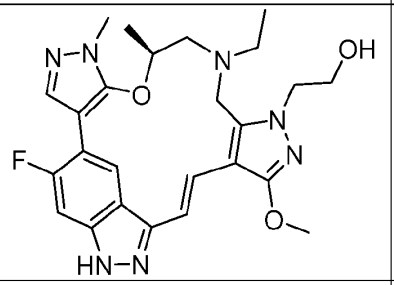
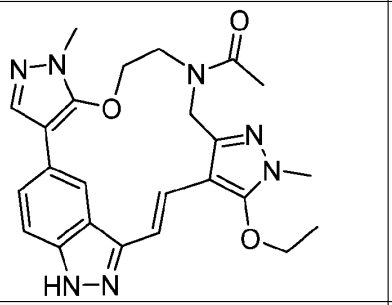
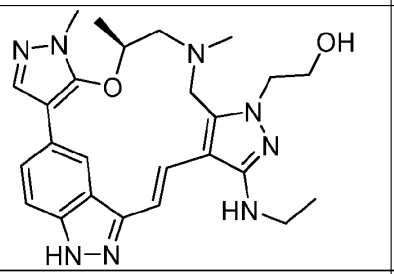
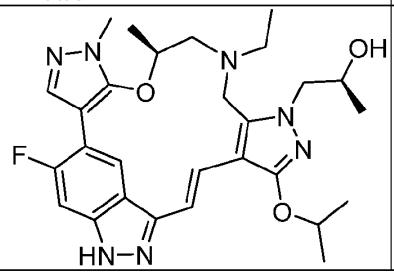
Ex #	Structure	Name
268		(2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile
269		(2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile
270		2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol
271		2-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol

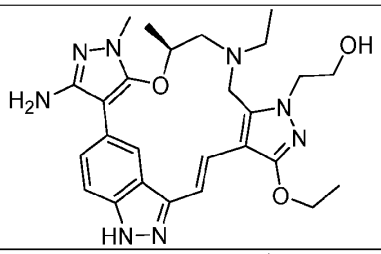
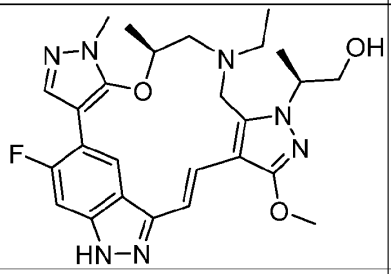
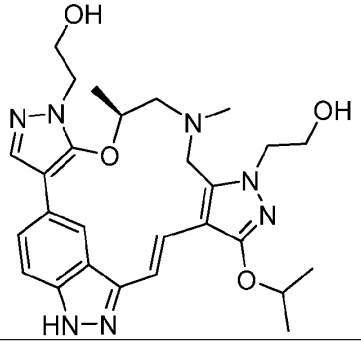
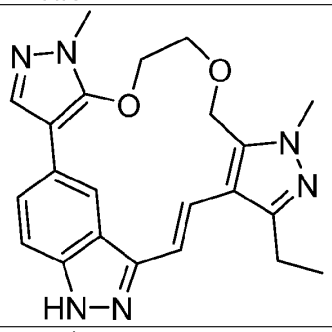
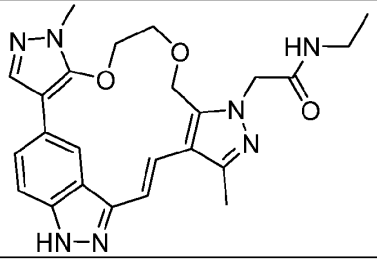
Ex #	Structure	Name
272		{[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile
273		{[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile
274		2-{(10*S*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
275		2-{(10*R*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
276		2-{(10*S*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

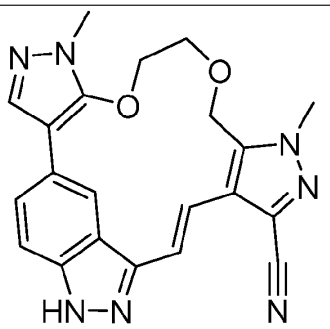
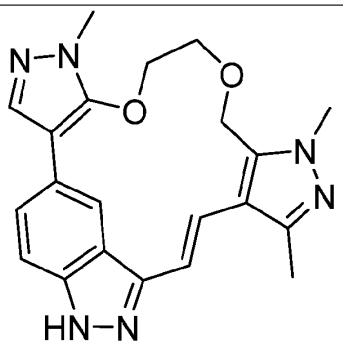
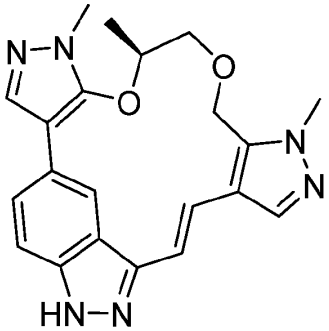
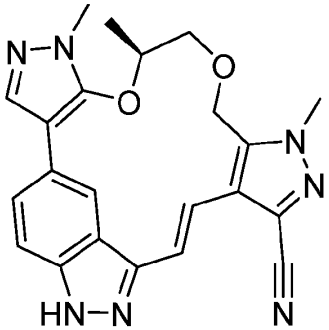
Ex #	Structure	Name
277		2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
278		(4a*S*,7a*S*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine
279		(4a*R*,7a*R*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine
280		(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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol
281		2-{(11*R*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol

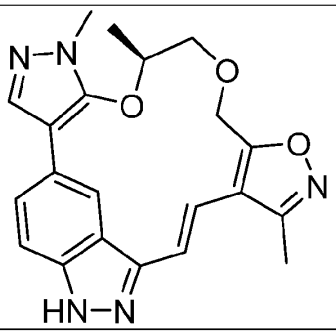
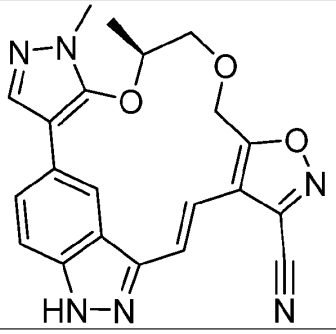
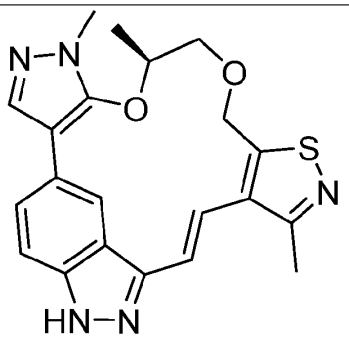
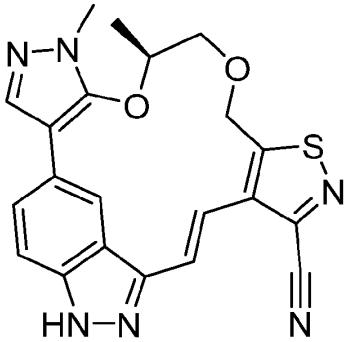
Ex #	Structure	Name
282		2-{(10*S*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol
283		2-[(11*R*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
284		2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
285		{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile
286		2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol

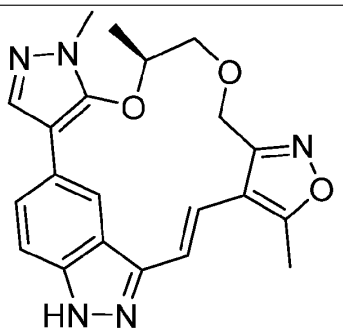
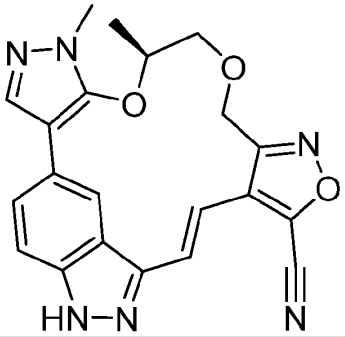
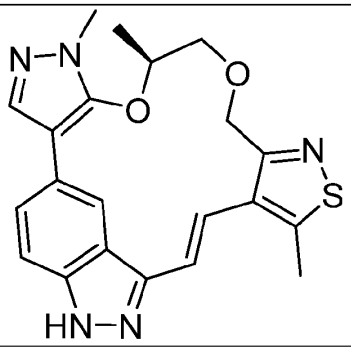
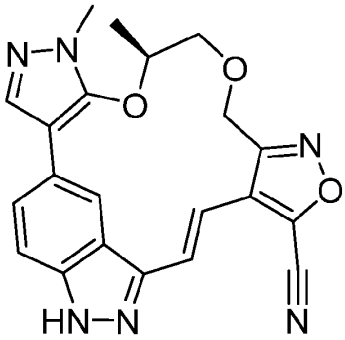
Ex #	Structure	Name
287		(2*S*)-2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
288		2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
289		(2*S*)-2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
290		(10*S*,17*E*)-16-ethoxy-12-ethyl-14-(2-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile
291		1-[(17*E*)-16-ethyl-8,15-dimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one

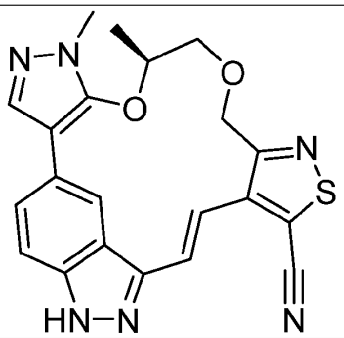
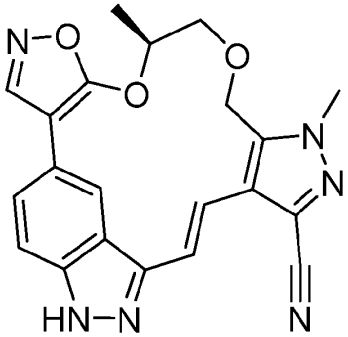
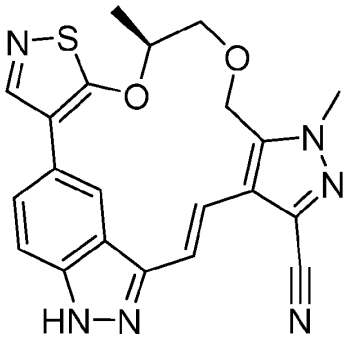
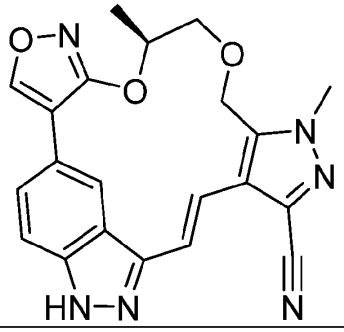
Ex #	Structure	Name
292		2-[(10*S*,17*E*)-16-ethoxy-6-ethynyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
293		2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
294		1-[(17*E*)-16-ethoxy-8,15-dimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one
295		2-[(10*S*,17*E*)-16-(ethylamino)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
296		(2*S*)-1-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol

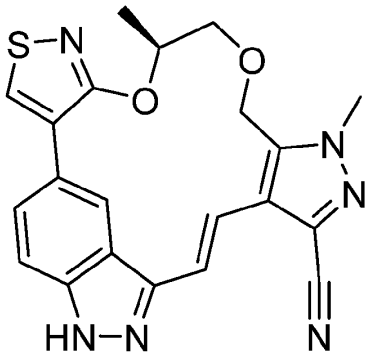
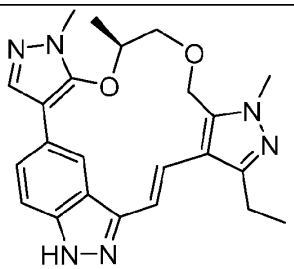
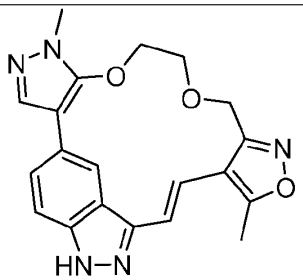
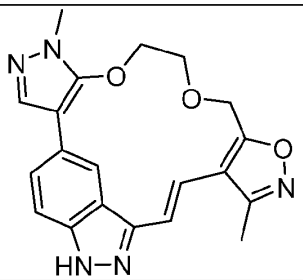
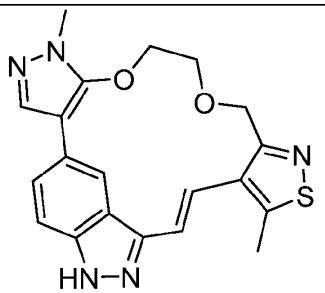
Ex #	Structure	Name
297		2-[(10*S*,17*E*)-6-amino-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol
298		(2*S*)-2-[(10*S*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol
299		2,2'-[(10*S*,17*E*)-10,12-dimethyl-16-[(propan-2-yl)oxy]-10,11,12,13-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-8,14(2*H*)-diyl]di(ethan-1-ol)
300		(17*E*)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole
301		2-[(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14(8*H*)-yl]-*N*-ethylacetamide

Ex #	Structure	Name
302		(17*E*)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole-16-carbonitrile
303		(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
304		(10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole
305		(10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c*′:6,7-*c*″]tripyrazole-16-carbonitrile

Ex #	Structure	Name
306		(10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole
307		(10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole-16-carbonitrile
308		(10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole
309		(10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole-16-carbonitrile

Ex #	Structure	Name
310		(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole
311		(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile
312		(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole
313		(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile

Ex #	Structure	Name
314		(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole-16-carbonitrile
315		(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]oxazole-16-carbonitrile
316		(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]thiazole-16-carbonitrile
317		(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]oxazole-16-carbonitrile

Ex #	Structure	Name
318		(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]thiazole-16-carbonitrile
319		(10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole
320		(17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole
321		(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole
322		(17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole

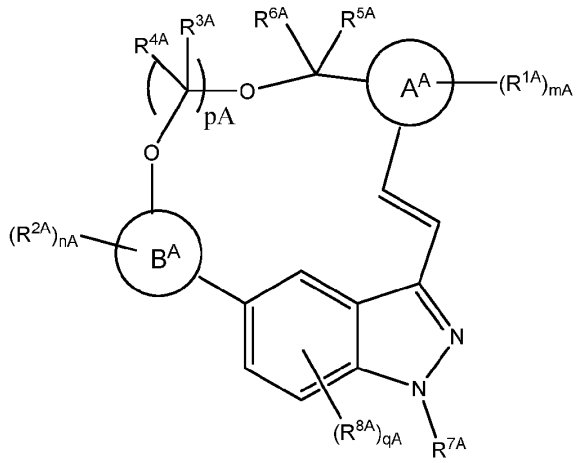
and pharmaceutically acceptable salts thereof.

[0897] 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.

ALTERNATIVE EMBODIMENTS

[0898] Certain compounds of the present disclosure are also described in the following alternative embodiments. The skilled person will recognize that the alternative embodiments described herein are consistent with embodiments described throughout the disclosure. The alternative embodiments describe certain aspects of the disclosure that are within the general teaching of the disclosure, and are described in a similar manner.

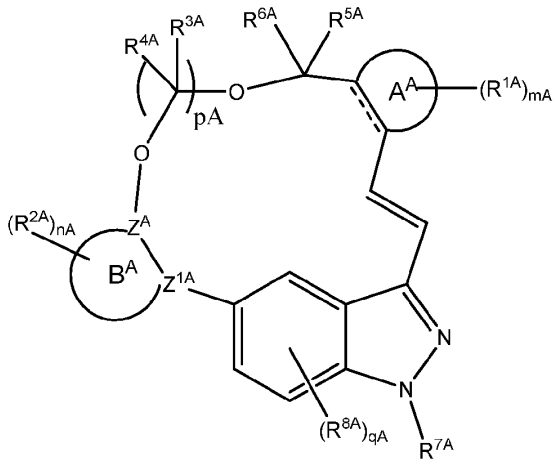
[0899] In some embodiments, the disclosure provides a compound of the formula IA, or a pharmaceutically acceptable salt thereof,



IA

[0900] wherein R^{1A}, R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, A^A, B^A, m^A, n^A, p^A, and q^A are as described herein.

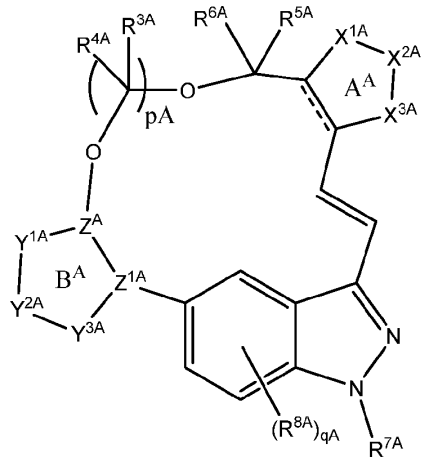
[0901] In some embodiments, the disclosure provides a compound of the formula IIA, or a pharmaceutically acceptable salt thereof,



IIA

[0902] wherein R^{1A}, R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, A^A, B^A, Z^A, Z^{1A}, m^A, n^A, p^A, q^A, and "▬▬▬" are as described herein.

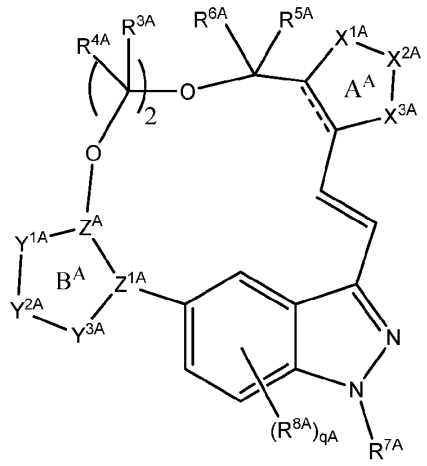
[0903] In some embodiments, the disclosure provides a compound of the formula IIIA, or a pharmaceutically acceptable salt thereof,



IIIA

[0904] wherein R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, A^A, B^A, X^{1A}, X^{2A}, X^{3A}, Z^A, Z^{1A}, Y^{1A}, Y^{2A}, Y^{3A}, p^A, q^A, and "▬▬▬" are as described herein.

[0905] In some embodiments, the disclosure provides a compound of the formula IVA, or a pharmaceutically acceptable salt thereof,



IVA

[0906] wherein R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, A^A, B^A, X^{1A}, X^{2A}, X^{3A}, Z^A, Z^{1A}, Y^{1A}, Y^{2A}, Y^{3A}, and q^A are as described herein.

[0907] In further aspects, the disclosure relates to a pharmaceutical composition comprising at least one compound of Formula (IA)-(IVA) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the disclosure may further comprise a pharmaceutically acceptable excipient.

[0908] In further aspects, the disclosure relates to a compound of Formula (IA)-(IVA), or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0909] 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 (IA)-(IVA), or a pharmaceutically acceptable salt thereof.

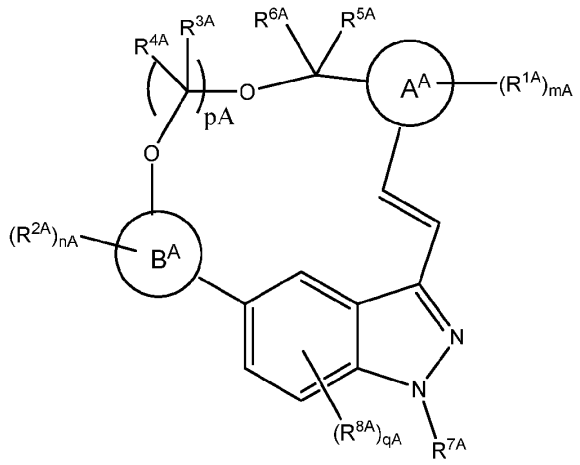
[0910] In further aspects, the disclosure relates to use of a compound of Formula (IA)-(IVA), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of disease, such as cancer, and the use of such compounds and salts for treatment of such diseases.

[0911] 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 (IA)-(IVA), 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*.

[0912] 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.

[0913] 1. A compound of the formula IA



IA

[0914] wherein

[0915] ring A^A and ring B^A are each independently a 5-membered heteroarylene;

[0916] each R^{1A}, R^{2A}, and R^{8A} when present, 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

[0917] each R^{1A} and R^{5A} or R^{6A}, can be taken together with the atom or atoms 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^{1A} and R^{5A} or R^{6A} are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$;

[0918] each R^{3A}, R^{4A}, R^{5A}, and R^{6A}, 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, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, 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 $-NO_2$; or two of R^{3A}, R^{4A}, R^{5A}, and R^{6A}, 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^{3A}, R^{4A}, R^{5A}, and R^{6A} are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$;

[0919] R^{7A} is independently 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 $-P(O)_2OR^c$;

[0920] 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, or 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;

[0921] m^A is 0, 1, 2, or 3;

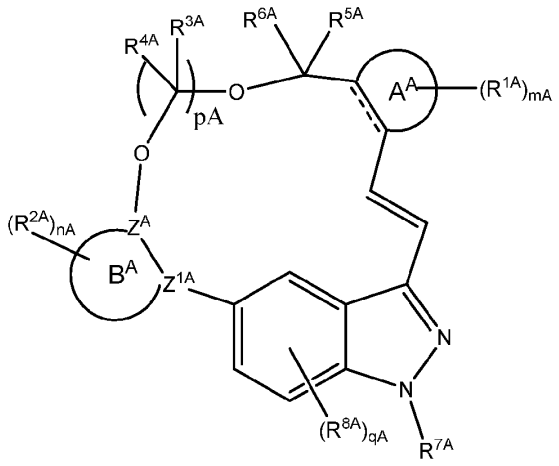
[0922] n^A is 0, 1, 2, or 3;

[0923] p^A is 2, 3, or 4; and

[0924] q^A is 0, 1, or 2;

[0925] or a pharmaceutically acceptable salt thereof.

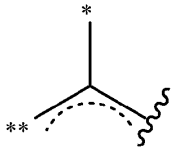
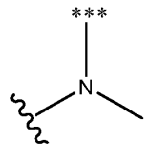
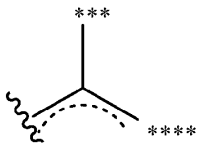
[0926] 2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, having the formula IIA



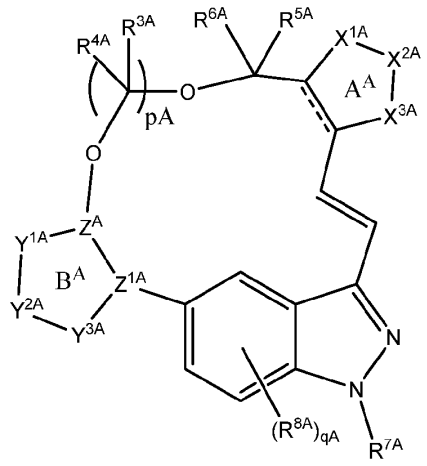
IIA

[0927] wherein

[0928] "------" is optionally a carbon-carbon single bond or a carbon-carbon double bond;

[0929] Z^A is  , wherein * is a point of covalent attachment to ether, ** is a point of covalent attachment to Z^{1A}, "~~~" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" represents the condition that between the points of attachment ** and "~~~", one bond is a single bond and one bond is a double bond; Z^{1A} is  or  wherein *** is a point of covalent attachment to indazole, **** is a point of covalent attachment to Z^A, "~~~" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" indicates the condition that between the points of attachment **** and "~~~", one bond is a single bond and one bond is a double bond; and ring B^A is a 5-membered heteroarylene.

[0930] 3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, having the formula IIIA



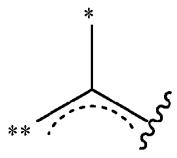
IIIA

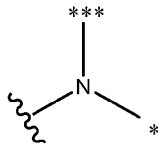
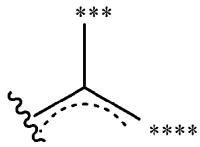
[0931] wherein

[0932] X^{1A}, X^{2A}, and X^{3A} are each independently –O-, -S-, =C(H)-, =C(R^{1A})-, -N(H)-, -N(R^{1A})- or =N- and ring A^A is a 5-membered heteroarylene, provided that at least one of X^{1A}, X^{2A}, and X^{3A} is not =C(H)-, or =C(R^{1A})-;

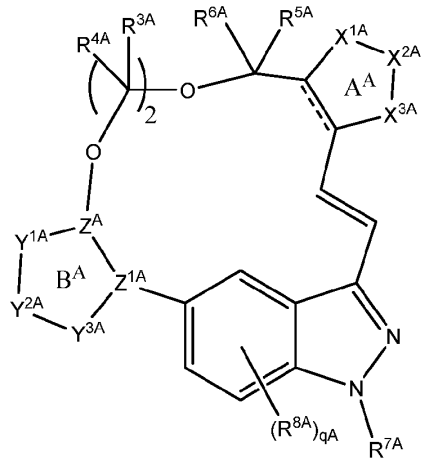
[0933] Y^{1A}, Y^{2A}, and Y^{3A} are each independently –O-, -S-, =C(H)-, =C(R^{2A})-, -N(H)-, -N(R^{2A})- or =N- and ring B is a 5-membered heteroarylene, provided that at least one of Y^{1A}, Y^{2A}, and Y^{3A} is not =C(H)-, or =C(R^{2A})-; and

[0934] "======" is optionally a carbon-carbon single bond or a carbon-carbon double bond;

[0935] Z^A is  , wherein * is a point of covalent attachment to ether, ** is a point of covalent attachment to Z^{1A}, "∿∿∿" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" represents the condition that between the points of attachment ** and "∿∿∿", one bond is a single bond and one bond is a double bond; Z^{1A} is

 or  wherein *** is a point of covalent attachment to indazole, **** is a point of covalent attachment to Z^A, "∿∿∿" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" indicates the condition that between the points of attachment **** and "∿∿∿", one bond is a single bond and one bond is a double bond; and ring B^A is a 5-membered heteroarylene.

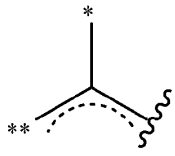
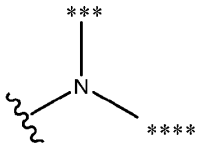
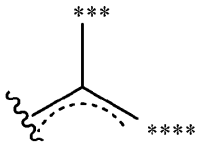
[0936] 4. The compound of any one of embodiments 1 to 3, or a pharmaceutically acceptable salt thereof, having the formula IVA



IVA

[0937] wherein

[0938] "======" is optionally a carbon-carbon single bond or a carbon-carbon double bond;

[0939] Z^A is  , wherein * is a point of covalent attachment to ether, ** is a point of covalent attachment to Z^{1A}, "∿∿∿" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" represents the condition that between the points of attachment ** and "∿∿∿", one bond is a single bond and one bond is a double bond; Z^{1A} is  or  wherein *** is a point of covalent attachment to indazole, **** is a point of covalent attachment to Z^A, "∿∿∿" represents a point of covalent attachment to a ring atom of ring B^A, and "⋰⋰⋰" indicates the condition that between the points of attachment **** and "∿∿∿", one bond is a single bond and one bond is a double bond; and ring B^A is a 5-membered heteroarylene.

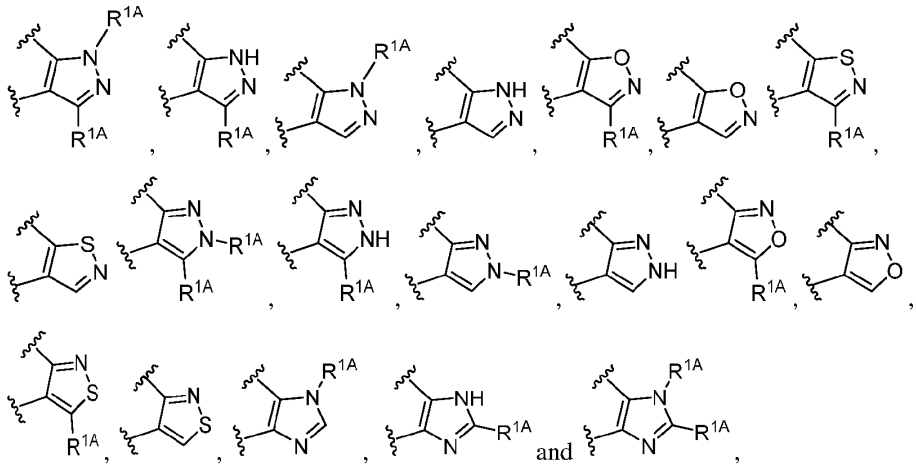
[0940] 5. The compound of any one of embodiments 1 to 3, wherein

[0941] X^{2A}, is –O-, -S-, -N(H)-, -N(R^{1A})- or =N-, X^{1A} and X^{3A} are each independently –O-, -S-, =C(H)-, =C(R^{1A})-, -N(H)-, -N(R^{1A})- or =N-, and ring A^A is a 5-membered heteroarylene; and

[0942] Y^{2A} is –O-, -S-, -N(H)-, -N(R^{2A})- or =N-, Y^{1A} and Y^{3A} are each independently –O-, -S-, =C(H)-, =C(R^{2A})-, -N(H)-, -N(R^{2A})- or =N-, and ring B^A is a 5-membered heteroarylene.

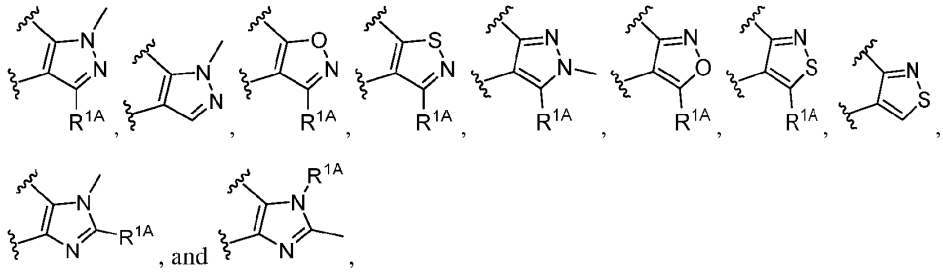
[0943] 6. The compound of any one of embodiments 1 to 5, or a pharmaceutically acceptable salt thereof, wherein

[0944] ring A^A is a 5-membered heteroarylene selected from the group consisting of



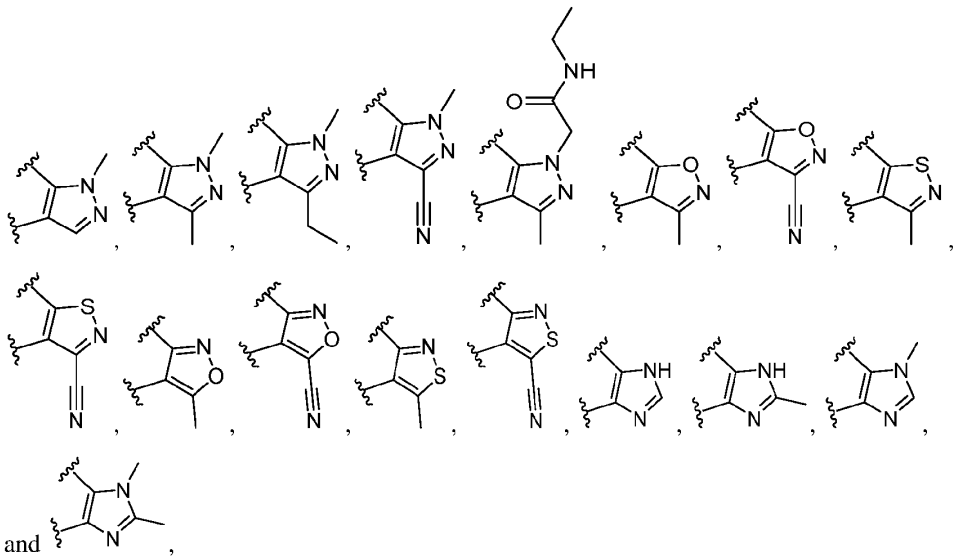
[0945] wherein each "〰" represents a point of covalent attachment, and each R^{1A} is independently as described herein.

[0946] 7. The compound of any one of embodiments 1 to 6, or a pharmaceutically acceptable salt thereof, wherein ring A^A is a 5-membered heteroarylene selected from the group consisting of



[0947] wherein each "〰" represents a point of covalent attachment, and R^{1A} is as described herein.

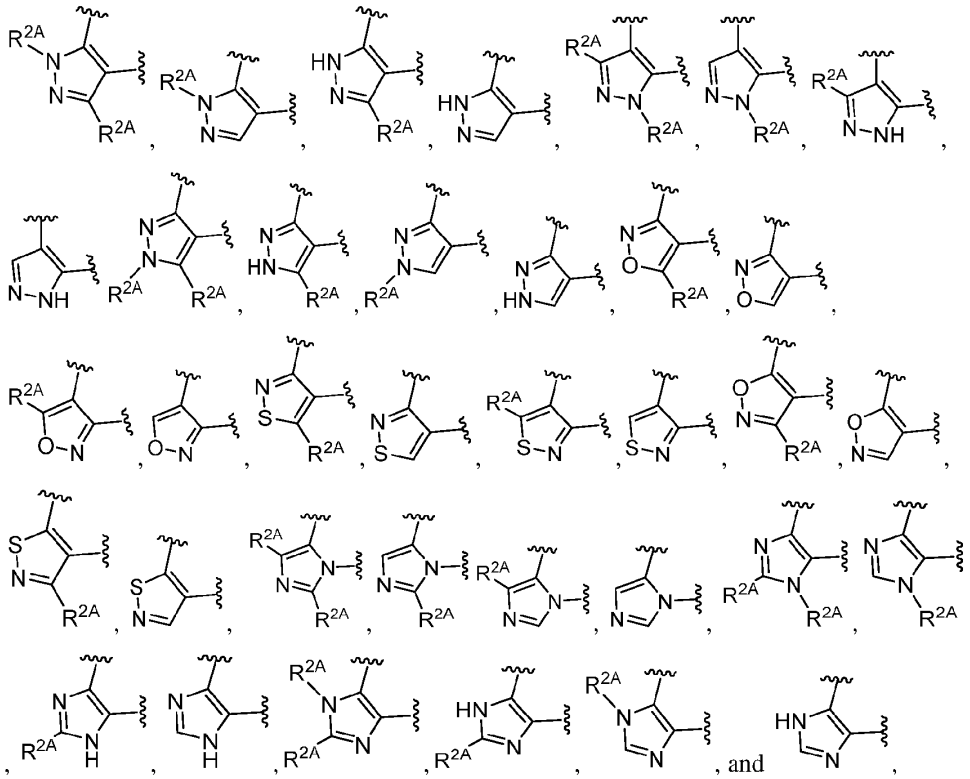
[0948] 8. The compound of any one of embodiments 1 to 6, or a pharmaceutically acceptable salt thereof, wherein ring A^A is a 5-membered heteroarylene selected from the group consisting of



and

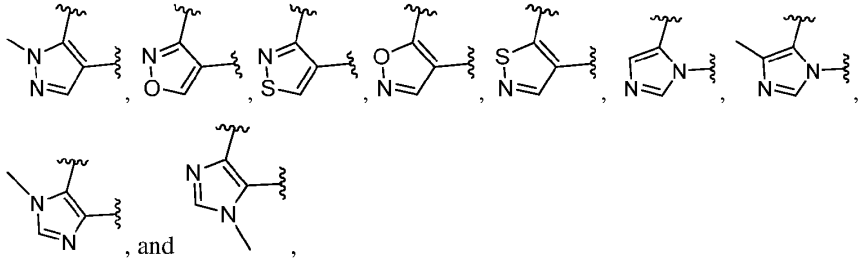
[0949] wherein each "〰" represents a point of covalent attachment.

[0950] 9. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein ring B^A is a 5-membered heteroarylene selected from the group consisting of



[0951] wherein each "〰" represents a point of covalent attachment, and each R^2 is independently as described herein.

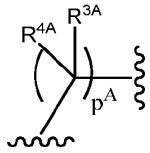
[0952] 10. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein ring B^A is a 5-membered heteroarylene selected from the group consisting of



, and

[0953] wherein each "〰" represents a point of covalent attachment.

[0954] 11. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein



[0955] is an ethylene, propylene, or butylene, wherein each hydrogen atom in ethylene, propylene, and butylene is independently optionally substituted by 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 $-NO_2$, and each "〰" represents a point of covalent attachment.

[0956] 12. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein one R^{3A} 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 $-NO_2$, or two or R^{3A} and/or R^{4A},

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^{3A} and/or R^{4A} are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$, and any remaining R^{3A} and R^{4A} are H.

[0957] 13. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein one R^{3A} 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^{3A} and R^{4A} are H.

[0958] 14. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein one R^{3A} is C_1-C_6 alkyl.

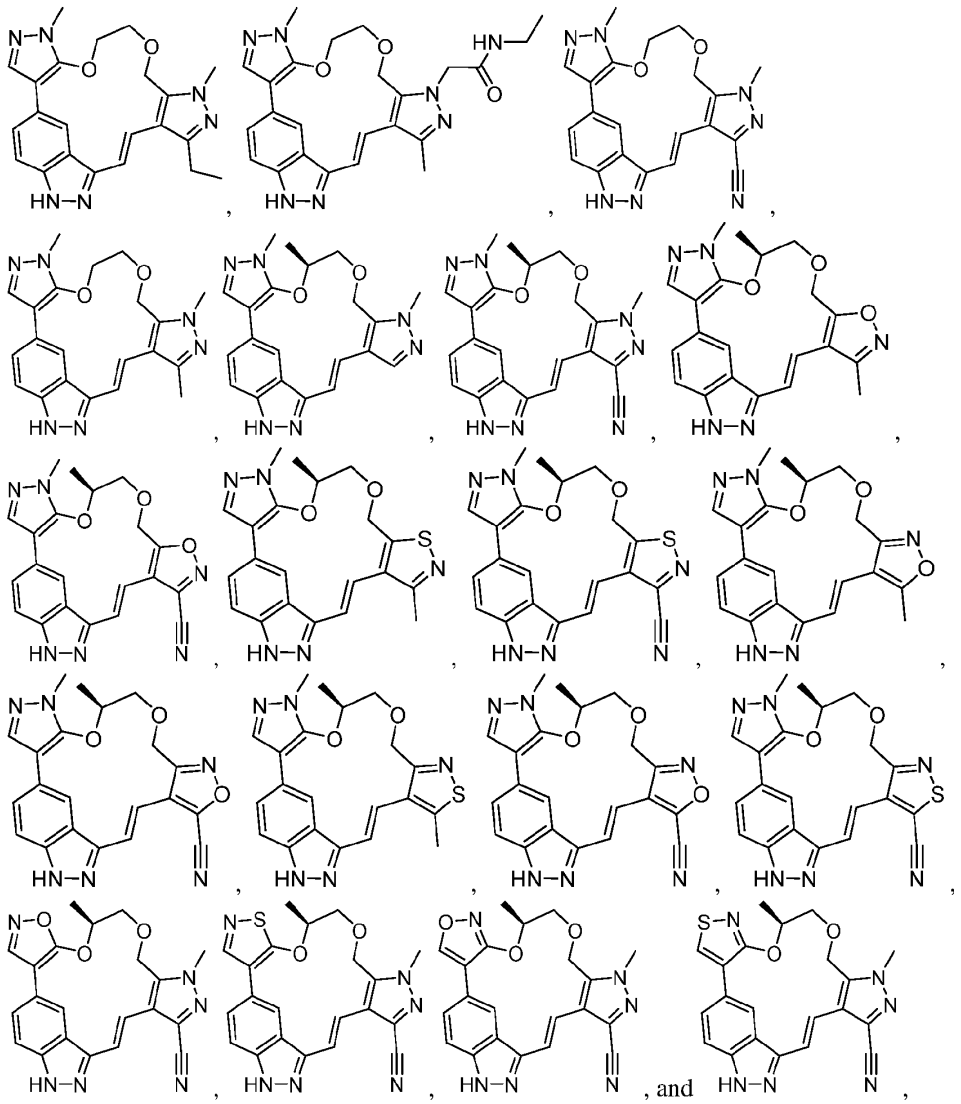
[0959] 15. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein one R^{3A} is methyl, and any remaining R^{3A} and R^{4A} are H.

[0960] 16. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein R^{5A} and R^{6A} are H

[0961] 17. The compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, wherein R^{7A} is H.

[0962] 18. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein q^A is 0.

[0963] 19. The compound of embodiment 1, selected from the group consisting of



[0964] or a pharmaceutically acceptable salt thereof.

[0965] 20. A pharmaceutical composition comprising a compound of any one of the preceding embodiments, and optionally one or more excipients.

[0966] 21. A method of treating disease in a subject comprising, administering a therapeutically effective amount of a compound of any one of embodiments 1 to 19, or a pharmaceutical composition of embodiment 20.

[0967] 22. A compound according to any one of embodiments 1 to 19, for use in a method of treating disease in a subject.

[0968] 23. Use of a compound according to any one of embodiments 1 to 19 in the

manufacture of a medicament for the treatment of disease in a subject.

[0969] In some embodiments, Ring A^A is a 5-membered heteroarylene.

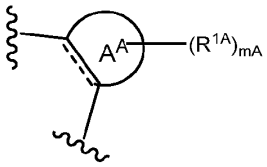
[0970] In some embodiments, Ring A^A is a 5-membered heteroarylene, wherein each R^{1A} when present, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -OR^a, -$OC(O)R^a$, -$OC(O)NR^aR^b$, -$OS(O)R^a$, -$OS(O)_2R^a$, -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, 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, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$, -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^{1A} and R^{5A} or R^{6A}, can be taken together with the atom or atoms 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^{1A} and R^{5A} or R^{6A} are taken together is independently optionally substituted by OR^e, $OC(O)R^e$, $OC(O)NR^eR^f$, -$OS(O)R^e$, $OS(O)_2R^e$, $OS(O)NR^eR^f$, -$OS(O)_2NR^eR^f$, -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.

[0971] In some embodiments, an R^{1A} of Ring A^A and an R^{5A} or R^{6A}, can be taken together with the atom or atoms 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^{1A} and R^{5A} or R^{6A} are taken together is independently optionally substituted by OR^e, $OC(O)R^e$, $OC(O)NR^eR^f$, -$OS(O)R^e$, $OS(O)_2R^e$, $OS(O)NR^eR^f$, $OS(O)_2NR^eR^f$, -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, -$P(O)R^eR^f$,

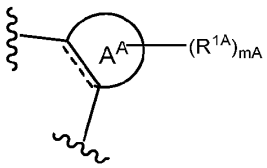
$-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $P(O)OR^e$, $-P(O)_2OR^e$, -CN, or NO_2.

[0972] In some embodiments, Ring A^A is pyrazolylene, isoxazolylene, isothiazolylene, imidazolylene wherein each is independently optionally substituted by 1, 2, or 3 R^{1A} (m of R^{1A}) each of which is independently selected from the group consisting of 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$.

[0973] In some embodiments, Ring A^A is of the formula

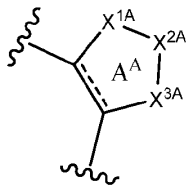


[0974] wherein "======" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "∿∿∿" represents a point of covalent attachment, and R^{1A} and m^A are as described herein. In some embodiments, Ring A^A is of the formula



[0975] wherein "======" is optionally a carbon-carbon single bond or a carbon-carbon double bond, each "∿∿∿" represents a point of covalent attachment, Ring A^A is a 5-membered heteroarylene, and R^{1A} and m^A are as described herein.

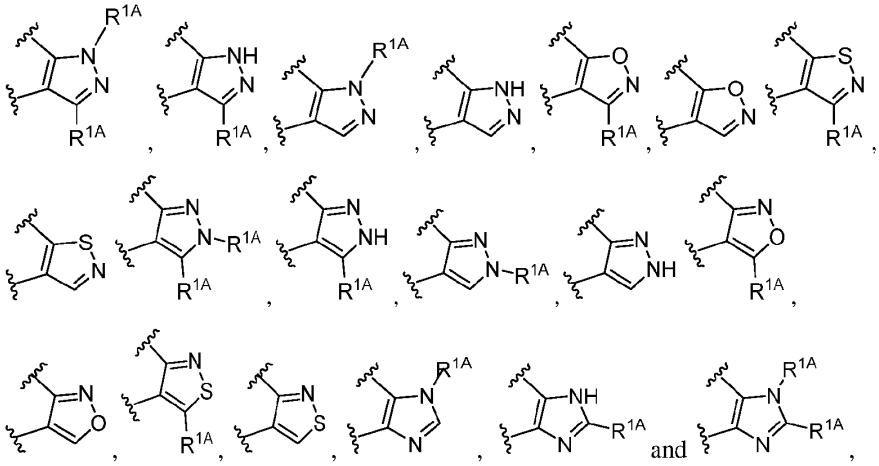
[0976] In some embodiments, Ring A^A is of the formula



[0977] 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^{1A})- or =N-, X^{1A} and X^{3A} are each independently –O-, -S-, =C(H)-, =C(R^{1A})-, -N(H)-, N(R^1)- or =N-, and ring A^A is a 5-membered heteroarylene, provided that at least one of X^{1A}, X^{2A}, and X^{3A} is not =C(H)-, or =C(R^1)-, Ring A^A is a 5-membered heteroarylene, and R^{1A} and m are as described herein.

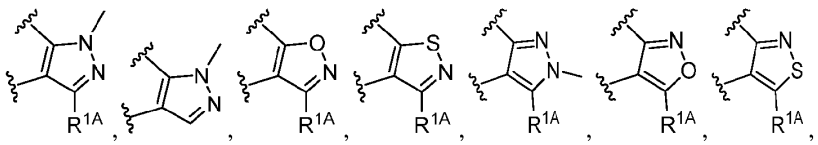
[0978] In some embodiments, m^A is 0, 1, 2, or 3. In some embodiments, m^A is 0, 1, or 2. In some embodiments, m^A is 0 or 1. In some embodiments, m^A is 0. In some embodiments, m^A is 1. In some embodiments, m^A is 2. In some embodiments, m^A is 3.

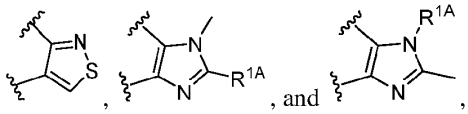
[0979] In some embodiments, ring A^A is a 5-membered heteroarylene selected from the group consisting of



[0980] wherein each "~~~" represents a point of covalent attachment, and each R^{1A} is independently as described herein.

[0981] In some embodiments, ring A^A is a 5-membered heteroarylene selected from the group consisting of

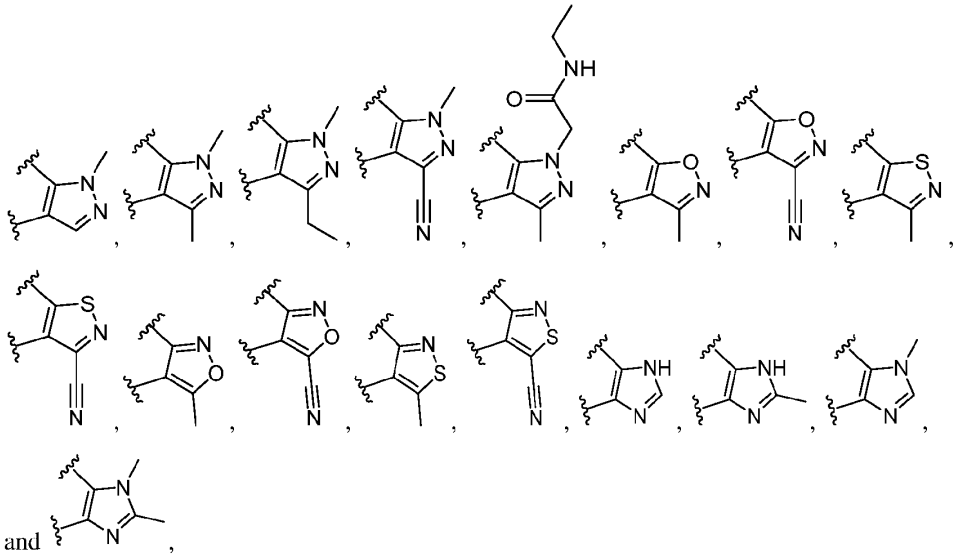




[0982] wherein each "〰" represents a point of covalent attachment, and R^{1A} is as described herein.

[0983] In some embodiments, R^{1A} 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, $-CN$, or $-NO_2$.

[0984] In some embodiments, ring A^A is a 5-membered heteroarylene selected from the group consisting of



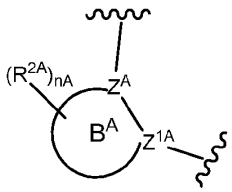
[0985] wherein each "〰" represents a point of covalent attachment.

[0986] In some embodiments, Ring B^A is 5-membered heteroarylene.

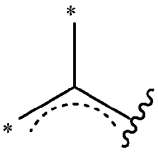
[0987] In some embodiments, Ring B^A is a 5-membered heteroarylene, wherein each R^{2A} when present, is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$,

$-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;.

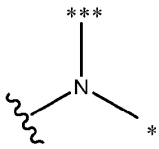
[0988] In some embodiments, Ring B^A is of the formula

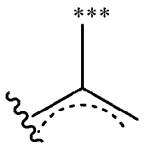


[0989] wherein each "〰" represents a point of covalent attachment, and R^{2A} and n^A are as described herein,

[0990] wherein Z^A is 

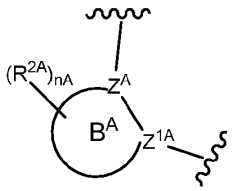
, wherein * is a point of covalent attachment to ether, ** is a point of covalent attachment to Z^{1A}, "〰" represents a point of covalent attachment to a ring atom of ring B^A, and "⌒" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^{1A} is



or 

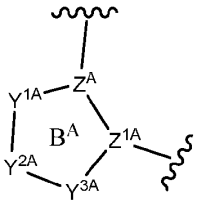
wherein *** is a point of covalent attachment to indazole, **** is a point of covalent attachment to Z^A, "〰" represents a point of covalent attachment to a ring atom of ring B^A, and "⌒" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond.

[0991] In some embodiments, Ring B^A is of the formula



[0992] wherein each "〰" represents a point of covalent attachment, Ring B^A is a 5-membered heteroarylene and Z^A, Z^{1A}, R^{2A} and n^A are as described herein.

[0993] In some embodiments, Ring B^A is of the formula



[0994] Wherein each "〰" represents a point of covalent attachment, Y^{1A}, Y^{2A}, and Y^{3A} are each independently –O-, -S-, =C(H)-, $=C(R^{2A})$-, -N(H)-, $-N(R^{2A})$- or =N-, and ring B is a 5-membered heteroarylene, provided that at least one of Y^{1A}, Y^{2A}, and Y^{3A} is not =C(H)-, or $=C(R^{2A})$-, and R^{2A}, Z^A, Z^{1A}, and n^A are as described herein.

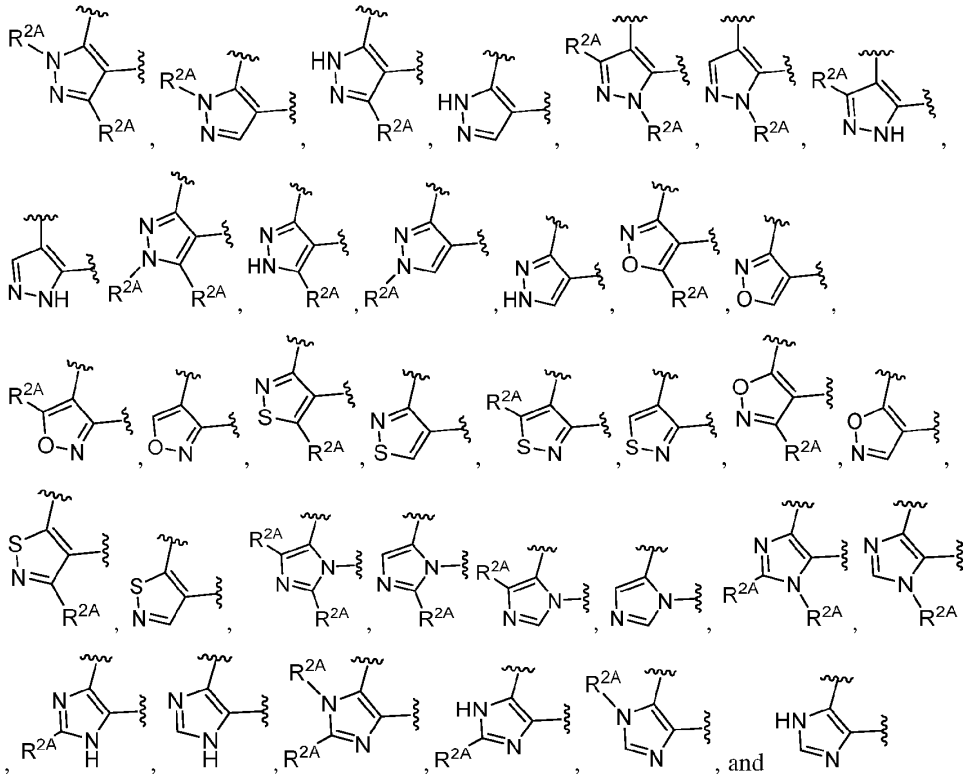
[0995] In some embodiments, Z^{1A} is N. In some embodiments, Z^{1A} is C.

[0996] In some embodiments, Ring B^A is pyrazolylene, isoxazolylene, isothiazolylene, imidazolylene wherein each is optionally substituted with 1, 2, or 3 R^{2A} (n^A of R^{2A}), each of which is independently selected from the group consisting of 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 $-NO_2$, 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, $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$,

-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.

[0997] In some embodiments, n^A is 0, 1, 2, or 3. In some embodiments, n^A is 0, 1, or 2. In some embodiments, n^A is 0 or 1. In some embodiments, n^A is 0. In some embodiments, n^A is 1. In some embodiments, n^A is 2. In some embodiments, n^A is 3.

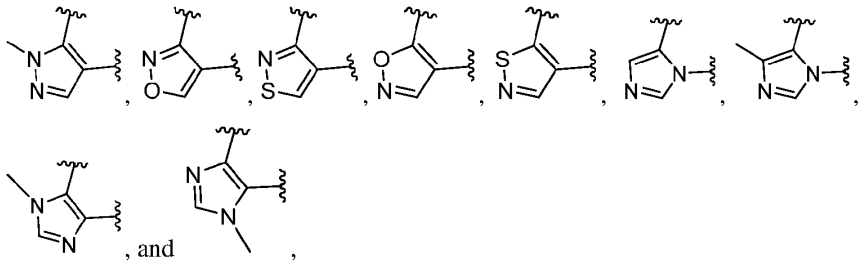
[0998] In some embodiments, ring B^A is a 5-membered heteroarylene selected from the group consisting of



, and

[0999] wherein each "〰" represents a point of covalent attachment, and each R^{2A} is independently as described herein.

[01000] In some embodiments, ring B^A is a 5-membered heteroarylene selected from the group consisting of



, and

[01001] wherein each "〰" represents a point of covalent attachment.

[01002] In some embodiments, R^{7A} is independently H, deuterium, -C(O)R^c, -C(O)OR^c, -C(O)N$R^c$$R^d$, -S(O)$_2NR^c$$R^d$, -P(O)$_2$$R^c$$R^d$, -P(O)$_2NR^c$$R^d$, or -P(O)$_2OR^c$.

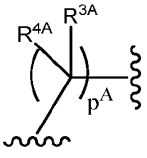
[01003] In some embodiments, R^{7A} is independently H.

[01004] In some embodiments, indazole is optionally substituted with 0, 1, or 2 R^{8A} (q of R^{8A}), each of which is independently selected from the group consisting of 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)N$R^a$$R^b$, -OS(O)$R^a$, -OS(O)$_2$$R^a$, -S$R^a$, -S(O)$R^a$, -S(O)$_2$$R^a$, -S(O)N$R^a$$R^b$, -S(O)$_2NR^a$$R^b$, -OS(O)N$R^a$$R^b$, -OS(O)$_2NR^a$$R^b$, -N$R^a$$R^b$, -N$R^a$C(O)$R^b$, -N$R^a$C(O)O$R^b$, -N$R^a$C(O)N$R^a$$R^b$, -N$R^a$S(O)$R^b$, -N$R^a$S(O)$_2$$R^b$, -N$R^a$S(O)N$R^a$$R^b$, -N$R^a$S(O)$_2NR^a$$R^b$, -C(O)$R^a$, -C(O)O$R^a$, -C(O)N$R^a$$R^b$, -P$R^a$$R^b$, -P(O)$R^a$$R^b$, -P(O)$_2$$R^a$$R^b$, -P(O)N$R^a$$R^b$, -P(O)$_2NR^a$$R^b$, -P(O)O$R^a$, -P(O)$_2OR^a$, -CN, or -NO$_2$, wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^c, -OC(O)R^c, -OC(O)N$R^c$$R^d$, -OC(=N)N$R^c$$R^d$, -OS(O)$R^c$, -OS(O)$_2$$R^c$, -OS(O)N$R^c$$R^d$, -OS(O)$_2NR^c$$R^d$, -S$R^c$, -S(O)$R^c$, -S(O)$_2$$R^c$, -S(O)N$R^c$$R^d$, -S(O)$_2NR^c$$R^d$, -N$R^c$$R^d$, -N$R^c$C(O)$R^d$, -N(C(O)$R^c$)(C(O)$R^d$), -N$R^c$C(O)O$R^d$, -N$R^c$C(O)N$R^c$$R^d$, -N$R^c$C(=N)N$R^c$$R^d$, -N$R^c$S(O)$R^d$, -N$R^c$S(O)$_2$$R^d$, -N$R^c$S(O)N$R^c$$R^d$, -N$R^c$S(O)$_2NR^c$$R^d$, -C(O)$R^c$, -C(O)O$R^c$, -C(O)N$R^c$$R^d$, -C(=N)N$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$, -P(O)$_2NR^c$$R^d$, -P(O)O$R^c$, -P(O)$_2OR^c$, -CN, or -NO$_2$.

[01005] In some embodiments, each R^{8A} when present, is independently hydrogen.

[01006] In some embodiments, q^A is 0, 1, or 2. In some embodiments, q^A is 0 or 1. In some embodiments, q^A is 0. In some embodiments, q^A is 1. In some embodiments, q^A is 2.

[01007] In some embodiments,



is an ethylene, propylene, or butylene, wherein each hydrogen atom in ethylene, propylene, and butylene is independently optionally substituted by 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)N$R^a$$R^b$, -OS(O)$R^a$, -OS(O)$_2$$R^a$, -S$R^a$, -S(O)$R^a$, -S(O)$_2$$R^a$, -S(O)N$R^a$$R^b$, -S(O)$_2NR^a$$R^b$, -OS(O)N$R^a$$R^b$, -OS(O)$_2NR^a$$R^b$, -N$R^a$$R^b$, -N$R^a$C(O)$R^b$, -N$R^a$C(O)O$R^b$, -N$R^a$C(O)N$R^a$$R^b$, -N$R^a$S(O)$R^b$, -N$R^a$S(O)$_2$$R^b$, -N$R^a$S(O)N$R^a$$R^b$, -N$R^a$S(O)$_2NR^a$$R^b$, -C(O)$R^a$, -C(O)O$R^a$, -C(O)N$R^a$$R^b$, -P$R^a$$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$_2$, and each "∿∿∿" represents a point of covalent attachment.

[01008] In some embodiments, p^A is 2, 3, or 4. In some embodiments, p^A is 2 or 3. In some embodiments, p^A is 2. In some embodiments, p^A is 3. In some embodiments, p^A is 4.

[01009] In some embodiments, one R^{3A} 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^{e}R^f, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)NR^{e}R^f, -OS(O)$_2$NR^{e}R^f, -SR^e, -S(O)R^e, -S(O)$_2$R^e, -S(O)NR^{e}R^f, -S(O)$_2$NR^{e}R^f, -NR^{e}R^f, -NR^{e}C(O)R^f, -NR^{e}C(O)OR^f, -NR^{e}C(O)NR^{e}R^f, -NR^{e}S(O)R^f, -NR^{e}S(O)$_2$R^f, -NR^{e}S(O)NR^{e}R^f, -NR^{e}S(O)$_2$NR^{e}R^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^f, -PR^{e}R^f, -P(O)R^{e}R^f, -P(O)$_2$R^{e}R^f, -P(O)NR^{e}R^f, -P(O)$_2$NR^{e}R^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO$_2$, or two or R^{3A} and/or R^{4A}, 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^{3A} and/or R^{4A} are taken together is independently optionally substituted by -OR^e, -OC(O)R^e, -OC(O)NR^{e}R^f, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)NR^{e}R^f, -OS(O)$_2$NR^{e}R^f, -SR^e, -S(O)R^e, -S(O)$_2$R^e, -S(O)NR^{e}R^f, -S(O)$_2$NR^{e}R^f, -NR^{e}R^f, -NR^{e}C(O)R^f, -NR^{e}C(O)OR^f, -NR^{e}C(O)NR^{e}R^f, -NR^{e}S(O)R^f, -NR^{e}S(O)$_2$R^f, -NR^{e}S(O)NR^{e}R^f, -NR^{e}S(O)$_2$NR^{e}R^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^f, -PR^{e}R^f, -P(O)R^{e}R^f, -P(O)$_2$R^{e}R^f, -P(O)NR^{e}R^f, -P(O)$_2$NR^{e}R^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO$_2$, and any remaining R^3 and R^4 are H.

[01010] In some embodiments, one R^{3A} 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^{e}R^f, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)NR^{e}R^f, -OS(O)$_2$NR^{e}R^f, -SR^e, -S(O)R^e, -S(O)$_2$R^e, -S(O)NR^{e}R^f, -S(O)$_2$NR^{e}R^f, -NR^{e}R^f, -NR^{e}C(O)R^f, -NR^{e}C(O)OR^f, -NR^{e}C(O)NR^{e}R^f, -NR^{e}S(O)R^f, -NR^{e}S(O)$_2$R^f, -NR^{e}S(O)NR^{e}R^f, -NR^{e}S(O)$_2$NR^{e}R^f, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^f, -PR^{e}R^f, -P(O)R^{e}R^f, -P(O)$_2$R^{e}R^f, -P(O)NR^{e}R^f, -P(O)$_2$NR^{e}R^f, -P(O)OR^e, -P(O)$_2$OR^e, -CN, or -NO$_2$, and any remaining R^3 and R^4 are H.

[01011] In some embodiments, one R^{3A} is C$_1$-C$_6$ alkyl. In some embodiments, one R^{3A} is methyl, and any remaining R^{3A} and R^{4A} are H.

[01012] In some embodiments, R^{5A} and R^{6A} are H.

[01013] In some embodiments, the disclosure provides a compound selected from the group consisting of

[01014] (17E)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole;

[01015] 2-[(17E)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazol-14(8H)-yl]-N-ethylacetamide;

[01016] (17E)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole-16-carbonitrile;

[01017] (17E)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole;

[01018] (10S,17E)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole;

[01019] (10S,17E)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole-16-carbonitrile;

[01020] (10S,17E)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-d][1,2]oxazole;

[01021] (10S,17E)-8,10-dimethyl-2,10,11,13-tetrahydro-8H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-d][1,2]oxazole-16-carbonitrile;

[01022] (10S,17E)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-d][1,2]thiazole;

[01023] (10S,17E)-8,10-dimethyl-2,10,11,13-tetrahydro-8H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-d][1,2]thiazole-16-carbonitrile;

[01024] (10S,17E)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-c][1,2]oxazole;

[01025] (10S,17E)-8,10-dimethyl-2,8,10,11-tetrahydro-13H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-c][1,2]oxazole-16-carbonitrile;

[01026] (10S,17E)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-c][1,2]thiazole;

[01027] (10S,17E)-8,10-dimethyl-2,8,10,11-tetrahydro-13H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-c][1,2]oxazole-16-carbonitrile;

[01028] (10S,17E)-8,10-dimethyl-2,8,10,11-tetrahydro-13H-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-c][1,2]thiazole-16-carbonitrile;

[01029] (10S,17E)-10,14-dimethyl-10,11,13,14-tetrahydro-2H-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-d][1,2]oxazole-16-carbonitrile;

[01030] (10S,17E)-10,14-dimethyl-10,11,13,14-tetrahydro-2H-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-d][1,2]thiazole-16-carbonitrile;

[01031] (10S,17E)-10,14-dimethyl-10,11,13,14-tetrahydro-2H-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-c][1,2]oxazole-16-carbonitrile;

[01032] (10S,17E)-10,14-dimethyl-10,11,13,14-tetrahydro-2H-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-c][1,2]thiazole-16-carbonitrile;

[01033] or a pharmaceutically acceptable salt thereof.

PHARMACEUTICAL COMPOSITIONS

[01034] 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.

[01035] Sterile compositions are also contemplated by the disclosure, including compositions that are in accord with national and local regulations governing such compositions.

[01036] 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.

[01037] 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.

[01038] 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.

[01039] 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.

[01040] 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.

[01041] 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.

[01042] 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.

[01043] 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.

[01044] The term "subject" refers to a mammalian patient in need of such treatment, such as a human.

[01045] 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, myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CML), 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, 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.

[01046] In one aspect, the compounds and pharmaceutical compositions of the disclosure specifically target EGFR. Thus, these compounds and pharmaceutical compositions can be used to prevent, reverse, slow, or inhibit diseases, such as cancers driven by the activity of EGFR. In some embodiments, the compounds described herein can target EGFR in a oncogenic driver mutation, such as L858R, Del19, Δ746-750, Δ746-750/T790M, Δ746-750/C979S, L858R/T790M, Del19/T790M, L858R/C979S, Del19/C979S, L858R/T790M/C979S, and Δ746-750/T790M/C979S. In some embodiments, the compounds described herein can target EGFR having one or more resistance mutations, such as such as resistance mutations. In some embodiments, the compounds described herein can inhibit EGFR in a oncogenic driver mutation, such as L858R, Del19, Δ746-750, Δ746-750/T790M, Δ746-750/C979S, L858R/T790M, Del19/T790M, L858R/C979S, Del19/C979S, L858R/T790M/C979S, and Δ746-750/T790M/C979S, and/or other emerging and established resistance mutations, while maintaining good selectivity over wild-type EGFR. In some embodiments, methods of treating a target cancer are described.

[01047] In one aspect, the compounds and pharmaceutical compositions of the disclosure specifically target PIM kinases. In some embodiments, the compounds described herein can target PIM kinase activity to overcome resistance mechanisms of chemotherapy, radiotherapy, anti-angiogenic therapies and targeted therapies. In some embodiments, methods of treating a target cancer, such as AML, are described.

[01048] In one aspect, the compounds and pharmaceutical compositions of the disclosure specifically target CLK kinases. In some embodiments, the compounds described

herein can target CLK kinase activity to treat diseases, such as cancers, through modulation of pre-mRNA splicing via inhibition of CLK kinase activity. In some embodiments, methods of treating a target cancer, such as myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia, AML, lung cancer, breast cancer, and pancreatic cancer are described.

[01049] In some embodiments, compounds as described herein can be useful in connection with the treatment of diseases, such as cancer, by inhibiting one or more of EGFR, including oncogenic driver mutations as described herein and/or resistance mutations, aberrant PIM kinases, and/or aberrant CLK kinases.

[01050] 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 EGFR, PIM, and/or CLK as described herein.

[01051] 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 EGFR, including oncogenic driver mutations as described herein and/or resistance mutations, 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).

[01052] 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

[01053] 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.

[01054] 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.

CHEMICAL SYNTHESIS METHODS

[01055] 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)-(XII) and (IA-IVA).

[01056] 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

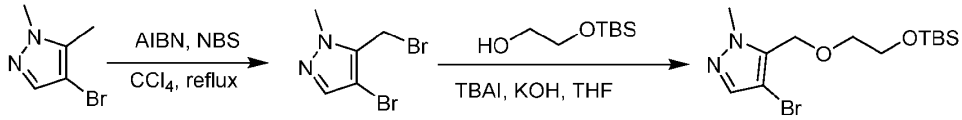
mL	milliliters
EtOAc	ethyl acetate
MHz	megahertz
ppm	parts per million
δ	chemical shift
s	singlet
d	doublet
t	triplet
q	quartet
quin	quintet
br	broad
m	multiplet
Hz	hertz
THF	tetrahydrofuran
°C	degrees Celsius
PE	petroleum ether
EA	ethyl acetate
R_f	retardation factor
N	normal
J	coupling constant
DMSO-d_6	deuterated dimethyl sulfoxide
n-BuOH	n-butanol
DIEA	n,n-diisopropylethylamine
TMSCl	trimethylsilyl chloride
min	minutes
hr	hours
Me	methyl
Et	ethyl
i-Pr	isopropyl
TLC	thin layer chromatography

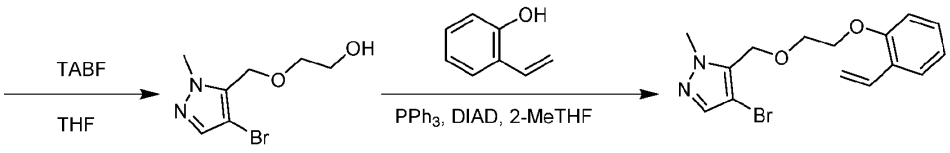
M	molar
Compd#	compound number
MS	mass spectrum
m/z	mass-to-charge ratio
Ms	methanesulfonyl
FDPP	pentafluorophenyl diphenylphosphinate
Boc	tert-butyloxycarbonyl
TFA	trifluoroacetic acid
Tos	toluenesulfonyl
DMAP	4-(dimethylamino)pyridine
mM	micromolar
ATP	adenosine triphosphate
IC_{50}	half maximal inhibitory concentration
U/mL	units of activity per milliliter
KHMDS	potassium bis(trimethylsilyl)amide
DIAD	diisopropyl azodicarboxylate
MeTHF	2-methyltetrahydrofuran
MOM	methoxymethyl
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DPPA	diphenyl phosphoryl azide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-diisopropylethylamine
SEM	[2-(Trimethylsilyl)ethoxy]methyl acetal
Hex	hexanes
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
MeCN (ACN)	Acetonitrile
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
Hunig's Base	*N*,*N*-diisopropylethylamine
TBAF	*Tert* butyl ammonium fluoride

PPh_3	Triphenyl phosphine
RT	Room Temperature
p-TSA	*Para*-Tolylsulfonic acid
t-BuOH	*Tert*-Butanol
$Pd(amphos)Cl_2$	Dichlorobis[di-tert-butyl(4-dimethylaminophenyl)phosphine]palladium(II)
mCPBA	*Meta*-Chloroperoxy benzoic acid
AcOH	Acetic Acid
DMAc	*N, N*-Dimethylformamide
BPD	4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane
MTBE	Methy *tert*-Butyl Ether
AIBN	2,2'-Azobis(2-methylpropionitrile)
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
TBAI	Tetrabutylammonium iodide
DHP	Dihydropyran
TBS	*tert*-Butyldimethylsilyl
TIPS	Triisopropylsilyl
THP	Tetrahydropyran
B_2pin_2	Bis(pinacolato)diboron

[01057] The compounds described herein can be prepared via conventional chemistry or following the general methods as shown below.

[01058] Preparation of 4-bromo-1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazole (A-2-1)





A-2-1

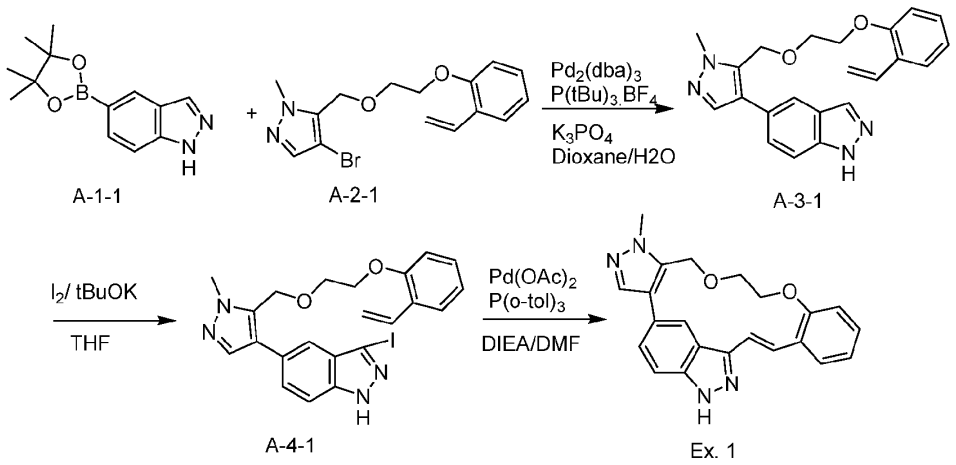
[01059] Step 1. To a solution of 4-bromo-1,5-dimethyl-pyrazole (15.0 g, 85.7 mmol, 1 eq) in CCl_4 (200 mL) was added AIBN (1.41 g, 8.57 mmol, 0.1 eq) and NBS (15.2 g, 85.7 mmol, 1 eq). The resulting mixture was stirred at 60 °C for 12 h. On completion, the mixture was concentrated. The residue was purified by column chromatography to give 4-bromo-5-(bromomethyl)-1-methyl-pyrazole (20 g, 78.76 mmol, 91.91% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ = 7.56 (s, 1H), 4.75 (s, 2H), 3.87 (s, 3H).

[01060] Step 2. To a solution of 4-bromo-5-(bromomethyl)-1-methyl-pyrazole (20.0 g, 78.8 mmol, 1 eq) in THF (400 mL) was added 2-[tert-butyl(dimethyl)silyl]oxyethanol (20.8 g, 118 mmol, 1.5 eq), TBAI (2.91 g, 7.88 mmol, 0.1 eq) and KOH (13.3 g, 236 mmol, 3 eq). The resulting mixture was stirred at 25 °C for 12 h. On completion, the mixture was concentrated. The residue was purified by column chromatography to give 2-[(4-bromo-2-methyl-pyrazol-3-yl)methoxy]ethoxy-tert-butyl-dimethyl-silane (13.19 g, 37.76 mmol, 47.94% yield) as a brown oil.

[01061] Step 3. To a solution of 2-[(4-bromo-2-methyl-pyrazol-3-yl)methoxy]ethoxy-tert-butyl-dimethyl-silane (13.1 g, 37.5 mmol, 1 eq) in THF (132 mL) was added TBAF•$3H_2O$ (17.8 g, 56.2 mmol, 1.5 eq). The resulting mixture was stirred at 25°C for 12 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography to give 2-[(4-bromo-2-methyl-pyrazol-3-yl)methoxy]ethanol (8.8 g, 37.43 mmol, 99.83% yield) as a colorless oil.

[01062] Step 4. The mixture of 2-[(4-bromo-2-methyl-pyrazol-3-yl)methoxy]ethanol (2.00 g, 8.51 mmol, 2 eq), 2-vinylphenol (511 mg, 4.25 mmol, 1 eq) and PPh_3 (2.45 g, 9.36 mmol, 2.2 eq) in 2-MeTHF (48 mL) was stirred at 25°C for 30 min, then DIAD (1.89 g, 9.36 mmol, 2.2 eq) was added dropwise to the mixture at 0°C, the resulting mixture was stirred for another 24 h at 25°C. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 3:1) to give 4-bromo-1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazole (590 mg, 1.75 mmol, 41.13% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.56 - 7.46 (m, 2H), 7.28 - 7.19 (m, 1H), 7.02 - 6.87 (m, 3H), 5.79 (dd, J = 1.6, 17.9 Hz, 1H), 5.24 (dd, J = 1.6, 11.2 Hz, 1H), 4.62 (s, 2H), 4.18 - 4.09 (m, 2H), 3.84 (s, 3H), 3.81 - 3.77 (m, 2H).

[01063] General Method A: Preparation of (11*E*)-1-methyl-1,18,19,21-tetrahydro-8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,4,12,13]benzodioxadiazacyclooctadecine



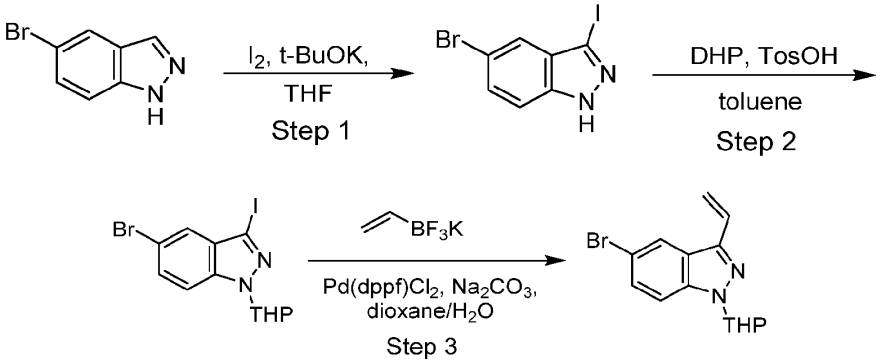
[01064] Step 1. To a mixture of 4-bromo-1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazole (567 mg, 1.68 mmol, 1 eq) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (492 mg, 2.02 mmol, 1.2 eq) in dioxane (12 mL)/H_2O (4 mL) was added K_3PO_4 (1.07 g, 5.04 mmol, 3 eq), tritert-butylphosphonium;tetrafluoroborate (48.8 mg, 0.168 mmol, 0.1 eq) and $Pd_2(dba)_3$ (77.0 mg, 84.1 mmol, 0.05 eq). The resulting mixture was stirred at 120 °C under N_2 for 24 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography give 5-[1-methyl-5-[2-(2-vinylphenoxy) ethoxymethyl]pyrazol-4-yl]-1H-indazole (380 mg, 1.01 mmol, 60.36% yield) as a colorless oil. LCMS: m/z 375.1 (M+1).

[01065] Step 2. To a solution of 5-[1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazol-4-yl]-1H-indazole (360 mg, 0.961 mmol, 1 eq) in THF (3.6 mL) was added tBuOK (324 mg, 2.88 mmol, 3 eq). The resulting mixture was stirred at 0°C for 5 min, then I_2 (317 mg, 1.25 mmol, 1.3 eq) in THF (1 mL) was added dropwise. The resulting mixture was stirred at 25 °C for another 2 h. On completion, the mixture was filtered and concentrated. The residue was purified by column chromatography to give 3-iodo-5-[1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazol-4-yl]-1H-indazole (345 mg, 0.690 mmol, 71.7% yield) as a yellow solid. LCMS: m/z 501.0 (M+1).

[01066] Step 3. To a solution of 3-iodo-5-[1-methyl-5-[2-(2-vinylphenoxy)ethoxymethyl]pyrazol-4-yl]-1H-indazole (100 mg, 0.200 mmol, 1 eq) in DMF (10 mL) was added tris-o-tolylphosphane (6.08 mg, 0.020 mmol, 0.1 eq), DIPEA (51.7 mg,

0.400 mmol, 2 eq) and $Pd(OAc)_2$ (2.24 mg, 0.01 mmol, 0.05 eq). The resulting mixture was stirred at 120 °C for 12h. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC to give Ex. 1 (20.42 mg, 0.0548 mmol, 27.43% yield) as an off-white solid.

[01067] Preparation of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (B-1-1)



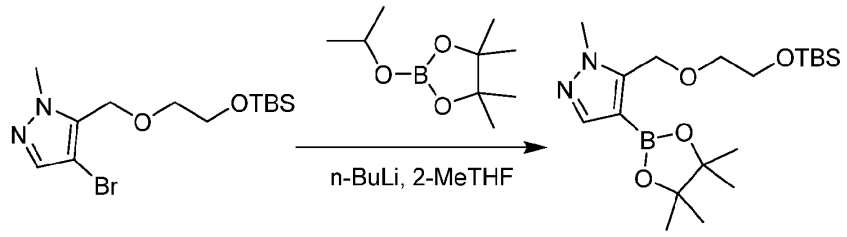
[01068] Step 1. To a solution of 5-bromo-1H-indazole (5.00 g, 25.3 mmol, 1 *eq*) in THF (50 mL) was added t-BuOK (5.70 g, 50.7 mmol, 2 *eq*) at 0°C followed by addition of a solution of I_2 (7.08 g, 27.9 mmol, 1.1 *eq*) in THF (50 mL). The reaction mixture was stirred at 25°C for 12 hrs. On completion, the residue was diluted with water and then extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-bromo-3-iodo-1H-indazole (8.10 g, 98.8% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.69 (s, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.55 - 7.53 (m, 2H). LCMS: (M+1: 324.4)

[01069] Step 2. To a mixture of 5-bromo-3-iodo-1H-indazole (8.10 g, 25.0 mmol, 1 *eq*) and TosOH (863 mg, 5.02 mmol, 0.2 *eq*) in toluene (200 mL) was added DHP (5.27 g, 62.7 mmol, 2.5 *eq*). The reaction mixture was stirred at 90°C for 12 hr. On completion, the residue was diluted with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (8.30 g, 81.2% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.75 - 7.70 (m, 1H), 7.62 - 7.58 (m, 2H), 5.83 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.89 - 3.82 (m, 1H), 3.75 - 3.67 (m, 1H), 2.35 - 2.29 (m, 1H), 2.01 - 1.93 (m, 2H), 1.74 - 1.67 (m, 1H), 1.59 - 1.53 (m, 2H). LCMS: (M+1: 408.7)

[01070] Step 3. To a mixture of 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (8.30 g, 20.3 mmol, 1 *eq*) and potassium hydride;trifluoro(vinyl)boron (2.73 g, 20.3 mmol, 1 *eq*) in

dioxane (80 mL) and H_2O (12 mL) were added $Pd(dppf)Cl_2$ (1.49 g, 2.04 mmol, 0.1 *eq*) and Na_2CO_3 (6.48 g, 61.1 mmol, 3 *eq*). The reaction mixture was stirred at 80°C for 12 hrs under N_2. On completion, the residue was diluted with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (6.00 g, 19.5 mmol, 95.7% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.24 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 11.6, 17.6 Hz, 1H), 6.14 (d, *J* = 18.0 Hz, 1H), 5.85 (d, *J* = 9.6 Hz, 1H), 5.53 (d, *J* = 11.6 Hz, 1H), 3.88 (d, *J* = 11.6 Hz, 1H), 3.78 - 3.69 (m, 1H), 2.43 - 2.31 (m, 1H), 2.06 - 1.91 (m, 2H), 1.79 - 1.66 (m, 1H), 1.58 (s, 2H).

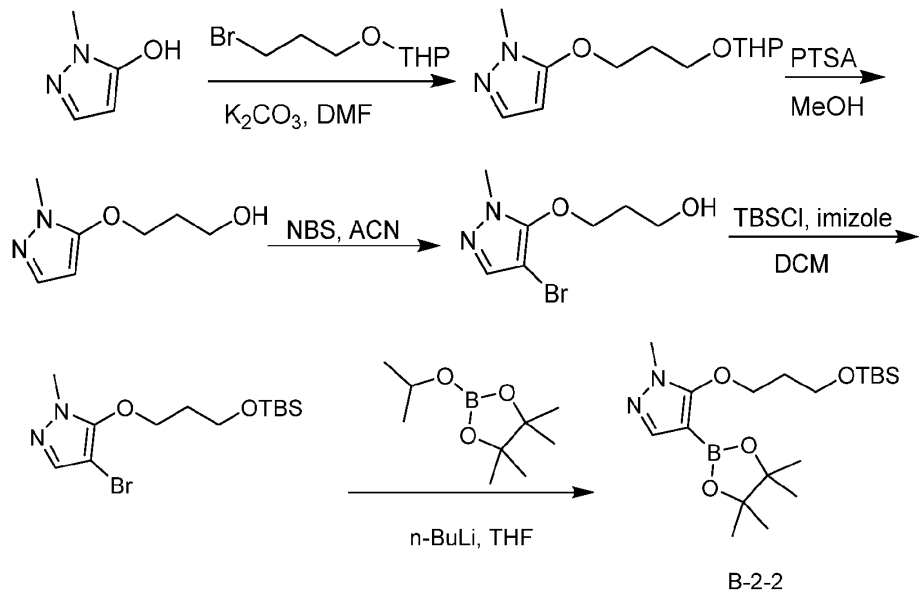
[01071] Preparation of tert-butyl-dimethyl-[2-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl] methoxy] ethoxy]silane (B-2-1)



B-2-1

[01072] To a solution of 2-[(4-bromo-2-methyl-pyrazol-3-yl)methoxy]ethoxy-tert-butyl-dimethyl-silane (2.0 g, 5.73 mmol, 1 eq) in 2-MeTHF (50 mL) was added n-BuLi (2.5 M, 3.44 mL, 1.5 eq) at -70°C. The mixture was stirred at -70°C for 0.5 hr. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 g, 11.4 mmol, 2 eq) was added and stirred at this temperature for 1.5 hrs. On completion, the mixture was added into NH_4Cl solution (60 mL), extracted with EA (3 X 100 mL), washed with brine (3 X 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=100/8) to give tert-butyl-dimethyl-[2-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl] methoxy] ethoxy]silane (1.54 g, 2.02 mmol, 35.29% yield, 52% purity) was obtained as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 4.58 (s, 2H), 3.92 (s, 3H), 3.79 - 3.77 (m, 2H), 3.75 - 3.72 (m, 2H), 1.31 (s, 12H), 0.89 (s, 9H), 0.07 (s, 6H).

[01073] Preparation of tert-butyl-dimethyl-[3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxypropoxy]silane (B-2-2)



[01074] Step 1. To a mixture of 2-methylpyrazol-3-ol (16.5 g, 168 mmol, 1 *eq*) and K_2CO_3 (69.5 g, 503 mmol, 3.00 *eq*) in DMF (700 mL) was added 2-(3-bromopropoxy)tetrahydropyran (56.1 g, 251 mmol, 1.5 *eq*). The resulting mixture was stirred at 40 °C for 12 hours. On completion, the mixture was added water (3 L) and extracted with ethyl acetate (500 ml * 5). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 1-methyl-5-(3-tetrahydropyran-2-yloxypropoxy)pyrazole (27.0 g, 112 mmol, 66.97% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 2.0 Hz, 1H), 4.59 - 4.54 (m, 1H), 4.15 - 4.09 (m, 2H), 3.88 (td, *J* = 6.4, 10.0 Hz, 1H), 3.80 (ddd, *J* = 3.2, 8.0, 11.2 Hz, 1H), 3.60 (s, 3H), 3.56 - 3.47 (m, 2H), 2.05 (t, *J* = 6.4 Hz, 2H), 1.83 - 1.74 (m, 1H), 1.72 - 1.65 (m, 1H), 1.57 - 1.47 (m, 4H).

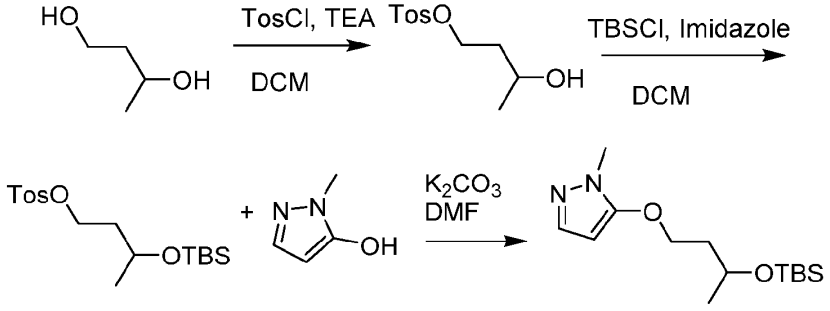
[01075] Step 2. A mixture of 1-methyl-5-(3-tetrahydropyran-2-yloxypropoxy)pyrazole (27.0 g, 112 mmol, 1 *eq*), PTSA (3.87 g, 22.4 mmol, 0.2 *eq*) in MeOH (40 mL) was stirred at 60 °C for 16 hours. On completion, the mixture was concentrated in vacuum. It was added $NaHCO_3$ solution to adjust pH to 7 and extracted with ethyl acetate (100 mL * 4). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 3-(2-methylpyrazol-3-yl)oxypropan-1-ol (11.9 g, 76.1 mmol, 67.81% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.19 (d, *J* = 2.0 Hz, 1H), 5.61 (d, *J* = 2.0 Hz, 1H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.58 - 3.53 (m, 2H), 3.52 (s, 3H), 1.86 (quin, *J* = 6.4 Hz, 2H).

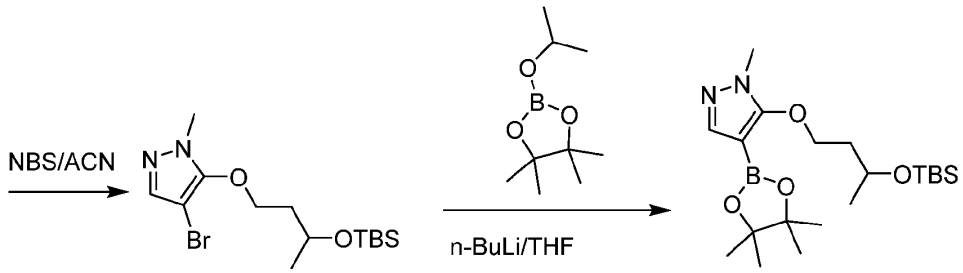
[01076] Step 3. A mixture of 3-(2-methylpyrazol-3-yl)oxypropan-1-ol (11.7 g, 74.9 mmol, 1 *eq*) in MeCN (250 mL) was added NBS (13.7 g, 77.1 mmol, 1.03 *eq*). The mixture was stirred at 25 °C for 1.5 hours. On completion, the mixture was concentrated in vacuum to give crude which was purified by prep-HPLC to give 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropan-1-ol (10.1 g, 42.9 mmol, 57.35% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (s, 1H), 4.40 (t, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.14 (s, 1H), 2.03 (quin, *J* = 6.0 Hz, 2H).

[01077] Step 4. To a solution of 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropan-1-ol (1.00 g, 4.25 mmol, 1.0 eq) in DCM (20 mL) was added imidazole (579 mg, 8.51 mmol, 2.0 eq). Then tert-butyl-chloro-dimethyl-silane (962 mg, 6.38 mmol, 782 µL, 1.5 eq) was added at 0 °C. The reaction mixture was stirred at 25 °C for 1 hr. The mixture was added to water (30 mL), extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy-tert-butyl-dimethyl-silane (1.40 g, 3.89 mmol, 91.4% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.38 (s, 1H), 4.28 (t, J = 6.0 Hz, 2H), 3.77 - 3.73 (m, 2H), 3.62 (s, 3H), 1.89 (t, J = 6.0 Hz, 2H), 0.86 (s, 9H), 0.04 (s, 6H).

[01078] Step 5. To a mixture of 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy-tert-butyl-dimethyl-silane (1.30 g, 3.72 mmol, 1.0 *eq*) in 2-MeTHF (20 mL) was added *n*-BuLi (1 M, 7.44 mL, 2.0 *eq*) at -78 °C for 0.5 hr, then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.08 g, 11.2 mmol, 2.28 mL, 3.0 *eq*) was added at -78 °C for 1 hr. The mixture was diluted with water (40 mL), extracted with EA (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give tert-butyl-dimethyl-[3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxypropoxy]silane (1.40 g, 1.17 mmol, 31.3% yield, 33.0% purity) as a yellow oil.

[01079] Preparation of tert-butyl-dimethyl-[1-methyl-3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl] oxy-propoxy] silane (B-2-3)





B-2-3

[01080] Step 1. To a solution of butane-1,3-diol (5.35 g, 59.4 mmol, 1.0 ***eq***) in DCM (50 mL) were added TEA (18.0 g, 178 mmol, 24.8 mL, 3.0 ***eq***) and DMAP (218 mg, 1.78 mmol, 0.03 ***eq***) followed by addition of 4-methylbenzenesulfonyl chloride (12.5 g, 65.3 mmol, 1.1 ***eq***) at 0 °C. The mixture was stirred at 0-20 °C for 16 hr, quenched with water (200 mL), and extracted with ethyl acetate (100 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 3-hydroxybutyl 4-methylbenzenesulfonate (15.2 g, crude) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.71 (s, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 4.16 (dd, *J* = 5.2, 10.0 Hz, 1H), 4.07 - 4.01 (m, 2H), 3.90 - 3.81 (m, 1H), 3.90 - 3.80 (m, 1H), 2.38 (s, 4H), 1.96 - 1.93 (m, 1H), 1.79 - 1.70 (m, 1H), 1.67 - 1.57 (m, 1H), 1.10 (d, *J* = 6.0 Hz, 3H).

[01081] Step 2. To a solution of 3-hydroxybutyl 4-methylbenzenesulfonate (15.0 g, 61.4 mmol, 1.0 ***eq***) in DCM (150 mL) and imidazole (8.36 g, 123 mmol, 2.0 ***eq***) was added TBSCl (11.1g, 73.7 mmol, 9.03 mL, 1.2 ***eq***) at 0 °C. The mixture was stirred at 25 °C for 1 hr. The mixture was quenched with water (500 mL) and extracted with ethyl acetate (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 3-[tert-butyl(dimethyl)silyl]oxybutyl 4-methylbenzenesulfonate (23.4 g, crude) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.86 (s, 1H), 7.84 (s, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 4.16 - 4.09 (m, 2H), 3.92 (ddd, *J* = 4.2, 6.0, 7.6 Hz, 1H), 2.59 (s, 3H), 1.83 - 1.65 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

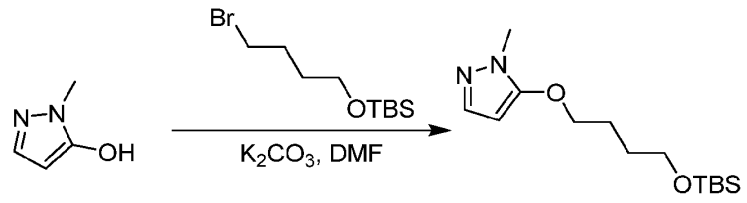
[01082] Step 3. To a solution of 2-methylpyrazol-3-ol (5.20 g, 53.0 mmol, 1.0 ***eq***) in DMF (50 mL) were added K_2CO_3 (22.0 g, 159 mmol, 3.0 ***eq***) and 3-[tert-butyl(dimethyl)silyl]oxybutyl 4-methylbenzenesulfonate (22.8 g, 63.6 mmol, 1.2 ***eq***). The mixture was stirred at 80 °C for 16 hr, quenched with water (200 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to

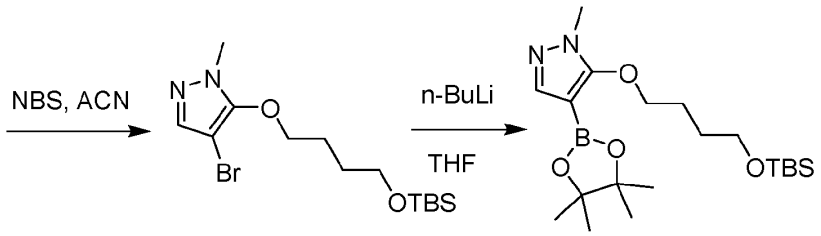
give tert-butyl-dimethyl-[1-methyl-3-(2-methylpyrazol-3-yl)oxy-propoxy]silane (8.2 g, 28.8 mmol, 54.4% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.18 (d, J = 2.0 Hz, 1H), 5.57 (d, J = 2.0 Hz, 1H), 4.13 - 3.99 (m, 3H), 3.52 (s, 3H), 1.92 - 1.82 (m, 1H), 1.73 (tdd, J = 5.2, 8.4, 13.8 Hz, 1H), 1.15 (d, J = 6.0 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H).

[01083] Step 4. To a solution of tert-butyl-dimethyl-[1-methyl-3-(2-methylpyrazol-3-yl) oxy-propoxy] silane (8.00 g, 28.12 mmol, 1.0 ***eq***) in ACN (80 mL) was added NBS (5.26 g, 29.5 mmol, 1.05 ***eq***) at 0 °C. The mixture was stirred at 0-25 °C for 2 h, and then quenched with sat. aqueous Na_2SO_3(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 to give [3-(4-bromo-2-methyl-pyrazol-3-yl)oxy-1-methyl-propoxy]-tert-butyl-dimethyl-silane (5.1 g, 13.70 mmol, 48.7% yield) as a red oil. LCMS: m/z 364.9 (M+1).

[01084] Step 5. To a solution of [3-(4-bromo-2-methyl-pyrazol-3-yl)oxy-1-methyl-propoxy]-tert-butyl-dimethyl-silane (5.00 g, 13.8 mmol, 1.0 *eq*) in THF (50 mL) was added n-BuLi (2.5 M, 13.8 mL, 2.5 *eq*) at -70 °C. The mixture was stirred at -70 °C for 1h. Then 2-isopropoxy-4,4,5-trimethyl-1,3,2-dioxaborolane (7.10 g, 41.3 mmol, 3.0 *eq*) was added. The mixture was stirred at -70 °C for 3h, then quenched with NH_4Cl (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give tert-butyl-dimethyl-[1-methyl-3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl] oxy-propoxy] silane (3.25 g, 5.70 mmol, 41.4% yield) as a colorless oil. LCMS: m/z 411.3 (M+1).

[01085] Preparation of tert-butyl-dimethyl-[4-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxybutoxy]silane (B-2-4)





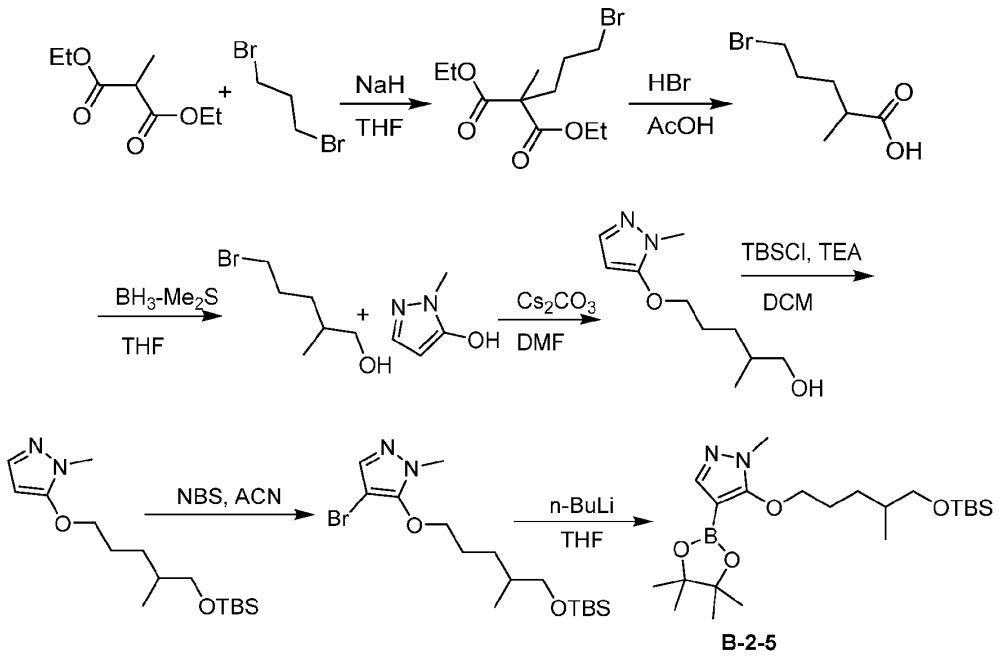
B-2-4

[01086] Step 1. To a solution of 2-methylpyrazol-3-ol (2.50 g, 25.5 mmol, 1 ***eq***) and 4-bromobutoxy-tert-butyl-dimethyl-silane (8.17 g, 30.6 mmol, 1.2 ***eq***) in DMF (50 mL) was added K_2CO_3 (10.6 g, 76.5 mmol, 3 ***eq***). The resulting mixture was stirred at 80 °C for 2 hr. On completion, the mixture was extracted with ethyl acetate (25 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 5-(4-((tert-butyldimethylsilyl)oxy)butoxy)-1-methyl-1H-pyrazole (5.30 g, 18.5 mmol, 65.0% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.17 (s, 1H), 5.58 (s, 1H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.66 - 3.66 (m, 1H), 3.67 - 3.60 (m, 1H), 3.53 - 3.49 (m, 3H), 1.80 - 1.72 (m, 2H), 1.64 - 1.55 (m, 2H), 1.40 - 1.32 (m, 1H), 0.86 (s, 10H), 0.05 - 0.02 (m, 6H).

[01087] Step 2. To a solution of tert-butyl-dimethyl-[4-(2-methylpyrazol-3-yl)oxybutoxy]silane (5.10 g, 17.9 mmol, 1 ***eq***) in ACN (50 mL) was added dropwise NBS (3.51 g, 19.7 mmol, 1.1 ***eq***) at 0 °C. On completion, the mixture was quenched with sat. aqueous 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. The residue was purified by column chromatography to give 4-bromo-5-(4-((tert-butyldimethylsilyl)oxy)butoxy)-1-methyl-1H-pyrazole (3.00 g, 8.22 mmol, 44.2% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ = 7.40 (s, 1H), 4.24 - 4.19 (m, 2H), 3.66 - 3.62 (m, 2H), 3.62 (s, 3H), 1.86 - 1.69 (m, 2H), 1.69 - 1.54 (m, 2H), 0.88 - 0.82 (m, 9H), 0.07 - -0.02 (m, 6H)

[01088] Step 3. 4-Bromo-5-(4-((tert-butyldimethylsilyl)oxy)butoxy)-1-methyl-1H-pyrazole was converted to B-2-4 using the same condition as Step 5 in B-2-2.

[01089] Preparation of tert-butyl-dimethyl-[2-methyl-5-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxy-pentoxy]silane (B-2-5)



B-2-5

[01090] Step 1. A mixture of diethyl 2-methylpropanedioate (20.0 g, 115 mmol, 19.6 mL, 1 *eq*) in THF (300 mL) the mixture was stirred at 0 °C followed by addition of NaH (11.5 g, 287 mmol, 60% purity, 2.5 *eq*). Then the mixture was stirred at 25 °C for 0.5 hr and 1,3-dibromopropane (69.5 g, 344 mmol, 35.1 mL, 3 *eq*) was added to the reaction mixture. And then the mixture was stirred at 25 °C for 1 h and at 60 °C for 16 h. On completion, the mixture was quenched by H_2O (250 mL) and extracted with EtOAc (150 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give diethyl 2-(3-bromopropyl)-2-methyl-propanedioate (18.8 g, 63.7 mmol, 55% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.22 - 4.14 (m, 4H), 3.39 (t, J = 6.4 Hz, 2H), 2.01 - 1.95 (m, 2H), 1.89 - 1.79 (m, 2H), 1.41 (s, 3H), 1.25 (t, J = 7.2 Hz, 6H).

[01091] Step 2. A solution of diethyl 2-(3-bromopropyl)-2-methyl-propanedioate (18.6 g, 63.0 mmol, 1 *eq*) and HBr in HOAc (93 mL, 48% purity) was heated to reflux for 16 h in a 100 °C. On completion, the mixture was quenched by H_2O (200 mL) and extracted with EtOAc (100 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give 5-bromo-2-methyl-pentanoic acid (9.10 g, 46.7 mmol, 74% yield) as a brown oil, which was used into the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.46 - 3.37 (m, 2H), 2.54 - 2.46 (m, 1H), 1.97 - 1.84 (m, 3H), 1.69 - 1.60 (m, 1H), 1.24 - 1.21 (m, 3H).

[01092] Step 3. To a solution of 5-bromo-2-methyl-pentanoic acid (9.00 g, 46.1 mmol, 1 *eq*) in THF (90 mL) at 0 °C was added BH_3-Me_2S (10 M, 23.1 mL, 5 *eq*). The mixture was stirred at 20 °C for 3h. On completion, the reaction mixture was quenched with MeOH (30 mL). The mixture was filtered and concentrated under reduced pressure to give 5-bromo-2-methyl-pentan-1-ol (9.37 g, crude) as a brown oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.53 - 3.45 (m, 2H), 3.44 - 3.37 (m, 2H), 1.96 - 1.83 (m, 2H), 1.68 - 1.63 (m, 2H), 1.20 - 1.15 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H).

[01093] Step 4. A mixture of 5-bromo-2-methyl-pentan-1-ol (9.37 g, 51.8 mmol, 1 *eq*), 2-methylpyrazol-3-ol (11.2 g, 114 mmol, 2.2 *eq*), Cs_2CO_3 (50.6 g, 155 mmol, 3 *eq*) in DMF (94 mL) was stirred at 80 °C for 16 h. On completion, the residue was diluted with H_2O (500 mL) and extracted with EtOAc (100 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give 2-methyl-5-(2-methylpyrazol-3-yl)oxy-pentan-1-ol (3.20 g, 16.1 mmol, 31% yield) as a brown oil. LCMS: m/z 199.0 (M+1).

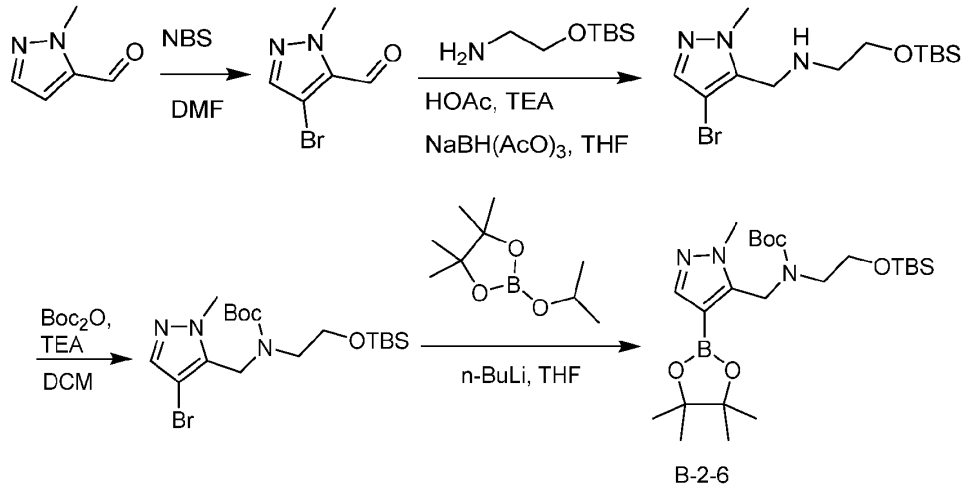
[01094] Step 5. A mixture of 2-methyl-5-(2-methylpyrazol-3-yl)oxy-pentan-1-ol (3.20 g, 16.1 mmol, 1 *eq*), TBSCl (3.65 g, 24.2 mmol, 2.97 mL, 1.5 *eq*), imidazole (2.20 g, 32.3 mmol, 2 *eq*) in DCM (18 mL) was stirred at 0 °C, and then at 25 °C for 16 h. On completion, the mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give tert-butyl-dimethyl-[2-methyl-5-(2-methylpyrazol-3-yl)oxy-pentoxy]silane (4.4 g, 14.1 mmol, 87% yield) as a brown oil. LCMS: m/z 313.6 (M+1).

[01095] Step 6. To a solution of tert-butyl-dimethyl-[2-methyl-5-(2-methylpyrazol-3-yl)oxy-pentoxy]silane (4.40 g, 14.1 mmol, 1 *eq*) in ACN (44 mL) was added NBS (2.51 g, 14.1 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0-25 °C for 3 h. On completion, the reaction mixture was quenched by addition of sat. aqueous Na_2SO_3 (25 mL) at 20 °C, and extracted with EtOAc (30 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give {[5-(4-bromo-2-methyl-pyrazol-3-yl)oxy-2-methyl-pentoxy]-tert-butyl-dimethyl-silane (3.30 g, 8.43 mmol, 60% yield) as a brown oil. LCMS: m/z 392.9 (M+1)

[01096] Step 7. To a solution of [5-(4-bromo-2-methyl-pyrazol-3-yl)oxy-2-methyl-pentoxy]-tert-butyl-dimethyl-silane (4.60 g, 11.75 mmol, 1 *eq*) in THF (70 mL) at -78 °C was added n-BuLi (2.5 M, 9.40 mL, 2 *eq*) and stirred at -78 °C for 0.5 h followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.56 g, 35.3 mmol, 7.19 mL, 3 *eq*). The mixture was stirred at -78 °C for 1.5 h. On completion, the mixture was quenched by sat.

aqueous NH_4Cl (50 mL) and extracted with EtOAc (50 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give tert-butyl-dimethyl-[2-methyl-5-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxy-pentoxy]silane (4.75 g, 10.8 mmol, 92% yield) as a brown oil. LCMS: 439.2 (M+1).

[01097] Preparation of tert-butyl N-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-N-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methyl]carbamate (B-2-6)



[01098] Step 1. To a mixture of 2-methylpyrazole-3-carbaldehyde (20.0 g, 181 mmol, 1 *eq*) in DMF (350 mL) was added NBS (32.3 g, 181 mmol, 1 *eq*) at 0 °C. The reaction mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was quenched with water (1000 mL), filtered and dried to afford 4-bromo-2-methyl-pyrazole-3-carbaldehyde (34.0 g, 179 mmol, 99% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.78 (s, 1H), 4.09 (s, 3H).

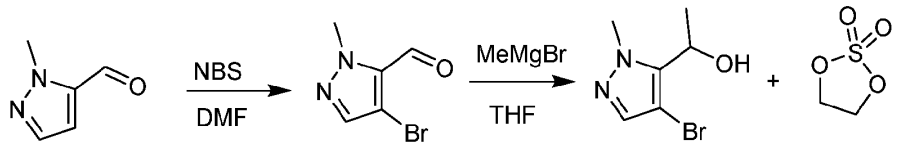
[01099] Step 2. To a mixture of 2-[tert-butyl(dimethyl)silyl]oxyethanamine (13.2 g, 75.6 mmol, 1.1 *eq*) in THF (20 mL) was added TEA (6.96 g, 68.7 mmol, 9.57 mL, 1 *eq*) followed by addition of 4-bromo-2-methyl-pyrazole-3-carbaldehyde (13.0 g, 68.7 mmol, 1 *eq*) and HOAc (4.13 g, 68.7 mmol, 3.93 mL, 1 *eq*). The reaction mixture was stirred at 60 °C for 0.5 hour. To the reaction mixture was then added $NaBH(OAc)_3$ (18.9 g, 89.4 mmol, 1.3 *eq*). The reaction mixture was stirred at 60°C for 12 hours. On completion, the mixture was diluted with water (90 mL) and extracted with EA (2 X 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified

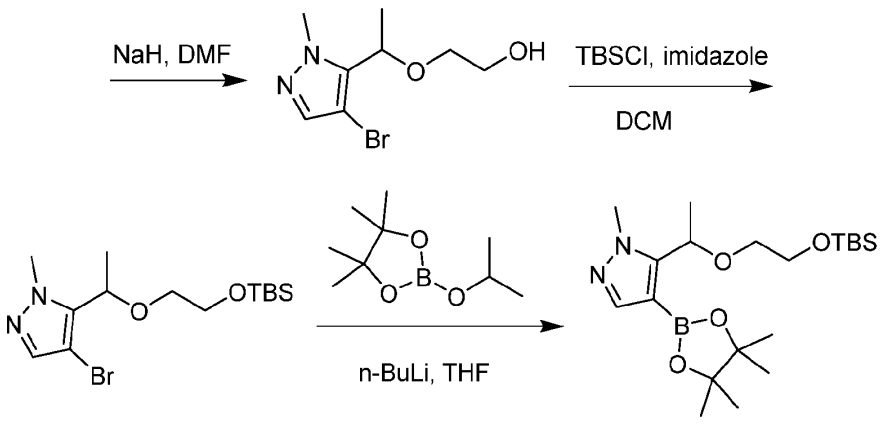
by column chromatography to afford N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl)silyl]oxy-ethanamine (6.00 g, 17.2 mmol, 25% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 3.83 - 3.82 (m, 3H), 3.75 (s, 2H), 3.58 (t, J = 6.0 Hz, 2H), 3.29 (s, 2H), 1.97 (s, 1H), 0.83 (s, 9H), 0.01 (m, 6H).

[01100] Step 3. To a mixture of N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl) silyl]oxy-ethanamine (11.0 g, 31.5 mmol, 1 *eq*) in DCM (100 mL) was added TEA (9.59 g, 94.7 mmol, 13.1 mL, 3 *eq*) and Boc_2O (10.3 g, 47.3 mmol, 10.8 mL, 1.5 *eq*). The reaction mixture was stirred at 25°C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography to afford tert-butyl N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-N-[2-[tert-butyl(dimethyl)silyl] oxyethyl]carbamate (9.40 g, 20.9 mmol, 66% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1H), 4.56 (s, 2H), 3.78 (s, 3H), 3.59 (t, J = 6.0 Hz, 2H), 3.20 - 3.10 (m, 2H), 1.44 - 1.36 (m, 9H), 0.86 (s, 9H), 0.02 (s, 6H)

[01101] Step 4. To a mixture of tert-butyl N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]carbamate (7.50 g, 16.7 mmol, 1 *eq*) in THF (100 mL) was added n-BuLi (2.5 M, 20.0 mL, 3 *eq*) at -70°C. The reaction mixture was stirred at -70°C for 0.5 hour followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.33 g, 50.1 mmol, 10.2 mL, 3 *eq*). The reaction mixture was stirred at -70°C for 1.5 hours. On completion, the residue was diluted with water (80 mL) and extracted with EA (2 X 90 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford tert-butyl N-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-N-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methyl]carbamate (7.00 g, 14.1 mmol, 84% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1H), 4.68 (s, 2H), 3.74 (s, 3H), 3.47 (s, 2H), 3.13 (s, 2H), 1.41 (s, 9H), 1.25 (s, 12H), 0.83 (s, 9H), -0.01 (s, 6H)

[01102] Preparation of 5-(1-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (B-2-7)





B-2-7

[01103] Step 1. To a solution of 2-methylpyrazole-3-carbaldehyde (25.0 g, 227 mmol, 1 eq) in DMF (250 mL) was added NBS (40.4 g, 227 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. To the mixture was added water (150 mL), and the mixture was extracted with EtOAc (50 mL*5). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 4-bromo-1-methyl-1H-pyrazole-5-carbaldehyde (40.0 g, 222 mmol, 93.2% yield) as a white solid. LCMS: m/z 190.8 (M+1)

[01104] Step 2. To a solution of 4-bromo-2-methyl-pyrazole-3-carbaldehyde (36.0 g, 190 mmol, 1 ***eq***) in THF (360 mL) was added MeMgBr (3 M, 95.23 mL, 1.5 ***eq***) at 0 °C after degassing and purging with N_2 for 3 times. The mixture was stirred at 25 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by addition NH_4Cl 600 mL at 0 °C, and then diluted with H_2O (100 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give 1-(4-bromo-1-methyl-1H-pyrazol-5-yl)ethanol (27.0 g, 132 mmol, 69.1% yield) as a yellow oil. LCMS: m/z 206.9 (M+1).

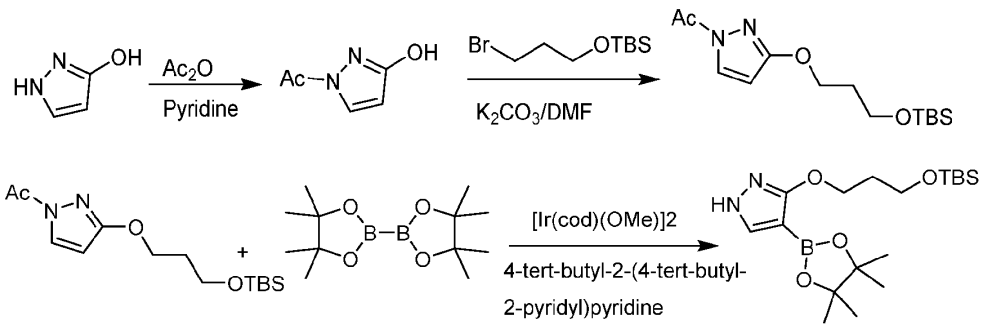
[01105] Step 3. To a solution of 1-(4-bromo-2-methyl-pyrazol-3-yl)ethanol (27.0 g, 131 mmol, 1 ***eq***) in DMF (270 mL) was added NaH (10.5 g, 263 mmol, 60% purity, 2 ***eq***) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then 1,3,2-dioxathiolane 2,2-dioxide (32.7 g, 263 mmol, 2 ***eq***) was added. The mixture was stirred at 25 °C for 16 hr. The mixture was quenched with aqueous HCl (1 M, 350 mL), and the mixture was extracted with EtOAc. The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 2-(1-(4-bromo-1-methyl-1H-pyrazol-5-yl)ethoxy)ethanol(40.0 g, 160 mmol, crude) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.15 (s, 3H), 7.99 - 7.90 (m, 8H), 7.48 - 7.44 (m, 1H), 4.84 - 4.68 (m, 1H),

4.26 - 4.03 (m, 2H), 3.87 (d, J = 5.8 Hz, 3H), 3.62 - 3.43 (m, 3H), 3.41 - 3.22 (m, 2H), 2.88 (s, 26H), 2.49 (t, J = 5.2 Hz, 19H), 1.44 - 1.36 (m, 3H).

[01106] Step 4. To a solution of 2-[1-(4-bromo-2-methyl-pyrazol-3-yl)ethoxy]ethanol (37.0 g, 148 mmol, 1 ***eq***) in DCM (370 mL) was added imidazole (20.2 g, 297 mmol, 2 ***eq***), TBSCl (33.6 g, 223 mmol, 1.5 ***eq***) at 0 °C. The mixture was stirred at 25 °C for 2 h and extracted with dichloromethane (60 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 4-bromo-5-(1-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-1-methyl-1H-pyrazole (11.0 g, 30.3 mmol, 20.4% yield) as a colorless oil. LCMS: m/z 364.9 (M+1).

[01107] Step 5. A mixture of 2-[1-(4-bromo-2-methyl-pyrazol-3-yl)ethoxy]ethoxy-tert-butyl-dimethyl-silane (5.8 g, 15.9 mmol, 1 ***eq***) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.91 g, 47.89 mmol, 3 ***eq***) in THF (58 mL) was degassed and purged with N_2 for 3 times followed by addition of n-BuLi (2.5 M, 19.15 mL, 3 ***eq***). The mixture was stirred at -68 °C for 2 h under N_2 atmosphere and then warmed to ambient temperature. The mixture was quenched with sat. aqueous 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 a residue. The residue was purified by column chromatography to give 5-(1-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.20 g, 12.4 mmol, 77.8% yield) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.45 (s, 1H), 5.18 - 5.11 (m, 1H), 3.92 - 3.84 (m, 3H), 3.70 - 3.59 (m, 2H), 3.34 - 3.26 (m, 1H), 3.24 - 3.17 (m, 1H), 1.43 - 1.39 (m, 3H), 1.24 (s, 12H), 0.85 - 0.80 (m, 9H), 0.00 (s, 6H).

[01108] Preparation of tert-butyl-dimethyl-[3-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl]oxy]propoxy]silane (B-2-8)



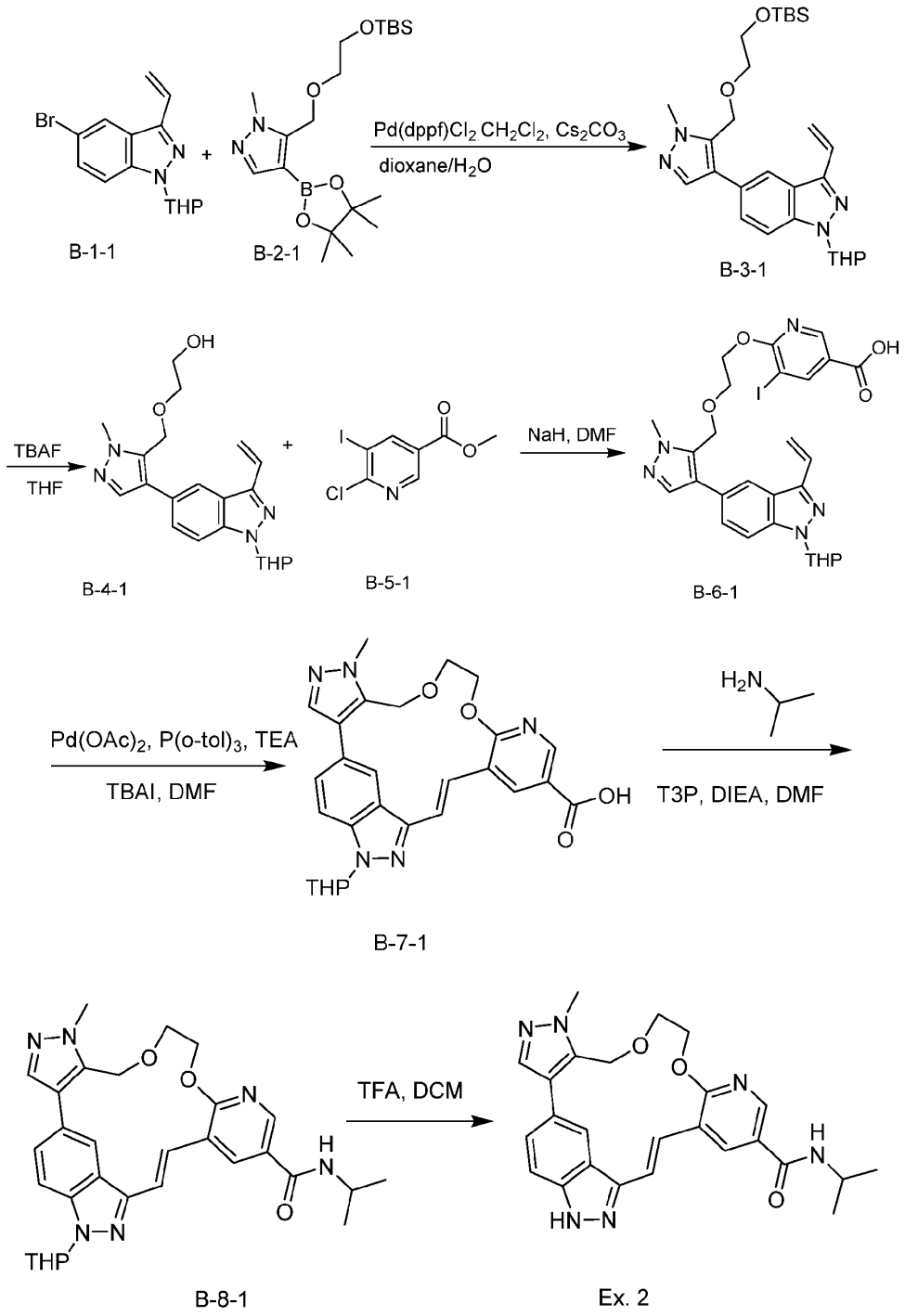
[01109] **Step 1.** To a mixture of 1H-pyrazol-3-ol (10.0 g, 119 mmol, 1 eq) in Pyridine

(50 mL) was stirred at 95 °C for 0.5 h. The acetic anhydride (12.1 g, 119 mmol, 1 eq) in pyridine (50 mL) was added to the mixture reaction. The reaction was stirred at 95 °C for 2.5 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (80 mL) and extracted with EtOAc (3 X 120 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue, which was triturated with PE (30 ml), filtered and dried under vacuo to afford 1-(3-hydroxypyrazol-1-yl)ethanone (12.0 g, 95.15 mmol, 80.00% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.97 (s, 1H), 8.13 (s, 1H), 6.00 (s, 1H), 2.47 (s, 3H).

[01110] Step 2. To a mixture of 1-(3-hydroxypyrazol-1-yl)ethanone (12.0 g, 95.2 mmol, 1 eq) and 3-bromopropoxy-tert-butyl-dimethyl-silane (26.5 g, 105 mmol, 1.1 eq) in DMF (100 mL) was added K_2CO_3 (39.4 g, 285 mmol, 3 eq). The reaction mixture was stirred at 60 °C for 4 h. On completion, the residue was diluted with water (300 mL) and extracted with EA (3 X 300mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford 1-[3-[3-[tertbutyl(dimethyl)silyl]oxypropoxy] pyrazol-1-yl]ethanone (24.0 g, 80.4 mmol, 84.5% yield) as yellow oil. LCMS: m/z 299.4 (M+1).

[01111] Step 3. To a mixture of 1-[3-[3-[tertbutyl(dimethyl)silyl]oxypropoxy] pyrazol-1-yl]ethenone (5.00 g, 16.7 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 (12.8 g, 50.3 mmol, 3 eq)in THF (50 mL) was added 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (899 mg, 3.35 mmol, 0.2 eq) and (1Z,5Z)-cycloocta-1,5-diene;2,4-dimethyl-BLAHbicyclo[1.1.0]butane (1.11 g, 1.68 mmol, 0.1 eq). The reaction mixture was stirred at 90 °C for 12 h. On completion, the residue was diluted with water (50 mL) and extracted with EA (3 X 80mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford tert-butyl-dimethyl-[3-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl]oxy]propoxy]silane (6.00 g, 15.7 mmol, 93.7% yield) as yellow solid. LCMS: m/z 383.1 (M+1)

[01112] General Method B: Preparation of (18*E*)-8-methyl-*N*-(propan-2-yl)-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4'',3'':13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide (Ex. 2)



[01113] Step 1. To a solution of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (381 mg, 1.24 mmol, 1 *eq*) and tert-butyl-dimethyl-[2-[[2-methyl-4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methoxy]ethoxy]silane (1.25 g, 1.86 mmol, 59% purity, 1.5*eq*) in mixture of solvent of dioxane (12 mL) and H_2O (3 mL) was added Cs_2CO_3 (1.21 g, 3.72 mmol, 3 *eq*) and ditertbutyl(cyclopentyl)phosphane;dichloropalladium;iron (80.8 mg, 124 umol, 0.1 *eq*) .The mixture was stirred at 90 °C for 8 hr under N2. On completion, the mixture was filtered , diluted with H_2O (50 mL), extracted with EA (3 X 50 mL), washed with brine (3 X 50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford tert-butyl-dimethyl-[2-[[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethoxy]silane (1.1 g, 2.21 mmol, 89.2% yield) as a brown oil.

[01114] Step 2. To a mixture of tert-butyl-dimethyl-[2-[[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethoxy]silane (1.20 g, 2.42 mmol, 1 *eq*) in THF (5 mL) was added TBAF (1 M, 3.62 mL, 1.5 *eq*) at 0°C. The reaction mixture was stirred at 25°C for 1 hr. On completion, the residue was diluted with water (30 mL), then the residue was extracted with EA (3 X 70mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography to give 2-[[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethanol (650 mg, 1.70 mmol, 70.3% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.98 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.54 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.03 (dd, *J* = 11.6, 18.0 Hz, 1H), 6.12 (d, *J* = 18.0 Hz, 1H), 5.85 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.53 (d, *J* = 11.6 Hz, 1H), 4.58 (s, 2H), 3.90 (s, 4H), 3.80 - 3.71 (m, 2H), 3.62 - 3.50 (m, 5H), 1.98 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 2H).

[01115] Step 3. To a mixture of 2-||2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethanol (50.0 mg, 0.130 mmol, 1 *eq*) in DMF (5 mL) was added NaH (7.84 mg, 0.196 mmol, 60% purity, 1.5 *eq*) at 0°C for 30min, then the methyl 6-chloro-5-iodo-pyridine-3-carboxylate (38.8 mg, 0.130 mmol, 1 *eq*) was added . The reaction mixture was stirred at 100°C for 12 hrs. On completion, the residue was diluted with water (5 mL), then the residue was extracted with EA (3 X 10mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by prep-HPLC to give 5-iodo-6-[2-[[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethoxy] pyridine-3-carboxylic acid (16.0 mg, 0.0254 mmol, 19% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.62 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 2.0 Hz, 1H), 7.96 (s, 1H), 7.70 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.50 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.99 (dd, *J* = 11.6, 18.0 Hz, 1H), 6.10 (dd, *J* = 0.8, 18.0 Hz, 1H), 5.80 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.50 - 5.45 (m, 1H), 4.70 (s, 2H), 4.57 - 4.53 (m, 2H), 3.95 - 3.89 (m, 6H), 3.78 -

3.71 (m, 1H), 2.42 - 2.36 (m, 1H), 2.09 - 1.91 (m, 3H), 1.82 - 1.69 (m, 1H), 1.63 - 1.54 (m, 2H).

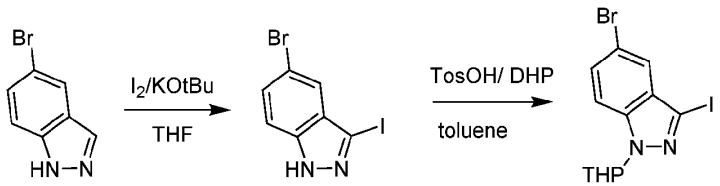
[01116] Step 4. To a mixture of 5-iodo-6-[2-[[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]methoxy]ethoxy]pyridine-3-carboxylic acid (16.0 mg, 0.0254 mmol, 1 *eq*) in DMF (1 mL) was added $Pd(OAc)_2$ (2.85 mg, 0.127 mmol, 0.5 *eq*), TEA (10.2 mg, 0.101 mmol, 4 *eq*),TBAI (0.94 mg, 0.00254 mmol, 0.1 *eq*) and $P(o\text{-}tolyl)_3$ (3.87 mg, 0.012.7 mmol, 0.5 *eq*). The reaction mixture was stirred at 60°C for 12 hrs. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give B-7-1 (12.0 mg, 23.9 umol, 94.1% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 13.32 - 12.85 (m, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 8.05 (d, *J* = 17.2 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.64 - 7.54 (m, 2H), 5.91 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.66 (s, 2H), 4.60 - 4.55 (m, 2H), 4.05 - 4.00 (m, 2H), 3.95 - 3.87 (m, 4H), 3.80 - 3.74 (m, 1H), 2.10 - 1.98 (m, 3H), 1.81 - 1.72 (m, 1H), 1.63 - 1.62 (m, 2H).

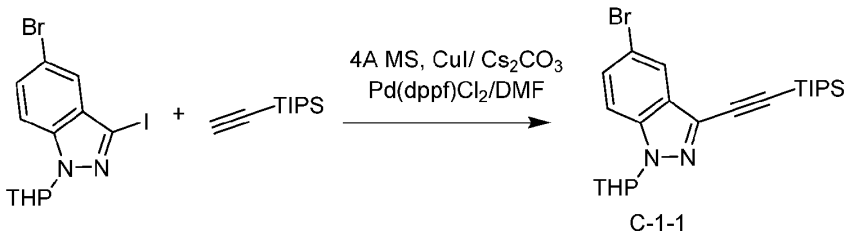
[01117] Step 5 To a mixture of B-7-1 (6.00 mg, 0.0119 mmol, 1 *eq*) in DCM (1 mL) were added T_3P (4.57 mg, 0.0143 mmol, 1.2 *eq*), DIEA (4.64 mg, 0.0358 mmol, 3 *eq*), and a solution of propan-2-amine (1.41 mg, 0.0239 mmol, 2 *eq*) in DCM (1 mL). The reaction mixture was stirred at 25°C for 1 hr. On completion, the residue was quenched with water (0.5 mL) and extracted with DCM (3 X 5mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give B-8-1 (6.00 mg, 0.011 mmol, 92.4% yield) as yellow oil.

[01118] Step 6. To a mixture of B-8-1 (6 mg, 0.011 mmol, 1 *eq*) in DCM (0.5 mL) was added TFA (770 mg, 6.75 mmol, 610 *eq*). The reaction mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC to give Ex. 2 (1.84 mg, 0.0032 mmol, 28.7% yield) as an off-white solid.

[01119] Ex. 3--Ex. 5 were prepared using General Method B with corresponding amines for the amide formation.

[01120] Preparation of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (C-1-1)





C-1-1

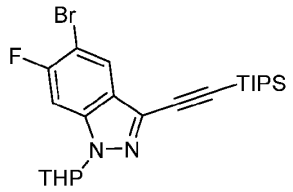
[01121] Step 1. A solution of 5-bromo-1H-indazole (21.0 g, 107 mmol, 1 ***eq***) in THF (250 mL) was cooled down on an ice bath and KOtBu (35.9 g, 320 mmol, 3 ***eq***) was added portion wise. The resulting slurry was stirred at 0 °C and a solution of I_2 (54.1 g, 213 mmol, 42.9 mL, 2 ***eq***) in THF (250 mL) was added dropwise. The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1H-indazole (120 g, 350 mmol, 82% yield, 94% purity) as a white solid. LCMS: 324.7 (M+1).

[01122] Step 2. To a mixture of 5-bromo-3-iodo-1H-indazole (25.0 g, 77.4 mmol, 1 ***eq***) and 3,4-dihydro-2H-pyran (13.0 g, 155 mmol, 2 ***eq***) in toluene (250 mL) was added 4-methylbenzenesulfonic acid (2.67 g, 15.5 mmol, 0.2 ***eq***). The mixture was stirred at 90 °C for 12 hours. On completion, the reaction was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (24.0 g, 58.9 mmol, 76% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 1.6 Hz, 1H), 7.54 - 7.44 (m, 2H), 5.68 (dd, *J* = 3.2, 9.1 Hz, 1H), 4.04 - 3.95 (m, 1H), 3.79 - 3.66 (m, 1H), 2.58 - 2.46 (m, 1H), 2.20 - 2.03 (m, 2H), 1.87 - 1.54 (m, 3H).

[01123] Step 3. To a mixture of 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (23.0 g, 56.5 mmol, 1 ***eq***) and ethynyl(triisopropyl)silane (11.3 g, 62.2 mmol, 1.1 ***eq***) in DMF (250 mL) was added Cs_2CO_3 (55.2 g, 170 mmol, 3 ***eq***), $Pd(dppf)Cl_2$ (2.48 g, 3.39 mmol, 0.06 ***eq***) and CuI (646 mg, 3.39 mmol, 0.06 ***eq***) under N_2. The mixture was stirred at 25 °C for 3 hours. On completion, the reaction was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford compound 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-

yl)ethynyl-triisopropyl-silane (II-1-1, 38.0 g, 79.9 mmol, 70% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.57 - 7.43 (m, 2H), 5.70 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.02 (bd, *J* = 11.2 Hz, 1H), 3.80 - 3.65 (m, 1H), 2.59 - 2.41 (m, 1H), 2.14 (d, *J* = 3.2 Hz, 1H), 2.08 (s, 1H), 1.79 - 1.70 (m, 2H), 1.67 (s, 1H), 1.22 - 1.18 (m, 18H), 1.18 - 1.14 (m, 3H).

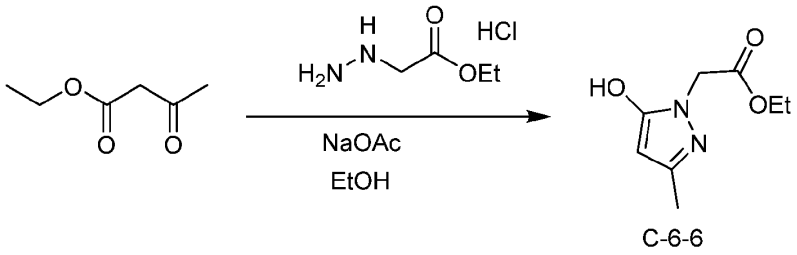
[01124] Preparation of 2-(5-bromo-6-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (C-1-2)



C-1-2

[01125] C-1-2 was prepared following similar methods as C-1-1 using 5-bromo-6-fluoro-1H-indazole as starting material.

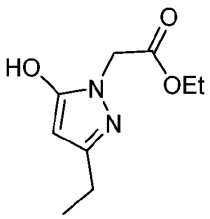
[01126] Preparation of Ethyl 2-(5-hydroxy-3-methyl-pyrazol-1-yl) acetate (C-6-6)



C-6-6

[01127] To a solution of ethyl 2-hydrazinoacetate;hydrochloride (19.0 g, 123 mmol, 1 ***eq***) in EtOH (200 mL) were added NaOAc (10.1 g, 123 mmol, 1 ***eq***) and ethyl 3-oxobutanoate (14.3 g, 123 mmol, 13.2 mL, 1 ***eq***). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was purified by column chromatography to provide ethyl 2-(5-hydroxy-3-methyl-pyrazol-1-yl) acetate (16.0 g, 86.9 mmol, 70.7% yield) as white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.41 (s, 2H), 4.27 - 4.14 (m, 2H), 3.25 (s, 2H), 2.11 (s, 3H), 1.28 (d, *J* = 7.2 Hz, 3H).

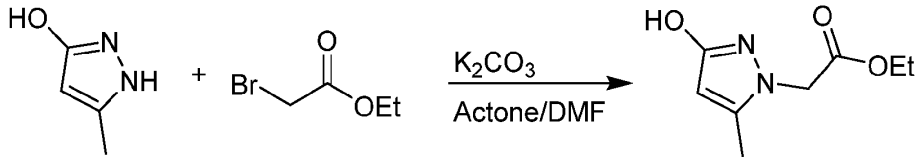
[01128] Preparation of Ethyl 2-(5-hydroxy-3-ethyl-pyrazol-1-yl) acetate (C-6-7)



C-6-7

[01129] C-6-7 was prepared with the same method as C-6-6 using ethyl 3-oxopentanoate as starting material.

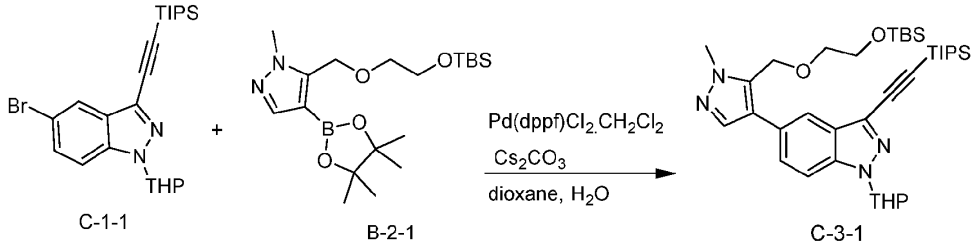
[01130] Preparation of ethyl 2-(3-hydroxy-5-methyl-pyrazol-1-yl)acetate (C-6-8)



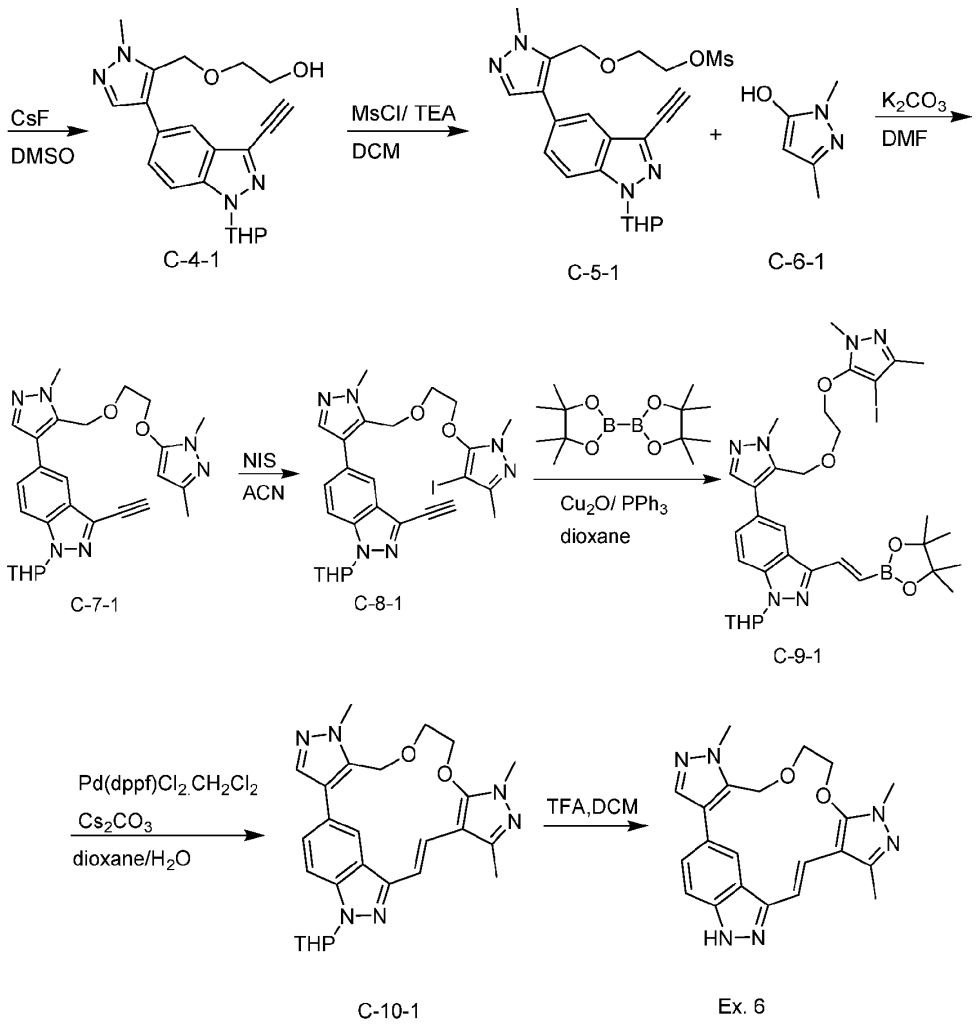
C-6-8

[01131] To a mixture of 5-methyl-1,2-dihydropyrazol-3-one (20.0 g, 204 mmol, 1 eq) and ethyl 2-bromoacetate (30.6 g, 183 mmol, 0.9 eq) in DMF (60 mL) and ACETONE (240 mL) was added K_2CO_3 (28.2 g, 204 mmol, 1 eq). The mixture was stirred at 20 °C for 3 h. On completion, the filter liquor was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (30 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to provide ethyl 2-(3-hydroxy-5-methyl-pyrazol-1-yl)acetate (10.0 g, 54.3 mmol, 26.6% yield) was as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.47 (s, 1H), 4.58 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

[01132] General Method C: Preparation of (17*E*)-8,14,16-trimethyl-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 6)



C-1-1 B-2-1 C-3-1



[01133] Step 1. A mixture of tert-butyl-dimethyl-[2-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methoxy]ethoxy]silane (11.7 g, 29.5 mmol, 1 ***eq***), 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (15.0 g, 32.5 mmol, 1.1 ***eq***), $Pd(dppf)Cl_2.CH_2Cl_2$ (2.41 g, 2.95 mmol, 0.1 ***eq***), Cs_2CO_3 (28.9 g, 88.6 mmol, 3 ***eq***) in dioxane (100 mL) and H_2O (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. After cooling down, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl-dimethyl-[2-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl] pyrazol-3-yl] methoxy] ethoxy] silane (14.2 g, 21.8 mmol, 73.9% yield) as a yellow oil. LCMS: m/z 651.8 (M+1)

[01134] Step 2. A mixture of tert-butyl-dimethyl-[2-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methoxy]ethoxy]silane (1.00 g, 1.54 mmol, 1 ***eq***) and CsF (2.10 g, 13.8 mmol, 9 ***eq***) in DMSO (10 mL) at 25 °C for 38 h. The mixture was diluted with H_2O (40 mL) and extracted with EtOAc (20 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by combi flash to give 2-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methoxy]ethanol (500 mg, 1.31 mmol, 85.6% yield) was obtained as a brown oil. LCMS: m/z 381.1 (M+1).

[01135] Step 3. To a mixture of 2-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methoxy]ethanol (500 mg, 1.31 mmol, 1 *eq*) in DCM (5 mL) was added TEA (665 mg, 6.57 mmol, 5 *eq*). The mixture was stirred at 0 °C followed by addition of MsCl (452 mg, 3.94 mmol, 3 *eq*). The mixture was stirred at 20 °C for 1 hr, and quenched with sat. aqueous $NaHCO_3$ (20 mL) and extracted with DCM (20 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give crude 2-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methoxy]ethyl methanesulfonate (580 mg, 1.26 mmol, 96.2% yield) as a brown oil. LCMS: m/z 459.1 (M+1).

[01136] Step 4. To a mixture of 2-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methoxy]ethyl methanesulfonate (560 mg, 1.22 mmol, 1 *eq*) and 2,5-dimethyl-4H-pyrazol-3-one (151 mg, 1.34 mmol, 1.1 *eq*) in DMF (14 mL) was added K_2CO_3 (506 mg, 3.66 mmol, 3 *eq*) . The reaction mixture was stirred at 60 °C for 12 h. The mixture was diluted with water (20 mL), and then extracted with EtOAc (3 * 20mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to give 5-[5-[2-(2,5-dimethylpyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-3-ethynyl-1-tetrahydropyran-2-yl-indazole (370 mg, 780 umol, 63.8% yield) as a brown oil. LCMS: m/z 475.0 (M+1).

[01137] Step 5. To a solution of 5-[5-[2-(2,5-dimethylpyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-3-ethynyl-1-tetrahydropyran-2-yl-indazole (360 mg, 0.759 mmol, 1 eq) in ACN (11 mL) was added NIS (154 mg, 0.683 mmol, 0.9 eq) at 0 °C. The mixture was stirred at 0 °C for 1h. The reaction mixture was quenched by addition of aqueous Na_2SO_3 solution (1 M, 15 mL) at 20 °C, and extracted with EtOAc (30 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give 3-ethynyl-5-[5-[2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-

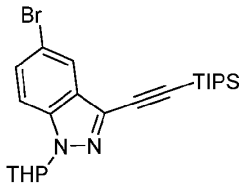
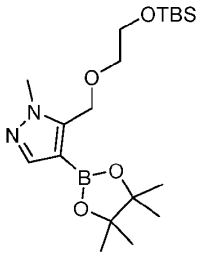
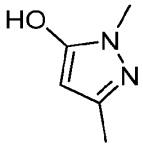
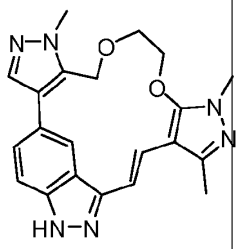
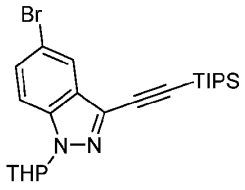
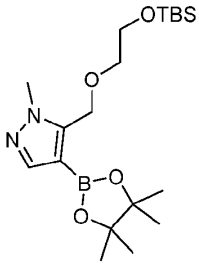
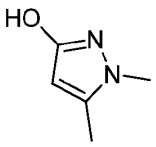
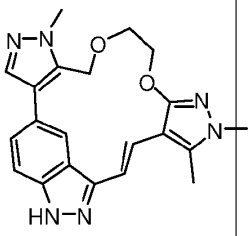
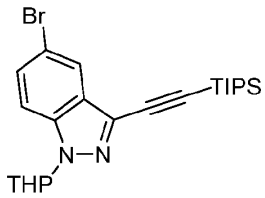
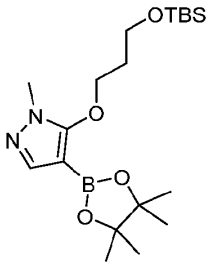
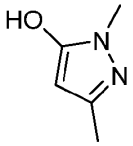
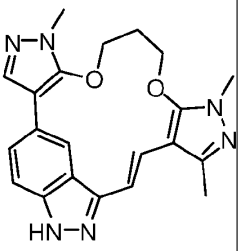
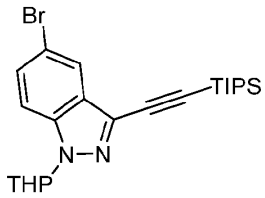
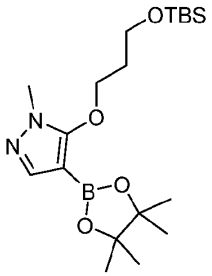
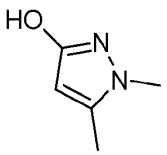
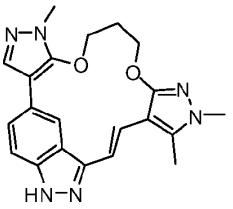
indazole (402 mg, 0.670 mmol, 88.3% yield) as a brown oil. LCMS: m/z 600.9 (M+1).

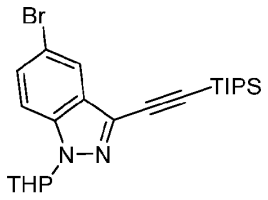
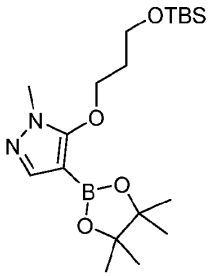
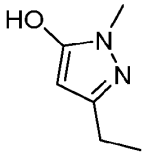
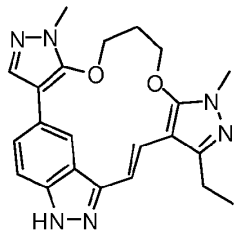
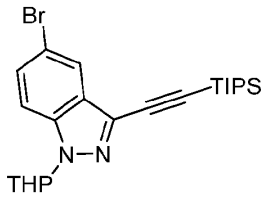
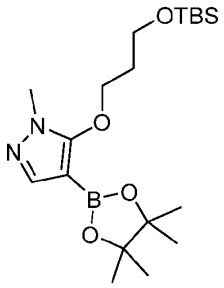
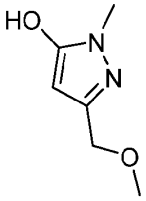
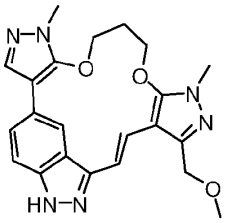
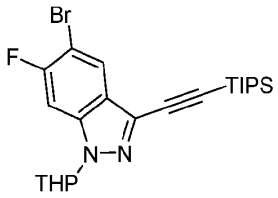
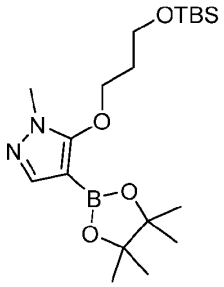
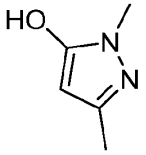
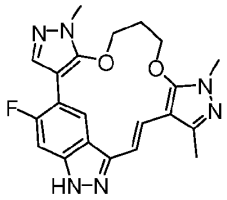
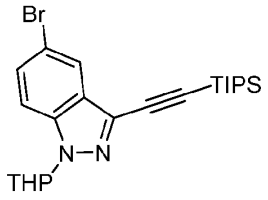
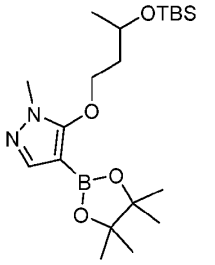
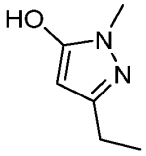
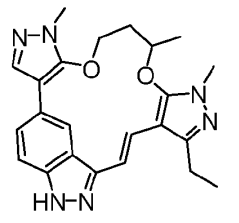
[01138] Step 6. To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (296 mg, 1.17 mmol, 2 *eq*) and PPh_3 (168 mg, 0.641 mmol, 1.1 *eq*) and cuprioxycopper (41.7 mg, 0.291 mmol, 0.5 *eq*) and 3-ethynyl-5-[5-[2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazole (350 mg, 0.583 mmol, 1 *eq*) in dioxane (10.5 mL). The reaction mixture was stirred at 60 °C for 16 hrs. The mixture was concentrated in vacuum and the residue was purified by column chromatography to give {5-[5-[2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazole (450 mg, crude) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.77 - 7.71 (m, 1H), 7.63 - 7.60 (m, 2H), 7.42 (dd, *J* = 1.6, 8.4 Hz,1H), 6.50 (d, *J* = 18.8 Hz, 1H), 5.75 (dd, *J* = 2.8, 8.8 Hz, 1H), 4.68 (s, 2H), 4.37 - 4.34 (m, 2H), 4.18 - 4.08 (m, 1H), 4.00 (s,2H), 4.03 - 3.98 (m, 1H), 3.79 - 3.73 (m, 3H), 3.59 (s, 3H), 3.23 - 3.20 (m, 1H), 2.65 - 2.50 (m, 1H), 2.26 - 2.18 (m, 1H), 2.16 (s,3H), 2.13 - 2.07 (m, 1H), 2.05 (s, 1H), 1.84 - 1.68 (m, 3H), 1.58 (s, 2H), 1.31 (s, 12H)

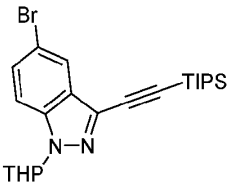
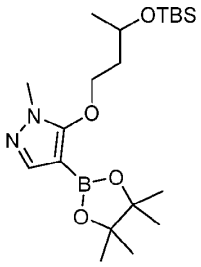
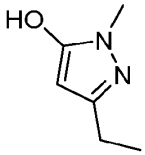
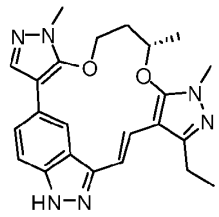
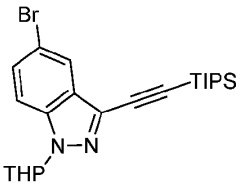
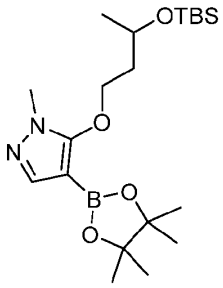
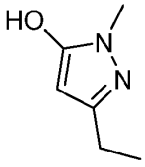
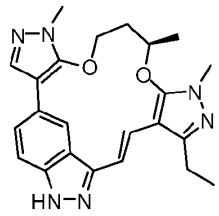
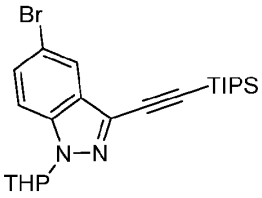
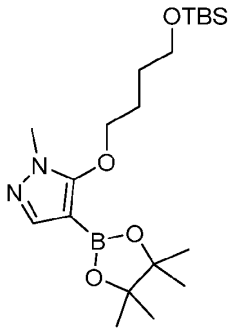
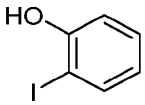
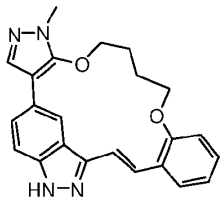
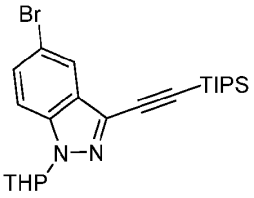
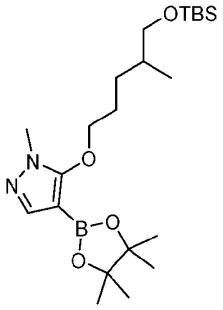
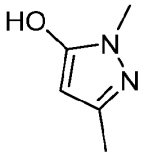
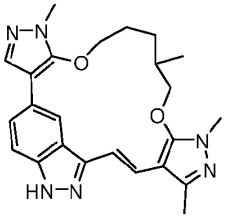
[01139] Step 7. A mixture of 5-[5-[2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxyethoxymethyl]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazole (400 mg, 0.549 mmol, 1 *eq*), Cs_2CO_3 (537 mg, 1.65 mmol, 3 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (44.8 mg, 0.0549 mmol, 0.1 *eq*) in dioxane (4 mL) and H_2O (0.8 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. The mixture was concentrated in vacuum and the residue was purified by column chromatography to give **C-10-1** (150 mg, 0.316 mmol, 57.6% yield) as a brown oil. LCMS: m/z 475.3 (M+1).

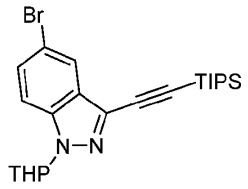
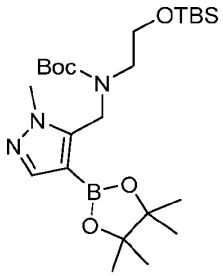
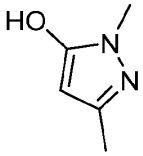
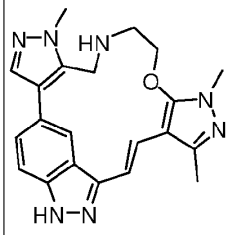
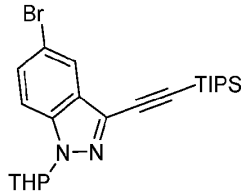
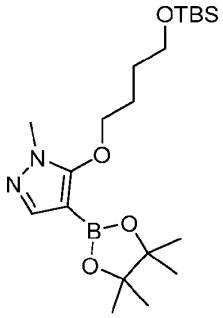
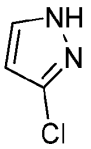
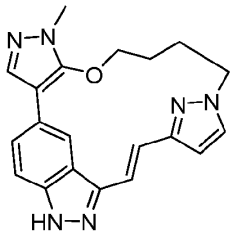
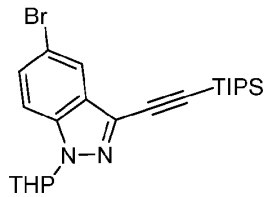
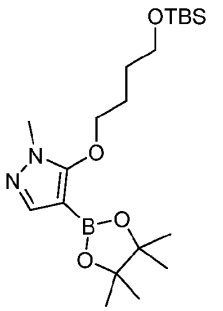
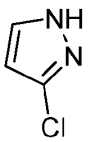
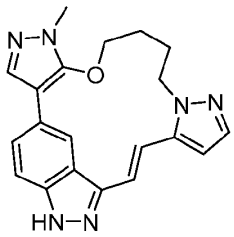
[01140] Step 8. To a solution of **C-10-1** (140 mg, 0.295 mmol, 1 eq) in DCM (7 mL) was added TFA (7 mL). The mixture was stirred at 20 °C for 1 h and then concentrated in vacuum. The residue was purified by column chromatography to give **Ex. 6** (20.0 mg, 0.0487 mmol, 16.5% yield) as a brown solid.

[01141] **Ex. 6—Ex. 20** were prepared with **General Method C** using corresponding C-1-X, B-2-X, and C-6-X as shown below. C-6-X compounds are commercially available or made via conventional methods. **Ex. 19** and **Ex. 20** were obtained as regio-isomers without iodination step (Step 5).

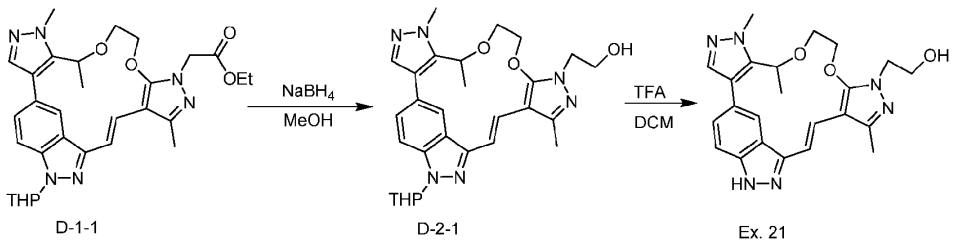
C-1-X	B-2-X	C-6-X	Ex. #
C-1-1 	B-2-1 	C-6-1 	Ex. 6 
C-1-1 	B-2-1 	C-6-2 	Ex. 7 
C-1-1 	B-2-2 	C-6-1 	Ex. 8 
C-1-1 	B-2-2 	C-6-2 	Ex. 9 

C-1-1 	B-2-2 	C-6-3 	Ex. 10 
C-1-1 	B-2-2 	C-6-4 	Ex. 11 
C-1-2 	B-2-2 	C-6-1 	Ex. 12 
C-1-1 	B-2-3 	C-6-3 	Ex. 13 

C-1-1 	B-2-3 	C-6-3 	Ex. 14 
C-1-1 	B-2-3 	C-6-3 	Ex. 15 
C-1-1 	B-2-4 	C-6-5 	Ex. 16 
C-1-1 	B-2-5 	C-6-1 	Ex. 17 

C-1-1 	B-2-6 	C-6-1 	Ex. 18 
C-1-1 	B-2-4 	C-6-6 	Ex. 19 
C-1-1 	B-2-4 	C-6-6 	Ex. 20 

General Method D: Preparation of 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(2*H*)-yl]ethan-1-ol (Ex. 21)

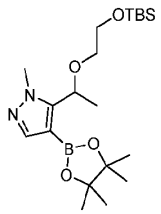
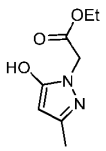
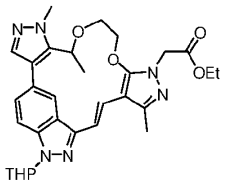
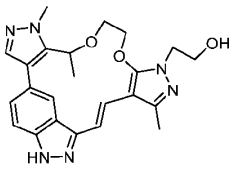
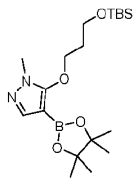
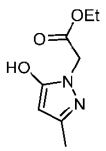
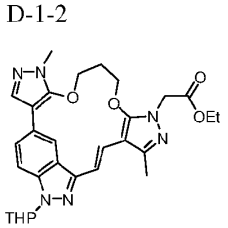
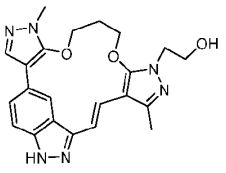


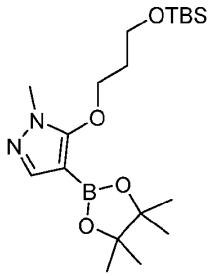
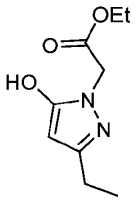
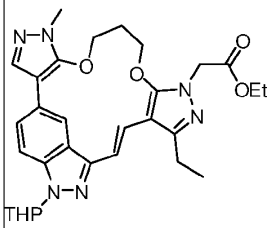
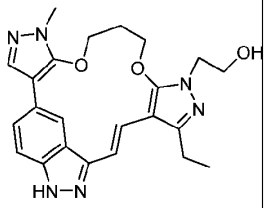
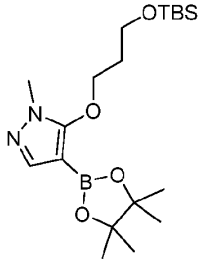
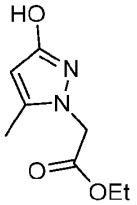
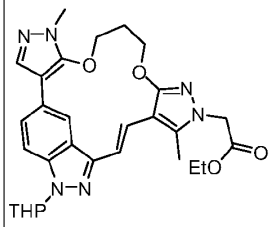
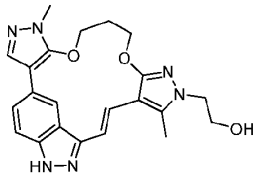
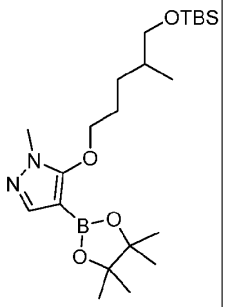
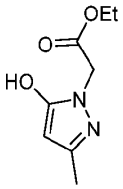
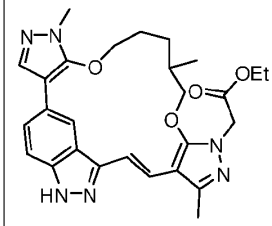
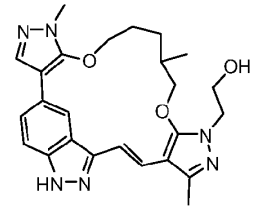
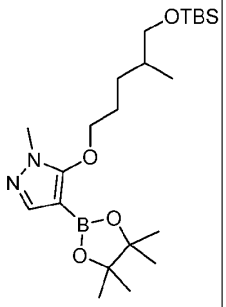
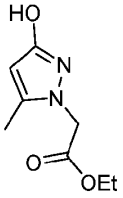
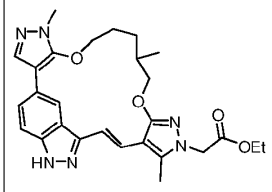
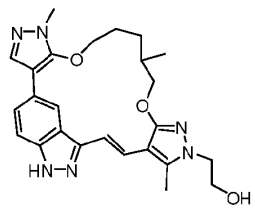
[01142] D-1-1 was prepared with General Method C.

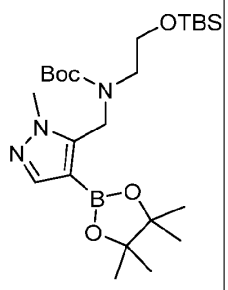
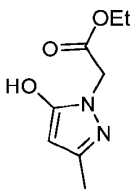
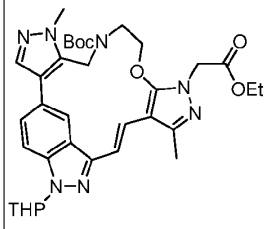
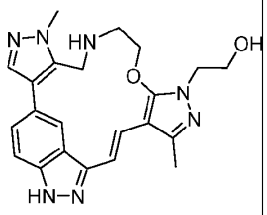
[01143] Step 1. To a solution of D-1-1 (70.00 mg, 0.125 mmol, 1 ***eq***) in MeOH (0.9 mL) was added $NaBH_4$ (47.24 mg, 1.25 mmol, 10 ***eq***) at 0°C. The mixture was stirred at 25 °C for 2 h and then quenched with water (2 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate=1:1) to give D-2-1 (58 mg, 0.11 mmol, 89.57% yield) as a yellow oil. LCMS: m/z 519.1 (M+1)

[01144] Step 2. To a solution of D-2-1 (18.0 mg, 0.0347 mmol, 1 ***eq***) in DCM (0.6 mL) was added TFA (0.66 mL). The mixture was stirred at 25 °C for 2 h and concentrated. The residue was purified by reverse-phase prep-HPLC to give Ex. 21 (2.32 mg, 0.005 mmol, 14.6% yield) as a white solid.

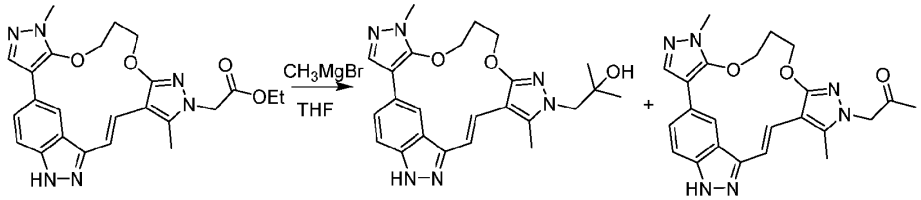
[01145] Ex. 21—Ex. 27 were prepared with General Method C&D using C-1-1, and the corresponding B-2-X, and C-6-X as shown below.

B-2-X	C-6-X	D-1-X	Ex. #
B-2-7 	C-6-6 	D-1-1 	Ex. 21 
B-2-2 	C-6-6 	D-1-2 	Ex. 22 

B-2-2 	C-6-7 	D-1-3 	Ex. 23 
B-2-2 	C-6-8 	D-1-4 	Ex. 24 
B-2-5 	C-6-6 	D-1-4 	Ex. 25 
B-2-5 	C-6-8 	D-1-5 	Ex. 26 

B-2-6	C-6-6	D-1-6	Ex. 27
			

[01146] General Method E: Preparation of 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-2-methylpropan-2-ol (Ex. 28) and 1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]propan-2-one (Ex. 29)



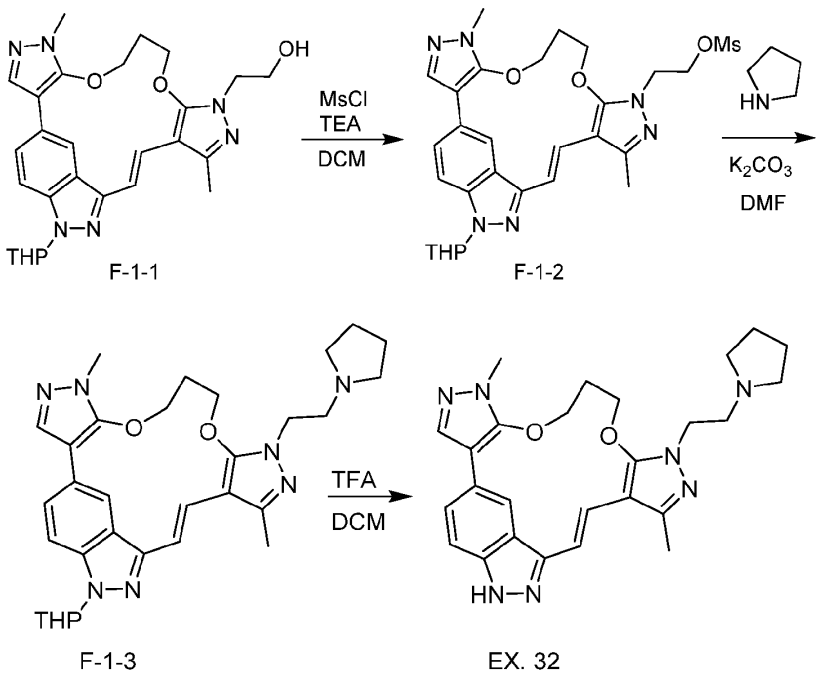
E-1-1 Ex. 28 Ex. 29

[01147] E-1-1 was prepared using General Method C.

[01148] To a solution of E-1-1 (100 mg, 0.216 mmol, 1 ***eq***) in THF (2 mL) was added MeMgBr (3 M, 1.44 mL, 20 ***eq***) at 0 °C. The mixture was stirred at 20 °C for 2 h. On completion. The reaction mixture was quenched by addition **NH_4Cl 10** mL at 0 °C, and then diluted with **H_2O (50** mL) and extracted with **EA 150** mL (**50** mL * **3**). The combined organic layers were dried over **Na_2SO_4,** filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give Ex. 28 (4.62 mg, 0.0103 mmol, 4.76% yield) as yellow solid, and Ex. 29 (2.12 mg, 0.0049 mmol, 2.27% yield) as yellow solid.

[01149] Ex. 30 and Ex. 31 were prepared with General Method E.

[01150] General Method F: Preparation of (17*E*)-8,16-dimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 32)



[01151] F-1-1 was prepared using General Method D.

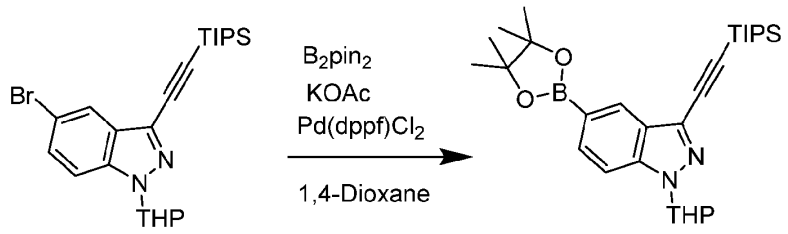
[01152] Step 1. To a solution of F-1-1 (100 mg, 0.198 mmol, 1 *eq*) in DCM (1 mL) was added TEA (100 mg, 0.991 mmol, 5 ***eq***) and MsCl (68.1 mg, 0.595 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was quenched by addition of sat. aqueous $NaHCO_3$ (**5** mL) at 0 °C, and then diluted with H_2O (20 mL) and extracted with DCM (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give F-2-1. LCMS: m/z 583.0 (M+1).

[01153] Step 2. To a solution of F-2-1 (110 mg, 0.189 mmol, 1 ***eq***) in DMF (1 mL) was added K_2CO_3 (78.3 mg, 0.566 mmol, 3 ***eq***) and pyrrolidine (26.9 mg, 0378 mmol, 2 ***eq***). The mixture was stirred at 80 °C for 2 h. On completion, the reaction mixture was diluted with H_2O (30 mL) and extracted with EA (30 mL * 3). The combined organic layers were washed with H_2O (30 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give F-3-1 (37.0 mg, 0.0664 mmol, 35.1% yield) as colorless oil. LCMS: m/z 558.4 (M+1).

[01154] Step 4. To a solution of F-3-1 (37.0 mg, 0.0664 mmol, 1 ***eq***) in DCM (1 mL) was added TFA (1 mL). The mixture was stirred at 20°C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to give Ex. 32 as TFA salt (4.12 mg, 0.0068 mmol, 10.2% yield) as brown solid.

[01155] Ex. 33 and Ex. 34 were prepared using General Method F.

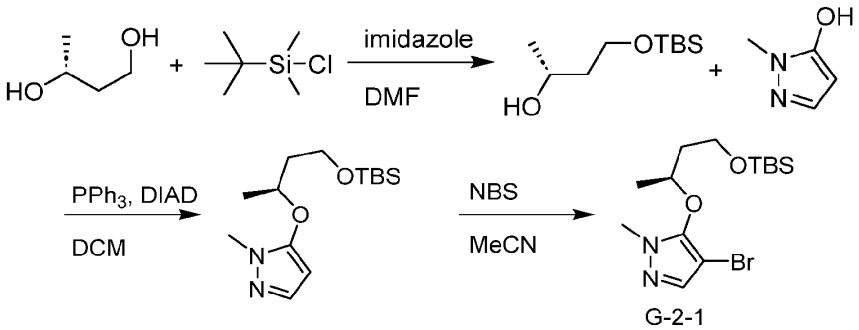
[01156] Preparation of triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (G-1-1)



G-1-1

[01157] To a solution of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (2 g, 4.33 mmol) in 1,4-Dioxane (20.86 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.43 g, 5.63 mmol) and Potassium Acetate (1.28 g, 13.00 mmol). The mixture was stirred as argon was bubbled through for 5 minutes, followed by addition of catalyst, $Pd(dppf)Cl_2$ (158.55 mg, 0.217 mmol). The vessel sealed and heat to 85 °C for 18 hr. The reaction was diluted with DCM (80 mL) and water (80 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 40 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (0-5% EA in Hexanes) provided triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (1.87 g, 3.68 mmol, 84.85% yield). LCMS: *m/z* 509.28 (M+1).

[01158] Preparation of [(3S)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxybutoxy]-tert-butyl-dimethyl-silane (G-2-1)



G-2-1

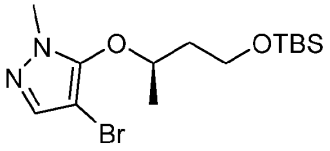
[01159] Step 1. To a solution of (3*R*)-butane-1,3-diol (2.03 g, 22.53 mmol, 2.02 mL) in DMF (42 mL) was added imidazole (1.84 g, 27.03 mmol) followed by addition of tert-butyl-chloro-dimethyl-silane (3.56 g, 23.65 mmol). The mixture was stirred at 0-22

°C for 4 hr. Reaction was diluted with DCM (150 mL) and water (150 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2x 50 mL). The combined organic layer was washed with 10% brine and dried over sodium sulfate. Flash column chromatography provided (2R)-4-[tert-butyl(dimethyl)silyl]oxybutan-2-ol (4.04 g, 19.77 mmol, 87.75% yield).

[01160] Step 2. To a solution of 2-methylpyrazol-3-ol (2.33 g, 23.72 mmol) , (2R)-4-[tert-butyl(dimethyl)silyl]oxybutan-2-ol (4.04 g, 19.77 mmol) and triphenylphosphine (7.78 g, 29.65 mmol) in anhydrous DCM (13.5 mL) at 0 °C was added DIAD (6.40 g, 31.63 mmol, 6.2 mL). The reaction mixture is stirred for 2 hr at 0-22 °C. Flash column chromatography provided tert-butyl-dimethyl-[(3S)-3-(2-methylpyrazol-3-yl)oxybutoxy]silane (3.2 g, 11.25 mmol, 56.91% yield).

[01161] Step 3. To a solution of tert-butyl-dimethyl-[(3S)-3-(2-methylpyrazol-3-yl)oxybutoxy]silane (5.62 g, 19.76 mmol) in acetonitrile (97 mL) was added NBS (3.52 g, 19.76 mmol). The reaction mixture was stirred at 0-22 °C for 3 hr and quenched with water (20 mL). Approximately 1/3 of acetonitrile was removed under reduced pressure. Remaining solution was worked up with DCM (75 mL) and water (75 mL). The aqueous layer was extracted twice more with DCM (2 x 30 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Flash column chromatography provided [(3S)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxybutoxy]-tert-butyl-dimethyl-silane (6.2 g, 17.06 mmol, 86.37% yield).

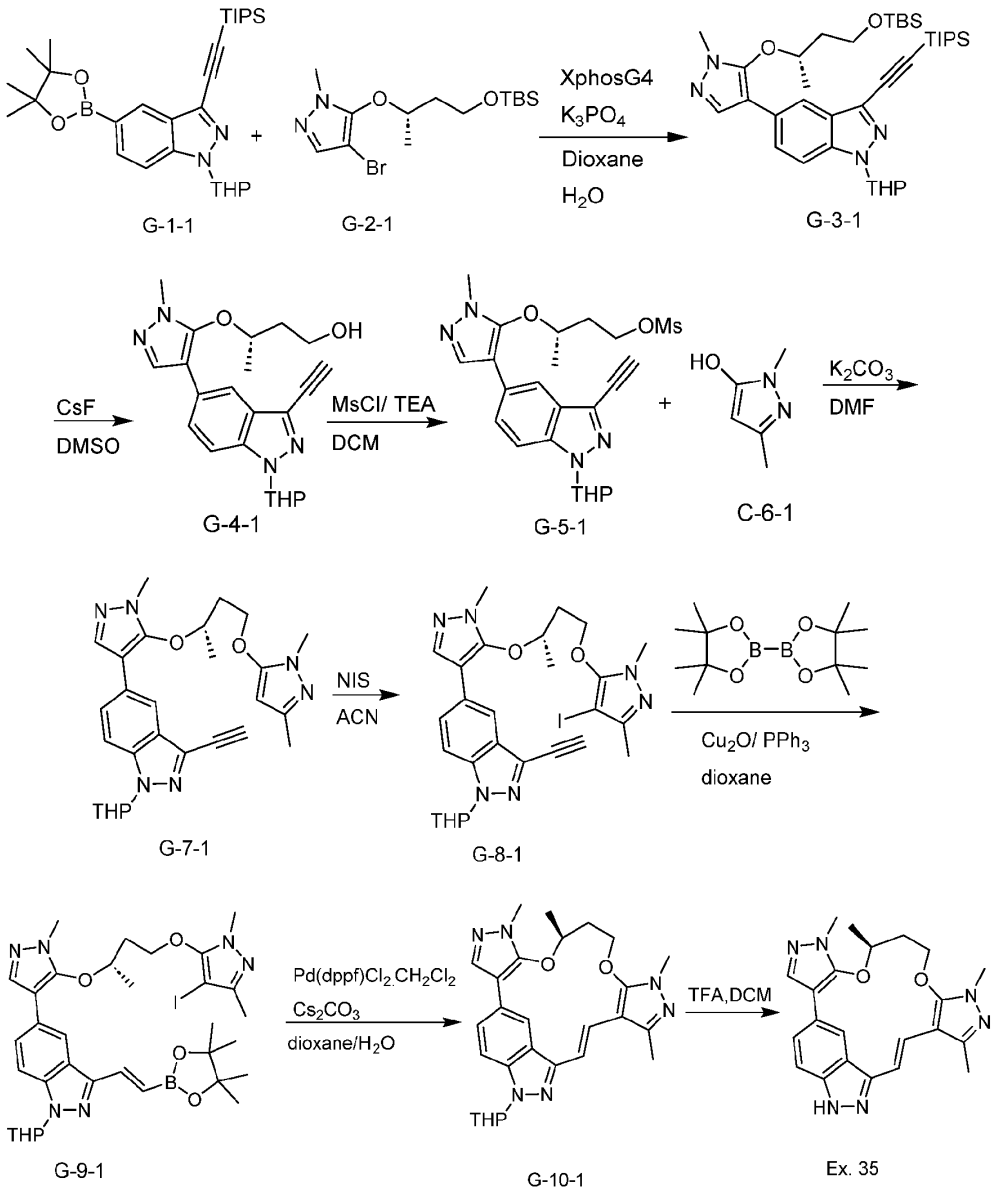
[01162] Preparation of [(3R)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxybutoxy]-tert-butyl-dimethyl-silane (G-2-2)



G-2-2

[01163] G-2-2 was prepared following the same methods as G-2-1 using (3*S*)-butane-1,3-diol as starting material.

[01164] General Method G: Preparation of (10*S*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole (Ex. 35)

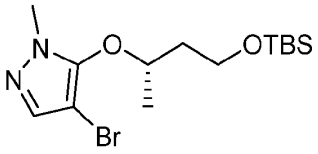
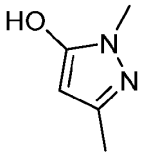
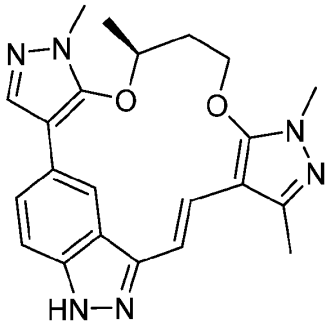
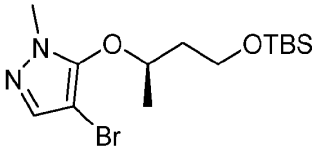
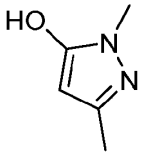
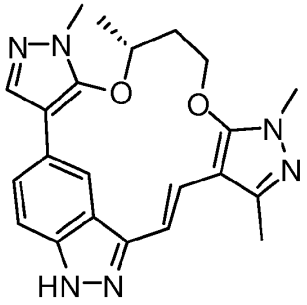
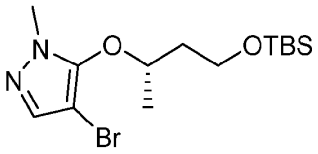
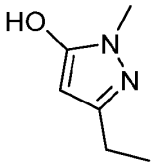
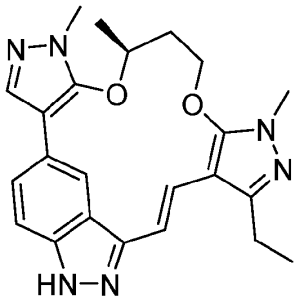


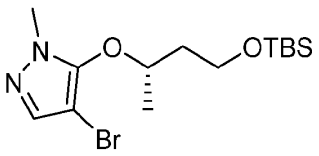
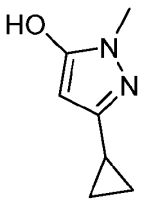
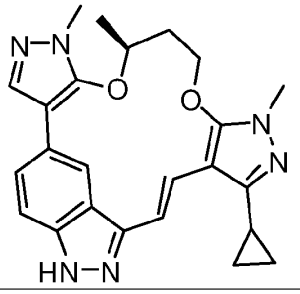
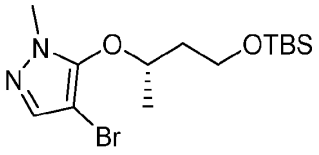
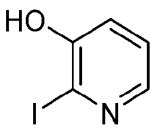
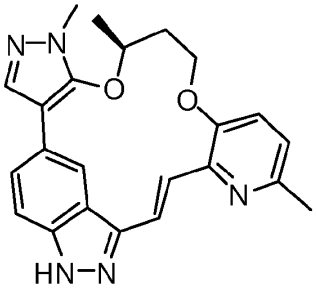
[01165] Step 1. To a solution of [(3S)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxybutoxy]-tert-butyl-dimethyl-silane (600 mg, 1.65 mmol) in 1,4-dioxane (5.8 mL) was added triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (834 mg, 1.64 mmol) and potassium phosphate tribasic (2 M in water, 2.46 mL). The reaction mixture was stirred as argon was bubbled through and the catalyst Xphos G4 (71 mg, 0.082mmol) was added. The reaction vessel was sealed and heated to 80 °C for 18 hr. Flash column chromatography provided **G-3-1** (561.15 mg, 0.843

mmol, 51.44% yield).

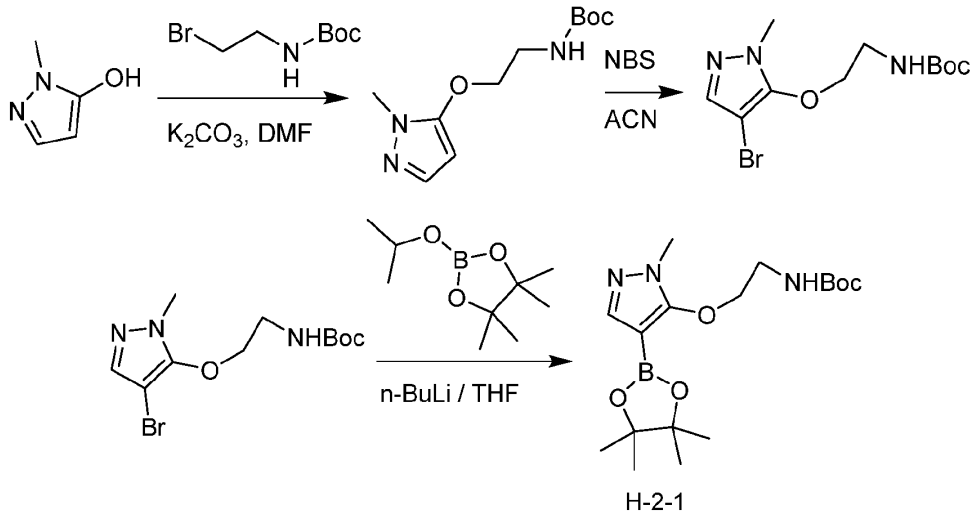
[01166] G-3-1 was converted to Ex. 35 using similar methods as Step 2-Step 8 in General Method C.

[01167] Ex. 35—Ex. 39 were prepared with General Method G using G-1-1, and the corresponding G-2-X, and C-6-X as shown below. C-6-X compounds are commercially available or made via conventional methods.

G-2-X	C-6-X	Ex. #
G-2-1 	C-6-1 	Ex. 35 
G-2-2 	C-6-1 	Ex. 36 
G-2-1 	C-6-3 	Ex. 37 

G-2-1 	C-6-9 	Ex. 38 
G-2-1 	C-6-10 	Ex. 39 

[01168] Preparation of tert-butyl N-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (H-2-1)



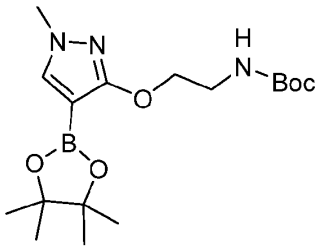
[01169] Step 1. To a mixture of 2-methylpyrazol-3-ol (5 g, 50.9 mmol, 1 *eq*) and tert-butyl *N*- (2-bromoethyl)carbamate (13.7 g, 61.1 mmol, 1.2 *eq*) in DMF (50 mL) was added K_2CO_3 (21.1 g, 152 mmol, 3 *eq*). The mixture was stirred at 80 °C for 2 hours. On

completion, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (40 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl N-[2-(2-methylpyrazol-3-yl) oxyethyl]carbamate (11 g, 45.5 mmol, 89.45% yield) as black oil. LCMS: m/z 242.2 (M+1).

[01170] Step 2. To a solution of tert-butyl-N-[2-(2-methylpyrazol-3-yl)oxyethyl]carbamate (2 g, 7.8 mmol, 1 *eq*) in ACN (20 mL) was added NBS (1.44 g, 8.1 mmol, 1.03 *eq*). The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was concentrated. The residue was purified by column chromatography to give tert-butyl N-[2-(4-bromo-2-methyl- pyrazol-3-yl)oxyethyl]carbamate (1.73 g, 66% yield) as red oil.

[01171] Step 3. To a mixture of tert-butyl N-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]carbamate (5.20 g, 16.2 mmol, 1 ***eq***) in THF (70 mL) was added n-BuLi (2.5 M, 16.9 mL, 2.6 ***eq***) at -78 °C. The mixture was stirred at -78 °C for 1 hour under N_2 followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.04 g, 32.5 mmol, 2 ***eq***). The mixture was stirred at -78 °C for 1 hour under N_2. On completion, the reaction mixture was quenched by addition MeOH (10 mL) and concentrated in vacuum to afford tert-butyl N-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (6 g, crude) as a yellow solid. LCMS: m/z 368.0 (M+1).

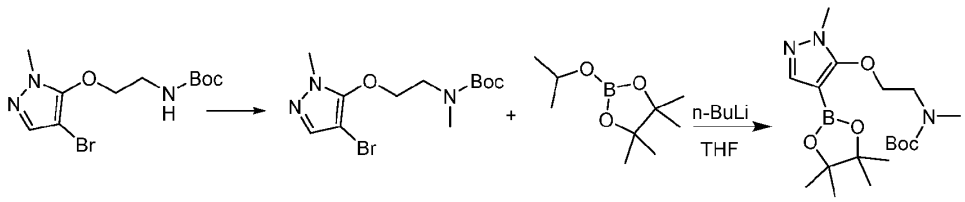
[01172] Preparation of tert-butyl N-[2-[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (H-2-2)



H-2-2

[01173] H-2-2 was prepared following similar methods as H-2-1.

[01174] Preparation of tert-butyl N-methyl-N-[3-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)pyrazol-3-yl]oxyethyl]carbamate (H-2-3)

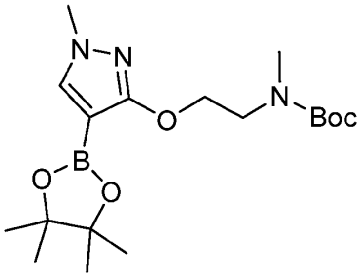


H-2-3

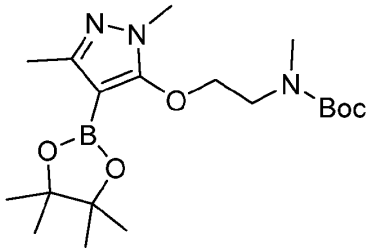
[01175] Step 1. To a solution of tert-butyl N-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]carbamate (20.0 g, 62.5 mmol, 1 eq) in DMF (120 mL) was added NaH (7.50 g, 187 mmol, 60% purity, 3 eq) at 0 °C and stirred for 30 mins. Then MeI (13.30g, 93.7 mmol, 1.5 eq) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1.5 hr. 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 concentrated. The residue was purified by column chromatography to give tert-butyl N-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-N-methyl-carbamate (20.0 g, 59.8 mmol, 95% yield) as a white oil. LCMS: m/z 336.7 (M+1).

[01176] Step 2. To a solution of tert-butyl N-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-N-methyl-carbamate (20. 0 g, 59. 8 mmol, 1 *eq*) in THF (200 mL) was added *n*-BuLi (2. 5 M, 23. 9 mL, 1 *eq*) at -78 °C, the mixture was stirred at this temperature for 30 mins followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22. 2 g, 119 mmol, 2 *eq*) dropwise at -78 °C. The mixture was stirred at -78 °C for 2 hr. On completion, the mixture was quenched with water (200 mL) and extracted with ethyl acetate (250 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography to give H-2-3 (21.2 g, 55.6 mmol, 92% yield) as a yellow oil. LCMS: m/z 381.9 (M+1).

[01177] Preparation of tert-butyl N-methyl-N-[3-[1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)pyrazol-3-yl]oxyethyl]carbamate (H-2-4) and tert-butyl N-methyl-N-[3-[2,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)pyrazol-3-yl]oxyethyl]carbamate (H-2-5)



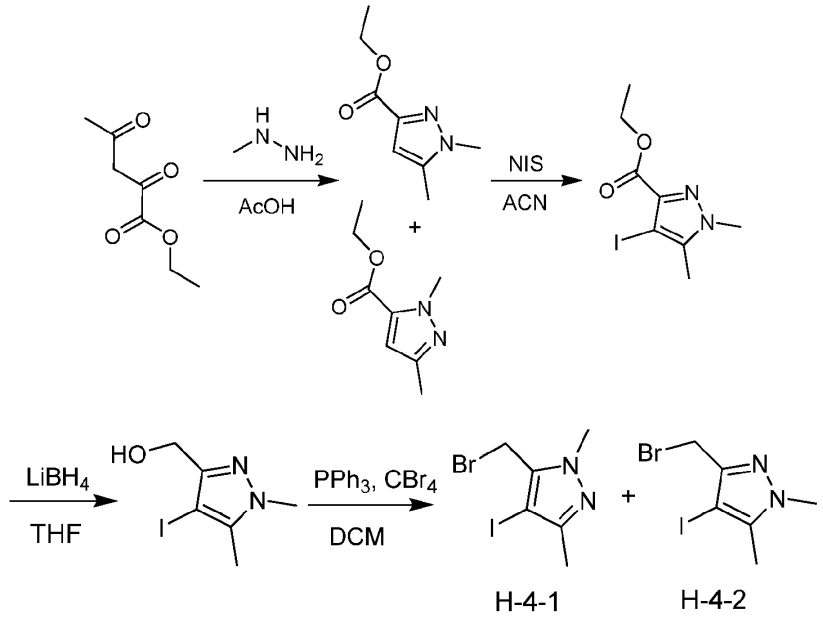
H-2-4



H-2-5

[01178] H-2-4 and H-2-5 were prepared with similar methods as H-2-3.

[01179] Preparation of 3-(bromomethyl)-4-iodo-2,5-dimethyl-pyrazole (H-4-1) and 3-(bromomethyl)-4-iodo-1,5-dimethyl-pyrazole (H-4-2)



H-4-1 H-4-2

[01180] Step 1. To a solution of ethyl 2, 4-dioxohexanoate (10.0 g, 58.1 mmol, 1 ***eq***) in AcOH (65.7 g, 1.09 mol, 18.8 ***eq***) was added methylhydrazine (7.45 g, 64.7 mmol, 40% purity, 1.11 ***eq***) at 0 °C. The mixture was stirred at 15 °C for 5 hours and concentrated in vacuum. The residue was purified by combi flash chromatography (120 g silica gel column, EtOAc in PE from 0% to 50%) to provide ethyl 5-ethyl-1-methyl-pyrazole-3-carboxylate (10.1 g, 55.5 mmol, 95.5% yield) as yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.59 (s, 1 H), 4.39 (q, *J* = 14.4, 7.2 Hz, 2 H), 3.85 (s, 3 H), 2.62 (q, *J* = 14.4, 7.2 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.6 Hz, 3 H).

[01181] Ethyl 5-ethyl-2-methyl-pyrazole-3-carboxylate (1.33 g, 7.30 mmol, 12.6% yield) was obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.65 (s, 1 H), 4.34 (q, *J*=7.2 Hz, 2 H), 4.18 - 4.11 (m, 4 H), 2.65 (q, *J* = 15.2, 7.6 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

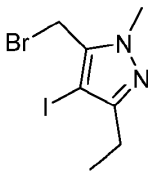
[01182] Step 2. To a solution of ethyl 1,5-dimethylpyrazole-3-carboxylate (3.00 g, 17.8 mmol, 1 ***eq***) in MeCN (30 mL) was added NIS (4.41 g, 19.6 mmol, 1.1 ***eq***) at 0 °C. The mixture was stirred at 25 °C for 3 hours. The residue was poured into ice-water (200 mL). The aqueous phase was extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography to give ethyl 4-iodo-1,5-dimethyl-pyrazole-3-carboxylate (4.20 g, 14.3 mmol, 80.1% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.41 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 2.35 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

[01183] Step 3. To a solution of ethyl 4-iodo-1,5-dimethyl-pyrazole-3-carboxylate (2.00 g, 6.80 mmol, 1 ***eq***) in THF (30 mL) was added $LiBH_4$ (296 mg, 13.6 mmol, 2 ***eq***) in three portions at 25 °C. The mixture was stirred at 25 °C for 1 hour. To the mixture was added aq. NH_4Cl (10 mL) dropwise at 0 °C under N_2. The mixture was stirred for 30 min. On completion, the aqueous phase was extracted with ethyl acetate (30 mL * 2). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give (4-iodo-1,5-dimethyl-pyrazol-3-yl)methanol (1.4 g, 81% yield) as a white solid. LCMS: 252.8 (M+1).

[01184] Step 4. To a mixture of (4-iodo-1,5-dimethyl-pyrazol-3-yl)methanol (300 mg, 1.19 mmol, 1 ***eq***) in DCM (10 mL) was added PPh_3 (468 mg, 1.79 mmol, 1.5 ***eq***) at 0 °C. Then to the mixture was added CBr_4 (592 mg, 1.79 mmol, 1.5 ***eq***) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated in vacuum. The residue was purified by column chromatography to give 3-(bromomethyl)-4-iodo-1,5-dimethyl-pyrazole (**H-4-2**, 260 mg, 69% yield, 100% purity) as a white solid. LCMS m/z 316.7 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.44 (s, 2H), 3.84 (s, 3H), 2.29 (s, 3H).

[01185] Ethyl 5-ethyl-2-methyl-pyrazole-3-carboxylate was converted to 3-(bromomethyl)-4-iodo-2,5-dimethyl-pyrazole (H-4-1) following similar methods.

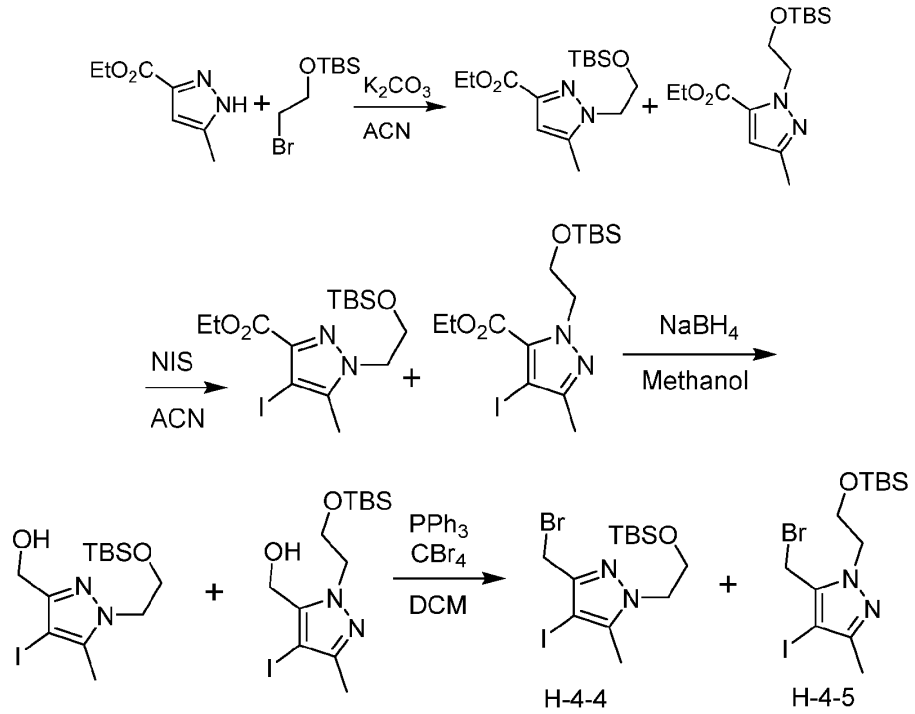
[01186] Preparation of 5-(bromomethyl)-3-ethyl-4-iodo-1-methyl-1H-pyrazole (H-4-3)



H-4-3

[01187] H-4-3 was prepared following similar methods as H-4-1.

[01188] Preparation of 2-[3-(bromomethyl)-4-iodo-5-methyl-pyrazol-1-yl]ethoxy-*tert*-butyl-dimethyl-silane (H-4-4) and 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethoxy-*tert*-butyl-dimethyl-silane (H-4-5)



[01189] Step 1. A mixture of ethyl 5-methyl-1*H*-pyrazole-3-carboxylate (1 g, 6.49 mmol), 2-bromoethoxy-*tert*-butyl-dimethyl-silane (3.10 g, 12.97 mmol, 2.78 mL), potassium carbonate, anhydrous (2.69 g, 19.46 mmol) in acetonitrile (28.5 mL) was stirred at room temperature overnight. The mixture was then diluted with water (15 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the crude residue was purified by flash column chromatography to furnish a mixture of ethyl 1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-5-methyl-pyrazole-3-carboxylate and ethyl 2-[2-[*tert*-

butyl(dimethyl)silyl]oxyethyl]-5-methyl-pyrazole-3-carboxylate (1.57 g, 5.01 mmol, 77.31% yield). LCMS: *m/z* 313.03 (M+1)

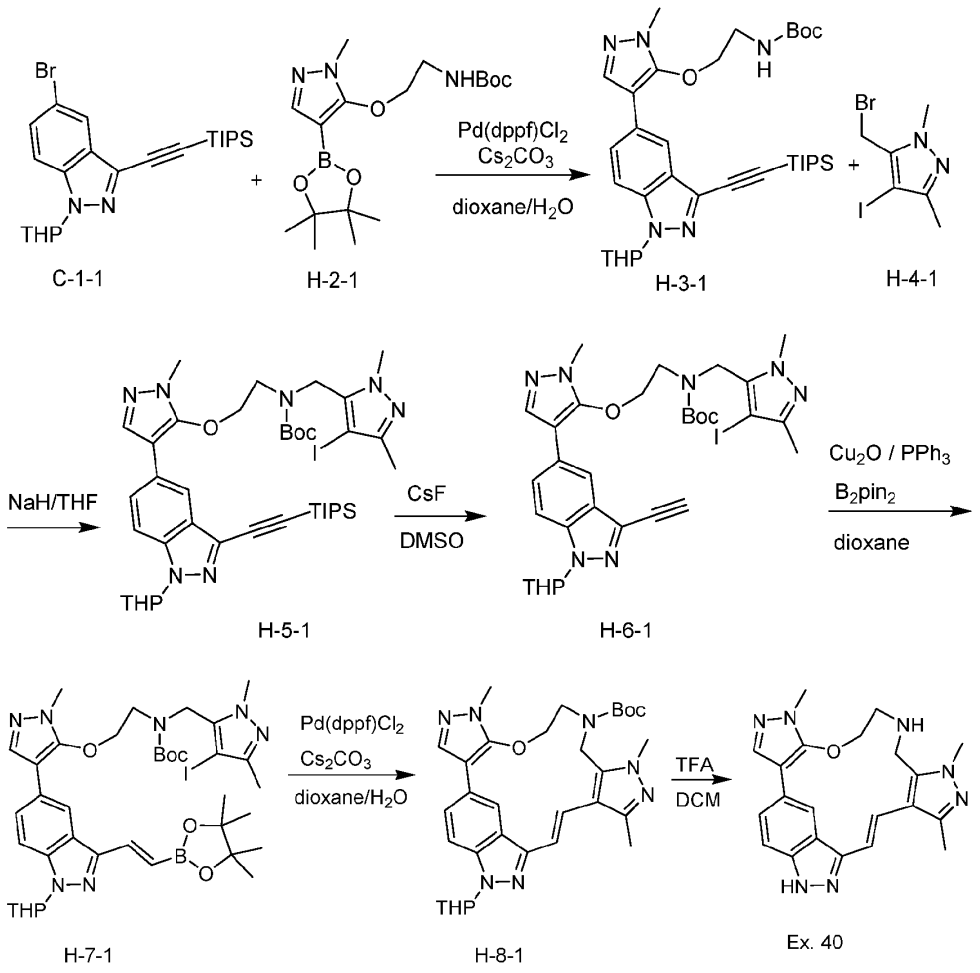
[01190] Step 2. A mixture of ethyl 1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-5-methyl-pyrazole-3-carboxylate and ethyl 2-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-5-methyl-pyrazole-3-carboxylate (785.00 mg, 2.51 mmol) was dissolved in acetonitrile (35 mL). *N*-Iodosuccinimide (2.26 g, 10.05 mmol) was added to this solution, and the mixture was heated to 60 °C for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to obtain a mixture of ethyl 1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazole-3-carboxylate and ethyl 2-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazole-3-carboxylate (0.97 g, 2.21 mmol, 88.08% yield). LCMS: *m/z* 438.82 (M+H).

[01191] Step 3. To a mixture of ethyl 1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazole-3-carboxylate and ethyl 2-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazole-3-carboxylate (0.97 g, 2.21 mmol) in methanol (11.65 mL) was added sodium borohydride (178.86 mg, 4.73 mmol) and the mixture was stirred overnight at room temperature. The reaction was then diluted with water (5 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, dried and purified by flash column chromatography to afford a mixture of [4-iodo-5-methyl-1-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]methanol and [4-iodo-5-methyl-2-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]methanol (745 mg, 2.02 mmol, 73.13% yield). LCMS: *m/z* 396.87 (M+H).

[01192] Step 4. To a mixture of [1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methanol and [2-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methanol (745 mg, 1.88 mmol) in DCM (15.41 mL) was added Triphenylphosphine (739.54 mg, 2.82 mmol) and Carbon tetrabromide (935.05 mg, 2.82 mmol, 273.41 µL) at 0 °C, and the mixture was stirred at room temperature for 4 hr. The reaction was quenched with water (10 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, dried and purified by flash column chromatography to afford 2-[3-(bromomethyl)-4-iodo-5-methyl-pyrazol-1-yl]ethoxy-*tert*-butyl-dimethyl-silane (H-4-4, 192 mg, 0.418 mmol, 22.24% yield) and 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethoxy-*tert*-butyl-dimethyl-silane (H-4-5, 564 mg, 1.23 mmol, 65.34% yield). LCMS: $[M+H]^+$ *m/z* = 458.73

[01193] General Method H: (17*E*)-8,14,16-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-

3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecine (Ex. 40)



[01194] Step 1. To a mixture of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (5.18 g, 11.2 mmol, 0.75 ***eq***) and tert-butyl N-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethyl]carbamate (5.50 g, 15.0 mmol, 1 ***eq***) in dioxane (80 mL) and H_2O (16 mL) were added Cs_2CO_3 (14.6 g, 44.9 mmol, 3 ***eq***) and $Pd(dppf)Cl_2$ (1.10 g, 1.50 mmol, 0.1 ***eq***). The mixture was stirred at 80 °C for 12 hours. On completion, the residue was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography followed by reversed-phase HPLC to afford tert-butyl N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (3.70 g, 39% yield, 100% purity) as a yellow oil. ^1H NMR (400 MHz,

DMSO-d_6) δ = 7.82 (d, J = 8.4 Hz, 1H), 7.75 - 7.70 (m, 2H), 7.02 (br s, 1H), 5.88 (d, J = 9.2 Hz, 1H), 3.92 (s, 2H), 3.90 (s, 1H), 3.79 - 3.73 (m, 1H), 3.70 (s, 3H), 3.24 (d, J = 5.6 Hz, 2H), 2.38 - 2.29 (m, 1H), 1.99 (s, 2H), 1.78 - 1.68 (m, 1H), 1.59 (s, 2H), 1.35 (s, 9H), 1.18 - 1.14 (m, 18H), 1.14 - 1.12 (m, 3H).

[01195] Step 2. To a mixture of tert-butyl N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (2.00 g, 3.22 mmol, 1 ***eq***) in THF (35 mL) was added NaH (386 mg, 9.65 mmol, 60.0% purity, 3 ***eq***) in portions at 0 °C. The mixture was stirred at 0 °C for 1 hour followed by addition of 5-(bromomethyl)-4-iodo-1,3-dimethyl-pyrazole (1.22 g, 3.86 mmol, 1.2 ***eq***). The mixture was stirred at 60 °C for 12 hours. On completion, the residue was diluted with H_2O (10 mL) and extracted with EtOA (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford tert-butyl N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (2.90 g, crude) as a yellow solid. LCMS: m/z 856.5 (M+1).

[01196] Step 3. To a mixture of tert-butyl N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (2.00 g, 2.34 mmol, 1 ***eq***) in DMSO (20 mL) was added CsF (710 mg, 4.67 mmol, 2 ***eq***). The mixture was stirred at 40 °C for 12 hours. On completion, the residue was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford tert-butyl N-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]carbamate (1.20 g, 68% yield, 93.2% purity) as a yellow solid. LCMS: m/z 700.4 (M+1).

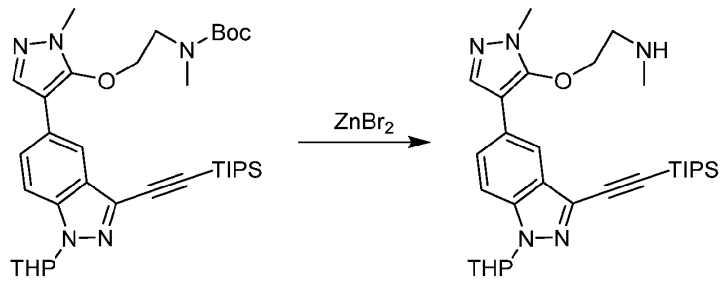
[01197] Step 4. To a mixture of tert-butyl N-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl] carbamate (1.75 g, 2.50 mmol, 1 ***eq***) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (952 mg, 3.75 mmol, 1.5 ***eq***) in dioxane (20 mL) were added Cu_2O (179 mg, 1.25 mmol, 0.5 ***eq***) and PPh_3 (656 mg, 2.50 mmol, 1 ***eq***) under N_2. The mixture was stirred at 100 °C for 12 hours. On completion, the residue was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The residue was purified by flash silica gel chromatography to afford tert-butyl N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (1.90 g, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (s, 1H), 7.78 - 7.71 (m, 1H), 7.70 - 7.64 (m, 1H), 7.59 (s, 1H), 7.57 - 7.55 (m, 1H), 6.52 (d, *J* = 18.8 Hz, 1H), 5.74 (dd, *J* = 2.8, 8.8 Hz, 1H), 4.62 (s, 2H), 4.04 - 3.85 (m, 4H), 3.80 - 3.68 (m, 5H), 3.38 (t, *J* = 6.0 Hz, 2H), 2.64 - 2.49 (m, 1H), 2.27 - 2.15 (m, 5H), 1.84 - 1.65 (m, 4H), 1.42 - 1.30 (m, 21H).

[01198] Step 5. To a mixture of tert-butyl N-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (1.90 g, 2.30 mmol, 1 ***eq***) in dioxane (20 mL) and H_2O (4 mL) were added $Pd(dppf)Cl_2$ (168 mg, 0.230 mmol, 0.1 ***eq***) and Cs_2CO_3 (1.50 g, 4.59 mmol, 2 *eq*) under N_2, The mixture was stirred at 80 °C for 12 hours. On completion, the residue was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford H-8-1 (600 mg, 45% yield) as a yellow solid. LCMS: 574.3 (M+1)

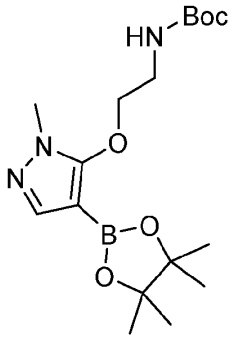
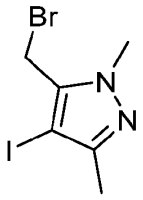
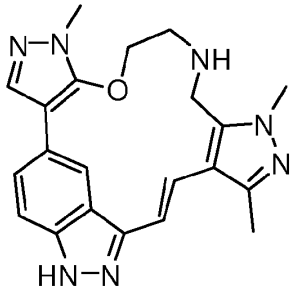
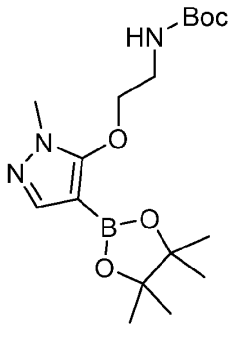
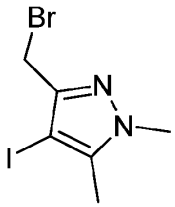
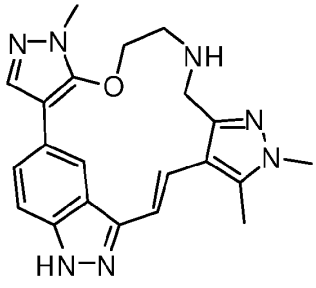
[01199] Step 6. To a mixture of H-8-1 (600 mg, 1.05 mmol, 1 ***eq***) in DCM (6 mL) was added TFA (4.62 g, 40.5 mmol, 38.7 *eq*). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was added $NaHCO_3$ until pH=7 ~ 8. After filtration, the filtrate was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford Ex. 40.

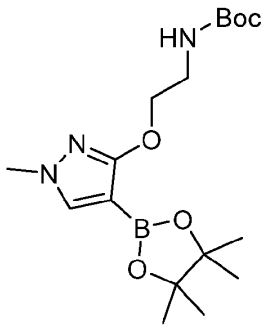
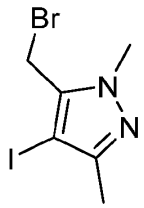
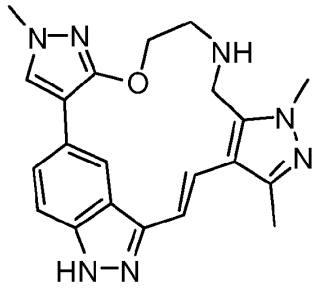
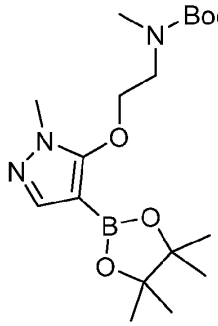
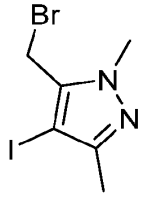
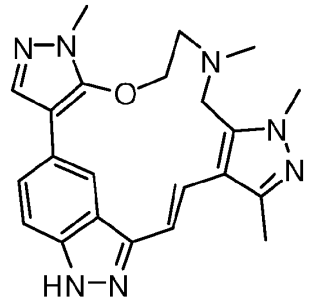
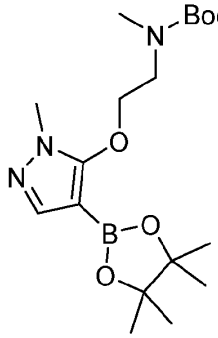
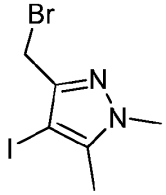
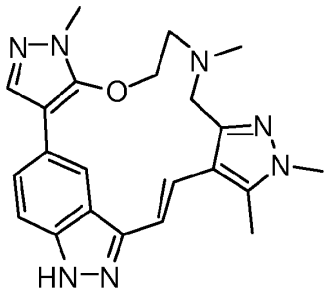
[01200] Ex. 40—Ex. 42 were prepared with General Method H using corresponding C-1-1, and the corresponding H-2-X, and H-4-X as shown in the table. Ex. 43—Ex. 47 were prepared with General Method H using C-1-1, and the corresponding H-2-X, and H-4-X with an additional de-Boc step after the first step as shown below:

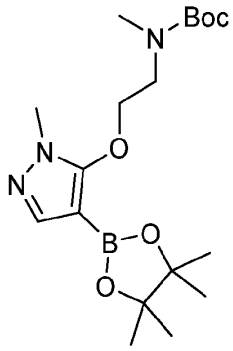
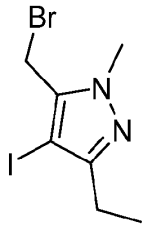
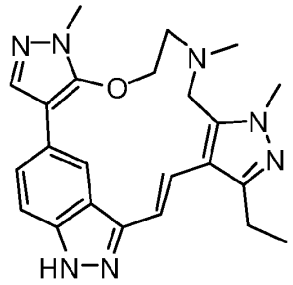
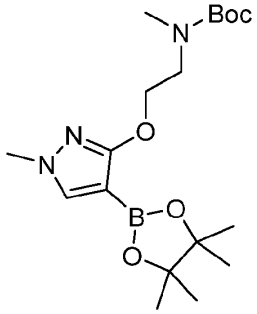
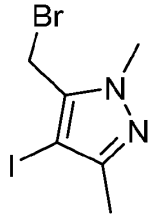
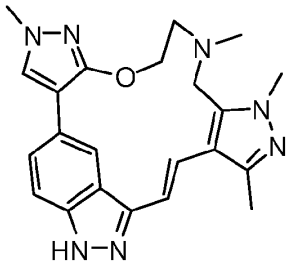
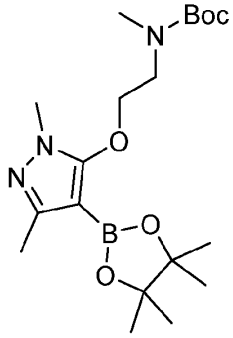
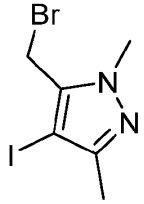
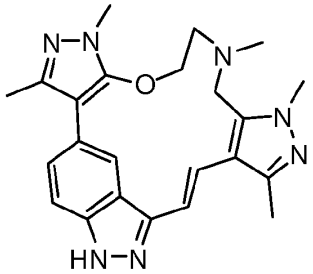


H-3-4 H-3-4b

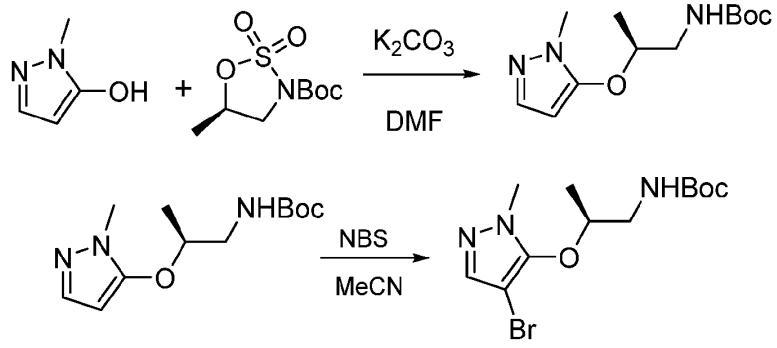
[01201] To a solution of tert-butyl N-methyl-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (6.00 g, 9.44 mmol, 1 *eq*) in DCM (120 mL) was added $ZnBr_2$ (10.6 g, 47. 1 mmol, 5 *eq*). The mixture was stirred at 25 °C for 12 hr. On completion, the mixture was concentrated to give N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-ethanamine (4.00 g, 7.47 mmol, 79% yield, crude) as a brown oil. LCMS: m/z 536.2 (M+1)

H-2-X	H-4-X	Ex. #
H-2-1 	H-4-1 	Ex. 40 
H-2-1 	H-4-2 	Ex. 41 

H-2-2 	H-4-1 	Ex. 42 
H-2-3 	H-4-1 	Ex. 43 
H-2-3 	H-4-2 	Ex. 44 

H-2-3 	H-4-3 	Ex. 45 
H-2-4 	H-4-1 	Ex. 46 
H-2-5 	H-4-1 	Ex. 47 

[01202] Preparation of *tert*-butyl *N*-[(2*S*)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]carbamate (I-2-1)

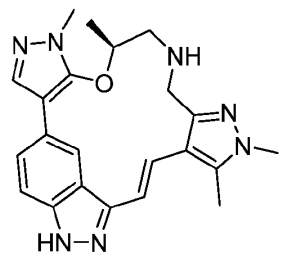


I-2-1

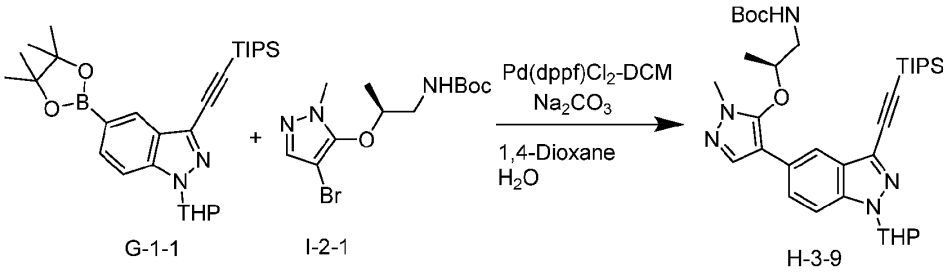
[01203] Step 1. A mixture of 2-methylpyrazol-3-ol (1.00 g, 10.2 mmol), tert-butyl (5*R*)-5-methyl-2,2-dioxo-oxathiazolidine-3-carboxylate (2.42 g, 10.2 mmol) in DMF (49 mL), and potassium carbonate, anhydrous (4.23 g, 30.6 mmol) was heated to 80 °C for 18 hr. The suspension was filtered over Celite and diluted with DCM (500 mL). A aqueous solution of citric acid (1 M, 100 mL) was added, and the mixture was stirred for 1 h until only product peak was observed by LCMS. The layers were separated, and the aqueous layer extracted with DCM (2 x 150 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the crude residue was purified by flash column chromatography to furnish *tert*-butyl *N*-[(2*S*)-2-(2-methylpyrazol-3-yl)oxypropyl]carbamate (2.59 g, 10.14 mmol, 99.5% yield). LCMS: *m/z* 255.99 (M+1).

[01204] Step 2. *tert*-butyl *N*-[(2*S*)-2-(2-methylpyrazol-3-yl)oxypropyl]carbamate (1.3 g, 5.09 mmol) was dissolved in acetonitrile (63 mL). *N*-Bromosuccinimide (1.04 g, 5.86 mmol) was added to this solution at 0 °C. The mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to obtain *tert*-butyl *N*-[(2*S*)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]carbamate (1.23 g, 3.68 mmol, 72.3% yield). LCMS: *m/z* 335.78 (M+1).

[01205] General Method I: (10*S*,17*E*)-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 48)



Ex. 48

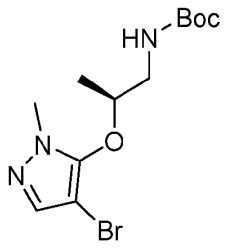
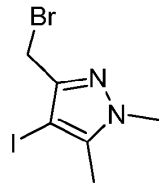
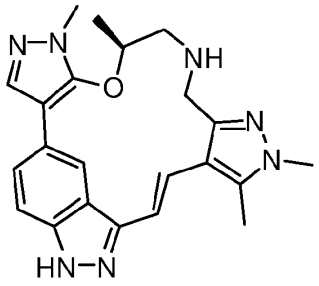
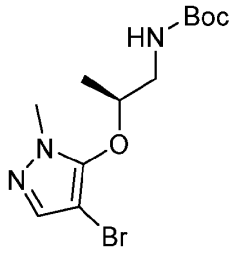
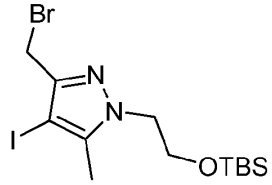
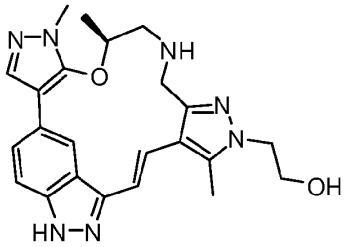
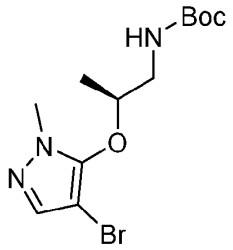
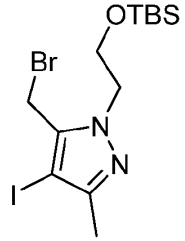
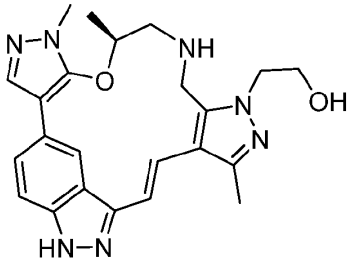


[01206] To *tert*-butyl *N*-[(2*S*)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]carbamate (564 mg, 1.69 mmol) and triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (944.08 mg, 1.86 mmol) in 1,4-dioxane (5 mL) and water (5 mL) was added Sodium carbonate (536.60 mg, 5.06 mmol). The mixture was stirred for 5 minutes as argon was bubbled through, followed by addition of catalyst Pd(dppf)Cl_2-DCM (68.91 mg, 0.0844 mmol). The vessel was sealed and heat to 85 °C for 18 hr. The reaction was diluted with DCM (20 mL) and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 20 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by flash column chromatography to obtain H-3-9 (657 mg, 1.03 mmol, 61.2% yield). LCMS: *m/z* 636.04 (M+1).

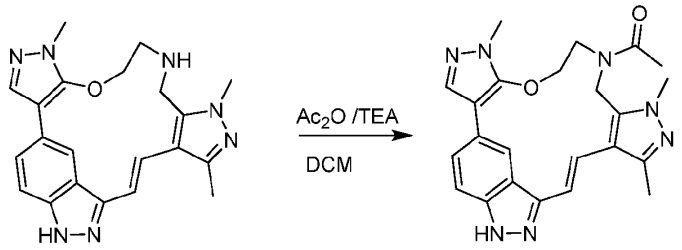
[01207] H-3-9 was converted to Ex. 48 following Step 2-Step 5 in General Method H.

[01208] Ex. 48—Ex. 50 were prepared with General Method I using G-1-1, and the corresponding I-2-X and H-4-X as shown in the Table.

I-2-X	H-4-X	Ex. #

I-2-1 	H-4-2 	Ex. 48 
I-2-1 	H-4-4 	Ex. 49 
I-2-1 	H-4-5 	Ex. 50 

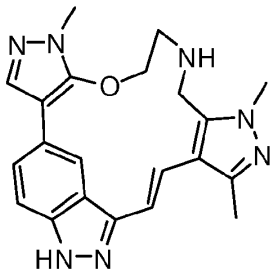
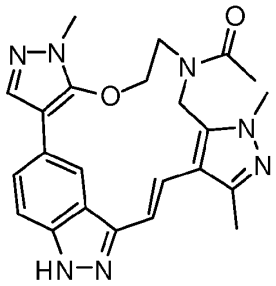
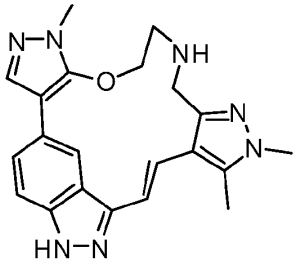
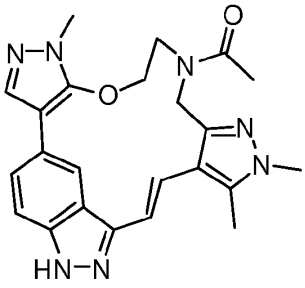
[01209] General Method J: 1-[(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one (Ex. 51)

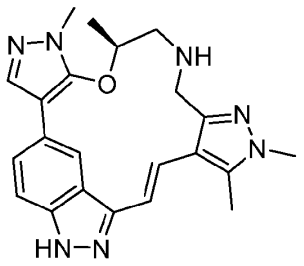
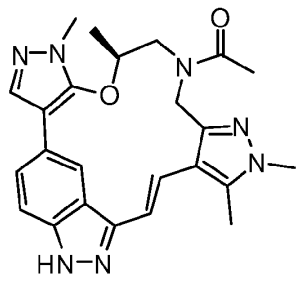
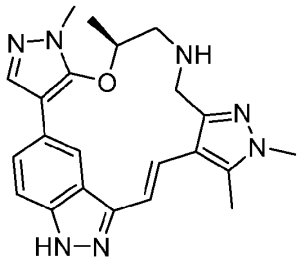
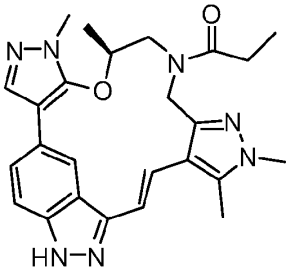


Ex. 40 **Ex. 51**

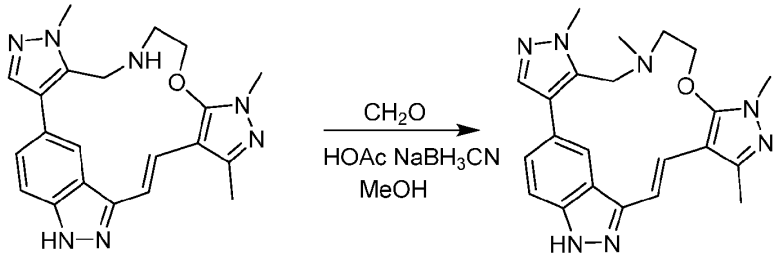
[01210] To a mixture of Ex. 38 (70.0 mg, 0.180 mmol, 1 *eq*) in DCM (2 mL) were added Ac2O (36.7 mg, 0.359 mmol, 2 *eq*) and TEA (72.8 mg, 0.719 mmol, 4 ***eq***). The mixture was stirred at 25 °C for 1 hour and quenched with addition of K_2CO_3 (30.0 mg) at 25°C. The reaction mixture was filtered, and the filtrate was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford Ex. 49 (59.1 mg, 0.129 mmol, 71.7% yield) as a white solid.

[01211] Ex. 49—Ex. 52 were prepared following General Method J using the corresponding starting materials as shown below:

Starting Material	Ex. #
Ex. 40 	Ex. 51 
Ex. 41 	Ex. 52 

Ex. 48 	Ex. 53 
Ex. 48 	Ex. 54 

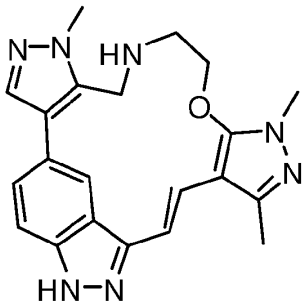
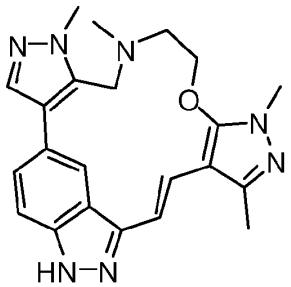
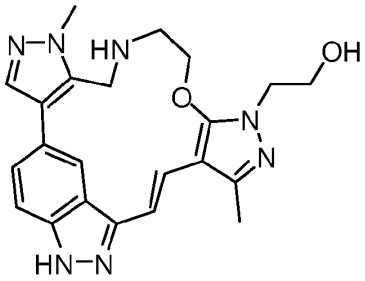
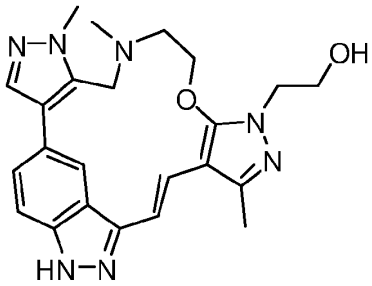
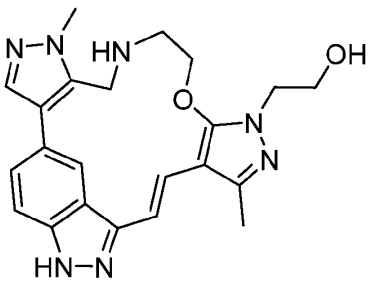
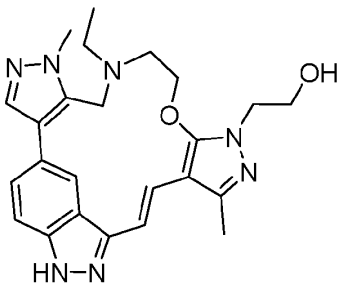
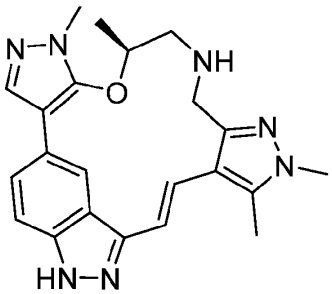
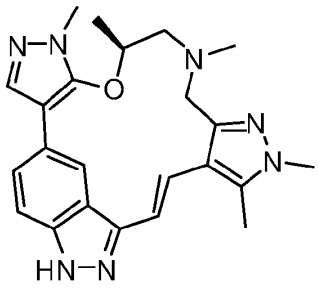
[01212] General Method K:

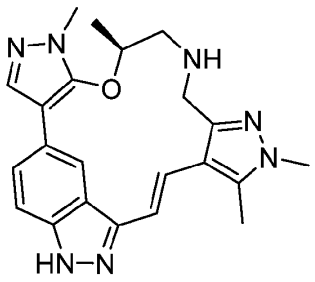
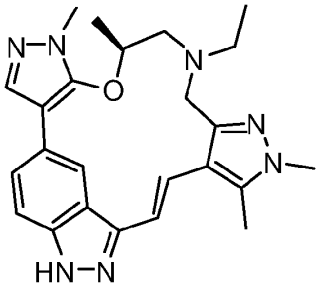
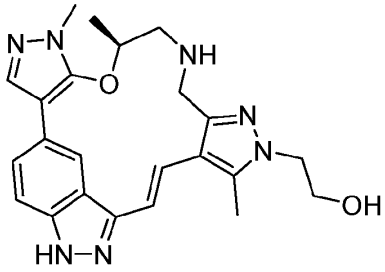
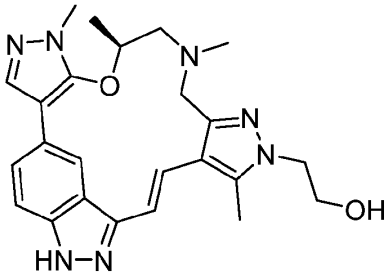
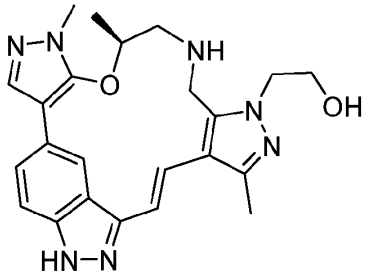
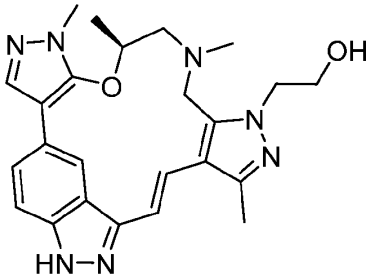


Ex. 18 Ex. 55

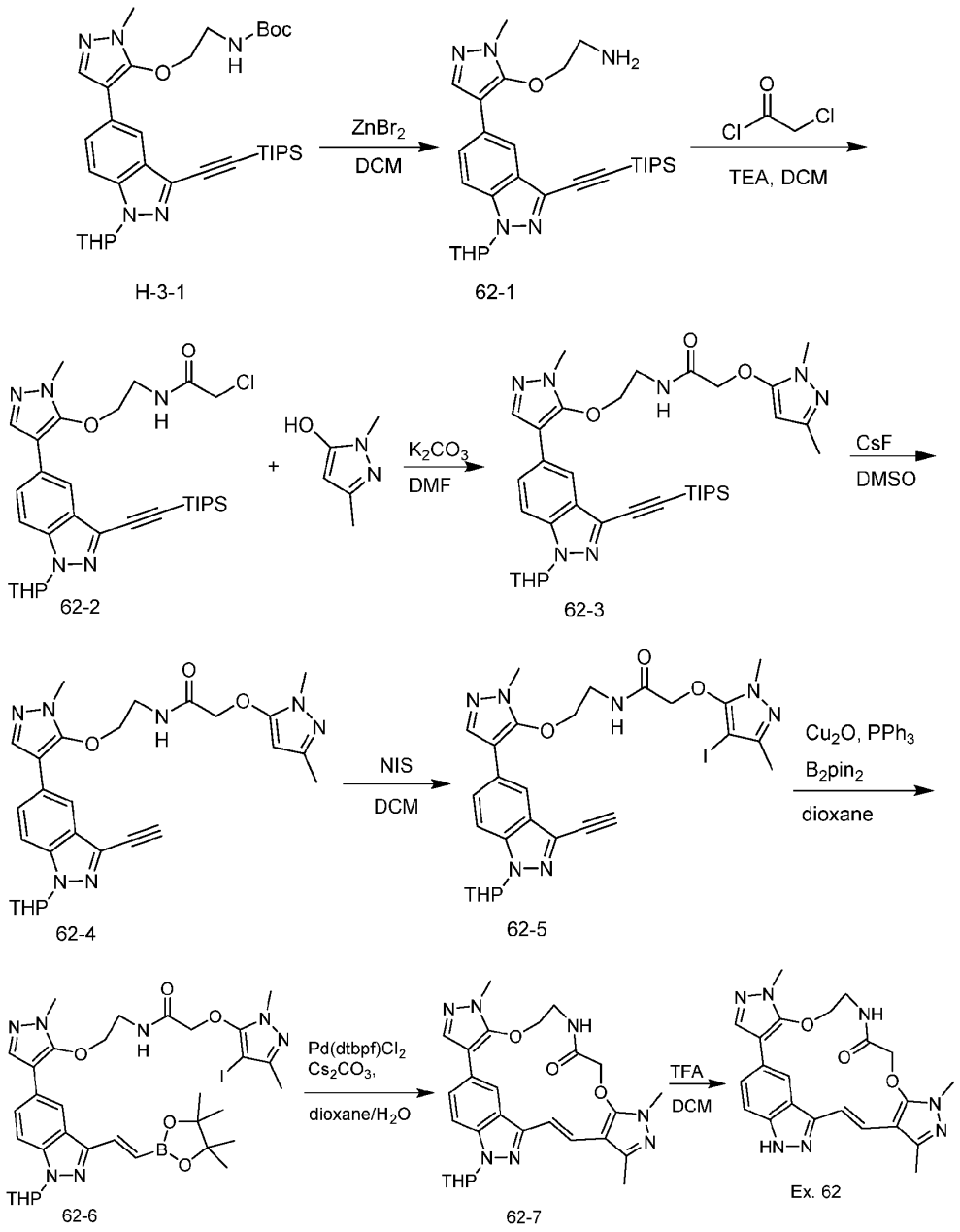
[01213] To a mixture of Ex. 18 (90.0 mg, 0.231 mmol, 1 *eq*) and HCHO (104 mg, 3.47 mmol, 15 *eq*) in MeOH (1 mL) was added HOAc (13.8 mg, 0.231 mmol, 13.2 uL, 1 *eq*) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hour. Then the reaction was added $NaBH_3CN$ (21.7 mg, 0.346 mmol, 1.5 *eq*). The reaction mixture was stirred at 25°C for 12 hours. On completion, the reaction mixture was quenched with water (0.05 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC afford to Ex. 55 as TFA salt (29.4 mg, 0.0562 mmol, 24% yield) as a white solid.

[01214] Ex. 55—Ex. 61 were prepared following General Method J using the corresponding starting materials as shown below:

Starting Material	Ex. #
Ex. 18 	Ex. 55 
Ex. 27 	Ex. 56 
Ex. 27 	Ex. 57 
Ex. 46 	Ex. 58 

Ex. 46 	Ex. 59 
Ex. 47 	Ex. 60 
Ex. 48 	Ex. 61 

[01215] Preparation of (19*E*)-8,16,18-trimethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one (Ex. 62)



[01216] Step 1. To a mixture of tert-butyl N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]carbamate (4.60 g, 7.40 mmol, 1 *eq*) in DCM (60 mL) was added $ZnBr_2$ (8.33 g, 36.9 mmol, 1.85 mL, 5 *eq*). The reaction mixture was stirred at 25°C for 16 hour. On completion, the residue was diluted with water (60 mL) and extracted with EA (2 X 70 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-[2-methyl-4-[1-tetrahydropyran-

2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl] oxyethanamine (4.00 g, 80% yield) as brown solid. LCMS: m/z 522.4 (M+1)

[01217] Step 2. To a mixture of 2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethanamine (2.40 g, 4.60 mmol, 1 eq) and 2-chloroacetyl chloride (779 mg, 6.90 mmol, 548 uL, 1.5 eq) in DCM (20 mL) was added TEA (465 mg, 4.60 mmol, 1 eq) at 0°C. The reaction mixture was stirred at 0°C for 1 hour. On completion, the residue was diluted with water (50mL) and extracted with EA (2 X 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford 2-chloro-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]acetamide (1.50 g, 2.51 mmol, 54% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (t, J = 5.6 Hz, 1H), 7.86 - 7.82 (m, 1H), 7.74 - 7.68 (m, 3H), 5.90 (dd, J = 2.0, 9.6 Hz, 1H), 4.10 - 4.06 (m, 2H), 4.03 (q, J = 7.2 Hz, 1H), 3.96 (t, J = 5.6 Hz, 2H), 3.73 - 3.69 (m, 3H), 3.47 - 3.41 (m, 2H), 2.39 - 2.32 (m, 1H), 2.07 - 1.95 (m, 3H), 1.82 - 1.70 (m, 1H), 1.64 - 1.56 (m, 2H), 1.19 - 1.15 (m, 21H).

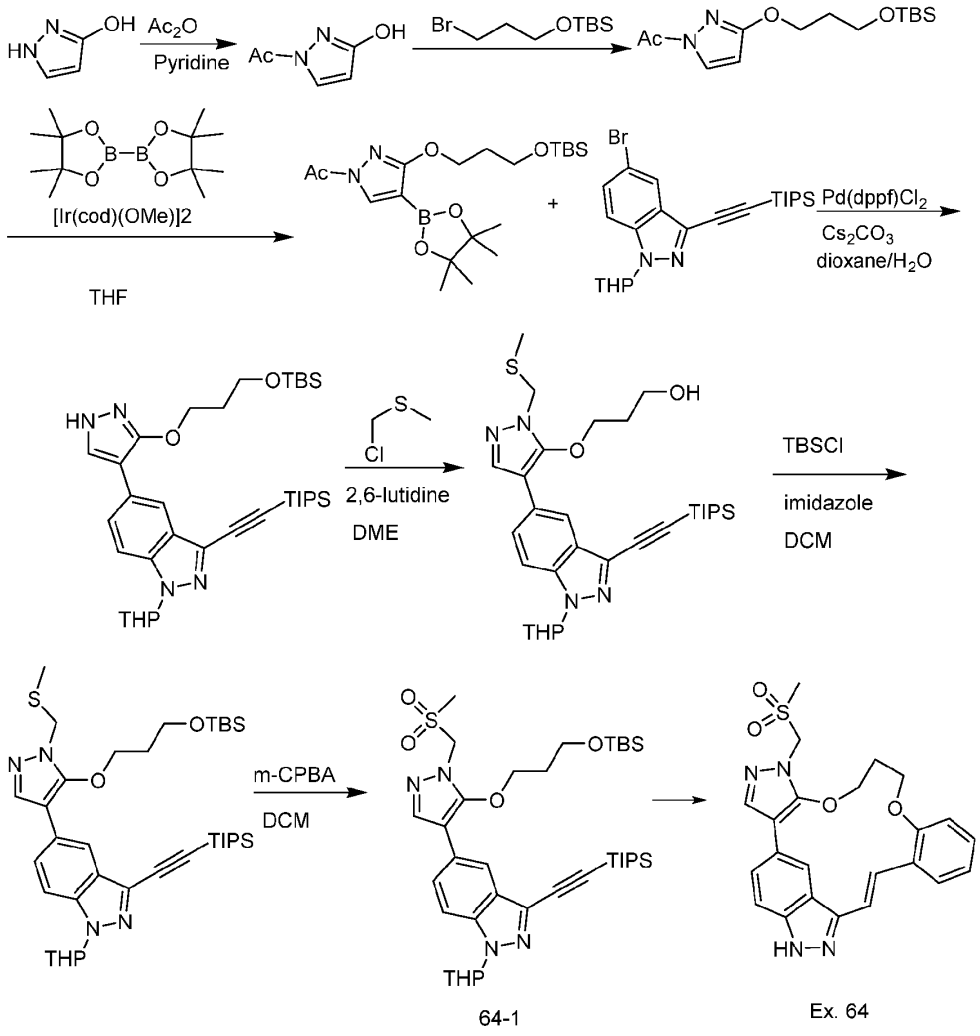
[01218] Step 3. To a mixture of 2-chloro-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]acetamide (1.40 g, 2.34 mmol, 1 *eq*) and 2,5-dimethylpyrazol-3-ol (341 mg, 3.04 mmol, 1.3 *eq*) in DMF (2 mL) was added K_2CO_3 (970 mg, 7.02 mmol, 3 *eq*). The reaction mixture was stirred at 40°C for 12 hours. On completion, the residue was diluted with water (30 mL) and extracted with EA(2 X 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-(2,5-dimethylpyrazol-3-yl)oxy-N-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl] acetamide (1.40 g, 2.08 mmol, 88% yield) as brown oil. LCMS: m/z 674.9 (M+1).

[01219] Step 4. To a mixture of 2-(2,5-dimethylpyrazol-3-yl)oxy-N-[2-[2-methyl-4-[1-tetrahydropyran -2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]acetamide (1.30 g, 1.93 mmol, 1 *eq*) in DMSO (10 mL) was added CsF (1.47 g, 9.65 mmol, 5 *eq*). The reaction mixture was stirred at 25°C for 1 hour. On completion, the residue was diluted with water (30 mL) and extracted with EA (2 X 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford 2-(2,5-dimethylpyrazol-3-yl)oxy-N-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl] acetamide (**62-4**, 560 mg, 1.08 mmol, 56% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (t, J = 5.6 Hz, 1H), 7.79 (s, 2H), 7.77 (s, 1H), 7.73 - 7.69 (m, 1H), 5.84 (dd, J = 2.4, 9.6 Hz, 1H), 5.40 (s, 1H), 4.59 (s, 1H), 4.50 (s, 2H), 4.00 - 3.94 (m, 2H), 3.90 - 3.83 (m, 1H),

3.77 - 3.71 (m, 1H), 3.68 (s, 3H), 3.51 (s, 3H), 3.49 (s, 1H), 2.55 - 2.51 (m, 1H), 2.38 - 2.29 (m, 1H), 2.02 (s, 1H), 2.01 (s, 3H), 1.99 - 1.94 (m, 1H), 1.81 - 1.69 (m, 1H), 1.63 - 1.54 (m, 2H)

[01220] 62-4 was converted to Ex. 62 following Step 5—Step 8 in General Method C.

[01221] Preparation of (11*E*)-1-[(methanesulfonyl)methyl]-19,20-dihydro-1*H*,8*H*,18*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,5,12,13]benzodioxadiazacyclooctadecine



[01222] Step 1. A mixture of 1H-pyrazol-3-ol (10.0 g, 119 mmol, 1 eq) in Py (50 mL) was stirred at 95 °C for 0.5 h. To the mixture was added a solution of acetic anhydride (12.1 g, 119 mmol, 11.1 mL, 1 eq) in pyridine (50 mL). The reaction was stirred at 95 °C for 2.5 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with

water (80 mL) and extracted with EA (3 X 120 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The reaction mixture was triturated with PE (30 ml), filtered and dried under vacuo to afford 1-(3-hydroxypyrazol-1-yl)ethanone (12.0 g, 95.15 mmol, 80.00% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.97 (s, 1H), 8.13 (s, 1H), 6.00 (s, 1H), 2.47 (s, 3H).

[01223] Step 2. To a mixture of 1-(3-hydroxypyrazol-1-yl)ethanone (12.0 g, 95.2 mmol, 1 eq) and 3-bromopropoxy-tert-butyl-dimethyl-silane (26.5 g, 105 mmol, 1.1 eq) in DMF (100 mL) was added K_2CO_3 (39.4 g, 285 mmol, 3 eq). The reaction mixture was stirred at 60 °C for 4 h. On completion, the residue was diluted with water (300 mL) and then extracted with EA (3 X 300 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford 1-[3-[3-[tertbutyl(dimethyl)silyl]oxypropoxy] pyrazol-1-yl]ethanone (24.0 g, 80.4 mmol, 84.5% yield) as yellow oil. LCMS: 299.4 (M+1).

[01224] Step 3. A mixture of 1-[3-[3-[tert-butyl(dimethyl)silyl]oxypropoxy]pyrazol-1-yl]ethanone (5.00 g, 16.7 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 (12.8 g, 50.3 mmol, 3 eq), 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (899 mg, 3.35 mmol, 0.2 eq), bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) (1.11 g, 1.68 mmol, 0.1 eq) in THF (50 mL) was stirred at 90 °C for 12 h. On completion, the residue was diluted with water (50 mL) and extracted with EA (3 X 80mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography to provide tert-butyl-dimethyl-|3-||4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl|oxy|propoxy|silane (6.00 g, 15.7 mmol, 93.7% yield) as yellow solid. LCMS: m/z 383.1 (M+1).

[01225] Step 4. A mixture of tert-butyl-dimethyl-[3-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl]oxy]propoxy]silane (7.00 g, 18.3 mmol, 1.0 ***eq***), 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (9.29 g, 20.1 mmol, 1.1 ***eq***), Cs_2CO_3 (17.9 g, 54.9 mmol, 3.0 ***eq***), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (1.19 g, 1.83 mmol, 0.1 ***eq***) in dioxane (150 mL) and H_2O (30 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 90 °C for 4 hr. under N_2 atmosphere. The mixture was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give tert-butyl-dimethyl-[3-[[4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-1H-pyrazol-3-yl]oxy]propoxy]silane (3.00 g, 4.52 mmol, 24.7% yield, 96% purity) as a brown oil. LCMS: m/z 638.0 (M+1)

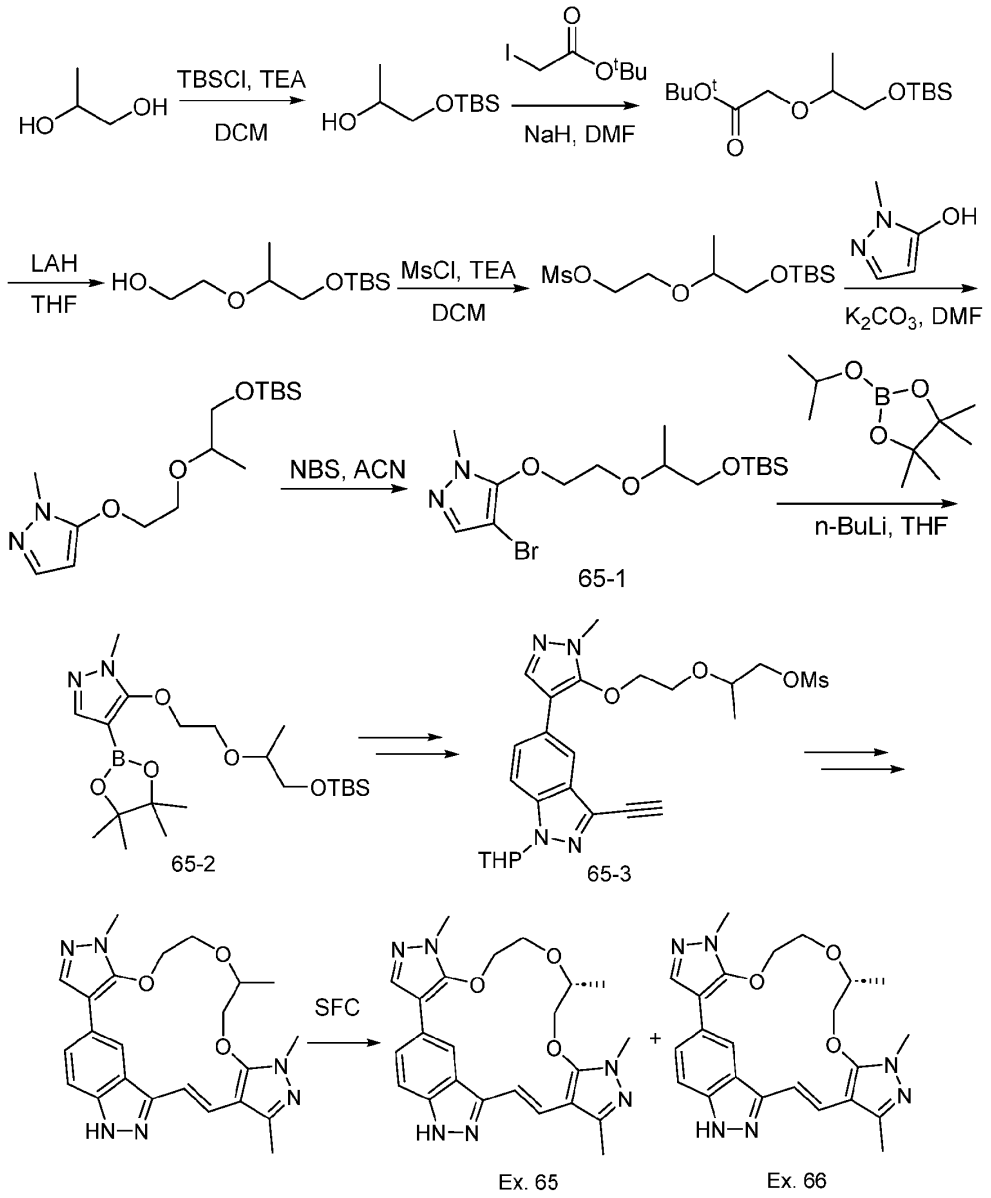
[01226] Step 5. To a solution of tert-butyl-dimethyl-[3-[[4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-1H-pyrazol-3-yl]oxy]propoxy]silane (1.50 g, 2.35 mmol, 1.0 ***eq***) in dioxane (20 mL) was added 2,6-dimethylpyridine (505 mg, 4.71 mmol, 2.0 ***eq***) and chloro(methylsulfanyl)methane (1.14 g, 11.8 mmol, 5.0 ***eq***). The mixture was stirred at 110 °C for 4 hr. After cooling down, the mixture was concentrated and the residue was purified by column chromatography to give 3-[2-(methylsulfanylmethyl)-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazol-3-yl]oxypropan-1-ol (500 mg, 0.841 mmol, 35.7% yield) as a colorless oil. LCMS: m/z 583.7 (M+1).

[01227] Step 6. To a solution of 3-[2-(methylsulfanylmethyl)-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropan-1-ol (1.00 g, 1.72 mmol, 1.0 ***eq***) in DCM (10 mL) was added imidazole (350 mg, 5.15 mmol, 3.0 ***eq***) and TBSCl (388 mg, 2.57 mmol, 1.5 ***eq***). The mixture was stirred at 25 °C for 3 hr, 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 concentrated. The residue was purified by column chromatography to give tert-butyl-dimethyl-[3-[2-(methylsulfanylmethyl)-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy]silane (900 mg, 1.29 mmol, 75.3% yield)as a colorless oil. LCMS: m/z 697.7 (M+1).

[01228] Step 7. To a solution of tert-butyl-dimethyl-[3-[2-(methylsulfanylmethyl)-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy]silane (1.20 g, 1.72 mmol, 1.0 ***eq***) in DCM (20 mL) was added m-CPBA (629 mg, 3.10 mmol, 85% purity, 1.8 ***eq***) at 0 °C. The mixture was quenched with sat. aqueous 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. The residue was purified by column chromatography to give tert-butyl-dimethyl-[3-[2-(methylsulfonylmethyl)-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy]silane (**64-1**, 720 mg, 987 mmol, 57.4 % yield) as a colorless oil. LCMS: m/z 729.2 (M+1).

[01229] 64-1 was converted to Ex. 64 following Steps 2,3,4,6,7 and 8 in General Method C using 2-iodophenol in Step 3.

[01230] Preparation of (13R,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole (Ex. 65) and (13S,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole (Ex. 66)



[01231] Step 1. To a solution of propane-1,2-diol (25.0 g, 328 mmol, 1 *eq*) in DCM (250 mL) was added TBSCl (49.5 g, 328 mmol, 1 *eq*) and imidazole (22.3 g, 328 mmol, 1 *eq*). The mixture was stirred at 25 °C for 3 hr. On completion, the mixture was quenched with water (400 mL) and extracted with ethyl acetate (400 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (55.0 g, 288 mmol, 87% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 4.44 (d, *J* = 4.6 Hz, 1H), 3.58 (td, *J* = 5.7, 11.2 Hz, 1H),

3.47 (dd, *J* = 5.4, 9.8 Hz, 1H), 3.32 – 3.25 (m, 1H), 1.02 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H).

[01232] Step 2. To a solution of 1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (10.0 g, 52.5 mmol, 1 *eq*) in THF (110 mL) was added NaH (4.20 g, 105 mmol, 60% purity, 2 *eq*) in batches at 0 °C. After addition, the mixture was stirred at this temperature for 30 mins, and then tert-butyl 2-iodoacetate (19.0 g, 78.8 mmol, 1.5 *eq*) in THF (5 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 1.5 hr. 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=40:1 to 30:1) to give tert-butyl 2-[2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethoxy]acetate (8.50 g, 27.9 mmol, 53% yield) as a colorless oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.11 (d, *J* = 5.8 Hz, 1H), 4.04 - 3.98 (m, 1H), 3.65 - 3.48 (m, 1H), 3.45 - 3.38 (m, 1H), 1.50 - 1.45 (m, 10H), 1.18 (dd, *J* = 6.0, 10.4 Hz, 3H), 0.90 (d, *J* = 4.4 Hz, 9H), 0.10 - 0.05 (m, 6H).

[01233] Step 3. To a solution of tert-butyl 2-((1-((tert-butyldimethylsilyl)oxy)propan-2-yl)oxy)acetate (8.50 g, 27.9 mmol, 1 *eq*) in THF (200 mL) was added LAH (1.06 g, 27.9 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hr. 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 a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to 4:1) to give 2-[2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethoxy]ethanol (4.40 g, 18.7 mmol, 67% yield) as a colorless oil

[01234] Step 4. To a solution of 2-[2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethoxy]ethanol (4.30 g, 18.3 mmol, 1 *eq*) in DCM (100 mL) was added TEA (9.28 g, 91.7 mmol, 5 *e*q), and then MsCl (12.6 g, 110 mmol, 6 eq) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was quenched with water (100 mL) and extracted with DCM (150 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 2-[2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethoxy]ethyl methanesulfonate (5.70 g, 18.2 mmol, 99% yield) as a yellow oil.

[01235] Step 5. To a solution of 2-[2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethoxy]ethyl methanesulfonate (5.70 g, 18.2 mmol, 1 *eq*) and 2-methylpyrazol-3-ol (3.58 g, 36.4 mmol, 2 *eq*) in DMF (80 mL) was added K_2CO_3 (7.56 g, 54.7 mmol, 3 *eq*). The mixture was stirred at 60 °C for 12 hr. On completion, the mixture was quenched with water (20 mL)

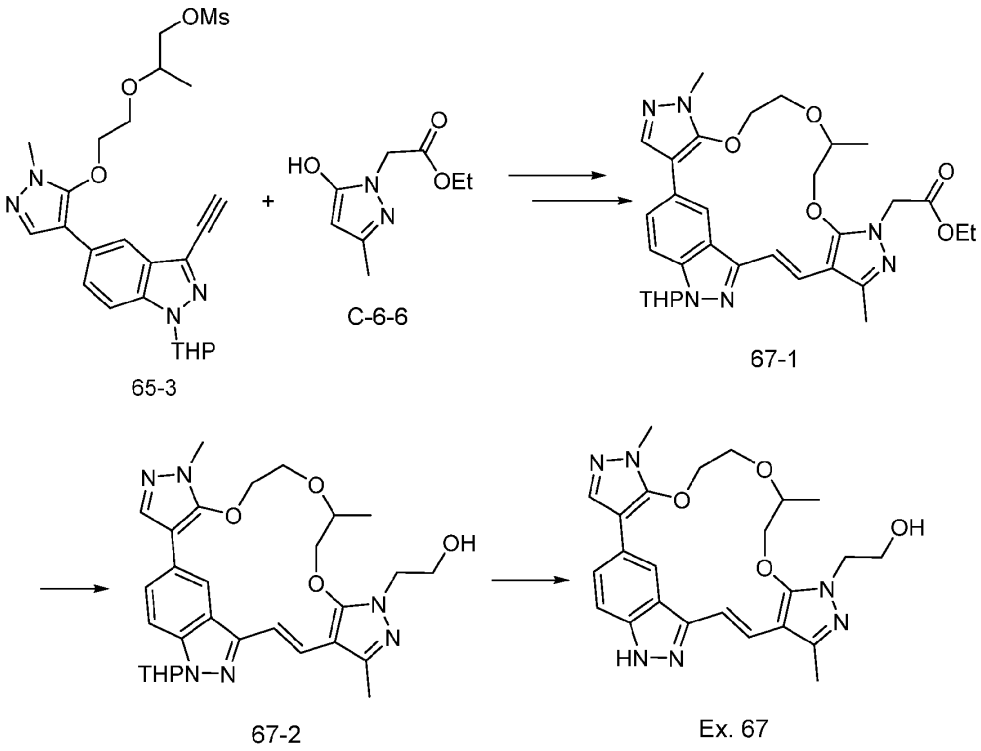
and extracted with ethyl acetate (25 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and the filtrated was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=5:1 to 4:1) to give tert-butyl-dimethyl-[2-[2-(2-methylpyrazol-3-yl)oxyethoxy]propoxy]silane (3.60 g, 11.4 mmol, 62% yield) as a yellow oil. LCMS:315.6 (M+1) *m/z*

[01236] Step 6. To a solution of tert-butyl-dimethyl-[2-[2-(2-methylpyrazol-3-yl)oxyethoxy]propoxy]silane (3.50 g, 11.13 mmol, 1 *eq*) in MeCN (60 mL) was added NBS (1.98 g, 11.1 mmol, 1 *eq*). The mixture was stirred at 25 °C for 2 hr. 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 a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=4:1 to 1:1 to give 2 2-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethoxy]propoxy-tert-butyl-dimethyl-silane (3.00 g, 7.63 mmol, 68% yield) as a yellow oil. LCMS: *m/z* 394.4 (M+1)

[01237] Step 7. To a solution of 2-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethoxy]propoxy-tert-butyl-dimethyl-silane (3.00 g, 7.63 mmol, 1 *eq*) in THF (80 mL) was added n-BuLi (2.5 M, 9.15 mL, 3 *eq*) at -78 °C. After addition, the mixture was stirred at this temperature for 30 min, and then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.26 g, 22.8 mmol, 3 *eq*) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 1.5 hr. 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, Petroleum ether/THF=8:1 to 6:1) to give tert-butyl-dimethyl-[2-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethoxy]propoxy]silane, 65-1 (2.40 g, 5.45 mmol, 71% yield) as a colorless oil. LCMS: *m/z* 441.2 (M+1)

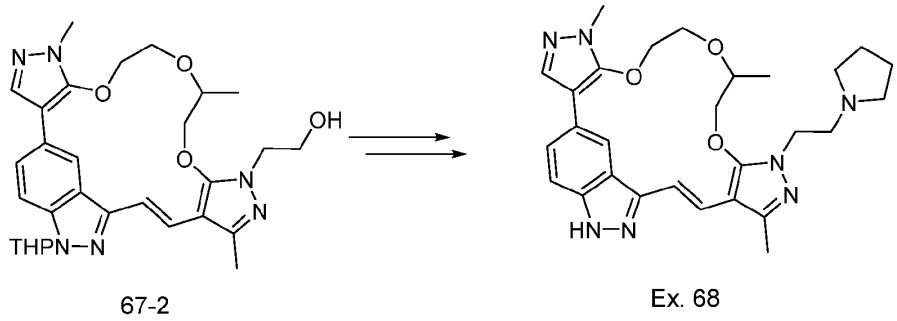
[01238] The remaining steps were performed according to Method G followed by SFC separation to provide the arbitrarily assigned isomers Ex. 65 and Ex 66.

[01239] Preparation of 2-[(19E)-8,13,18-trimethyl-2,8,10,11,13,14-hexahydro-16H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazol-16-yl]ethan-1-ol (Ex. 67)



[01240] Ex 67 was prepared from 65-3 and C-6-6 via General Method C and General Method D.

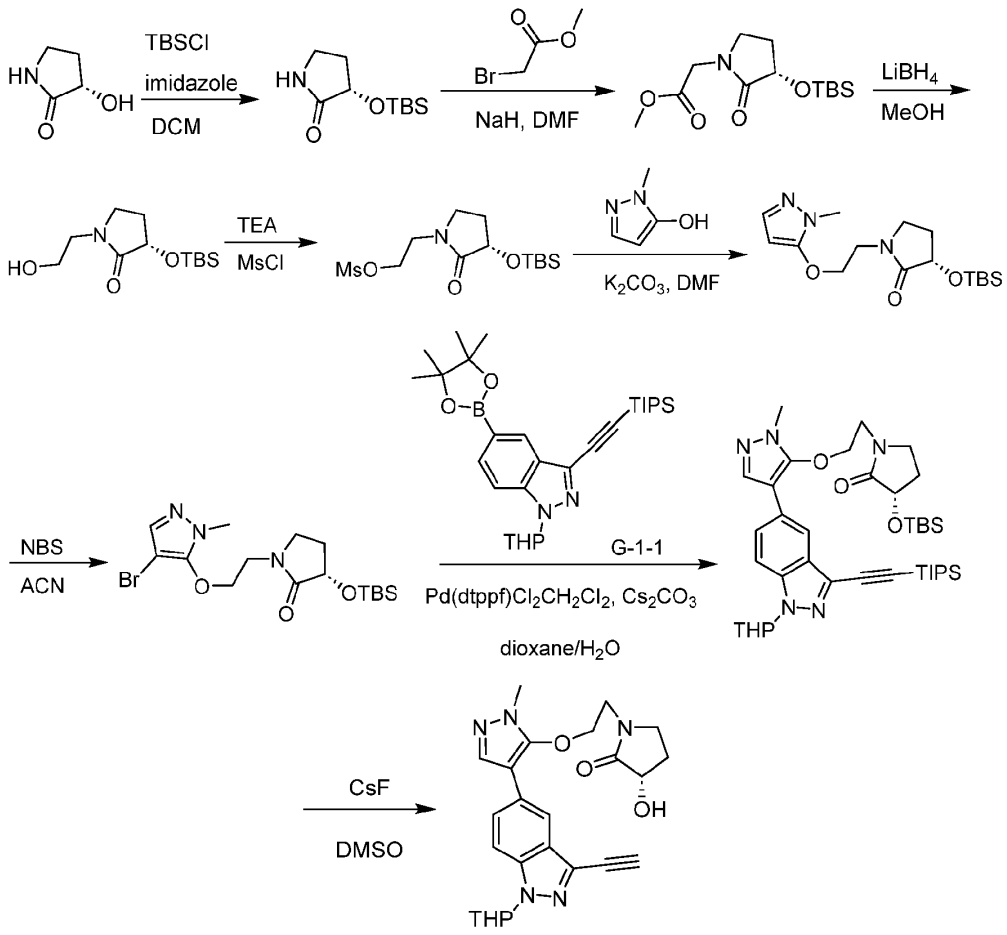
[01241] Preparation of (19*E*)-8,13,18-trimethyl-16-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole (Ex. 68)



[01242] Ex. 68 was prepared from 67-2 in a similar manner to Method F.

[01243] Ex. 69 was prepared from D-1-3 and (3S)-pyrrolidin-3-ol via General Method D and General Method F.

[01244] Preparation of 3R)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-(2-iodophenoxy)pyrrolidin-2-one (I-70)



I-70

[01245] Step 1. A mixture of (3S)-3-hydroxypyrrolidin-2-one (21.3 g, 210 mmol, 1 *eq*) and TBSCl (47.6 g, 316 mmol, 38.7 mL, 1.5 *eq*), and imidazole (28.7 g, 421 mmol, 2 *eq*) in DCM (220 mL) at 0 °C, and then the mixture was stirred at 25 °C for 16 h. On completion, the mixture was quenched by H_2O (200 mL) and extracted with EtOAc (80 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (220 g silica gel column, EA in PE from 0-100%) to give (3S)-3-[tert-butyl(dimethyl)silyl]oxypyrrolidin-2-one (49.0 g, 196 mmol, 93% yield, 86% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.27 (t, *J* = 7.6 Hz, 1H), 3.44 - 3.36 (m, 1H), 3.27 (td, *J* = 7.6, 9.6 Hz, 1H), 2.38

(dd, *J* = 3.2, 12.8 Hz, 1H), 2.05 (d, *J* = 8.0, 12.8 Hz, 1H), 0.93 (s, 9H), 0.16 (d, *J* = 7.2 Hz, 6H). LCMS: *m/z* 216.2 (M+1)

[01246] Step 2. A mixture of (3S)-3-[tert-butyl(dimethyl)silyl]oxypyrrolidin-2-one (21.0 g, 97.5 mmol, 1 *eq*) in DMF (189 mL) the mixture was stirred at 0 °C added NaH (5.85 g, 146 mmol, 116 uL, 60% purity, 1.5 *eq*). Then the mixture was stirred at 0 °C for 0.5 h. Then added methyl 2-bromoacetate (22.4 g, 146 mmol, 13.8 mL, 1.5 *eq*), and then the mixture was stirred at 0 °C for 0.5 h. On completion, the mixture was quenched by H_2O (400 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (220 g silica gel column, THF in PE from 0-100%) to give methyl 2-[(3S)-3-[tert-butyl(dimethyl)silyl]oxy-2-oxo-pyrrolidin-1-yl]acetate (27.8 g, 96.7 mmol, 99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.37 (t, *J* = 8.0 Hz, 1H), 4.29 - 4.21 (m, 1H), 3.86 (d, *J* = 17.6 Hz, 1H), 3.75 - 3.70(m, 3H), 3.44 - 3.32 (m, 2H), 2.49 - 2.29 (m, 1H), 2.09 - 1.92 (m, 1H), 0.91 (s, 9H), 0.15 (d, *J* = 7.2 Hz, 6H). LCMS: *m/z* 288.4 (M+1)

[01247] Step 3. A mixture of methyl 2-[(3S)-3-[tert-butyl(dimethyl)silyl]oxy-2-oxo-pyrrolidin-1-yl]acetate (26.8 g, 93 mmol, 1 *eq*) in MeOH (480 mL) at 0 °C, added $LiBH_4$ (10.2 g, 466 mmol, 5 *eq*) and then the mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched by NH_4Cl (60 mL).The mixture was filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (120 g silica gel column, THF in PE from 0--100%) to give (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-(2-hydroxyethyl)pyrrolidin-2-one (22.0 g, 84.8 mmol, 91% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.39 - 4.33 (m, 1H), 3.84 - 3.75 (m, 2H), 3.51 - 3.31 (m, 4H), 2.81 - 2.61 (m, 1H), 2.42 - 2.25 (m, 1H), 1.99 (d, *J* = 8.4, 12.8 Hz, 1H), 0.92 (s, 9H), 0.16 (d, *J* = 6.8 Hz, 6H). LCMS: *m/z* 260.2 (M+1)

[01248] Step 4. To a solution of (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-(2-hydroxyethyl)pyrrolidin-2-one (10.5 g, 40.5 mmol, 1 *eq*) in DCM (105 mL) was added TEA (20.5 g, 202 mmol, 28.2 mL, 5 *eq*) and MsCl (13.9 g, 121 mmol, 9.40 mL, 3 *eq*) and then the mixture was stirred at 20 °C for 1 h. On completion, the mixture was quenched by $NaHCO_3$ (80 mL) and extracted with DCM (70 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give 2-[(3S)-3-[tert-butyl(dimethyl)silyl]oxy-2-oxo-pyrrolidin-1-yl]ethyl methanesulfonate (13.0 g, 38.5 mmol, 95 % yield) as a brown oil.

[01249] Step 5. To a solution of 2-[(3S)-3-[tert-butyl(dimethyl)silyl]oxy-2-oxo-pyrrolidin-1-yl]ethyl methanesulfonate (13.0 g, 38.5 mmol, 1 *eq*) and 2-methylpyrazol-3-ol

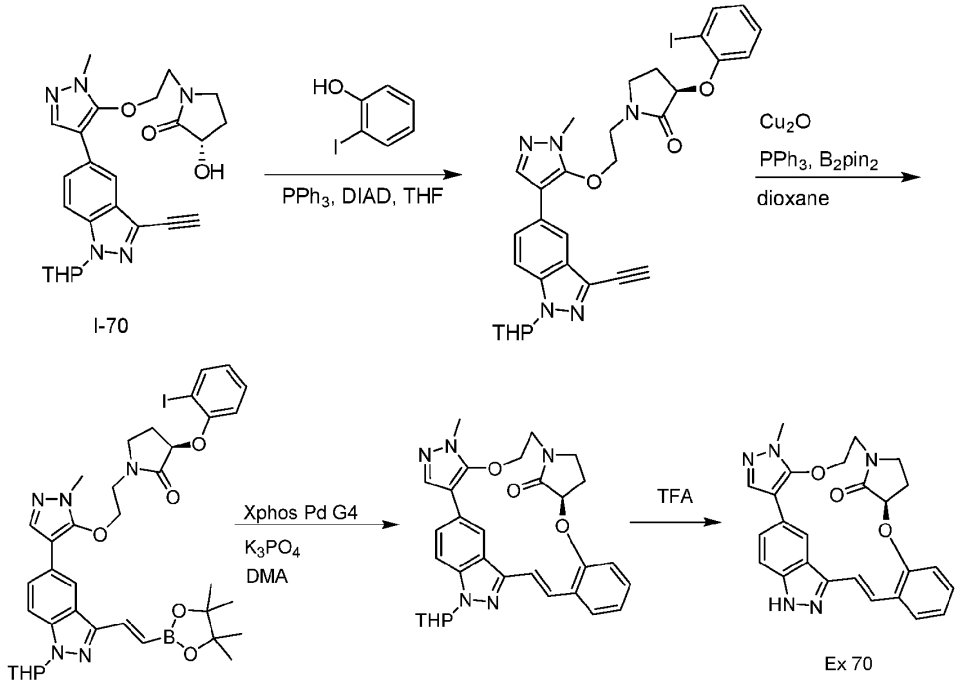
(4.91 g, 50.1 mmol, 1.3 *eq*) in DMF (180 mL) was added K_2CO_3 (16.0 g, 116 mmol, 3 *eq*). The mixture was stirred at 80 °C for 16 h. On completion, the mixture was quenched by H_2O (400 mL) and extracted with EtOAc (100 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (120 g silica gel column, THF in PE from 0-100%) to give (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-[2-(2-methylpyrazol-3-yl)oxyethyl]pyrrolidin-2-one (11.5 g, 33.9 mmol, 88% yield) as a colorless oil. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.63 (s, 1H), 5.67 - 5.58 (m, 1H), 4.19 - 4.11 (m, 2H), 4.06 (d, *J* = 7.2, 11.8 Hz, 1H), 3.91 - 3.84 (m, 2H), 3.84 - 3.76 (m, 1H), 3.39 (s, 3H), 2.40 (d, *J* = 6.8, 14.4 Hz, 1H), 2.11 - 1.98 (m, 1H), 0.89 - 0.86 (m, 9H), 0.18 (d, *J* = 11.8 Hz, 6H). LCMS: *m/z* 340.0 (M+1)

[01250] Step 6. To a solution of (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-[2-(2-methylpyrazol-3-yl)oxyethyl]pyrrolidin-2-one (8.20 g, 24.2 mmol, 1 *eq*) in ACN (82 mL) was added NBS (4.30 g, 24.2 mmol, 1 *eq*) and 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the reaction mixture was quenched by addition solvent Na_2SO_3 50 mL at 20 °C, and extracted with EtOAc (40 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (120 g silica gel column, EA in PE from 0-100%) to give (3S)-1-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-3-[tert-butyl(dimethyl)silyl]oxy-pyrrolidin-2-one (4.10 g, 9.80 mmol, 41% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 - 7.27 (m, 1H), 4.44 - 4.39 (m, 2H), 4.36 - 4.31 (m, 1H), 3.79 - 3.68 (m, 2H), 3.67 - 3.65 (m, 3H), 3.57 - 3.50 (m, 1H), 3.46 - 3.39 (m, 1H), 2.43 - 2.31 (m, 1H), 2.03 - 1.92 (m, 1H), 1.89 - 1.82 (m, 1H), 0.95- 0.89 (m, 1H), 0.92 (s, 8H), 0.23 - 0.11 (m, 6H). LCMS: *m/z* 419.7 (M+1)

[01251] Step 7. A mixture of triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (3.98 g, 7.82 mmol, 1 *eq*), (3S)-1-[2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethyl]-3-[tert-butyl(dimethyl)silyl]oxy-pyrrolidin-2-one (3.60 g, 8.60 mmol, 1.1 *eq*), Cs_2CO_3 (7.65 g, 23.5 mmol, 3 *eq*) and Pd(dppf)Cl2-DCM (510 mg, 0.782 mmol, 0.1 *eq*) in dioxane (80 mL) and H_2O (16 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, the mixture was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (120 g silica gel column, THF in PE from 0--100%) to give (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (4.15 g, 5.76 mmol, 74% yield) as a black brown oil. LCMS: *m/z* 720.7 (M+1)

[01252] Step 8. A mixture of (3S)-3-[tert-butyl(dimethyl)silyl]oxy-1-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (4.00 g, 5.55 mmol, 1 *eq*) and CsF (5.06 g, 33.3 mmol, 1.23 mL, 6 *eq*) in DMSO (40 mL) at 25 °C for 2 h. On completion, the residue was diluted with H_2O 100 mL and extracted with EtOAc (30 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (12 g silica gel column, MeOH in DCM from 0-100%) to give (3S)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-hydroxy-pyrrolidin-2-one (1.40 g, 3.11 mmol, 56% yield) a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.87 - 7.82 (m, 1H), 7.77 (s, 2H), 7.67 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.70 - 6.58 (m, 1H), 5.58(dd, *J* = 1.6, 5.6 Hz, 1H), 4.67 - 4.59 (m, 1H), 4.11 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.04 - 3.99 (m, 2H), 3.92 - 3.83 (m, 1H), 3.80- 3.72 (m, 1H), 3.68 (s, 3H), 3.60 - 3.48 (m, 2H), 2.38 - 2.23 (m, 2H), 2.21 - 2.15 (m, 2H), 2.07 - 1.99 (m, 2H), 1.79 - 1.68 (m,2H), 1.60 (d, *J* = 3.6 Hz, 2H). LCMS: *m/z* 450.1(M+1)

[01253] General Method L. Preparation of (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one (Ex. 70)



[01254] Step 1. The mixture of (3S)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-hydroxy-pyrrolidin-2-one (1.30 g, 2.89

mmol, 1 *eq*), 2-iodophenol (1.40 g, 6.36 mmol, 718 uL, 2.2 *eq*) and PPh_3 (1.67 g, 6.36 mmol, 2.2 *eq*) in 2-MeTHF (65 mL) was stirred at 25 °C for 30 min, then DIAD (1.29 g, 6.36 mmol, 1.24 mL, 2.2 *eq*) was added dropwise to the mixture at 0 °C, the resulting mixture was stirred for another 2 h at 25 °C under N_2. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (40 g silica gel column, THF in PE from 0-100%) to give (3R)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-(2-iodophenoxy)pyrrolidin-2-one (1.35 g, 2.07 mmol, 72% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (s, 1H), 7.78 - 7.75 (m, 1H), 7.68 - 7.64 (m, 1H), 7.60 - 7.54 (m, 2H), 7.34 -7.29 (m, 1H), 7.27 - 7.23 (m, 1H), 6.80 - 6.74 (m, 1H), 5.73 (d, *J* = 3.2, 9.2 Hz, 1H), 4.86 - 4.79 (m, 1H), 4.16 - 4.09 (m, 2H),4.08 - 3.95 (m, 2H), 3.78 (s, 3H), 3.68 (t, *J* = 5.2 Hz, 3H), 3.49 - 3.42 (m, 1H), 2.60 - 2.46 (m, 2H), 2.34 (dd, *J* = 2.8, 13.6 Hz, 1H), 2.21 - 2.13 (m, 1H), 2.13 - 2.06 (m, 1H), 1.81 - 1.64 (m, 4H). LCMS: *m/z* 651.9 (M+1)

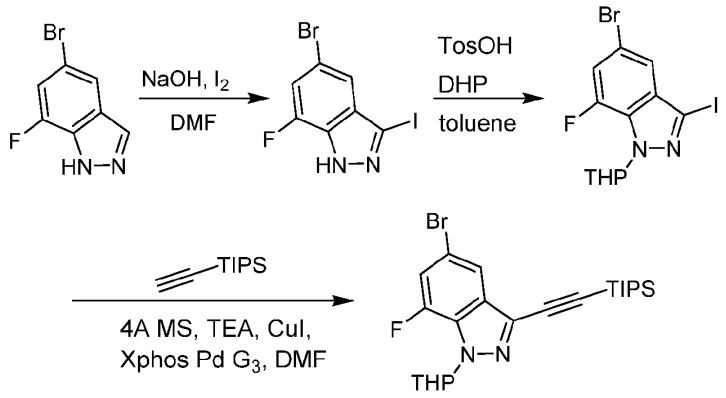
[01255] Step 2. A mixture of (3R)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-(2-iodophenoxy)pyrrolidin-2-one (650 mg, 0.998 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (507 mg, 2.00 mmol, 2 *eq*), triphenylphosphine (288 mg, 1.10 mmol, 1.1 *eq*), Cu_2O (71.4 mg, 0.499 mmol, 51.0 uL, 0.5 *eq*) in dioxane (26 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 4 h under N_2 atmosphere. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (20 g silica gel column, THF in PE from 0-100%) to give (3R)-3-(2-iodophenoxy)-1-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (475 mg, 0.61 mmol, 61 % yield) as a brown oil.

[01256] Step 3. A mixture of (3R)-3-(2-iodophenoxy)-1-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (450 mg, 0.577 mmol, 1 *eq*), Xphos Pd G4 (49.7 mg, 0.058 mmol, 0.1 *eq*), K_3PO_4 (367 mg, 1.73 mmol, 3 *eq*) in DMA (23 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2h under N_2 atmosphere. On completion, the reaction mixture was quenched by addition solvent H_2O 40 mL at 20 °C, and extracted with EtOAc (30 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrate in vacuum to give crude. The residue was purified by combi flash (4 g silica gel column, MeOH in DCM from 0-100%) to give (13R,21E)-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-

1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (110 mg, 0.209 mmol, 36% yield) as a brown oil.

[01257] Step 4. To a solution of (13R,21E)-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (100 mg, 0.190 mmol, 1 *eq*) in DCM (5 mL) was added TFA (7.70 g, 67.5 mmol, 5.00 mL, 355 *eq*). The mixture was stirred at 20 °C for 1 h. On completion the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (4 g silica gel column, MeOH in DCM from 0-10%) to give (13R,21E)-5-methyl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (31.03 mg, 0.065 mmol, 34% yield, 92.9% purity) a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 8.19 (s, 1H), 7.77 - 7.71 (m, 1H), 7.70 - 7.65 (m, 2H), 7.64 - 7.59 (m, 1H), 7.59 -7.52 (m, 2H), 7.36 - 7.28 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 4.45 - 4.38 (m,1H), 4.36 - 4.26 (m, 1H), 4.15 - 4.04 (m, 2H), 3.85 (s, 3H), 3.57 (t, *J* = 8.8 Hz, 1H), 3.46 - 3.40 (m, 1H), 2.45 - 2.32 (m, 1H),2.27 - 2.18 (m, 1H)

[01258] Preparation of 2-(5-bromo-7-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-71)



I-71

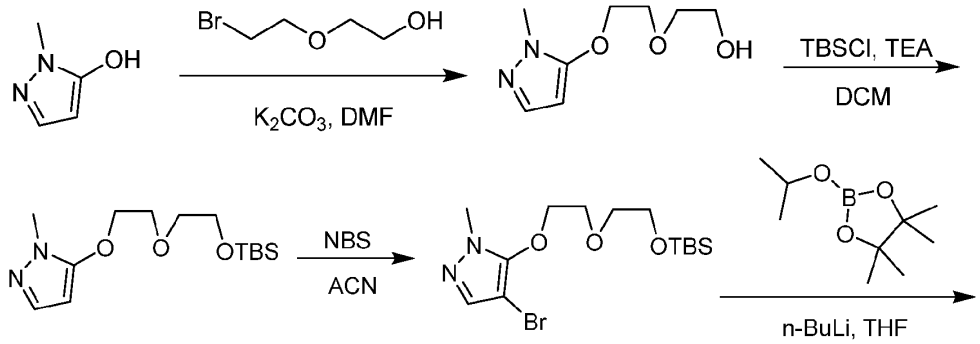
[01259] Step 1. To mixture of 5-bromo-7-fluoro-1H-indazole (5.00 g, 23.3 mmol, 1 *eq*) and I_2 (11.8 g, 46.51 mmol, 2 *eq*) in DMF (100 mL) was added NaOH (2.79 g, 69.8 mmol, 3 *eq*), the mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (300 mL) and extracted with ethyl acetate (125 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

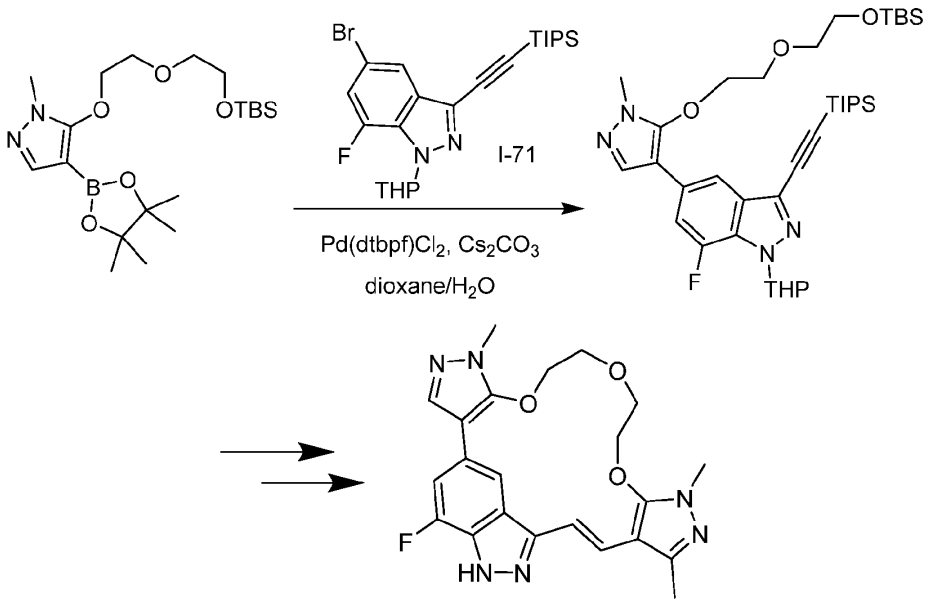
acetate=10:1) to give 5-bromo-7-fluoro-3-iodo-1H-indazole (7.50 g, 22.0 mmol, 95% yield) as a yellow solid. LCMS: *m/z* 340.4 (M+1).

[01260] Step 2. To a solution of 5-bromo-7-fluoro-3-iodo-1H-indazole (6.50 g, 19.1 mmol, 1 *eq*) in toluene (65 mL) was added 3,4-dihydro-2H-pyran (3.98 g, 47.3 mmol, 2.48 *eq*) and DHP (321 mg, 3.81 mmol, 0.2 *eq*), the mixture was stirred at 90 °C for 16 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE : THF=10:1) to give 5-bromo-7-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole (9.00 g, 18.9 mmol, 99% yield, 89% purity) as a yellow solid.

[01261] Step 3. To a mixture of 5-bromo-7-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole (3.00 g, 7.06 mmol, 1 *eq*), ethynyl(triisopropyl)silane (2.57 g, 14.1 mmol, 2 *eq*), TEA (10.9 g, 108 mmol, 15 *eq*), XPhos Pd G3 (597 mg, 0.706 mmol, 0.1 *eq*) and CuI (67.2 mg, 0.353 mmol, 0.05 *eq*) in ACN (30 mL) and stirred at 25 °C for 3 h under N_2. On completion, the mixture was quenched with water (80 mL) and extracted with ethyl acetate (35 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=10:1) to give 2-(5-bromo-7-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (4.00 g, 7.01 mmol, 99 % yield, 84% purity) as a yellow oil. LCMS: *m/z* 480.8 (M+1).

[01262] Preparation of (19*E*)-22-fluoro-8,16,18-trimethyl-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole (Ex. 71)





Ex. 71

[01263] Step 1. To a mixture of 2-methylpyrazol-3-ol (18.2 g, 185 mmol, 1 *eq*), 2-(2-bromoethoxy)ethanol (47.0 g, 278 mmol, 1.5 *eq*) and K_2CO_3 (76.9 g, 556 mmol, 3 *eq*) in DMF (200 mL), the mixture was stirred at 80 °C for 16 h. On completion, the mixture was quenched with water (600 mL) and extracted with DCM: MeOH (10:1) (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, MeOH: DCM = 10 : 1) to give 2-[2-(2-methylpyrazol-3-yl)oxyethoxy]ethanol (25.0 g, 134 mmol, 72% yield) as a yellow oil. LCMS: *m/z* 186.9 (M+1).

[01264] Step 2. To a mixture of 2-[2-(2-methylpyrazol-3-yl)oxyethoxy]ethanol (25.0 g, 134 mmol, 1 *eq*) and imidazole (27.4 g, 403 mmol, 3 *eq*) in DCM (250 mL) was added TBSCl (28.3 g, 188 mmol, 1.4 *eq*), the mixture was stirred at 25 °C for 3 h. On completion, the mixture was quenched with water (800 mL) and extracted with DCM (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl-dimethyl-[2-[2-(2-methylpyrazol-3-yl)oxyethoxy]ethoxy]silane (45.0 g, crude) as a yellow oil. LCMS: *m/z* 301.6 (M+1).

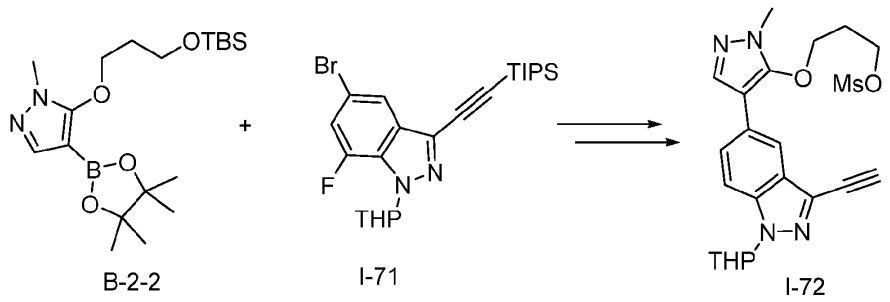
[01265] Steps 3-4 were performed in a similar manner to those of steps 2-3 for the synthesis of intermediate H-2-1.

[01266] Step 5. To a mixture of tert-butyl-dimethyl-[2-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxyethoxy]ethoxy]silane (2.00 g, 4.69 mmol, 1 *eq*), 2-(5-bromo-7-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-

silane (2.70 g, 5.63 mmol, 1.2 *eq*), Cs_2CO_3 (4.58 g, 14.1 mmol, 3 *eq*) and $Pd(dppf)Cl_2.CH_2Cl_2$ (383 mg, 0.469 mmol, 0.1 *eq*) in dioxane (40 mL) and H_2O (8 mL), the mixture was stirred at 90 °C for 16 h under N_2. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF = 3:1) to give tert-butyl-[2-[2-[4-[7-fluoro-1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-yl]oxyethoxy]ethoxy]-dimethyl-silane (1.96 g, 2.80 mmol, 60% yield) as a yellow oil. LCMS: *m/z* 699.9 (M+1).

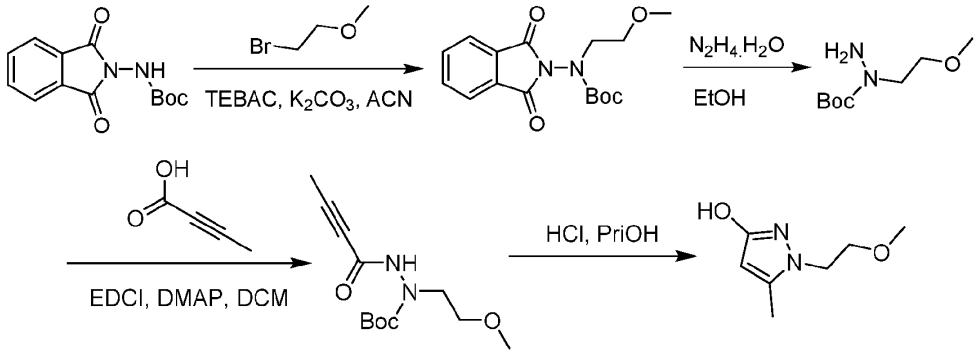
[01267] The remaining steps were performed in a manner similar to those described in General Method G to give Ex. 71.

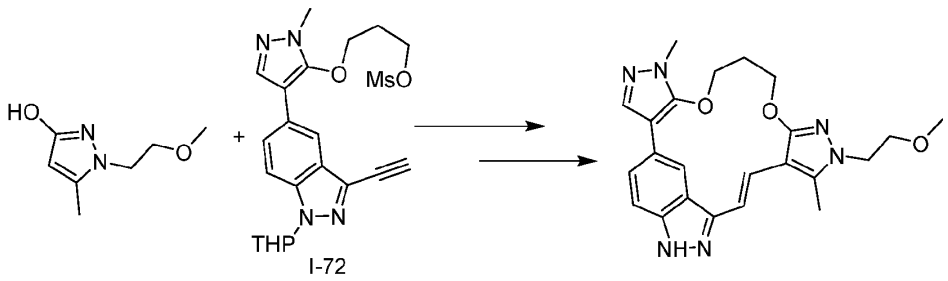
[01268] Preparation of (17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (I-72)



[01269] I-72 was synthesized in a manner similar to steps 1-3 in General Method C.

[01270] Preparation of (17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 72)





[01271] Step 1. To a solution of tert-butyl N-(1,3-dioxoisoindolin-2-yl)carbamate (5 g, 19.0 mmol, 1 *eq*) in ACN (40 mL) was added 1-bromo-2-methoxy-ethane (5.30 g, 38.1 mmol, 3.58 mL, 2 *eq*) and benzyl(triethyl)ammonium;chloride (1.74 g, 7.63 mmol, 0.4 *eq*) and K_2CO_3 (7.90 g, 57.1 mmol, 3 *eq*). The mixture was stirred at 55 °C for 12 hours. On completion, the mixture was filtered and concentrated to give a residue. The crude product was used into the next step without further purification to give tert-butyl N-(1,3-dioxoisoindolin-2-yl)-N-(2-methoxyethyl)carbamate (6.1 g, 99% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 8.03 - 7.89 (m, 4H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.51 - 3.43 (m, 2H), 3.20 - 3.12 (m, 3H), 1.45 (s, 4H), 1.24 (s, 5H)

[01272] Step 2. To a solution of tert-butyl N-(1,3-dioxoisoindolin-2-yl)-N-(2-methoxyethyl)carbamate (6 g, 18.7 mmol, 1 *eq*) in EtOH (100 mL) was added $N_2H_4.H_2O$ (6.31 g, 123 mmol, 6.12 mL, 98% purity, 6.59 *eq*). The mixture was stirred at 80 °C for 1 hour. On completion, the reaction mixture was quenched by addition H_2O 200 mL at 25°C, and then extracted with EA (100 mL * 3). The combined organic layers were washed with NaCl (aq.) 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification get the title compound tert-butyl N-amino-N-(2-methoxyethyl)carbamate (3.5 g, 98% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 4.39 (s, 2H), 3.46 - 3.42 (m, 2H), 3.41 - 3.37 (m, 2H), 3.23 (s, 3H), 1.40 (s, 9H)

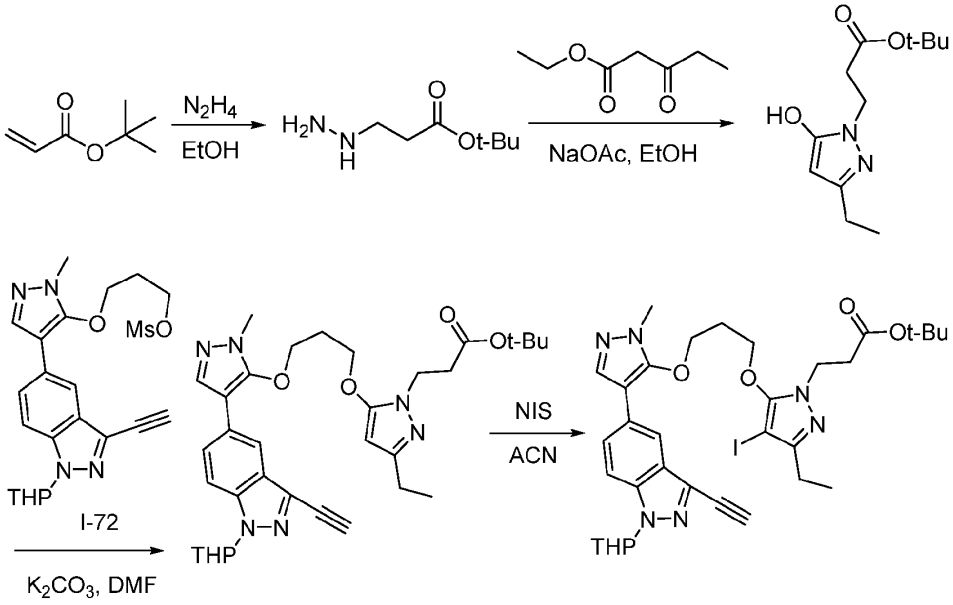
[01273] Step 3. To a solution of but-2-ynoic acid (625 mg, 7.44 mmol, 1 *eq*) and DMAP (90.8 mg, 0.743 mmol, 0.1 *eq*) in DCM (5 mL) was added dropwise tert-butyl N-amino-N-(2-methoxyethyl)carbamate (1.5 g, 7.88 mmol, 1.06 *eq*) at 0°C. And then EDCI (1.57 g, 8.18 mmol, 1.1 *eq*) was added was in five equal portions over 50 min at 0°C. The resulting mixture was stirred at 25 °C for 1.5 hours. On completion, the reaction mixture was quenched by addition HCl (aq.) 10 mL at 25°C, and then diluted with HCl (aq.) 10 mL and extracted with EA (15 mL * 3). The combined organic layers were washed with NaCl (aq.) 10 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification get the

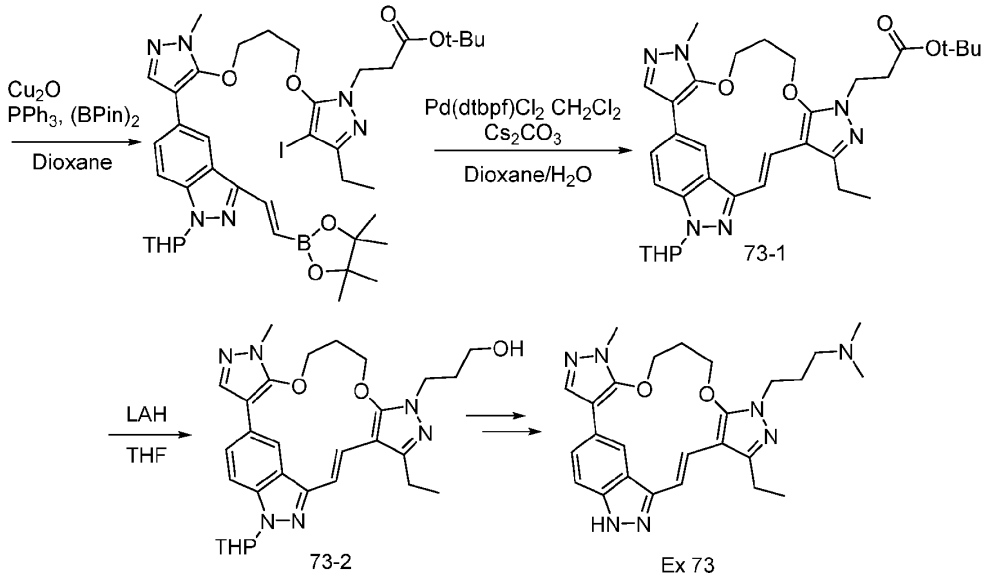
title compound tert-butyl N-(but-2-ynoylamino)-N-(2-methoxyethyl)carbamate (1.5 g, 78% yield) as a yellow oil.

[01274] Step 4. To a solution of tert-butyl N-(but-2-ynoylamino)-N-(2-methoxyethyl)carbamate (1.5 g, 5.85 mmol, 1 *eq*) and propan-2-ol (5.89 g, 97.9 mmol, 16.7 *eq*) was added HCl (4 M, 3.2 mL, 2.2 *eq*). The mixture was stirred at 63 °C for 30 hours. On completion, the resulting residue was then charged with CH_3CN (100 mL, 10 mL/g) and concentrated in vacuo. The solids were filtered, washed with CH_3CN (2 × 40 mL), and then the filter liquor dried under vacuum at ambient temperature. The crude was used into the next step without further purification get the title compound 1-(2-methoxyethyl)-5-methyl-pyrazol-3-ol (300 mg, 32% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 9.39 (s, 1H), 5.22 (s, 1H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.20 (s, 3H), 2.11 (s, 3H)

[01275] The remaining steps were performed in a similar manner to General Method C to give Ex 72.

[01276] Preparation of 3-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-*N*,*N*-dimethylpropan-1-amine (Ex. 73)





[01277] Step 1. To a solution of tert-butyl prop-2-enoate (10.0 g, 78.0 mmol, 11 mL, 1 *eq*) in EtOH (100 mL) was added $N_2H_4.H_2O$ (4.78 g, 93.6 mmol, 5 mL, 98% purity, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. Tert-butyl 3-hydrazinopropanoate (11.7 g, 73.0 mmol, 94% yield) was obtained as yellow oil.

[01278] To a solution of tert-butyl 3-hydrazinopropanoate (11.7 g, 73.0 mmol, 1 *eq*) in EtOH (130 mL) was added NaOAc (8.99 g, 110 mmol, 1.5 *eq*) and ethyl 3-oxopentanoate (11.6 g, 80.3 mmol, 1.1 *eq*). The mixture was stirred at 80 °C for 16 h. 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 0/1). tert-butyl 3-(3-ethyl-5-hydroxy-pyrazol-1-yl)propanoate (17.0 g, 70.6 mmol, 97% yield) was obtained as black brown oil. LCMS: *m/z* 241.0 (M+1).

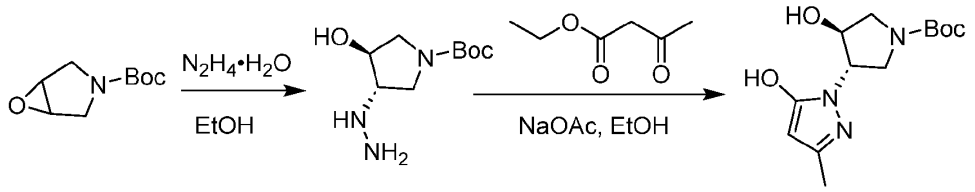
[01279] Steps 3-6 were done in a similar manner to General Method C.

[01280] Step 7. To a solution of tert-butyl 3-[(17E)-15-ethyl-5-methyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]propanoate (500 mg, 0.829 mmol, 1 *eq*) in THF (10 mL) was added $LiAlH_4$ (94.5 mg, 2.49 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was quenched by addition MeOH 10 mL at 0 °C. The residue was purified by column chromatography (SiO_2, DCM/MeOH=1/0 to 10/1). 3-[(17E)-15-ethyl-5-methyl-21-tetrahydropyran-2-yl-7,11-dioxa-

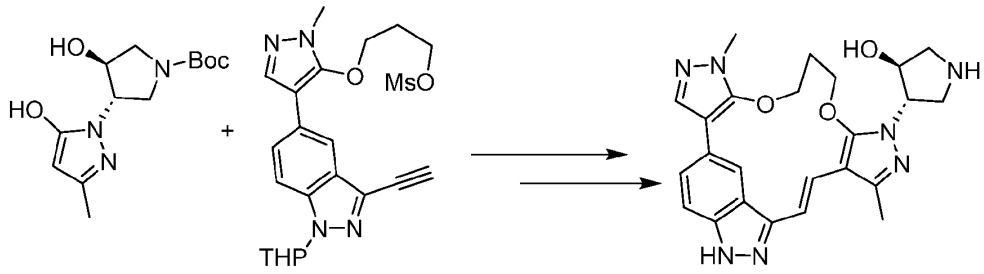
4,5,13,14,20,21-hexazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]propan-1-ol (290 mg, 0.544 mmol, 66% yield) was obtained as yellow solid. LCMS: *m/z* 603.0 (M+1).

[01281] The remaining steps were done in a similar manner to General Method F with dimethylamine in step 2 to give Ex. 73.

[01282] Preparation of (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]pyrrolidin-3-ol (Ex. 74)



74-1



74-1 I-72 Ex 74

[01283] Step 1. To a mixture of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (6.70 g, 36.1 mmol, 1 *eq*) in EtOH (70 mL) was added $N_2H_4.H_2O$ (5.83 g, 114 mmol, 5.66 mL, 98% purity, 3.16 *eq*) at 0°C. The reaction mixture was stirred at 60°C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo* afford to tert-butyl (3S,4S)-3-hydrazino-4-hydroxy-pyrrolidine-1-carboxylate (7.50 g, 34.5 mmol, 95% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.02 (s, 1H), 3.44 (d, *J* = 7.2 Hz, 1H), 3.32 - 3.26 (m, 2H), 3.18 - 3.06 (m, 2H), 2.98 (d, *J* = 6.0 Hz, 1H), 1.38 (s, 9H).

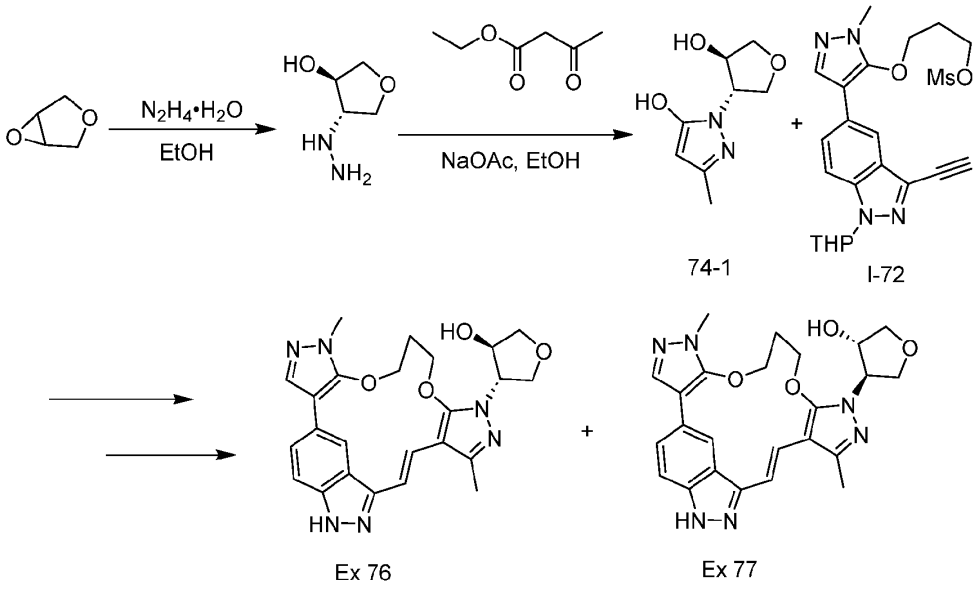
[01284] Step 2. To a mixture of tert-butyl (3S,4S)-3-hydrazino-4-hydroxy-pyrrolidine-1-carboxylate (7.50 g, 34.5 mmol, 1 *eq*) and ethyl 3-oxobutanoate (4.94 g, 37.9 mmol, 4.80 mL, 1.1 *eq*) in EtOH (80 mL) was added NaOAc (4.25 g, 51.7 mmol, 1.5 *eq*). The reaction mixture was stirred at 80°C for 12 hours. On completion, the residue was diluted with water (70 mL) and extracted with EA (2 X 70 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by

column chromatography afford tert-butyl (3S,4S)-3-hydroxy-4-(5-hydroxy-3-methyl-pyrazol-1-yl)pyrrolidine-1-carboxylate (5.90 g, 20.8 mmol, 60% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.87 (s, 1H), 5.49 - 5.36 (m, 1H), 5.25 - 5.11 (m, 1H), 4.45 (d, J = 4.4 Hz, 1H), 4.26 (s, 1H), 3.66 - 3.56 (m, 2H), 3.41 (s, 1H), 3.18 - 3.12 (m, 1H), 2.02 - 1.97 (m, 3H), 1.40 (d, J = 4.8 Hz, 9H).

[01285] The remaining steps were performed in a similar manner to those in General Method C to afford racemic Example 74.

[01286] Racemic Ex. 75 was synthesized using Method K starting from racemic Ex. 74

[01287] Preparation of (3*R*,4*S*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]oxolan-3-ol (Ex. 76) and (3*S*,4*R*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]oxolan-3-ol (Ex. 77)

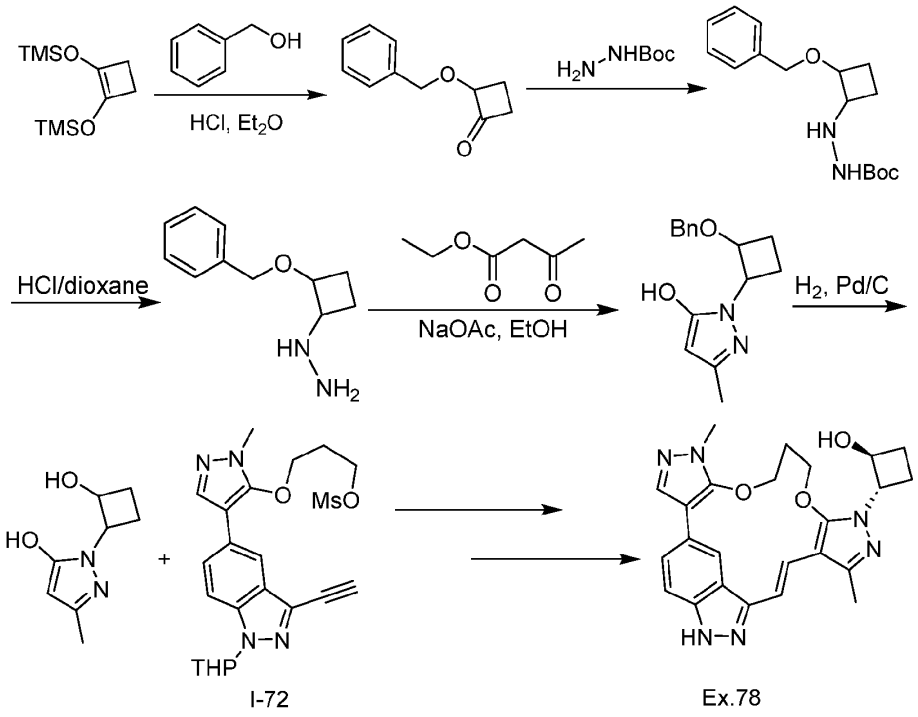


[01288] Step 1. To a solution of 3,6-dioxabicyclo[3.1.0]hexane (1.00 g, 11.6 mmol, 1 *eq*) in EtOH (39 mL) was added $N_2H_4.H_2O$ (1.48 g, 29.0 mmol, 98% purity, 2.5 *eq*) at 0 °C. The reaction was stirred at 25 °C for 10 min, then heated at 60 °C and stirred for 16 h. On completion, the mixture was concentrated to give (3R,4S)-4-hydrazinotetrahydrofuran-3-ol (770 mg, 6.52 mmol, 56% yield) as a white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.04 - 4.02 (m, 1H), 3.79 - 3.69 (m, 3H), 3.49 (d, J = 2.4 Hz, 1H), 3.48 - 3.45 (m, 2H), 3.44(d, J = 1.6 Hz, 1H), 3.05 - 3.02 (m, 1H)

[01289] Step 2. The mixture of (3R,4S)-4-hydrazinotetrahydrofuran-3-ol (3.05 g, 25.8 mmol, 1 *eq*), ethyl 3-oxobutanoate (3.36 g, 25.8 mmol, 1 *eq*) and NaOAc (2.12 g, 25.8 mmol, 1 *eq*) in EtOH (60 mL) was stirred at 80 °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=1:3) to give 2-[(3S,4R)-4-hydroxytetrahydrofuran-3-yl]-5-methyl-pyrazol-3-ol, (74-1) (2.65 g, 14.4 mmol, 56% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.82 (br d, *J* = 1.6 Hz, 1H), 5.35 (br d, *J* = 4.0 Hz, 1H), 5.15 (s, 1H), 4.51 - 4.45 (m, 1H), 4.37 (br s, 1H), 4.06 (br t, *J* = 8.0 Hz, 1H), 3.98 - 3.91 (m, 1H), 3.73 - 3.66 (m, 1H), 3.62 - 3.54 (m, 1H), 2.00 (s, 3H). LCMS: *m/z* 184.9 (M+1)

[01290] The remaining steps were performed in a similar manner to those in General Method C followed by SFC separation to give the arbitrarily assigned Example 76 and Example 77.

[01291] Preparation of (*rac*)-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]cyclobutan-1-ol (Ex. 78)



[01292] Step 1. A mixture of trimethyl-(2-trimethylsilyloxycyclobuten-1-yl)oxy-silane (5.00 g, 21.7 mmol, 1 *eq*), phenylmethanol (2.82 g, 26.0 mmol, 1.2 *eq*), in HCl/dioxane (4 M, 10.8 mL, 2 *eq*), was stirred at 80 °C for 4 h. 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 10:1) to give 2-benzyloxycyclobutanone (3.02 g, 78% yield) as colorless oil.

[01293] Step 2. To a mixture of tert-butyl N-aminocarbamate (405 mg, 3.06 mmol, 1.2 *eq*) and 2-benzyloxycyclobutanone (450 mg, 2.55 mmol, 1 *eq*) in MeOH (4.5 mL) was added AcOH (153 mg, 2.55 mmol, 146. uL, 1 *eq*) to adjust pH=6. The mixture was stirred at 25 °C for 0.2 h. Then $NaBH_3CN$ (481 mg, 7.66 mmol, 3 *eq*) was added to the mixture, the mixture was stirred at 25 °C for 12 h. On completion, the mixture was quenched with water (1 mL) 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 tert-butyl N-[(2-benzyloxycyclobutyl)amino]carbamate (372 mg, 1.27 mmol, 50% yield) as a colorless oil. LCMS: *m/z* 192.9 (M+1-100)

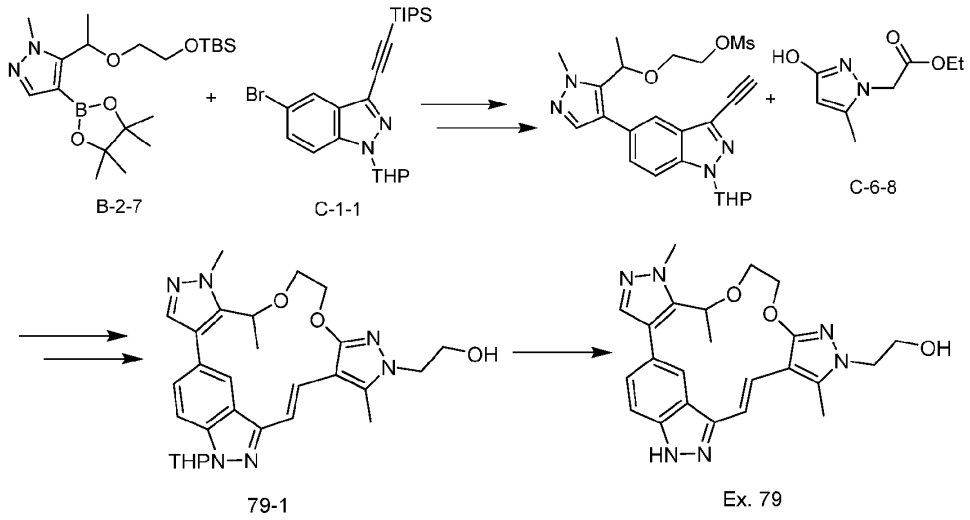
[01294] Step 3. To a solution of tert-butyl N-[(2-benzyloxycyclobutyl)amino]carbamate (342 mg, 1.17 mmol, 1 *eq*) in DCM (3 mL) was added HCl/dioxane (4 M, 7 mL, 22.9 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was concentrated to give (2-benzyloxycyclobutyl)hydrazine (267 mg, crude, HCl) as a red oil. LCMS: *m/z* 192.9 (M+1)

[01295] Step 4. To a solution of (2-benzyloxycyclobutyl)hydrazine (267 mg, 1.17 mmol, 1 *eq*, HCl) in EtOH (2.7 mL) was added NaOAc (96.0 mg, 1.17 mmol, 1 *eq*) and ethyl 3-oxobutanoate (152 mg, 1.17 mmol, 1 *eq*). The mixture was stirred at 80 °C for 2 h. On completion, the mixture 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 2-(2-benzyloxycyclobutyl)-5-methyl-pyrazol-3-ol (92.0 mg, 0.356 mmol, 30 % yield) as a red oil. LCMS: *m/z* 259.1 (M+1)

[01296] Step 5. To a solution of 2-(2-benzyloxycyclobutyl)-5-methyl-pyrazol-3-ol (540 mg, 2.09 mmol, 1 *eq*) in MeOH (20 mL), and HCl/dioxane (2 mL) was added Pd/C (130 mg, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 for several times. The mixture was stirred under H_2 (50 psi) at 50 °C for 16 h. On completion, the mixture was concentrated to give 2-(2-hydroxycyclobutyl)-5-methyl-pyrazol-3-ol (475 mg, crude) as a colorless oil. LCMS: *m/z* 168.9 (M+1)

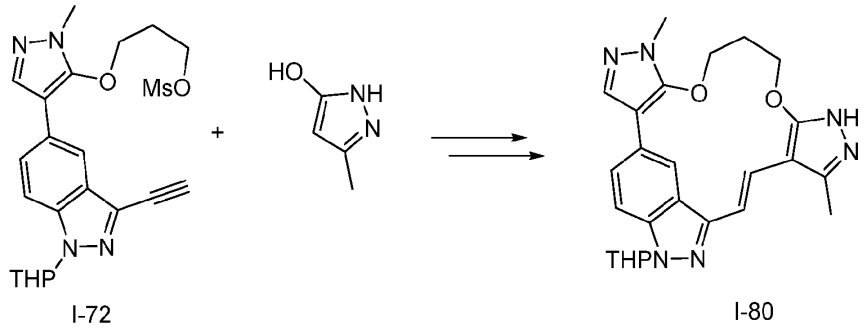
[01297] The remaining steps were performed in a similar manner to those described in General Method C to afford racemic Ex. 78.

[01298] Preparation of 2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15(2*H*)-yl]ethan-1-ol (Ex 79)



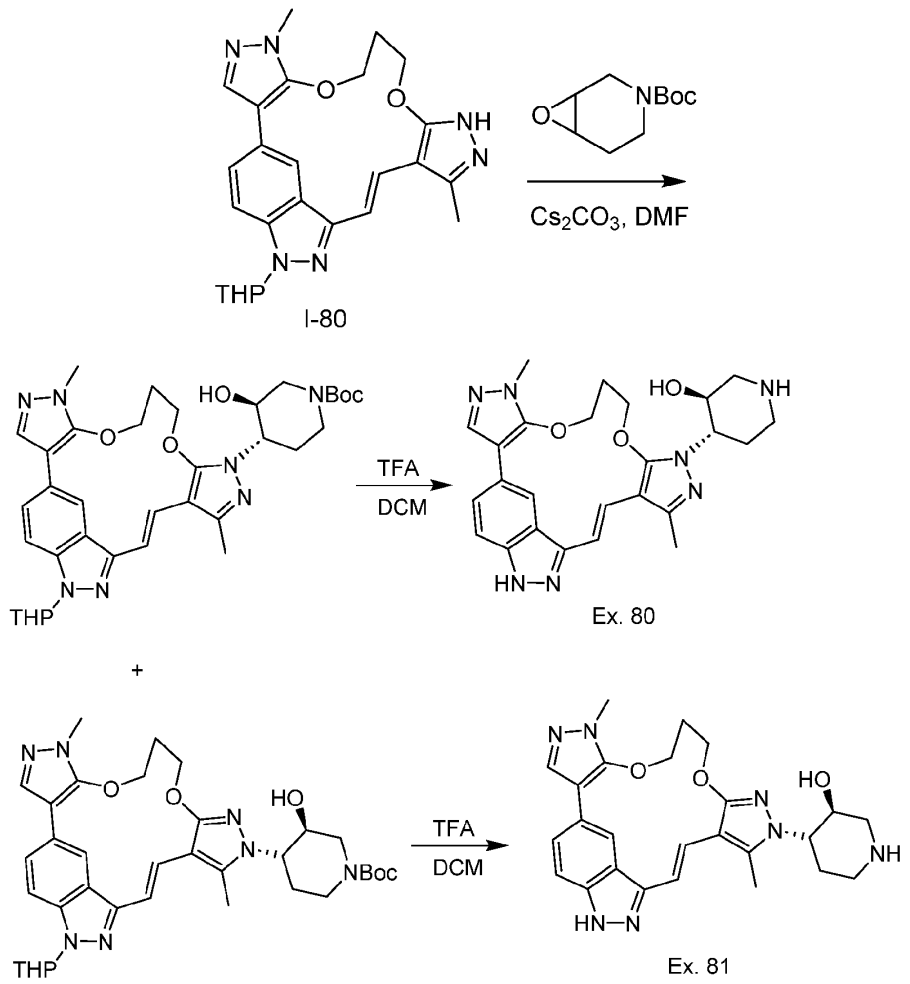
[01299] Ex. 79 was synthesized in a manner similar to those described in General Method C and General Method D with the appropriate intermediates shown.

[01300] Synthesis of (17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa 1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (I-80)



[01301] I-80 was prepared in a manner similar to those described in General Method G and Method L. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (s, 1H), 7.80 (s, 1H), 7.64 - 7.59 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 2H), 5.73 - 5.64 (m, 1H), 4.58 - 4.33 (m, 4H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 4H), 2.63 - 2.51 (m, 4H), 2.38 (s, 2H), 2.17 (d, *J* = 5.2 Hz, 1H), 2.08 (d, *J* = 12.4 Hz, 1H), 1.83 - 1.75 (m, 2H), 1.67 (s, 1H). LCMS: *m/z* 461.2 (M+1)

[01302] Preparation of (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol (Ex. 80) and (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]piperidin-3-ol (Ex. 81)

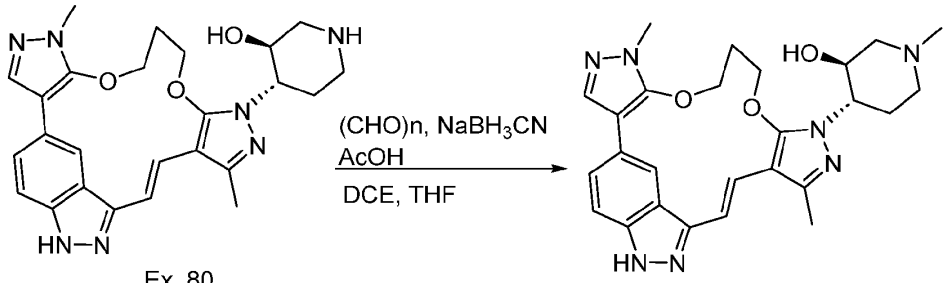


[01303] Step 1. To a solution of I-80 (150 mg, 0.325 mmol, 1 *eq*) in DMF (8 mL) was added Cs_2CO_3 (318 mg, 0.977 mmol, 3 *eq*) and tert-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (324 mg, 1.63 mmol, 5 *eq*). The mixture was stirred at 70 °C for 16 hours. On completion, the mixture was concentrated in *vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 52%-82%,15min) to give tert-butyl (3S,4S)-4-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]-3-hydroxy-piperidine-1-carboxylate (15 mg, 0.022 mmol, 7 % yield) as yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 - 8.55 (m, 1H), 7.82 - 7.74 (m, 1H), 7.65 - 7.59 (m, 1H), 7.57 - 7.48 (m, 2H), 7.11 - 6.98 (m, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 4.69 - 4.23 (m, 6H), 4.22 - 4.15 (m, 1H), 4.13 - 4.06 (m, 1H), 4.03 - 3.93 (m, 1H), 3.79 (d, *J* = 7.6 Hz, 3H), 2.96 - 2.66 (m, 2H), 2.64 - 2.52 (m,

3H), 2.50 (s, 1H), 2.48 - 2.40 (m, 1H), 2.38 - 2.34 (m, 1H), 2.20 - 2.04 (m, 3H), 1.96 - 1.86 (m, 1H), 1.79 (t, J = 8.8 Hz, 2H), 1.68 - 1.63 (m, 3H), 1.49 (s, 9H); LCMS: *m/z* 660.0 (M+1) and tert-butyl (3S,4S)-4-((E)-11,55-dimethyl-21-(tetrahydro-2H-pyran-2-yl)-11H,21H,51H-6,10-dioxa-2(5,3)-indazola-1(4,5),5(4,3)-dipyrazolacyclodecaphan-3-en-51-yl)-3-hydroxypiperidine-1-carboxylate (15 mg, 0.022 mmol, 7 % yield) as yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 - 8.54 (m, 1H), 7.82 - 7.75 (m, 1H), 7.64 - 7.59 (m, 1H), 7.57 - 7.50 (m, 2H), 7.12 - 7.00 (m, 1H), 5.67 (d, J = 10.0 Hz, 1H), 4.67 - 4.27 (m, 6H), 4.23 - 4.16 (m, 1H), 4.14 - 4.08 (m, 1H), 4.02 - 3.93 (m, 1H), 3.81 - 3.74 (m, 4H), 2.91 - 2.68 (m, 2H), 2.60 - 2.52 (m, 3H), 2.50 (s, 1H), 2.48 - 2.42 (m, 1H), 2.35 (d, J = 4.4 Hz, 1H), 2.19 - 2.05 (m, 3H), 1.94 - 1.88 (m, 1H), 1.84 - 1.71 (m, 4H), 1.50 - 1.48 (m, 9H); LCMS: *m/z* 660.1 (M+1).

[01304] The remaining steps were performed in a similar manner to the final deprotection in General Method C to give racemic Ex. 80 and racemic Ex. 81.

[01305] Preparation of (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol (Ex. 82)

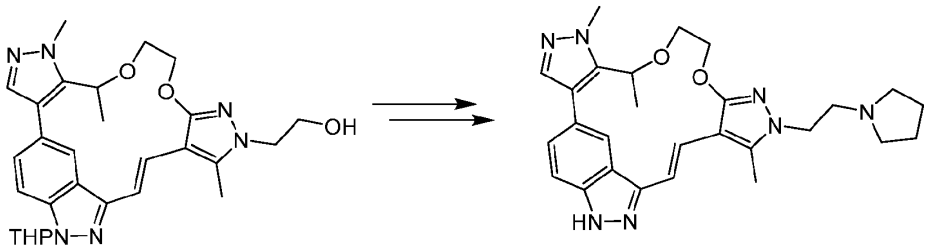


Ex. 80 Ex. 82

[01306] Step 1. To a solution of (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol (7 mg, 0.012 mmol, 1 *eq*, TFA) in DCE (1 mL) and THF (0.5 mL) was added AcOH (5.50 mg, 0.092 mmol, 6 *eq*) and PARAFORMALDEHYDE (30 mg). The mixture was stirred at 25 °C for 0.5 hour. Then $NaBH(OAc)_3$ (9.71 mg, 0.046 mmol, 3 *eq*) was added to the mixture and the mixture was stirred at 25 °C for 15.5 hours. On completion, the mixture was concentrated in *vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 35%-65%,15min) to give (*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol (4.16 mg, 0.008 mmol, 54% yield) as yellow solid.

[01307] Example 83 was synthesized from racemic Ex. 81 in a similar manner to the procedure used for Ex. 82.

[01308] Preparation of (17*E*)-8,9,16-trimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 84)

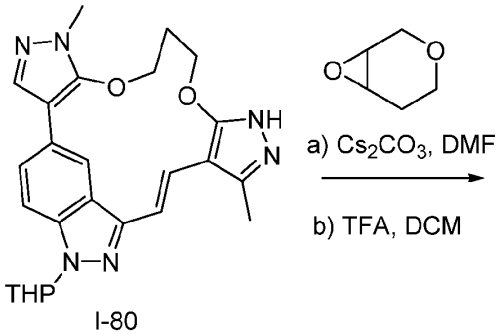


79-1 Ex. 84

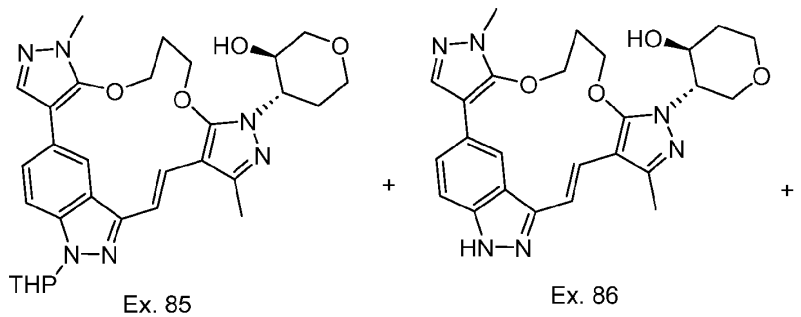
[01309] Example 84 was synthesized from 79-1 and appropriate amine following the procedures of General Method F.

[01310] Preparation of (*rac*)-1,5-anhydr-3o-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol (Ex. 85), (*rac*)-1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol (Ex. 86), (*rac*)-1,5-anhydro-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol (Ex. 87), and 1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol

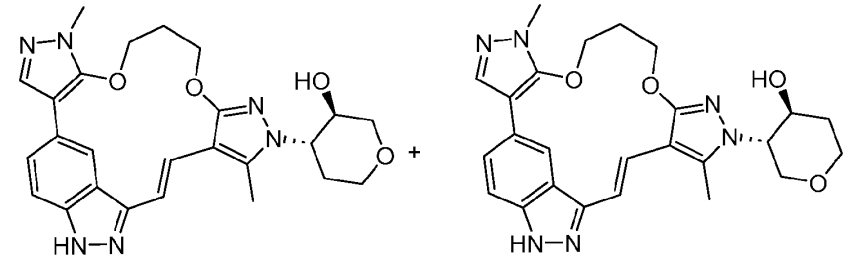
[01311] (Ex. 88).



I-80



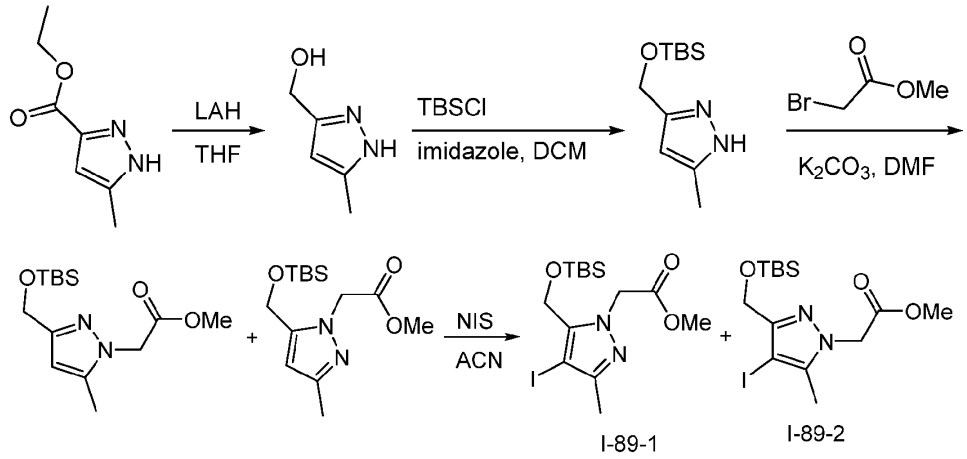
Ex. 85 Ex. 86



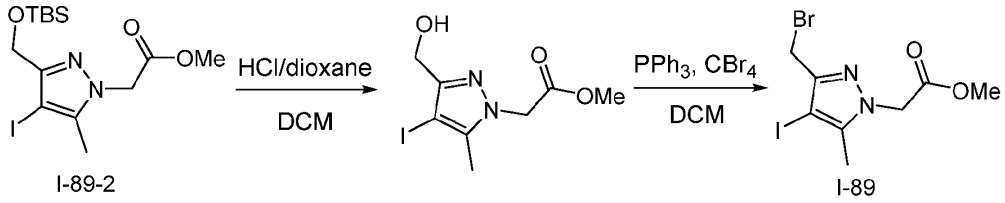
Ex. 87 Ex. 88

[01312] Steps 1 and 2 were performed in a similar manner to those of Example 80 to give arbitrarily assigned racemic Ex. 85, Ex. 86, Ex. 87, and Ex. 88.

[01313] Preparation of 2-[3-(bromomethyl)-4-iodo-5-methyl-pyrazol-1-yl]acetate (I-89).



I-89-1 I-89-2



[01314] Step 1. To a mixture of ethyl 5-methyl-1H-pyrazole-3-carboxylate (10.0 g, 64.8 mmol, 1 eq) in THF (100 mL) was added LAH (2.95 g, 77.8 mmol, 1.2 eq), the reaction mixture was stirred at 0°C for 2 hours. On completion, the mixture was slowly added to water (3 ml), saturated sodium hydroxide (3 ml) and water (9 ml) to quench. The reaction mixture was filtered and concentrated under reduced pressure to afford (5-methyl-1H-pyrazol-3-yl)methanol (3.40 g, 30.3 mmol, 46% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.89 (s, 1H), 4.36 (s, 2H), 2.16 (s, 3H).

[01315] Step 2. To a mixture of (5-methyl-1H-pyrazol-3-yl)methanol (25.0 g, 222 mmol, 1 *eq*) in DCM (300 mL) was added imidazole (30.3 g, 445 mmol, 2 *eq*) and TBSCl (50.4 g, 334 mmol, 40.9 mL, 1.5 *eq*) at 0°C, the reaction mixture was stirred at 25°C for 12 hours. On completion, the residue was diluted with water (300 mL) and extracted with DCM (2 X 300 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford tert-butyl-dimethyl-[(5-methyl-1H-pyrazol-3-yl)methoxy]silane (65.0 g, 90% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 - 12.09 (m, 1H), 5.90 (s, 1H), 4.55 (s, 2H), 2.17 (s, 3H), 0.86 (s, 9H), 0.05 - 0.02 (m, 6H).

[01316] Step 3. A mixture of methyl 2-bromoacetate (40.5 g, 265 mmol, 25.0 mL, 2 *eq*), tert-butyl-dimethyl-[(5-methyl-1H-pyrazol-3-yl)methoxy]silane (30.0 g, 132 mmol, 1 *eq*), K_2CO_3 (54.9 g, 397 mmol, 3 *eq*) in DMF (300 mL). The mixture was stirred at 80 °C for 16 hours. On completion, the reaction mixture was filtered and then the residue was diluted with water (500 mL) and extracted with EA (2 X 500 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford methyl 2-[3-[[tert-butyl(dimethyl)silyl] oxymethyl] -5- methyl-pyrazol-1-yl]acetate and methyl 2-[5- [[tert-butyl (dimethyl)silyl]oxymethyl]-3- methyl-pyrazol-1-yl]acetate (21.2 g, 35.5 mmol, 52% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.98 (s, 1H), 4.94 (s, 2H), 4.91 (s, 2H), 3.65 (s, 3H), 2.17 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H).

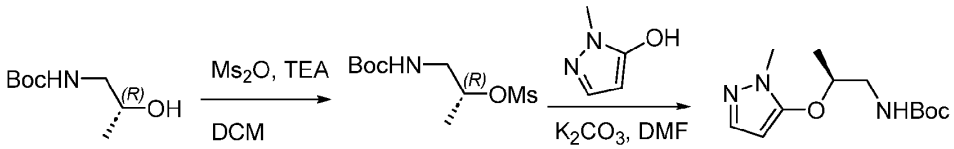
[01317] Step 4. To a mixture of methyl 2-[5-[[tert-butyl(dimethyl)silyl] oxymethyl]-3-methyl -pyrazol-1-yl] acetate and methyl 2-[3-[[tert-butyl (dimethyl) silyl] oxymethyl] -5-methyl-pyrazol-1-yl]acetate (21.2 g, 35.5 mmol, 1 *eq*) in ACN (200 mL) was added NIS (7.99 g, 35.5 mmol, 1 *eq*), the reaction mixture was stirred at 25°C for 12 hours. On

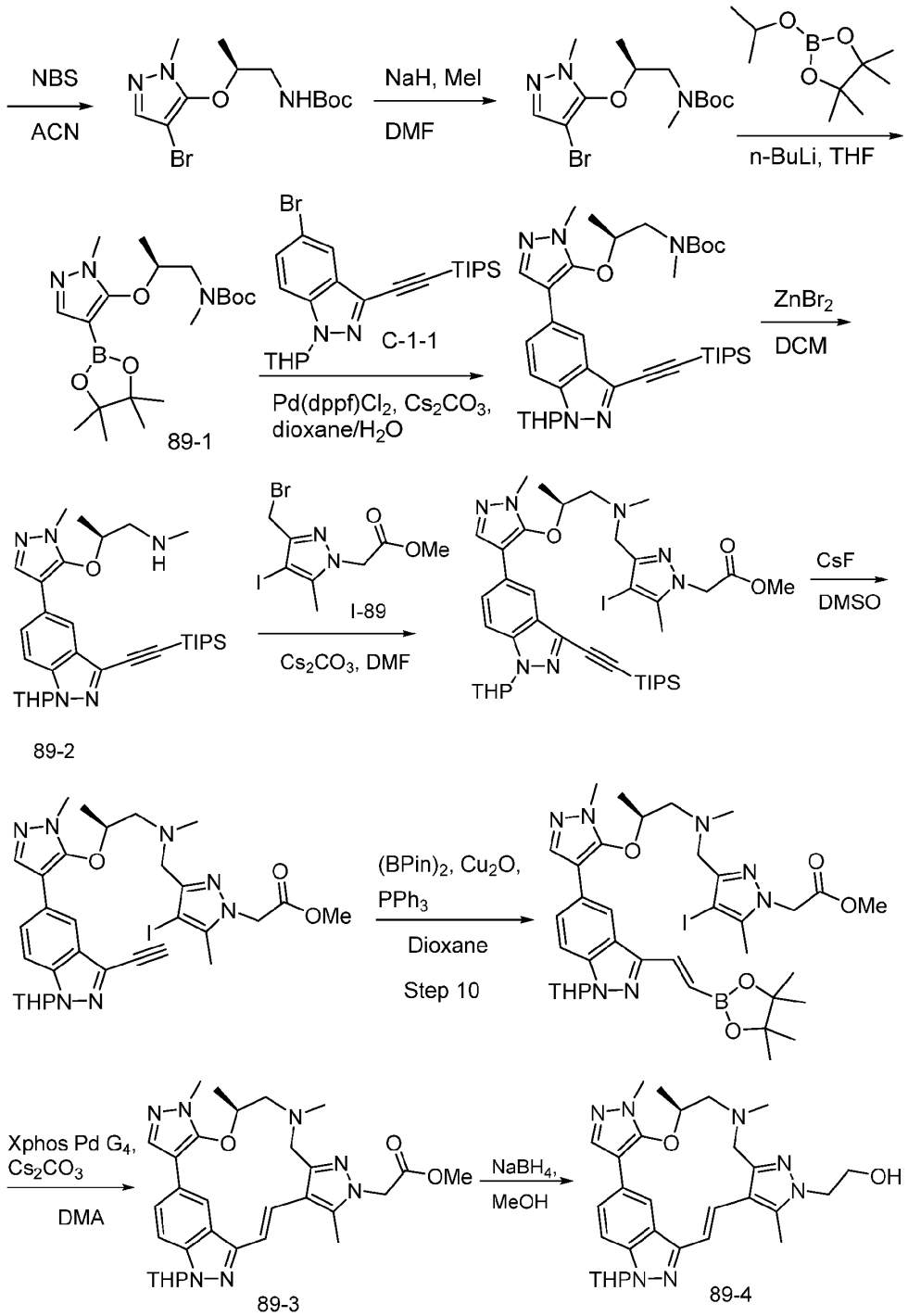
completion, the residue was diluted with water (200 mL) and extracted with EA (2 X 200 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford methyl 2-[5-[[tert-butyl (dimethyl) silyl]oxymethyl] -4-iodo-3-methyl -pyrazol-1-yl]acetate (13.0 g, 30.6 mmol, 86% yield) yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.09 (s, 2H), 4.48 (s, 2H), 3.68 (s, 3H), 2.20 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H). and methyl 2-[3-[[tert-butyl(dimethyl) silyl]oxymethyl] -4-iodo-5- methyl-pyrazol -1-yl] acetate (6.19 g, 14.5 mmol, 41% yield) as yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.03 (s, 2H), 4.64 (s, 2H), 3.65 (s, 3H), 2.11 (s, 3H), 0.85 (s, 9H), 0.06 (s, 6H).

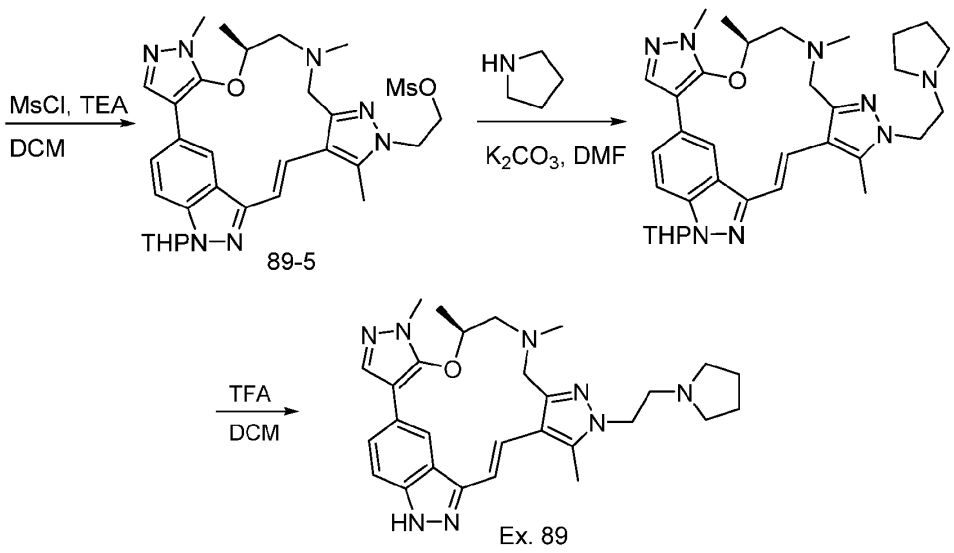
[01318] Step 5. To a mixture of methyl 2-[3-[[tert-butyl(dimethyl)silyl]oxymethyl]-4-iodo-5-methyl-pyrazol-1-yl]acetate (12.0 g, 28.2 mmol, 1 *eq*) in DCM (170 mL) was added HCl/dioxane (4 M, 20 mL, 2.83 *eq*). The reaction mixture was stirred at 25 °C for 12 hour. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with water (100 mL) and extracted with EA (2 X 100 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography afford to methyl 2-[3-(hydroxymethyl)-4-iodo-5-methyl-pyrazol-1-yl]acetate (7.9 g, 25.4 mmol, 90% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.23 (s, 4H), 5.08 (s, 2H), 4.28 (s, 2H), 2.19 (s, 3H). LCMS: *m/z* 311.0 (M+1).

[01319] Step 6. To a mixture of methyl 2-[3-(hydroxymethyl)-4-iodo-5-methyl-pyrazol-1-yl]acetate (6.70 g, 21.6 mmol, 1 *eq*) in DCM (70 mL) was added CBr_4 (10.7 g, 32.4 mmol, 1.5 *eq*) and PPh_3 (8.50 g, 32.4 mmol, 1.5 *eq*) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. On completion, the residue was diluted with water (80 mL) and extracted with EA (2 X 90 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford methyl 2-[3-(bromomethyl)-4-iodo-5-methyl-pyrazol-1-yl]acetate (9.60 g, crude) as white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.14 (s, 2H), 4.48 (s, 2H), 3.69 (s, 3H), 2.21 (s, 3H). LCMS: *m/z* 372.9 (M+1).

[01320] General Method M: Preparation of (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 89)




NBS
ACN
NHBoc
Br
NaH, MeI
DMF
NBoc
n-BuLi, THF
89-1
C-1-1
TIPS
THP
Pd(dppf)Cl2, Cs2CO3,
dioxane/H2O
THPN–N
ZnBr2
DCM
89-2
I-89
Cs2CO3, DMF
CsF
DMSO
OMe
(BPin)2, Cu2O,
PPh3
Dioxane
Step 10
Xphos Pd G4,
Cs2CO3
DMA
89-3
NaBH4,
MeOH
OH
89-4



[01321] Step 1. To a mixture of tert-butyl N-[(2R)-2-hydroxypropyl]carbamate (30.0 g, 171 mmol, 1 *eq*) in DCM (250 mL) was added TEA (51.9 g, 513 mmol, 71.4 mL, 3 *eq*) and MsCl (23.5 g, 205 mmol, 15.9 mL, 1.2 *eq*) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was diluted with water (1000 mL) and extracted with EA(2 X 800 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford to [(1R)-2-(tert-butoxycarbonylamino)-1-methyl-ethyl] methanesulfonate (29.0 g, 114 mmol, 66% yield) as yellow oil.

[01322] Step 2. To a mixture of [(1R)-2-(tert-butoxycarbonylamino)-1-methyl-ethyl] methanesulfonate (29.0 g, 114 mmol, 1 *eq*) and 2-methylpyrazol-3-ol (13.4 g, 137 mmol, 1.2 *eq*) in DMF (200 mL) was added K_2CO_3 (47.4 g, 343 mmol, 3 *eq*). The reaction mixture was stirred at 80 °C for 12 hours. On completion, the residue was diluted with water (300 mL) and extracted with EA (2 X 300 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* afford to tert-butyl N-[(2S)-2-(2-methylpyrazol-3-yl)oxypropyl]carbamate (29.0 g, 113 mmol, 99% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 2H), 7.22 (d, J = 2.0 Hz, 1H), 4.32 - 4.23 (m, 1H), 3.56 (s, 3H), 3.27 - 3.14 (m, 2H), 1.41 (s, 12H); LCMS: *m/z* 256.3 (M+1).

[01323] Step 3. To a mixture of tert-butyl N-[(2S)-2-(2-methylpyrazol-3-yl)oxypropyl]carbamate (29.0 g, 113 mmol, 1 *eq*) in ACN (300 mL) was added NBS (22.2 g, 124 mmol, 1.1 *eq*) at 0°C. The reaction mixture was stirred at 25 °C for 2 hours. On completion, the residue was diluted with water (200 mL) and extracted with EA (2 X 150 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography afford tert-butyl N-

[(2S)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]carbamate (15.4 g, 46.0 mmol, 40% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H), 7.09 (t, J = 5.6 Hz, 1H), 4.58 - 4.49 (m, 1H), 3.61 (s, 3H), 3.19 (t, J = 6.0 Hz, 2H), 1.37 (s, 9H), 1.22 (d, J = 6.2 Hz, 3H).

[01324] Step 4. To a mixture of tert-butyl N-[(2S)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl] carbamate (15.4 g, 46.0 mmol, 1 *eq*) in DMF (150 mL) was added NaH (3.69 g, 92.1 mmol, 60% purity, 2 *eq*) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour. Then MeI (7.85 g, 55.29 mmol, 3.44 mL, 1.2 *eq*) was added. The reaction mixture was stirred at 25 °C for 12 hours. On completion, the residue was diluted with water (150 mL) and extracted with EA (2 X 200 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography afford tert-butyl N-[(2S)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]-N-methyl-carbamate (11.0 g, 31.59 mmol, 69 % yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 - 7.33 (m, 1H), 4.68 (brs, 1H), 3.61 (s, 3H), 3.43 (s, 2H), 2.88 (s, 3H), 1.37 (s, 9H), 1.22 - 1.19 (m, 3H).

[01325] Step 5 was conducted in a similar manner to step 4 in synthesis of B-2-4 to afford tert-butyl N-methyl-N-[(2S)-2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxypropyl] carbamate (6.00 g, 15.1 mmol, 48% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H), 5.14 - 4.84 (m, 1H), 3.54 (s, 3H), 3.48 - 3.37 (m, 2H), 2.88 - 2.78 (m, 3H), 1.37 (s, 9H), 1.17 - 1.15 (m, 3H), 1.07 (s, 12H); LCMS: *m/z* 396.2 (M+1).

[01326] Step 6 was conducted in a similar manner to step 1 in General Method C.

[01327] Step 7. To a mixture of tert-butyl N-methyl-N-[(2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropyl]carbamate (4.70 g, 7.23 mmol, 1 *eq*) in DCM (50 mL) was added $ZnBr_2$ (8.14 g, 36.1 mmol, 5 *eq*). The reaction mixture was stirred at 25 °C for 3 hours. On completion, the residue was diluted with water (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford (2S)-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl] pyrazol-3-yl]oxy-propan-1-amine (3.00 g, 5.46 mmol, 75% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 - 7.81 (m, 1H), 7.75 (s, 1H), 7.72 - 7.65 (m, 2H), 5.93 - 5.86 (m, 1H), 4.29 - 4.20 (m, 1H), 3.97 - 3.87 (m, 2H), 3.79 - 3.74 (m, 1H), 3.73 (s, 3H), 3.49 - 3.39 (m, 1H), 2.95 - 2.88 (m, 1H), 2.86 - 2.80 (m, 1H), 2.39 - 2.34 (m, 3H), 2.04 - 1.96 (m, 2H), 1.81 - 1.70 (m, 1H), 1.59 (s, 2H), 1.18 - 1.13 (m, 21H), 1.07 (s, 3H); LCMS: *m/z* 550.7 (M+1).

[01328] Step 8. To a mixture of (2S)-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (2.90 g, 5.27 mmol, 1 *eq*) and methyl 2-[3-(bromomethyl)-4-iodo-5-methyl-pyrazol-1-yl]acetate (3.93 g, 10.5 mmol, 2 *eq*) in DMF (30 mL) was added Cs_2CO_3 (5.16 g, 15.8 mmol, 3 *eq*). The reaction mixture was stirred at 25 °C for 4 hours. On completion, the residue was diluted with water (60 mL) and extracted with EA (2 X 60 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford methyl 2-[4-iodo-5-methyl-3-[[methyl-[(2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropyl]amino]methyl] pyrazol-1-yl]acetate (4.00 g, 4.75 mmol, 90% yield) as yellow oil. LCMS: *m/z* 842.6 (M+1).

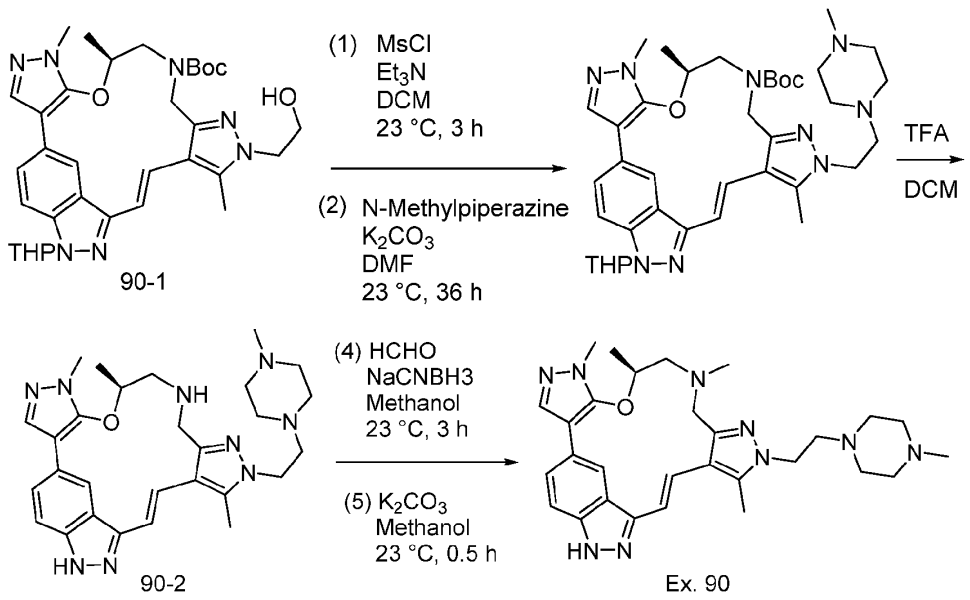
[01329] Steps 9 and 10 were performed in a similar manner to step 3 and 4 of General Method H.

[01330] Step 11. To a mixture of methyl 2-[4-iodo-5-methyl-3-[[methyl-[(2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl] indazol-5-yl]pyrazol-3-yl]oxypropyl]amino]methyl]pyrazol-1-yl]acetate (500 mg, 0.614 mmol, 1 *eq*) in DMA (4 mL) was added Cs_2CO_3 (600 mg, 1.84 mmol, 3 *eq*) and Xphos Pd G_4 (52.8 mg, 0.061 mmol, 0.1 *eq*). The reaction mixture was stirred at 90 °C for 1 hour. On completion, the residue was diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography afford to methyl 2-[(8S,17E)-5,8,10,15-tetramethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$] hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]acetate (250 mg, 0.446 mmol, 72% yield) as yellow oil. LCMS: *m/z* 842.6 (M+1).

[01331] Step 12 was performed in a similar manner to step 1 of General Method D.

[01332] The remaining steps were performed in a similar manner to General Method F to give Ex. 89 (32.3 mg) as yellow solid.

[01333] Preparation of (10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(4-methylpiperazin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 90)

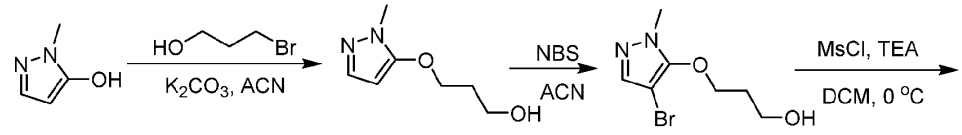


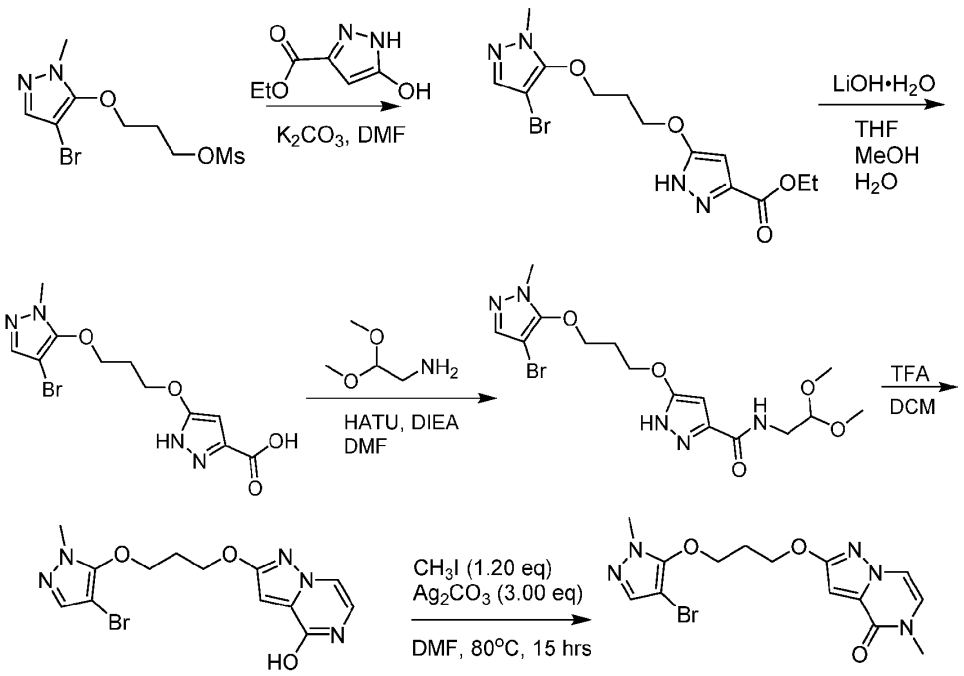
[01334] 90-1 was an intermediate in the synthesis of Ex. 49.

[01335] 90-1 was converted to 90-2 in a similar manner to General Method F.

[01336] Step 4. To a solution of 90-2 (0.7 mg, 0.0014 mmol) in Methanol (0.1 mL) was added Formaldehyde, 37% w/w aq. soln., (61.14 µg, 0.002 mmol), followed by Sodium cyanoborohydride (102.37 µg, 0.002 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water (0.5 mL), extracted with ethyl acetate (3 x 1 mL), washed with brine and dried over sodium sulfate. The volatiles were evaporated in vacuo and the crude residue was taken up in methanol (60 µL) and to this mixture was added Potassium carbonate (562 µg, 0.004 mmol), and the mixture was stirred for 30 minutes. The reaction was then diluted with water (0.5 mL), extracted with DCM (3 x 1 mL) and the combined organic layers were evaporated in vacuo. The crude residue was purified by preparative HPLC (C18, 21mm x100mm, MeCN in water with 0.035% TFA) to obtain Ex. 90.

[01337] Preparation of 2-[3-(4-bromo-2-methyl-pyrazol-3-yl) oxypropoxy]-4-methoxy-pyrazolo[1,5-a]pyrazine (I-91)





I-91

[01338] Step 1. To a solution of 2-methylpyrazol-3-ol (20.0 g, 203 mmol, 1 *eq*) in ACN (200 mL) was added K_2CO_3 (84.5 g, 611 mmol, 3 *eq*) and 3-bromopropan-1-ol (28.3 g, 203 mmol, 18.4 mL, 1 *eq*). The mixture was stirred at 25°C for 16 hr. On completion, the reaction mixture was concentrated under reduced pressure to remove ACN. The residue was purified by column chromatography (SiO_2, DCM/MeOH=10/1 to 1/1) to give 3-(2-methylpyrazol-3-yl)oxypropan-1-ol (27.3 g, 175 mmol, 85% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28 - 7.22 (m, 1H), 5.48 (d, *J* = 1.6 Hz, 1H), 4.26 - 4.05 (m, 2H), 3.86 - 3.70 (m, 2H), 3.65 - 3.52 (m, 3H), 2.13 - 1.95 (m, 2H). LCMS: *m/z* 156.9 (M+1)

[01339] Step 2. To a solution of 3-(2-methylpyrazol-3-yl)oxypropan-1-ol (27.0 g, 172 mmol, 1 *eq*) in ACN (180 mL) was added NBS (30.7 g, 172 mmol, 1 *eq*). The mixture was stirred at 20 °C for 1 hr. On completion, the reaction mixture was quenched by addition Na_2SO_3 (200 mL) at 0°C, and then diluted with H_2O (250 mL). The mixture was separated and extracted with DCM 600 mL (300 mL * 2). The combined organic layers were washed with sat NaCl (500 mL), dried over Na_2SO_4, filtered and filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3/1) to give 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropan-1-ol (21.1 g, 89.7 mmol, 52 % yield) as a yellow oil. LCMS: *m/z* 234.6

[01340] Step 3. To a solution of 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropan-1-ol (21.1 g, 89.7 mmol, 1 *eq*) in DCM (200 mL) was added TEA (27.2 g, 269 mmol, 37.5 mL, 3 *eq*) and MsCl (20.5 g, 179 mmol, 13.9 mL, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was quenched by addition $NaHCO_3$ 50 mL at 0°C, and then diluted with H_2O (200 mL) and extracted with DCM (200 mL * 3). The combined organic layers were washed with H_2O (100 mL *3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to give 3-(4-bromo-2-methyl-pyrazol-3-yl) oxypropyl methanesulfonate (28.0 g, 89.4 mmol, 100 % yield) as brown oil.

[01341] Step 4. To a solution of 3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl methanesulfonate (28.0 g, 89.4 mmol, 1 *eq*) in DMF (120 mL) was added K_2CO_3 (37.1 g, 268 mmol, 3 *eq*) and ethyl 5-hydroxy-1H-pyrazole-3-carboxylate (13.3 g, 84.9 mmol, 0.95 *eq*) at 20 °C. The mixture was stirred at 60 °C for 16 hr. On completion, the reaction mixture was diluted with H_2O (400 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with sat. NaCl (250 mL), dried over Na_2SO_4, filtered and filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1) to give ethyl 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-1H-pyrazole-3-carboxylate (17.3 g, 46.4 mmol, 52 % yield) as a white solid.

[01342] Step 5. To a solution of ethyl 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-1H-pyrazole-3-carboxylate (14.0 g, 37.5 mmol, 1 *eq*) in THF (20 mL), MeOH (20 mL), H_2O (10 mL) and $LiOH.H_2O$ (1.57 g, 37.5 mmol, 1 *eq*). The mixture was stirred at 20 °C for 15 hr. On completion, the reaction mixture was diluted with H_2O (50 mL) and then 0.5 M aq. HCl solution (50 mL) was added until the pH=5 and extracted with EtOAc (40 mL * 3). The combined organic layers were washed with sat. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc (50 mL). Then the mixture was filtered to give 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-1H-pyrazole-3-carboxylic acid (8.00 g, 23.2 mmol, 62% yield, crude purity) as a white solid. LCMS: *m/z* 346.5 (M+1)

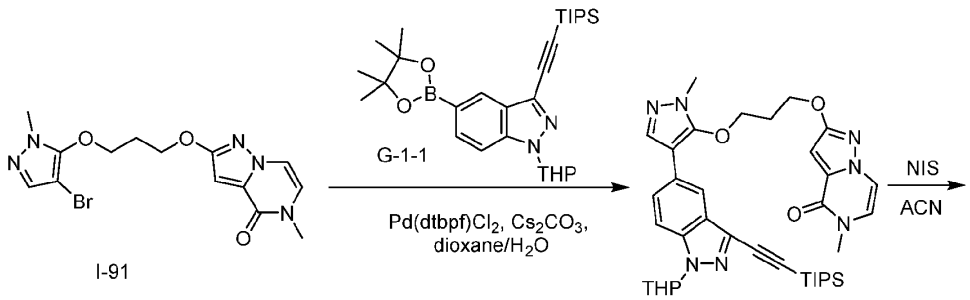
[01343] Step 6. To a solution of 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-1H-pyrazole-3-carboxylic acid (8.00 g, 23.2 mmol, 1 *eq*) in DMF (80 mL) was added 2,2-dimethoxyethanamine (3.66 g, 34.7 mmol, 3.79 mL, 1.5 *eq*), HATU (13.2 g, 34.8 mmol, 1.5 *eq*) and DIEA (8.99 g, 69.5 mmol, 12.1 mL, 3 *eq*). The mixture was stirred at 20 °C for 2 hr. On completion, the reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (50 mL * 5). The combined organic layers were washed with aq NaCl solution (500

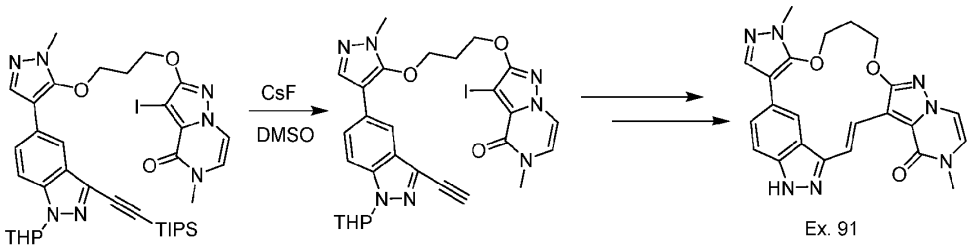
mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1) to give 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-N-(2,2-dimethoxyethyl)-1H-pyrazole-3-carboxamide (8.80 g, 20.4 mmol, 87% yield) as a white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (s, 1H), 6.64 (s, 1H), 6.02 (s, 1H), 4.48 (t, *J* = 5.2 Hz, 1H), 4.44 (t, *J* = 6.4Hz, 2H), 4.37 (t, *J* = 6.4 Hz, 2H), 3.66 (s, 3H), 3.58 (t, *J* = 5.6 Hz, 2H), 3.44 (s, 6H), 2.31 - 2.18 (m, 2H). LCMS: *m/z* 455.5 (M+Na)

[01344] Step 7. To a solution of 5-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-N-(2,2-dimethoxyethyl)-1H-pyrazole-3- carboxamide (6.00 g, 13.9 mmol, 1 *eq*) in DCM (60 mL) was added TFA (12 mL). The mixture was stirred at 20 °C for 2 hrs. On completion, the reaction mixture was concentrated under reduced pressure to remove DCM and give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 1/1) to give 2-[3-(4-bromo-2-methyl-pyrazol-3-yl) oxypropoxy]pyrazolo[1,5-a]pyrazin-4-ol (4.61 g, 12.5 mmol, 90% yield) as a white solid. LCMS: *m/z* 367.9 (M+1)

[01345] Step 8. At 20 °C, a solution of 2-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]pyrazolo[1,5-a]pyrazin-4-ol (4.60 g, 12.5 mmol, 1 *eq*) in DMF (30 mL) was added CH_3I (2.13 g, 14.9 mmol, 1.2 *eq*) and Ag_2CO_3 (10.3 g, 37.5 mmol, 3 *eq*). The mixture was stirred 80 °C for 8 h. On completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (50 mL * 3). The organic phase was separated, washed with H_2O (300 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=10/1 to 1/1) to give 2-[3-(4-bromo-2-methyl-pyrazol-3-yl) oxypropoxy]-4-methoxy-pyrazolo[1,5-a]pyrazine (3.00 g, 7.85 mmol, 62% yield) a yellow solid. LCMS: *m/z* 381.9 (M+1)

[01346] Preparation of (20*E*)-8,18-dimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3",4":10',11';4"',3"':14',15'][1,5]dioxacyclopentadecino[6',7':3,4]pyrazolo[1,5-*a*]pyrazin-19(18*H*)-one (Ex. 91)





Ex. 91

[01347] Step 1. A mixture of 2-[3-(4-bromo-2-methyl-pyrazol-3-yl)oxypropoxy]-5-methyl-pyrazolo[1,5-a]pyrazin-4-one (3.00 g, 7.85 mmol, 1 *eq*), triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3- yl] ethynyl] silane (4.79 g, 9.42 mmol, 1.2 *eq*), Cs_2CO_3 (7.67 g, 23.5 mmol, 3 *eq*)and ditertbutyl (cyclopentyl)phosphane;dichloropalladium;iron (511 mg, 0.785 mmol, 0.1 *eq*) in H_2O (12 mL) and dioxane (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, the mixture was diluted with H_2O (200 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with sat. NaCl solution (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=10/1 to 2/1) to give 5-methyl-2-[3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy] pyrazolo [1,5-a]pyrazin-4-one (4.40 g, 6.43 mmol, 81% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.53 - 7.47 (m, 3H), 7.15 (d, J = 6.0 Hz, 1H), 6.42 (d, J = 6.0 Hz,1H), 6.28 (s, 1H), 5.64 (dd, J = 2.8, 9.2 Hz, 1H), 4.30 (t, J = 6.0 Hz, 2H), 4.12 - 3.94 (m, 4H), 3.68 (s, 5H), 3.44 (s, 3H), 2.46 (s, 1H), 2.15 - 2.04 (m, 3H), 2.03 - 1.94 (m, 2H), 1.85 (s, 3H), 1.77 - 1.65 (m, 3H), 1.20 (s, 4H), 1.12 - 1.10 (m, 18H). LCMS: *m/z* 683.9 (M+1)

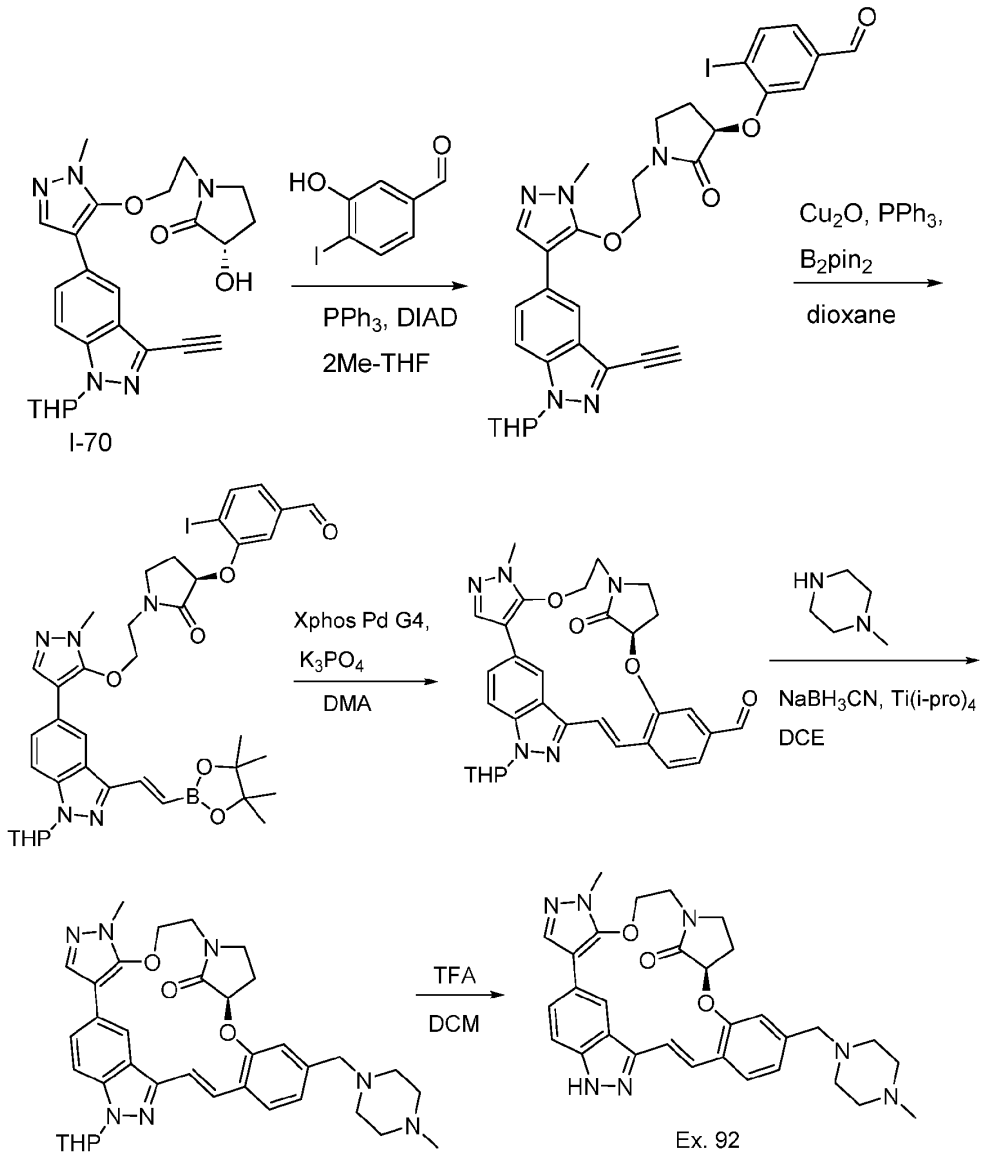
[01348] Step 2. To a solution of 5-methyl-2-[3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy]pyrazolo[1,5-a] pyrazin-4-one (4.40 g, 6.43 mmol, 1 *eq*) in ACN (70 mL) was added NIS (2.17 g, 9.65 mmol, 1.5 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the reaction mixture was quenched by addition sat. Na_2SO_3 solution (50 mL) at 0°C, then diluted with H_2O (20 mL) and extracted with EA (30 mL * 2). The combined organic layers were washed with sat. NaCl solution (50 mL) and 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=10/1 to 2/1) to give 3-iodo-5-methyl-2-[3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazol-3-yl]oxypropoxy]pyrazolo[1,5-a]pyrazin-4-one (3.80 g, 4.69 mmol, 72% yield) as a yellow

solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 6.45 (d, *J* = 6.0 Hz, 1H), 5.66 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.38 (t, *J* = 6.0 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 4.05 (q, *J* = 7.2 Hz, 1H), 4.01 - 3.88 (m, 4H), 3.76 - 3.61 (m, 1H), 3.41 (s, 3H), 2.54 - 2.38 (m, 2H), 2.20 - 1.90 (m, 13H),1.80 - 1.56 (m, 5H), 1.20 - 1.17 (m, 4H), 1.11 (s, 14H). LCMS: *m/z* 810.3 (M+1)

[01349] Step 3. To a solution of 3-iodo-5-methyl-2-[3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropoxy]pyrazolo[1,5-a] pyrazine-4-one (3.80 g, 4.69 mmol, 1 *eq*) in DMSO (20 mL) was added CsF (712 mg, 4.69 mmol, 1 *eq*). The mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was quenched by addition sat. NH_4Cl solution (10 mL), then diluted with H_2O (50 mL) and extracted with EA (30 mL * 4). The combined organic layers were washed with H_2O (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=10/1 to 1/1) to give 2-[3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropoxy]-3-iodo-5-methyl-pyrazolo[1,5-a]pyrazin-4-one (2.79 g, 4.27 mmol, 90% yield) a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.51 - 7.42 (m, 1H), 7.13 (d, *J*= 6.0 Hz, 1H), 6.44 (d, *J* = 6.0 Hz, 1H), 5.66 (dd, *J* = 2.8, 8.9 Hz, 1H), 5.23 (s, 1H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 4.00 - 3.89 (m, 1H), 3.83 (s, 3H), 3.75 - 3.63 (m, 1H), 3.50 - 3.37 (m, 3H), 3.32 (s, 1H), 2.55 (s, 1H), 2.50 - 2.39 (m, 2H), 2.21 - 2.10 (m, 3H), 1.79 - 1.56 (m, 3H). LCMS: *m/z* 653.9 (M+1)

[01350] The remaining steps were performed in a manner similar to those described in General Method L to give Ex. 91.

[01351] Preparation of (10*R*,16*E*)-3-methyl-13-[(4-methylpiperazin-1-yl)methyl]-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one (Ex. 92)



[01352] Step 1 through 3 were performed in a similar manner to those described in General Method L from I-70.

[01353] Step 4. To a solution of (13R,21E)-5-methyl-31-oxo-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29)

[01354] ,2(6),3,15(20),16,18,21,23,26(30),27-decaene-17-carbaldehyde (50 mg, 0.090 mmol, 1 *eq*) and 1-methylpiperazine (36.2 mg, 0.361 mmol, 40.1 uL, 4 *eq*) in DCE (5 mL) was added $Ti(i\text{-}PrO)_4$ (51.3 mg, 0.181 mmol, 53.3 uL, 2 *eq*). The mixture was stirred at 20 °C

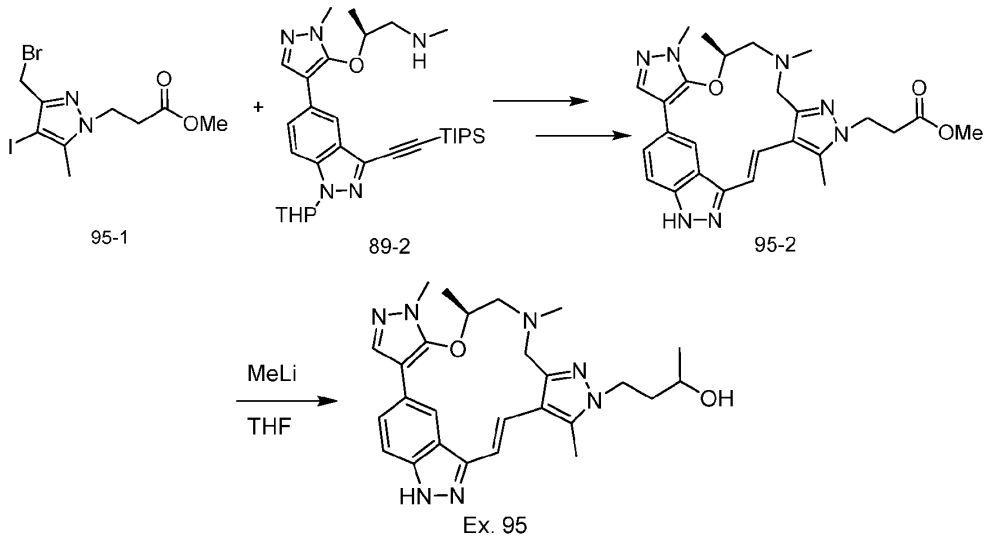
for 1 h, then $NaBH_3CN$ (17.0 mg, 0.271 mmol, 3 *eq*) was added and the mixture was stirred at 20 °C for 2 h. On completion, the mixture was filtered and the filtrate was concentrated in vacuum to give crude. The residue was purified by combi flash (12 g silica gel column, THF in PE from 0-100%) to give (13R,21E)-5-methyl-17-[(4-methylpiperazin-1-yl)methyl]-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (20 mg, 0.031 mmol, 35% yield) as a brown oil. LCMS: *m/z* 638.2 (M+1).

[01355] Step 5 was performed in a similar manner to the last step in General Method C to give Ex. 92.

[01356] Example 93 was made following the procedures of General Method M.

[01357] Example 94 was made in a similar manner to Ex. 92.

[01358] Preparation of 4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol (Ex. 95)



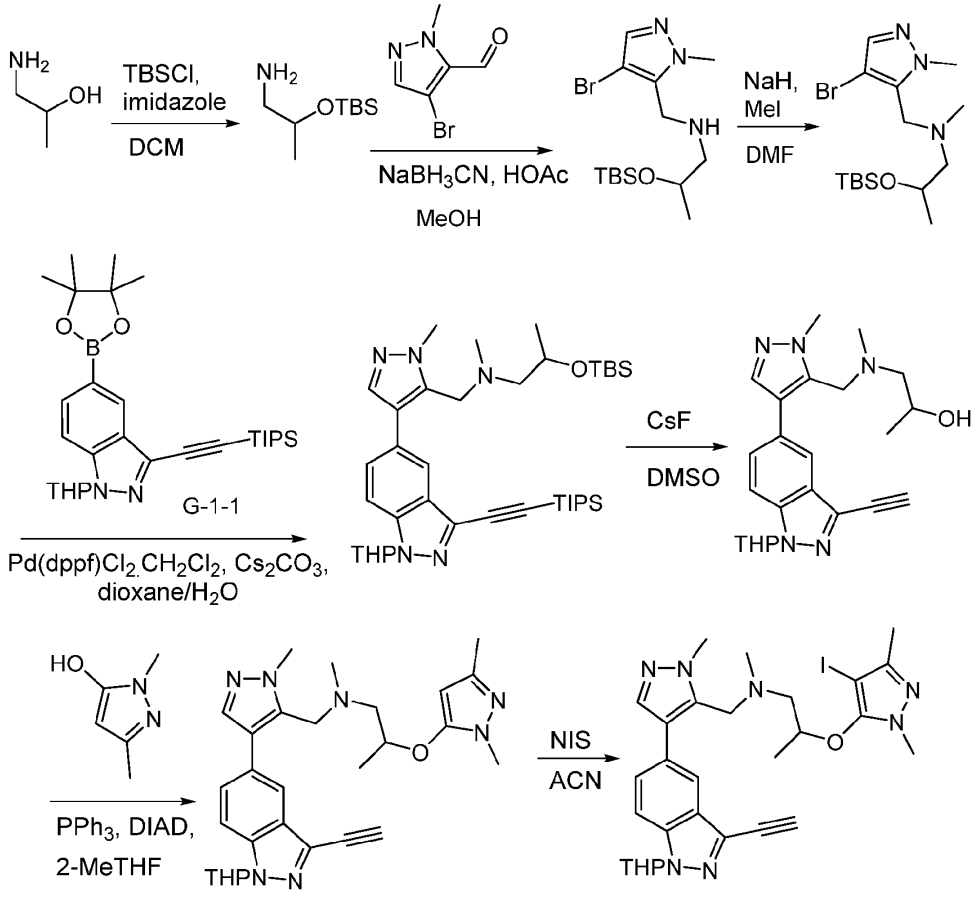
[01359] 95-1 was synthesized in the same manner as I-89 starting with methyl 3-bromopropanoate.

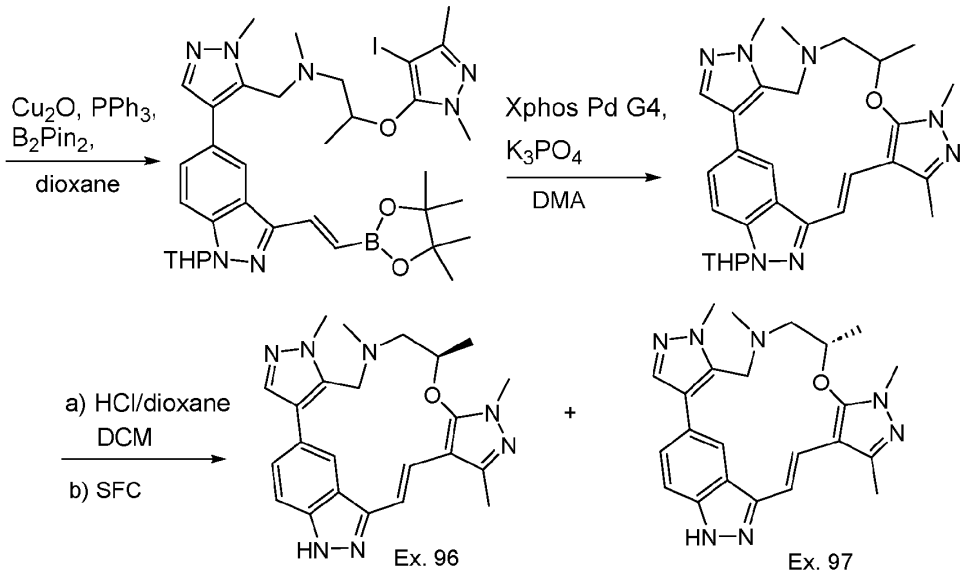
[01360] 95-1 and 89-2 were combined following the procedures described in General Method M to afford 95-2.

[01361] Step 2. A mixture of methyl 3-[(8S,17E)-5,8,10,15-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$] hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]propanoate (20 mg, 0.041 mmoL, 1 *eq*) in

THF (1 mL) was degassed and purged with N_2 for 3 times, MeLi (1.6 M, 25.5 uL, 1 *eq*) was added at 0 °C, and then the mixture was stirred at 20 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was quenched by addition sat. NH_4Cl 10 mL at 0 °C, and then diluted with H_2O 30 mL and extracted with EA (3*30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (Phenomenex C18 150*25mm*10um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 5%-35%, 8min) to give Ex. 95 (0.58 mg, 0.001 mmol, 3% yield, 92% purity) as a white solid.

[01362] General Method N: Preparation of (12*R*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 96) and (12*S*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 97).





[01363] Step 1. To a solution of 1-aminopropan-2-ol (10.0 g, 133 mmol, 10.4 mL, 1 *eq*) in DCM (100 mL) was added TBSCl (22.1 g, 146 mmol, 18.0 mL, 1.1 *eq*) and imidazole (18.1 g, 266 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with DCM (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 2-[tert-butyl (dimethyl)silyl]oxypropan-1-amine (13.7 g, 72.4 mmol, 54% yield) as colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.76 - 3.70 (m, 1H), 2.63 - 2.50 (m, 2H), 1.07 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H).

[01364] Step 2. To a solution of 4-bromo-2-methyl-pyrazole-3-carbaldehyde (8.46 g, 44.8 mmol, 1 *eq*) and 2-[tert-butyl(dimethyl)silyl]oxypropan-1-amine (12.7 g, 67.1 mmol, 1.5 *eq*) in MeOH (90 mL) was added HOAc (2.69 g, 44.8 mmol, 2.56 mL, 1 *eq*) to adjust pH to 6 and then $NaBH_3CN$ (5.63 g, 89.5 mmol, 2 *eq*) was added. The mixture was stirred at 25 °C for 2 h. On completion, the reaction mixture was quenched by water (5 mL) at 25 °C, and then filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl)silyl]oxy-propan-1-amine (19.4 g, 42.8 mmol, 96% yield, 80% purity) as light yellow liquid. LCMS: *m/z* 364.2 (M+1).

[01365] Step 3. To a solution of N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl)silyl]oxy-propan-1-amine (18.4 g, 40.6 mmol, 80% purity, 1 *eq*) in DMF (185 mL) was added NaH (3.24 g, 81.1 mmol, 60% purity, 2 *eq*) at 0 °C and stirred for 0.5 h,

and then MeI (8.63 g, 60.8 mmol, 3.79 mL, 1.5 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 15.5 h. On completion, the reaction mixture was quenched by sat. NH_4Cl 50 mL at 0 °C, and then diluted with H_2O 300 mL and extracted with EA (80 mL * 3). The combined organic layers were washed with H_2O (150 mL * 2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl)silyl]oxy-N-methyl-propan-1-amine (12.7 g, 33.7 mmol, 83% yield) as colorless liquid. LCMS: *m/z* 377.8 (M+1).

[01366] Step 4. A mixture of N-[(4-bromo-2-methyl-pyrazol-3-yl)methyl]-2-[tert-butyl(dimethyl)silyl]oxy-N-methyl-propan-1-amine (1.00 g, 2.66 mmol, 1 *eq*), triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (1.49 g, 2.92 mmol, 1.1 *eq*), Cs_2CO_3 (2.60 g, 7.97 mmol, 3 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (217 mg, 0.266 mmol, 0.1 *eq*) and H_2O (2 mL) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 2-[tert-butyl(dimethyl)silyl]oxy-N-methyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]propan-1-amine (1.36 g, 2.01 mmol, 76% yield) as yellow oil. LCMS: *m/z* 678.8 (M+1).

[01367] Step 5. To a solution of 2-[tert-butyl(dimethyl)silyl]oxy-N-methyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl] propan-1-amine (6.52 g, 9.61 mmol, 1 *eq*) in DMSO (70 mL) was added CsF (17.5 g, 115 mmol, 12 *eq*). The mixture was stirred at 40 °C for 16 h. On completion, the reaction mixture was diluted with H_2O 150 mL and extracted with EA (50 mL * 3). The combined organic layers were washed with H_2O (150 mL * 2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 1-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl-methyl-amino] propan-2-ol (1.99 g, 4.89 mmol, 51% yield) as orange oil. LCMS: *m/z* 407.9 (M+1).

[01368] Step 6. A mixture of 1-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl-methyl-amino]propan-2-ol (800 mg, 1.96 mmol, 1 *eq*), 2,5-dimethylpyrazol-3-ol (484 mg, 4.32 mmol, 2.2 *eq*), PPh_3 (1.13 g, 4.32 mmol, 2.2 *eq*) in 2-MeTHF (4 mL) was stirred at 25 °C for 0.5 h, and then DIAD (873 mg, 4.32 mmol, 840 uL, 2.2 *eq*) was added at 0 °C, 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 to give 2-(2,5-dimethylpyrazol-3-yl)oxy-N-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]-N-methyl-propan-1-amine (410 mg, 0.817 mmol, 42% yield) as yellow oil. LCMS: *m/z* 502.1 (M+1).

[01369] Step 7. To a solution of 2-(2,5-dimethylpyrazol-3-yl)oxy-N-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]-N-methyl-propan-1-amine (360 mg, 0.718 mmol, 1 *eq*) in ACN (5 mL) was added NIS (153 mg, 0.682 mmol, 0.95 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the reaction mixture was quenched by sat. Na_2SO_3 8 mL at 0 °C, and then diluted with H_2O 30 mL and extracted with EA 30 mL (10 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 column chromatography to give N-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]-2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-N-methyl-propan-1-amine (276 mg, 0.440 mmol, 61% yield) as yellow solid. LCMS: *m/z* 628.1 (M+1).

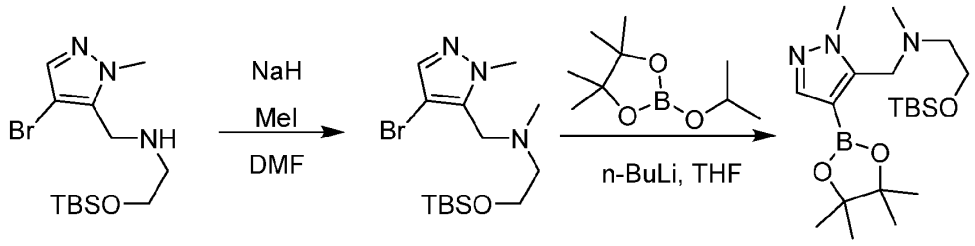
[01370] Step 8. A mixture of N-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]-2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-N-methyl-propan-1-amine (266 mg, 0.424 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (215 mg, 0.848 mmol, 2 *eq*), PPh_3 (111 mg, 0.424 mmol, 1 *eq*), Cu_2O (30.3 mg, 0.212 mmol, 21.7 uL, 0.5 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. On completion, the reaction mixture was filtered and the solution was diluted with H_2O 20 mL and extracted with EA 30 mL (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-N-methyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl] indazol-5-yl]pyrazol-3-yl]methyl]propan-1-amine (264 mg, 0.349 mmol, 82% yield) as colorless oil. LCMS: *m/z* 756.1 (M+1).

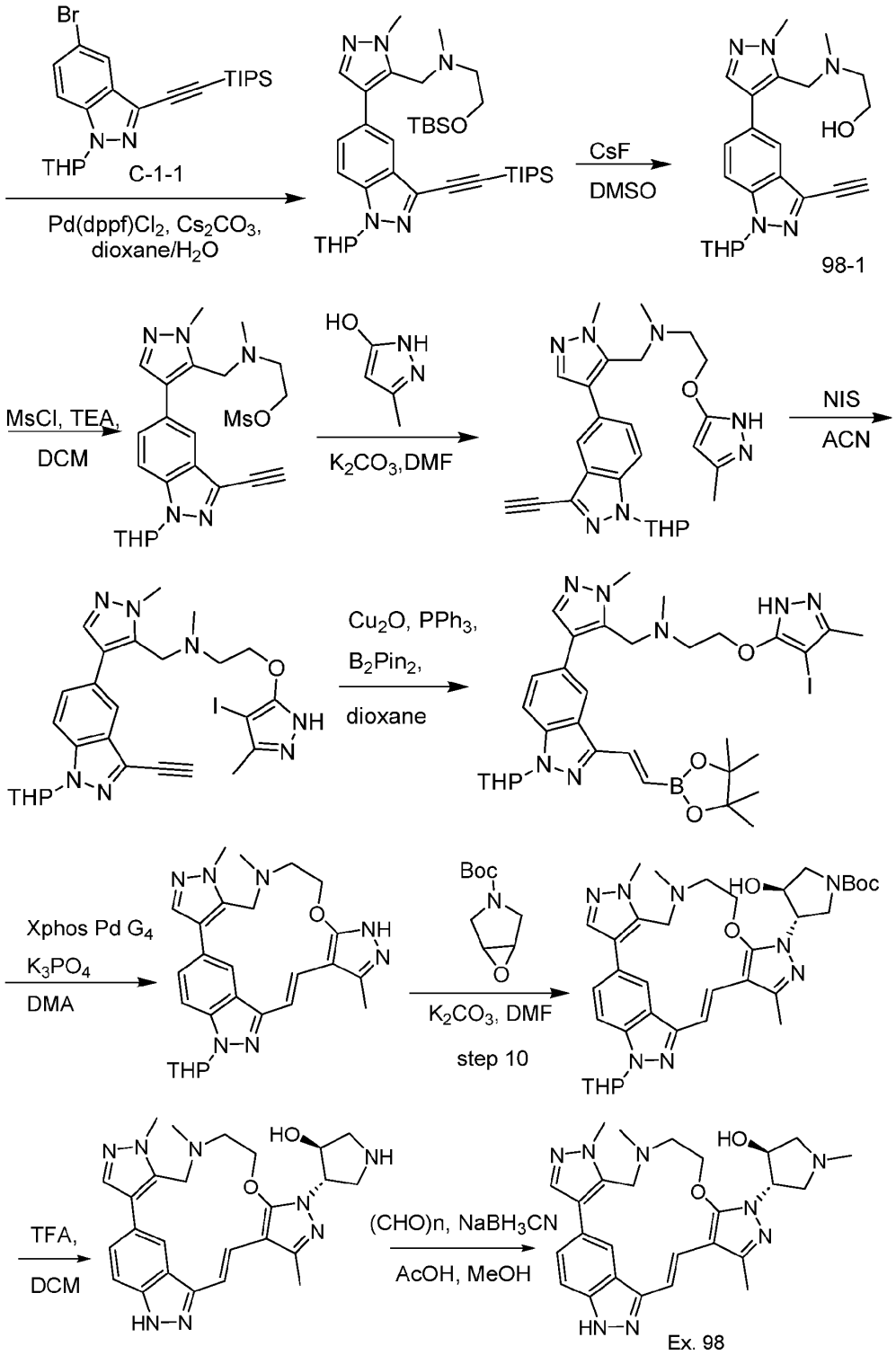
[01371] Step 9. A mixture of 2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-N-methyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl] indazol-5-yl]pyrazol-3-yl]methyl]propan-1-amine (201 mg, 0.266 mmol, 1 *eq*), Xphos Pd G4 (22.9 mg, 0.027 mmol, 0.1 *eq*), K_3PO_4 (169 mg, 0.798 mmol, 3 *eq*) in DMA (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was diluted with H_2O 50

mL and extracted with EA 60 mL (20 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 column chromatography to give (17E)-5,8,10,13,15-pentamethyl-21-tetrahydropyran-2-yl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (32.0 mg, 0.064 mmol, 24% yield) as colorless oil. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 9.07 - 8.31 (m, 1H), 7.76 - 7.61 (m, 1H), 7.57 - 7.41 (m, 2H), 5.66 (s, 1H), 4.67 - 4.56 (m, 1H), 3.99 (s, 1H), 3.92 - 3.79 (m, 3H), 3.76 - 3.67 (m, 3H), 3.61 - 3.52 (m, 3H), 3.45 - 3.39 (m, 1H), 3.31 (s, 1H), 2.98 - 2.85 (m, 1H), 2.81 (d, J = 0.8 Hz, 1H), 2.37 - 2.30 (m, 3H), 2.21 (s, 3H), 2.10 - 1.97 (m, 3H), 1.88 - 1.82 (m, 2H), 1.23 - 1.11 (m, 3H), 1.02 - 0.79 (m, 1H). LCMS: *m/z* 502.0 (M+1).

[01372] Step 10. To a solution of (17E)-5,8,10,13,15-pentamethyl-21-tetrahydropyran-2-yl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6), 3,12(16),14,17,19,22(26),23-nonaene (30.0 mg, 0.060 mmol, 1 *eq*) in DCM (2 mL) was added HCl/dioxane (4 M, 2 mL, 134 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [0.1%NH_3H_2O MeOH]; B%: 40%-40%, C2.55; 30min) to give crude material (17.4 mg, 0.042 mmol, 70% yield) as a white solid. This material was further purified by SFC (Column: Chiralcel OD-3 50x4.6mm I.D., 3um Mobile phase: Phase A for CO_2, and Phase B for MeOH (0.05%DEA); Gradient elution: MeOH (0.05% DEA) in CO_2 from 5% to 40% Flow rate: 3mL/min; Detector: PDA; Column Temp: 35C; Back Pressure: 100Bar") to give two peak. Each peak was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 20%-50%, 10min) to give arbitrarily assigned Ex. 96 and Ex. 97.

[01373] Preparation of (rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol (Ex. 98).




Br
TIPS
N–N
THP
C-1-1
Pd(dppf)Cl2, Cs2CO3,
dioxane/H2O
TBSO
CsF
DMSO
HO
98-1
MsCl, TEA,
DCM
MsO
K2CO3,DMF
NIS
ACN
Cu2O, PPh3,
B2Pin2,
dioxane
I
Xphos Pd G4
K3PO4
DMA
Boc
K2CO3, DMF
step 10
NBoc
TFA,
DCM
(CHO)n, NaBH3CN
AcOH, MeOH
Ex. 98

[01374] Steps 1 was conducted in a similar manner to step 3 in General Method N.

[01375] Step 2 was conducted in a similar manner to step 3 in the synthesis of intermediate B-2-4.

[01376] Steps 3 and 4 were conducted in a similar manner to steps 4 and 5 in General Method N.

[01377] Step 5-8 were conducted in a similar manner to steps 3-6 in General Method G.

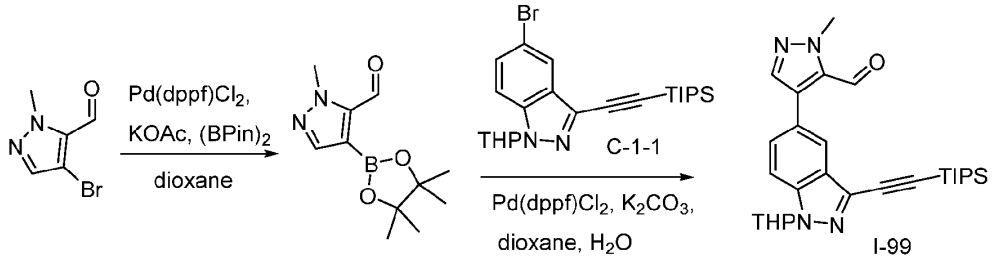
[01378] Step 9 were conducted in a similar manner to step 9 in General Method N.

[01379] Step 10. To a solution of (17E)-5,8,15-trimethyl-21-tetrahydropyran-2-yl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (80.0 mg, 0.168 mmol, 1 *eq*) and tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (187 mg, 1.01 mmol, 6 *eq*) in DMF (6 mL) was added Cs_2CO_3 (165 mg, 0.506 mmol, 3 *eq*). The mixture was stirred at 70 °C for 12 h. On completion, the mixture was quenched with water (10 mL) and extracted with EA (15 mL × 3), the organic layer was concentrated in vacuum to give the residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=2:1 to 2:1) to give (rac)-tert-butyl (4R)-3-hydroxy-4-[(17E)-5,8,15-trimethyl-21-tetrahydropyran-2-yl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5. 2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl] pyrrolidine-1-carboxylate (50.0 mg, 0.076 mmol, 44% yield) as a yellow oil. LCMS: *m/z* 659.6 (M+1).

[01380] Step 11 was conducted in a similar manner to the last step in General Method C.

[01381] Step 12. To a solution of 4-[(17E)-5,8,15-trimethyl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]pyrrolidin-3-ol (40 mg, 0.084 mmol, 1 *eq*) in MeOH (1 mL) was added $(CHO)_n$ (8.61 mg, 0.253 mmol, 3 *eq*) and AcONa (69.1 mg, 10 *eq*) and then $NaBH_3CN$ (10.5 mg, 0.168 mmol, 2 *eq*) was added at 25 °C. The mixture was stirred at 25 °C for 4 h. On completion, the mixture was quenched with water (10 mL) and extracted with EA (15 mL × 3), the organic layer was concentrated in vacuum to give the residue. The residue was further purification by pre-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 0%-27%, 10min) to give (rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol (3.82 mg, 0.008 mmol, 9 % yield) as a white solid.

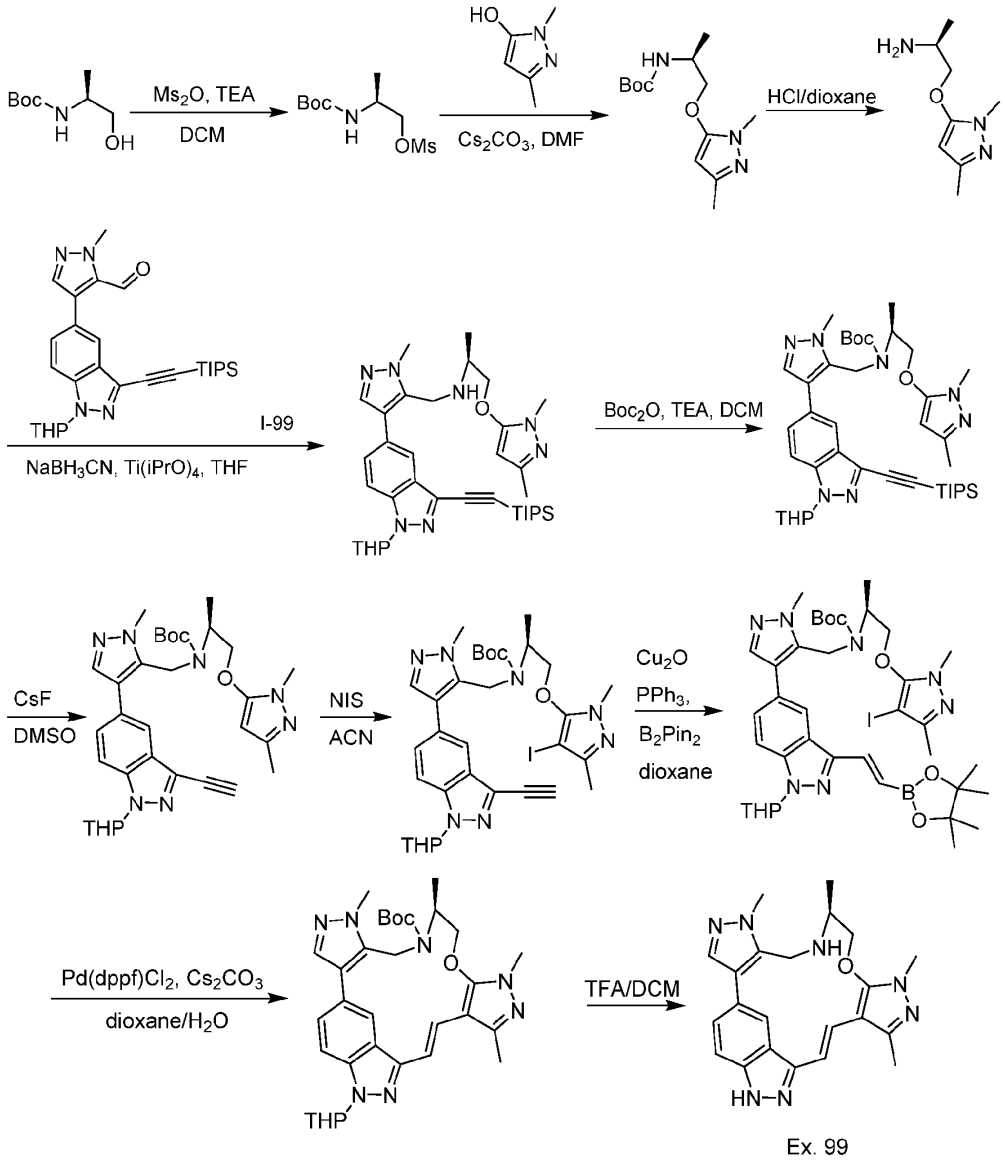
[01382] Preparation of 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl] pyrazole-3-carbaldehyde (I-99)



[01383] Step 1. A mixture of 4-bromo-2-methyl-pyrazole-3-carbaldehyde (20 g, 106 mmol, 1 eq) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (53.7 g, 212 mmol, 2 eq), $Pd(dppf)Cl_2$ (7.74 g, 10.6 mmol, 0.1 eq), KOAc (31.2 g, 317 mmol, 3 eq) in dioxane (200 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was partitioned between ethyl acetate (200 mL × 3) and water (500 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 to give 2-methyl-4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) pyrazole-3-carbaldehyde (32 g, 94.9 mmol, 90% yield) as light-yellow solid. ^1H NMR (400 MHz, DMSO-*d6*) δ = 10.11 (s, 1H), 7.73 (s, 1H), 4.08 (s, 3H), 1.30 (s, 12H); LCMS: *m/z* 491.3 (M+1).

[01384] Step 2. To a solution of 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-3-carbaldehyde (9.97 g, 42.3 mmol, 1.3 eq) and 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (15 g, 32.5 mmol, 1 eq) in dioxane (150 mL) and H_2O (50 mL) was added $Pd(dppf)Cl_2$ (2.38 g, 3.25 mmol, 0.1 eq) and K_2CO_3 (13.5 g, 97.5 mmol, 3 eq). The mixture was stirred at 90 °C for 2 h. On completion, the reaction mixture was diluted with H_2O (500 mL) and extracted with EtOAc (200 mL x 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 to give 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl] pyrazole-3-carbaldehyde (5.5 g, 9.30 mmol, 29% yield) as a white solid. LCMS: *m/z* 491.3 (M+1).

[01385] Preparation of (11*S*,17*E*)-8,11,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 99).



[01386] Step 1. To a solution of tert-butyl N-[(1S)-2-hydroxy-1-methyl-ethyl]carbamate (6 g, 34.2 mmol, 1 eq) in DCM (50 mL) was added TEA (6.93 g, 68.5 mmol, 9.5 mL, 2 eq), and then methylsulfonyl methanesulfonate (11.9 g, 68.5 mmol, 2 eq) was added at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was partitioned between dichloromethane (100 mL) and water (300 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue to give [(2S)-2-(tert-butoxycarbonylamino)propyl] methanesulfonate (8 g,

crude) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.75 (s, 1H), 4.03 (d, J = 5.6 Hz, 2H), 3.74 (td, J = 6.4, 13.2 Hz, 1H), 3.16 (s, 3H), 1.38 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H).

[01387] Step 2. To a solution of [(2S)-2-(tert-butoxycarbonylamino) propyl] methanesulfonate (8 g, 31.6 mmol, 1 eq) and 2, 5-dimethylpyrazol-3-ol (4.25 g, 37.9 mmol, 1.2 eq) in DMF (80 mL) was added Cs_2CO_3 (20.6 g, 63.2 mmol, 2 eq). The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (250 mL) and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine 120 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl N-[(1S)-2-(2, 5-dimethylpyrazol-3-yl) oxy-1-methyl-ethyl] carbamate (4 g, 13.5 mmol, 91% purity) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.41 (s, 1H), 3.84 (s, 2H), 3.83 - 3.77 (m, 1H), 3.43 (s, 3H), 2.02 (s, 3H), 1.38 (s, 9H), 1.08 (d, J = 6.4 Hz, 3H). LCMS: *m/z* 270.2(M+1)

[01388] Step 3. To a solution of tert-butyl N-[(1S)-2-(2, 5-dimethylpyrazol-3-yl) oxy-1-methyl-ethyl] carbamate (4 g, 14.9 mmol, 1 eq) in HCl/dioxane (40 mL) and DCM (40 mL). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was concentrated to give a residue to give (2S)-1-(2, 5-dimethylpyrazol-3-yl) oxypropan-2-amine (3 g, crude) as a white solid. LCMS: *m/z* 170.3(M+1)

[01389] Step 4. To a solution of 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazole-3-carbaldehyde (1.5 g, 3.06 mmol, 1 eq) and (2S)-1-(2,5-dimethylpyrazol-3-yl)oxypropan-2-amine (1.26 g, 6.11 mmol, 2 eq, HCl) in THF (20 mL) was added Ti(i-PrO)$_4$ (1.74 g, 6.11 mmol, 1.8 mL, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 1 hour, and then $NaBH_3CN$ (288 mg, 4.59 mmol, 1.5 eq) was added. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with water (30 mL) and extracted with EA (200 ml), filtered and filter liquor was concentrated to give a residue. The residue was purified by column chromatography to give (2S)-1-(2,5-dimethylpyrazol-3-yl)oxy-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl] pyrazol-3-yl]methyl]propan-2-amine (670 mg, 0.520 mmol, 17 % yield) as yellow oil. LCMS: *m/z* 644. 7 (M+1)

[01390] Step 5. To a solution of (2S)-1-(2, 5-dimethylpyrazol-3-yl) oxy-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2- triisopropylsilylethynyl) indazol-5-yl] pyrazol-3-yl] methyl] propan-2-amine (600 mg, 0.932 mmol, 1 eq) and Boc_2O (407 mg, 1.86 mmol, 2 eq) in DCM (5 mL) was added TEA (283 mg, 2.80 mmol, 3 eq). The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine 20 mL, dried over

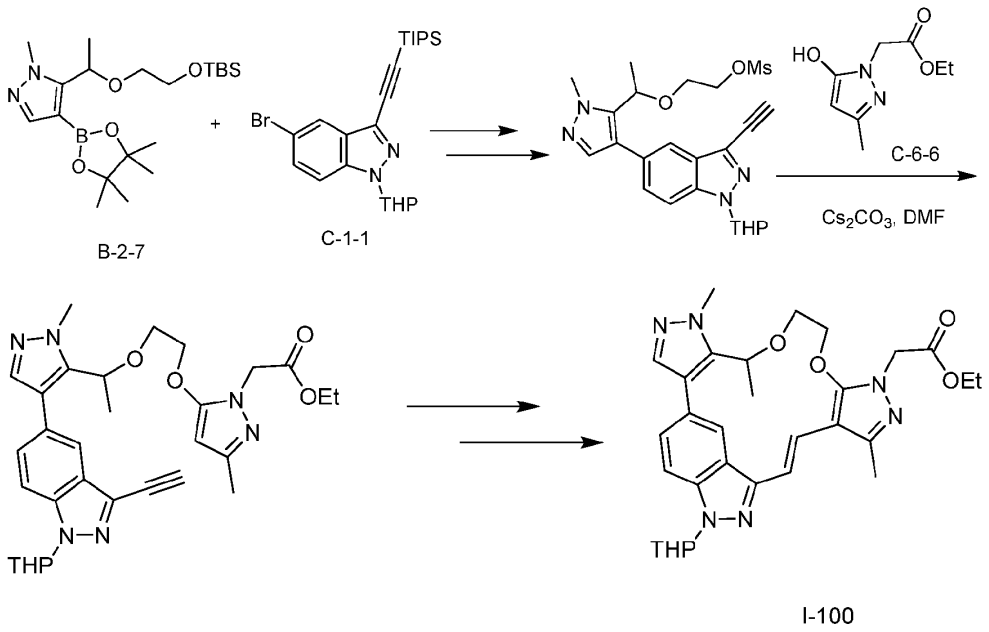
Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl N-[(1S)-2-(2,5-dimethylpyrazol-3-yl)oxy-1-methyl-ethyl]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl] carbamate (400 mg, 0.425 mmol, 46% yield) as a white oil. LCMS: *m/z* 744.5 (M+1)

[01391] Step 6. To a solution of tert-butyl N-[(1S)-2-(2, 5-dimethylpyrazol-3-yl) oxy-1-methyl-ethyl]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3- (2-triisopropylsilylethynyl) indazol-5-yl] pyrazol-3-yl] methyl] carbamate (400 mg, 0.538 mmol, 1 eq) in DMSO (5 mL) was added CsF (245 mg, 1.61 mmol, 3 eq). The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl N-[(1S)-2-(2,5-dimethylpyrazol-3-yl)oxy-1-methyl-ethyl]-N-[[4-(3-ethynyl-1-tetrahydropyran-2-ylindazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]carbamate (360 mg, 0.515 mmol, 96% yield) was obtained as a yellow oil. LCMS: *m/z* 588.5 (M+1)

[01392] Step 7. To a solution of tert-butyl N-[(1S)-2-(2, 5-dimethylpyrazol-3-yl) oxy-1-methyl-ethyl]-N-[[4-(3-ethynyl-1-tetrahydropyran-2-ylindazol- 5-yl)-2-methyl-pyrazol-3-yl] methyl] carbamate (360 mg, 0.613 mmol, 1 eq) in ACN (2 mL) was added NIS (152 mg, 0.674 mmol, 1.1 eq). The mixture was stirred at 25 °C for 4 h. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl N-[[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]methyl]-N-[(1S)-2-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-1-methyl-ethyl]carbamate (380 mg, 0.447 mmol, 73 % yield) as a yellow oil. LCMS: *m/z* 714.1 (M+1)

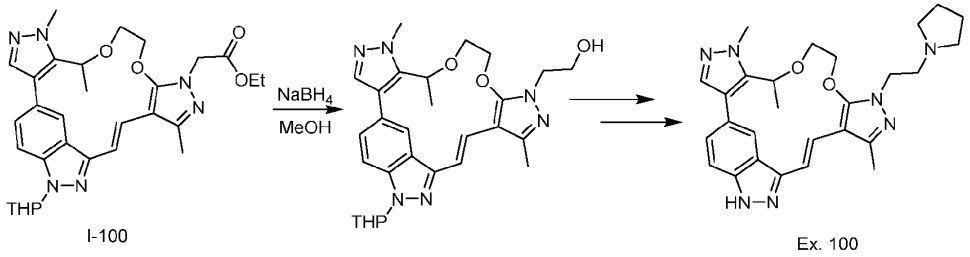
[01393] The remaining steps were conducted in a manner similar to those described in General Method H to give Ex. 99

[01394] Preparation of ethyl 2-[(17E)-5,7,15-trimethyl-21-tetrahydropyran-2-yl-8,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetate (I-100)



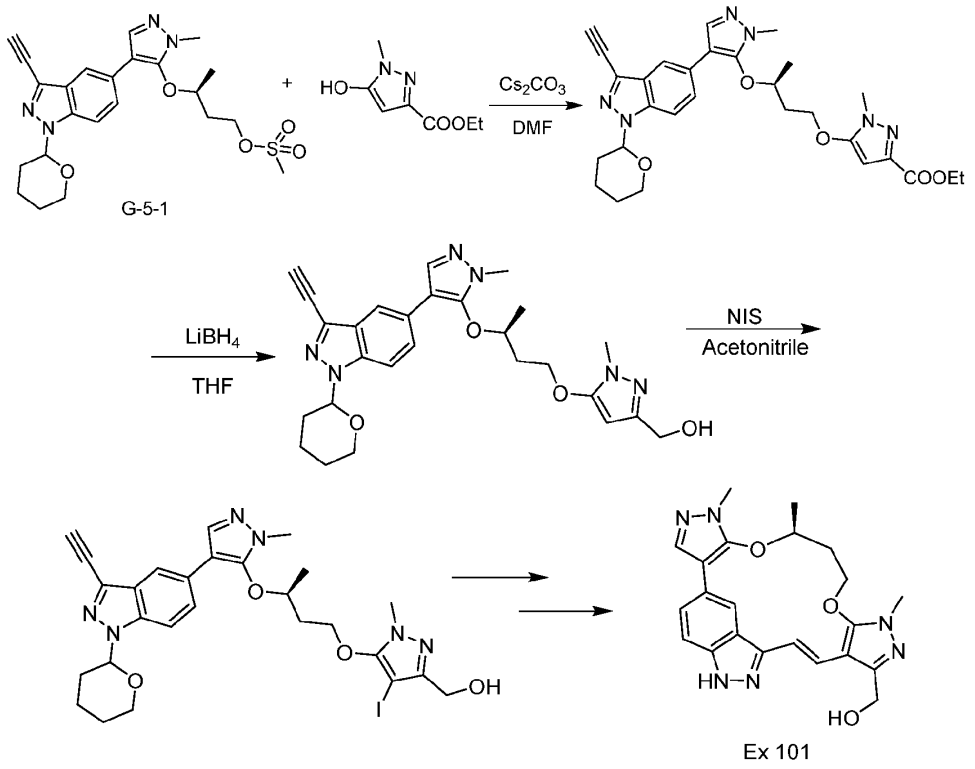
[01395] I-100 was prepared in a similar manner to those described in General Method C.

[01396] Preparation of (17*E*)-8,9,16-trimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 100)



[01397] I-100 was converted to Ex. 100 following procedures described in General Method D and F using the appropriate amine.

[01398] Preparation of [(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-16-yl]methanol (Ex. 101)



Ex 101

[01399] Step 1. To ethyl 5-hydroxy-1-methyl-pyrazole-3-carboxylate (180.05 mg, 1.06 mmol) in DMF (5 mL) was added base, Cesium carbonate (517.11 mg, 1.59 mmol) and stirred for 30 minutes followed by [(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutyl] methanesulfonate (250 mg, 0.529 mmol) . Stirred at 22 °C for 22 hr. Diluted with DCM and cooled. Solids were filtered and washed with DCM. Reaction was diluted with DCM and water (25 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g, 50-100 % EA in Hexanes) provided ethyl 5-[(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutoxy]-1-methyl-pyrazole-3-carboxylate (300.63 mg, 0.55 mmol, quantitative yield). Take forward without further purification. LCMS: *m/z* 547.0 (M+1)

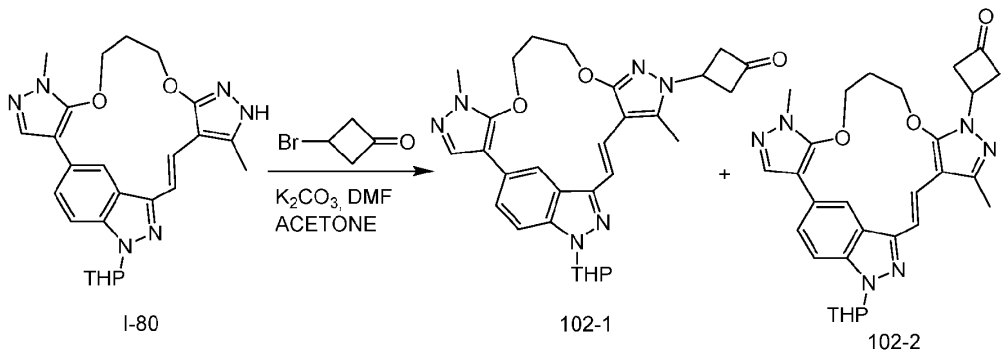
[01400] Step 2. To ethyl 5-[(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutoxy]-1-methyl-pyrazole-3-carboxylate (250 mg, 0.457 mmol) in THF (3 mL) was added lithium borohydride (13.56 mg, 0.686. mmol, 12.63 µL). Stir at 0 °C for 18 hr as temp increases to RT. reaction was quenched with 1 mL of water and 1 mL of 2 M NaOH (aq), stir vigorously and worked up with DCM and water (10 mL each).

The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-60% 1:3 DCM:MeOH in EA) provided [5-[(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutoxy]-1-methyl-pyrazol-3-yl]methanol (75 mg, 0.147 mmol, 33 % yield). LCMS: *m/z* 505.2 (M+1)

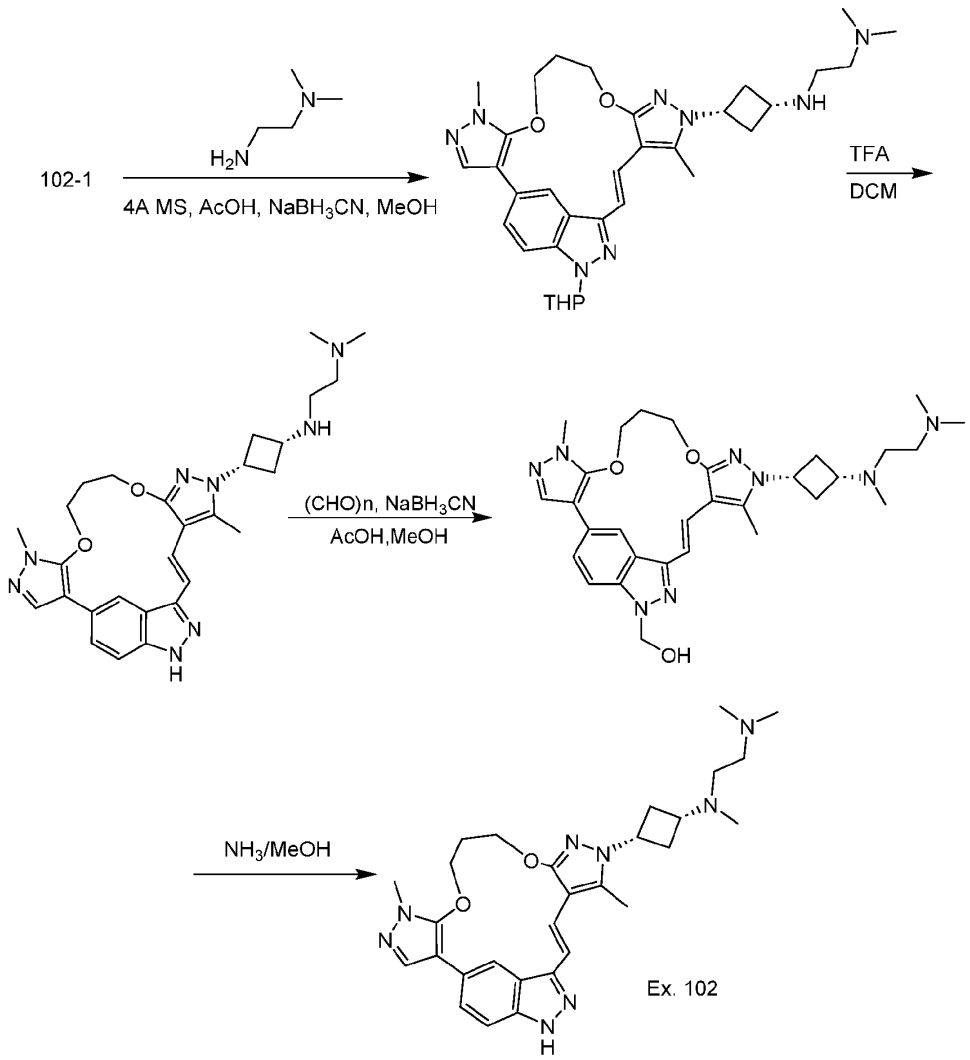
[01401] Step 3. To [5-[(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutoxy]-1-methyl-pyrazol-3-yl]methanol (75 mg, 0.149 mmol) in Acetonitrile (3 mL) was added NIS (36.79 mg, 0.164 mmol). Stir at 22 °C for 18 hr. Quenched with water and worked up with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography twice (automated system, 12g silica, 0-10% Methanol in DCM) provided [5-[(3S)-3-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxybutoxy]-4-iodo-1-methyl-pyrazol-3-yl]methanol (72.22 mg, 0.115 mmol, 77 % yield). LCMS: *m/z* 630.6 (M+1)

[01402] The remaining steps were conducted according to General Method L to give Ex. 101.

[01403] Preparation of N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-15-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine (Ex. 102)



I-80 102-1 102-2



[01404] Step 1. To a mixture of (17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-nonaene (65.0 mg, 0.141 mmol, 1 *eq,*) and 3-bromocyclobutanone (18.9 mg, 0.127 mmol, 0.9 *eq*) in DMF (1 mL) and acetone (3 mL) was added K_2CO_3 (19.5 mg, 0.141 mmol, 1 *eq*), the mixture was stirred at 23 °C for 10 h. On completion, the reaction mixture was partitioned between 2-MeTHF (3 mL × 3) and water (3 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=1:0 to 1:2) to give 3-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-

nonaen-14-yl] cyclobutanone (32.0 mg, 0.061 mmol, 42% yield) as white solid. LCMS: *m/z* 529.1 (M+1) and its regioisomer, 102-2, as a white solid. LCMS: *m/z* 529.1 (M+1)

[01405] To a mixture of 3-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12, 15,17,19,22(26),23-nonaen-14-yl]cyclobutanone (20.0 mg, 0.038 mmol, 1 *eq*), N',N'-dimethylethane-1,2-diamine (4.00 mg, 0.045 mmol, 1.2 *eq*) and 4A MS (0.038 mmol, 1 *eq*) in MeOH (0.5 mL) was added AcOH to adjust pH=6, the reaction mixture was stirred at 23 °C for 0.5 h, then $NaBH_3CN$ (4.76 mg, 0.076 mmol, 2 *eq*) was added at 23 °C, the reaction mixture was stirred at 23 °C for 2 h. On completion, the mixture was filtered and concentrated to give a residue. The crude product was purified by prep-HPLC purification (column: Welch Ultimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 18%-48%,10min) to give N-[3-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$. $0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-nonaen-14-yl]cyclobutyl]-N',N'-dimethyl-ethane-1,2-diamine (11.0 mg, 0.018 mmol, 48% yield) as green gum. LCMS: *m/z* 601.2 (M+1)

[01406] Step 3. To a solution of N-[3-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12, 15,17,19,22(26),23-nonaen-14-yl]cyclobutyl]-N',N'-dimethyl-ethane-1,2-diamine (11.0 mg, 0.0183 mmol, 1 *eq*) and DCM (0.5 mL) was added in TFA (41.8 mg, 0.366 mmol, 20 *eq*), the resulting mixture was stirred at 23 °C for 1.5 h. On completion, the mixture was concentrated to give a residue. The crude product was purified by prep-HPLC purification (column: Welch Ultimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 8%-38%,10min) to give N-[3-[(17E)-5,15-dimethyl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3, 12,15,17,19,22(26),23-nonaen-14-yl]cyclobutyl]-N',N'-dimethyl-ethane-1,2-diamine (8.00 mg, 0.015 mmol, 84% yield) as green solid. LCMS: *m/z* 517.0 (M+1)

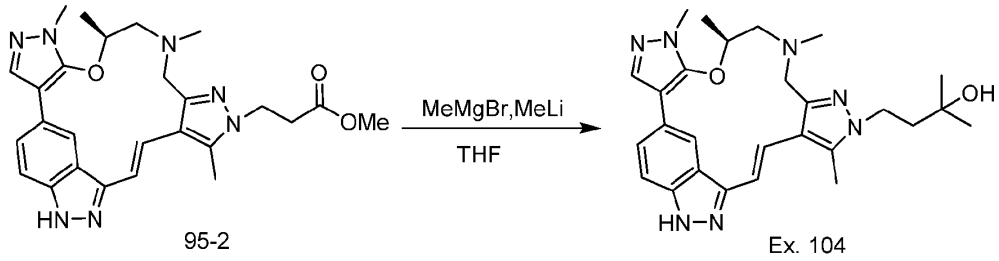
[01407] Step 4. The mixture of N-[3-[(17E)-5,15-dimethyl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]cyclobutyl]-N',N'-dimethyl-ethane-1,2-diamine (8.00 mg, 0.015 mmol, 1 *eq*) and formaldehyde (4.65 mg, 0.154 mmol, 10 *eq*) in MeOH (0.5 mL) was added AcOH to adjust pH=6, then the mixture was stirred at 25 °C for 0.5 h, Then $NaBH_3CN$ (1.95 mg, 0.031 mmol, 2 *eq*) was added to the mixture and stirred for another 12 h at 25 °C. On completion, the mixture was quenched with water (1 mL) and concentrated in vacuo to give [(17E)-14-[3-[2-(dimethylamino)ethyl-methyl-amino]cyclobutyl]-5,15-dimethyl-7,11-dioxa-4,5,13,14,20,21-

hexazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}] hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-nonaen-21-yl]methanol (5.00 mg, 0.009 mmol, 57% yield) as a green solid. LCMS: *m/z* 561.2 (M+1)

[01408] Step 5. The solution of [(17E)-14-[3-[2-(dimethylamino)ethyl-methyl-amino]cyclobutyl]-5,15-dimethyl-7,11-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}] hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-nonaen-21-yl]methanol (4.00 mg, 0.007 mmol, 1 *eq*) in NH_3/MeOH (0.5 mL) was stirred at 25 °C for 1 h. On completion, the mixture was concentrated to give a residue. The crude product was purified by prep-HPLC purification (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 3%-33%,10min) to give Ex. 102 (2.33 mg, 0.0044 mmol, 61% yield, TFA salt) as yellow gum.

[01409] Ex. 103 was prepared in a similar manner described in the synthesis of Ex. 102 from 102-2.

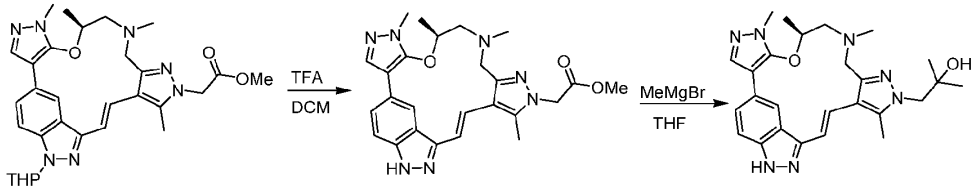
[01410] Preparation of 2-methyl-4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol (Ex. 104)



95-2 Ex. 104

[01411] Step 1. A mixture of methyl 3-[(8S,17E)-5,8,10,15-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]propanoate (60 mg, 0.122 mmol, 1 *eq*) in THF (1 mL) was degassed and purged with N_2 for 3 times, MeMgBr (3 M, 408 uL, 10 *eq*) and MeLi (4.8M, 76.6 uL, 1 *eq*) was added at 0 °C, and then the mixture was stirred at 20 °C for 0.5 h under N_2 atmosphere. On completion, the reaction mixture was quenched by addition sat. NH_4Cl 10 (mL) at 0 °C, and then diluted with H_2O (30 mL) and extracted with EA 90 (3*30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (Welch Ultimate C18 150*25mm*5um; mobile phase: [water (TFA)-ACN]; B%: 10%-40%, 10min) to give Ex. 104 (3.09 mg, 0.0062 mmol, 5% yield, 98% purity) as a brown gum.

[01412] Preparation of 2-methyl-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol (Ex. 105)

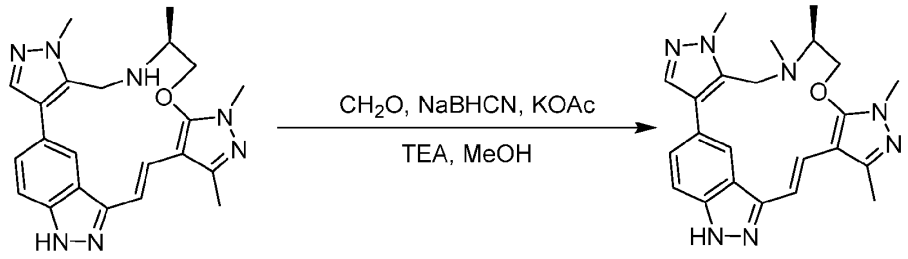


89-2 Ex. 105

[01413] Step 1. To a mixture of methyl 2-[(8S,17E)-5,8,10,15-tetramethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6), 3,12,15,17,19,22(26),23-nonaen-14-yl]acetate (120 mg, 0.214 mmol, 1 *eq*) in DCM (1 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 62.9 *eq*). The reaction mixture was stirred at 25°C for 0.5 hour. On completion, the residue was diluted with water (20 mL) and extracted with EA (2 X 20 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 5%-35%,10min) to afford methyl 2-[(8S,17E)-5,8,10,15-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$] hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]acetate (80.0 mg, 0.168 mmol, 78% yield) as yellow solid. LCMS: *m/z* 476.4 (M+1)

[01414] Step 2. To a mixture of methyl 2-[(8S,17E)-5,8,10,15-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26), 23-nonaen-14-yl]acetate (40.0 mg, 0.084 mmol, 1 *eq*) in THF (2 mL) was added MeMgBr (3 M, 140 uL, 5 *eq*). The reaction mixture was stirred at 25°C for 4 hours. On completion, the residue was diluted with water (20 mL) and extracted with EA (2 X 20 mL). The combined organic layers was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 7%-27%, 9min) to afford Ex.105 (1.68 mg, 0.003 mmol, 3% yield, 97% purity, FA) as white solid.

[01415] Preparation of (11*S*,17*E*)-8,10,11,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 106)

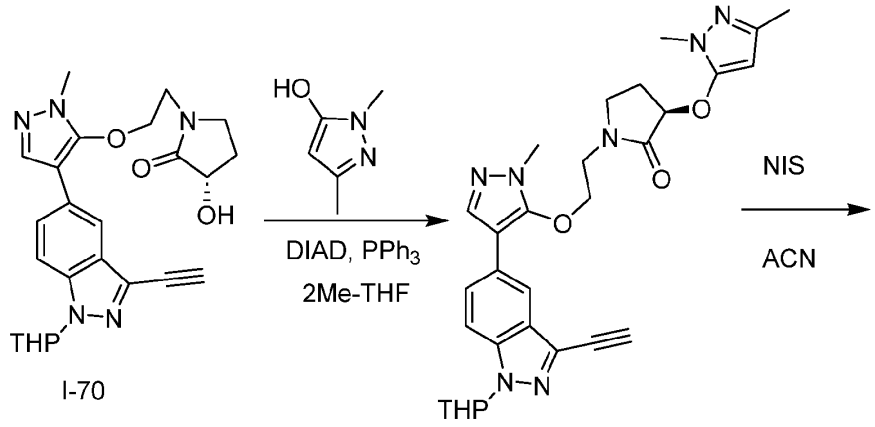


Ex. 99 Ex. 106

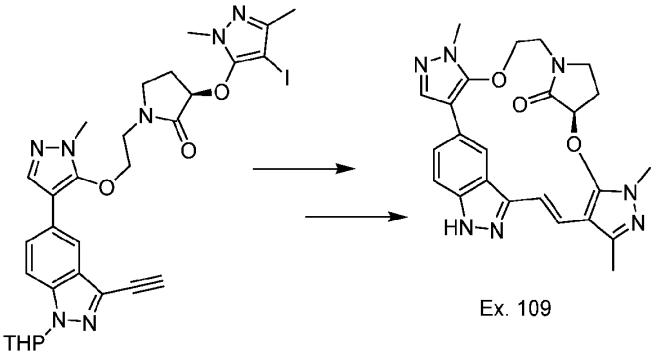
[01416] Step 1. To a solution of (9S,17E)-5,9,13,15-tetramethyl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19, 22(26), 23-nonaene (25 mg, 0.062 mmol, 1 eq) in MeOH (1 mL) added TEA (18.8 mg, 0.186 mmol , 3 eq), and then formaldehyde (2.23 mg, 0.074 mmol, 1.2 eq), KOAc (12.2 mg, 0.124 mmol, 2 eq) was added. The mixture above was stirred at 25 °C for 30 minutes, then $NaBH_3CN$ (4.67 mg, 0.074 mmol, 1.2 eq) was added. The mixture was stirred at 25 °C for 0.5 h. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 13%-43%,9min) to give Ex. 106 (7.84 mg, 0.019 mmol, 30% yield, 95% purity) as white solid.

[01417] Ex. 107 and 108 were made during the synthesis of Ex. 102 and 103.

[01418] Preparation of (10*R*,15*E*)-3,12,14-trimethyl-5,6,9,10,12,18-hexahydro-3*H*,8*H*-19,21-etheno-7,10-methanotripyrazolo[3,4-*i*:3',4'-*m*:4",3"-*q*][1,8,4]dioxazacyclooctadecin-24-one (Ex. 109)



I-70



Ex. 109

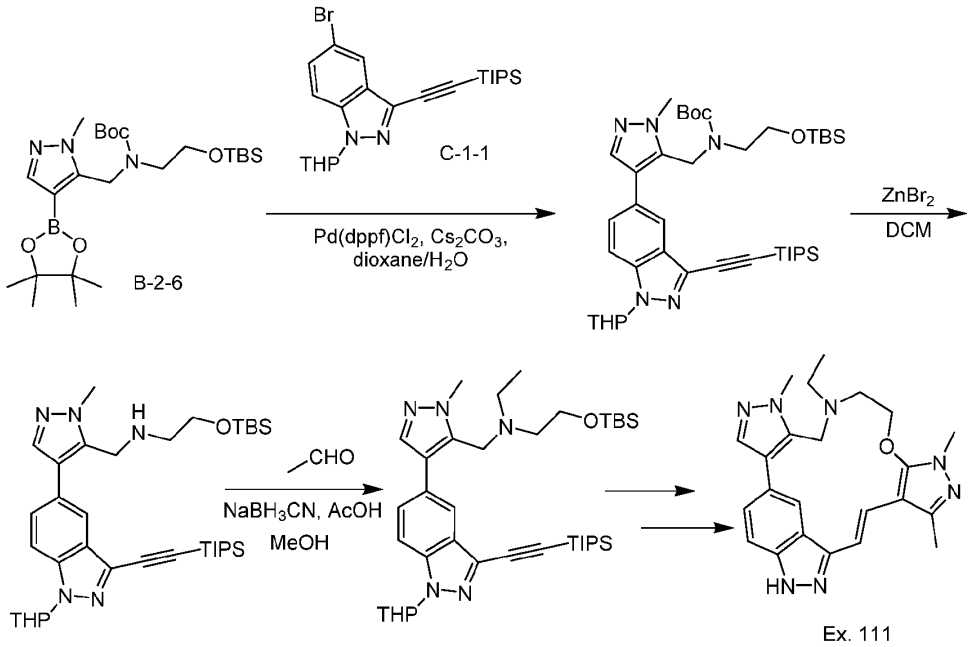
[01419] Step 1. The mixture of (3S)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-hydroxy-pyrrolidin-2-one (500 mg, 1.11 mmol, 1 *eq*) 2,5-dimethylpyrazol-3-ol (274.40 mg, 2.45 mmol, 11.04 uL, 2.2 *eq*) and PPh_3 (642 mg, 2.45 mmol, 2.2 *eq*) in 2-MeTHF (5 mL) was stirred at 25 °C for 30 min, then DIAD (495 mg, 2.45 mmol, 476 uL, 2.2 *eq*) was added dropwise to the mixture at 0 °C, the mixture was stirred for another 2 h at 25 °C under N_2 atmosphere. On completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by combi flash (12 g silica gel column, THF in PE from 0-100%) to give (3R)-3-(2,5-dimethylpyrazol-3-yl)oxy-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (502 mg, 0.923 mmol, 83% yield) as a brown oil. LCMS: *m/z* 544.2 (M+1)

[01420] Step 2. To a solution of (3R)-3-(2,5-dimethylpyrazol-3-yl)oxy-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (480 mg, 0.883 mmol, 1 *eq*) in ACN (15 mL) was added NIS (179 mg, 0.795 mmol, 0.9 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1 h. On completion, the reaction mixture was quenched with water saturated solution of Na_2SO_3 (30 mL) at 20 °C, and extracted with EtOAc (20 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give crude. The residue was purified by combi flash (12 g silica gel column, THF in PE from 0-100%) to give (3R)-1-[2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl]-3-(4-iodo-2,5-dimethyl-pyrazol-3-yl)oxy-pyrrolidin-2-one (395 mg, 0.590 mmol, 67% yield) as a brown oil. LCMS: *m/z* 670.1 (M+1)

[01421] The remaining steps were conducted in a manner similar to those described in General Method L to afford Ex. 109

[01422] Ex. 110 was prepared in a manner like those described in General Method N starting with step 6, with intermediates C-6-3 and 98-1. Then TFA/DCM in the final deprotection as described in General Method L.

[01423] Preparation of (17*E*)-10-ethyl-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex.111)



Ex. 111

[01424] Step 1. A mixture of tert-butyl N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methyl]carbamate, B-2-6 (5 g, 10.0 mmol, 1 *eq*), 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane, C-1-1 (5.12 g, 11.1 mmol, 1.1 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (824 mg, 1.01 mmol, 0.1 *eq*), and Cs_2CO_3 (9.86 g, 30.2 mmol, 3 *eq*) in dioxane (100 mL) and H_2O (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, 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 flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/PE @ 70 mL/min) to give tert-butyl N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]carbamate (4.09 g, 5.45 mmol, 54% yield) as a yellow oil. LCMS: *m/z* 750.5 (M+1)

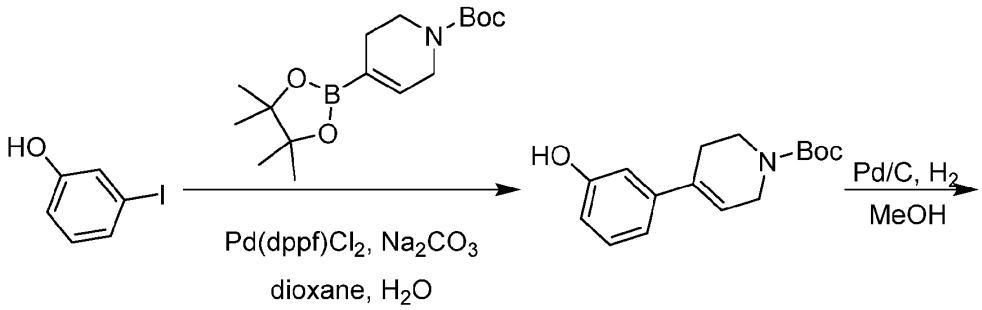
[01425] Step 2. To a solution of tert-butyl N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-

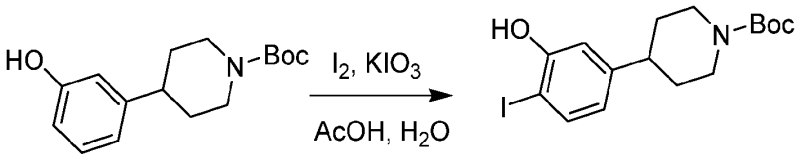
yl]methyl]carbamate (4.09 g, 5.45 mmol, 1 *eq*) in DCM (70 mL) was added $ZnBr_2$ (3.68 g, 16.3 mmol, 818 uL, 3 *eq*). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was quenched by H_2O (150 mL) and extracted with DCM (70 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give crude. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/PE @ 50 mL/min) to give 2-[tert-butyl(dimethyl)silyl]oxy-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]ethanamine (1 g, 1.54 mmol, 28% yield) as a yellow oil. LCMS: *m/z* 650.4 (M+1)

[01426] Step 3. To a solution of 2-[tert-butyl(dimethyl)silyl]oxy-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]ethanamine (1 g, 1.54 mmol, 1 *eq*) and acetaldehyde (203 mg, 1.85 mmol, 258 uL, 40% purity, 1.2 *eq*) in MeOH (15 mL) was added $NaBH_3CN$ (116 mg, 1.85 mmol, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 1 h. On completion, the mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/PE @ 40 mL/min) to give 2-[tert-butyl(dimethyl)silyl]oxy-N-ethyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]ethanamine (1.18 g, crude) as a yellow oil. LCMS: *m/z* 678.4 (M+1)

[01427] 2-[tert-butyl(dimethyl)silyl]oxy-N-ethyl-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]ethanamine was converted to Ex. 111 via processes similar to those described in General Method N using TFA/DCM in the final deprotection.

[01428] Preparation of tert-butyl 4-(3-hydroxy-4-iodo-phenyl)piperidine-1-carboxylate (I-112).



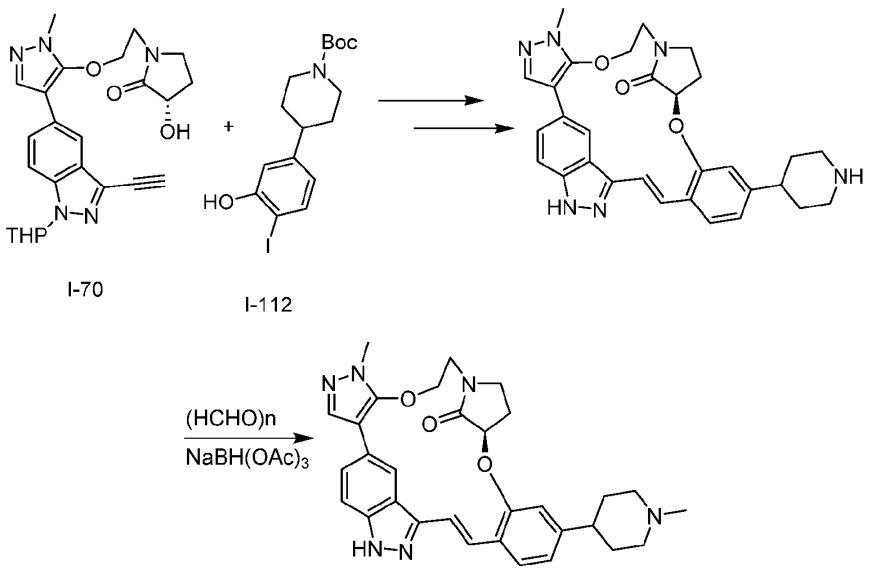


I-112

[01429] Step 1. To a solution of 3-bromophenol (2 g, 11.6 mmol, 1 *eq*) in dioxane (15 mL) and H_2O (2.1 mL) was added $Pd(dppf)Cl_2$ (846 mg, 1.16 mmol, 0.1 *eq*) and Na_2CO_3 (3.68 g, 34.7 mmol, 3 *eq*) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.57 g, 11.6 mmol, 1 *eq*). The mixture was stirred at 80 °C for 2 h .On completion, the residue was diluted with H_2O 80 mL and extracted with EA (80 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=1/0 to 4/1) to give tert-butyl 4-(3-hydroxyphenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (3 g, 10.90 mmol, 94% yield) as a black solid. LCMS: *m/z* 220.0 (M-56+1)

[01430] Step 2. A mixture of tert-butyl 4-(3-hydroxyphenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.46 g, 12.57 mmol, 1 eq), Pd/C (0.35 g, 10% purity) in MeOH (40 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 2 h under H_2 atmosphere. On completion, the reaction mixture was filtrated and the filtrated was concentrated in vacuum to give tert-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (3.45 g, 12.4 mmol, 99 % yield) as brown oil. LCMS: *m/z* 222.0 (M-56+1)

[01431] Step 3. To a solution of tert-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (3 g, 10.8 mmol, 1 *eq*) in H_2O (5 mL) and AcOH (20 mL) was added I_2 (1.37 g, 5.41 mmol, 1.09 mL, 0.5 *eq*) and 2-iodopropane (368 mg, 2.16 mmol, 216 uL, 0.2 *eq*) .The mixture was stirred at 25 °C for 2 h. On completion, the residue was diluted with H_2O 70 mL and extracted with EA (70 mL * 3). The combined organic layers were washed with H_2O (20 mL * 3), 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 5/1) to give tert-butyl 4-(3-hydroxy-4-iodo-phenyl)piperidine-1-carboxylate I-112 (2.02 g, 5.01 mmol, 46% yield) as a white solid. LCMS: *m/z* 348.0 (M-56+1)



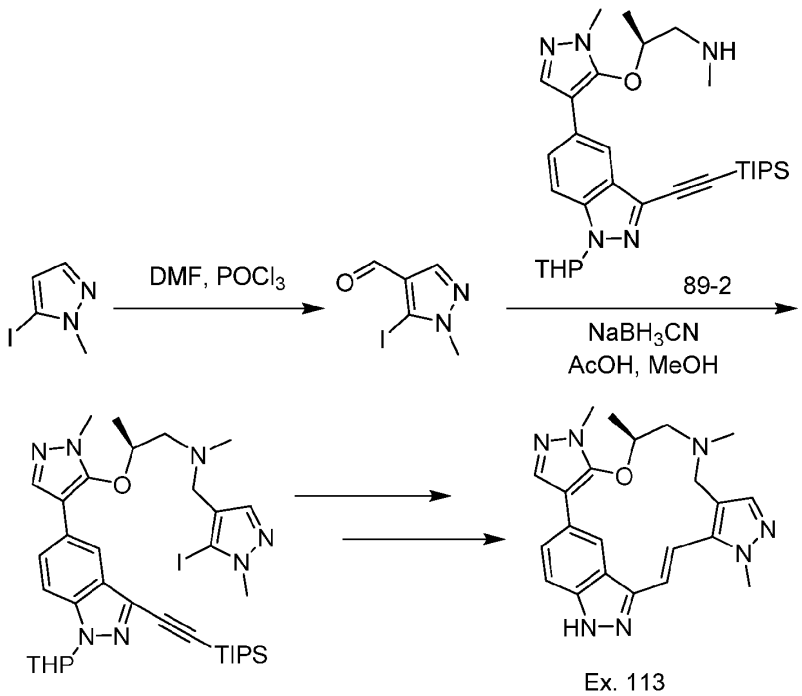
I-70 I-112

Ex. 112

[01432] Step 1. I-112 and I-70 was converted to (13R,21E)-5-methyl-17-(4-piperidyl)-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one using process described in General Method L.

[01433] Step 2. To a solution of (13R,21E)-5-methyl-17-(4-piperidyl)-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15 (20),16,18,21,23,26(30),27-decaen-31-one (40 mg, 0.076 mmol, 1 *eq*) in MeOH (4 mL) was added KOAc (150 mg, 1.52 mmol, 20 *eq*) and $NaBH(OAc)_3$ (32.3 mg, 0.152 mmol, 2 *eq*). The mixture was stirred at 20 °C for 0.5 h, then HCHO (11.4 mg, 0.381 mmol, 10.5 uL, 5 *eq*) was added, the mixture was stirred at 20 °C for 0.5 h. On completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 7%-37%,10min) to give Ex. 112 (3.69 mg, 0.007 mmol, 9% yield, 100% purity) as a yellow solid.

[01434] Preparation of (10*S*,17*E*)-8,10,12,16-tetramethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 113)



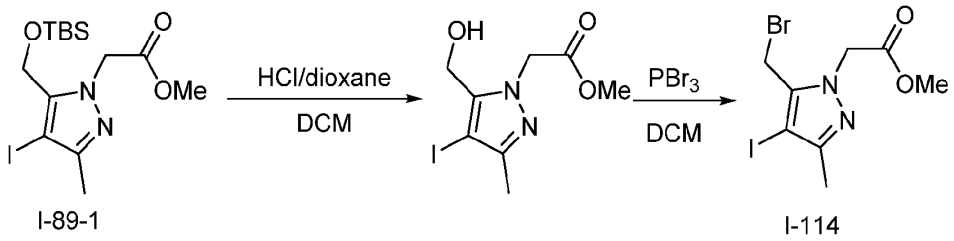
Ex. 113

[01435] Step 1. The solution of 5-iodo-1-methyl-pyrazole (5.00 g, 24.0 mmol, 1 *eq*) in DMF (25 mL) was added $POCl_3$ (11.0 g, 72.1 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 4 h. On completion, the solution was added to sat. K_2CO_3 aqueous solution (7 mL), the mixture was extracted with EA (50 mL*2), the organic layer was washed with brine (10 mL), dried over Na2SO4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF=3:1 to 3:1) to give 5-iodo-1-methyl-pyrazole-4-carbaldehyde (1.18 g, 5.00 mmol, 21% yield) as a yellow solid. LCMS: *m/z* 236.9 (M+1)

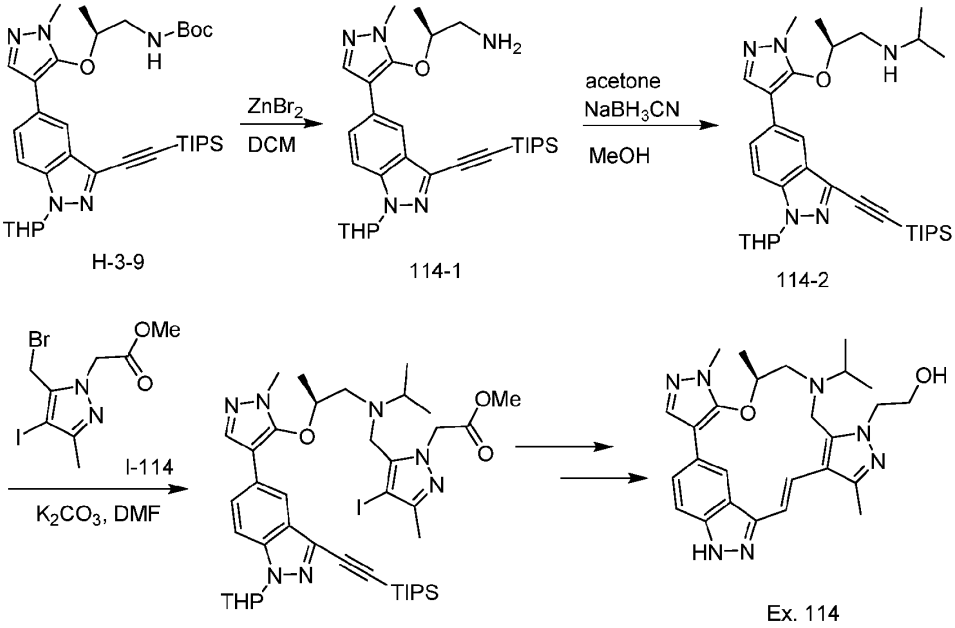
[01436] Step 2. The solution of 5-iodo-1-methyl-pyrazole-4-carbaldehyde (141 mg, 0.600 mmol, 1 *eq*) in MeOH (5 mL) was added 89-2 (330 mg, 0.600 mmol, 1 *eq*) and AcOH (36.0 mg, 0.600 mmol, 1 *eq*), the resulting mixture was stirred at 25 °C for 30 min, then $NaBH_3CN$ (75.4 mg, 1.20 mmol, 2 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was quenched by addition water 10 mL. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF=1:1 to 1:1) to give (2S)-N-[(5-iodo-1-methyl-pyrazol-4-yl)methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (210 mg, 0.272 mmol, 45% yield) as a yellow solid. LCMS: *m/z* 770.1 (M+1)

[01437] The remaining steps was conducted similarly to those detailed in General Method H to afford Ex. 113.

[01438] Preparation of methyl 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]acetate (I-114)



[01439] I-114 was made similarly to I-89 from I-89-2. 1H NMR (400 MHz, DMSO-d6) δ 5.13 (s, 2H), 4.70 (s, 2H), 3.67 (s, 3H), 2.11 (s, 3H).



Ex. 114

Step 1. To a mixture of H-3-9 (6.56 g, 10.3 mmol, 1 eq) in DCM (80 mL) was added ZnBr2 (11.6 g, 51.5 mmol, 5 eq), the reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was concentrated in vacuo and then the residue was diluted with water (100 mL) and extracted with EA (2 X 100 mL). The combined organic layers was dried over Na2SO4, filtered and concentrated in vacuo to afford compound (2S)-2-[2-methyl-4-[1-tetrahydropyran-2- yl-3-(2-triisopropylsilylethynyl)indazol -5-yl]pyrazol-3-yl]oxypropan-1-amine (5.80 g, 90% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.69 (s, 1H), 5.88 (d, J = 9.6

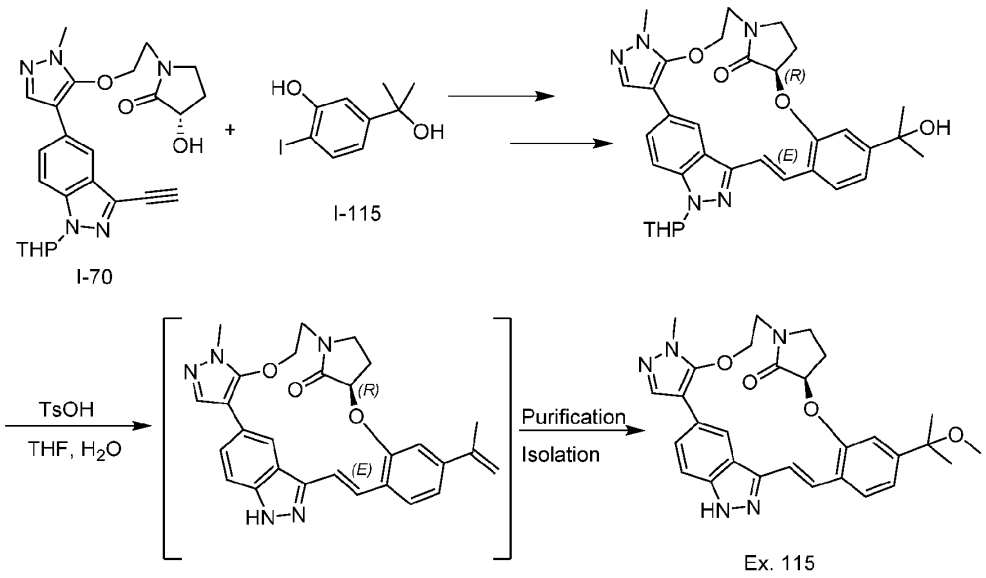
Hz, 1H), 4.23 (td, *J* = 6.0, 12.0 Hz, 1H), 4.15 (dt, *J* = 2.8, 5.6 Hz, 1H), 4.05 - 4.00 (m, 2H), 3.92 (s, 1H), 3.89 (s, 1H), 3.72 (s, 3H), 2.88 - 2.79 (m, 1H), 2.77 - 2.70 (m, 1H), 2.41 - 2.31 (m, 1H), 2.03 (d, *J* = 4.0 Hz, 1H), 1.99 (s, 3H), 1.79 - 1.69 (m, 1H), 1.59 (s, 2H), 1.19 (s, 1H), 1.17 (d, *J* = 1.6 Hz, 2H), 1.15 (s, 18H)

[01440] Step 2. To a mixture of (2S)-2-[2-methyl-4- [1-tetrahydropyran -2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazol-3-yl]oxypropan-1-amine (4.14 g, 7.73 mmol, 1 eq) in MeOH (40 mL) was added acetone (1.35 g, 23.1 mmol, 1.70 mL, 3 eq), the reaction mixture was stirred at 25°C for 0.5 hour, and then NaBH3CN (728 mg, 11.5 mmol, 1.5 eq) was added to the reaction mixture, the reaction mixture was stirred at 25 °C for 1 hour. On completion, the residue was diluted with water (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers was dried over Na2SO4, filtered and concentrated in vacuo to afford compound (2S)-N- isopropyl -2- [2- methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (3.29 g, 5.69 mmol, 73% yield) as yellow oil. LCMS: *m/z* 578.3 (M+1)

Step 3. To a mixture of (2S) -N- isopropyl -2- [2-methyl-4- [1-tetrahydropyran-2- yl-3- (2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (1.15 g, 1.99 mmol, 1 *eq*) in DMF (30 mL) was added K_2CO_3 (825 mg, 5.97 mmol, 3 *eq*) and I-114 (2.97 g, 7.96 mmol, 4 *eq*), the mixture was stirred at 25°C for 12 hours. On completion, the residue was diluted with water (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford compound methyl 2-[4-iodo-5- [[isopropyl -[(2S) -2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropyl]amino]methyl]-3-methyl-pyrazol-1-yl]acetate (1.53 g, 1.76 mmol, 88% yield) as yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 7.95 (s, 2H), 7.82 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 5.88 (dd, J = 2.4, 9.6 Hz, 2H), 5.75 (s, 1H), 4.03 (q, J = 7.2 Hz, 1H), 3.60 (d, J = 0.8 Hz, 3H), 3.50 (s, 2H), 3.49 (s, 3H), 3.44 - 3.42 (m, 2H), 2.38 - 2.31 (m, 2H), 2.12 (s, 1H), 2.09 (d, J = 4.0 Hz, 1H), 2.05 (s, 3H), 1.99 (s, 4H), 1.95 - 1.90 (m, 1H), 1.59 (d, J = 3.2 Hz, 3H), 1.24 (s, 3H), 1.16 - 1.16 (m, 6H), 1.15 (s, 18H).

[01441] The remaining steps were conducted similarly to those described in General Method M to afford Ex. 114.

[01442] Preparation of (10*R*,16*E*)-13-(2-methoxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one (Ex. 115)

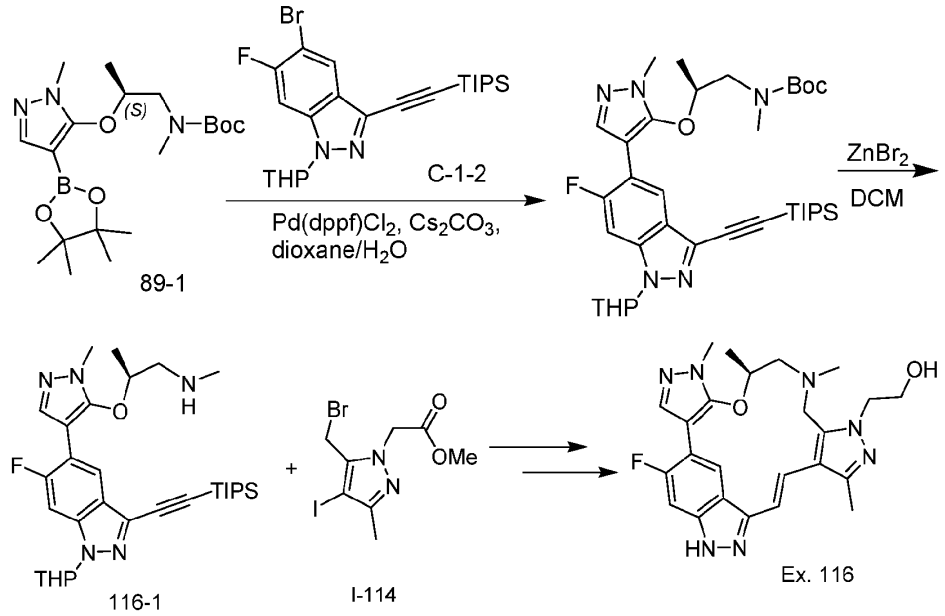


[01443] I-115 was prepared similarly to those described in General Method E.

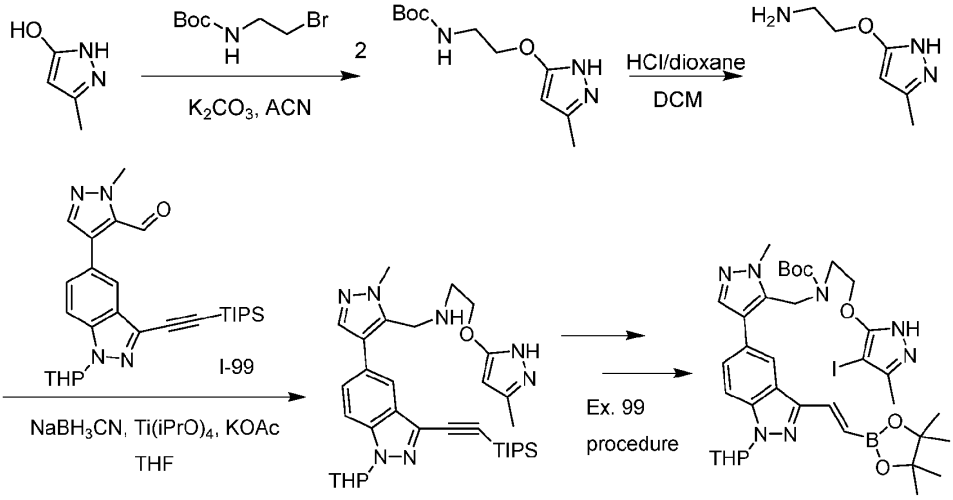
[01444] I-70 and I-115 were converted to (13R,21E)-17-(1-hydroxy-1-methyl-ethyl)-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one in a manner similar to those described in General Method L.

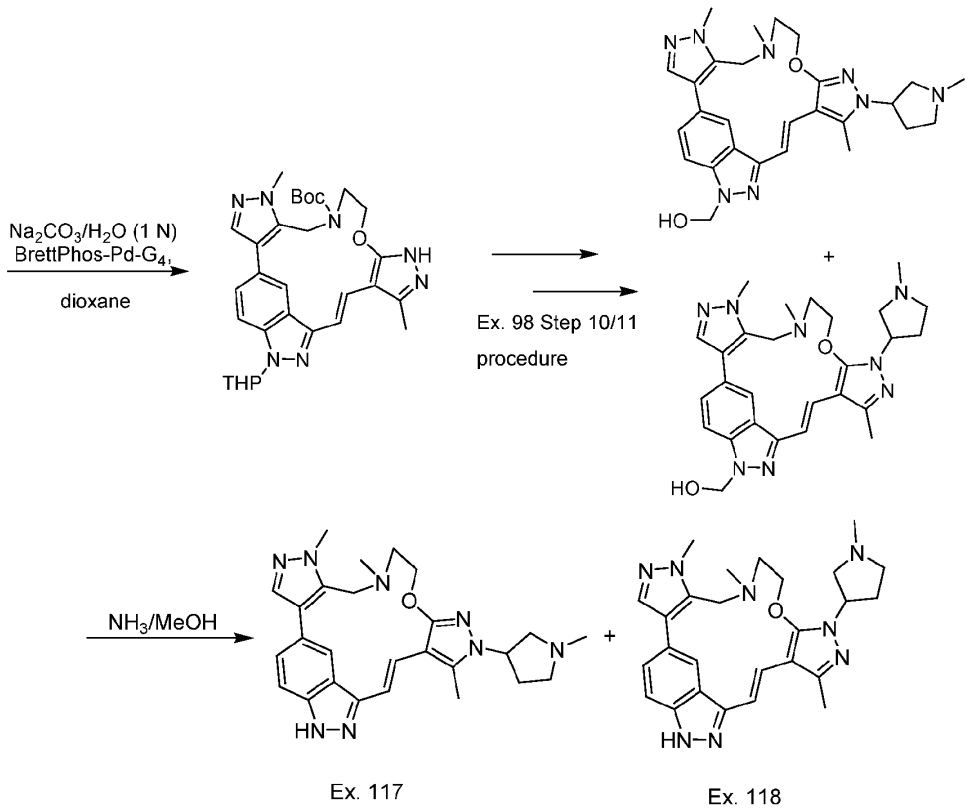
[01445] To a solution of (13R,21E)-17-(1-hydroxy-1-methyl-ethyl)-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo [21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20), 16,18,21,23,26(30),27-decaen-31-one (50.0 mg, 0.086 mmol, 1 eq) in THF (1 mL) and H2O (0.2 mL) was added TsOH (22.1 mg, 0.129 mmol, 1.5 eq). The mixture was stirred at 70 °C for 1h. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 33%-63%, 58min) to give Ex. 115 (10.06 mg, 0.019 mmol, 22 % yield, 98.3% purity) as a white solid.

[01446] Ex. 116 was prepared similarly to those described in General Method M from intermediate C-1-2, 89-1, and I-114.



[01447] Preparation of(17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 117) and (17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 118)





[01448] Step 1. To a mixture of 3-methyl-1H-pyrazol-5-ol (3.00 g, 30.5 mmol, 1 *eq*), tert-butyl N-(2-bromoethyl)carbamate (6.85 g, 30.5 mmol, 1 *eq*) in ACN (60 mL) was added K_2CO_3 (12.6 g, 91.7 mmol, 2 *eq*). The mixture was stirred at 100 °C for 4 hours. On completion, the mixture was poured into the water (50 mL), extracted with EA (40 mL * 3), the combined organic layers were washed with brine (50 mL * 2), 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 = 10/1 to 2/1) to give tert-butyl N-[2-[(3-methyl-1H-pyrazol-5-yl)oxy]ethyl]carbamate (3.60 g, 48% yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.52 (s, 1H), 6.94 (t, J = 5.2 Hz, 1H), 5.41 (s, 1H), 3.98 - 3.93 (m, 2H), 3.27 - 3.19 (m, 3H), 2.13 (s, 3H), 1.38 (s, 9H).

[01449] Step 2. To a mixture of tert-butyl N-[2-[(3-methyl-1H-pyrazol-5-yl)oxy]ethyl]carbamate (1.50 g, 6.22 mmol, 1 *eq*) in DCM (10 mL) was added HCl/dioxane (4 M, 3 mL) and the mixture was stirred at 20 °C for 10 minutes. On completion, the mixture was concentrated under reduced pressure to give 2-[(3-methyl-1H-pyrazol-5-yl)oxy] ethanamine (870 mg, 78% yield, HCl) as a brown oil.

[01450] Step 3. To a mixture of 2-[(3-methyl-1H-pyrazol-5-yl)oxy]ethanamine (870 mg, 4.90 mmol, 1 *eq*, HCl), 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazole-3-carbaldehyde (1.92 g, 3.92 mmol, 0.8 *eq*), KOAc (4.81 g, 48.9 mmol, 10 *eq*) in THF (30 mL) was added $Ti(i\text{-}PrO)_4$ (6.96 g, 24.4 mmol, 5 *eq*). The mixture was stirred at 80 °C for 11.5 hours under N_2 atmosphere. Then the mixture was cooled to 25 °C. $NaBH_3CN$ (615 mg, 9.80 mmol, 2 *eq*) was added into the mixture and stirred for 0.5 hours at 25 °C. On completion, the reaction mixture was poured into H_2O (100 mL) and stirred for 10 minutes, filtered to give the mother liquor. The mother liquor was extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=8:1 to 4:1) to give 2-[(3-methyl-1H-pyrazol-5-yl)oxy]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]methyl]ethanamine (1.20 g, 39% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.58 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.50 (s, 1H), 7.40 - 7.33 (m, 1H), 5.69 - 5.64 (m, 1H), 4.03 (d, *J* = 3.6 Hz, 1H), 3.93 (s, 3H), 3.73 - 3.65 (m, 1H), 3.31 (t, *J* = 7.2 Hz, 2H), 2.86 - 2.81 (m, 2H), 2.77 (s, 3H), 2.30 (t, *J* = 8.0 Hz, 2H), 2.12 (s, 3H), 2.04 (d, *J* = 8.8 Hz, 1H), 1.97 - 1.90 (m, 2H), 1.74 - 1.66 (m, 2H), 1.64 - 1.56 (m, 1H), 1.12 - 1.07 (m, 21H).

[01451] Steps 4-8 were conducted similarly to those described for Ex 99.

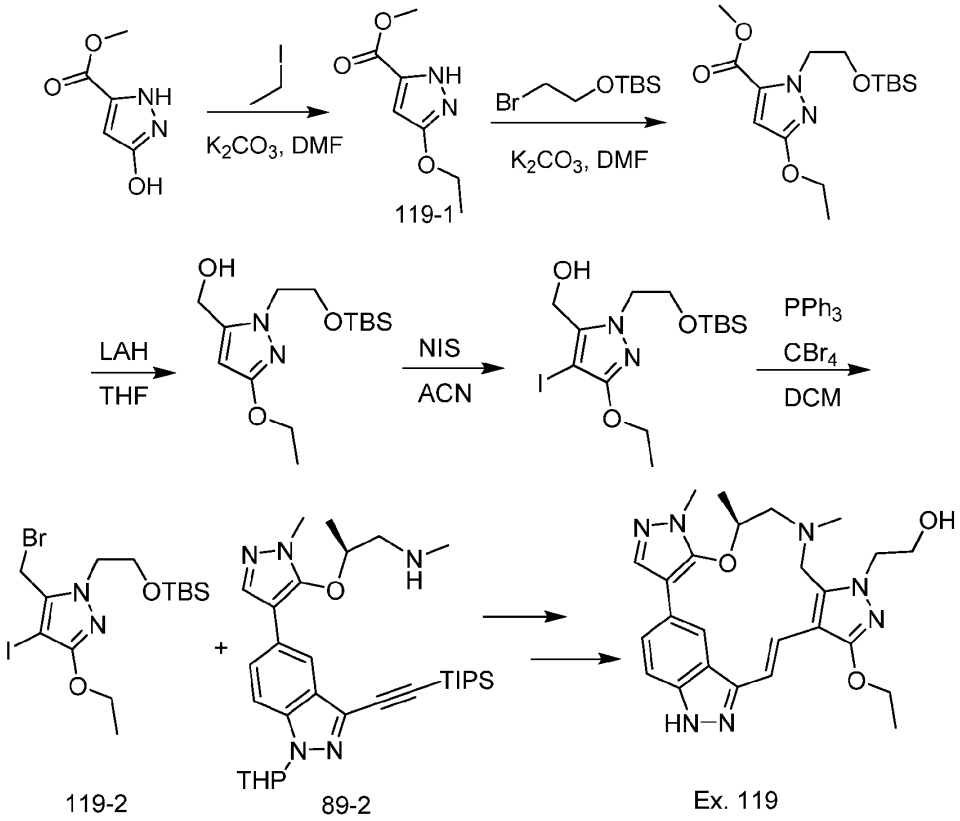
[01452] Step 9. To a mixture of tert-butyl N-[2-[(4-iodo-3-methyl-1H-pyrazol-5-yl)oxy]ethyl]-N-[[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]methyl]carbamate (500 mg, 0.614 mmol, 1 *eq*), a solution of Na_2CO_3 in water (1 N, 1.2 mL, 3 *eq*), dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino) phenyl] phenyl]palladium(1+) (56.5 mg, 0.061 mmol, 0.1 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 80 °C for 2 hours under N_2 atmosphere. On completion, the mixture was concentrated to give the residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to 2:1) to give the compound tert-butyl (17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-11-oxa-4,5,8,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$. $0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylate (189 mg, 54% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 - 7.59 (m, 3H), 6.91 (s, 1H), 5.66 - 5.58 (m, 1H), 5.00 (s, 2H), 4.37 (s, 2H), 4.08 - 3.96 (m, 1H), 3.81 (s, 3H), 3.71 - 3.65 (m, 6H), 3.62 (d, *J* = 5.2 Hz, 2H), 2.58 - 2.47 (m, 1H), 2.41 (s, 3H), 2.15 - 1.98 (m, 3H), 1.36 (s, 9H).

[01453] Steps 10 and 11 were conducted in a manner similar to those described for Ex. 98, steps 10-11.

[01454] Step 12. A mixture of (17E)-5,8,15-trimethyl-13-(1-methylpyrrolidin-3-yl)-11-oxa-4,5,8,13,14, 20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17, 19,22(26),23-nonaene (4.00 mg, 0.0085 mmol, 1 *eq*) in NH_3/MeOH (2 M, 2 mL) was stirred at 20 °C for 0.5 hours. On completion, the mixture was concentrated to give the residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; B%: 20%-50%,min) to give Ex. 117 (2.84 mg, 64% yield, FA) as a gum brown.

[01455] Ex. 118 was obtained in the same fashion as Ex. 117

[01456] General Method O. Preparation of 2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 119)



[01457] Step 1. To a solution of methyl 3-hydroxy-1H-pyrazole-5-carboxylate (15.0 g, 105 mmol, 1 *eq*), iodoethane (16.4 g, 105 mmol, 8.44 mL, 1 *eq*) in DMF (150 mL) was added K_2CO_3 (43.7 g, 316 mmol, 3 *eq*). The mixture was stirred at 80 °C for 2 hr. On

completion, the mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (50 mL × 3), the combined organic phase was washed with sat. NaCl (200 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 80:20) to give methyl 3-ethoxy-1H-pyrazole-5-carboxylate (10.4 g, 61.1 mmol, 58% yield) as a white solid. LCMS: *m/z* 171.1 (M+1)

[01458] Step 2. To a solution of methyl 3-ethoxy-1H-pyrazole-5-carboxylate (10.0 g, 58.7 mmol, 1 *eq*), 2-bromoethoxy-tert-butyl-dimethyl-silane (21.0 g, 88.1 mmol, 1.5 *eq*) in DMF (100 mL) was added NaI (8.81 g, 58.7 mmol, 1 *eq*), K_2CO_3 (24.3 g, 176 mmol, 3 *eq*). The mixture was stirred at 60 °C for 16 hr. On completion, the mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic phase was washed with sat. NaCl (80 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 17:83) to give methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-ethoxy-1H-pyrazole-5-carboxylate(12.7 g, 38.6 mmol, 66% yield) as a yellow liquid. LCMS: *m/z* 329.5 (M+1)

[01459] Step 3. To a solution of methyl 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-pyrazole-3-carboxylate (12.0 g, 36.5 mmol, 1 *eq*) in THF (120 mL) was added $LiAlH_4$ (1.39 g, 36.5 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hr. On completion, the mixture was quenched with MeOH (150 mL) at 0 °C, and the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 75:25) to give (1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-ethoxy-1H-pyrazol-5-yl)methanol(12.7 g, 38.6 mmol, 66% yield) as a yellow liquid. LCMS: *m/z* 301.1 (M+1)

[01460] Step 4. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-pyrazol-3-yl]methanol (7.00 g, 23.3 mmol, 1 *eq*) in ACN (70 mL) was added NIS (4.72 g, 20.9 mmol, 0.9 *eq*) at 0 °C The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was quenched with sat. Na_2SO_3 (200 mL) at 0 °C and extracted with ethyl acetate (50 mL × 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, Petroleum ether/Ethyl acetate=1:0 to 80:20) to give (1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-ethoxy-4-iodo-1H-pyrazol-5-yl)methanol (7.70 g, 18.0 mmol, 66% yield) as a yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.60 (d, *J* = 2.0 Hz, 2H), 4.30 - 4.25 (m, 2H), 4.23 (dt, *J* = 2.4, 4.8 Hz, 2H), 3.95 -3.90 (m, 2H), 3.33 (br s, 1H), 1.45 - 1.39 (m, 3H), 0.84 (d, *J* = 2.0 Hz, 9H), 0.02 - 0.01 (m, 6H). LCMS: *m/z* 427.0 (M+1)

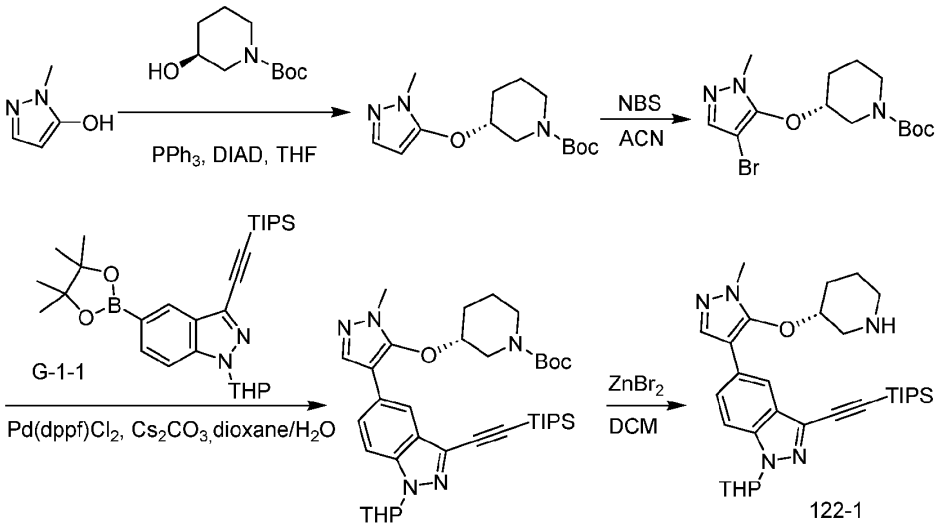
[01461] Step 5. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methanol (3.50 g, 8.21 mmol, 1 *eq*), PPh_3 (2.58 g, 9.85 mmol, 1.2 *eq*) in DCM (35 mL) was added CBr_4 (3.27 g, 9.85 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was diluted with water (50 mL) and extracted with DCM (30 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 (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 80:20) to give 5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-ethoxy-4-iodo-1Hpyrazole, 119-2. (2.90 g, 5.93 mmol, 72% yield) as a yellow oil. LCMS: *m/z* 490.8 (M+1)

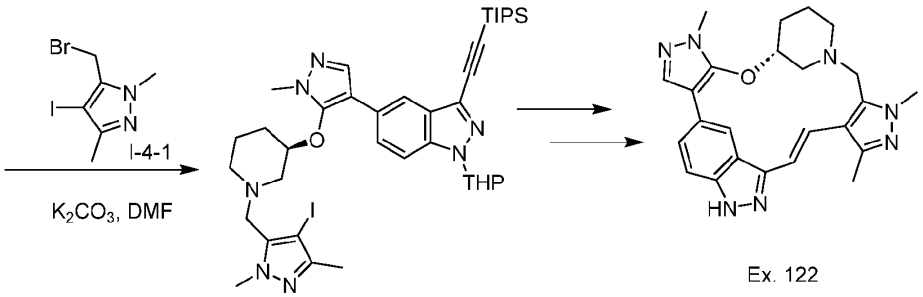
[01462] The remaining steps were conducted similarly to General Method H to give Ex. 119.

[01463] Ex. 120 was prepared in a manner similar to those described in General Method H using 89-2 in step 2.

[01464] Ex. 121 was prepared following procedures described in General Method M using tert-butyl N-[(2S)-2-hydroxypropyl]carbamate in step 1.

[01465] Preparation of (10*R*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine (Ex. 122)





[01466] Step 1. To a solution of 2-methylpyrazol-3-ol (5.0 g, 50.9 mmol, 1.0 *eq*) and tert-butyl (3S)-3-hydroxypiperidine-1-carboxylate (15.4 g, 76.5 mmol, 1.5 *eq*), PPh_3 (16.0 g, 61.2 mmol, 1.2 *eq*) in THF (50 mL) was stirred at 0 °C for 0.5 hr under N_2 atmosphere. Then DIAD (12.4 g, 61.2 mmol, 11.9 mL, 1.2 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=1/0 to 4/1) and reversed-phase HPLC (0.1% FA condition 0%-50% ACN) to give tert-butyl (3R)-3-(2-methylpyrazol-3-yl)oxypiperidine-1-carboxylate (2.80 g, 9.35 mmol, 18% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$-*d*) δ = 7.30 (s, 1H), 5.52 (br s, 1H), 5.14 - 4.84 (m, 1H), 4.17 - 4.12 (m, 1H), 3.79 - 3.68 (m, 1H), 3.61 (s, 3H), 3.58 - 3.50 (m, 1H), 3.31 (d, *J* = 17.2 Hz, 1H), 1.99 - 1.77 (m, 4H), 1.38 (s, 9H). LCMS: *m/z* 282.1 (M+1)

[01467] Step 2. To a solution of tert-butyl (3R)-3-(2-methylpyrazol-3-yl)oxypiperidine-1-carboxylate (2.0 g, 7.11 mmol, 1.0 *eq*) in ACN (20 mL) was added NBS (1.27 g, 7.11 mmol, 1.0 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hr. On completion, the mixture was quenched with water saturated Na_2SO_3 (100 mL), extracted with ethyl acetate (45 mL × 3), the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=1/0 to 2/1) to give tert-butyl (3R)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxypiperidine-1-carboxylate (1.20 g, 3.33 mmol, 47% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$-*d*) δ = 7.29 (s, 1H), 4.68 (br d, *J* = 3.6 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.65 (s, 3H), 3.59 - 3.54 (m, 1H), 3.41 - 3.23 (m, 2H), 1.93 - 1.83 (m, 4H), 1.42 (br s, 9H).

[01468] Step 3. A mixture of tert-butyl (3R)-3-(4-bromo-2-methyl-pyrazol-3-yl)oxypiperidine-1-carboxylate (1.05 g, 2.91 mmol, 1.0 *eq*), triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (1.78 g, 3.50 mmol, 1.2 *eq*) , Cs_2CO_3 (2.85 g, 8.74 mmol, 3.0 *eq*), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (190 mg, 0.291 mmol, 0.1 *eq*) in dioxane (10 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the

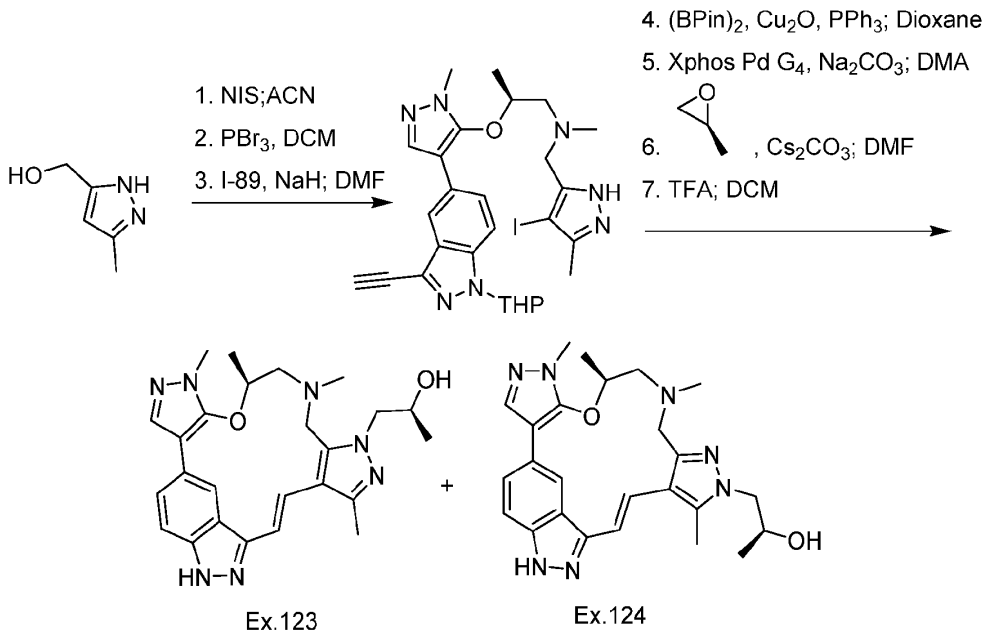
mixture was stirred at 80 °C for 4 hr under N_2 atmosphere. On completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (30 mL × 3), the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give tert-butyl (3R)-3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazol-3-yl]oxypiperidine-1-carboxylate (1.56 g, 2.10 mmol, 72% yield) as a brown oil. LCMS: *m/z* 662.4 (M+1)

[01469] Step 4. To a solution of tert-butyl (3R)-3-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypiperidine-1-carboxylate (1.5 g, 2.27 mmol, 1.0 *eq*) in DCM (20 mL) was added $ZnBr_2$ (2.55 g, 11.3 mmol, 5.0 *eq*). The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was diluted 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 a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH= 1/0 to 0/1) to give triisopropyl-[2-[5-[1-methyl-5-[[(3R)-3-piperidyl]oxy]pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazol-3-yl]ethynyl]silane (600 mg, 0.918 mmol, 40% yield,) as a colorless gum. LCMS: *m/z* 562.5 (M+1)

[01470] Step 5. To a solution of triisopropyl-[2-[5-[1-methyl-5-[[(3R)-3-piperidyl]oxy]pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazol-3-yl]ethynyl]silane (570 mg, 1.01 mmol, 1.0 *eq*) and 5-(bromomethyl)-4-iodo-1,3-dimethyl-pyrazole (383 mg, 1.22 mmol, 1.2 *eq*) in DMF (10 mL) was added K_2CO_3 (421 mg, 3.04 mmol, 3.0 *eq*). The mixture was stirred at 80 °C for 16 hr. On completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (25 mL × 3), the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 2-[5-[5-[[(3R)-1-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methyl]-3-piperidyl]oxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazol-3-yl]ethynyl-triisopropyl-silane (800 mg, crude) as a colorless oil. LCMS: *m/z* 796.6 (M+1)

[01471] Steps 6-9 were conducted in a similar manner to those described in General Method H to give Ex. 122.

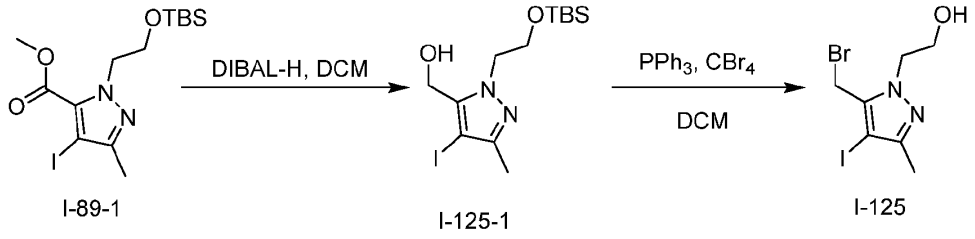
[01472] (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-2-ol (Ex. 123) and (2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol (Ex. 124)



[01473] Steps 1-3 was conducted according to General Method O.

[01474] Steps 4-7 were conducted similarly to those described in Ex. 98 to give Ex. 123 and Ex. 124.

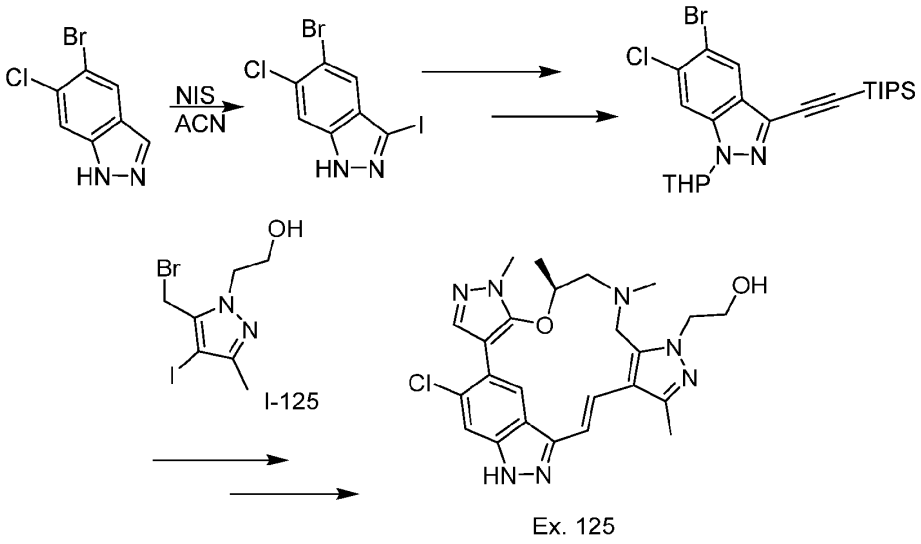
[01475] Preparation of 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethanol (I-125)



[01476] Step 1. To a solution of methyl 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazole-3-carboxylate (2.00 g, 4.71 mmol, 1 *eq*) in THF (40 mL) was added DIBAL-H (268 mg, 7.07 mmol, 1.5 *eq*) at 0°C .The mixture was stirred at 0 °C for 12 hr. 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 concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1 to 1:1) to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-methyl-pyrazol-3-yl]methanol (700 mg, 2.59 mmol, 54% yield) as a yellow oil. LCMS: *m/z* 397.1 (M+1)

[01477] Step 2. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methanol (2.5 g, 6.31 mmol, 1 *eq*) and PPh_3 (2.48 g, 9.46 mmol, 1.5 *eq*) in DCM (40 mL) was added dropwise CBr_4 (3.14 g, 9.46 mmol, 1.5 *eq*) at 0 °C. The resulting mixture was stirred at 25 °C for 4 hr. On completion, the mixture was quenched with water (20 mL) and extracted with DCM (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/Ethyl acetate=0:1 to 0:1) to give 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethanol (264 mg, 0.765 mmol, 12 % yield) as a white solid. LCMS: *m/z* 344.7 (M+1)

[01478] Preparation of 2-[(10*S*,17*E*)-19-chloro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 125)



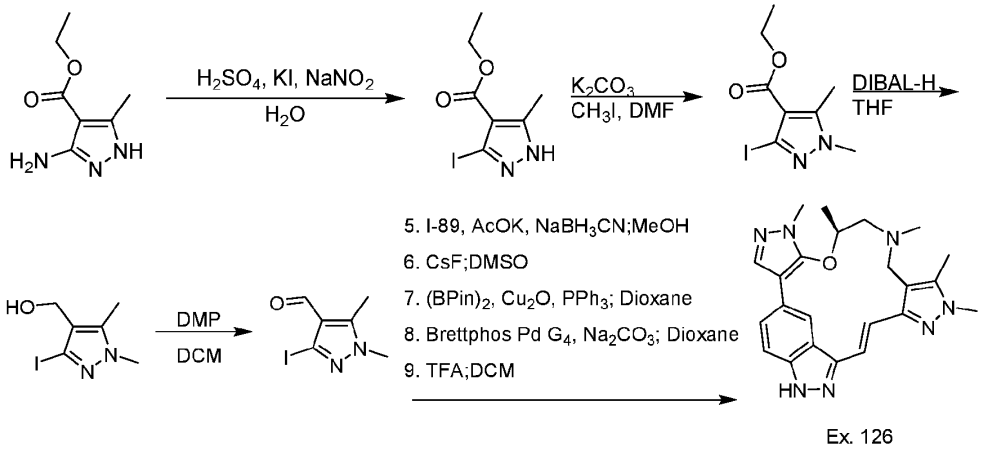
Ex. 125

[01479] Step 1. To a solution of 5-bromo-6-chloro-1H-indazole (5.00 g, 21.6 mmol, 1 *eq*) in ACN (200 mL) was added NIS (7.29 g, 32.4 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 4 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 concentrated to give 5-bromo-6-chloro-3-iodo-1H-indazole (7.70 g, 99% yield) as a red solid. LCMS: *m/z* 356.8 (M+1)

[01480] Steps 2-3 were conducted in a manner similar to those described for C-1-1.

[01481] Steps 4-10 were conducted in a manner similar to those described in General Method M using I-125 in step 6 to afford Ex. 125.

[01482] Preparation of (10*S*,17*E*)-8,10,12,14,15-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 126)



Ex. 126

[01483] Step 1. Ethyl 3-amino-5-methyl-1H-pyrazole-4-carboxylate (5.00 g, 29.5 mmol, 1 *eq*) was added in portions to a solution of H_2SO_4 (15 mL) in H_2O (12 mL) at 0° C. The resulting solution was stirred at 0° C for 30 min. A solution of $NaNO_2$ (3.06 g, 44.3 mmol, 1.5 *eq*) in H_2O (12 mL) was added dropwise to the reaction mixture at 0° C. The resulting solution was stirred at 0° C for another hour. A solution of KI (10.5 g, 63.2 mmol, 2.14 *eq*) in H_2O (12.5 mL) was then added dropwise. The resulting solution was stirred at 25° C for 8 h. On completion, the mixture was quenched with water (50 mL) and extracted with ethyl acetate (20 mL X 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF=1:0 to 4:1) to give ethyl 3-iodo-5-methyl-1H-pyrazole-4-carboxylate (3.00 g, 36% yield) as an orange solid. LCMS: *m/z* 280.9 (M+1)

[01484] Step 2. To a solution of ethyl 3-iodo-5-methyl-1H-pyrazole-4-carboxylate (1 g, 3.57 mmol, 1 eq) in DMF (10 mL) was added K2CO3 (1.48 g, 10.7 mmol, 3 eq) and CH3I (658 mg, 4.64 mmol, 1.3 eq). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (10 mL X 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO2, PE:THF=1:0 to 100:13) to give ethyl 3-iodo-1,5-dimethyl-pyrazole-4- carboxylate (530 mg, 50% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.25 - 4.18 (m, 2H), 3.76 (s, 3H), 2.48 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 294.9 (M+1)

[01485] Step 3. To a solution of ethyl 3-iodo-1,5-dimethyl-pyrazole-4-carboxylate (500 mg, 1.70 mmol, 1 *eq*) in THF (6 mL) was degassed and purged with N_2 for 3 times, and then DIBAL-H (1 M, 4 mL, 2.5 *eq*) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 h under N_2 atmosphere. On completion, the mixture was quenched with MeOH (30 mL), filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane : Methanol=1:0 to 10:1) to give (3-iodo-1,5-dimethyl-pyrazol-4-yl)methanol (380 mg, 88 % yield) as white solid. LCMS: *m/z* 252.9 (M+1)

[01486] Step 4. To a solution of (3-iodo-1,5-dimethyl-pyrazol-4-yl)methanol (320 mg, 1.27 mmol, 1 eq) in DCM (5 mL) was added DMP (646 mg, 1.52 mmol, 1.2 eq). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with aq. Na2SO3 (10 mL) and extracted with DCM (8 mL X 5), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 3-iodo-1,5-dimethyl-pyrazole-4-carbaldehyde (250 mg, 78 % yield) as white solid. LCMS: *m/z* 250.9 (M+1)

[01487] Steps 5. The mixture of (2S)-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2- triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (458 mg, 0.833 mmol, 1 *eq*) and 3-iodo-1,5-dimethyl-pyrazole-4-carbaldehyde (250 mg, 0.999 mmol, 1.2 *eq*) in MeOH (3 mL) was added AcOK (817 mg, 8.33 mmol, 10 *eq*). The mixture was stirred at 25 °C for 0.2 h. Then $NaBH_3CN$ (157 mg, 2.50 mmol, 3 *eq*) was added to the mixture, the mixture was stirred at 25 °C for 12 h. On completion, the mixture was quenched with water (1 mL) and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:TFH=1:0 to 2:1) to give (2S)-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (402 mg, 61% yield) as white solid. LCMS: *m/z* 784.3 (M+1)

[01488] Steps 6-7 were conducted in a manner similar to those described in General Method N

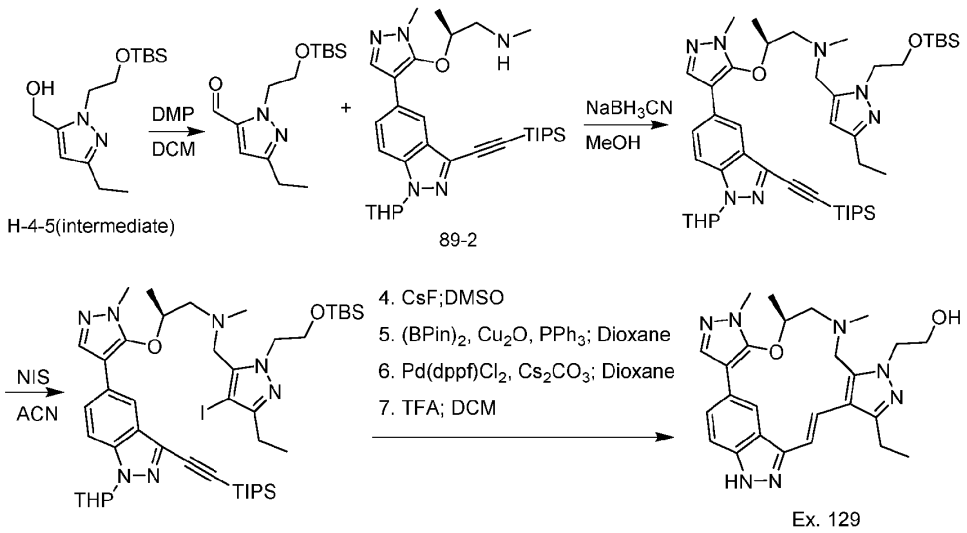
[01489] Step 8. To a solution of (2S)-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N-methyl-2- [2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (158 mg, 0.209 mmol, 1 *eq*) in dioxane (8 mL) was added Na_2CO_3 (1.5 M, 418 uL, 3 *eq*) and BrettPhos (Pd, G4) (19.2 mg, 0.021 mmol, 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 2 h under N_2 atmosphere. On completion, the mixture 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 1:2) to

give (8S,17E)-5,8,10,13,14-pentamethyl-21- tetrahydropyran-2-yl-7-oxa-4,5,10,14,15,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12,15,17,19,22(26),23-nonaene (61.0 mg, 58 % yield) as white oil. LCMS: *m/z* 502.2 (M+1)

[01490] Step 9 was conducted in a manner similar to General Method N to afford Ex. 126.

[01491] Preparation of Ex. 127 and Ex. 128 were prepared in a manner similar to those described for Ex. 123 and 124 using (2R)-2-methyloxirane.

[01492] Preparation of 2-[(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol. (Ex. 129)



[01493] Step 1. To a mixture of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethyl-pyrazol-3-yl] methanol (3.50 g, 12.3 mmol, 1 *eq*) in DCM (40 mL) was added DMP (7.83 g, 18.4 mmol, 1.5 *eq*) at 0 °C, the reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture were quenched with sat.$Na_2S_2O_3$ (15 mL) and sat.$NaHCO_3$ (15 mL) under stirring, then the mixture was diluted with water (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford compound 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethyl-pyrazole-3-carbaldehyde (3.05 g, 87% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 6.82 (s, 1H), 4.53 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 5.2 Hz, 2H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H), 0.74 (s, 9H), -0.12 - -0.18 (m, 6H).

[01494] Step 2. To a mixture of (2S)-N-methyl-2-[2-methyl-4- [1-tetrahydropyran -2-yl-3- (2- triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (5.34 g, 9.72

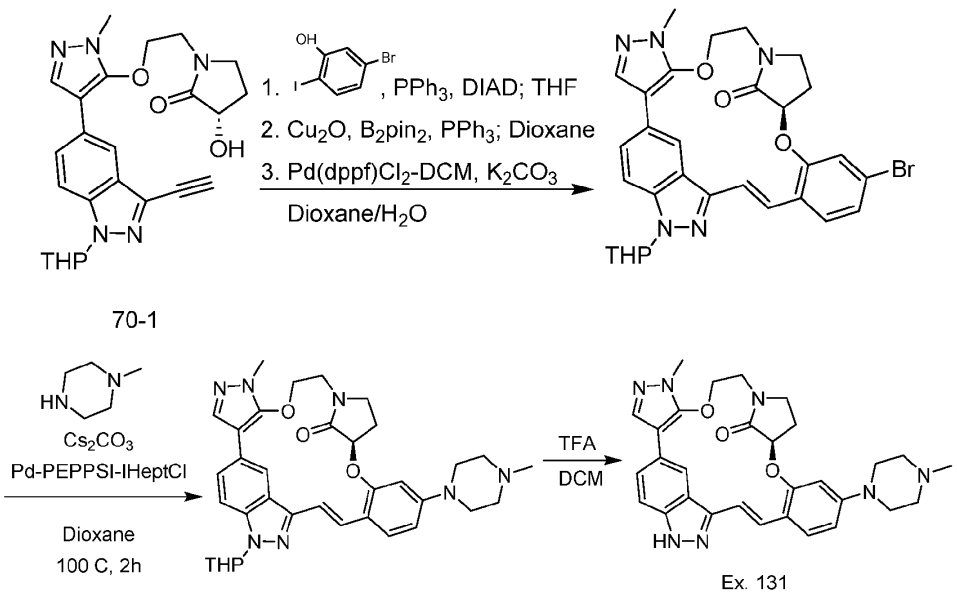
mmol, 0.9 *eq*) in MeOH (40 mL) was added 2-[2- [tertbutyl (dimethyl) silyl] oxyethyl] -5-ethyl –pyrazole-3-carbaldehyde (3.05 g, 10.8 mmol, 1 *eq*) and $NaBH_3CN$ (1.02 g, 16.2 mmol, 1.5 *eq*), the reaction mixture was stirred at 25 °C for 12 hours. On completion, the mixture was diluted with water (50 mL) and extracted with EA (2 × 50 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford compound t(2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethyl- pyrazol-3-yl]methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (7.50 g, 85% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.66 - 7.65 (m, 1H), 7.64 - 7.61 (m, 1H), 5.90 -5.86 (m, 1H), 5.76 (d, *J* = 1.6 Hz, 1H), 4.17 - 4.10 (m, 2H), 4.10 - 4.05 (m, 1H), 4.03 (d, *J* = 7.2 Hz, 1H), 4.00 - 3.95 (m, 2H), 3.94 - 3.87 (m, 2H), 3.86 - 3.83 (m, 1H), 3.77 - 3.75 (m, 2H), 3.66 (s, 3H), 3.41 (d, *J* = 4.8 Hz, 2H), 2.65 (dd, *J* = 5.6, 12.8 Hz, 1H), 2.60 - 2.54 (m, 1H), 2.47 - 2.45 (m, 1H), 2.43 (d, *J* = 7.6 Hz, 2H), 2.39 - 2.33 (m, 1H), 2.04 (d, *J* = 14.4 Hz, 2H), 1.99 (s, 3H), 1.95 (s, 1H), 1.59 (s, 2H), 1.19 - 1.18 (m, 2H), 1.17 (d, *J* = 1.6 Hz, 2H), 1.15 (s, 18H), 1.11 - 1.08 (m, 6H), 0.69 (s, 9H).

[01495] Step 3. To a mixture of (2S)-N-[[2-[2-[tert-butyl(dimethyl) silyl]oxyethyl] -5-ethyl-pyrazol -3-yl]methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (1.08 g, 1.32 mmol, 1 *eq*) in ACN (15 mL) was added NIS (446 mg, 1.98 mmol, 1.5 *eq*) at 0°C, the reaction mixture was stirred at 25 °C for 8 hours. On completion, the reaction mixture was quenched with sat.Na_2SO_3 solution (5 mL) under stirring, and then the residue was diluted with water (20 mL) and extracted with EA (2 × 20 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford compound (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-5-ethyl -4-iodo-pyrazol-3-yl] methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (1.40 g, crude) as yellow oil. LCMS: *m/z* 942.4 (M+1)

[01496] Steps 4-7 were conducted in a manner similar to those described in General Method H to give Ex. 129.

[01497] Ex. 130 was prepared in a manner similar to those described in Ex. 126 starting in step 2 with 3-iodo-5-methyl-1H-pyrazole-4-carboxylate.

[01498] Preparation of (10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 131)



[01499] Steps 1-2 are described in General Method L.

[01500] Step 3. A mixture of (3R)-3-(5-bromo-2-iodo-phenoxy)-1-[2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethyl]pyrrolidin-2-one (200 mg, 0.233 mmol, 1.00 *eq*), K_2CO_3 (64.4 mg, 0.466 mmol, 2.00 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (19.0 mg, 0.023 mmol, 0.10 *eq*) in dioxane (10 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 90 °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, Dichloromethane/Methanol=10/1 to 5/1) to give (13R,21E)-17-bromo-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.$1^{10,13}$.$0^{2,6}$.$0^{15,20}$.$0^{26,30}$]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (54.0 mg, 0.089 mmol, 38% yield) as brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.01 (s, 1H), 7.81 - 7.74 (m, 2H), 7.72 - 7.66 (m, 1H), 7.65 - 7.60 (m, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 1H), 5.91 - 5.84 (m, 1H), 5.16 (s, 1H), 4.39 - 4.28 (m, 1H), 4.12 - 4.05 (m, 1H), 3.89 (s, 6H), 3.84 - 3.84 (m, 1H), 3.80 - 3.76 (m, 3H), 3.60 - 3.41 (m, 2H), 2.47 - 2.36 (m, 2H), 2.19 - 2.02 (m, 2H), 1.83 - 1.69 (m, 1H), 1.60 (s, 2H). LCMS: *m/z* 606.1 (M+1)

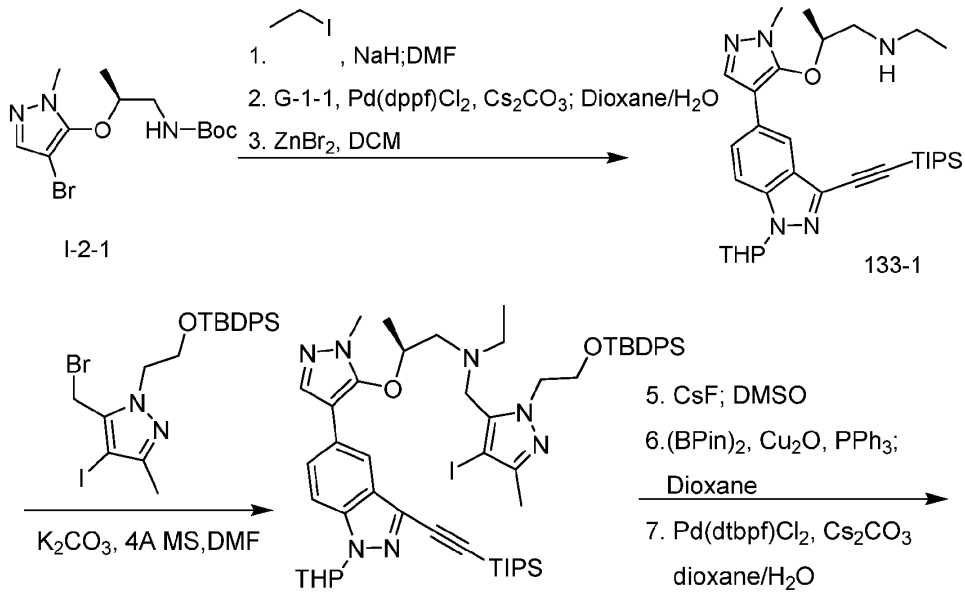
[01501] Step 4. A mixture of (13R,21E)-17-bromo-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.$1^{10,13}$.$0^{2,6}$.$0^{15,20}$.$0^{26,30}$]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (44.0 mg, 0.073 mmol, 1.00 *eq*), 1-methylpiperazine (8.75 mg, 0.087 mmol, 1.20 *eq*), Cs_2CO_3 (71.2 mg, 0.218 mmol, 3.00 *eq*),

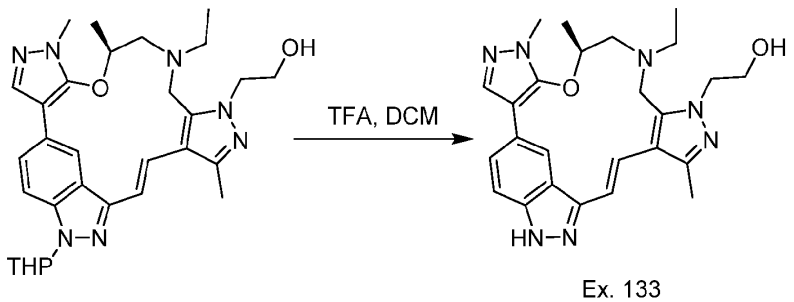
Pd-PEPPSI-IHeptCl (7.08 mg, 0.0073 mmol, 0.10 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 2 h under N_2 atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane/Methanol=1/0 to 10/1) to give (13R,21E)-5-methyl-17-(4-methylpiperazin-1-yl)-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.1^{10,13}.0^{2,6}.0^{15,20}.0^{26,30}]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (44.0 mg, 0.071 mmol, 97% yield) as brown solid. LCMS: *m/z* 624.4 (M+1)

[01502] Step 5 was conducted in a manner described in General Method L to give Ex. 131.

[01503] Ex. 132 was prepared in a manner similar to those described in Ex. 131 starting with the appropriate phenol.

[01504] Preparation ofv2-[(10*S*,17*E*)-12-ethyl-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 133)





Ex. 133

[01505] Example 133 was prepared following procedures similar to those described in General Method M with variations in steps 4 and 7 as detailed.

[01506] Steps 1-3, General Method M

[01507] Step 4. To a mixture of (2S)-N-ethyl-2-[2-methyl-4- [1-tetrahydropyran-2-yl-3- (2- triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (390 mg, 0.691 mmol, 1 eq) and 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethoxy-tert-butyl-diphenyl-silane (1.21 g, 2.08 mmol, 3 eq), made similarly to I-114, in DMF (5 mL) was added K_2CO_3 (286 mg, 2.08 mmol, 3 eq) and 4A MS (1.00 g, 0.691 mmol, 1 eq), the reaction mixture was stirred at 50 °C for 12 hours. On completion, the residue was diluted with water (10 mL) and extracted with EA (2 × 10 mL). The combined organic layers was dried over Na2SO4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, 80/20%DCM:DCM/MeOH, DCM/MeOH=10:1) to afford compound ((2S)-N- [[2-[2-[tert-butyl(diphenyl)silyl] oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methyl]-N-ethyl- 2-[2-methyl-4-[1-tetrahydropyran -2- yl -3- (2- triisopropylsilylethynyl) indazol - 5-yl] pyrazol- 3-yl] oxy-propan -1- amine (717 mg, 0.672 mmol, 97% yield) as yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 7.95 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 - 7.72 (m, 1H), 7.65 (s, 1H), 7.64 - 7.61 (m, 1H), 7.44 - 7.39 (m, 4H), 7.33 (s, 6H), 5.90 - 5.85 (m, 1H), 4.22 - 4.17 (m, 2H), 3.92 (s, 2H), 3.87 (s, 1H), 3.78 (t, J = 4.8 Hz, 3H), 3.60 (s, 3H), 3.57 - 3.48 (m, 2H), 2.64 (dd, J = 4.8, 13.6 Hz, 2H), 2.43 (d, J = 7.6 Hz, 1H), 2.35 - 2.28 (m, 3H), 2.09 (s, 3H), 2.01 - 1.92 (m, 2H), 1.82 - 1.66 (m, 2H), 1.58 (s, 2H), 1.26 - 1.22 (m, 2H), 1.16 - 1.11 (m, 20H), 1.07 (s, 10H)

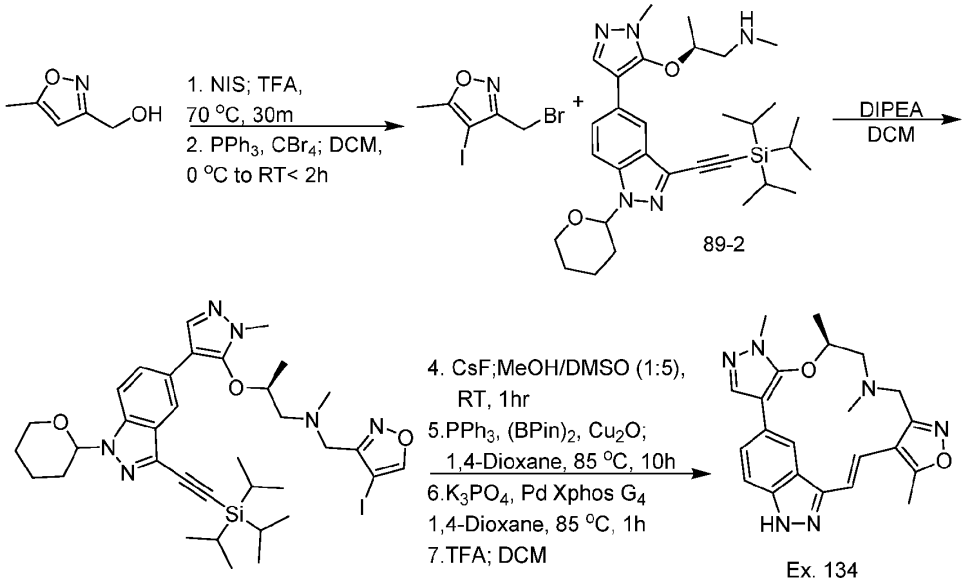
[01508] Steps 5-6 conducted according to General Method M.

[01509] Step 7. To a mixture of 2-[5-[[ethyl-[(2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5 -tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxypropyl]amino]methyl]-4-iodo-3-methyl-pyrazol-1-yl]ethanol (70.0 mg, 0.088 mmol, 1 eq) in dioxane (1 mL) and H2O (0.2 mL) was added Cs2CO3 (85.5 mg, 0.262 mmol, 3 eq) and ditert-butyl(cyclopentyl) phosphane;dichloropalladium;iron (5.71 mg, 0.009 mmol, 0.1 eq). The reaction mixture was stirred at 90 °C for 1 hour. On completion, the residue was

diluted with water (20 mL) and extracted with EA (2 × 20 mL). The combined organic layers was dried over Na2SO4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO2, 80/20%DCM:DCM/MeOH, DCM/MeOH=10:1) to afford 2-[(8S,17E)-10-ethyl-5,8,15-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]ethanol (30.0 mg, 0.055 mmol, 62% yield) as yellow oil. LCMS: *m/z* 546.4 (M+1)

[01510] Step 8. Ex. 133 was prepared following procedure described in General Method M.

[01511] General Method P. Preparation of(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine (Ex. 134)



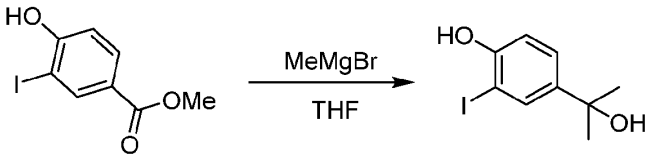
[01512] Steps 1-2 were conducted according to procedures described in General Method O.

[01513] Step 3. Step 3. To (2S)-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine, 100 mg, 0.182 mmol) in anhydrous DCM (1 mL) was added DIPEA (0.546 mmol, 95 µL) followed by 3-(bromomethyl)-4-iodo-5-methyl-isoxazole (66 mg, 0.218 mmol). Stirred at RT for 18 hr. Flash column chromatography (automated system, 12g silica, 0-60% EA in Hexanes) provided (2S)-N-[(4-iodo-5-methyl-isoxazol-3-yl)methyl]-N-methyl-2-[2-methyl-4-[1-

tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (73.2 mg, 0.095 mmol, 52 % yield). LCMS: *m/z* 771.1 (M+1)

[01514] Steps 4-7 were conducted in a manner similar to those described in General Method M to give Ex. 134.

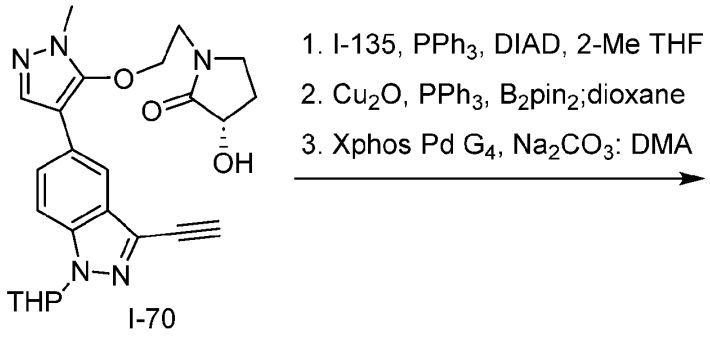
[01515] Preparation of I-135



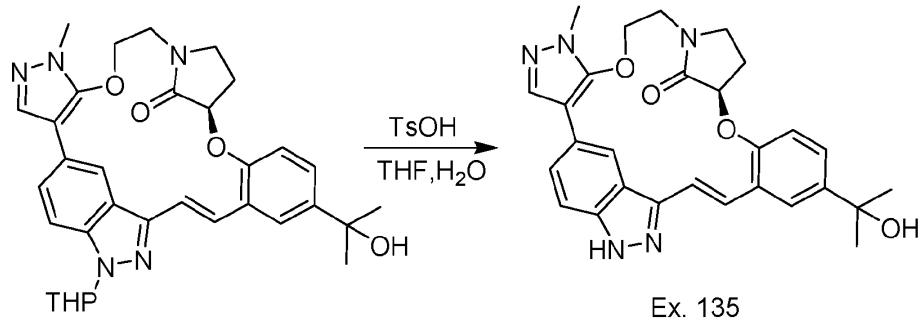
I-135

[01516] I-135 was prepared in a manner similar to those described for Ex. 105

[01517] Preparation of (10*R*,16*E*)-14-(2-hydroxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one (Ex. 135)



I-70



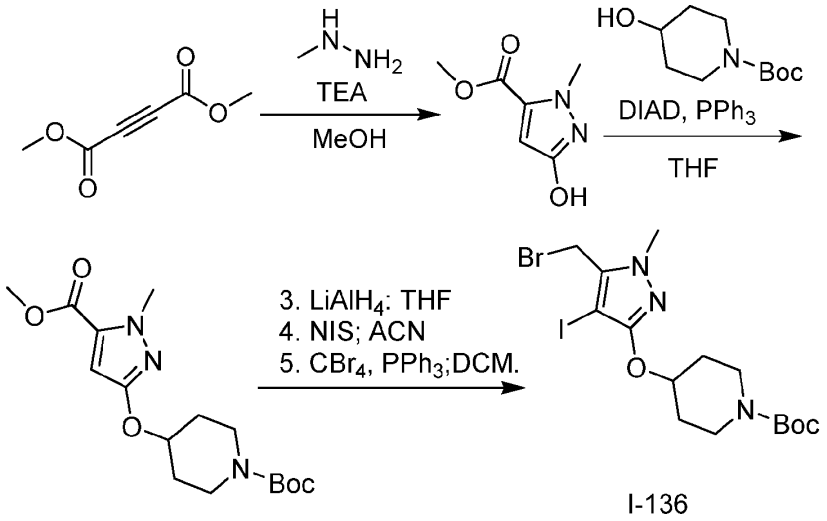
Ex. 135

[01518] Steps 1-3 were conducted in a similar manner to those described in General Method L.

[01519] Step 4. The mixture of (13R,21E)-18-(1-hydroxy-1-methyl-ethyl)-5-methyl-25-tetrahydropyran-2-yl-7,14-dioxa-4,5,10,24,25-pentazahexacyclo[21.5.2.110,13.02,6.015,20.026,30]hentriaconta-1(29),2(6),3,15(20),16,18,21,23,26(30),27-decaen-31-one (45.0

mg, 0.077 mmol, 1 *eq*) and TsOH (19.9 mg, 0.115 mmol, 1.5 *eq*) in H_2O (0.4 mL) and THF (2 mL) was stirred at 60 °C for 1 h. On completion, the mixture was diluted with DCM (10 mL) and adjusted to pH = 8 with sat. $NaHCO_3$ (20ml). The mixture was extracted with DCM (10 mL*3), and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give the residue. The residue was then purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 19%-49%,8min) to give Ex. 135 (7.63 mg, 0.137 mmol, 18 % yield, 98.3% purity, FA) as an off-white solid.

[01520] Preparation of tert-butyl 4-[5-(bromomethyl)-4-iodo-1-methyl-pyrazol-3-yl]oxypiperidine-1-carboxylate (I-136)



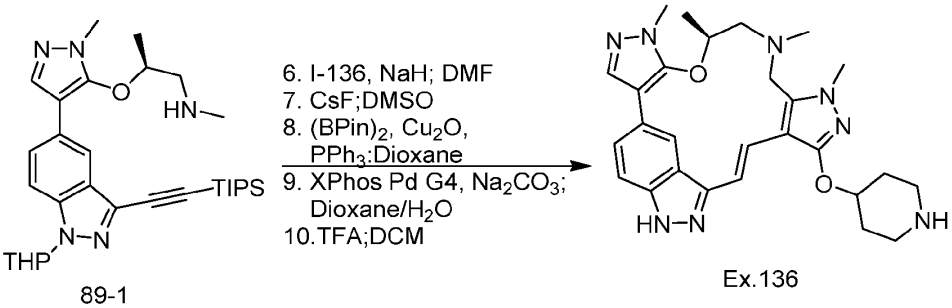
[01521] Step 1. To a solution of dimethyl but-2-ynedioate (50.0 g, 352 mmol, 1.00 *eq*) in MeOH (500 mL) was added TEA (71.2 g, 704 mmol, 97.9 mL, 2.00 *eq*) and Methylhydrazine;sulfuric acid (50.7 g, 352 mmol, 1.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. On completion, the mixture was concentrated in reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate (24.0 g, 154 mmol, 44% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.03 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H).

[01522] Step 2. To a solution of methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate (2.00 g, 12.8 mmol, 1.00 *eq*) in THF (15 mL) was added tert-butyl 4-hydroxypiperidine-1-carboxylate (5.16 g, 25.6 mmol, 2.00 *eq*) , PPh_3 (6.72 g, 25.6 mmol, 2.00 *eq*).The mixture was stirred at 25 °C for 1h. DIAD (5.18 g, 25.6 mmol, 4.98 mL, 2.00 *eq*) was added into the

mixture at 0 °C. The mixture was stirred at 25 °C for 15 h under N_2. On completion, the mixture was concentrated in reduced pressure. The crude product was triturated with petroleum ether at 25 °C for 10 min. The filtrate was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 2/1) to give tert-butyl 4-(5-methoxycarbonyl-1-methyl-pyrazol-3-yl) oxypiperidine-1-carboxylate (4.35 g, 12.8 mmol, 100% yield) as a yellow oil. LCMS: *m/z* 284.1 (M+1)

[01523] Steps 3-5 were performed in a manner similar to those described in the synthesis of 119-2 to give I-136.

[01524] Preparation of(10*S*,17*E*)-8,10,12,14-tetramethyl-16-[(piperidin-4-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 136)

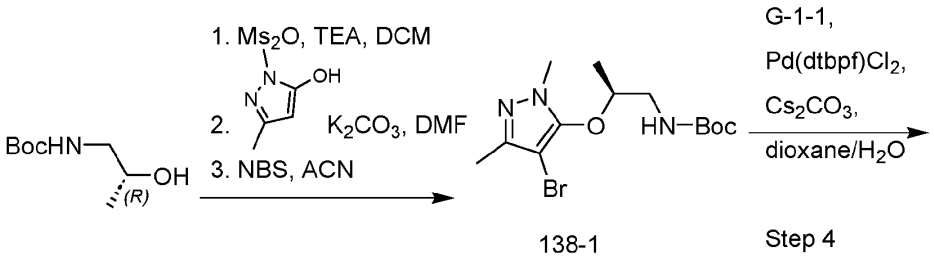


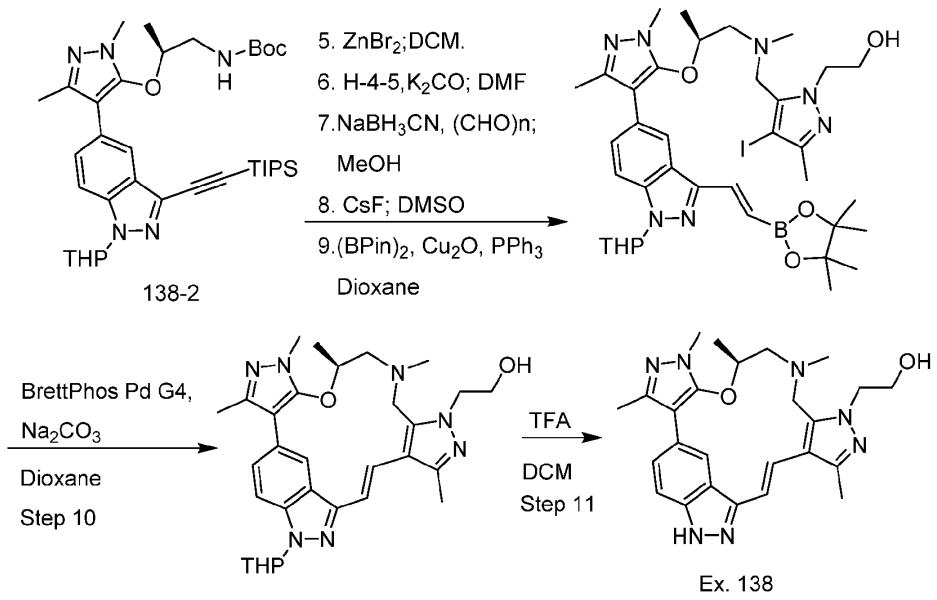
[01525] Steps 6-8 were conducted in manner similar to those described in General Method H

[01526] Step 9-10 was conducted in a manner similar to those described in General Method L to afford Ex. 136.

[01527] Ex. 137 was prepared in a similarly to Ex. 122 using 119-2 in step 5.

[01528] General Method Q. Preparation of 2-[(10*S*,17*E*)-6,8,10,12,16-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-o (Ex. 138)





[01529] Steps 1-3 were conducted in a manner similar to those described in General Method M.

[01530] Step 4 was conducted in a manner similar to that described in General Method I.

[01531] Steps 5 were conducted in a manner similar to those described in General Method M.

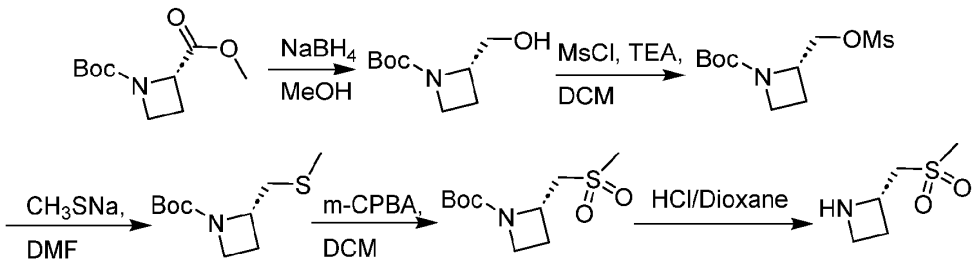
[01532] Step 6. To a solution of (2S)-2-[2,5-dimethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilyle thynyl)indazol-5-yl]pyrazol-3-yl]oxypropan-1-amine (2.60 g, 4.73 mmol, 1 *eq*) and 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]ethoxy-tert-butyl-diphenyl-silane (3.31 g, 5.67 mmol, 1.2 *eq*) in DMF (60 mL) was added K_2CO_3 (1.96 g, 14.1 mmol, 3 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (180 mL) and extracted with EA (125 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (2S)-N-[[2-[2-[tert-butyl(diphenyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methyl]-2-[2,5-dimethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyra zol-3-yl]oxy-propan-1-amine (3.20 g, 3.04 mmol, 64% yield) as a yellow oil. LCMS: *m/z* 1052.6 (M+1)

[01533] Step 7. To a solution of (2S)-N-[[2-[2-[tert-butyl(diphenyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methyl]-2-[2,5-dimethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilyl ethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (3.20 g, 3.04 mmol, 1 *eq*) and $(CHO)_n$ (621 mg, 18.2 mmol, 6 *eq*) in MeOH (50 mL) was added $NaBH_3CN$ (382 mg, 6.08 mmol, 2.0 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the

mixture was filtered and concentrated to give (2S)-N-[[2-[2-[tert-butyl(diphenyl)silyl]oxyethyl]-4-iodo-5-methyl-pyrazol-3-yl]methyl]-2-[2,5-dimethyl -4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-N-methyl-propan-1-amine (3.20 g, 3.00 mmol, 98% yield) as a white solid. LCMS: *m/z* 1066.3(M+1)

[01534] Remaining steps 8-11 were conducted according to Ex. 126 to give Ex. 138.

[01535] Preparation of (2S)-2-(methylsulfonylmethyl)azetidine, (I-139)



I-139

[01536] Step 1. To a solution of O1-tert-butyl O2-methyl (2S)-azetidine-1,2-dicarboxylate (5.00 g, 23.2 mmol, 1 *eq*) in MeOH (80 mL) was added $NaBH_4$ (4.39 g, 116 mmol, 5 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, The mixture was quenched with water (120 mL) and extracted with ethyl acetate (125 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl (2S)-2-(hydroxymethyl)azetidine-1-carboxylate (5.00 g, crude) as a colourless oil

[01537] Step 2. To a solution of tert-butyl (2S)-2-(hydroxymethyl)azetidine-1-carboxylate (4.30 g, 22.9 mmol, 1 *eq*) in DCM (100 mL) was added TEA (11.6 g, 114 mmol, 5 *eq*) and MsCl (15.7 g, 137 mmol, 6 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched with water (100 mL) and extracted with DCM (120 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl (2S)-2-(methylsulfonyloxymethyl) azetidine-1-carboxylate (8.00 g, crude) as a yellow oil.

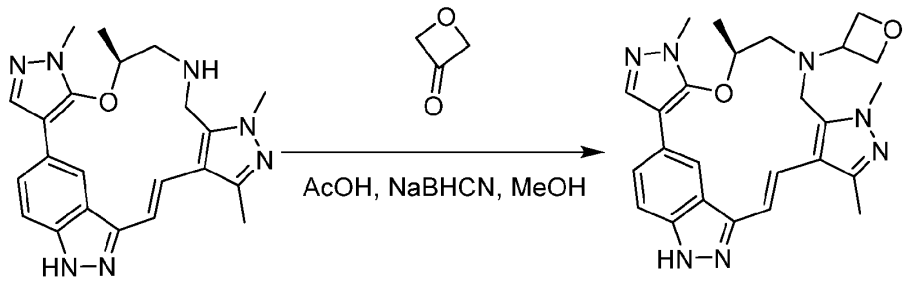
[01538] Step 3. To a solution of tert-butyl (2S)-2-(methylsulfonyloxymethyl)azetidine-1-carboxylate (7.00 g, 26.3 mmol, 1 *eq*) in DMF (160 mL) was added NaSMe (3.70 g, 52.7 mmol, 2 *eq*). The mixture was stirred at 25 °C for 3 h. On completion, the mixture was quenched with water (400 mL) and extracted with EA (250 mL × 3), the residue was purified by column chromatography (SiO_2, PE/EA=2:1 to 1:1) to give tert-butyl (2S)-2-(methylsulfanylmethyl)azetidine-1-carboxylate (5.60 g, 25.7 mmol, 97% yield) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ = 4.28 (qdd, *J* = 2.8, 5.6, 8.4 Hz, 1H), 3.69 (br d, *J* = 7.6 Hz, 1H), 3.32 (s, 1H), 2.86 - 2.71 (m, 2H), 2.32 - 2.20 (m, 1H), 2.08 (s, 3H), 1.92 (tdd, *J* = 6.4, 9.2, 11.2 Hz, 1H), 1.37 (s, 9H)

[01539] Step 4. To a solution of tert-butyl (2S)-2-(methylsulfanylmethyl)azetidine-1-carboxylate (5.50 g, 25.3 mmol, 1 *eq*) in DCM (100 mL) was added m-CPBA (16.3 g, 75.9 mmol, 80% purity, 3 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, the mixture was quenched with water (100 mL) and extracted with DCM (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/EA=2:1 to 1:1) to give tert-butyl (2S)-2-(methylsulfonylmethyl)azetidine-1-carboxylate (6.20 g, 24.8 mmol, 98% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.58 - 4.48 (m, 1H), 3.84 - 3.72 (m, 2H), 3.64 - 3.52 (m, 2H), 3.00 (s, 3H), 2.44 - 2.32 (m, 1H), 2.19 (tdd, J = 6.8, 8.8, 11.2 Hz, 1H), 1.38 (s, 9H)

[01540] Step 5. To a solution of tert-butyl (2S)-2-(methylsulfonylmethyl)azetidine-1-carboxylate (2.00 g, 8.02 mmol, 1 *eq*) in DCM (10 mL) was added HCl/dioxane (4 M, 2 mL, 1 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was concentrated to give (2S)-2-(methylsulfonylmethyl)azetidine, I-39 (1.50 g, crude) as a white solid.

[01541] Ex. 139 was prepared in a manner similar to those described in General Method L and in the synthesis of Ex. 131 using I-139 in the appropriate step.

[01542] Preparation of (10*S*,17*E*)-8,10,14,16-tetramethyl-12-(oxetan-3-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 140)



I-140 Ex. 140

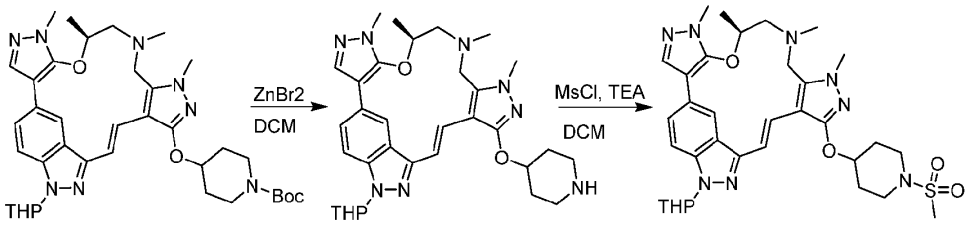
[01543] (8S,17E)-5,8,13,15-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19, 22(26),23-nonaene, I-140 was prepared via Method I and H using starting materials: G-1-1, H-4-1, and I-2-1 in Ex. 40, 41, and 48, respectively.

[01544] Ex. 140 was prepared in a manner like those described in General Method K using oxetan-3-one and I-140.

[01545] Ex. 141 was synthesized according to the methods described in General Method P starting with the appropriate alcohol.

[01546] Ex. 142 was prepared from 138-2 and 119-2 in a similar manner to those described in the synthesis of Ex. 114 and General Method M.

[01547] Preparation of (10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 143)



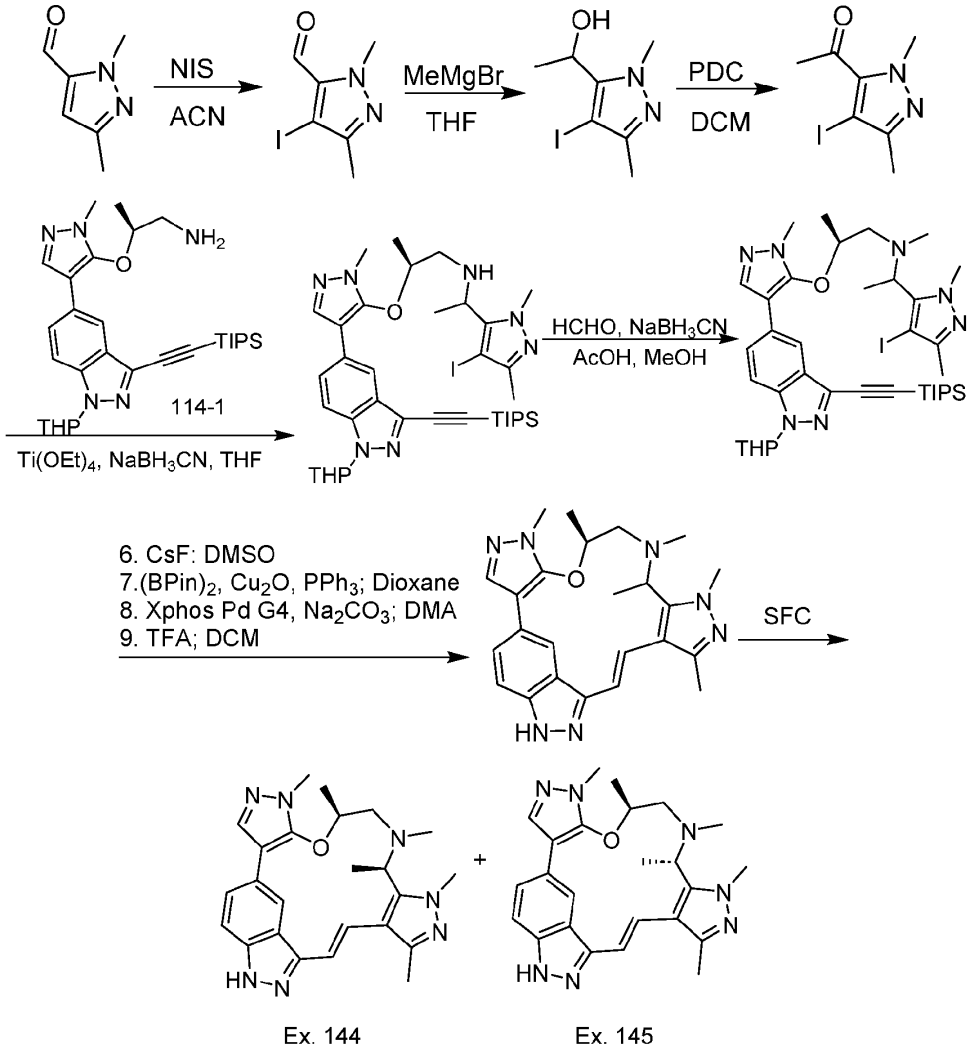
Ex. 143

[01548] Step 1. To a solution of tert-butyl 4-[[(8S,17E)-5,8,10,13-tetramethyl-21 -tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]oxy]piperidine-1-carboxylate from Ex. 136 (200 mg, 0.291 mmol, 1 *eq*) in DCM (2 mL) was added $ZnBr_2$ (197 mg, 0.874 mmol, 3 *eq*). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was poured into water (20 mL), the aqueous phase was extracted with DCM (5 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2,DCM: MeOH= 10:1) to give (8S,17E)-5,8,10,13-tetramethyl-15-(4-piperidyloxy)-21-tetrahydropyran-2-yl-7- oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (85.0 mg, 0.145 mmol, 50% yield) as a yellow solid. LCMS: *m/z* 587.4 (M+1)

[01549] Step 2. To a solution of (8S,17E)-5,8,10,13-tetramethyl-15-(4-piperidyloxy)-21- tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (40.0 mg, 0.068 mmol, 1 *eq*) in DCM (1 mL) was added TEA (10.4 mg, 0.102 mmol, 1.5 *eq*) and methylsulfonyl methanesulfonate (14.3 mg, 0.082 mmol, 1.2 *eq*).The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was concentrated. The residue was purified by prep-HPLC (column: Welch Ultimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];B%: 15%-45%, 10min) to give Ex. 143 (2.17 mg, 0.004 mmol, 5 % yield) as a white solid.

[01550] Preparation of (10*S*,13*R*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecine (Ex. 144) and (10*S*,13*S*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 145)



[01551] Step 1. To a solution of 2,5-dimethylpyrazole-3-carbaldehyde (1 g, 8.06 mmol, 1 *eq*) in ACN (10 mL) was added NIS (2.72 g, 12.08 mmol, 1.5 *eq*).The mixture was stirred at 80 °C for 12 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to 5:1) to give 4-iodo-2,5-dimethyl-pyrazole-3-carbaldehyde (1.62 g, 6.48 mmol, 80% yield) as a brown solid. 1H NMR (400 MHz, DMSO-d_6) δ = 9.71 (s, 1H), 4.03 (s, 3H), 2.18 (s, 3H)

[01552] Step 2 was performed in similar manner to those described in Ex. I-135

[01553] Step 3. To a solution of 1-(4-iodo-2,5-dimethyl-pyrazol-3-yl)ethanol (950 mg, 3.57 mmol, 1 *eq*) in DCM (30 mL) was added PDC (2.01 g, 5.36 mmol, 1.5 *eq*) under N_2 .The mixture was stirred at 40 °C for 12 h. On completion, the mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1 to 3:1) to give 1-(4-iodo-2,5-dimethyl-pyrazol-3-yl)ethanone (820 mg, 3.11 mmol, 87% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ = 3.95 (s, 3H), 2.68 (s, 3H), 2.18 (s, 3H)

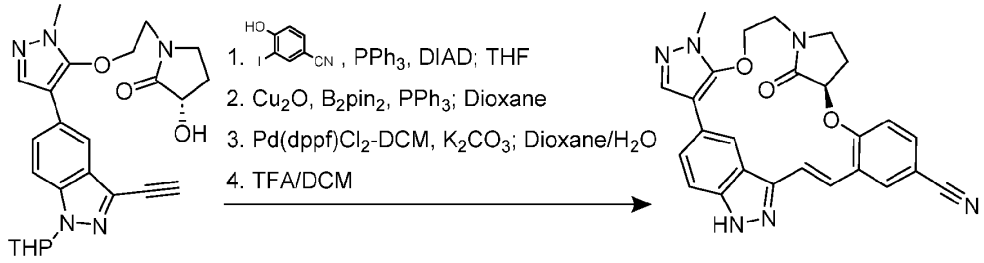
[01554] Step 4. To a solution of (2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropan-1-amine (430 mg, 0.802 mmol, 1 *eq*) in THF (6 mL) was added 1-(4-iodo-2,5-dimethyl-pyrazol-3-yl)ethanone (423 mg, 1.61 mmol, 2 *eq*) and $Ti(OEt)_4$ (732 mg, 3.21 mmol, 4 *eq*), the resulting mixture was stirred at 70 °C for 4 h, then $NaBH_3CN$ (302 mg, 4.82 mmol, 6 *eq*) was added. The mixture was stirred at 25 °C for 12 h. On completion, the reaction mixture was partitioned between ethyl acetate (10 mL × 3) and water (10 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=2:1 to 2:1) to give (2S)-N-[1-(4-iodo-2,5-dimethyl-pyrazol-3-yl)ethyl]-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (500 mg, crude) as a yellow solid.

[01555] Step 5 was conducted in a manner similar to those described in

[01556] Step 6-9 was conducted in a manner similar to those described in General Method M.

[01557] Step 10. The residue was purified by SFC(column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [Neu-MeOH];B%:35%, isocratic elution mode) to give arbitrarily assigned Ex. 144 (10.5 mg, 0.024 mmol, 52% yield) as a yellow solid and Ex. 145(4.36 mg, 0.010 mmol, 22% yield) as a yellow solid.

[01558] Preparation of (10*R*,16*E*)-3-methyl-25-oxo-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine-14-carbonitrile (Ex. 146).

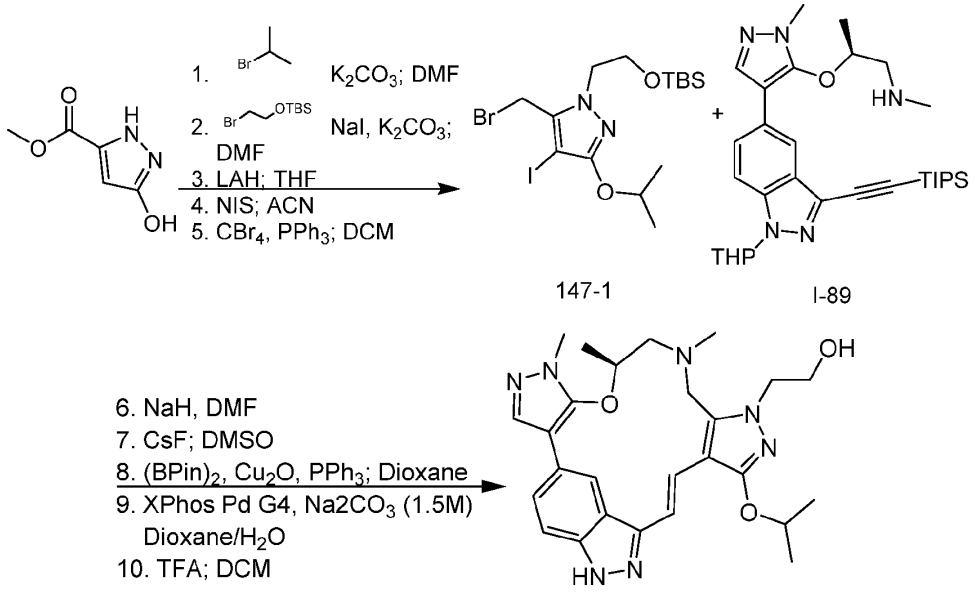


70-1

Ex. 146

[01559] Ex. 146 was prepared in a manner similar to those described in Ex. 131 and General Method L.

[01560] Preparation of 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 147)



147-1

I-89

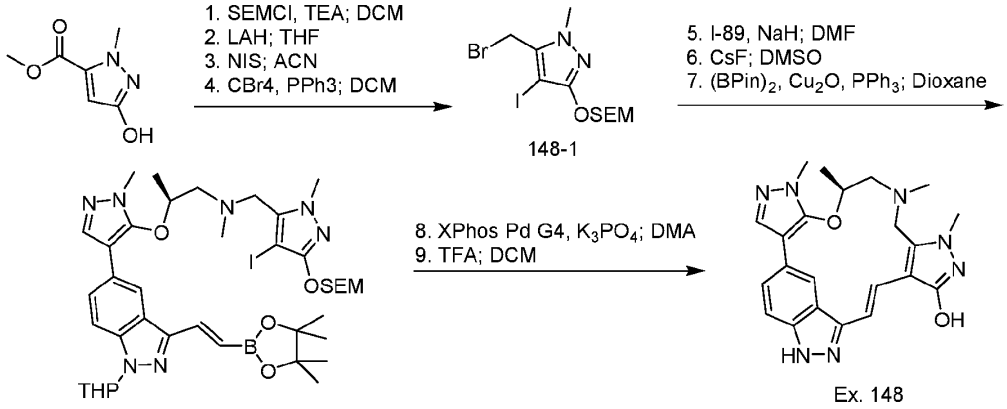
Ex. 147

[01561] Steps 1-5 were conducted in a similar manner to those described in General Method O.

[01562] Steps 6-8 were conducted in a similar manner to those described in General Method H.

[01563] Steps 9-10 were conducted in a similar manner to those described in General Method M to afford Ex. 147

[01564] Preparation of (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (Ex. 148)



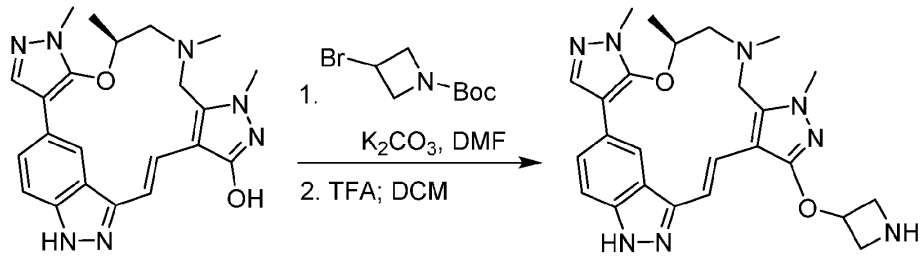
[01565] Step 1. To a solution of methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate (8 g, 51.2 mmol, 1 *eq*) in DCM (100 mL) was added SEM-Cl (25.6 g, 154 mmol, 3 *eq*) and TEA (31.1 g, 307 mmol, 6 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was concentrated 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 methyl 2-methyl-5-(2-trimethylsilylethoxymethoxy)pyrazole-3-carboxylate (6.43 g, 22.5 mmol, 44% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.33 - 6.31 (m, 1H), 5.25 - 5.24 (m, 2H), 4.06 - 4.04 (m, 3H), 3.87 (s, 3H), 3.80 - 3.75 (m, 2H), 1.01 - 0.95 (m, 2H), 0.01 (s, 9H). LCMS: *m/z* 287.0 (M+1)

[01566] Steps 2-4 were conducted in a manner similar to those described in General Method O.

[01567] Steps 5-7 were conducted in a manner similar to those described in General Method H.

[01568] Steps 8-9 were conducted in a manner similar to those described in General Method M to afford Ex. 148.

[01569] Preparation of (10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 149)

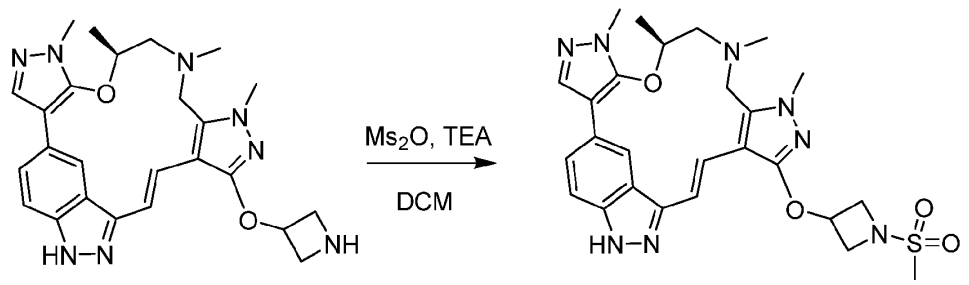


Ex. 148 Ex. 149

[01570] Step 1. To a solution of Ex. 148 (80 mg, 0.191 mmol, 1 *eq*) in DMF (1 mL) was added K_2CO_3 (79.1 mg, 0.572 mmol, 3 *eq*) and tert-butyl 3-bromoazetidine-1-carboxylate (90.1 mg, 0.381 mmol, 2 *eq*). The mixture was stirred at 80 °C for 5 h. On completion, the reaction mixture was filtrated to remove K_2CO_3, and concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=1/0 to 0/1) to give tert-butyl 3-[[(8S,17E)-5,8,10,13-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]oxy]azetidine-1-carboxylate (70 mg, 0.122 mmol, 64% yield) as yellow solid. LCMS: *m/z* 575.3 (M+1)

[01571] Step 2. To a solution of tert-butyl 3-[[(8S,17E)-5,8,10,13-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]oxy]azetidine-1-carboxylate (18 mg, 0.0313 mmol, 1 *eq*) in DCM (1 mL) was added TFA (308 mg, 2.70 mmol, 0.2 mL, 86.2 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC(column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 1%-31%, 10min) to give Ex. 149 (1.23 mg, 0.0023 mmol, 7 % yield, 97% purity, FA) as off-white solid.

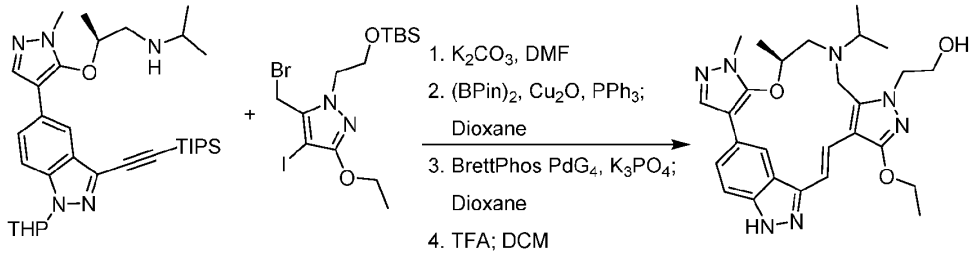
[01572] Preparation of (10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 150)



Ex. 149 Ex. 150

[01573] Step 1. To a solution of Ex. 149 (63 mg, 0.133 mmol, 1 *eq*) in DCM (1 mL) was added TEA (40.3 mg, 0.398 mmol, 55.4 µL, 3 *eq*) and methylsulfonyl methanesulfonate (34.7 mg, 0.199 mmol, 1.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 15%-45%,10min) to give Ex. 150 (10.23 mg, 0.018 mmol, 14 % yield, 98.29% purity) as white solid.

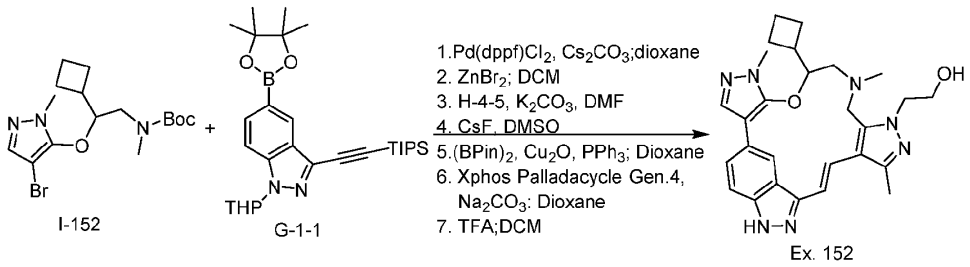
[01574] Preparation of 2-[(10*S*,17*E*)-16-ethoxy-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-o (Ex. 151)



114-2 119-2 Ex. 151

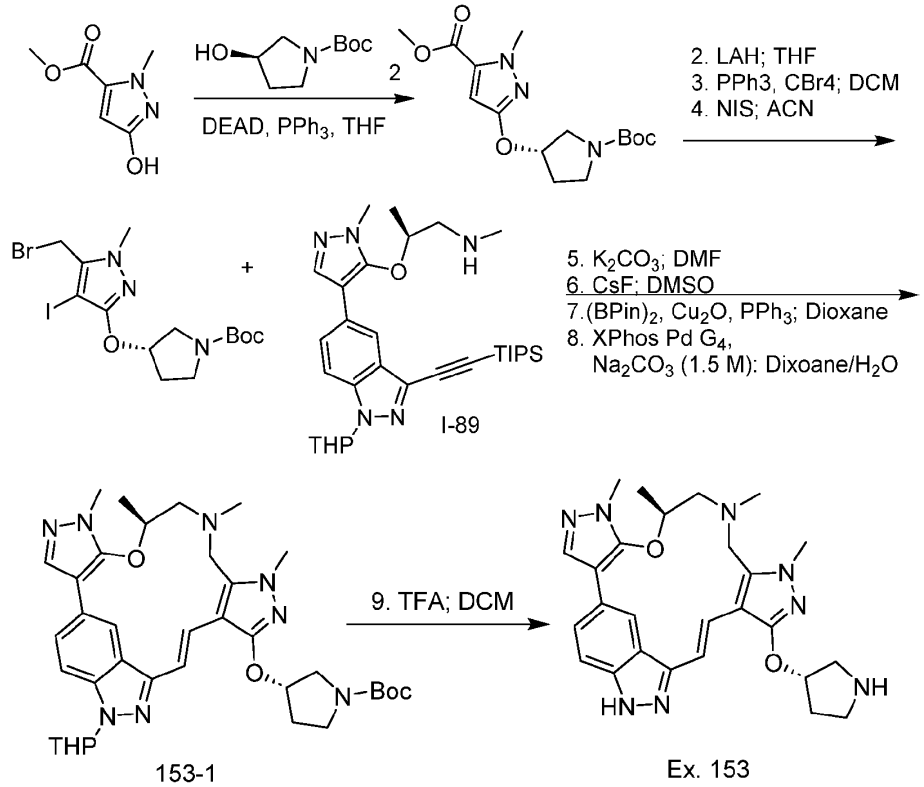
[01575] Ex. 151 was prepared in a manner similar to those described in the synthesis of Ex. 114 and General Method Q with starting materials from intermediates of Ex. 114 and General Method O.

[01576] Preparation of 2-[(17*E*)-10-cyclobutyl-8,12,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 152)



[01577] I-152 (General Method M) and G-1-1 were combined in a manner described in General Method I and General Method M to afford Ex. 152.

[01578] Preparation of (10*S*,17*E*)-8,10,12,14-tetramethyl-16-{[(3*S*)-pyrrolidin-3-yl]oxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 153)



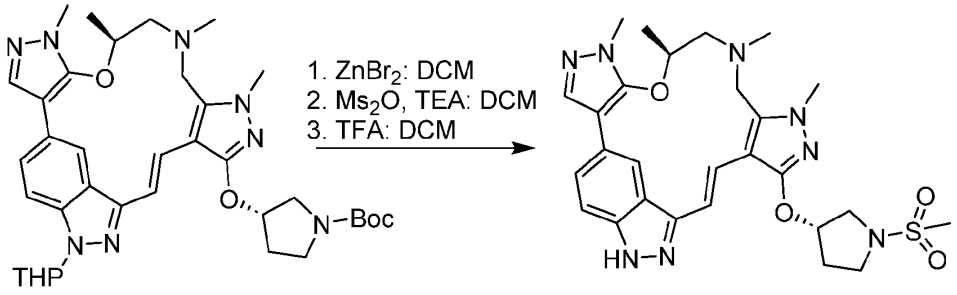
[01579] Step 1. A mixture of methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate (2.5 g, 16.0 mmol, 1.0 *eq*), tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate (6.00 g, 32.0 mmol, 2.0 *eq*), PPh_3 (8.40 g, 32.0 mmol, 2.0 *eq*) in THF (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 0.5 h under N_2 atmosphere. Then was added DIAD (6.48 g, 32.0 mmol, 6.23 mL, 2.0 *eq*) at 0 °C. The mixture was stirred

at 25 °C for 16 hr 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 2:1) to give methyl 5-[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy-2-methyl-pyrazole-3-carboxylate (4.42 g, 13.1 mmol, 82% yield, 97% purity) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.15 (s, 1H), 5.11 - 5.01 (m, 1H), 4.02 (s, 3H), 3.85 (s, 3H), 3.77 - 3.71 (m, 1H), 3.64 - 3.53 (m, 2H), 3.50 - 3.45 (m, 1H), 2.24 - 2.01 (m, 2H), 1.47 - 1.44 (m, 9H). LCMS: *m/z* 270.1 (M-56+1)

[01580] Steps 2 to 4 were conducted in a manner similar to those described in General Method O.

[01581] Steps 5-8 were conducted in a manner similar to those described in General Method M.

[01582] Preparation of (10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 154)



153-1 Ex. 154

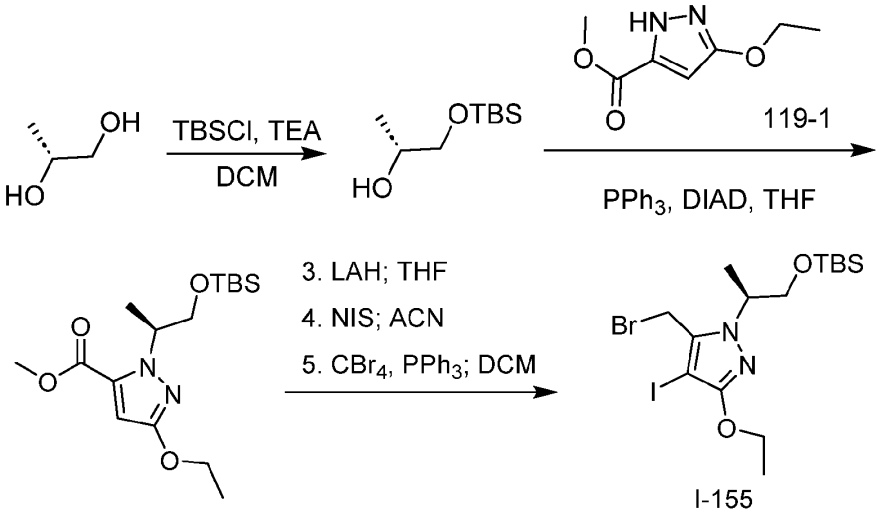
[01583] Step 1. To a solution of tert-butyl (3S)-3-[[(8S,17E)-5,8,10,13-tetramethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaen-15-yl]oxy]pyrrolidine-1-carboxylate (40 mg, 0.059 mmol, 1.0 *eq*) in DCM (2 mL) was added $ZnBr_2$ (67 mg, 0.297 mmol, 5.0 *eq*). The mixture was stirred at 25 °C for 16 hr. On completion the mixture was diluted with water (15 mL) and extracted with ethyl acetate (10 mL × 3), the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give (8S,17E)-5,8,10,13-tetramethyl-15-[(3S)-pyrrolidin-3-yl]oxy-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaene (30 mg, crude) as a colorless oil. LCMS: *m/z* 573.4 (M+1)

[01584] Step 2. To a solution of (8S,17E)-5,8,10,13-tetramethyl-15-[(3S)-pyrrolidin-3-yl]oxy-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-

heptazapentacycl[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaene (30 mg, 0.0523 mmol, 1.0 *eq*) in DCM (1 mL) was added TEA (7.95 mg, 0.079 mmol, 10.9 uL, 1.5 *eq*) and methylsulfonyl methanesulfonate (10.9 mg, 0.063 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 hr. The mixture was quenched with water (15 mL) and extracted with ethyl acetate (5 mL × 3), the combined organic phase was washed with brine dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give (8S,17E)-5,8,10,13-tetramethyl-15-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaene (30 mg, crude) as a colorless oil. LCMS: *m/z* 651.3 (M+1)

[01585] Step 3. To a solution of (8S,17E)-5,8,10,13-tetramethyl-15-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaene (30 mg, 0.0461 mmol, 1.0 *eq*) in DCM (2 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 292 *eq*). The mixture was stirred at 25 °C for 2 hr. On completion the mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];B%: 12%-42%, 10min) to give Ex. 154 (120 μg, 2.01e-4 mmol, 4.36e-1% yield, 95% purity) as a off-white gum.

[01586] Preparation of [(2S)-2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl]propoxy]-tert-butyl-dimethyl-silane, I-155.



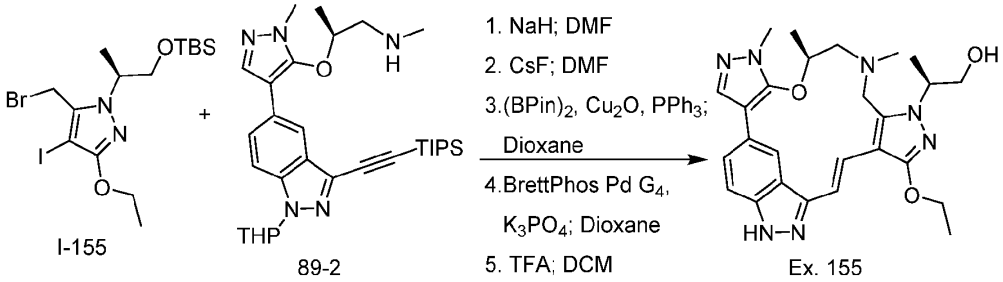
[01587] Step 1. To a solution of (2R)-propane-1,2-diol (25 g, 329 mmol, 1 *eq*), TEA (99.7 g, 986 mmol, 3 *eq*) in DCM (250 mL) was added TBSCl (52.0 g, 345 mmol, 1.05 *eq*) at

0 °C. The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=1:0 to 95:5) to give (2R)-1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (42 g, 220 mmol, 67 % yield) as yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ = 3.85 - 3.76 (m, 1H), 3.58 (dd, *J* = 3.6, 10.0 Hz, 1H), 3.34 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.53 (d, *J* = 3.2 Hz, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.93 - 0.85 (m, 9H), 0.10 - 0.02 (m, 5H).

[01588] Step 2. A mixture of methyl 3-ethoxy-1H-pyrazole-5-carboxylate (3 g, 17.6 mmol, 1 eq), (2R)-1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (7.38 g, 38.8 mmol, 2.2 *eq*), PPh_3 (10.2 g, 38.8 mmol, 2.2 *eq*) in THF (30 mL) was degassed and purged with N_2 for 3 times at 0 °C and stirred for 0.5 h, then DIAD (7.84 g, 38.8 mmol, 7.54 mL, 2.2 *eq*) was added at 0 °C, then the mixture was stirred at 25 °C for 1.5 h under N_2 atmosphere. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with EA (50 mL * 3), 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 methyl 2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-ethoxy-pyrazole-3-carboxylate (3.2 g, 9.34 mmol, 53% yield) as yellow oil. LCMS: *m/z* 343.4 (M+1)

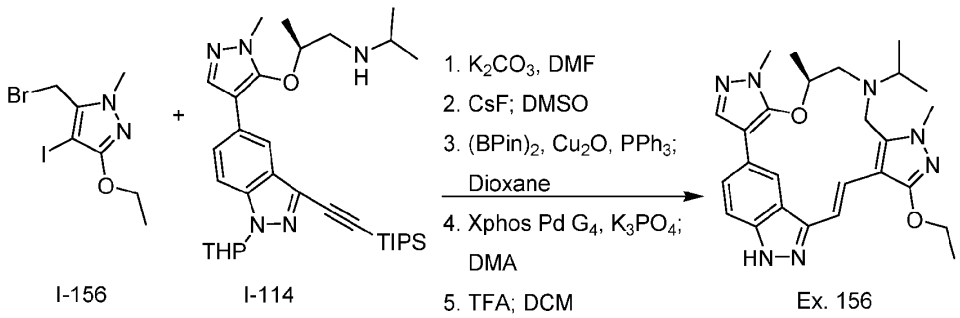
[01589] Steps 3-5 were conducted in a manner similar to those described in the synthesis of General Method O to afford [(2S)-2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl]propoxy]-tert-butyl-dimethyl-silane, I-155. LCMS: *m/z* 503.0 (M+1)

[01590] Preparation of (2*S*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Ex. 155)



[01591] Ex. 155 was prepared with I-155 and 89-2 in a manner similar to those described in General Method H and General Method Q.

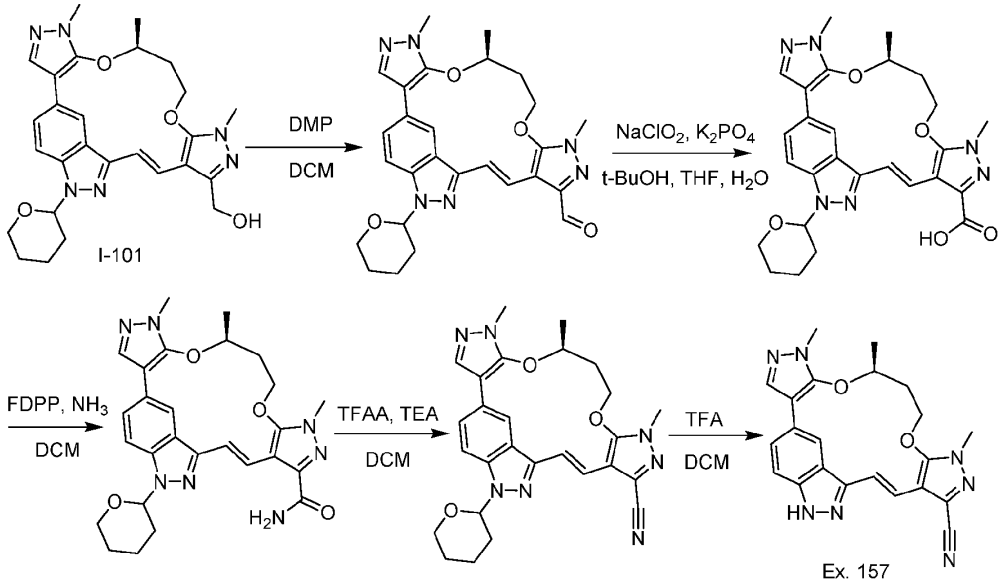
[01592] Preparation of (10*S*,17*E*)-16-ethoxy-8,10,14-trimethyl-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 156)



[01593] Methyl 5-hydroxy-2-methyl-pyrazole-3-carboxylate was converted to I-156 in a manner similar to those described in General Method O. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.40 (s, 2H), 4.28 - 4.20 (m, 2H), 3.80 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 346.8 (M+1)

[01594] I-156 and 114-2 were combined in a manner similar to those described in General Method M to afford Ex. 156.

[01595] Preparation of (10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile (Ex. 157)



[01596] Step 1. To [(13E,25S)-25,30,31-trimethyl-32-tetrahydropyran-2-yl-34,36-dioxa-27,28,29,30,31,32-hexazapentacyclohexacosa-

3,5(16),6(27),13,17,19(23),20(24),21(28),22(29)-nonaen-22-yl]methanol (19.87 mg, 0.039 mmol) from Ex. 101 in DCM (1 mL) was added Dess-Martin Periodinane (20 mg, 0.047 mmol) at -78 °C, the mixture was allowed to stir and warm to ambient over 18 hr. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 3 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) provided (13E,25S)-25,30,31-trimethyl-32-tetrahydropyran-2-yl-34,36-dioxa-27,28,29,30,31,32-hexazapentacyclohexacosa-3,5(16),6(27),13,17,19(23),20(24),21(28),22(29)-nonaene-22-carbaldehyde (12.53 mg, 0.025 mmol, 63% yield). LCMS: *m/z* 503.1 (M+1)

[01597] Step 2. To a solution of (13E,25S)-25,30,31-trimethyl-32-tetrahydropyran-2-yl-34,36-dioxa-27,28,29,30,31,32-hexazapentacyclohexacosa-3,5(16),6(27),13,17,19(23),20(24),21(28),22(29)-nonaene-22-carbaldehyde (9.2 mg, 0.018 mmol) in tert-butanol (500 µL) was added a solution of 2-methylbut-2-ene (9.63 mg, 0.137 mmol, 15 µL) in THF (500 µL), followed by sodium chlorite (8.9 mg, 0.099 mmol) and Potassium phosphate dibasic (38 mg, 0.220 mmol) in Water (500 µL). The mixture was stirred at ambient temperature for 18 hr. Reaction was diluted with DCM and 2 M HCl (4 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 4 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-10% methanol in DCM with 0.2 mL AcOH added) provided (13E,24S)-24,30,31-trimethyl-32-tetrahydropyran-2-yl-35,37-dioxa-27,28,29,30,31,32-hexazapentacyclohexacosa-3,5(15),6(27),13,16,18(22),19(23),20(28),21(29)-nonaene-21-carboxylic acid (9.49 mg, 0.018 mmol, 100% yield) . Taken forward without further purification assuming quantitative yield. LCMS: *m/z* 519.0 (M+1)

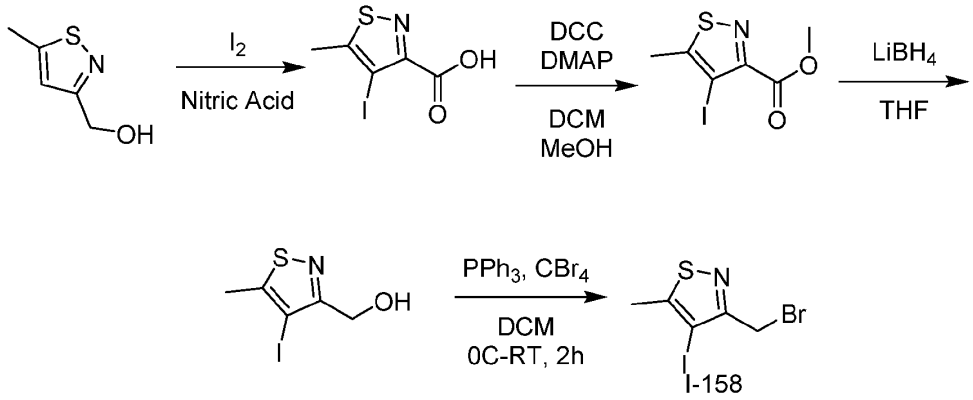
[01598] Step 3. To (13E,24S)-24,30,31-trimethyl-32-tetrahydropyran-2-yl-35,37-dioxa-27,28,29,30,31,32-hexazapentacyclohexacosa-3,5(15),6(27),13,16,18(22),19(23),20(28),21(29)-nonaene-21-carboxylic acid (9.2 mg, 0.018 mmol) in DCM (1 mL) was added NH_3 (0.4 M, 887.07 µL) and followed by FDPP (8.18 mg, 0.021 mmol) . Stir at 22 °C for 18 hr. Reaction was quenched with 2M Na_2CO_3 (aq) (1 mL) and the mixture was stirred vigorously. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 3 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) provided (13E,24S)-24,31,32-trimethyl-33-tetrahydropyran-2-yl-35,37-dioxa-

28,29,30,31,32,33-hexazapentacyclohexacosa-3,5(15),6(28),13,16,18(22),19(23),20(29),21(30)-nonaene-21-carboxamide (1.59 mg, 0.003 mmol, 17 % yield). LCMS: *m/z* 518.3 (M+1)

[01599] Step 4. To (13E,24S)-24,31,32-trimethyl-33-tetrahydropyran-2-yl-35,37-dioxa-28,29,30,31,32,33-hexazapentacyclohexacosa-3,5(15),6(28),13,16,18(22),19(23),20(29),21(30)-nonaene-21-carboxamide (1.59 mg, 0.003 mmol) in DCM (200 µL) at 0 °C was added TEA (3.73 mg, 0.037 mmol, 5 µL) and TFAA (3.87 mg, 0.018 mmol, 2.6 µL) and stirred for 2 hr, then at RT for a half hour. Quenched with water (10 mL) and extracted with DCM (3 X 10mL). Flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) provided (13E,25S)-25,31,32-trimethyl-33-tetrahydropyran-2-yl-34,36-dioxa-28,29,30,31,32,33-hexazapentacyclohexacosa-3,5(16),6(28),13,17,19(23),20(24),21(29),22(30)-nonaene-22-carbonitrile (810.00 µg, 0.002 mmol, 53% yield). LCMS: *m/z* 500.2 (M+1)

[01600] Step 5. To (13E,25S)-25,31,32-trimethyl-33-tetrahydropyran-2-yl-34,36-dioxa-28,29,30,31,32,33-hexazapentacyclohexacosa-3,5(16),6(28),13,17,19(23),20(24),21(29),22(30)-nonaene-22-carbonitrile (810.00 µg, 0.002 mmol) in DCM (1 mL) was added TFA (745.00 mg, 6.53 mmol, 0.5 mL) . Stir at 22 °C for 3 hr. Volatiles removed under reduced pressure. Flash column chromatography (automated system, 12g silica, 0-5% MeOH in DCM) provided Ex. 157 (0.39 mg, 8.24e-4 mmol, 51 % yield, 87.8% purity).

[01601] Preparation of 3-(bromomethyl)-4-iodo-5-methyl-isothiazole, I-158



[01602] Step 1. To (5-methylisothiazol-3-yl)methanol (300 mg, 2.32 mmol) in concentrated Nitric Acid (209.04 mg, 2.32 mmol, 5 mL, 70% purity) was added Iodine (648 mg, 2.55 mmol). Mixture was stirred for 45 min at 80 °C. Cooled to 0 °C and slowly quenched with aq. sodium bisulfite solution (1M, 10 mL). Reaction was diluted

with DCM and water (20 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Salts were filtered and filtrate was concentrated to approximately 5-10 mL, hexanes (20mL) was added and solids precipitated. Cooled for several hours and solids filtered and washed with hexanes. Dried under high vacuum to give 4-iodo-5-methyl-isothiazole-3-carboxylic acid (465 mg, 1.73 mmol, 74% yield). LCMS: *m/z* 269.8 (M+1)

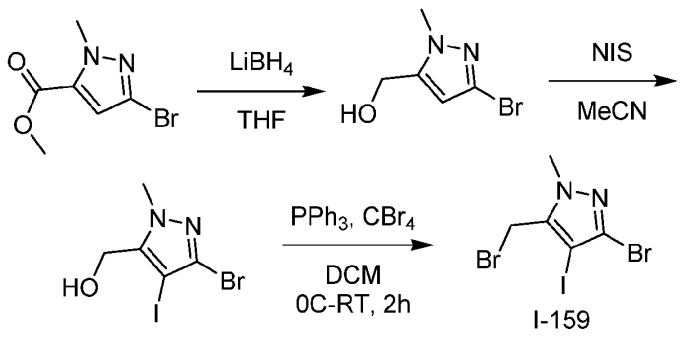
[01603] Step 2. To 4-iodo-5-methyl-isothiazole-3-carboxylic acid (465 mg, 1.73 mmol) in DCM (2.5 mL) and methanol (2.5 mL) was added DCC (428 mg, 2.1 mmol), followed by DMAP (21 mg, 0.173 mmol). Stirred at 22 °C for 20 hr. Reaction was diluted with DCM and water (20 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-40% EA in Hexanes) provided methyl 4-iodo-5-methyl-isothiazole-3-carboxylate (347 mg, 1.23 mmol, 71% yield).

[01604] To methyl 4-iodo-5-methyl-isothiazole-3-carboxylate (347 mg, 1.23 mmol) in THF (5.86 mL) was added lithium borohydride (53.40 mg, 2.45 mmol). Stirred as temperature increased over 1 hr. Reaction was cooled and quenched with water (5 mL) carefully. Reaction was diluted with DCM and water (30 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 15 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-60% EA in Hexanes) provided (4-iodo-5-methyl-isothiazol-3-yl)methanol (222 mg, 0.870 mmol, 71 % yield). LCMS: *m/z* 255.8 (M+1)

[01605] Step 4. To (4-iodo-5-methyl-isothiazol-3-yl)methanol (222 mg, 0.870 mmol) in DCM (5 mL) was added triphenylphosphine (410.89 mg, 1.57 mmol). Cooled to 0 °C and carbon tetrabromide (346.4 mg, 1.04 mmol) was added. Stirred for 2 hr as temperature increases to ambient. Quenched with water and worked up with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-40% EA in Hexanes) provided 3-(bromomethyl)-4-iodo-5-methyl-isothiazole, I-158 (181.54 mg, 0.571 mmol, 66 % yield). LCMS: *m/z* 317.6/319.3 (M/M+2)

[01606] Ex. 158 was prepared from I-158 and 89-2 in a manner similar to those described in General Method P and General Method M.

[01607] Preparation of -bromo-5-(bromomethyl)-4-iodo-1-methyl-pyrazole, I-159

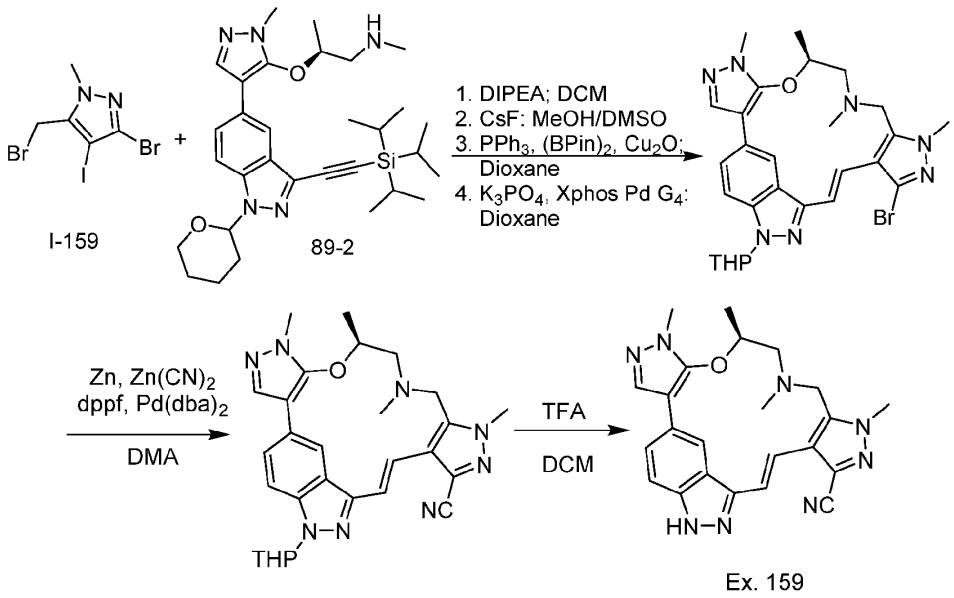


[01608] Step 1. Step 1. To methyl 5-bromo-2-methyl-pyrazole-3-carboxylate (500 mg, 2.28 mmol) in THF (11.41 mL) at 0 °C was added, $LiBH_4$ (74.6 mg, 3.42 mmol). Stirred as temperature increase to RT over 18 hr. An additional 45 mg of $LiBH_4$ added and the mixture was stirred at ambient temperature for additional 2 hr. Reaction was quenched with water at 0 °C and the reaction was worked up with DCM and water (30 mL). The aqueous layer was extracted with DCM (2x 20mL). The combined organic layer was washed with brine and dried over sodium sulfate. The filtrate was concentrated and residue was crystallized with EA (10mL) and Hexanes (30 mL) to afford (5-bromo-2-methyl-pyrazol-3-yl)methanol (333 mg, 1.74 mmol, 76 % yield). LCMS: *m/z* 190.9/192.9 (M/M+2)

[01609] Step 2. To (5-bromo-2-methyl-pyrazol-3-yl)methanol (333 mg, 1.74 mmol) in acetonitrile (8.7 mL) was added NIS (470.6 mg, 2.09 mmol). Stirred at 22 °C for 18 hr and then quenched with water (5 mL) and worked up with DCM and water (30 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Filtrate was concentrated after filtration. Residue was crystallized with EA and Hexanes to afford (5-bromo-4-iodo-2-methyl-pyrazol-3-yl)methanol (488 mg, 1.54 mmol, 88 % yield) as a beige solid. LCMS: *m/z* 316.7/318.7 (M/M+2)

[01610] Step 3. To (5-bromo-4-iodo-2-methyl-pyrazol-3-yl)methanol (100 mg, 0.316 mmol) in DCM (2 mL) was added triphenylphosphine (149 mg, 0.568 mmol). Cooled to 0 °C and carbon tetrabromide (125.6 mg, 0.379 mmol) was added. Stirred as temperature increases to ambient for 1.5h. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 3 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-30% EA in Hexanes) provided -bromo-5-(bromomethyl)-4-iodo-1-methyl-pyrazole, I-159 (68.24 mg, 0.180 mmol, 57 % yield). LCMS: *m/z* 377.7 (M-1)

[01611] Preparation of (10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile (Ex. 159)



[01612] Steps 1-4 were prepared from I-159 and 89-2 in a manner similar to those described in General Method P and General Method M.

[01613] Step 5.To (14E,25S)-23-bromo-25,30,31,33-tetramethyl-32-tetrahydropyran-2-yl-35-oxa-27,28,29,30,31,32,33-heptazapentacyclohexacosa-4,6(16),7(27),14,17,19(24),20,22(28),23(29)-nonaene (9.76 mg, 0.017 mmol) in DMA (1 mL) was added zinc (2.3 mg, 0.035 mmol) and zinc cyanide (22.3 mg, 0.190 mmol), argon was bubbled through as dppf (5.73 mg, 0.010 mmol) was added followed by Pd(dba)2 (2.97 mg, 0.0052 mmol) . Stir under argon for about 5 minutes. The vessel was closed and heated to 120 °C and stirred for 6 hr. Reaction was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography twice(automated system, 12g silica, 0-10% MeOH in DCM, then 0-10% MeOH/DCM (1/3) in EA) provided (14E,26S)-26,32,33,35-tetramethyl-34-tetrahydropyran-2-yl-37-oxa-29,30,31,32,33,34,35-heptazapentacyclohexacosa-4,6(17),7(29),14,18,20(25),21,23(30),24(31)-nonaene-24-carbonitrile (3.85 mg, 0.008 mmol, 44 % yield). LCMS: *m/z* 513.0 (M+1)

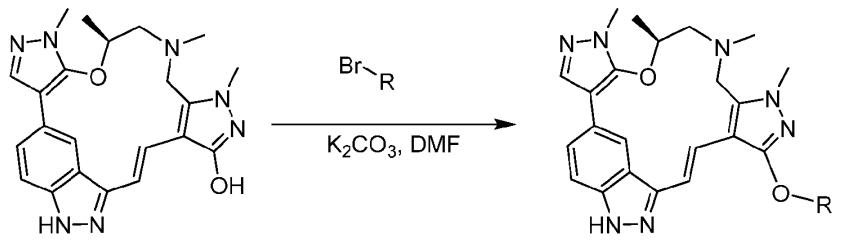
[01614] Step 6. To (14E,26S)-26,32,33,35-tetramethyl-34-tetrahydropyran-2-yl-37-oxa-29,30,31,32,33,34,35-heptazapentacyclohexacosa-

4,6(17),7(29),14,18,20(25),21,23(30),24(31)-nonaene-24-carbonitrile (3.85 mg, 0.008 mmol) in dcm (1 mL) was added TFA (6.53 mmol, 0.5 mL) . Stir at 22 °C for 18 hr. Volatiles removed under reduced pressure. Sample re-diluted with DCM and TEA (200uL) added. Flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) provided Ex. 159 (1.85 mg, 0.004 mmol, 53 % yield, 92.77% purity).

[01615] Ex. 160 was prepared with 122-1 and I-156 in a similarly to Ex. 122.

[01616] Ex. 161 was prepared in a manner similar to those described in General Method K using (1-ethoxycyclopropoxy)-trimethyl-silane and I-140.

[01617] General Method R. Preparation of (10*S*,17*E*)-8,10,12,14-tetramethyl-16-(2,2,2-trifluoroethoxy)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex.162) and {[(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (Ex. 163)



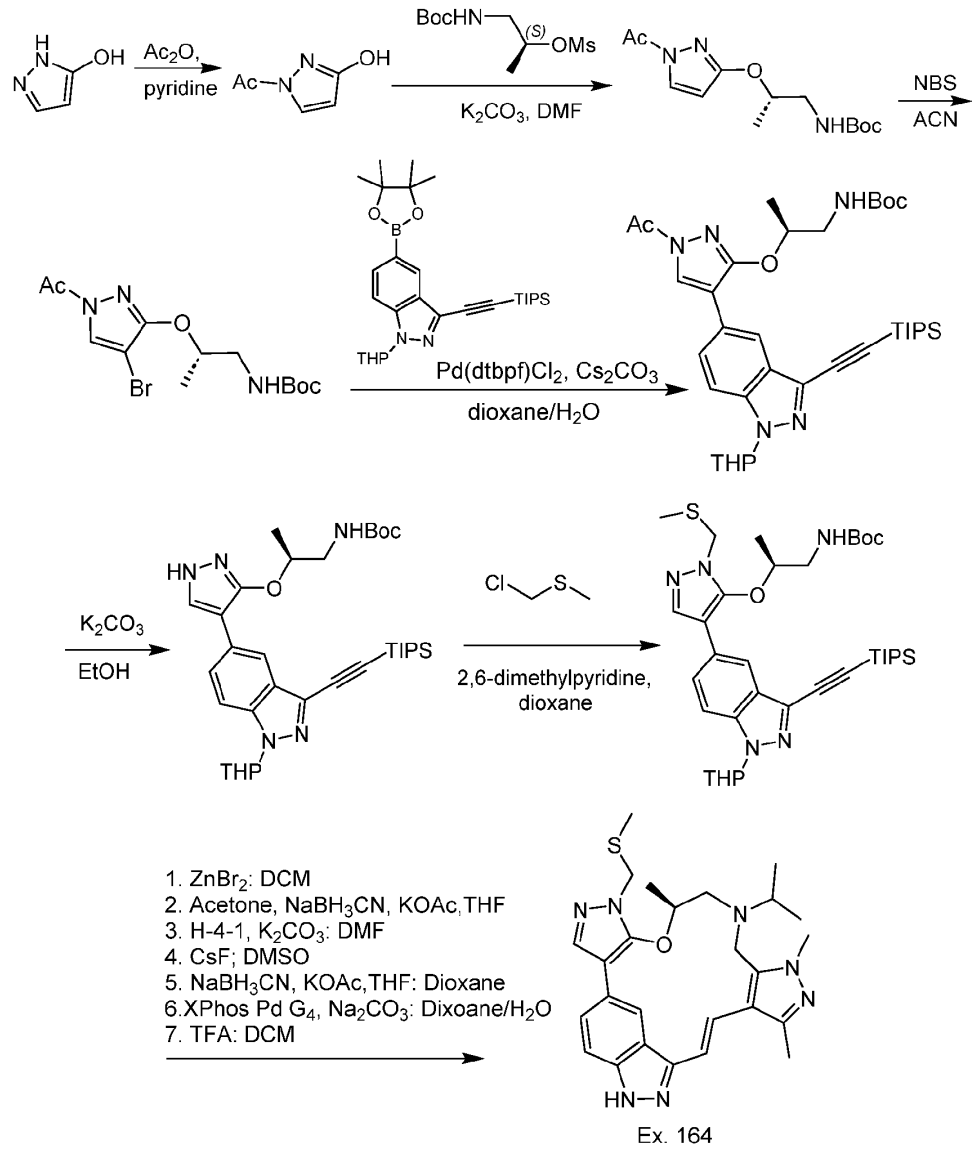
Ex. 148

Ex. 162, R= CH_2CF_3
Ex. 163, R=CH_2CN

[01618] Ex. 148 was converted to Ex. 162 and 163 in the same fashion using the corresponding bromide.

[01619] Step 1. To a solution of (8S,17E)-5,8,10,13-tetramethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-ol (20 mg, 0.048 mmol, 1 *eq*) in DMF (0.5 mL) was added 2-bromo-1,1,1-trifluoro-ethane (15.5 mg,0.095 mmol, 2 *eq*) and K_2CO_3 (19.8 mg, 0.143 mmol, 3 *eq*). The mixture was stirred at 80 °C for 3 h. On completion, the mixture was filtrated to remove K_2CO_3. The solvent was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 28%-58%,10min) to give Ex. 162 (3.58 mg, 0.007 mmol, 13.71% yield, FA) as yellow solid.

[01620] Preparation of (10*S*,17*E*)-10,14,16-trimethyl-8-[(methylsulfanyl)methyl]-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 164)



Ex. 164

[01621] Step 1. The mixture of 1H-pyrazol-5-ol (10.0 g, 118 mmol, 1.00 *eq*) in Py (100 mL) was stirred at 95 °C for 0.5 h, then acetyl acetate (12.1 g, 118 mmol, 11.1 mL, 1.00 *eq*) was dissolve in Py (30.0 mL) was added in the reaction mixture., the mixture was stirred at 95 °C for 2.5 h. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE (100 mL) at 30 °C for 10 min to give 1-(3-hydroxypyrazol-1-yl)ethanone (14.8 g, 114 mmol, 96% yield, 97% purity) as a light yellow solid. LCMS: *m/z* 149.1(M+23)

[01622] Step 2. To a mixture of 1-(3-hydroxypyrazol-1-yl)ethanone (10.0 g, 79.3 mmol, 1.00 *eq*) and [(1S)-2-(tert-butoxycarbonylamino)-1-methyl-ethyl] methanesulfonate

(22.1 g, 87.2 mmol, 1.10 *eq*) in DMF (200 mL) was added K_2CO_3 (32.9 g, 238 mmol, 3.00 *eq*). The mixture was stirred at 80 °C for 16 h. On completion, the reaction mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/ Petroleum ether gradient @100 mL/min) to give tert-butyl *N*-[(2S)-2-(1-acety lpyrazol-3-yl) oxypropyl] carbamate (49.0 g, 77.8 mmol, 98% yield, 45% purity) as a light yellow oil. LCMS: *m/z* 306.1 (M+23)

[01623] Step 3. To a solution of tert-butyl *N*-[(2S)-2-(1-acetylpyrazol-3-yl)oxypropyl]carbamate (25.0 g, 88.2 mmol, 1.00 *eq*) in ACN (150 mL) was added NBS (7.85 g, 44.1 mmol, 0.50 *eq*) at 0 °C. Then the mixture was stirred at 0 °C for 1 h. On completion, the mixture was quenched by Na_2SO_3 (100 mL) and extracted with EtOAc (40 mL*3). The combined organic layer was washed with brine (100 mL*2), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum to give crude. The residue was purified by combi flash (100 g silica gel column, EtOAc in PE from 0% to 100%) to give tert-butyl N-[(2S)-2-(1-acetyl-4-bromo-pyrazol-3-yl)oxypropyl] carbamate (5.70 g, 15.7 mmol, 18% yield) as brown oil. LCMS: *m/z* 385.9 (M+23)

[01624] Step 4 was conducted in a manner similar to those described in General Method I with G-1-1. LCMS: *m/z* 664.5 (M+1)

[01625] Step 5. To a solution of tert-butyl *N*-[(2S)-2-[1-acetyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5- yl] pyrazol-3-yl]oxypropyl]carbamate (2.40 g, 3.61 mmol, 1.00 *eq*) in EtOH (1 mL) was added K_2CO_3 (1.50 g, 10.8 mmol, 3.00 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was concentrated in vacuum to give a residue. The residue was purified by combi flash (40 g silica gel column, EtOAc in PE from 0% to 100%) to give tert-butyl *N*-[(2S)-2-[[4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]-1H-pyrazol-3- yl] oxy] propyl] carbamate (1.90 g, 3.06 mmol, 85% yield) as brown oil. LCMS: *m/z* 622.5 (M+1)

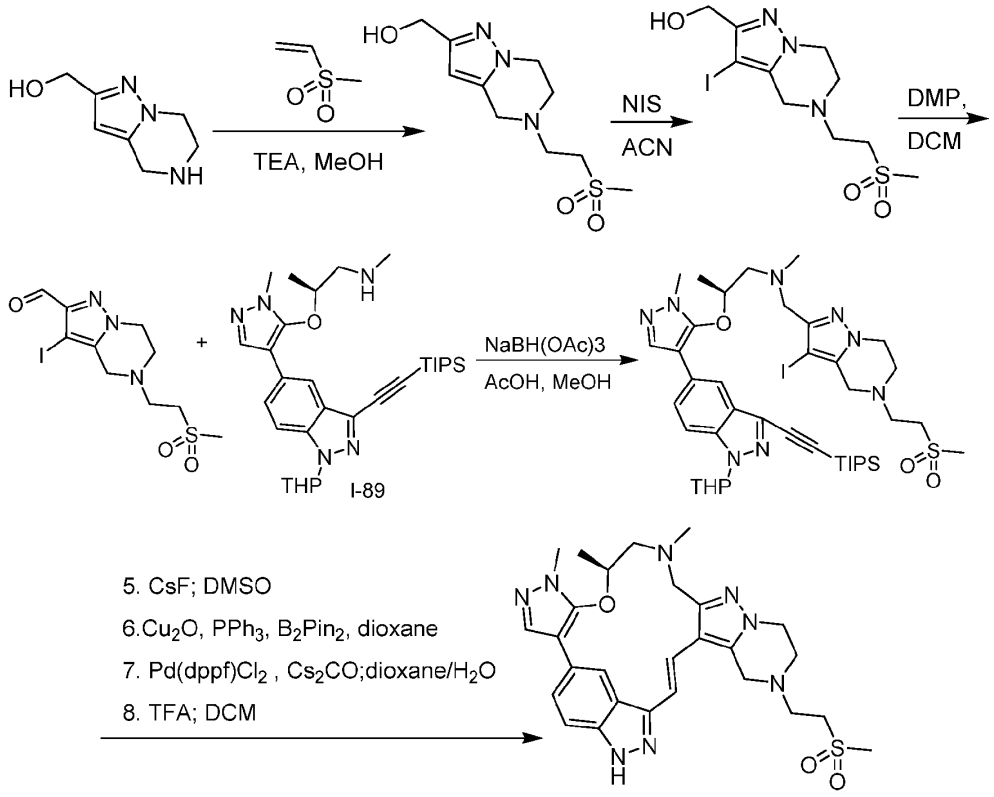
[01626] Step 6. To a solution of tert-butyl *N*-[(2S)-2-[[4-[1-tetrahydropyran-2-yl-3-(2-triisopropy lsilylethynyl)indazol-5-yl]-1Hpyrazol-3-yl]oxy]propyl]carbamate (3.80 g, 6.11 mmol, 1.00 *eq*) and chloro(methylsulfanyl)methane (2.95 g, 30.6 mmol, 2.57 mL, 5.00 *eq*) in dioxane (40 mL) was added 2,6-dimethylpyridine (1.31 g, 12.2 mmol, 1.42 mL, 2.00 *eq*). The mixture was stirred at 110 °C for 4 h. On completion, the mixture was concentrated in vacuum to give crude. The residue was purified by combi flash (40 g silica gel column, EtOAc in PE from 0% to 100%) to give tert-butyl *N*-[(2S)-2-[2-(methylsulfany lmethyl) -4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5- yl] pyrazol-3-yl]oxypropyl]carbamate (2.10 g, 3.08 mmol, 50% yield) as brown oil. ^{1}H NMR (400 MHz,

DMSO-d_6) δ = 7.96 - 7.89 (m, 1H), 7.87 - 7.80 (m, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.13 - 7.01 (m, 1H),6.02 - 5.91 (m, 1H), 5.30 - 5.18 (m, 2H), 4.29 - 4.18 (m, 1H), 3.89 - 3.79 (m, 1H), 3.29 - 3.14 (m, 2H), 2.66 - 2.56 (m, 3H), 2.52- 2.39 (m, 1H), 1.92 - 1.75 (m, 1H), 1.73 - 1.62 (m, 2H), 1.24 - 1.21 (m, 13H), 1.20 - 1.11 (m, 21H). LCMS: *m/z* 682.5 (M+1)

[01627] tert-butyl *N*-[(2S)-2-[2-(methylsulfany lmethyl) -4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5- yl] pyrazol-3-yl]oxypropyl]carbamate was converted to Ex. 164 in a manner similar to those described in General Method M.

[01628] Ex. 165 was prepared in a manner similar to those described in General Method K using acetaldehyde and I-140.

[01629] Preparation of (10*S*,20*E*)-18-[2-(methanesulfonyl)ethyl]-8,10,12-trimethyl-2,8,10,11,12,13,16,17,18,19-decahydro-3,5-ethenopyrazino[1',2':1,5]pyrazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine (Ex. 166)



Ex.166

[01630] Step 1. The reaction mixture of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylmethanol (1.00 g, 6.53 mmol, 1 eq) and 1-methylsulfonylethylene (2.08 g, 19.5 mmol, 1.72 mL, 3 eq) in EtOH (7 mL) was stirred at 60 °C for 1 hour. On completion, the reaction

mixture was filtered and the filtrate was concentrated in vacuo to afford [5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]methanol (1.30 g, 5.01 mmol, 76% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.94 (s, 1H), 4.93 (t, J = 5.6 Hz, 1H), 4.34 (d, J = 5.2 Hz, 2H), 4.00 (t, J = 5.2 Hz, 2H), 3.68 (s, 2H), 3.00 (s, 3H), 2.97 - 2.89 (m, 4H), 2.50 (s, 2H)

[01631] Step 2. The reaction mixture of [5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]methanol (1.30 g, 5.01 mmol, 1 *eq*) in ACN (15 mL) was add NIS (1.35 g, 6.02 mmol, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was quenched with sat. NaS_2O_3 (8 mL), diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give [3-iodo-5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]methanol (1.40 g, 3.63 mmol, 73% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.95 (t, J = 5.4 Hz, 1H), 4.30 (d, J = 5.6 Hz, 2H), 4.05 (t, J = 5.2 Hz, 2H), 3.56 (s, 2H), 3.43 (t, J = 6.8 Hz, 2H), 3.01 (s, 3H), 3.00 - 2.93 (m, 4H). LCMS: *m/z* 385.9 (M+1)

[01632] Step 3. To a solution of [3-iodo-5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]methanol (1 g, 2.60 mmol, 1 *eq*) in DCM (15 mL) was added DMP (1.65 g, 3.89 mmol, 1.21 mL, 1.5 *eq*). The reaction mixture was stirred at 25°C for 1 hour. On completion, the reaction mixture was quenched with sat. NaS_2O_3 (8 mL) and sat. $NaHCO_3$ (8 mL). The reaction mixture was diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO2, PE: EA=50:1 to PE: EA=0:1) to afford 3-iodo-5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-2-carbaldehyde (1.50 g, crude) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.86 - 9.80 (m, 1H), 4.24 (t, J = 5.4 Hz, 2H), 3.66 (s, 2H), 3.44 (t, J = 6.8 Hz, 2H), 3.07 - 3.02 (m, 4H), 3.01 (s, 3H). LCMS: *m/z* 383.8 (M+1)

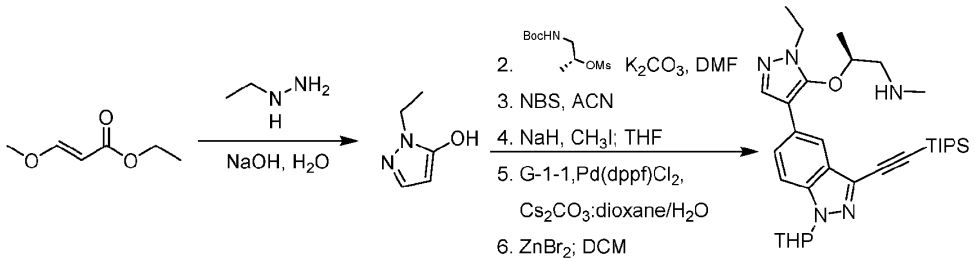
[01633] Step 4. The reaction mixture of (2S)-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (1.51 g, 2.74 mmol, 0.75 *eq* in THF (8 mL) was added TEA (370 mg, 3.65 mmol, 508 uL, 1 *eq*). Then 3-iodo-5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-2-carbaldehyde (1.4 g, 3.65 mmol, 1 *eq*) and HOAc (219 mg, 3.65 mmol, 1 *eq*) was added to the reaction mixture above. The reaction mixture was stirred at 25°C for 0.5 hour. Then $NaBH(OAc)_3$ (1.16 g, 5.48 mmol, 1.5 *eq*) was added. The reaction mixture was stirred at 25 °C for 1 hour. On completion, the residue was diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and

concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, PE:EA=50:1 to PE:EA=0:1) to give (2S)-N-[[3-iodo-5-(2-methylsulfonylethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]methyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (1.23 g, 1.34 mmol, 37% yield) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.82 (d, J = 8.9 Hz, 1H), 7.78 (s, 1H), 7.70 - 7.65 (m, 2H), 5.92 - 5.86 (m, 1H), 4.22 - 4.13 (m, 1H), 4.02 - 3.97 (m, 2H), 3.90 (br d, J = 10.6 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.69 (s, 3H), 3.52 (s, 2H), 3.43 - 3.41 (m, 2H), 3.30 (br s, 3H), 3.00 (s, 4H), 2.98 - 2.92 (m, 4H), 2.67 (br dd, J = 5.3, 12.8 Hz, 1H), 2.42 - 2.31 (m, 2H), 2.07 - 2.04 (m, 3H), 1.80 - 1.70 (m, 1H), 1.59 (br s, 2H), 1.18 - 1.14 (m, 24H). LCMS: *m/z* 917.2 (M+1)

[01634] Steps 5-8 were conducted in a similar manner to those described in General Method H to afford Ex. 166

[01635] Ex. 167 was prepared in a similar manner to those described in General Method M with tert-butyl (S)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate as starting material and intermediates G-1-1, and H-4-2 where appropriate.

[01636] Preparation of (2S)-2-[2-ethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-N-methyl-propan-1-amine (I-168)



I-168

[01637] Step 1. To a mixture of ethyl (E)-3-ethoxyprop-2-enoate (1 g, 6.94 mmol, 1 *eq*) and ethylhydrazine;oxalic acid (1.04 g, 6.94 mmol, 1 *eq*) in water (20 mL) was added NaOH (277 mg, 6.94 mmol, 1 *eq*). The mixture was stirred at 50 °C for 2 hours. On completion, the mixture was cooled to 20 °C and extracted with DCM/i-Pr-OH (20 mL X 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 2-ethylpyrazol-3-ol (700 mg, 6.24 mmol, 90% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.52 (d, *J* = 12.4 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 3.98 - 3.89 (m, 2H), 1.27 - 1.21 (m, 3H).

[01638] Steps 2-4 were conducted according to General Method M.

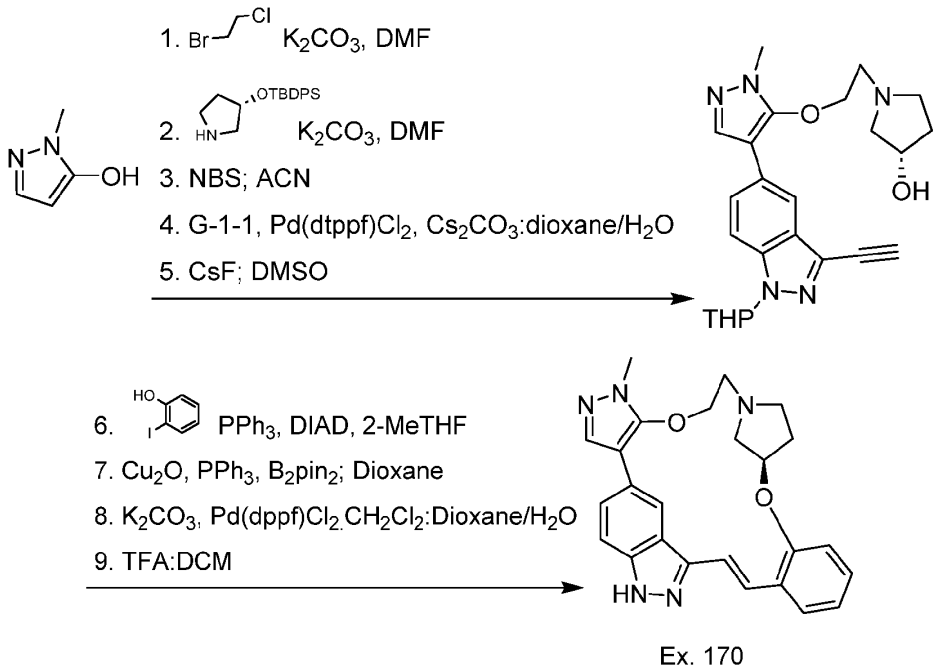
[01639] Step 5 was conducted according to General Method I.

[01640] Step 6. To a solution of tert-butyl N-[(2S)-2-[2-ethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxypropyl]-N-methyl-carbamate (0.72 g, 1.08 mmol, 1 *eq*) in DCM (10 mL) was added $ZnBr_2$ (1.47 g, 6.51 mmol, 6 *eq*). The mixture was stirred at 25 C for 14 hours. 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 a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane / Methanol=1:0 to 0:1) to give (2S)-2-[2-ethyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-N-methyl-propan-1-amine (400 mg, 0.709 mmol, 65% yield) as yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 - 7.76 (m, 1H), 7.65 - 7.57 (m, 3H), 5.76 - 5.68 (m, 1H), 4.36 - 4.24 (m, 1H), 4.13 - 4.09 (m, 2H), 3.85 - 3.57 (m, 2H), 2.89 - 2.67 (m, 2H), 2.64 - 2.36 (m, 5H), 2.05 (s, 3H), 1.78 - 1.73 (m, 3H), 1.70 - 1.64 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H), 1.21 - 1.17 (m, 21H).

[01641] Ex. 168 was prepared from I-168 and 119-2 in a similar manner to those described in General Method M.

[01642] Ex. 169 was prepared from I-168 and 147-1 in a similar manner to those described in General Method M.

[01643] Preparation of (10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine (Ex. 170)



Ex. 170

[01644] Steps 1-5 are described in General Method M.

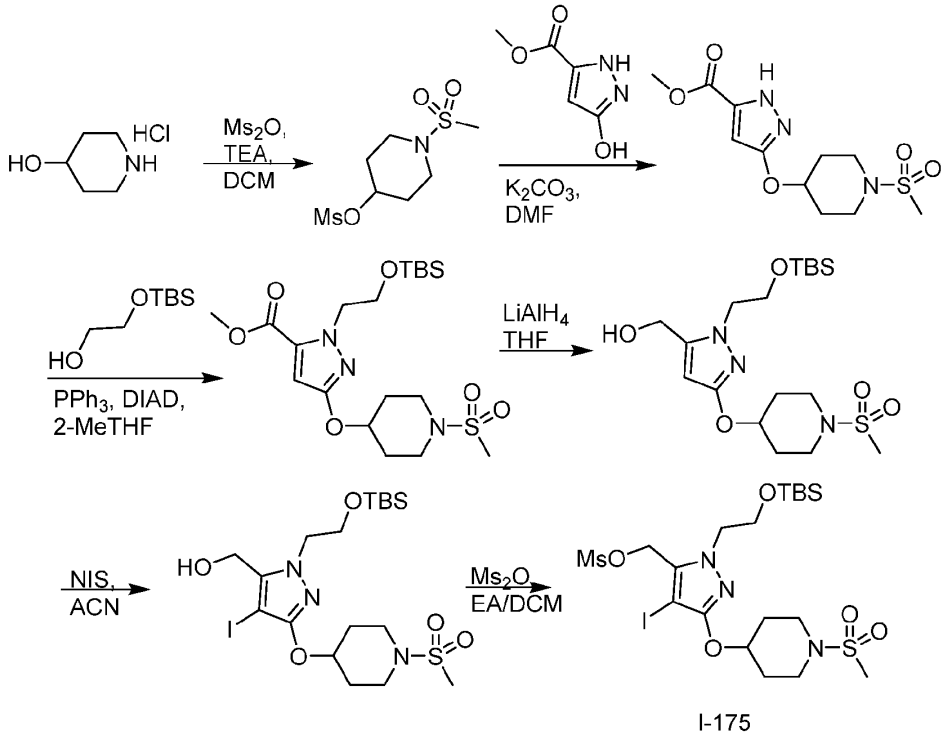
[01645] Steps 6-9 were conducted in similar manner to those described in General Method L and General Method H to afford Ex. 170.

[01646] Ex. 171 was prepared as described in the synthesis for Ex. 155 starting with (2S)-propane-1,2-diol instead.

[01647] Ex. 172 was prepared in manner similar to those described in General Method M from 116-1 and 119-2

[01648] Ex. 173 and Ex. 174 were prepared in a manner described in General Method P starting from appropriate alcohol, (3-cyclopropylisoxazol-5-yl)methanol and (3-ethylisoxazol-5-yl)methanol, respectively.

[01649] Preparation of [2-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-4-iodo-5-[(1-methylsulfonyl-4-piperi dyl)oxy]pyrazol-3-yl]methyl methanesulfonate, (I-175)



[01650] Step 1. To a mixture of piperidin-4-ol (5.00 g, 36.3 mmol, 1 *eq*, HCl), TEA (11.0 g, 109 mmol, 3 *eq*) in DCM (50 mL) was added bis(methylsulfonyl)methane (9.39 g, 54.5 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 12 hours. On completion, the mixture was quenched by water (100 mL), and extracted with DCM (50 mL * 2), The combined organic layers were washed with aq. NaCl (50 mL * 2), filtered and concentrated under reduced pressure to give 1-(methylsulfonyl)piperidin-4-yl methanesulfonate (6.75 g,

26.2 mmol, 53% yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.85 - 4.82(m, 1H), 3.28 - 3.26 (m, 1H), 3.21 (s, 3H), 3.17 - 3.14 (m, 2H), 2.83 (s, 3H), 2.02 - 1.97 (m, 2H), 1.47 - 1.44 (m, 2H).

[01651] Step 2. To a solution of (1-methylsulfonyl-4-piperidyl) methanesulfonate (6.75 g, 26.2 mmol, 1.5 *eq*) and ethyl 3-hydroxy1H-pyrazole-5-carboxylate (2.73 g, 17.5 mmol, 1 *eq*) in DMF (50 mL) was added K_2CO_3 (7.25 g, 52.5 mmol, 3 *eq*). The mixture was stirred at 90 °C for 14 hours. On completion, the mixture was partitioned between ethyl acetate (20 mL * 3) and water (100 mL), the combined organic phase was dried over anhydrous sodium sulfate, concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 1:2) to give ethyl 3-[(1-methylsulfonyl-4-piperidyl)oxy]-1H-pyrazole-5-carboxylate (1.50 g, 4.73 mmol, 27% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (s, 1H), 6.16 (s, 1H), 4.78 - 4.64 (m, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.43 - 3.21 (m, 4H), 2.74 (s, 3H), 2.10 - 1.91 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H).

[01652] Step 3. A mixture of ethyl 3-[(1-methylsulfonyl-4-piperidyl)oxy]-1H-pyrazole-5-carboxylate (1.50 g, 4.73 mmol, 1 *eq*), 2-[tert-butyl(dimethyl)silyl]oxyethanol (833 mg, 4.73 mmol, 1 *eq*), PPh_3 (2.73 g, 10.4 mmol, 2.2 *eq*) in 2-MeTHF (15 mL) was degassed and purged with N_2 for 3 times, and then DIAD (2.39 g, 11.8 mmol, 2.5 *eq*) was added to the mixture dropwise at 0 °C and the mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. On completion, the reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 2:1) to give ethyl 2-|2-|tert-butyl(dimethyl)silyl|oxyethyl|-5-|(1-methylsulfonyl-4-piperidyl)oxy]pyrazole-3-carboxylate (2.00 g, 4.20 mmol, 89% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.19 (s, 1H), 4.70 (quin, *J* = 4.4 Hz, 1H), 4.56 (t, *J* = 5.6 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.43 - 3.27 (m, 4H), 2.80 (s, 3H), 2.05 - 2.02 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.81 (s, 9H), -0.04 - -0.09 (m, 6H).

[01653] Step 4. To a mixture of ethyl 2-[2-[tert-butyl(dimethl)silyl]oxyethyl]-5-[(1-methylsulfonyl-4-piperidyl)oxy]pyrazole-3- carboxylate (2.27 g, 4.77 mmol, 1 *eq*) in THF (20 mL) was added $LiAlH_4$ (181mg, 4.77 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1 hour under N_2 atmosphere. On completion, the reaction mixture was quenched with water (0.5 mL), 15% NaOH (0.5 mL) and water (0.5 mL), the mixture was concentrated to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(1-methylsulfonyl-4-piperidyl) oxy]pyrazol-3-yl]methanol (1.00 g, 2.31 mmol, 48% yield) as a brown oil. LCMS: *m/z* 434.2 (M+1)

[01654] Step 5. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(1-methylsulfonyl-4-piperidyl)oxy]pyrazol-3- yl]methanol (900 mg, 2.08 mmol, 1 *eq*) in ACN (10 mL) was added NIS (467 mg, 2.08 mmol, 1 *eq*). The mixture was stirred at 0 °C for 0.5 hour. On completion, the mixture was quenched with sat. Na_2SO_3 (20 mL) aqueous solution and extracted with ethyl acetate (25 mL * 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-[(1-methylsulfonyl-4-piperidyl)oxy]pyrazol-3-yl]methanol (1.15 g, 2.06 mmol, 99% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.88 - 4.80 (m, 1H), 4.59 (s, 2H), 4.29 - 4.19 (m, 2H), 3.97 - 3.86 (m, 2H), 3.46 - 3.29 (m, 4H), 3.27 - 3.01 (m, 1H), 2.83 (s, 3H), 2.11 - 1.96 (m, 4H), 0.82 (s, 9H), 0.00 (s, 6H). LCMS: *m/z* 560.5 (M+1)

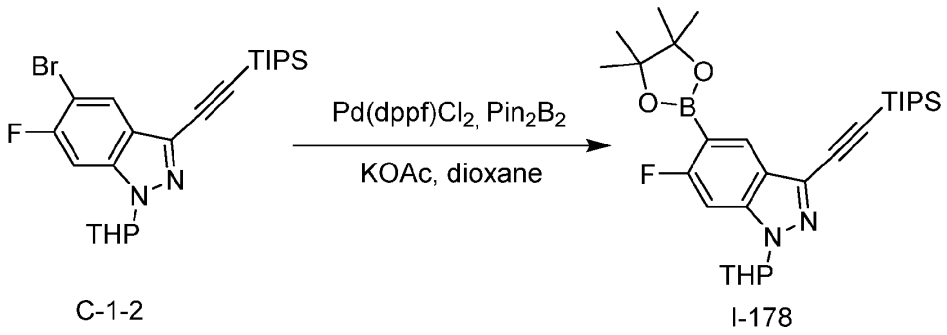
[01655] Step 6. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-[(1-methylsulfonyl-4-piperidyl)oxy]pyrazol -3- yl]methanol (600 mg, 1.07 mmol, 1 *eq*) in DCM (5 mL) was added methylsulfonyl methanesulfonate (560 mg, 3.22 mmol, 3 *eq*) and TEA (326 mg, 3.22 mmol, 3 *eq*). The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated to give [2-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-4-iodo-5-[(1-methylsulfonyl-4-piperi dyl)oxy]pyrazol-3-yl]methyl methanesulfonate (654 mg, 1.03 mmol, 96% yield) as brown oil. LCMS: *m/z* 638.0 (M+1)

[01656] I-175 was converted to Ex. 175 following procedures described in General Method M.

[01657] Ex. 176 was prepared following procedures described in General Method M and General Method I starting with the appropriate alcohol, tert-butyl (3R)-3-hydroxypiperidine-1-carboxylate, boronic ester G-1-1, and bromide H-4-1 at the appropriate steps.

[01658] Ex. 177 was prepared from 119-2 and 133-1 following procedures similar to those described in General Method H.

[01659] Preparation of 2-[6-fluoro-1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazol-3-yl] ethynyl-triisopropyl-silane, I-178



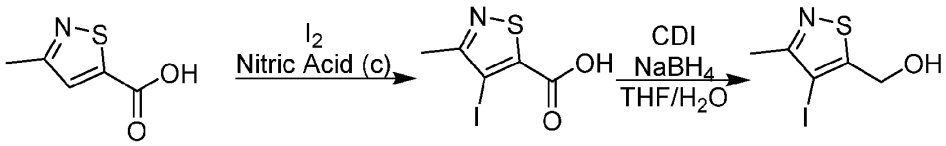
C-1-2 I-178

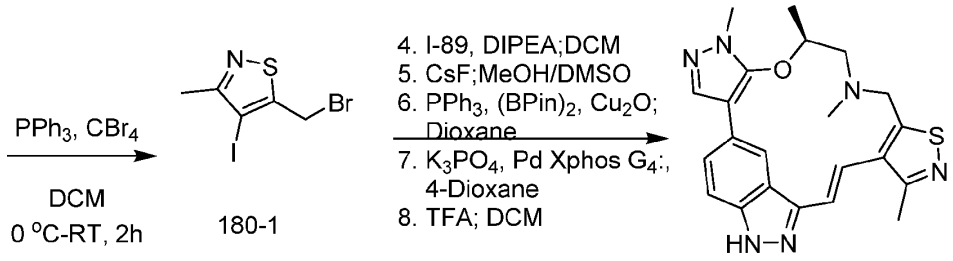
[01660] Step 1. A mixture of 2-(5-bromo-6-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl) ethynyl-triisopropyl-silane (8 g, 16.7 mmol, 1 *eq)*, Pin_2B_2 (6.36 g, 25.1 mmol, 1.5 *eq*), KOAc (4.91 g, 50.1 mmol, 3 *eq*) and cyclopentyl (diphenyl) phosphane;dichloromethane;dichloropalladium;iron (1.36 g, 1.67 mmol, 0.1 *eq*) in dioxane (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. On completion, the reaction was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EA=1:0 to 20:1) to give 2-[6-fluoro-1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazol-3-yl] ethynyl-triisopropyl-silane (5.50 g, 9.92 mmol, 59% yield, 95% purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 2.4 Hz, 1H), 7.24 - 7.19 (m, 1H), 5.62 (d, *J* = 2.8, 9.2 Hz, 1H), 4.08 - 4.00 (m, 1H), 3.79 - 3.66 (m, 1H), 2.60 - 2.38 (m, 1H), 2.15 - 2.08 (m, 1H), 1.78 - 1.71 (m, 2H), 1.69 - 1.65 (m, 1H), 1.42 (s, 3H), 1.38 (s, 13H), 1.20 - 1.18 (m, 18H).

[01661] Ex. 178 was prepared via procedures described Ex. 122 from the appropriate alcohol, tert-butyl (3S)-3-hydroxypiperidine-1-carboxylate, I-178, and I-156 in the appropriate steps.

[01662] Ex. 179 were prepared in a manner described in General Method P starting from appropriate alcohol, (3-isopropylisoxazol-5-yl)methanol.

[01663] Preparation of Ex. 180





Ex. 180

[01664] Step 1. To 3-methylisothiazole-5-carboxylic acid (438 mg, 3.06 mmol) was added Nitric Acid (275.41 mg, 3.06 mmol, 6 mL, 70% purity) and iodine (931.81 mg, 3.67 mmol). Heated to 100 °C for 3 hr. Cooled in an ice bath and carefully quenched with 1M sodium bisulfite (aq. 3 mL). Reaction was diluted with DCM and water (20 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Filtrate was concentrated under reduced pressure and the residue crystallized with EA/Hex to afford 4-iodo-3-methyl-isothiazole-5-carboxylic acid (350 mg, 1.30 mmol, 43 % yield). Mother liquor was purified by flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) provided 4-iodo-3-methyl-isothiazole-5-carboxylic acid (350 mg, 1.30 mmol, 43 % yield). LCMS: *m/z* 270.0 (M+1)

[01665] Step 2. To 4-iodo-3-methyl-isothiazole-5-carboxylic acid (400 mg, 1.49 mmol) in THF (5 mL) was added CDI (494.17 mg, 3.05 mmol) and stirred for 2h at RT. The mixture was added slowly to a solution of Sodium Borohydride (281.22 mg, 7.43 mmol, 261.84 µL) in water (2.5 mL). Allowed to stir for 5 minutes and then quenched with concentrated HCl carefully until pH is approximately 2. Reaction was diluted with EA and water (10 mL) and the layers were separated. The aqueous layer was extracted again with EA (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Aqueous layer was re-extracted with DCM (3 x 20 mL). Flash column chromatography (automated system, 12g silica, 0-45% EA in Hexanes) provided (4-iodo-3-methyl-isothiazol-5-yl)methanol (176 mg, 0.690 mmol, 46 % yield). LCMS: *m/z* 255.8 (M+1)

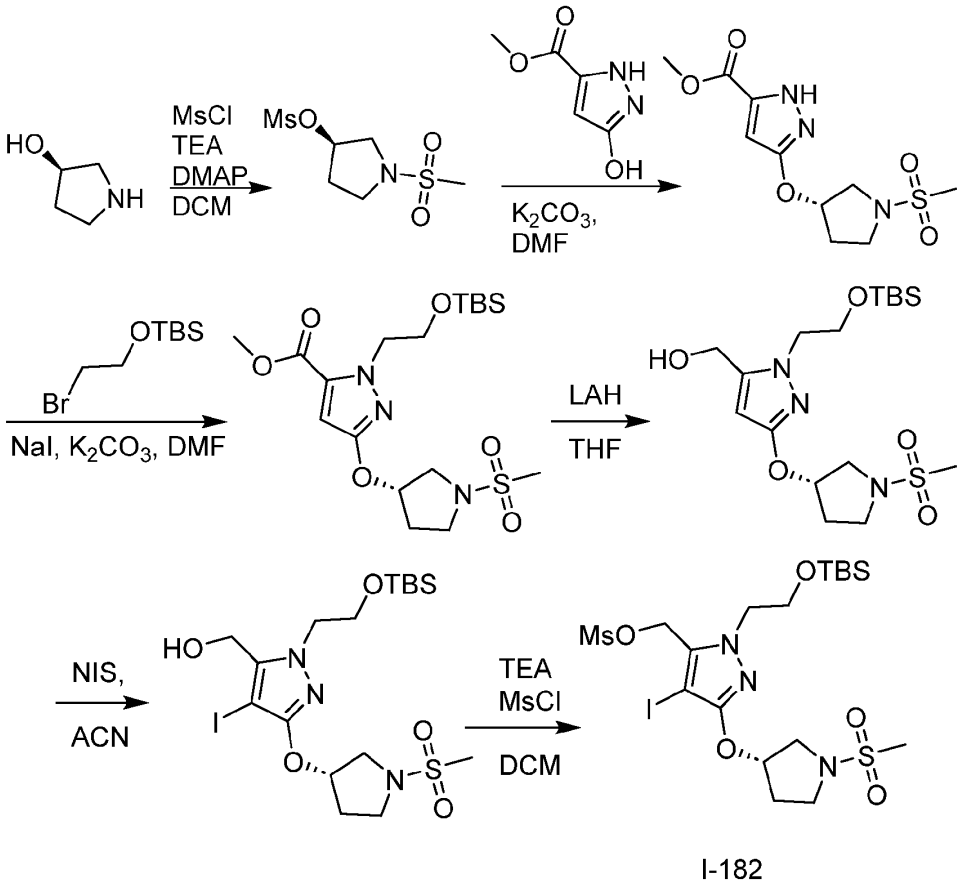
[01666] Step 3. To (4-iodo-3-methyl-isothiazol-5-yl)methanol (100 mg, 0.392 mmol) in DCM (2 mL) was added triphenylphosphine (206 mg, 0.784 mmol) followed by carbon tetrabromide (195 mg, 0.588 mmol). Stir at 0 °C for 18 hr as temperature increases to ambient. Quenched with water (1 mL) and worked up with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The

combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-30% EA in Hexanes) provided 5-(bromomethyl)-4-iodo-3-methyl-isothiazole, 180-1 (89 mg, 0.280 mmol, 71 % yield). LCMS: *m/z* 317.7/319.7 (M/M+2)

[01667] 5-(bromomethyl)-4-iodo-3-methyl-isothiazole was combined with 89-2 and converted to Ex. 180 via methods described in General Method P.

[01668] Ex. 181 was prepared in a similar manner to those described in General Method M using 116-1 and 147-1.

[01669] Preparation of[2-[2-[tert-butyl (dimethyl)silyl]oxyethyl]-4-iodo-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-pyraz ol-3-yl]methyl methanesulfonate (I-182)



I-182

[01670] Step 1. To a mixture of (3R)-pyrrolidin-3-ol (10.0 g, 115 mmol, 1 *eq*) in DCM (100 mL) was added TEA (58.1 g, 574 mmol, 79.9 mL, 5 *eq*) and MsCl (52.6 g, 459 mmol, 4 *eq*), DMAP (1.40 g, 11.5 mmol, 0.1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was quenched with dilute citric acid (300 mL). The mixture was

separated and the aqueous layer was extracted with DCM (100 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated to give to give [(3R)-1-methylsulfonylpyrrolidin-3-yl] methanesulfonate (20.5 g, crude) as a yellow solid.

[01671] Step 2. To a solution of [(3R)-1-methylsulfonylpyrrolidin-3-yl] methanesulfonate (1.40 g, 5.75 mmol, 1.1 *eq*), methyl 3-hydroxy-1H-pyrazole-5-carboxylate (743 mg, 5.23 mmol, 1 *eq*) in DMF (14 mL) was added K_2CO_3 (2.17 g, 15.7 mmol, 3 *eq*). The mixture was stirred at 60 °C for 16 h. On completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic phase was washed with water (50 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF=1:1) to give methyl 3-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-1H-pyrazole-5-carboxylate (530 mg, crude) as a white solid. LCMS: *m/z* 290.0 (M+1)

[01672] Step 3. To a solution of methyl 3-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-1H-pyrazole-5-carboxylate (2.31 g, 7.98 mmol, 1 *eq*) in DMF (20 mL) was added NaI (1.20 g, 7.98 mmol, 1 *eq*), 2-bromoethoxy-tert-butyl-dimethyl-silane (2.87 g, 12.0 mmol, 1.5 *eq*) and K_2CO_3 (3.31 g, 24.0 mmol, 3 *eq*), then the mixture was stirred at 60 °C for 16 h. On completion, the mixture was diluted with water (60 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with water (60 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF=1:1) to give methyl 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy -pyrazole-3-carboxylate (2.04 g, crude) as a yellow oil. LCMS: *m/z* 448.6 (M+1)

[01673] Step 4. To a mixture of methyl 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-pyrazole-3-carboxylate (2.14 g, 4.78 mmol, 1 *eq*) in THF (20 mL) was added $LiAlH_4$ (327 mg, 8.61 mmol, 1.8 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (0.3 ml) and 15% aq. NaOH (0.3 ml) drop by drop, then water (1 ml). The residue was purified by column chromatography (SiO_2, PE: THF=1:1) to give [2-[2-[tert-butyl (dimethyl)silyl]oxyethyl]-5-(1-methylsulfonylpyrrolidin-3-yl)oxy-pyrazol-3-yl]methanol (1.10 g, crude) as a white oil. LCMS: *m/z* 420.0 (M+1)

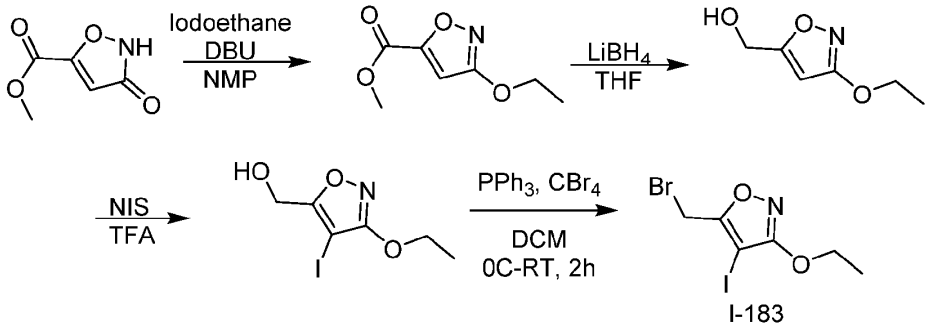
[01674] Step 5. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-(1-methylsulfonyl pyrrolidin-3-yl)oxy-pyrazol-3-yl]methanol (1.05 g, 2.50 mmol, 1 *eq*) in ACN (10 mL) was added NIS (619 mg, 2.75 mmol, 1.1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with sat. Na_2SO_3 (30 mL) at 0 °C and

extracted with DCM (10 mL × 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: THF=2:1) to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl] oxy-pyrazol-3-yl]methanol (1.33 g, crude) as a white solid. LCMS: *m/z* 546.1 (M+1)

[01675] Step 6. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-pyrazol-3-yl]methanol (1.06 g, 1.94 mmol, 1 *eq*) in DCM (10 mL) was added TEA (590 mg, 5.83 mmol, 3 *eq*), and then methylsulfonyl methanesulfonate (508 mg, 2.91 mmol, 1.5 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was quenched with dilute citric acid (30 mL). The mixture was separated and the aqueous layer was extracted with DCM (10 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue to give [2-[2-[tert-butyl (dimethyl)silyl]oxyethyl]-4-iodo-5-[(3S)-1-methylsulfonylpyrrolidin-3-yl]oxy-pyraz ol-3-yl]methyl methanesulfonate, I-181 (1.17 g, crude) as a yellow oil. LCMS: *m/z* 624.0 (M+1)

[01676] I-182 was combined with 89-2 and converted to Ex. 182 in a manner similar to those described in General Method M.

[01677] Preparation of 5-(bromomethyl)-3-ethoxy-4-iodoisoxazole (I-183)



[01678] Step 1. To methyl 3-oxoisoxazole-5-carboxylate (1 g, 6.99 mmol) in NMP (21.37 mL) was added DBU (1.38 g, 9.08 mmol, 1.36 mL). Stir as argon is bubbled through and Iodoethane (1.09 g, 6.99 mmol, 561.82 µL) was added slowly at 0 °C. Stirred as temperature is kept cold for the next 4 hours then allowed to slowly warm to RT overnight. The reaction was diluted with DCM (50 mL) and cooled. HCl (aq) (2M, 50mL) was added slowly while stirring at 0 °C. The layers were partition and the organic layer was concentrated. The residue was loaded onto a silica plug and eluted with 30% EA in Hexanes (500 mL). The filtrate was concentrated to give a light orange oil. Re-dissolved in DCM (20mL) and washed with brine followed by sodium bicarbonate (sat.) then dried over sodium

sulfate. After filtration and concentration, methyl 3-ethoxyisoxazole-5-carboxylate (1.04 g, 6.08 mmol, 87 % yield) was obtained. LCMS:*m/z* 172.0 (M+1)

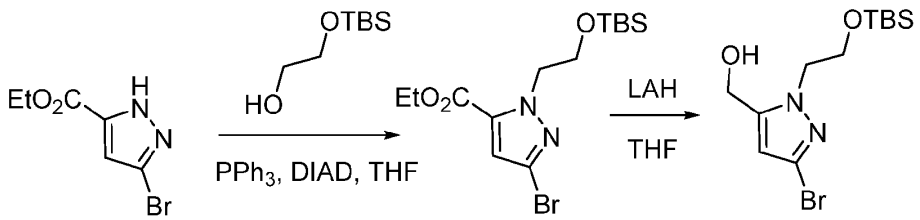
[01679] Step 2. To methyl 3-ethoxyisoxazole-5-carboxylate (500 mg, 2.92 mmol) in THF (12.96 mL) was added $LiBH_4$ (127 mg, 5.8mmol) under argon at 0 °C. Stir for 0.5 hr and reaction was diluted with DCM and water (30 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-30% EA in Hexanes) provided (3-ethoxyisoxazol-5-yl)methanol (263 mg, 1.84 mmol, 63 % yield). LCMS:*m/z* 144.1 (M+1)

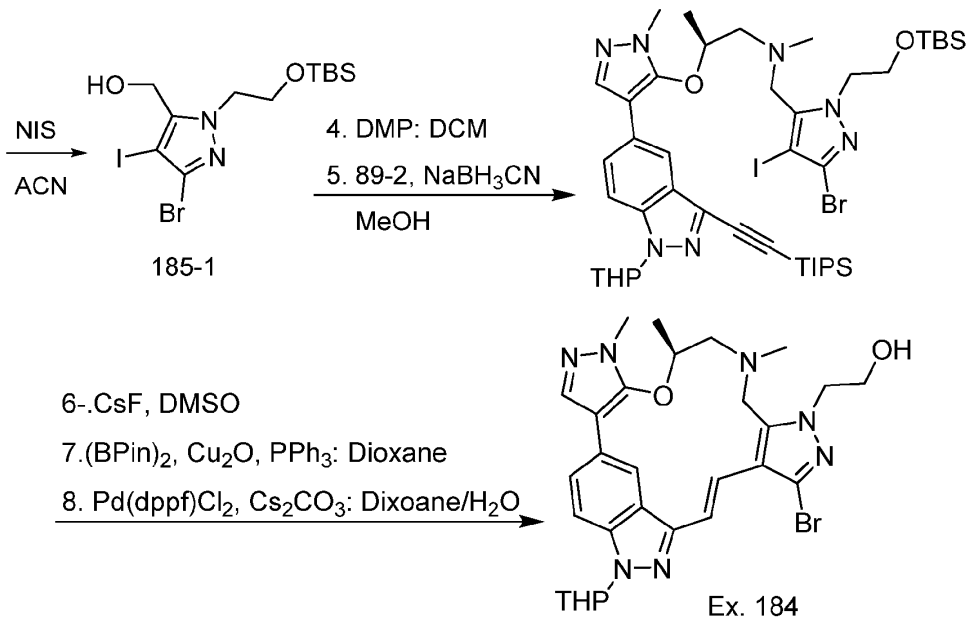
[01680] Step 3. To (3-ethoxyisoxazol-5-yl)methanol (263 mg, 1.84 mmol) in TFA (4 mL) was added NIS (620.06 mg, 2.76 mmol). Stir at 70 °C for 0.5 hr. Reaction was diluted with DCM and water (20 mL) after cooling and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system with ELSD, 12g silica, 0-30% EA in Hexanes) provided (3-ethoxy-4-iodo-isoxazol-5-yl)methanol (264 mg, 0.981 mmol, 53 % yield). LCMS:*m/z* 269.9 (M+1)

[01681] Step 4. To (3-ethoxy-4-iodo-isoxazol-5-yl)methanol (130 mg, 0.483 mmol) in DCM (2.5 mL) was added Triphenylphosphine (253 mg, 0.966 mmol) followed by carbon tetrabromide (240 mg, 0.725 mmol) at 0 °C. Stirred for 2 hr. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 3 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-30% EA in Hexanes) provided 5-(bromomethyl)-3-ethoxy-4-iodo-isoxazole (140 mg, 0.422 mmol, 87 % yield). LCMS:*m/z* 331.7 (M+1)

[01682] I-183 was combined with 89-2 and converted to Ex. 183 following procedures similar to those described in General Method P.

[01683] Preparation of 2-[(10*S*,17*E*)-16-bromo-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 184)





[01684] Step 1. To a solution of ethynyl(triisopropyl)silane (33.4 g, 183 mmol, 41 mL, 2.5 *eq*) in THF (200 mL) at −78 °C was added n-BuLi (2.5 M, 88 mL, 3 *eq*) under N_2. The mixture was stirred at the -78 °C for 1 hr, and then $BF_3.Et_2O$ (26.0 g, 183 mmol, 23 mL, 2.5 *eq*) was added. After 0.2 hr, methyl 3-chloro-3-oxo-propanoate (10.0 g, 73.2 mmol, 7.82 mL, 1 *eq*) in THF (50 mL) was added. The mixture was stirred at -78 °C for 2 h. On completion, the mixture was quenched with sat. NH_4Cl (500 mL) and water (500 mL) and extracted with ethyl acetate (500 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (60.0 g, crude) as an orange oil. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1) to give methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (9.96 g, 35.3 mmol, 17% yield) as a red oil. ^1H NMR (400 MHz, $CDCl_3$-*d*) δ = 11.78 - 11.58 (m, 1H), 3.78 - 3.74 (m, 4H), 3.62 - 3.60 (m, 1H), 1.11 - 1.10 (m, 21H).

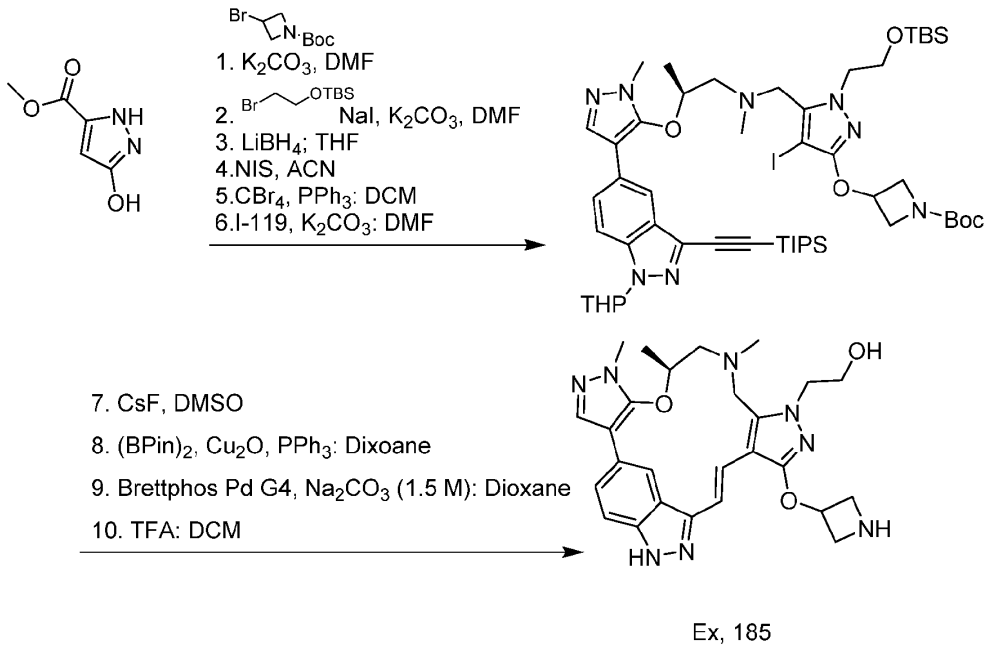
[01685] Step 2. To a solution of methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (6.83 g, 24.2 mmol, 1 *eq*) in MeOH (70 mL) was added methylhydrazine (3.34 g, 29.0 mmol, 4 mL, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 hr. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH=1:0 to 10:1) to give 2-methyl-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (3.15 g, 10.3 mmol, 43% yield, 91% purity) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.46 - 11.02 (m, 1H), 5.48 (s, 1H), 3.50 (s, 3H), 1.07 (s, 21H); LCMS: *m/z* 279.2 (M+1).

[01686] Step 3. To a solution of 2-methyl-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (1.00 g, 3.59 mmol, 1 *eq*) in dioxane (10 mL) was added 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (1.21 g, 3.95 mmol, 1.1 *eq*) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (307 mg, 0.359 mmol, 0.1 *eq*) then the mixture was added K_2CO_3 (993 mg, 7.18 mmol, 2 *eq*) under N_2. The mixture was stirred at 100 °C for 3 hr. 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 10/1) to give 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (960 mg, 1.77 mmol, 49% yield, 93% purity) as a brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 11.60 - 10.26 (m, 1H), 8.15 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 6.97 (dd, *J* = 11.4, 18.0 Hz,1H), 6.05 (d, *J* = 18.0 Hz, 1H), 5.84 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.50 (d, *J* = 12.4 Hz, 1H), 3.88 (br d, *J* = 11.2 Hz, 1H), 3.79 - 3.71 (m, 1H), 3.63 (s, 3H), 2.45 - 2.31 (m, 2H), 2.08 - 2.00 (m, 1H), 1.96 (br dd, *J* = 2.4, 13.1 Hz, 1H), 1.76 (td, *J* = 3.2, 6.3 Hz,2H), 1.59 (br d, *J* = 3.6 Hz, 3H), 1.05 - 1.01 (m, 18H); LCMS: *m/z* 505.2 (M+1).

[01687] Steps 4-5 were conducted similarly to Ex. 192

[01688] Steps 6-8 were conducted according to General Method H to afford Ex. 184.

[01689] Preparation of 2-{(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 185)



Ex, 185

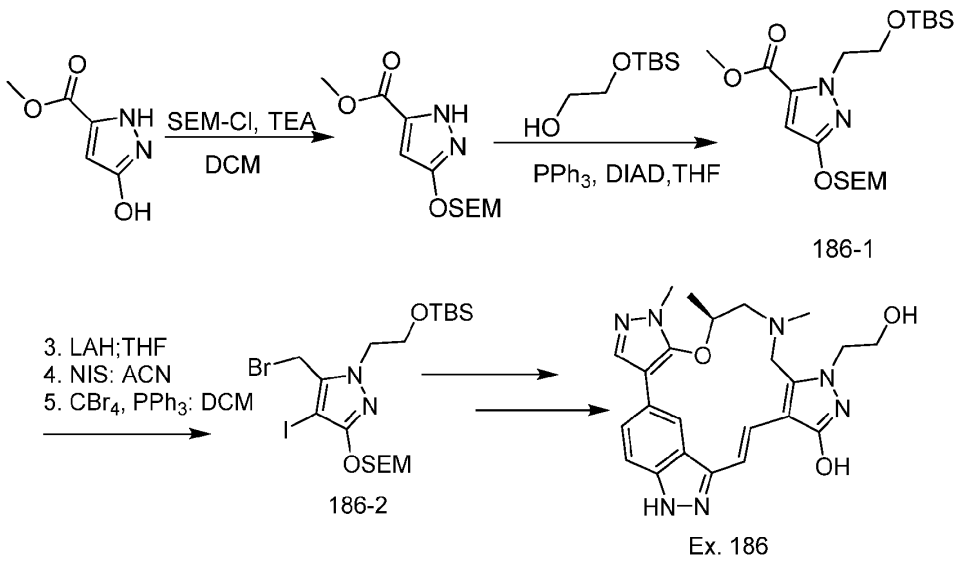
[01690] Steps 1-2 were conducted following procedures described in General Method O.

[01691] Step 3. A mixture of methyl 5-(1-tert-butoxycarbonylazetidin-3-yl)oxy-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]pyrazole-3-carboxylate (3.70 g, 8.12 mmol, 1.00 *eq*) in THF (40 mL), added $LiBH_4$ (1.77 g, 81.2 mmol, 10.0 *eq*) at 0 °C and then the mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was quenched by addition NH_4Cl (80 mL) at 0 °C and extracted with EA (70 mL * 3). The combined organic layers were dried over Na_2SO_4. 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 tert-butyl 3-[1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-(hydroxymethyl)pyrazol-3-yl]oxyazetidine-1-carboxylate (2.60 g, 6.08 mmol, 75% yield) as a white solid. LCMS: *m/z* 428.3 (M+1)

[01692] Steps 4- 5 were conducted following procedures described in General Method O.

[01693] Steps 6-10 were conducted following procedures described in General Method Q to afford Ex. 185.

[01694] Preparation of (10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol (Ex. 186)



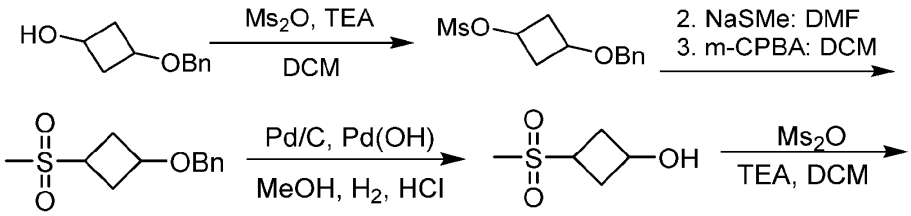
[01695] Step 1. To a mixture of methyl 3-hydroxy-1H-pyrazole-5-carboxylate (20.0 g, 140 mmol, 1.00 *eq*), TEA (85.0 g, 844 mmol, 117 mL, 6.00 *eq*) in DCM (200 mL) was added SEM-Cl (70.3 g, 422 mmol, 3.00 *eq*) at 0 °C and then the mixture was stirred at 25 °C

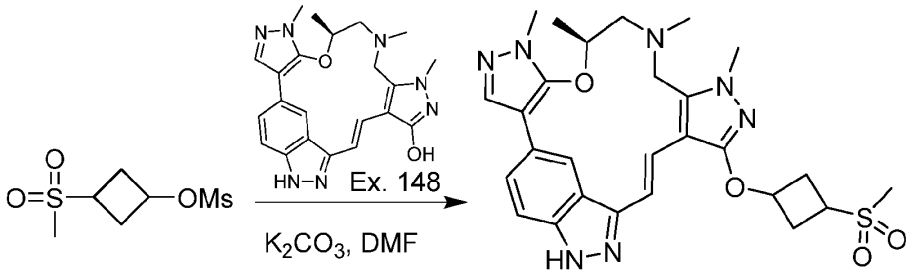
for 2 h. On completion, the mixture was quenched with water (200 mL) and extracted with DCM (55 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 0:1) to give methyl 3-(2-trimethylsilylethoxymethoxy)-1H-pyrazole-5-carboxylate (11.1 g, 40.9 mmol, 29% yield) as pink solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.32 - 6.30 (m, 1H), 5.28 - 5.25 (m, 2H), 3.88 - 3.86 (m, 3H), 3.78 - 3.73 (m, 2H), 1.25 - 1.18 (m, 2H), 0.96 - 0.92 (m, 2H), -0.03 - -0.04 (m, 9H). LCMS: *m/z* 273.2 (M+1)

[01696] Step 2. A mixture of methyl 3-(2-trimethylsilylethoxymethoxy)-1H-pyrazole-5-carboxylate (10.0 g, 36.7 mmol, 1.00 *eq*), 2-[tert-butyl(dimethyl)silyl]oxyethanol (14.2 g, 80.7 mmol, 2.20 *eq*), PPh_3 (21.1 g, 80.7 mmol, 2.20 *eq*) in THF (100 mL) was degassed and purged with N_2 for 3 times, and then DIAD (16.3 g, 80.7 mmol, 15.7 mL, 2.20 *eq*) was added at 0 °C, the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. On completion, the mixture was quenched with water (150 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=1:0 to 4:1) to give methyl 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-(2-trimethylsilylethoxymethoxy)pyrazole-3-carboxylate, 186-1 (10.0 g, 23.2 mmol, 63.0% yield) as yellow oil. LCMS: *m/z* 431.6 (M+1)

[01697] 186-1 was converted to Ex. 186 in a manner similar to those described in the synthesis of Ex. 148.

[01698] Preparation of (10*S*,17*E*)-16-{[3-(methanesulfonyl)cyclobutyl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 187)





Ex. 187

[01699] Step 1. To a solution of 3-benzyloxycyclobutanol (1.00 g, 5.61 mmol, 1 *eq*) and TEA (1.70 g, 16.8 mmol, 2 mL, 3 *eq*) in DCM (10 mL) was added methylsulfonyl methanesulfonate (1.47 g, 8.42 mmol, 1.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (20 mL) and extracted with DCM (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, DCM/MeOH=10:0 to 0:1) to give (3-benzyloxycyclobutyl) methanesulfonate (1.30 g, 5.07 mmol, 90% yield) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.30 (m, 5H), 4.72 - 4.60 (m, 1H), 4.48 - 4.40 (m, 2H), 3.81 - 3.68 (m, 1H), 3.02 - 2.96 (m, 3H), 2.89 - 2.79 (m, 2H), 2.40 - 2.29 (m, 2H).

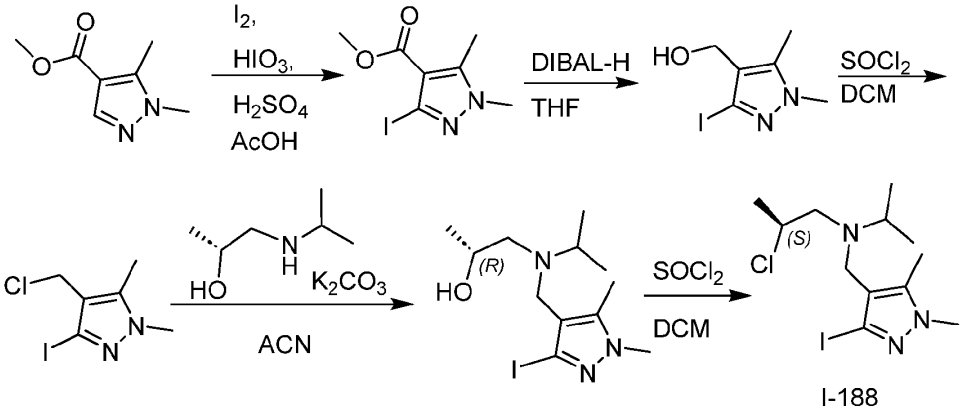
[01700] Steps 2-3 were conducted following procedures similar to those described in the synthesis of I-139.

[01701] Step 4. A mixture of (3-methylsulfonylcyclobutoxy)methylbenzene (100 mg, 0.416 mmol, 1 *eq*), Pd/C (20 mg, 0.416 mmol, 10% purity, 1 *eq*) and $Pd(OH)_2$ (20 mg, 0.014 mmol, 10% purity, 2 *eq*) in MeOH (1 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 25 °C for 16 h under H_2 atmosphere at 50 Psi. On completion, the mixture was filtrated to remove Pd/C and $Pd(OH)_2$ to give 3-(methylsulfonyl)cyclobutan-1-ol (60 mg crude) as a white solid.

[01702] Step 5. To a solution of 3-methylsulfonylcyclobutanol (60 mg, 0.399 mmol, 1 *eq*) and TEA (121 mg, 1.20 mmol, 3 *eq*) in DCM (3 mL) was added methylsulfonyl methanesulfonate (139 mg, 0.799 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the mixture was extracted with water (10 mL) and DCM (10 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF=10:0 to 0:1) to give (3-methylsulfonylcyclobutyl) methanesulfonate (87 mg, 0.381 mmol, 95% yield) as a white solid. ^{1}H NMR (400 MHz, CDCl*3-d*) δ = 5.18 (m, 1H), 3.76 - 3.66 (m, 1H), 2.96 (s, 3H), 2.92 (td, *J* = 4.0, 7.6 Hz, 2H), 2.82 - 2.80 (m, 3H), 2.78 - 2.70 (m, 2H).

[01703] Step 6. (3-methylsulfonylcyclobutyl) methanesulfonate was combined with Ex. 148 in a manner similar to those described in General Method R to afford Ex. 187

[01704] Preparation of (2R)-2-chloro-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N-isopropyl-propan -1-amine, I-188.



[01705] Step 1. A mixture of methyl 1,5-dimethylpyrazole-4-carboxylate (3.50 g, 22.7 mmol, 1 *eq*), I_2 (4.61 g, 18.1 mmol, 0.8 *eq*) and iodic acid (1.88 g, 10.6 mmol, 0.47 *eq*) in H_2SO_4 (9.4 mL) and AcOH (26 mL) was stirred at 90 °C for 5 h. On completion, the mixture was treated with AcONa (5.60 g), and the AcOH was vacuum-distilled. The residue was dissolved in EA (50 mL), washed in succession with sat. $NaHCO_3$ (50 mL * 2) and sat. Na_2SO_3 (50 mL * 2) solutions, and 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 methyl 3-iodo-1,5-dimethyl-pyrazole-4-carboxylate (1.75 g, 6.25 mmol, 27% yield) as a white solid. LCMS: *m/z* 280.9 (M+1)

[01706] Step 2. A solution of methyl 3-iodo-1,5-dimethyl-pyrazole-4-carboxylate (1.75 g, 6.25 mmol, 1 *eq*) in THF (20 mL) was degassed and purged with N_2 for 3 times, and then DIBAL-H (1 M, 15.6 mL, 2.5 *eq*) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 2 h under N_2 atmosphere. On completion, the mixture was quenched with water (0.6 mL), 15% NaOH (0.6 mL), and water (1.5 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, PE:THF=1:0 to 2:1) to give (3-iodo-1,5-dimethyl-pyrazol-4-yl)methanol (1.57 g, 6.23 mmol, 100 % yield) as a white solid. LCMS: *m/z* 252.9 (M+1)

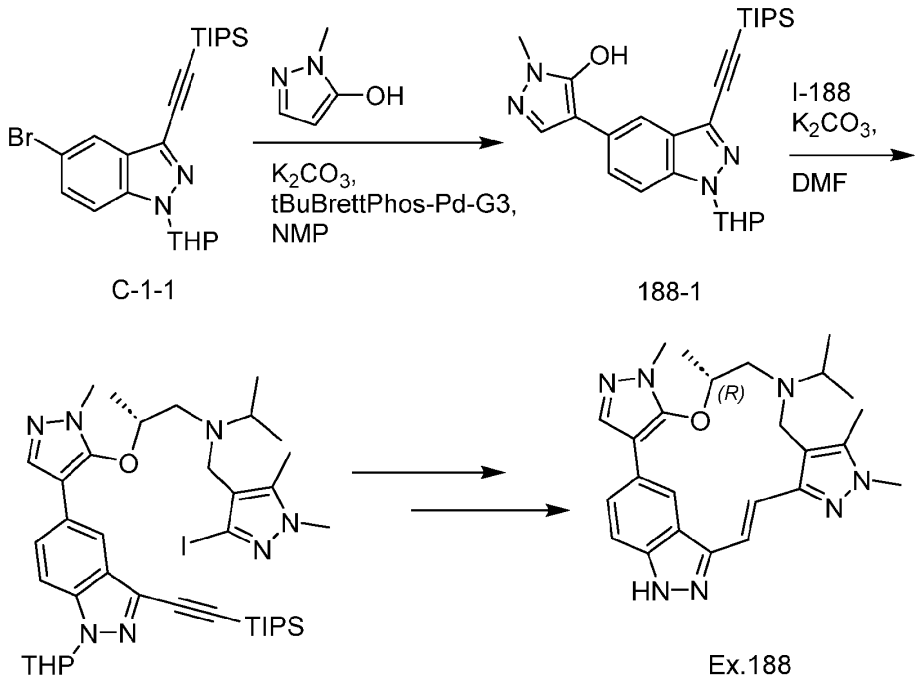
[01707] Step 3. To a solution of (3-iodo-1,5-dimethyl-pyrazol-4-yl)methanol (1.34 g, 5.33 mmol, 1 *eq*) in DCM (14 mL) was added $SOCl_2$ (1.90 g, 15.9 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was concentrated to give

4-(chloromethyl)-3-iodo-1,5-dimethyl-pyrazole (1.44 g, 5.32 mmol, 100% yield) as a white solid.

[01708] Step 4. To a mixture of 4-(chloromethyl)-3-iodo-1,5-dimethyl-pyrazole (1.44 g, 5.32 mmol, 1 *eq*) and (2R)-1-(isopropylamino)propan-2-ol (686 mg, 5.86 mmol, 1.1 *eq*) in ACN (15 mL) was added K_2CO_3 (2.21 g, 15.9 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 h. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane : Methanol =1:0 to 15:1) to give (2R)-1- [(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl-isopropyl-amino]propan-2-ol (1.5 g, 4.27 mmol, 80% yield) as colorless oil. LCMS: *m/z* 352.2 (M+1)

[01709] Step 5. To a solution of (2R)-1-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl-isopropyl- amino]propan-2-ol (1 g, 2.85 mmol, 1 *eq*) in DCM (10 mL) was added TEA (864 mg, 8.54 mmol, 1.19 mL, 3 *eq*) and $SOCl_2$ (406 mg, 3.42 mmol, 248 µL, 1.2 *eq*). The mixture was stirred at 25 °C for 0.5 h. On completion, the mixture was concentrated to give (2R)-2-chloro-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N-isopropyl-propan -1-amine, I-188 (950 mg, 2.57 mmol, 90% yield) as a yellow solid. LCMS: *m/z* 370.0 (M+1)

[01710] Preparation of (10*R*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex.188)

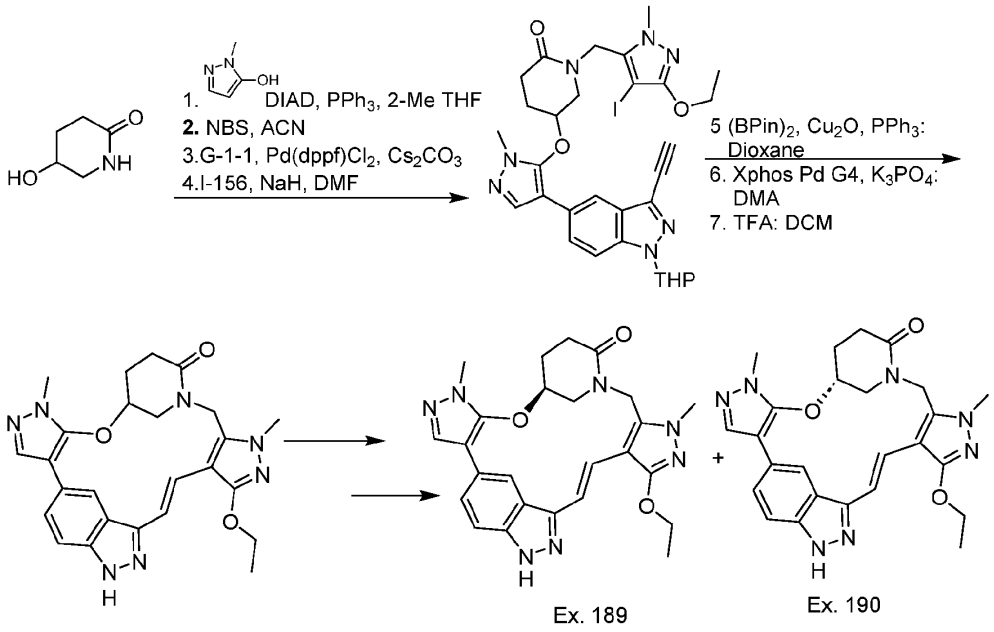


[01711] Step 1. To a solution of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (5.00 g, 10.8 mmol, 1 *eq*) in NMP (120 mL) was added 2-methylpyrazol-3-ol (1.28 g, 13.0 mmol, 1.2 *eq*) and K_2CO_3 (2.99 g, 21.6 mmol, 2 *eq*), then [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (370 mg, 0.433 mmol, 0.04 *eq*) was added. The mixture was stirred at 130 °C for 2 h under N_2 atmosphere. On completion, the mixture was quenched by adding water (400 mL) and then filtered to produce a reddish brown solid. The residue was purified by column chromatography (SiO_2, DCM: THF=2:1 to 2:1) to give 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl] pyrazol-3-ol (2.71 g, 5.66 mmol, 52% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.76 (br s, 4H), 5.92 - 5.81 (m, 1H), 3.90 (br d, J = 11.6 Hz, 1H), 3.82 - 3.70 (m, 1H), 3.67 - 3.54 (m, 2H), 2.70 (s, 3H), 2.42 - 2.30 (m, 1H), 2.06 - 1.95 (m, 2H), 1.80 - 1.70 (m, 1H), 1.22 - 1.11 (m, 21H). LCMS: *m/z* 479.2 (M+1)

[01712] Step 2. To a mixture of 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl]pyrazol-3-ol (1.48 g, 3.08 mmol, 1.2 *eq*) and (2R)-2-chloro-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N-isopropyl-propan-1-amine (950 mg, 2.57 mmol, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (1.07 g, 7.71 mmol, 3 *eq*). The mixture was stirred at 60 °C for 12 h. On completion, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (15 mL X 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (2S)-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N- isopropyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (2.45 g, crude) as a brown oil. LCMS: *m/z* 812.7 (M+1)

[01713] (2S)-N-[(3-iodo-1,5-dimethyl-pyrazol-4-yl)methyl]-N- isopropyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine was converted to Ex. 188 following procedures described in the synthesis of General Method Q.

[01714] Preparation of (10*S*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one (Ex. 189) and (10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one (Ex. 190)

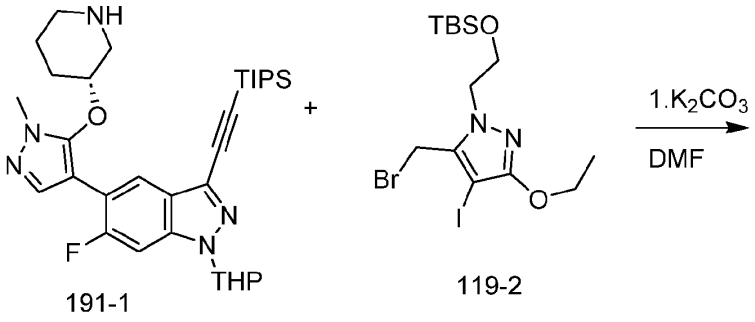


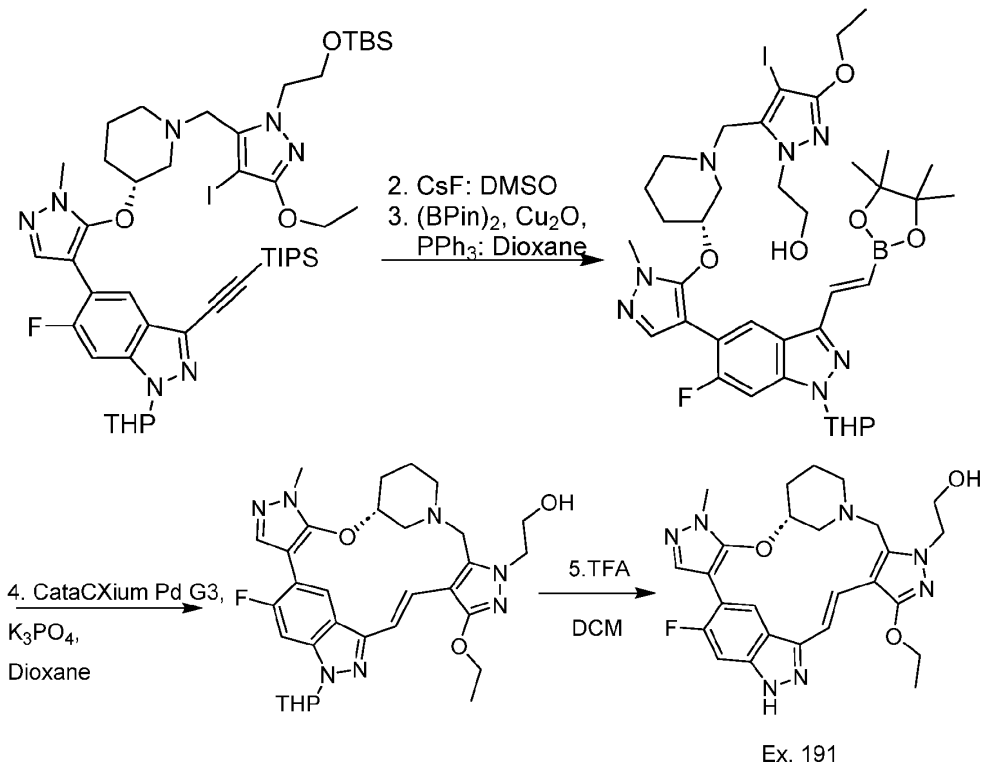
[01715] Steps 1-4 were conducted in a manner similar to those described in Ex. 122.

[01716] Steps 5-7 were conducted in a manner similar to those described in General Method L to afford a racemate.

[01717] Purification by SFC (column: DAICEL CHIRALCEL OX (250mm*30mm,10um);mobile phase: [CO2-ACN/i-PrOH(0.1% NH_3H_2O)];B%:65%, isocratic elution mode) afforded the arbitrarily assigned isomers Ex. 189 and Ex 190.

[01718] Preparation of 2-[(10*R*,19*E*)-18-ethoxy-22-fluoro-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-o (Ex. 191)





[01719] 191-1, tert-butyl-[2-[3-ethoxy-5-[[(3R)-3-[4-[6-fluoro-1- tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-yl]oxy-1-piperidyl]methyl]-4-iodo-pyrazol-1-yl]ethoxy]-dimethyl-silane, was prepared similarly to Ex. 176, following procedures described in General Method M and General Method I starting with the appropriate alcohol, tert-butyl (3R)-3-hydroxypiperidine-1-carboxylate and boronic ester I-178.

[01720] Step 1. To a solution of 2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl]ethoxy-tert

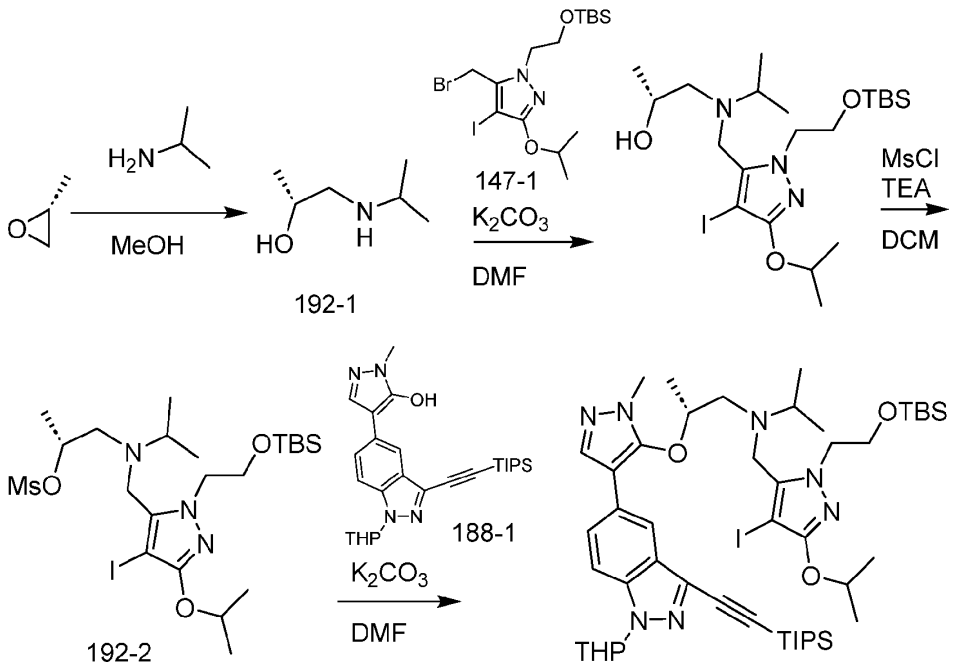
-butyl-dimethyl-silane (1.52 g, 3.1 mmol, 1.2 *eq*) and 2-[6-fluoro-5-[1-methyl-5-[[(3R)-3-piperidyl]oxy]pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazol-3-yl]ethynyl-triisopropyl-silane (1.5 g, 2.59 mmol, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (1.07 g, 7.76 mmol, 3 *eq*). The mixture was stirred at 80 °C for 2 hr. On completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (30 mL*3). The combined organic layers were washed with brine (30 mL * 3), dried over Na_2SO_4, filtered and concentrated to give tert-butyl-[2-[3-ethoxy-5-[[(3R)-3-[4-[6-fluoro-1- tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-yl]oxy-1-piperidyl]methyl]-4-iodo-pyrazol-1-yl]ethoxy]-dimethyl-silane (2.25 g, crude) as a red oil. LCMS: *m/z* 988.5

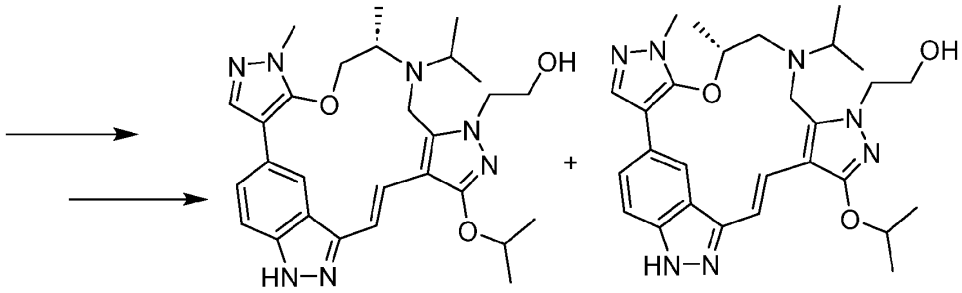
[01721] Steps 2-3 were performed according to those described in General Method M.

[01722] Step 4. A mixture of 2-[3-ethoxy-5-[[(3R)-3-[4-[6-fluoro-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]-2-methyl-pyrazol-3-yl]oxy-1-piperidyl]methyl]-4-iodo-pyrazol-1-yl]ethanol (95 mg, 0.112 mmol, 1 eq), CataCXium A Pd G3 (8.18 mg, 0.011 mmol, 0.1 eq), K3PO4 (71.5 mg, 0.337 mmol, 3 eq) in dioxane (1 mL) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N2 atmosphere. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH=0/20 to 1/20) to give 2-[(8R,19E)-17-ethoxy-26-fluoro-5-methyl-23-tetrahydropyran-2-yl-7-oxa- 4,5,12,15,16,22,23-heptazahexacyclo[19.5.2.18,12.02,6.014,18.024,28]nonacosa-1(27),2(6),3,14(18),16,19,21,24(28),25-nonaen-15-yl]ethanol (28 mg, 0.047 mmol, 42% yield) as a red oil. LCMS: *m/z* 592.3 (M+1)

[01723] Step 5 was conducted via General Method M to afford Ex. 191.

[01724] General Method S. Preparation of 2-{(11*S*,17*E*)-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 192) and 2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 193)





Ex. 192 Ex. 193

[01725] Step 1. To a solution of (2R)-2-methyloxirane (5.00 g, 86.0 mmol, 1 *eq*) and propan-2-amine (15.2 g, 258 mmol, 3 *eq*) in MeOH (80 mL). The mixture was stirred at 25 °C for 14 hours. On completion, the mixture was concentrated to give (2R)-1-(isopropylamino) propan-2-ol (8.60 g, 73.3 mmol, 85% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.76 - 3.66 (m, 1H), 2.85 - 2.69 (m, 2H), 2.40 - 2.27 (m, 1H), 2.19 - 1.94 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.09 - 1.04 (m, 6H).

[01726] Step 2. To a solution of (2R)-1-(isopropylamino) propan-2-ol (325 mg, 2.78 mmol, 1 *eq*) and 2-[5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl] ethoxy-tert-butyl-dimethyl-silane, 147-1 (1.40 g, 2.78 mmol, 1 *eq*, in DMF (20 mL) was added K_2CO_3 (1.15 g, 8.35 mmol, 3 *eq*). The mixture was stirred at 25 °C for 14 hours. 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 concentrated to give (2R)-1-[[2-[2-[tert-butyl(dimethyl) silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-isopropyl-amino]propan-2-ol (1.50 g, 2.78 mmol, 99% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.87 - 4.74 (m, 1H), 4.31 - 4.09 (m, 2H), 3.93 - 3.82 (m, 2H), 3.80 - 3.56 (m, 3H), 2.88 (s, 2H), 2.40 - 2.23 (m, 2H), 1.37 - 1.32 (m, 6H), 1.08 (d, *J* = 6.4 Hz, 6H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.81 (s, 9H), -0.04 - -0.12 (m, 6H). LCMS: *m/z* 540.1 (M+1)

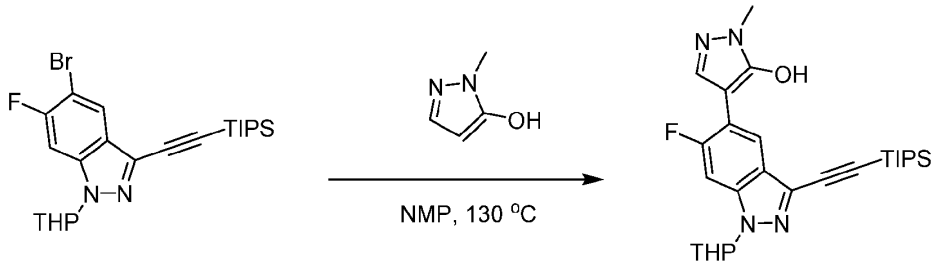
[01727] Step 3. To a solution of (2R)-1-[[2-[2-[tert-butyl(dimethyl) silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl] methyl-isopropyl-amino] propan-2-ol (1.40 g, 2.59 mmol, 1 *eq*) in DCM (20 mL) was added methylsulfonyl methanesulfonate (1.36 g, 7.78 mmol, 3 *eq*) and TEA (656 mg, 6.49 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 0.5 hours. On completion, the mixture was quenched with water (10 mL) and extracted with DCM (5 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give [(1R)-2-[[2-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-4-iodo-5-

isopropoxy-pyrazol-3-yl]methyl-isopropyl-amino]-1-methyl-ethyl] methanesulfonate (1.60 g, 2.59 mmol, 99% yield) as yellow oil. LCMS: *m/z* 618.8 (M+1)

[01728] Step 4. To a solution of [(1R)-2-[[2-[2-[tert-butyl(dimethyl) silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl] methyl-isopropyl-amino]-1-methyl-ethyl] methanesulfonate (1.60 g, 2.59 mmol, 1 *eq*) and 2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl) indazol-5-yl] pyrazol-3-ol (1.24 g, 2.59 mmol, 1 *eq*) in DMF (30 mL) was added K_2CO_3 (1.07 g, 7.77 mmol, 3 *eq*). The mixture was stirred at 80 °C for 0.5 hours. 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 concentrated to give (2R)-N-((1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl)-N-isopropyl-2-((1-methyl-4-(1-(tetrahydro-2H-pyran-2-yl)-3-((triisopropylsilyl)ethynyl)-1H-indazol-5-yl)-1H-pyrazol-5-yl)oxy)propan-1-amine (2.50 g, 2.50 mmol, 96% yield) as yellow oil. LCMS: *m/z* 1000.4 (M+1)

[01729] Intermediate was taken forward following procedures described in General Method L Upon purification by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient:14%-44% B over 10 min), 2 isomers were isolated and determined to be inverted General Method S from step 4 and unexpected double inversion by-product, Ex. 193.

[01730] Preparation of 4-[6-fluoro-1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-ol (I-194)



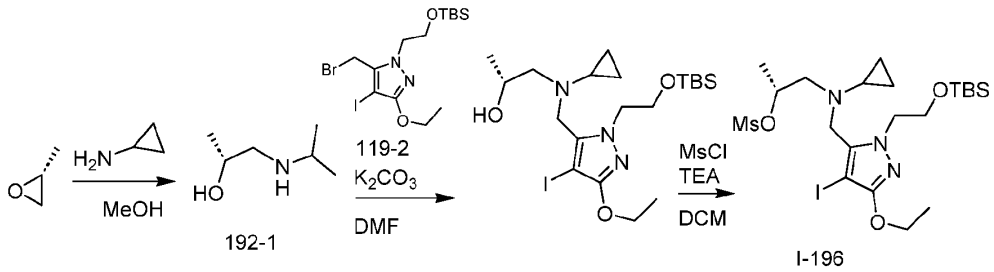
C-1-2 I-194

[01731] Step 1. To a solution of 2-(5-bromo-6-fluoro-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (1.20 g, 2.50 mmol, 1 *eq*) in NMP (20 mL) was added 2-methylpyrazol-3-ol (295 mg, 3.00 mmol, 1.2 *eq*) and K_2CO_3 (692 mg, 5.01 mmol, 2 *eq*), then the mixture was added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl) phenyl]phosphane (107 mg, 0.125 mmol, 0.05 *eq*), degassed and purged with N_2 for 3 times. On completion, the mixture was stirred at 130 °C for 0.5 h under N_2 atmosphere to give 4-[6-fluoro-1-tetrahydropyran-2-yl-3-(2-

triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-ol (1.2 g, crude) as a brown liquid in NMP (20 mL) used to next step. LCMS: *m/z* 497.3(M+1)

[01732] Ex. 194 and 195 were isolated from prep-HPLC following preparations described in General Method S using I-194 in step 3.

[01733] Preparation of [(1R)-2-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-cyclopropyl-amino]-1-methyl-ethyl] methanesulfonate, I-196.



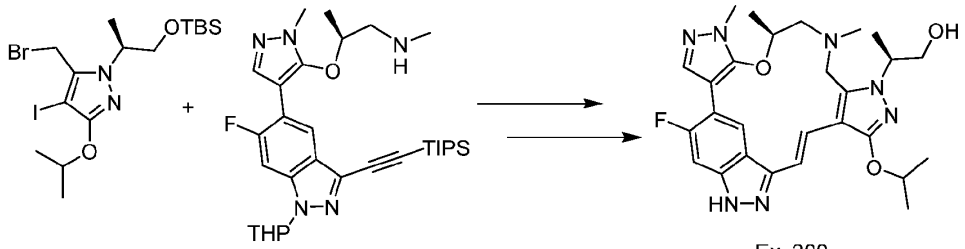
I-196

[01734] I-196 was synthesized according to General Method S using cyclopropylamine, 192-1, and 119-2.

[01735] Ex. 196, 197, and 198 were isolated from synthesis described in General Method S from I-196 and 188-1 in step 4.

[01736] Ex. 199 was prepared from 191-1 and 147-1 following preparations similar to those described in the synthesis of Ex. 191.

[01737] Preparation of (2*S*)-2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol (Ex. 200)



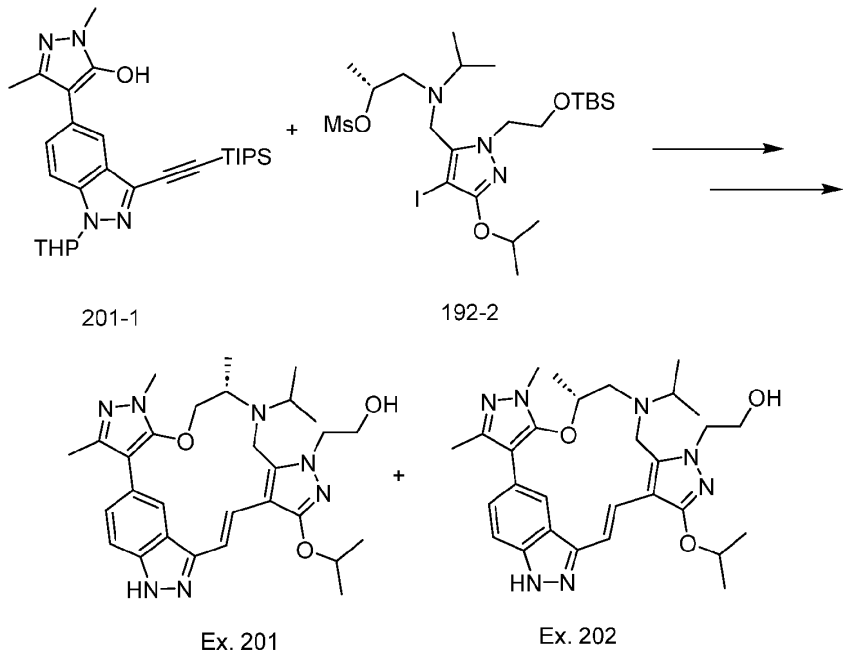
200-1 116-1 Ex. 200

[01738] 200-1 was prepared in a manner similar to those described in the synthesis of I-155.

[01739] Ex. 200 was prepared from 200-1 and 116-1 following the procedures described in General Method M.

[01740] Preparation of 2-{(11*S*,17*E*)-6,8,11-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 201) and 2-{(10*R*,17*E*)-6,8,10-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 202)



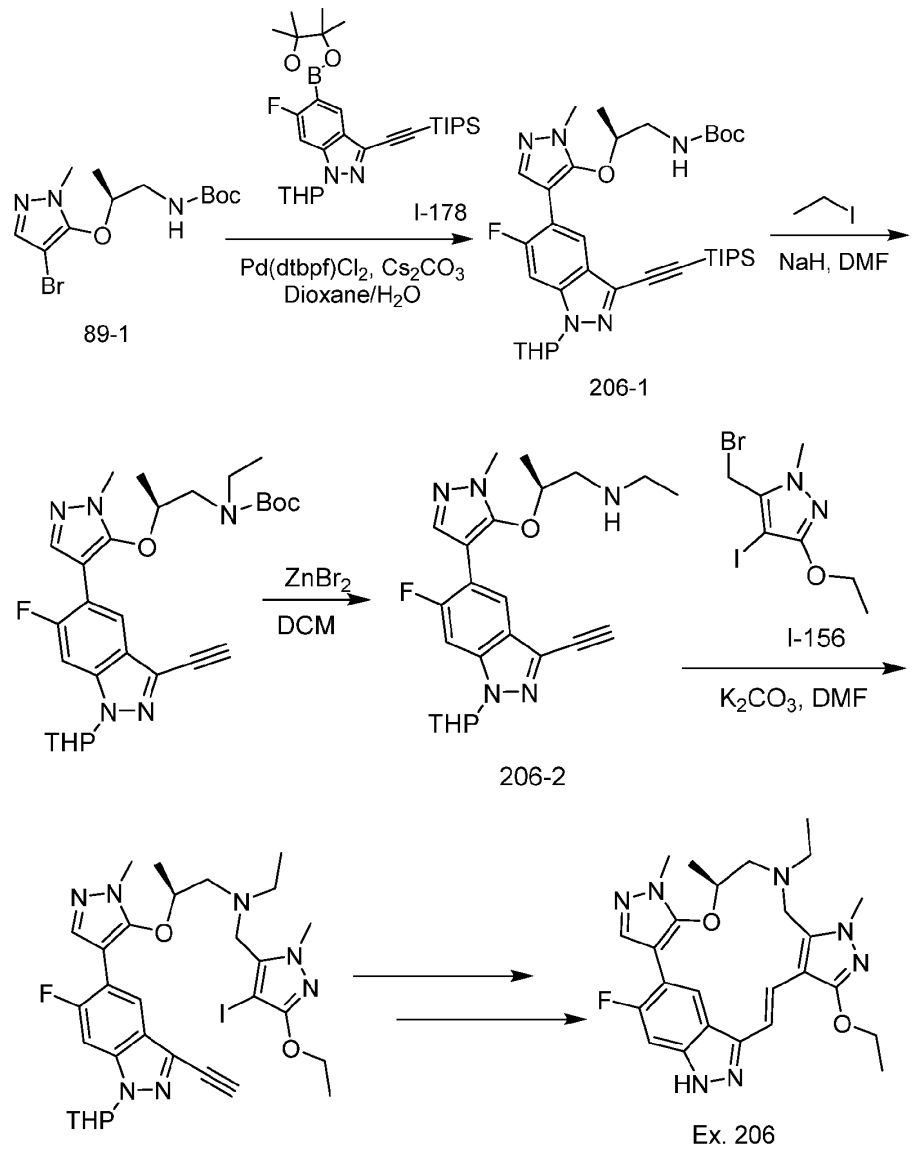
[01741] 201-1 was prepared from C-1-2 and 2,5-dimethylpyrazol-3-ol following procedure described in the synthesis of 188-1.

[01742] 201-1 and 192-2 were combined in a manner similar to those described in General Method S to afford inverted product Ex. 201 and unexpected double inverted, Ex. 202.

[01743] Ex. 203 was prepared via methods described in General Method R from starting material, Ex. 186.

[01744] 201-1 was reacted with I-196 in a manner described in General Method S to afford inverted product Ex. 204 and unexpected double inverted, Ex. 205.

[01745] Preparation of (10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine (Ex. 206)



[01746] Step 1. To a solution of tert-butyl N-[(2S)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]carbamate (1.50 g, 4.49 mmol, 1 *eq*) and 2-[6-fluoro-1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl-triisopropyl-silane (2.60 g, 4.94 mmol, 1.1 *eq*) in dioxane (30 mL) and H_2O (6 mL) was added dicesium;carbonate (4.39 g, 13.4 mmol, 3 *eq*) and ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (292 mg, 0.449 mmol, 0.1 *eq*). The mixture was stirred at 80 °C for 1 h under N_2. 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 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 N-[(2S)-2-[4-[6-fluoro-1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (2.54 g, 3.88 mmol, 87% yield) as a brown oil. LCMS: *m/z* 654.8 (M+1)

[01747] Step 2. To a solution of tert-butyl N-[(2S)-2-[4-[6-fluoro-1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (2.20 g, 3.36 mmol, 1 *eq*) in DMF (22 mL) was added NaH (538 mg, 13.5 mmol, 60% purity, 4 *eq*) stirred at 0 °C for 30 min. Then the mixture was added CH_3CH_2I (1.05 g, 6.73 mmol, 2 *eq*) at 0 °C and stirred at 25 °C for 1 h. On completion, the mixture was quenched with sat. NH_4Cl (40 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, PE:THF=1:0 to 3:1) to give tert-butyl N-ethyl-N-[(2S)-2-[4-(3-ethynyl-6-fluoro-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (739 mg, 1.41 mmol, 42% yield) as a yellow solid. LCMS: *m/z* 548.2 (M+1)

[01748] The remaining steps were conducted similarly those described in General Method Q steps 5 and 7-9 to afford Ex. 206.

[01749] Ex. 207 was prepared similarly to General Method S from 192-1, 200-1, and then 188-1 at the appropriate steps and assigned as the double inverted by product.

[01750] Ex. 208 was prepared from Ex. 184 using procedure described in Ex. 159 step 5 and final deprotection described in General Method N.

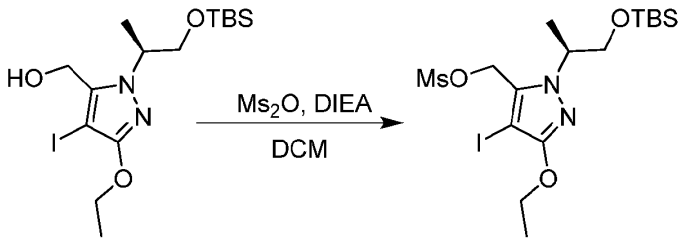
[01751] Ex. 209 was prepared from 133-1 and 148-1 similarly to General Method Q.

[01752] Ex. 210 was prepared following General Method Q from 186-2 and 116-1.

[01753] Ex. 210 was converted to Ex. 211 in a similar manner described in General Method R.

[01754] Ex. 212 and Ex. 213 were prepared similarly to that of General Method S from 188-1 and the appropriate mesylate synthesized from 147-1 and cyclopropylamine.

[01755] Preparation of [2-[(1S)-2-[tert-butyl (dimethyl) silyl] oxy-1-methyl-ethyl]-5-ethoxy-4-iodo-pyrazol-3-yl] methyl methanesulfonate, I-214



I-214

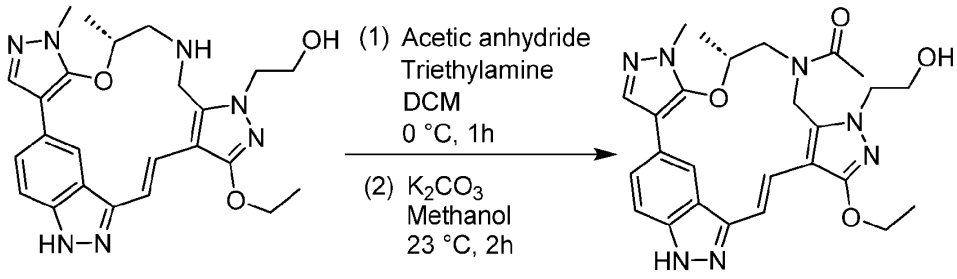
[01756] To a solution of [2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methanol (3.00 g, 6.81 mmol, 1.00 eq, from I-155) in DCM (30 mL) was added methylsulfonyl methanesulfonate (2.37 g, 13.6 mmol, 2.00 *eq*) and DIEA (2.64 g, 20.4 mmol, 3.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the reaction was concentrated under vacuum to give [2-[(1S)-2-[tert-butyl (dimethyl) silyl] oxy-1-methyl-ethyl]-5-ethoxy-4-iodo-pyrazol-3-yl] methyl methanesulfonate (9.00 g, crude) as a yellow solid.

[01757] Ex. 214 was obtained from I-214 and 116-1 following procedures detailed in the General Method Q.

[01758] Ex. 215 was prepared following procedures described in the synthesis of Ex. 133 steps 1-5 and then General Method L from the following starting materials and intermediates: I-2-1, I-178, and I-155.

[01759] Ex. 216 was prepared following procedures described in the synthesis of Ex. 133 steps 1-5 and then General Method L from the following starting materials and intermediates: I-2-1, 1-178, and 147-1.

[01760] Preparation of1-[(10*R*,17*E*)-16-ethoxy-14-(2-hydroxyethyl)-8,10-dimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one (Ex. 217)

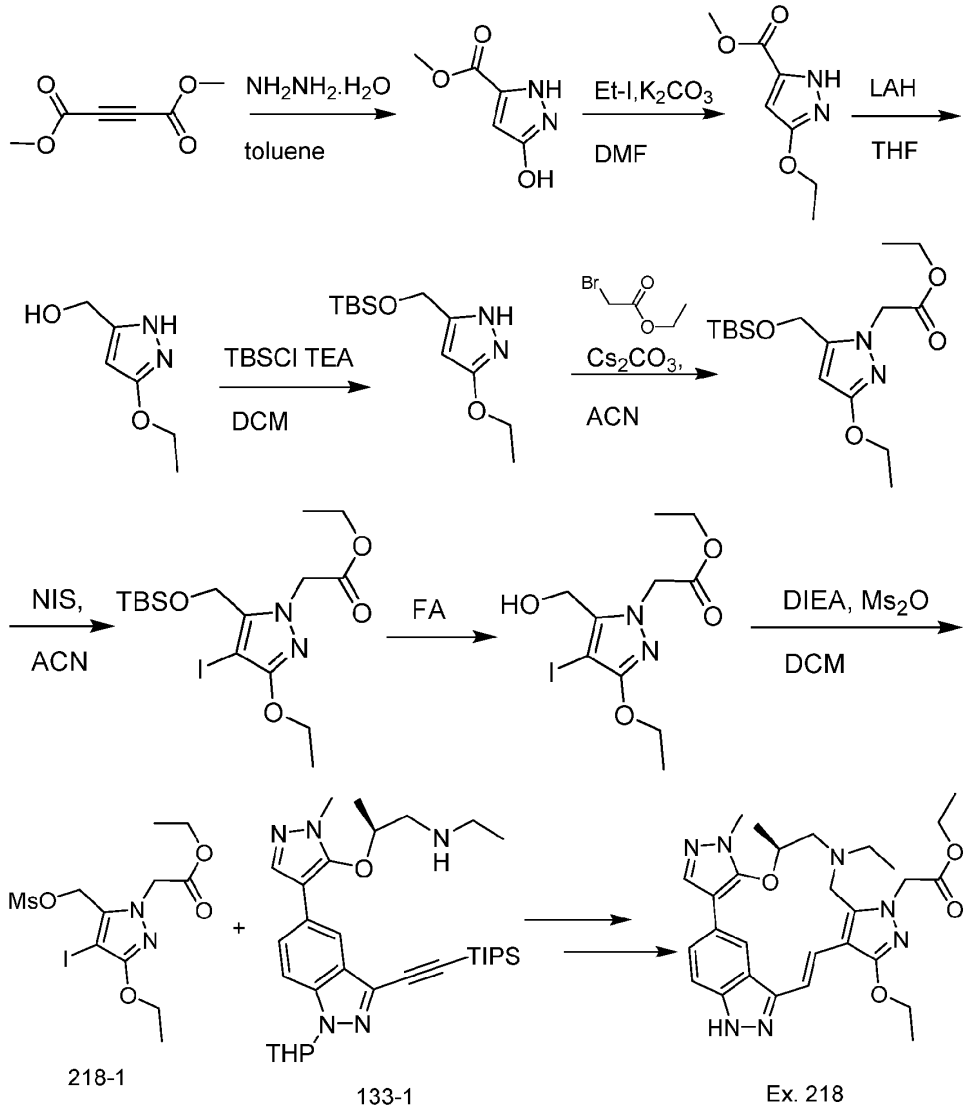


Ex. 197 Ex. 217

[01761] Step 1 was conducted according to General Method J and gave a mixture of over acetylated products. The mixture was taken forward to step 2.

[01762] Step 2. To the mixture in Methanol (1 mL) was added Potassium carbonate (35.43 mg, 0.256 mmol) and the suspension was stirred for 2 h at 23 °C. The mixture was then diluted with water (0.3 mL) and extracted with DCM (3 x 1 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by preparative HPLC (C18, 21mm x100mm, MeCN in water with 0.035% TFA) to furnish Ex. 217 (1.04 mg, 0.002 mmol, 39 % yield, TFA).

[01763] Preparation of ethyl [(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]acetate (Ex. 218)



[01764] Step 1. The solution of dimethyl but-2-ynedioate (50.0 g, 352 mmol, 1.00 *eq*) in toluene (250 mL) was added $NH_2NH_2 \cdot H_2O$ (23.4 g, 457 mmol, 22.6 mL, 98% purity, 1.30 *eq*). The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was filtrated and concentrated under reduced pressure to remove solvent and get crude product. The crude product was washed with PE(250 mL) and triturated with Methanol (200 mL) at 20 °C for 20 min to give methyl 3-hydroxy-1H-pyrazole-5-carboxylate (40.5 g, 285 mmol, 81% yield) as light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.80 (s, 1H), 3.78 - 3.48 (m, 3H). LCMS: *m/z* 143.2 (M+1)

[01765] Step 2. To a solution of methyl 3-hydroxy-1H-pyrazole-5-carboxylate (20.0 g, 141 mmol, 1.00 *eq*) in DMF (200 mL) was added K_2CO_3 (58.4 g, 422 mmol, 3.00 *eq*) and iodoethane (22.0 g, 140 mmol, 11.3 mL, 1.00 *eq*). The mixture was stirred at 80 °C for 4 hr. On completion, the reaction mixture was partitioned between ethyl acetate (50 mL × 5) and water (300 mL), the combined organic phase was washed with water (100 × 2) and dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Tetrahydrofuran=1/1 to 0/1) to give methyl 3-ethoxy-1H-pyrazole-5-carboxylate (17.7 g, 104 mmol, 74% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.22 - 12.96 (m, 1H), 6.34 - 6.08 (m, 1H), 4.19 - 4.07 (m, 2H), 3.81 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 171.1 (M+1)

[01766] Step 3. To a solution of methyl 3-ethoxy-1H-pyrazole-5-carboxylate (17.0 g, 99.9 mmol, 1.00 *eq*) in THF (250 mL) was added LAH (7.58 g, 200 mmol, 2.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 6 hr. On completion, the reaction mixture was diluted with EA (50 mL), quenched with H_2O (8 mL) and adjusted with 15% NaOH (8 mL). The combined organic layers were dried over Na_2SO_4 with stirring 10 min at 25 °C, filtered and concentrated under reduced pressure to give (3-ethoxy-1H-pyrazol-5-yl)methanol (4.30 g, 30.3 mmol, 30 % yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.71 (br s, 1H), 5.52 (s, 1H), 5.29 - 5.12 (m, 1H), 4.41 - 4.35 (m, 2H), 4.06 - 4.03 (m, 2H), 1.26 (s, 3H).

[01767] Step 4. To a solution of (3-ethoxy-1H-pyrazol-5-yl) methanol (4.30 g, 30.3 mmol, 1.00 *eq*) in DCM (50 mL) was added TBSCl (5.47 g, 36.3 mmol, 4.45 mL, 1.20 *eq*) and TEA (9.18 g, 90.8 mmol, 12.6 mL, 3.00 *eq*). The mixture was stirred at 25 °C for 8 hr. 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/Tetrahydrofuran=3/1 to 1/1) to give tert-butyl-[(3-ethoxy-1H-pyrazol-5-yl) methoxy]-dimethyl-silane (4.60 g, 17.9 mmol, 59% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.74 (br s, 1H), 5.54 (d, *J* = 2.0 Hz, 1H), 4.59 - 4.53 (m, 2H), 4.09 - 4.02 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.89 - 0.85 (m, 9H), 0.07 - 0.03 (m, 6H). LCMS: *m/z* 257.1 (M+1)

[01768] Step 5. To a solution of tert-butyl-[(3-ethoxy-1H-pyrazol-5-yl)methoxy]-dimethyl-silane (5.47 g, 21.3 mmol, 1.00 *eq*) in ACN (50 mL) was added ethyl 2-bromoacetate (5.35 g, 32.0 mmol, 3.54 mL, 1.50 *eq*) and Cs_2CO_3 (20.9 g, 64.0 mmol, 3.00 *eq*). The mixture was stirred at 80 °C for 2.5 hr. On completion, the mixture was filtered, washed with ethyl acetate (50 mL) and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=4/1 to 1/1) to give ethyl 2-[5-[[tert-butyl (dimethyl) silyl] oxymethyl]-3-ethoxy-pyrazol-1-yl] acetate (5.82 g, 17.0 mmol, 80% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.64 (s, 1H), 4.80 (s, 2H), 4.58 (s, 2H), 4.15 - 4.01 (m, 4H), 1.29 - 1.16 (m, 6H), 0.88 - 0.84(m, 9H), 0.05 (s, 6H). LCMS: *m/z* 343.1 (M+1)

[01769] Step 6. To a solution of ethyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3-ethoxy-pyrazol-1-yl]acetate (5.76 g, 16.8 mmol, 1.00 *eq*) in ACN (90 mL) was added NIS (3.78 g, 16.8 mmol, 1.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 4 hr. On completion, the mixture was quenched with saturated solution of Na_2SO_3 (12 mL) and partitioned between ethyl acetate(30 mL × 3) and water (90 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/Tetrahydrofuran=4/1 to 3/1) to give ethyl 2-[5-[[tert-butyl (dimethyl) silyl] oxymethyl]-3-ethoxy-4-iodo-pyrazol-1-yl] acetate (7.10 g, 15.2 mmol, 90% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.94 - 4.89 (m, 2H), 4.60 (s, 2H), 4.13 (qd, *J* = 7.2, 9.2 Hz, 4H), 1.32 - 1.27 (m, 3H), 1.22 -1.17 (m, 3H), 0.87 - 0.84 (m, 9H), 0.08 - 0.04 (m, 6H). LCMS: *m/z* 468.9 (M+1)

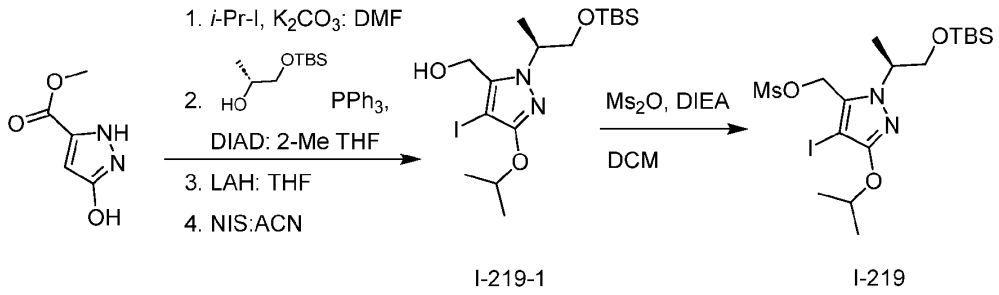
[01770] Step 6. A solution of ethyl 2-[5-[[tert-butyl (dimethyl) silyl] oxymethyl]-3-ethoxy-4-iodo-pyrazol-1-yl] acetate (6.84 g, 14.6 mmol, 1.00 *eq*) in HCOOH (35 mL) was stirred at 25 °C for 7 hr. On completion, the reaction mixture was partitioned between ethyl acetate (200 mL) and water (200 mL), the combined organic phase was washed with water (60 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Tetrahydrofuran=5/1 to 1/1) to give ethyl 2-[3-ethoxy-5-(hydroxymethyl)-4-iodo-pyrazol-1-yl]acetate (1.82 g, 5.14 mmol, 35% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.39 (t, *J* = 5.6 Hz, 1H), 4.94 (s, 2H), 4.38 (d, *J* = 5.6 Hz, 2H), 4.13 (dq, *J* = 1.6, 7.2 Hz, 4H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 355.0 (M+1)

[01771] Step 7. To a solution of ethyl 2-[3-ethoxy-5-(hydroxymethyl)-4-iodo-pyrazol-1-yl]acetate (500 mg, 1.41 mmol, 1.00 *eq*) in DCM (5 mL) was added DIEA (547 mg, 4.24 mmol, 738 μL, 3.00 *eq*) firstly and methylsulfonyl methanesulfonate (492 mg, 2.82 mmol, 2.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the reaction

mixture was concentrated under reduced pressure to give ethyl 2-[3-ethoxy-4-iodo-5-(methylsulfonyloxymethyl) pyrazol-1-yl] acetate (610 mg, crude) as brown oil. LCMS: *m/z* 432.8 (M+1)

[01772] 2-[3-ethoxy-4-iodo-5-(methylsulfonyloxymethyl) pyrazol-1-yl] acetate was converted to Ex. 218 after combining with 133-1 following procedures described in the synthesis of Ex. 191.

[01773] Preparation of (S)-(1-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4-iodo-3-isopropoxy-1H-pyrazol-5-yl)methyl methanesulfonate, I-219



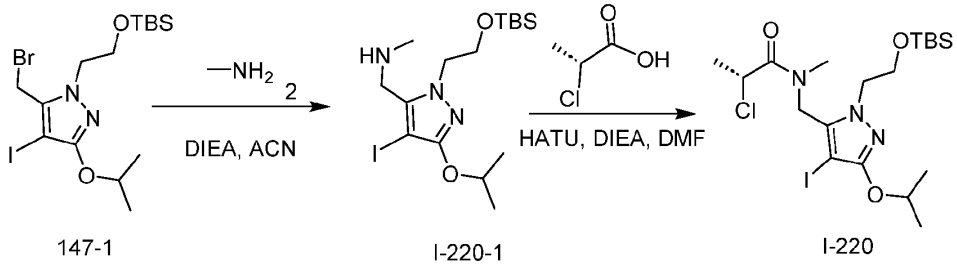
I-219-1 I-219

[01774] Steps 1 to 4 were conducted in a manner similar to those described in the synthesis of I-155.

[01775] Step 5 was conducted in a manner similar to that described in the synthesis of I-214.

[01776] I-219 was combined with 206-2 following procedures described in General Method M and Q to afford Ex. 219.

[01777] Preparation of (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl] methyl]-2-chloro-N-methyl-propanamide, I-220



147-1 I-220-1 I-220

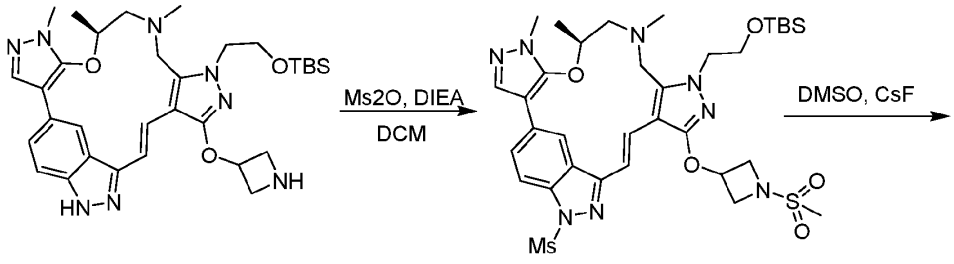
[01778] Step 1. To a solution of 2-[5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl] ethoxy-tert-butyl-dimethyl-silane (2.00 g, 3.97 mmol, 1 *eq*) and methanamine (536 mg, 7.95 mmol, 2 *eq*, HCl) in ACN (20 mL) was added DIEA (7.95 mmol, 1.4 mL, 2 *eq*). The mixture was stirred at 60 °C for 0.5 hours. 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, 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 1-[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methyl-methanamine (660 mg, 1.46 mmol, 36% yield) as colorless oil. LCMS: *m/z* 454.4 (M+1)

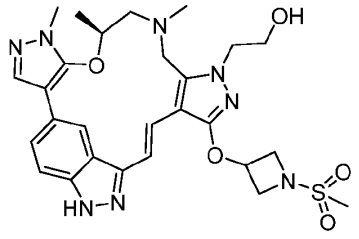
[01779] Step 2. To a solution of 1-[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methyl-methanamine (610 mg, 1.35 mmol, 1 *eq*) and (2S)-2-chloropropanoic acid (218 mg, 2.02 mmol, 1.5 *eq*) in DMF (5 mL) was added HATU (1.02 g, 2.69 mmol, 2 *eq*) and DIEA (521 mg, 4.04 mmol, 3 *eq*). The mixture was stirred at 25 °C for 0.5 hours. On completion, the mixture was 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 (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl] methyl]-2-chloro-N-methyl-propanamide, I-220 (200 mg, 0.367 mmol, 27% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.90 - 4.79 (m, 1H), 4.78 - 4.66 (m, 2H), 4.64 - 4.50 (m, 1H), 4.20 - 4.08 (m, 2H), 3.93 - 3.76 (m, 2H), 3.12 - 2.80 (m, 3H), 1.76 - 1.63 (m, 3H), 1.38 - 1.35 (m, 6H), 0.83 - 0.79 (m, 9H), -0.04 - -0.10 (m, 6H). LCMS: *m/z* 544.2 (M+1)

[01780] Ex. 220 was prepared from I-220 and 188-1 in a manner similar to those described in General Method M.

[01781] Preparation of 2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4'',3''-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 221)



From 185



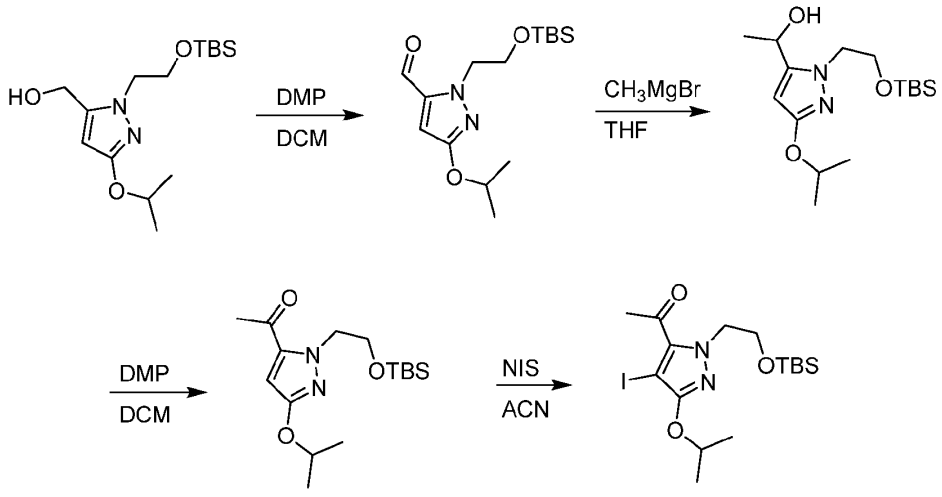
Ex. 221

[01782] Step 1 was conducted according to the synthesis of I-214 starting with intermediate from the synthesis of Ex. 185.

[01783] Step 2. To a solution of tert-butyl-dimethyl-[2-[(8S,17E)-5,8,10-trimethyl-21-methylsulfonyl-15-(1-methylsulfonylazetidin-3-yl)oxy-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaen-13-yl]ethoxy]silane (50.0 mg, 0.065 mmol, 1.00 *eq*) in DMSO (0.5 mL) was added CsF (29.4 mg, 0.193 mmol, 3.00 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:6%-36% B over 10 min) to give 2-[(8S,17E)-5,8,10-trimethyl-15-(1-methylsulfonylazetidin-3-yl)oxy-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaen-13-yl]ethanol, Ex. 221 (1.89 mg, 0.003 mmol, 5 % yield) as an off-white solid.

[01784] Ex. 222 was prepared from Ex. 218 following procedures described in Ex. 105.

[01785] Preparation of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethenone, I-223



I-223

[01786] Step 1. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazol-3-yl]methanol (1 g, 3.18 mmol, 1 *eq.* from Ex. 147) in DCM (15 mL) was added DMP (1.62 g, 3.82 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 4 hours. On completion, the mixture was filtered and concentrated to give 2-[2-[tert-

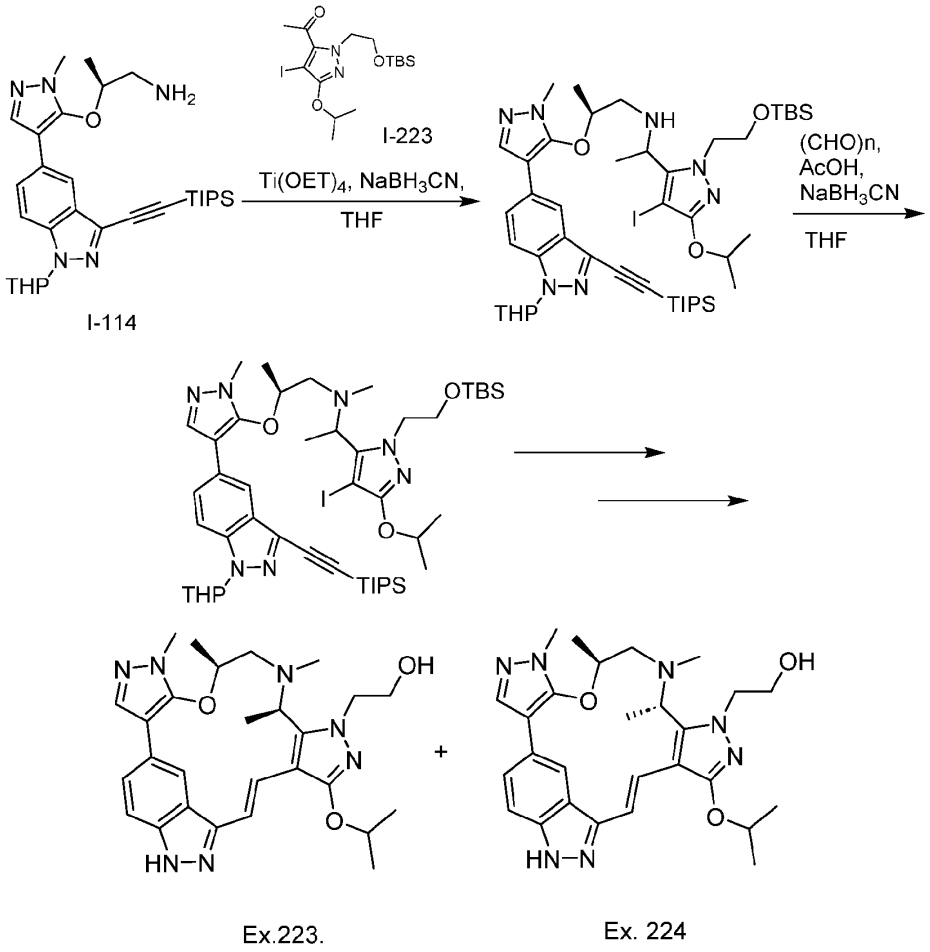
butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazole-3-carbaldehyde (800 mg, 2.56 mmol, 80% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (s, 1H), 6.22 - 6.21 (m, 1H), 4.73 (td, *J* = 6.0, 12.3 Hz, 1H), 4.52 - 4.47 (m, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 1.36 (d, *J* = 6.0 Hz, 6H), 0.84 - 0.81 (m, 9H), -0.03 - -0.08 (m, 6H). LCMS: *m/z* 313.4 (M+1)

[01787] Step 2. A solution of 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazole-3-carbaldehyde (800 mg, 2.56 mmol, 1 *eq*) in THF (10 mL) at 0°C. The mixture was degassed and purged with N_2 for 3 times, and then bromo(methyl)magnesium (3 M, 1 mL, 1.5 *eq*) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hour under N_2 atmosphere. On completion, the reaction mixture was partitioned between ethyl acetate (10 mL × 3) and water (10 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazol-3-yl]ethanol (700 mg, 2.13 mmol, 83% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.58 (s, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 4.72 - 4.62 (m, 1H), 4.21 - 4.15 (m, 2H), 4.05 - 3.98 (m, 1H), 3.93 - 3.88 (m, 1H), 3.78 - 3.73 (m, 1H), 1.53 (d, *J* = 6.4 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 6H), 0.83 (d, *J* = 0.8 Hz, 9H), 0.01 (d, *J* = 1.6 Hz, 6H). LCMS: *m/z* 329.2 (M+1)

[01788] Step 3. To a solution of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazol-3-yl]ethanol (640 mg, 1.95 mmol, 1 *eq*) in DCM (1 mL) was added DMP (991 mg, 2.34 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 4 hours. 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 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazol-3-yl]ethanone (550 mg, 1.68 mmol, 86% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.14 (s, 1H), 4.79 - 4.71 (m, 1H), 4.56 - 4.51 (m, 2H), 3.90 - 3.85 (m, 2H), 2.45 (s, 1H), 1.35 (d, *J* = 6.0 Hz, 6H), 0.84 - 0.82 (m, 9H), -0.02 - -0.05 (m, 6H). LCMS: *m/z* 327.2 (M+1)

[01789] Step 4. To a solution of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-isopropoxy-pyrazol-3-yl]ethanone (500 mg, 1.53 mmol, 1 *eq*) in ACN (6 mL) was added NIS (413 mg, 1.84 mmol, 1.2 *eq*). The mixture was stirred at 0 °C for 14 hours. On completion, the reaction mixture was partitioned between ethyl acetate (10 mL × 3) and water (10 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethanone (600 mg, 1.33 mmol, 86% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.92 - 4.84 (m, 1H), 4.48 (t, *J* = 5.6 Hz, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 2.74 (s, 3H), 1.39 - 1.36 (m, 6H), 0.85 - 0.82 (m, 9H), -0.01 - -0.05 (m, 6H). LCMS: *m/z* 453.0 (M+1)

[01790] Preparation of 1-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]-2-methylpropan-2-ol (Ex. 223) and 2-{(10*S*,13*S*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 224)



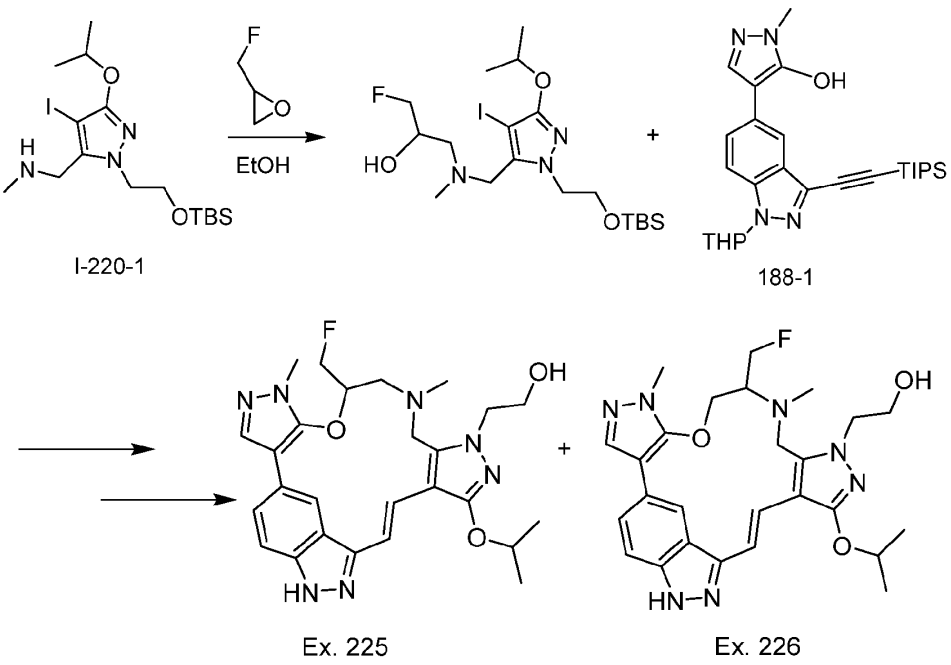
[01791] Step 1. To a mixture of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethanone (580 mg, 1.28 mmol, 1 *eq*), (2S)-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl] oxypropan-1-amine (686 mg, 1.28 mmol, 1 *eq*) in THF (10 mL) was added $Ti(OEt)_4$ (1.17 g, 5.13 mmol, 4 *eq*) at 25 °C for 1 hour, then $NaBH_3CN$ (483 mg, 7.69 mmol, 6 *eq*) was added at 70 °C. The mixture was stirred at 70 °C for 13 hours. On completion, the reaction mixture was partitioned between ethyl acetate (20 mL × 3) and water (10 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (2S)-N-[1-

[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethyl]-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (600 mg, 0.617 mmol, 48% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 - 7.74 (m, 1H), 7.66 - 7.57 (m, 3H), 5.78 - 5.69 (m, 1H), 4.17 - 4.09 (m, 5H), 2.05 (s, 7H), 1.56 (s, 24H), 1.39 - 1.32 (m, 9H), 1.30 - 1.24 (m, 9H), 0.85 - 0.81 (m, 9H), 0.02 - -0.06 (m, 6H). LCMS: *m/z* 973.3 (M+1)

[01792] Step 2. To a solution of (2S)-N-[1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethyl]-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (570 mg, 0.586 mmol, 1 *eq*) in THF (6 mL) was added AcOH (35.2 mg, 0.586 mmol, 1 *eq*), $(HCHO)_n$ (570 mg) and $NaBH_3CN$ (55.2 mg, 0.879 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 14 hours. On completion, the reaction mixture was partitioned between ethyl acetate (10 mL × 3) and water (10 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (2S)-N-[1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine (420 mg, 0.425 mmol, 72% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 - 7.66 (m, 2H), 7.61 - 7.53 (m, 1H), 7.50 - 7.38 (m, 1H), 5.79 - 5.69 (m, 1H), 4.88 - 4.74 (m, 1H), 4.40 (s, 1H), 4.18 - 4.03 (m, 3H), 3.98 - 3.85 (m, 4H), 3.80 - 3.71 (m, 2H), 2.72 - 2.43 (m, 3H), 2.22 - 2.09 (m, 2H), 2.03 - 1.91 (m, 2H), 1.77 (d, *J* = 9.2 Hz, 2H), 1.72 - 1.64 (m, 1H), 1.36 (d, *J* = 2.8 Hz, 8H), 1.30 - 1.25 (m, 3H), 1.19 (s, 21H), 1.14 - 1.01 (m, 3H), 0.82 (d, *J* = 4.0 Hz, 9H), -0.05 (dd, *J* = 2.4, 5.6 Hz, 6H)

[01793] (2S)-N-[1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]ethyl]-N-methyl-2-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-propan-1-amine was taken forward in a manner similar to those described in General Method M followed by SFC separation to afford Ex. 223 and Ex. 224.

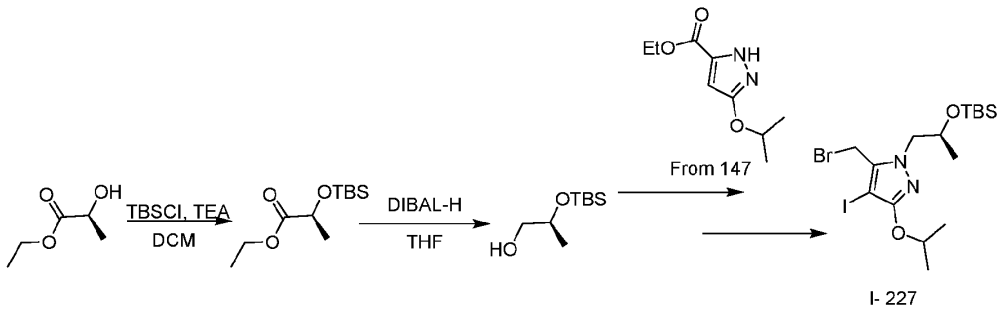
[01794] Preparation2-{(17*E*)-10-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 225) and 2-{(17*E*)-11-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 226)



[01795] Step 1. To a solution of 2-(fluoromethyl)oxirane (671 mg, 8.82 mmol, 2 *eq*) and 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methyl-methanamine (2.00 g, 4.41 mmol, 1 *eq*) in EtOH (20 mL) was added. The mixture was stirred at 70 °C for 16 h. 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=100/1 to 5/1) to give 1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-3-fluoro-propan-2-ol (1.60 g, 2.93 mmol, 66% yield, 97% purity) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.88 - 4.77 (m, 1H), 4.55 - 4.30 (m, 2H), 4.27 - 4.11 (m, 2H), 3.94 (d, *J* = 4.0 Hz, 1H), 3.93 - 3.87 (m, 2H), 3.77 - 3.55 (m, 2H), 2.68 - 2.46 (m, 2H), 2.28 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 6H), 0.81 (s, 9H), -0.07 (s, 6H).

[01796] 1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-3-fluoro-propan-2-ol was combined with 188-1 according to procedures described in General Method S to afford Ex. 225 and inverted by product Ex. 226.

[01797] Preparation of (S)-5-(bromomethyl)-1-(2-((tert-butyldimethylsilyl)oxy)propyl)-4-iodo-3-isopropoxy-1H-pyrazole, I-227



[01798] Step 1. To a solution of ethyl (2S)-2-hydroxypropanoate (5.00 g, 42.3 mmol, 1 *eq*) in DCM (50 mL) was added IMIDAZOLE (8.64 g, 127 mmol, 3 *eq*), and then TBSCl (9.57 g, 63.5 mmol, 1.5 *eq*) was added at 0°C. The mixture was stirred at 25 °C for 2 h. On completion, the reaction mixture was partitioned between DCM (60 mL × 3) and water (50 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/EA=10:1 to 10:1) to give ethyl (2S)-2-|tert-butyl(dimethyl)silyl| oxypropanoate (9.70 g, 41.7 mmol, 99% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.38 - 4.29 (m, 1H), 4.14 - 4.04 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.87 - 0.85 (m, 9H), 0.05 (d, J = 3.2 Hz, 6H)

[01799] Step 2. To a solution of ethyl (2S)-2-[tert-butyl(dimethyl)silyl]oxypropanoate (8.70 g, 37.4 mmol, 1 *eq*) in THF (87 mL) was added DIBAL-H (1 M, 74.8 mL, 2 *eq*) at 0°C under N_2 atmosphere. The mixture was stirred 25 °C for 4 h. On completion, water (3 mL), 15% NaOH (3 mL) and water (7.5 mL) was added successively, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 10:1) to give (2S)-2-| tert-butyl(dimethyl)silyl]oxypropan-1-ol (4.87 g, 25.6 mmol, 68% yield) as a white oil.^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.53 (t, J = 5.6 Hz, 1H), 3.80 - 3.66 (m, 1H), 3.30 - 3.09 (m, 2H), 1.09 - 0.99 (m, 3H), 0.87 -0.84 (m, 8H), 0.04 (d, J = 0.8 Hz, 6H)

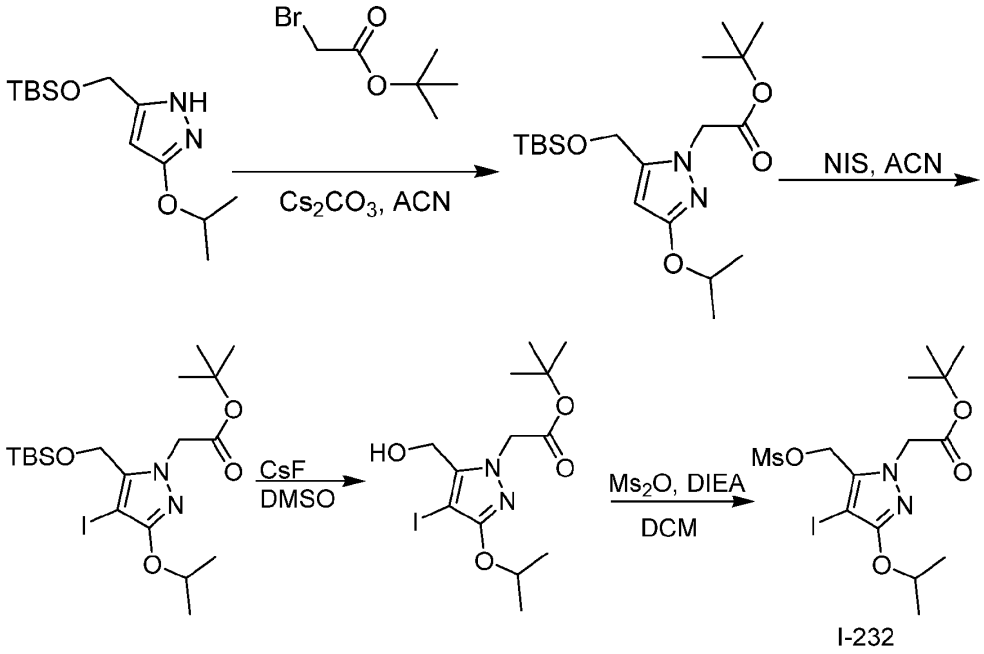
[01800] The remaining steps were conducted similarly to those described in Ex. 186-2 using (2S)-2-[tert-butyl(dimethyl)silyl]oxypropan-1-ol and ethyl 3-isopropoxy-1H-pyrazole-5-carboxylate (from Ex. 147) to afford I-227

[01801] Ex. 227 was prepared in a manner similar to those described in General Method S from ethylamine, I-227 in step 2 and 188-1 in step 4.

[01802] Inverted Ex. 228 and double inverted Ex. 229 was isolated from Prep-HPLC following syntheses like those described in General Method S from I-214 in step 2 and I-194 in step 4.

[01803] Inverted Ex. 230 and double inverted Ex. 231 was isolated from Prep-HPLC following syntheses like those described in General Method S from I-219 in step 2 and I-194 in step 4.

[01804] Preparation of tert-butyl 2-[4-iodo-3-isopropoxy-5-(methylsulfonyloxymethyl) pyrazol-1-yl] acetate, I-232



I-232

[01805] Step 1. To a solution of tert-butyl 2-bromoacetate (25.2 g, 129 mmol, 1.40 *eq*) in ACN (250 mL) was added tert-butyl-[(3-isopropoxy-1H-pyrazol-5-yl)methoxy]-dimethyl-silane (25.0 g, 92.4 mmol, 1.00 *eq*, from Ex. 147) and Cs_2CO_3 (90.3 g, 277 mmol, 3.00 *eq*). The mixture was stirred at 80 °C for 2.5 hr. On completion, the mixture was diluted with water (250 mL) and extracted with ethyl acetate (300 mL * 3) and washed with saturated NaCl (300 mL * 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3-isopropoxy-pyrazol-1-yl]acetate (31.0 g, crude) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.74 (s, 1H), 4.67 (s, 2H), 4.64 - 4.58 (m, 1H), 4.56 (s, 2H), 1.41 - 1.39 (m, 9H), 1.23 (d, J = 6.0 Hz, 6H), 0.86 (s, 9H), 0.05 (s, 6H). LCMS: *m/z* 385.3 (M+1)

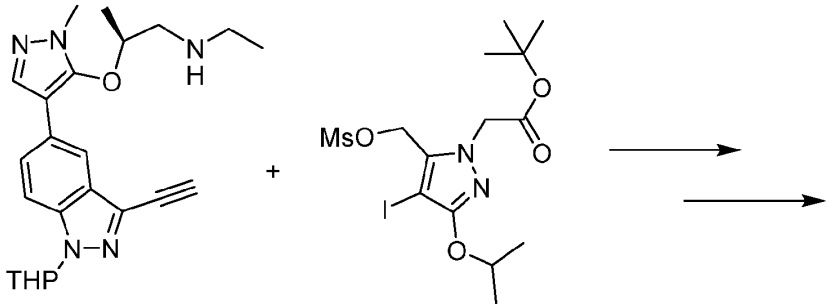
[01806] Step 2. To a solution of tert-butyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-3-isopropoxy-pyrazol-1-yl]acetate (30.0 g, 78.0 mmol, 1.00 *eq*) in ACN (300 mL) was added NIS (17.5 g, 78.0 mmol, 1.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1 hr. On completion, the mixture was quenched with water (300 mL) and extracted with EA (300 mL

*3). The combined organic layers were washed with brine (300 mL *3), dried over Na_2SO_4, filtered and concentrated to give tert-butyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-4-iodo-3-isopropoxy-pyrazol-1-yl]acetate (31.0 g, crude) as a red oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.80 (s, 2H), 4.75 - 4.70 (m, 1H), 4.57 (s, 2H), 1.40 (s, 9H), 1.26 (d, J = 6.0 Hz, 6H), 0.87 (s, 9H), 0.08 (s, 6H).

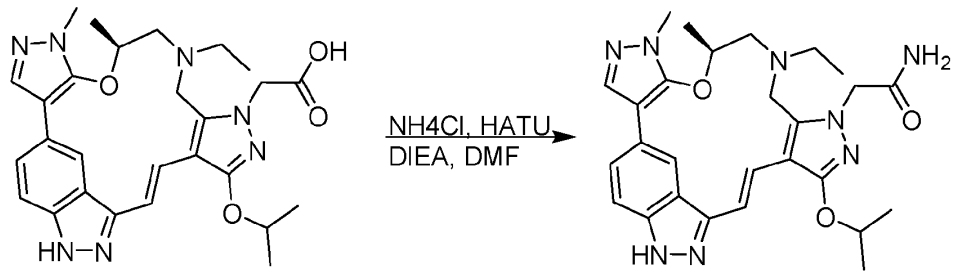
[01807] Step 3. To a solution of tert-butyl 2-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-4-iodo-3-isopropoxy-pyrazol-1-yl]acetate (3.00 g, 5.88 mmol, 1.00 *eq*) in DMSO (30 mL) was added CsF (2.68 g, 17.6 mmol, 3.00 *eq*) at 25 °C. The mixture was stirred at 25°C for 1 hr. On completion, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (80 mL*3) and washed with saturated NaCl (100 ml *3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 2-[5-(hydroxymethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl]acetate (2.28 g, crude) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.37 (t, J = 5.6 Hz, 1H), 4.81 (s, 2H), 4.75 - 4.70 (m, 1H), 4.36 (d, J = 5.6 Hz, 2H), 1.42 - 1.41 (m, 9H), 1.26 (d, J = 6.0 Hz, 6H).

[01808] Step 4. To a solution of tert-butyl 2-[5-(hydroxymethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl]acetate (2.50 g, 6.31 mmol, 1.00 *eq*) in DCM (25 mL) was added DIEA (3.26 g, 25.2 mmol, 4.40 mL, 4.00 *eq*) at 0 °C. Then methylsulfonylmethanesulfonate (2.20 g, 12.6 mmol, 2.00 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was quenched with water (30 mL) and extracted with DCM (30 mL *3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give tert-butyl 2-[4-iodo-3-isopropoxy-5-(methylsulfonyloxymethyl) pyrazol-1-yl] acetate (3.00 g, crude) as a brown oil. LCMS: *m/z* 496.8 (M+1)

[01809] Preparation of 2-{(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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}acetamide (Ex. 232)



133-1 I-232



232-1 Ex. 232

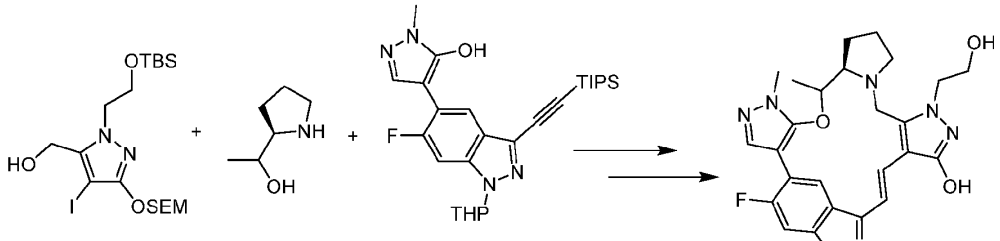
[01810] I-232 was combined with 133-1 following procedures similar to those described in General Method M to afford 232-1.

[01811] To a solution of 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetic acid (30.0 mg, 0.058 mmol, 1.00 *eq*) in THF (1 mL) was added DIEA (14.9 mg, 0.115 mmol, 2.00 *eq*) and HATU (32.9 mg, 0.087 mmol, 1.50 *eq*) for 0.5 h, the mixture was added NH_4Cl (3.09 mg, 0.058 mmol, 1.00 *eq*) stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated in vacuum. The mixture was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:10%-40% B over 10 min) to give Ex. 232 as a yellow solid.

[01812] Ex. 233 was prepared in the same manner as Ex. 188 with the appropriate linker.

[01813] Ex. 234 was prepared from Ex. 210 and 2-iodopropane following preparations described in General Method R.

[01814] Preparation of (52R,E)-16-fluoro-71-(2-hydroxyethyl)-21,4-dimethyl-11H,21H,71H-3-oxa-1(5,3)-indazola-2(4,5),7(5,4)-dipyrazola-5(2,1)-pyrrolidinacyclononaphan-8-en-73-ol, I-235



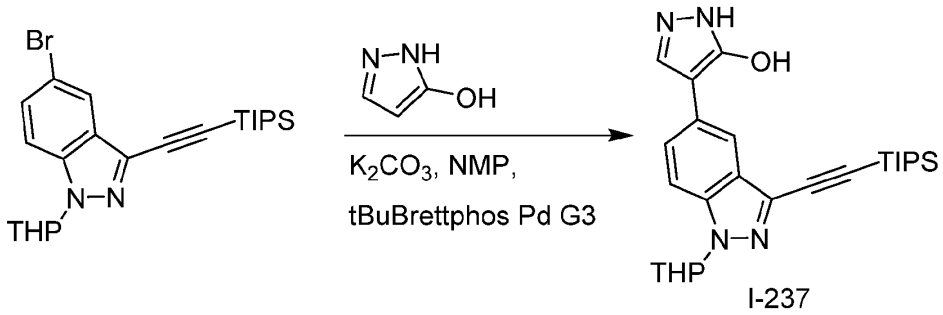
from 186-2 1-[(2R)-pyrrolidin-2-yl] ethanol I-194 I-235

[01815] I-235 was synthesized following procedures described in General Method P and General M from the intermediates and starting material listed.

[01816] I-235 was combined with bromomethylcyclopropane following preparations described in General Method R to afford Ex. 235.

[01817] Ex. 236 was prepared in a similar manner to those described in General Method M with tert-butyl (S)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate as starting material and intermediates G-1-1, and I-156 where appropriate.

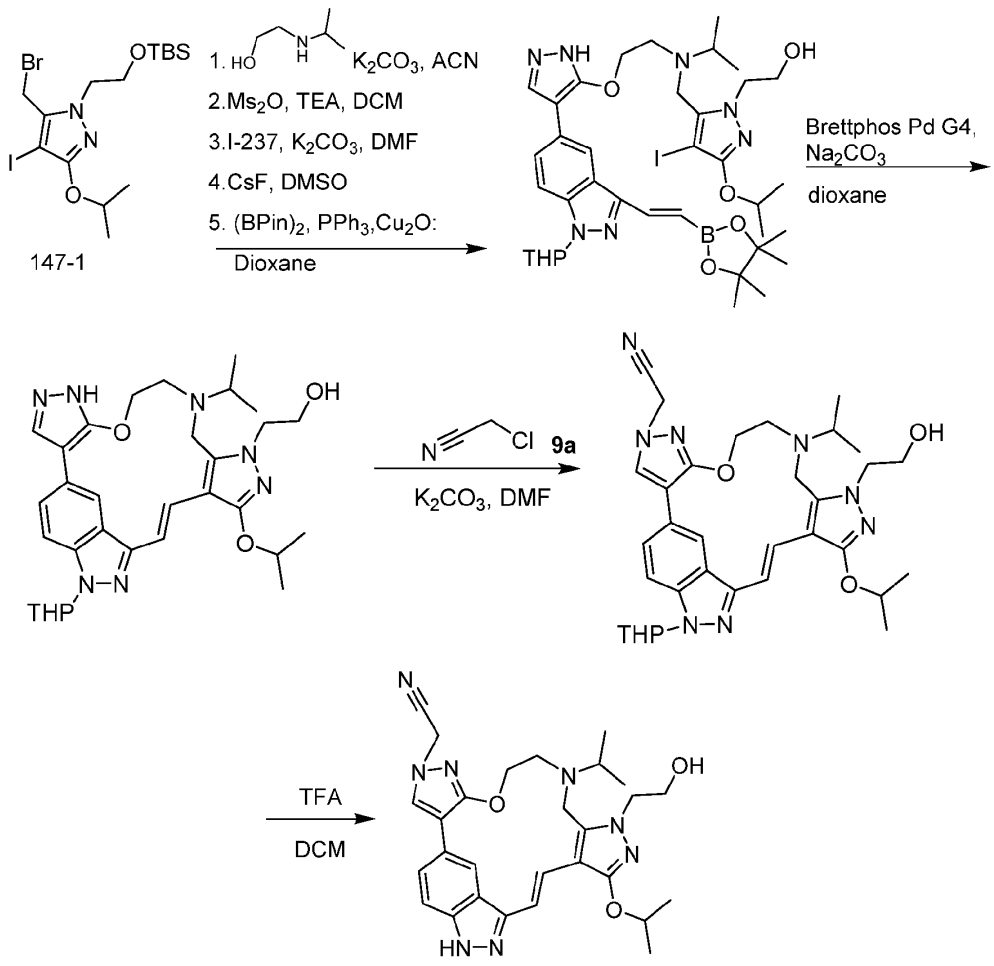
[01818] Preparation of 4-[1-tetrahydropyran-2-yl-3-(2-triisopro pylsilylethynyl) indazol-5-yl]-1H-pyrazol-5-ol, I-237



I-237

[01819] Step 1. The mixture of 1H-pyrazol-5-ol (109 mg, 1.30 mmol, 1.2 *eq*), 2-(5-bromo-1-tetrahyd ropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (500 mg, 1.08 mmol, 1 *eq.*), tBuBrettphos (46.3 mg, 0.054 mmol, 0.05 *eq*), K_2CO_3 (299 mg, 2.17 mmol, 2 *eq*) in NMP (20 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 quenched by addition H_2O 250 mL and extracted with EA (200 mL * 3). The combined organic layers were washed with NaCl 300 mL, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0:1) to give 4-[1-tetrahydropyran-2-yl-3-(2-triisopro pylsilylethynyl) indazol-5-yl]-1H-pyrazol-5-ol (130 mg, 0.279 mmol, 26% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.00 - 11.46 (m, 1H), 10.48 - 9.89 (m, 1H), 8.02 (s, 1H), 7.87 (s, 1H), 7.71 - 7.59 (m, 2H),3.82 (br d, J = 11.2 Hz, 1H), 3.72 - 3.61 (m, 2H), 2.34 - 2.20 (m, 2H), 1.93 - 1.83 (m, 4H), 1.73 - 1.60 (m, 2H), 1.09 - 1.06 (m, 21H)

[01820] Preparation of {(17*E*)-14-(2-hydroxyethyl)-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-7-yl}acetonitrile (Ex. 237)



Ex. 237

[01821] Steps 1 through 5 were conducted in a manner similar to those described for General Method S.

[01822] Step 6 was conducted according to General Method Q.

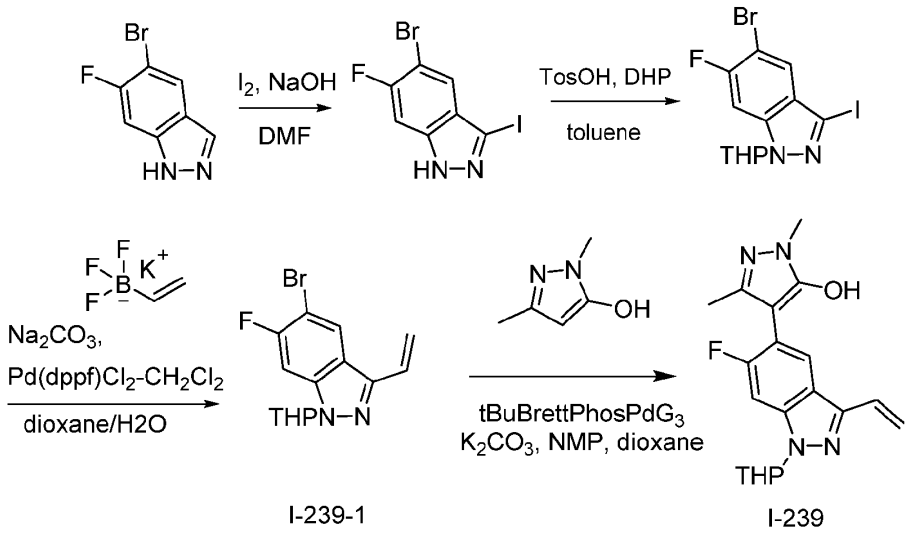
[01823] Step 7. To a solution of 2-[(17E)-15-isopropoxy-10-isopropyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(25),2(6),3, 12(16),14,17,19,22(26),23-nonaen-13-yl]ethanol (40.0 mg, 0.070 mmol, 1 *eq*), 2-chloroacetonitrile (10.4 mg, 0.138 mmol, 2 *eq)* in DMF (0.6 mL) was added K_2CO_3 (28.8 mg, 0.208 mmol, 3 *eq*). The mixture was stirred at 60 °C for 1 h. On completion, the mixture was diluted with water (2 mL) and extracted with ethyl acetate (1 mL × 3). The combined organic phase was washed with water (2 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF=1:2) to give 2-[(17E)-

13-(2-hydroxyethyl)-15-isopropoxy-10-isopropyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-hepta zapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23 -nonaen-5-yl]acetonitrile (12.0 mg, 0.020 mmol, 28% yield) as a yellow solid. LCMS: *m/z* 615.3 (M+1)

[01824] Step 8. To a solution of 2-[(17E)-13-(2-hydroxyethyl)-15-isopropoxy-10-isopropyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$. $0^{22,26}$]hexacosa-1(25),2,5,12(16),14,17,19,22(26),23-nonaen-4-yl]acetonitrile (9.00 mg, 0.015 mmol, 1 *eq*) in DCM (1 mL) was added TFA (460 mg, 4.04 mmol, 1 mL, 275 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters xbridge 150*25mm 10um;mobile phase: [water (NH_4HCO_3)-ACN];gradient:29%-59% B over 10 min) to Ex. 237 (1.76 mg, 0.003 mmol, 23 % yield) as a white solid.

[01825] Ex. 238 was prepared in a similar manner to those described in General Method M with tert-butyl 3-hydroxyazetidine-1-carboxylate as starting material and intermediates G-1-1, and I-156 where appropriate.

[01826] Preparation of 4-(6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-3-vinyl-1H-indazol-5-yl)-1,3-dimethyl-1H-pyrazol-5-ol, I-239



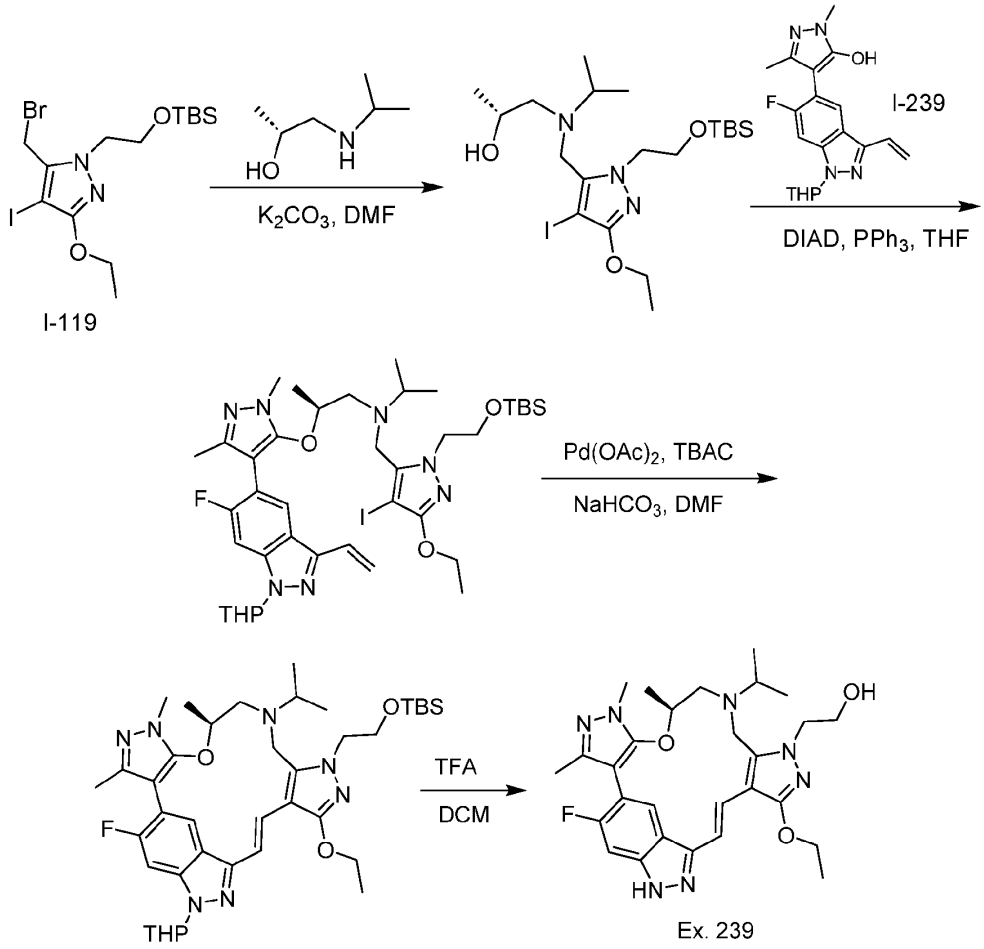
[01827] Steps 1 and 2 were performed in a similar manner to synthesis of C-1-1.

[01828] Step 3. To a solution of 5-bromo-6-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole (9.50 g, 22.4 mmol, 1 *eq*) in dioxane (100 mL) and H_2O (20 mL) was added potassium;trifluoro(vinyl)boranuide (2.99 g, 22.4 mmol, 1 *eq*), Na_2CO_3 (7.11 g, 67 mmol, 3

eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.83 g, 2.24 mmol, 0.1 *eq*) at 25 °C under N_2, then the mixture was stirred at 80 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (150 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 under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~15% THF/Petroleum ether gradient @ 80 mL/min). Compound 5-bromo-6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazole (4.30 g, 13.2 mmol, 59% yield) as a yellow solid.

[01829] Step 4 was conducted in a manner similar to those described in I-237 to give I-239.

[01830] General Method T: Preparation of 2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 239)



[01831] Step 1. To a solution of 2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl] ethoxy-tert-butyl-dimethyl-silane (1.00 g, 2.04 mmol, 1 *eq*) in DMF (10 mL) was added (2R)-1-(isopropylamino) propan-2-ol (240 mg, 2.04 mmol, 1 *eq*) and K_2CO_3 (847 mg, 6.13 mmol, 3 *eq*). The mixture was stirred at 80 °C for 2 h. On completion, the mixture was diluted with H_2O (20 mL) and extracted with EA (30 mL * 3). The combined organic layers was dried over Na_2SO_4, filtered and the filtrate was 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 (2R)-1-[[2-[2-[tert-butyl (dimethyl) silyl] oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl] methyl-isopropyl-amino] propan-2-ol (760 mg, 1.45 mmol, 71% yield) was obtained as yellow oil. LCMS: *m/z* 526.5 (M+1)

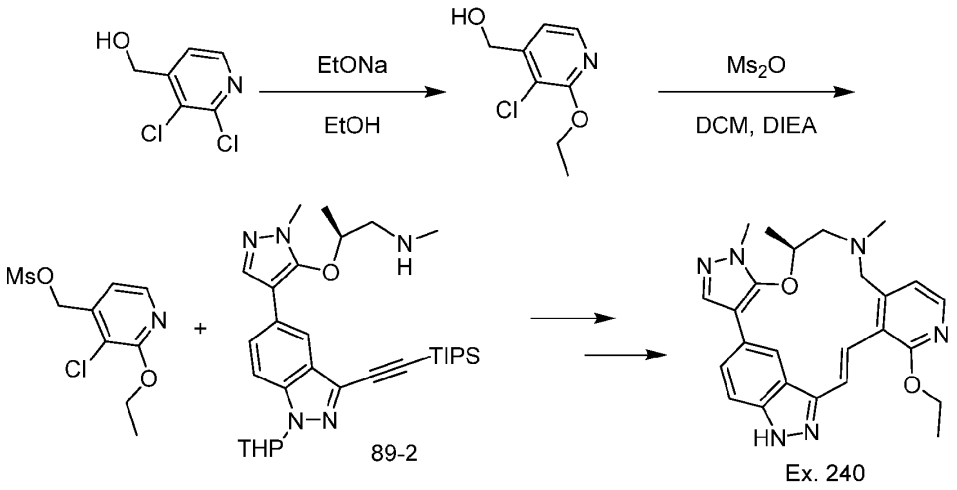
[01832] Step 2. A mixture of (2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-isopropyl-amino]propan-2-ol (545 mg, 1.04 mmol, 1 *eq*), 4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2,5-dimethyl-pyrazol-3-ol (443 mg, 1.24 mmol, 1.2 *eq*), PPh_3 (598 mg, 2.28 mmol, 2.2 *eq*) in THF (3 mL) was degassed and purged with N_2 for 3 times, and stirred at 25 °C for 0.5 h, and then DIAD (461 mg, 2.28 mmol, 2.2 *eq*) was added at 0 °C, the mixture was stirred at 25 °C for 1.5 h 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 (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl]-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2,5-dimethyl-pyrazol-3-yl]oxy-N-isopropyl-propan-1-amine (800 mg, 0.926 mmol, 89% yield) as a yellow oil. LCMS: *m/z* 864.3 (M+1)

[01833] Step 3. A mixture of (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl]-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2,5-dimethyl-pyrazol-3-yl]oxy-N-isopropyl-propan-1-amine (501 mg, 0.580 mmol, 1 eq), TBAC (161 mg, 0.580 mmol, 1 eq), NaHCO3 (122 mg, 1.45 mmol, 2.5 eq) and Pd(OAc)2 (26.1 mg, 0.116 mmol, 0.2 eq) in DMF (6 mL) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 140 °C for 1 h under N2 atmosphere. On completion, the reaction mixture was diluted with H2O (30 mL) and extracted with EA (30 mL * 3). The combined organic layers were washed with H2O (20 mL * 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/THF=1/0 to 0/1) to give tert-butyl-[2-[(8S,17E)-15-ethoxy-24-fluoro-10-isopropyl-3,5,8-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26]hexacosa-

1(24),2(6),3,12(16),14,17,19,22,25-nonaen-13-yl]ethoxy]-dimethyl-silane (360 mg, 0.489 mmol, 84% yield) as a brown oil. LCMS: *m/z* 736.3 (M+1)

[01834] Step 4. To a solution of tert-butyl-[2-[(8S,17E)-15-ethoxy-24-fluoro-10-isopropyl-3,5,8-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(24),2(6),3,12(16),14,17,19,22,25-nonaen-13-yl]ethoxy]-dimethyl-silane (130 mg, 0.177 mmol, 1 *eq*) in DCM (1.5 mL) was added TFA (2.30 g, 20.2 mmol, 1.5 mL, 114 *eq*). The mixture was stirred at 25 °C for 1h. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 12%-42% B over 10 min) to give Ex. 239 (16.7 mg, 0.028 mmol, 16 % yield, 96.50% purity, FA) as a white solid.

[01835] Preparation of (10*S*,18*E*)-17-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[4,3-*f*][1,4]oxazacyclopentadecine, Ex. 240



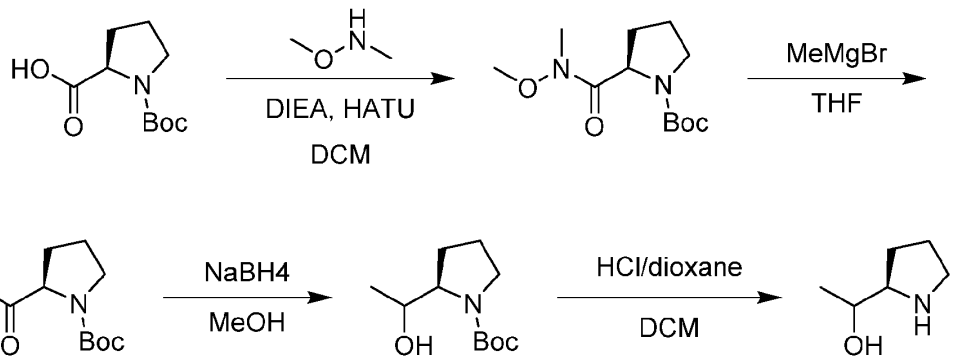
[01836] Step 1. Freshly prepared EtONa in EtOH (from Na (4.84 g, 210 mmol, 12.5 *eq*) in dry EtOH (25 mL)) was added dropwise to a solution of (2,3-dichloro-4-pyridyl)methanol (3.00 g, 16.8 mmol, 1 *eq*) in EtOH (40 mL). The mixture was stirred at 80 °C for 16 h. LCMS showed part of the reactant 1 was remained and one peak with desired mass was detected. Then freshly prepared EtONa in EtOH (from Na (4.84 g, 210 mmol, 12.5 *eq*) in dry EtOH (25 mL)) was added to the reaction solution. On completion, the mixture was concentrated under reduced pressure to give a residue. The residue was quenched with H_2O (300 mL) and extracted with EtOAc (3*300 mL). The combined organic layers were washed with brine (3*200mL), dried over Na_2SO_4 and concentrated in vacuum. The residue

was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give (3-chloro-2-ethoxy-4-pyridyl)methanol (1.48 g, 6.27 mmol, 37% yield, 79% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.09 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 5.2 Hz, 1H), 5.59 (t, J = 5.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H). LCMS: m/z 188.0 (M+1).

[01837] Step 2. To a solution of (3-chloro-2-ethoxy-4-pyridyl)methanol (1.45 g, 7.73 mmol, 1 *eq*), DIEA (3.00 g, 23.1 mmol, 4.04 mL, 3 *eq*) in DCM (30 mL) at 0 °C was added methylsulfonylmethanesulfonate (2.02 g, 11.5 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was concentrated under reduced pressure to give (3-chloro-2-ethoxy-4-pyridyl)methyl methanesulfonate (2.05 g, 7.72 mmol, 100% yield, crude) as a yellow solid. LCMS: m/z 265.9 (M+1).

[01838] 3-chloro-2-ethoxy-4-pyridyl)methyl methanesulfonate was combined with 89-2 in a manner similar to those described in Ex. 191 to afford Ex. 240 as a white solid.

[01839] Preparation of 1-((R)-pyrrolidin-2-yl)ethan-1-ol, I-241



I-241

[01840] Step 1. To a solution of (2R)-1-tert-butoxycarbonylpyrrolidine-2-carboxylic acid (20.0 g, 92.9 mmol, 1 *eq*), N-methoxymethanamine (6.24 g, 102 mmol, 1.10 *eq*), DIEA (24.0 g, 185 mmol, 2.00 *eq*), HATU (38.8 g, 102 mmol, 1.10 *eq*) in DCM (200 mL). The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was diluted with water (300 mL) and extracted with DCM (60 mL × 3). The combined organic phase was washed with water (200 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=1:0 to 90:10) to give tert-butyl (R)-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate(11.0 g, 42.5 mmol, 46% yield) as a yellow oil. LCMS: m/z 159.1 (M+1-100).

[01841] Step 2. To a solution of tert-butyl (2R)-2-[methoxy(methyl)carbamoyl]pyrrolidine-1-carboxylate (10.0 g, 38.7 mmol, 1.00 *eq*) in THF

(100 mL) was added bromo(methyl)magnesium (3 M, 38.7 mL, 3.00 *eq*) at -78 °C under atmosphere. The mixture was stirred at -78 °C for 2 hr. On completion, the reaction mixture was quenched with sat. NH_4Cl (200 mL) at 0 °C, and then diluted with H_2O (150 mL) and extracted with EA (60 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 column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 1:1) to give tert-butyl (R)-2-acetylpyrrolidine-1-carboxylate (7.00 g, 32.8 mmol, 85% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.37 - 4.13 (m, 1H), 3.60 - 3.38 (m, 2H), 2.31 - 2.00 (m, 4H), 1.92 - 1.76 (m, 3H), 1.52 - 1.37 (m, 9H).

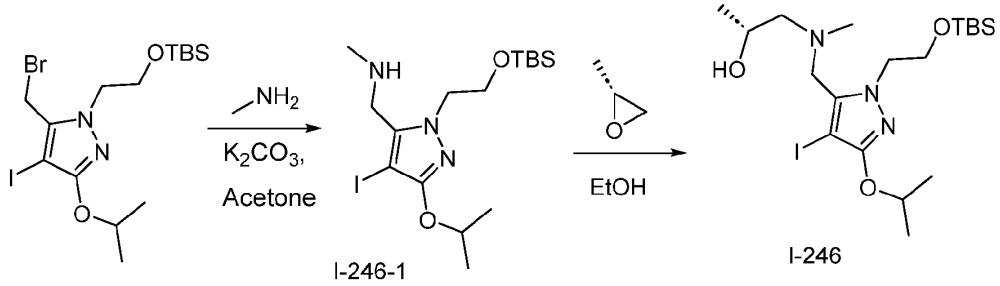
[01842] Step 3. To a solution of tert-butyl (2R)-2-acetylpyrrolidine-1-carboxylate (6.50 g, 30.4 mmol, 1.00 *eq*) in MeOH (65 mL) was added $NaBH_4$ (3.46 g, 91.4 mmol, 3.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hr. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 1:1) to give tert-butyl (2R)-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (5.60 g, 26.0 mmol, 85% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.01 - 3.81 (m, 1H), 3.77 - 3.45 (m, 2H), 3.31 - 3.20 (m, 1H), 2.05 - 1.64 (m, 4H), 1.46 (s, 9H), 1.16 - 1.03 (m, 3H). LCMS: *m/z* 116.2 (M+1-100)

[01843] Step 4. To a solution of tert-butyl (2R)-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (1.00 g, 4.64 mmol, 1.00 *eq*) in DCM (10 mL) was added HCl/dioxane (4 M, 2.00 mL, 1.72 *eq*). The mixture was stirred at 25 °C for 2 hr. On completion, the mixture was concentrated to give 1-((R)-pyrrolidin-2-yl)ethan-1-ol, I-241 (700 mg, crude) as a white oil.

[01844] I-241 was combined with 119-2, then 188-1 following synthesis described in General Method S to give 3 compounds after prep HPLC: arbitrarily assigned stereo isomers Ex. 241, Ex. 242, and rearranged by product Ex. 243

[01845] I-241 and 119-2 were combined with I-194 in the same way to afford arbitrarily assigned Ex. 243, ex. 244, and rearranged by product Ex. 245.

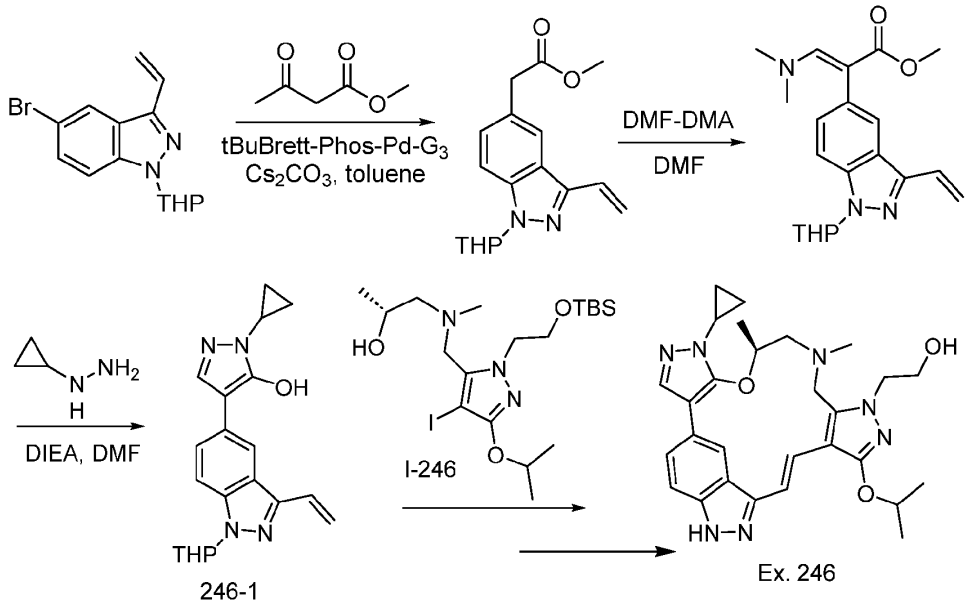
[01846] Preparation of (2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methylamino]propan-2-ol (I-246).



[01847] Step 1. To a solution of 2-[5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl]ethoxy-tert-butyl-dimethyl-silane (2.00 g, 3.97 mmol, 1 *eq*) in acetone (50 mL) was added methanamine (2 M, 19.9 mL, 10 *eq*) and K_2CO_3 (1.65 g, 11.9 mmol, 3 *eq*) . The mixture was stirred at 20 °C for 1 hour. On completion, the mixture was filtered and concentrated to give the crude compound. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1) to give 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methyl-methanamine (800 mg, 1.76 mmol, 44% yield) as a brown oil. LCMS: *m/z* 454.3 (M+1).

[01848] Step 2. To a solution of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methylmethanamine (800 mg, 1.76 mmol, 1 *eq*) in EtOH (5 mL) was added (2R)-2-methyloxirane (123 mg, 2.12 mmol, 1.2 *eq*) . The mixture was concentrated to give (2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methylamino]propan-2-ol (520 mg, 1.02 mmol, 58% yield) as a brown oil. LCMS: *m/z* 512.0 (M+1).

[01849] Preparation of 2-{(10*S*,17*E*)-8-cyclopropyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 246)



[01850] Step 1. A mixture of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (5.00 g, 16.3 mmol, 1 *eq*), methyl 3-oxobutanoate (2.83 g, 24.4 mmol, 1.5 *eq*), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6- dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (695 mg, 0.814 mmol, 0.05 *eq*), Cs_2CO_3 (15.9 g, 48.8

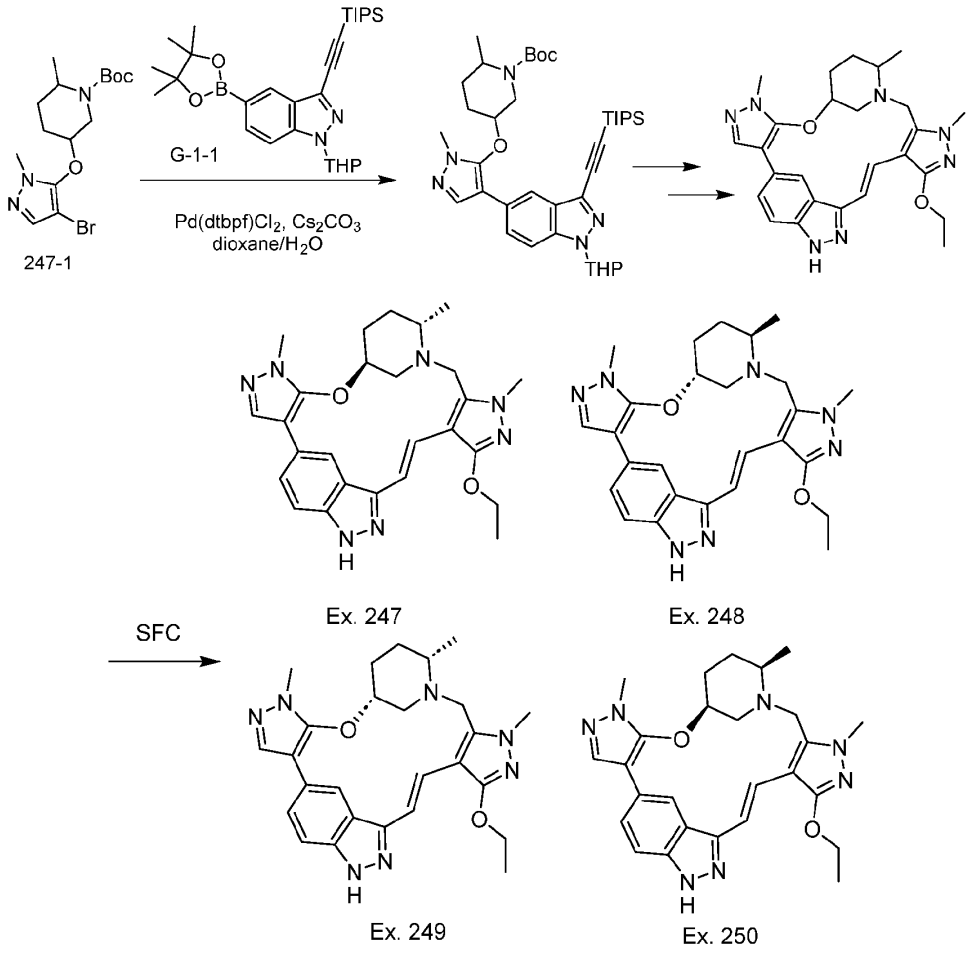
mmol, 3 *eq*) in toluene. (60 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 12 hours under N_2 atmosphere. On completion, the reaction mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (80 g silica gel column, THF in PE from 0% to 10%) to give methyl 2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)acetate (3.10 g, 10.3 mmol, 63% yield) as a brown oil.

[01851] Step 2. To a solution of methyl 2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)acetate (3.10 g, 10.3 mmol, 1 *eq*) in DMF (20 mL) was added DMF-DMA (1.84 g, 15.5 mmol, 1.5 *eq*). The mixture was stirred at 60 °C for 16 hours. On completion, the reaction mixture was concentrated in vacuum to give methyl (E)-3-(dimethylamino)-2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)prop-2-enoate (3.60 g, 10.1 mmol, 98% yield) as a brown oil. LCMS: *m/z* 356.2 (M+1).

[01852] Step 3. To a solution of methyl (E)-3-(dimethylamino)-2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)prop-2-enoate (3.60 g, 10.1 mmol, 1 *eq*), cyclopropylhydrazine;hydrochloride (1.65 g, 15.2 mmol, 1.5 *eq*) in DMF (30 mL) was added DIEA (6.55 g, 50.6 mmol, 5 *eq*). The mixture was stirred at 60 °C for 1 hour. On completion, the reaction mixture was poured into water (100 mL), extracted with ethyl acetate (50 mL * 3), the combined organic layers were washed with brine (40 mL * 2), 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=10/1 to 0/1) to give 2-cyclopropyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (1.80 g, 5.14 mmol, 51% yield) as a brown oil. LCMS: *m/z* 351.2 (M+1).

[01853] The remaining steps were conducted according to General Method T from 246-1 and I-246 to afford Ex. 246.

[01854] Preparation of (10*S*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine, (10*R*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine, (10*R*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine, and (10*S*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine (Ex. 247-250)



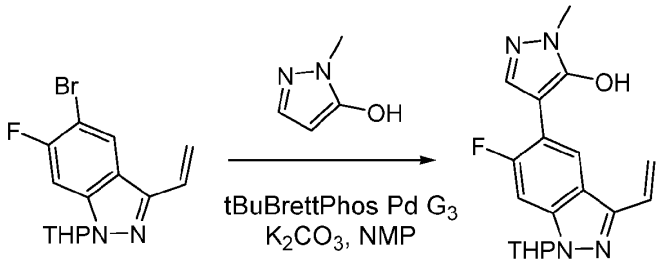
[01855] Step 1. A mixture of tert-butyl 5-(4-bromo-2-methyl-pyrazol-3-yl)oxy-2-methyl-piperidine-1-carboxylate (1.5 g, 4.01 mmol, 1 *eq,* from General Method M), triisopropyl-[2-[1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazol-3-yl]ethynyl]silane (1.63 g, 3.21 mmol, 0.8 *eq*), ditert-butyl(cyclopentyl)phosphane; dichloropalladium;iron (130 mg, 0.200 mmol, 0.05 *eq*), Cs_2CO_3 (1.31 g, 4.01 mmol, 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 12 hours under N_2 atmosphere. On completion the reaction mixture was quenched by addition H_2O (100 mL), and extracted with EA (100mL * 3). The combined organic layers were washed with sat. NaCl (100 mL), concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1) to give tert-butyl 2-methyl-5-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-

5-yl]pyrazol-3-yl]oxy-piperidine-1-carboxylate (2 g, 2.96 mmol, 73% yield) as a white solid. LCMS: *m/z* 676.4 (M+1)

[01856] tert-butyl 2-methyl-5-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-piperidine-1-carboxylate was converted to mixtures of isomers: tert-butyl 2-methyl-5-[2-methyl-4-[1-tetrahydropyran-2-yl-3-(2-triisopropylsilylethynyl)indazol-5-yl]pyrazol-3-yl]oxy-piperidine-1-carboxylate via General Method M.

[01857] SFC separation resulted in 4 compounds that were arbitrarily assigned as Ex. 247, Ex. 248, Ex. 249, and Ex. 250.

[01858] Preparation of 4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-ol (I-251).

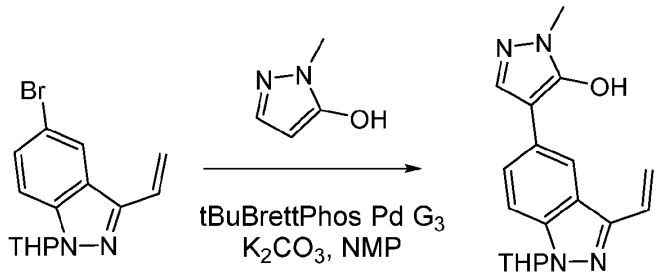


I-239-1 I-251

[01859] I-239-1 was converted to I-251 following procedure detailed in the synthesis of I-237.

[01860] Ex. 251 was isolated as a byproduct from a mixture obtained from I-251 and I-246 following General Method T.

[01861] Preparation of I-252

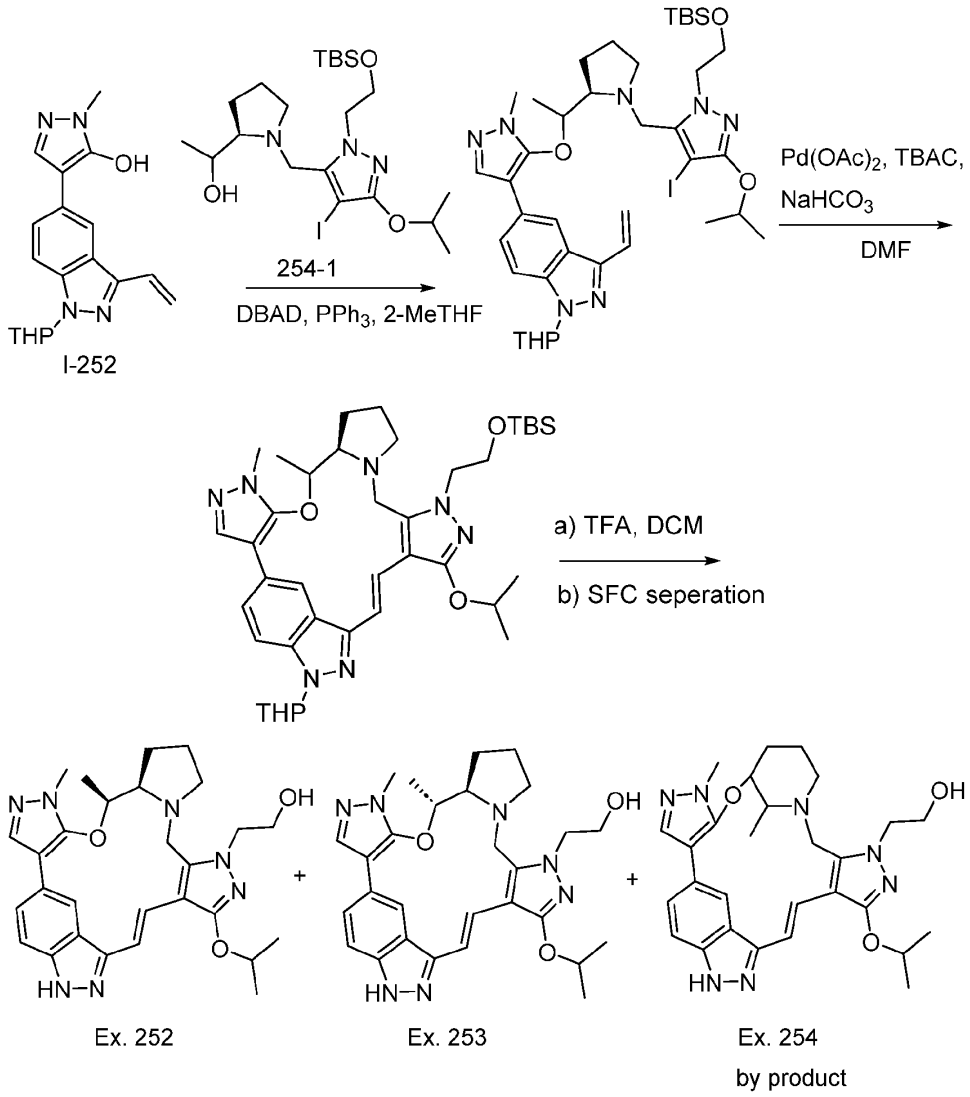


B-1-1 I-252

[01862] I-252 was prepared according to synthesis of I-237 from B-1-1.

[01863] General Method U: Preparation of 2-[(8a*R*,9*S*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

n]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol (Ex. 252), 2-[(8a*R*,9*R*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol (Ex. 253), and 2-[(19*E*)-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol (Ex.254)



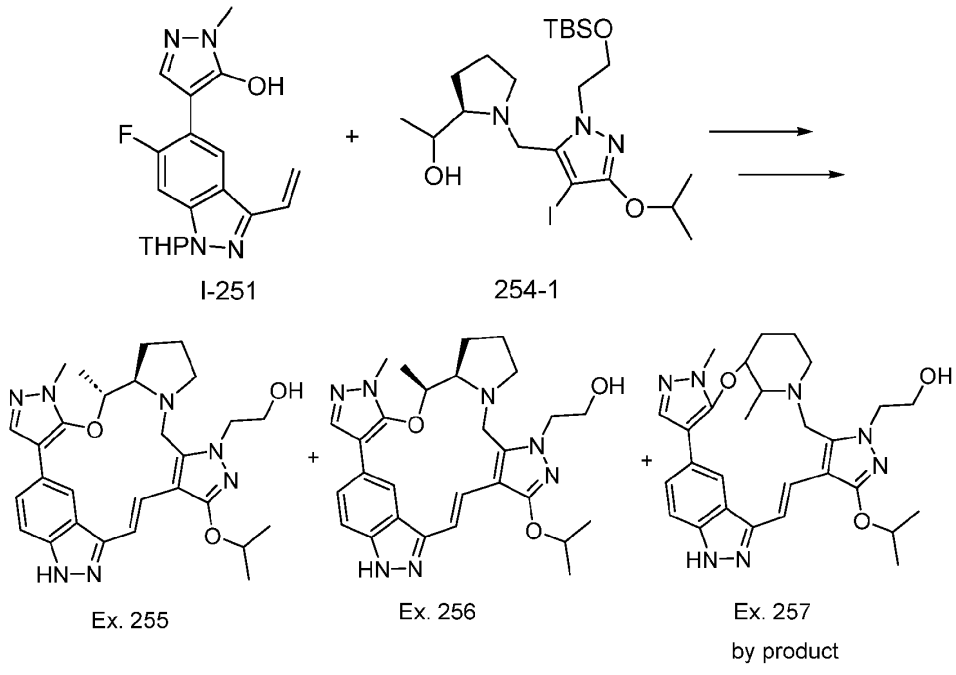
[01864] 254-1 was synthesized from I-241 and 147-1 following General Method T.

[01865] Step 1. A mixture of 1-[(2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl]pyrrolidin-2-yl]ethanol (1.00 g, 1.86 mmol, 1 *eq*), 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (965 mg, 2.98 mmol,

1.6), DBAD (942 mg, 4.09 mmol, 2.2 *eq*), PPh_3 (1.07 g, 4.09 mmol, 2.2 *eq*) was degassed and purged with N_2 for 3 times, then 2-methyltetrahydrofuran (10 mL) was degassed and purged with N_2 for 3 times again, and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. On completion, the mixture was concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=3:1 to 1:2) to give tert-butyl-[2-[4-iodo-3-isopropoxy-5-[[(2R)-2-[1-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethyl]pyrrolidin-1-yl]methyl]pyrazol-1-yl]ethoxy]-dimethyl-silane (1.20 g, 1.42 mmol, 76% yield) as white solid. LCMS: *m/z* 844.3 (M+1).

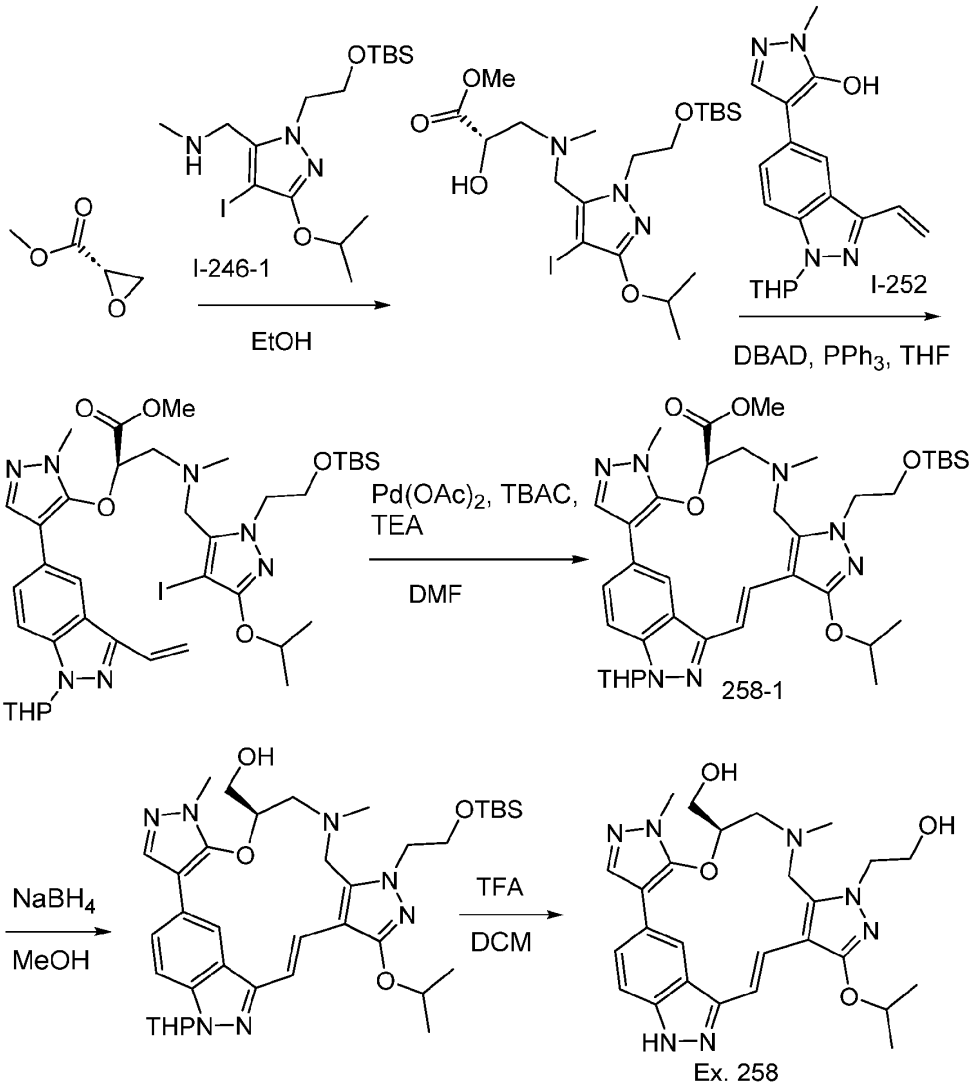
[01866] Steps 2 and 3 were performed in a similar manner to General Method T followed by SFC separation to give Ex. 252, Ex. 253 and by product 254. Absolute stereochemistry of 253 was determined by X-ray analysis.

[01867] Preparation of 2-[(8a*R*,9*R*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol (Ex. 255), 2-[(8a*R*,9*S*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol (Ex. 256), and 2-[(19*E*)-22-fluoro-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol (Ex.257)



[01868] Examples 255, 256 and 257 were synthesized using the procedure of General Method U starting with I-251 and 254-1. SFC separation was used to obtain arbitrarily assigned 255 and 256 as well as by product 257.

[01869] Preparation of 2-{(10*R*,17*E*)-10-(hydroxymethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 258).



[01870] Step 1. To a solution of methyl (2S)-oxirane-2-carboxylate (1.01 g, 9.92 mmol, 3 *eq*) 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methyl-methanamine (1.50 g, 3.31 mmol, 1 *eq*) in EtOH (15 mL). The mixture was stirred at 80 °C for 2 h. On completion. The mixture was filtered and concentrated to give methyl

(2R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-2-hydroxy-propanoate (2.00 g, 3.24 mmol, 98% yield, 90% purity) as a yellow oil. LCMS: *m/z* 557.0 (M+1).

[01871] Step 2. To a solution of methyl (2S)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-2-hydroxy-propanoate (1.90 g, 3.42 mmol, 1 *eq*), 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (1.66 g, 5.13 mmol, 1.5) in THF (50 mL) was added PPh_3 (1.97 g, 7.52 mmol, 2.2 *eq*) and DBAD (1.73 g, 7.52 mmol, 2.2 *eq*). The mixture was stirred at 25 °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=2:1 to 1:1) to give methyl (2R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propanoate (2.5F0 g, 2.90 mmol, 85% yield) as a yellow solid. LCMS: *m/z* 862.2 (M+1).

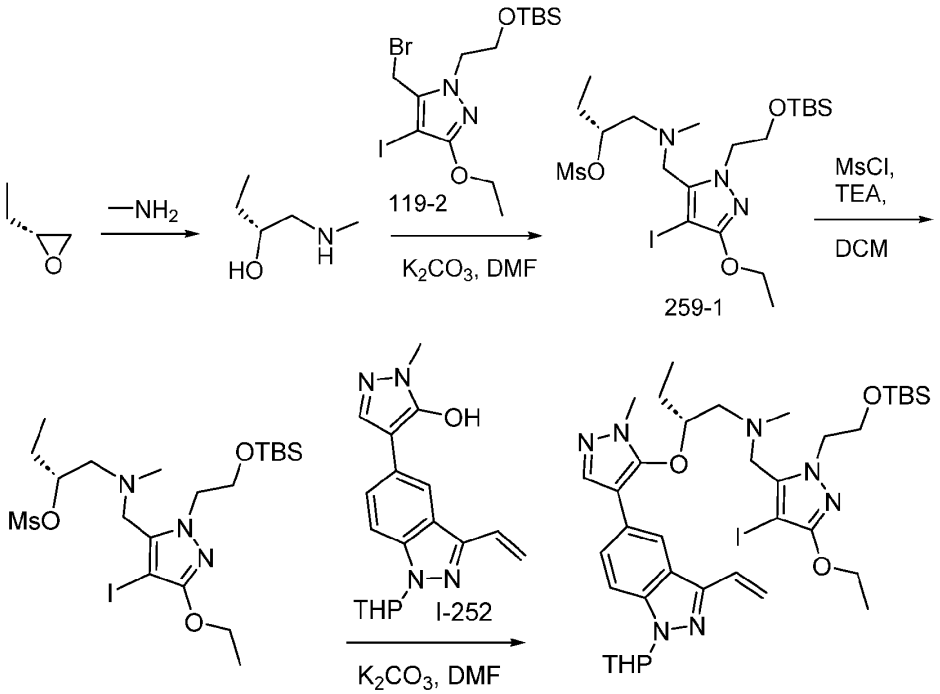
[01872] Step 3. To a solution of methyl (2R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propanoate (2.50 g, 2.90 mmol, 1 *eq*), TEA (1.17 g, 11.6 mmol, 4 *eq*) in DMF (250 mL) was added $Pd(OAc)_2$ (97.7 mg, 0.435 mmol, 0.15 *eq*) and TBAC (806 mg, 2.90 mmol, 1 *eq*). The mixture was stirred at 100 °C for 2 h. On completion, the mixture was quenched with water (200 mL) and extracted with ethyl acetate (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=1:1 to 0:1) to give methyl (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylate (1.00 g, 1.36 mmol, 47% yield) as a white solid. LCMS: *m/z* 736.3 (M+1).

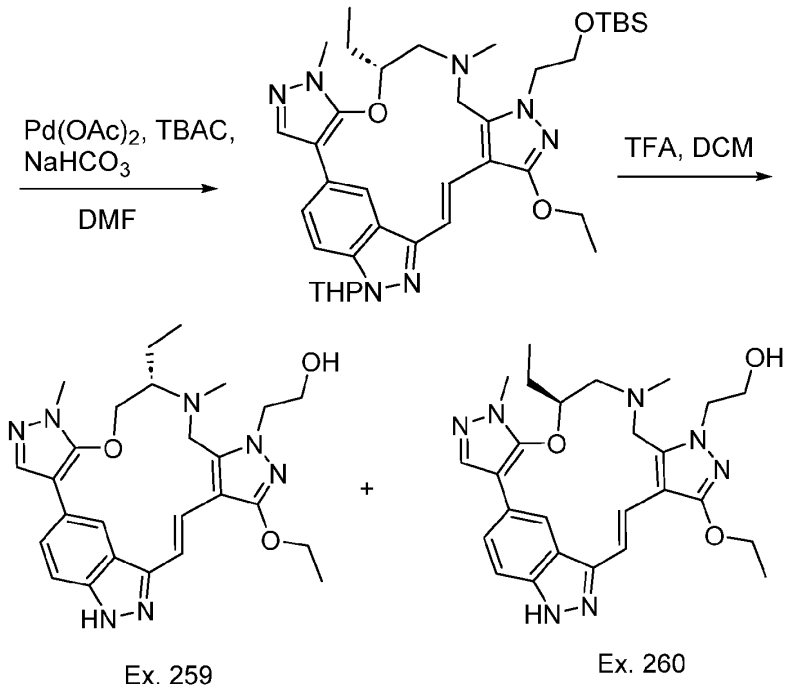
[01873] Step 4. To a solution of methyl (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptaza pentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylate (200 mg, 0.272 mmol, 1 *eq*) in MeOH (1 mL) was added $NaBH_4$ (103 mg, 2.72 mmol, 10 *eq*). 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 concentrated to give[(8R,17E)-13-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14, 20,21-

heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-8-yl]methanol (190 mg, 0.269 mmol, 98% yield) as a white solid. LCMS: *m/z* 706.3 (M+1).

[01874] Step 5. To a solution of [(8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-8-yl]methanol (120 mg, 0.169 mmol, 1 *eq*) in DCM (2 mL) was added TFA (3.07 g, 26.9 mmol, 2 mL, 158 *eq*) .The mixture was stirred at 25 °C for 1hr. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=30:1 to 15:1) to give 2-{(10*R*,17*E*)-10-(hydroxymethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (31.31 mg, 0.062 mmol, 36 % yield) as a white solid.

[01875] General Method V: Preparation of 2-[(11*S*,17*E*)-16-ethoxy-11-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 259), and 2-[(10*S*,17*E*)-16-ethoxy-10-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 260)





Ex. 259 Ex. 260

[01876] Step 1. To a solution of (2R)-2-ethyloxirane (2.00 g, 27.7 mmol, 1 *eq*) was added $MeNH_2$ (23.6 mL, 2.13 *eq*). The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was quenched by addition H_2O (30 mL) and extracted with EA (30mL * 3) to give the compound (2R)-1-(methylamino)butan-2-ol (2 g, 19.3 mmol, 69% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.61 - 3.44 (m, 1H), 2.90 - 2.51 (m, 2H), 2.39 - 2.26 (m, 3H), 2.26 - 2.21 (m, 1H), 1.43 - 1.33 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H).

[01877] Step 2. To a solution of (2R)-1-(methylamino)butan-2-ol (1.00 g, 9.69 mmol, 1 *eq*) 2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl]ethoxy-tert-butyl-dimethyl-silane (4.74 g, 9.69 mmol, 1 *eq*) in DMF (30 mL) was added K_2CO_3 (4.02 g, 29 mmol, 3 *eq*). The mixture was stirred at 80 °C for 1 hour. On completion, the reaction mixture was quenched by addition H_2O (100 mL) and extracted with EA (80mL * 3). The combined organic layers were washed with NaCl (100 ML), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1) to give the compound (2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]butan-2-ol (600 mg, 1.17 mmol, 12% yield) as a white solid. LCMS: *m/z* 512.1 (M+1).

[01878] Step 3. To a solution of (2R)-1-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]butan-2-ol (400 mg, 0.782 mmol, 1 *eq*) in DCM (8 mL) was added MsCl (1.17 mmol, 90 µL, 1.5 *eq*) and TEA (2.35 mmol, 350 µL, 3

eq). The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was quenched with sat. $NaHCO_3$ (25 mL). The mixture was separated and the aqueous layer was extracted with DCM (20 mL * 2). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated to give the compound [(1R)-1-[[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]methyl]propyl] methanesulfonate (400 mg, 0.678 mmol, 86% yield) as a white solid. LCMS: *m/z* 590.3 (M+1).

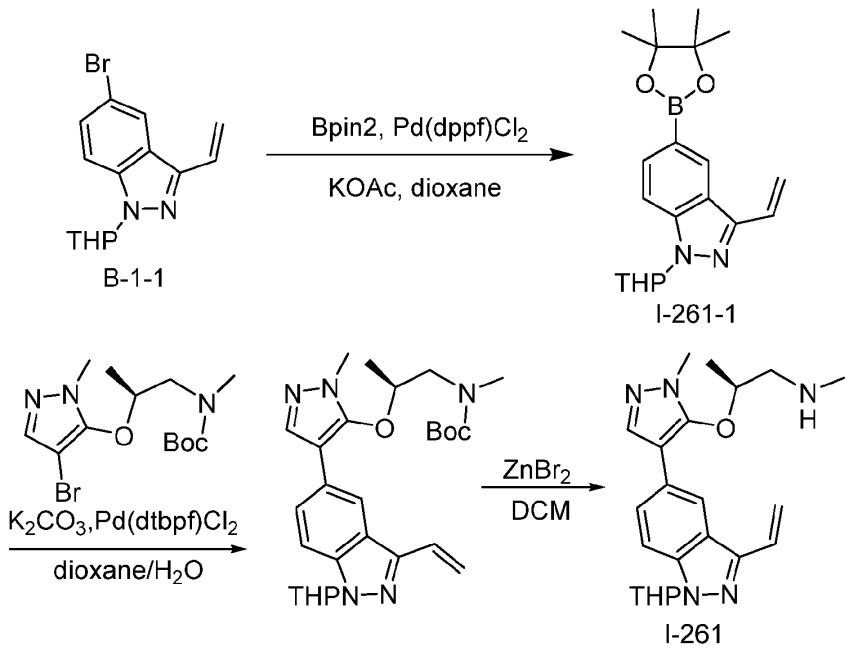
[01879] Step 4. To a solution of [(1R)-1-[[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]methyl]propyl] methanesulfonate (350 mg, 0.593 mmol, 1 *eq*) 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (192 mg, 0.593 mmol, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (246 mg, 1.78 mmol, 3 *eq*). The mixture was stirred at 80 °C for 1 hour. On completion the reaction mixture was quenched by addition H_2O (30 mL) and extracted with EA(30mL * 3). The combined organic layers were washed with NaCl (30 mL), filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1) to give the compound (2R)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl]-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-butan-1-amine (400 mg, 0.489 mmol, 82 % yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.97 (br d, *J* = 14.0 Hz, 1H), 7.63 - 7.48 (m, 3H), 7.03 (ddd, *J* = 3.2, 11.6, 18 Hz, 1H), 6.10 (d, *J* = 18.0 Hz, 1H), 5.69 (br d, *J* = 9.6 Hz, 1H), 5.52 (d, *J* = 11.6a Hz, 1H), 4.29 - 4.17 (m, 3H), 4.11 - 3.94 (m, 3H), 3.89 - 3.64 (m, 7H), 2.63 - 2.49 (m, 1H), 2.23 - 2.12 (m, 2H), 2.05 (br d, *J* = 8.4 Hz, 1H), 1.96 (s, 2H), 1.78 (br s, 4H), 1.69 - 1.52 (m, 2H), 1.44 - 1.34 (m, 4H), 0.86 - 0.75 (m, 12H), -0.04 - -0.15 (m, 6H); LCMS: *m/z* 818.4 (M+1).

[01880] Step 5. A mixture of (2R)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl]-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-butan-1-amine (400 mg, 0.489 mmol, 1 *eq*), $Pd(OAc)_2$ (21.9 mg, 0.098 mmol, 0.2 *eq*), TBAC (135 mg, 0.489 mmol, 136 µL, 1 *eq*) and $NaHCO_3$ (1.22 mmol, 47.5 µL, 2.5 *eq*) in DMF (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 1hour under N_2 atmosphere. On completion the reaction mixture was quenched by addition H_2O (15 mL) and extracted with EA(15mL * 3). The combined organic layers were washed with NaCl (15 mL), filtered and concentrated under reduced pressure to give the compound tert-butyl-[2-[(8R,17E)-15-ethoxy-8-ethyl-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-

nonaen-13-yl]ethoxy]-dimethyl-silane (210 mg, 0.304 mmol, 62 % yield) as a white solid. LCMS: *m/z* 690.3 (M+1).

[01881] Step 6. To a solution of tert-butyl-[2-[(8R,17E)-15-ethoxy-8-ethyl-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$. $0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]ethoxy]-dimethyl-silane (280 mg, 0.405 mmol, 1 *eq*) in DCM (5 mL) was added TFA (46.2 mg, 0.405 mmol, 30.1 μL, 1 *eq*) .The mixture was stirred at 25 °C for 1 hour . On completion the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to remove solvent. The crude product was purified by reversed-phase column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:14%-44% B over 11 min to give 2-[(11*S*,17*E*)-16-ethoxy-11-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (1.77 mg, 0.0035 mmol, 8.52e-1% yield, 96% purity) as a white solid and 2-[(10*S*,17*E*)-16-ethoxy-10-ethyl-8,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (4.13 mg, 0.0082 mmol, 2.01% yield, 97% purity) as a white solid.

[01882] Preparation of (2S)-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (I-261).



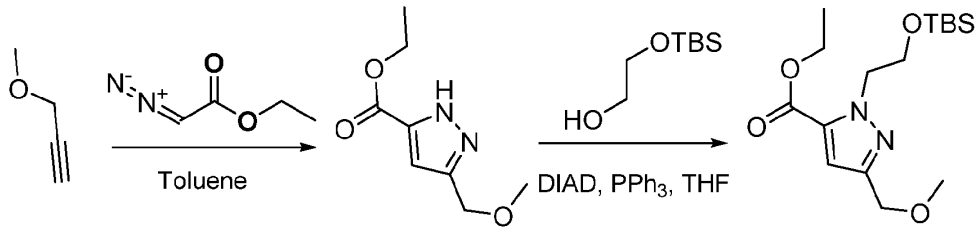
[01883] Step 1. A mixture of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (8.00 g, 26.0 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

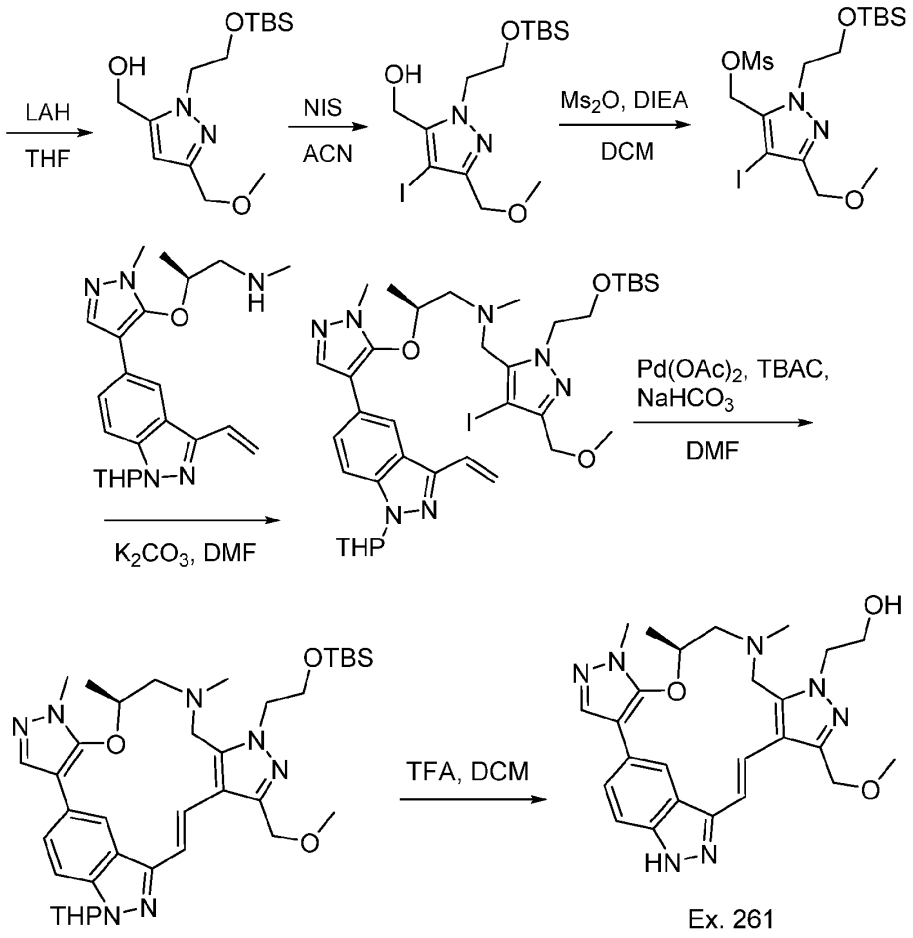
1,3,2-dioxaborolane (7.27 g, 28.6 mmol, 1.1 *eq*), potassium; acetate (3.83 g, 39.1 mmol, 1.5 *eq*), cyclopentyl(diphenyl)phosphane; dichloropalladium; iron (1.91 g, 2.60 mmol, 0.1 *eq*) in dioxane (150 mL) was degassed and purged with N_2 for 3 times. Then the mixture was stirred at 90 °C for 5 h under N_2 atmosphere. On completion, the mixture was concentrated to give 1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-indazole (9.20 g, crude) as yellow oil. LCMS: *m/z* 355.1 (M+1)

[01884] Step 2. A mixture of tert-butyl N-[(2R)-2-(4-bromo-2-methyl-pyrazol-3-yl)oxypropyl]-N-methyl-carbamate (8.45 g, 24.3 mmol, 1 *eq*) from Ex. 89, 1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-indazole (8.60 g, 24.3 mmol, 1 *eq*), K_2CO_3 (6.71 g, 48.6 mmol, 2 *eq*), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (1.58 g, 2.43 mmol, 0.1 *eq*) in dioxane (140 mL) and H_2O (28 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. On completion, the mixture was dried over Na_2SO_4, 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 tert-butyl N-methyl-N-[(2S)-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) pyrazol-3-yl] oxypropyl] carbamate (4.40 g, 8.88 mmol, 36% yield) as brown oil. LCMS: *m/z* 496.2 (M+1).

[01885] Step 3. To a solution of tert-butyl N-methyl-N-[(2S)-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxypropyl]carbamate (500 mg, 1.01 mmol, 1 *eq*) in DCM (5 mL) was added $ZnBr_2$ (681 mg, 3.03 mmol, 3 *eq*). The mixture was stirred at 25 °C for 16 h. On completion, the reaction was concentrated under vacuum to give (2S)-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (2.00 g, 0.961 mmol, 95 % yield, 19% purity) as a yellow oil. LCMS: *m/z* 396.2 (M+1).

[01886] General Method W: Preparation of 2-[(10*S*,17*E*)-16-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 261)





Ex. 261

[01887] Step 1. A mixture of 3-methoxyprop-1-yne (15.0 g, 214 mmol, 17.6 mL, 1 *eq*) and ethyl 2-diazoacetate (24.4 g, 214 mmol, 1 *eq*) in toluene (150 mL) was stirred at 115 °C for 2 h. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~1% THF/Petroleum ether gradient @ 100 mL/min) to give ethyl 3-(methoxymethyl)-1H-pyrazole-5-carboxylate (6.15 g, 28.7mmol, 13% yield, 86% purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 6.82 (s, 1H), 4.54 (s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.42 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); LCMS: *m/z* 185.1 (M+1).

[01888] Step 2. To a mixture of ethyl 3-(methoxymethyl)-1H-pyrazole-5-carboxylate (5.95 g, 32.3 mmol, 1 *eq*), 2-[tert-butyl(dimethyl)silyl]oxyethanol (11.4 g, 64.6 mmol, 2 *eq*) and PPh_3 (18.6 g, 71.1 mmol, 2.2 *eq*) in THF (60 mL) was added DIAD (14.4 g, 71.1 mmol, 13.8 mL, 2.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the

reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; X g SepaFlash® Silica Flash Column, Eluent of 0~5% THF/Petroleum ether gradient @ 100 mL/min) to give ethyl 2-[2-[tert-butyl (dimethyl) silyl]oxyethyl]-5-(methoxymethyl)pyrazole-3-carboxylate (13.0 g, 32.3 mmol, 99% yield, 85% purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 6.84 (s, 1H), 4.70 (t, *J* = 5.6 Hz, 2H), 4.47 (s, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.97 - 3.91 (m, 2H), 3.42 - 3.37 (m, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 0.83 - 0.79 (m, 10H), -0.05 - -0.11 (m, 7H); LCMS: *m/z* 343.5 (M+1).

[01889] Step 3. To a mixture of ethyl 2-[2-[tert-butyl (dimethyl)silyl]oxyethyl]-5-(methoxy methyl) pyrazole-3-carboxylate (12.5 g, 31.0 mmol, 1 *eq*) in THF (130 mL)was added $LiAlH_4$ (2.5 M, 13.7 mL, 1.1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the reaction mixture was quenched by addition of 15% NaOH. 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 (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-(methoxymethyl)pyrazol-3-yl]methanol (4.00 g, 12.9 mmol, 42% yield, 97% purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 6.23 (s, 1H), 4.62 (s, 2H), 4.45 (s, 2H), 4.30 (t, *J* = 4.8 Hz, 2H), 4.01 (t, *J* = 4.8 Hz,2H), 3.39 (s, 3H), 0.82 (s, 9H), 0.00 - -0.02 (m, 6H); LCMS: *m/z* 301.4 (M+1).

[01890] Step 4. To a mixture of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-(methoxymethyl)pyrazol-3-yl]methanol (1.00 g, 3.33 mmol, 1 *eq*) in ACN (10 mL) was added NIS (599 mg, 2.66 mmol, 0.8 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1h. Then NIS (449 mg, 1.77 mmol, 0.6 *eq*) was added and the reaction mixture was stirred at 25 °C for 1 h. On completion, the mixture was quenched with sat. Na_2SO_3 (50 mL) at 0 °C and extracted with ethyl acetate (50 mL × 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, Petroleum ether/Ethyl acetate=0/1 to 1/1) to give [2-[2-[tert-butyl (dimethyl)silyl]oxyethyl]-4-iodo-5-(methoxymethyl)pyrazol-3-yl]methanol (637 mg, 1.37 mmol, 41% yield, 92% purity) as a light yellow oil. LCMS: *m/z* 427.3 (M+1).

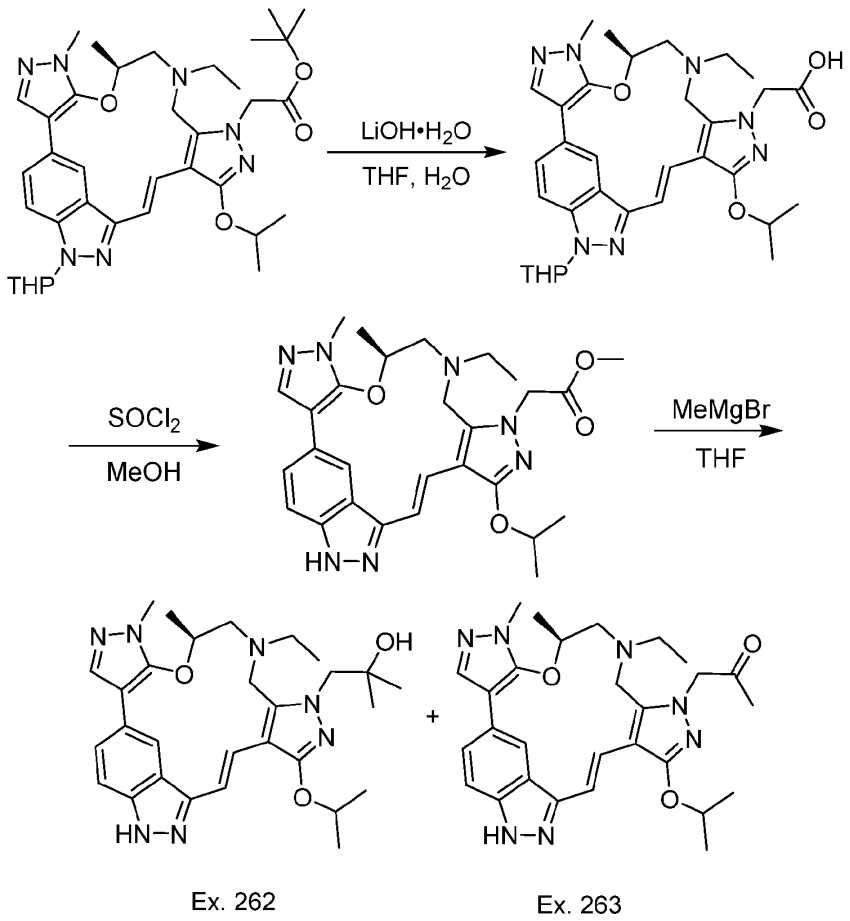
[01891] Step 5. To a mixture of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-(methoxymethyl)pyrazol-3-yl]methanol (587 mg, 1.38 mmol, 1 *eq*) and DIEA (534 mg, 4.13 mmol, 719 µL, 3 *eq*) in DCM (5 mL) was added methylsulfonyl methanesulfonate (479 mg, 2.75 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the mixture was poured into water (50 mL) aqueous solution, the aqueous phase was extracted

with DCM (50 mL × 2). The combined organic phase was washed with brine (30 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give [2-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-4-iodo-5-(methoxymethyl)pyrazol-3-yl]methyl methanesulfonate (694 mg, crude)was obtained as a yellow oil. LCMS: *m/z* 505.0 (M+1).

[01892] Step 6. To a mixture of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-(methoxymethyl)pyrazol-3-yl]methyl methanesulfonate (686 mg, 1.36 mmol, 0.25 *eq*) and (2S)-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) pyrazol-3-yl]oxy-propan-1-amine (2.15 g, 5.44 mmol, 1 *eq*) in DMF (20 mL) was added K_2CO_3 (2.25 g, 16.3 mmol, 3 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the mixture was poured into water (80 mL) aqueous solution, the aqueous phase was extracted with ethyl acetate (60 mL × 2). The combined organic phase was washed with brine (50 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 1/1) to give (2S)-N-[[2-[2-[tert-butyl (dimethyl) silyl]oxyethyl]-4-iodo-5-(methoxymethyl)pyrazol-3-yl]methyl]-N-methyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (393 mg, 0.489 mmol, 9% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 8.00 (s, 1H), 7.58 (s, 1H), 7.55 (s, 2H), 6.99 (s, 1H), 6.12 (d, *J* = 18.0 Hz, 1H), 5.69 (br d, *J* = 9.6 Hz, 1H), 5.54 (d, *J* = 11.4 Hz, 1H), 4.40 - 4.33 (m, 1H), 4.32 - 4.23 (m, 1H), 4.22 - 4.14 (m, 1H), 4.08 (d, *J* = 11.0 Hz, 1H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.81 - 3.73 (m, 2H), 3.71 (s, 3H), 3.61 (br d, *J* = 4.0 Hz, 2H), 3.39 (s, 3H), 3.00 - 2.86 (m, 2H), 2.68 - 2.51 (m, 2H), 2.43 (dd, *J* = 6.0, 12.8 Hz, 1H), 2.21 - 2.13 (m, 1H), 2.06 (s, 3H), 1.78 (t, *J* = 9.2 Hz, 2H), 1.70 - 1.62 (m, 1H), 1.57 (s, 3H), 0.78 (s, 9H), -0.12 (d, *J* = 4.0 Hz, 6H). LCMS: *m/z* 804.3 (M+1).

[01893] Steps 7 and 8 were performed in a similar manner to General Method V to give 2-[(10*S*,17*E*)-16-(methoxymethyl)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (7.81 mg, 0.016 mmol, 39 % yield, 100% purity) as a white solid.

[01894] Preparation of 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}-2-methylpropan-2-ol (Ex. 262) and 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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-one (Ex. 263)



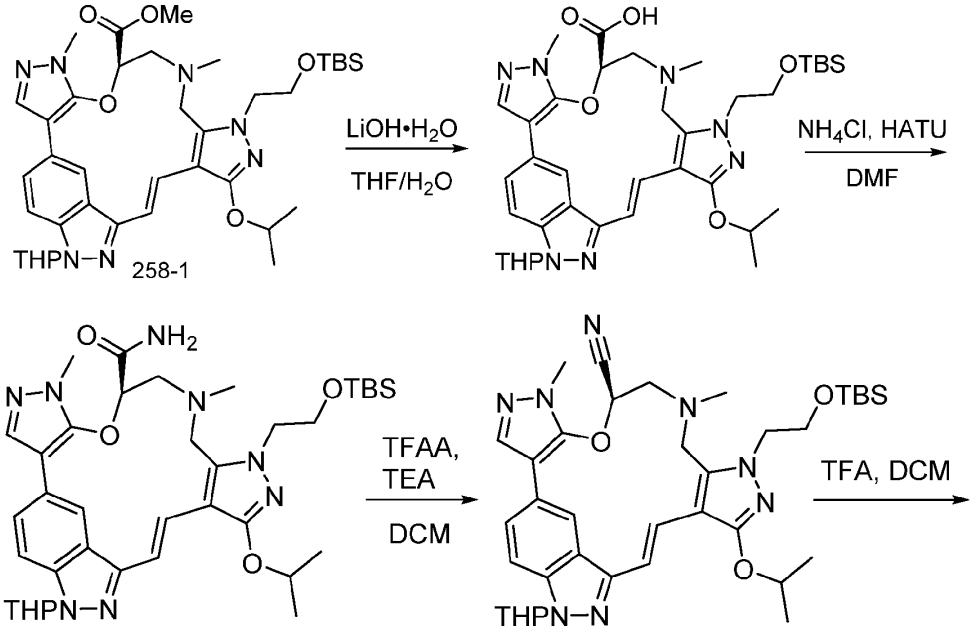
[01895] Step 1. A mixture of tert-butyl 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012, 16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetate (60.0 mg, 0.091 mmol, 1 *eq,* from Ex. 232) in H_2O (0.25 mL) and THF (0.5 mL) was added LiOH•H_2O (6.53 mg, 0.272 mmol, 3 *eq*) at 0 °C. Then the mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated in vacuo to give 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetic acid (55.0 mg, 0.072 mmol, 79% yield, 79% purity) as a brown solid. LCMS: *m/z* 604.1 (M+1)

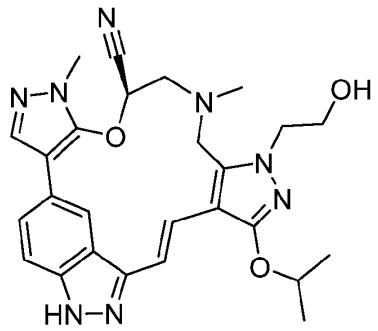
[01896] Step 2. To a solution of 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetic acid (54.0 mg, 0.089 mmol, 1 *eq*) in MeOH (1 mL) was added $SOCl_2$ (19.1 mg, 0.161 mmol, 1.8 *eq*) at -15

°C. The mixture was stirred at 25 °C for 16 h. On completion, the solvent was lyophilized and to give desired compound to give methyl 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02, 6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetate (45.0 mg, 0.069 mmol, 77% yield, 82% purity) as a yellow solid. LCMS: *m/z* 534.1 (M+1)

[01897] Step 3. A mixture of methyl 2-[(8S,17E)-10-ethyl-15-isopropoxy-5,8-dimethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetate (40.0 mg, 0.075 mmol, 1 *eq*) in THF (1 mL) was degassed and purged with N_2 for 3 times, and then MeMgBr (3 M, 125 μL, 5 *eq*) was added at 0 °C. Then the mixture was stirred at 25 °C for 4 h under N_2 atmosphere. On completion, the mixture was quenched with MeOH (1 mL). The mixture was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:24%-54% B over 8 min) and lyophilized to give Ex. 262 (1.94 mg, 0.003 mmol, 4% yield, 93.29% purity, FA) as a white solid, and Ex. 263 (1.54 mg, 0.003 mmol, 4% yield, 100% purity, FA) as a white solid.

[01898] Preparation of (10*R*,17*E*)-14-(2-hydroxyethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-10-carbonitrile (Ex. 264)





Ex. 264

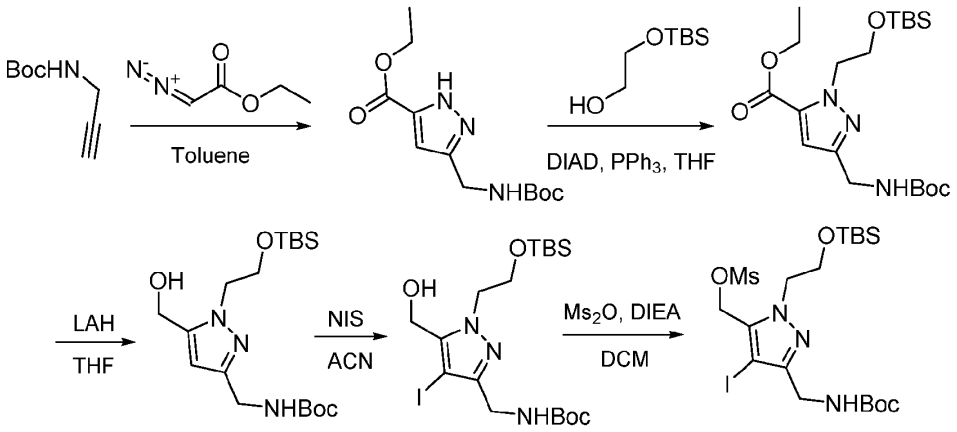
[01899] Step 1. To a solution of methyl (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptaza pentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylate (700 mg, 0.953 mmol, 1 *eq*) in THF (9 mL) and H_2O (3 mL) was added LiOH.H_2O (120 mg, 2.86 mmol, 3 *eq*). The mixture was stirred at 25 °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 concentrated to give (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran -2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylic acid (700 mg, crude) as a white solid. LCMS: *m/z* 720.3 (M+1).

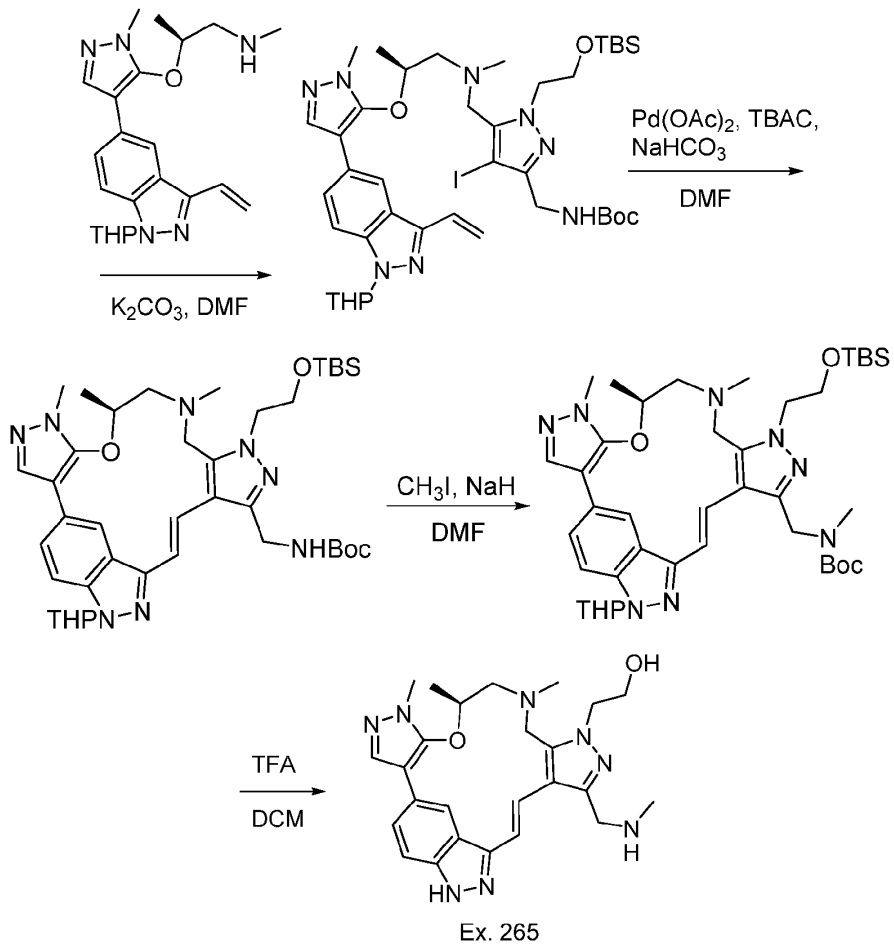
[01900] Step 2. To a solution of (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxylic acid (700 mg, 0.972 mmol, 1 *eq*) in DMF (20 mL) was added NH_4Cl (520 mg, 9.72 mmol, 10 *eq*), DIEA (376 mg, 2.92 mmol, 3 *eq*), and then HATU (1.11 g, 2.92 mmol, 3 *eq*) was added dropwise at 0 °C. The mixture was stirred at 25 °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 concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=2:1 to 1:1) to give (8R,17E)-13-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10, 13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3, 12(16),14,17,19,22(26),23-nonaene-8-carboxamide (500 mg, 0.695 mmol, 71% yield) as a white solid. LCMS: *m/z* 719.2 (M+1).

[01901] Step 3. To a solution of (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carboxamide (480 mg,0.667 mmol, 1 *eq*) in $CHCl_3$ (10 mL) was added TEA (229 mg, 2.27 mmol, 3.4 *eq*) and TFAA (238 mg, 1.13 mmol, 1.7 *eq*). The mixture was stirred at 0 °C for 2 h. On completion, The mixture was quenched with water (20 mL) and extracted with DCM (25 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carbonitrile (400 mg, 0.570 mmol, 85% yield) as a yellow oil. LCMS: *m/z* 701.7 (M+1).

[01902] Step 4. To a solution of (8R,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-15-isopropoxy-5,10-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.0^{2,6}.0^{12,16}.0^{22,26}]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carbonitrile (400 mg, 0.570 mmol, 1 *eq*) in DCM (3 mL) was added TFA (33.6 mmol, 2.50 mL, 59 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was filtered and concentrated to give a residue. The crude product was triturated with EA (10 mL) at 25 °C for 5 mines to give (8R,17E)-13-(2-hydroxyethyl)-15-isopropoxy-5,10-dimethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.0^{2,6}. 0^{12,16}.0^{22,26}] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-8-carbonitrile (132.93 mg, 0.264.50 mmol, 46 % yield) as a white solid.

[01903] Preparation of 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 265)





Ex. 265

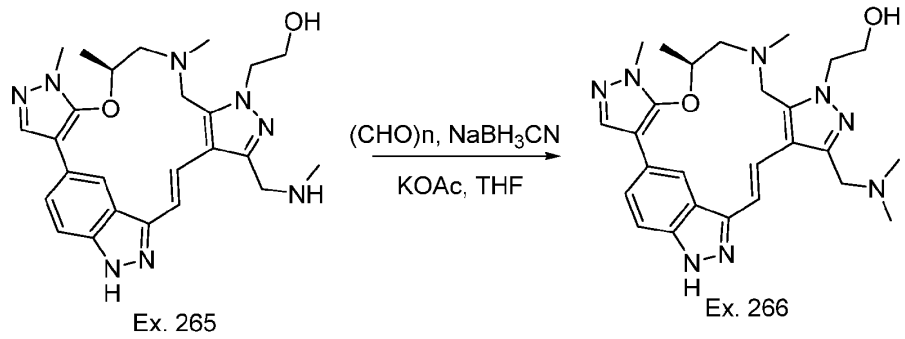
[01904] Steps 1 through 7 followed the procedures of General Method W steps 1 through 7.

[01905] Step 8. To a solution of tert-butyl N-[[(8S,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]methyl]carbamate (0.250 g, 0.328 mmol, 1.00 *eq*) in DMF (2.50 mL) was added NaH (26.3 mg, 0.657 mmol, 60% purity, 2.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. CH_3I (69.9 mg, 0.492 mmol, 30.7 μL, 1.50 *eq*) was added into the mixture at 0 °C. The mixture was stirred at 25 °C for 3.5 h. On completion, the mixture was poured into NH_4Cl (50.0 mL) aqueous, the aqueous phase was extracted with ethyl acetate (20.0 mL × 3). The combined organic phase was washed with brine (20.0 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give tert-butyl N-[[(8S,17E)-13-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5,8,10-trimethyl-

21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]methyl]-N-methyl-carbamate (0.170 g, 0.219 mmol, 67% yield) as a yellow solid. LCMS: *m/z* 775.6 (M+1).

[01906] Step 9 was performed in a similar manner to the last step in General Method W to give 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (2.6 mg, 0.0053 mmol, 3 % yield, 96.4% purity, FA) as a white solid.

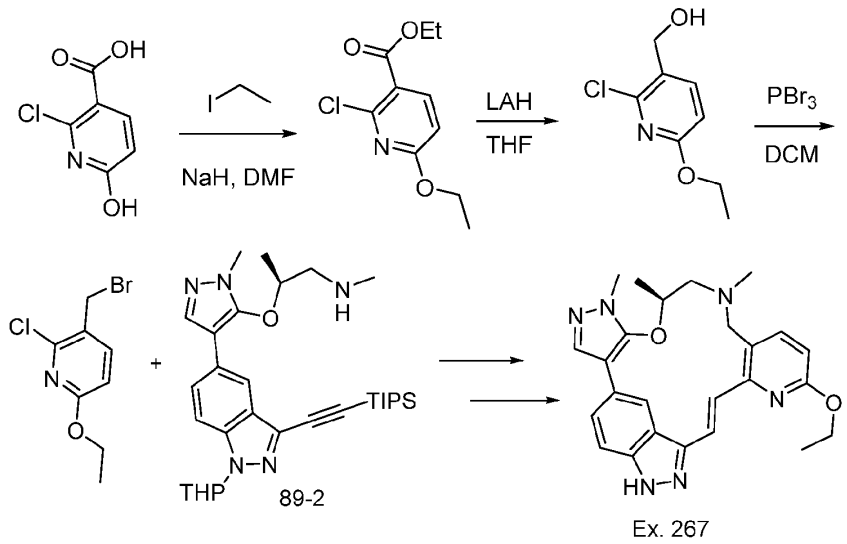
[01907] Preparation of 2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 266)



Ex. 265 Ex. 266

[01908] Step 1. To a solution of 2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (40.0 mg, 0.084 mmol, 1.00 *eq*) in THF (0.100 mL) was added KOAc (82.4 mg, 0.839 mmol, 10.0 *eq*) and HCHO (12.6 mg, 0.420 mmol, 11.6 μL, 5.00 *eq*). The mixture was stirred at 25 °C for 0.5 h. $NaBH_3CN$ (10.6 mg, 0.168 mmol, 2.00 *eq*) was added into the mixture. On completion, the mixture was stirred at 25 °C for 0.5 h. The reaction was concentrated under vacuum. The residue was purified by prep-HPLC (column: Welch Ultimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];gradient:0%-30% B over 10 min)to give 2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (0.52 mg, 9.38e-4 mmol, 1 % yield, 96.8% purity, FA) as a yellow solid.

[01909] Preparation of (10*S*,18*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[3,2-*f*][1,4]oxazacyclopentadecine (Ex. 267)



[01910] Step 1. To a solution of 2-chloro-6-hydroxy-pyridine-3-carboxylic acid (6.00 g, 34.5 mmol, 1 *eq*) in DMF (120 mL) at 0 °C , then was added NaH (4.98 g, 124 mmol, 60% purity, 3.6 *eq*) at 0 °C for 0.5 h. EtI (26.9 g, 172 mmol, 13.8 mL, 5 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 16 hours. On completion, the mixture was slowly quenched with water (300 mL), extracted with EA (3*300 mL). The combined organic layers were washed with brine (3*300 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, PE/THF=1/0 to 20/1) to give ethyl 2-chloro-6-ethoxy-pyridine-3-carboxylate (4.40 g, 19.1 mmol, 55% yield) as a yellow oil. 1H NMR (400 MHz, CHLOROFORM-d) δ = 8.12 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.52 - 4.25 (m, 4H), 1.40 (dt, *J* =2.8, 7.1 Hz, 6H). LCMS: *m/z* 230.0 (M+1)

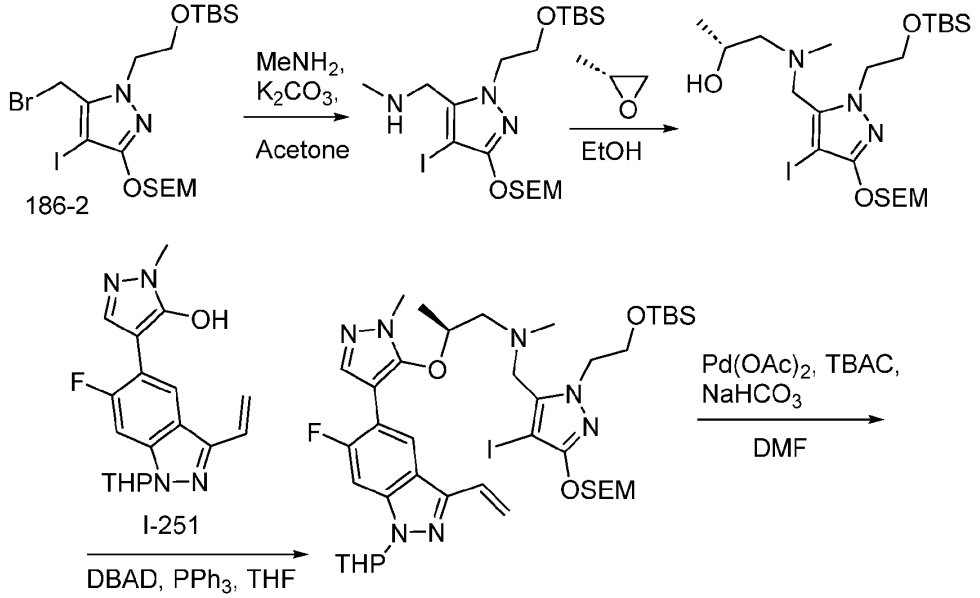
[01911] Step 2. To a solution of ethyl 2-chloro-6-ethoxy-pyridine-3-carboxylate (4.40 g, 19.1 mmol, 1 *eq*) in THF (44 mL) was added $LiAlH_4$ (2.5 M, 9.20 mL, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. On completion, the mixture was slowly added to water (0.9 ml), 15% sodium hydroxide (0.9 ml) and was added water (2.7 ml) to quench. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (20 g silica gel column, THF in PE from 0% to 20%) to give (2-chloro-6-ethoxy-3-pyridyl) methanol (2.85 g, 15.1 mmol, 79% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.69 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.09 (d, *J* = 11.2 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 188.0 (M+1)

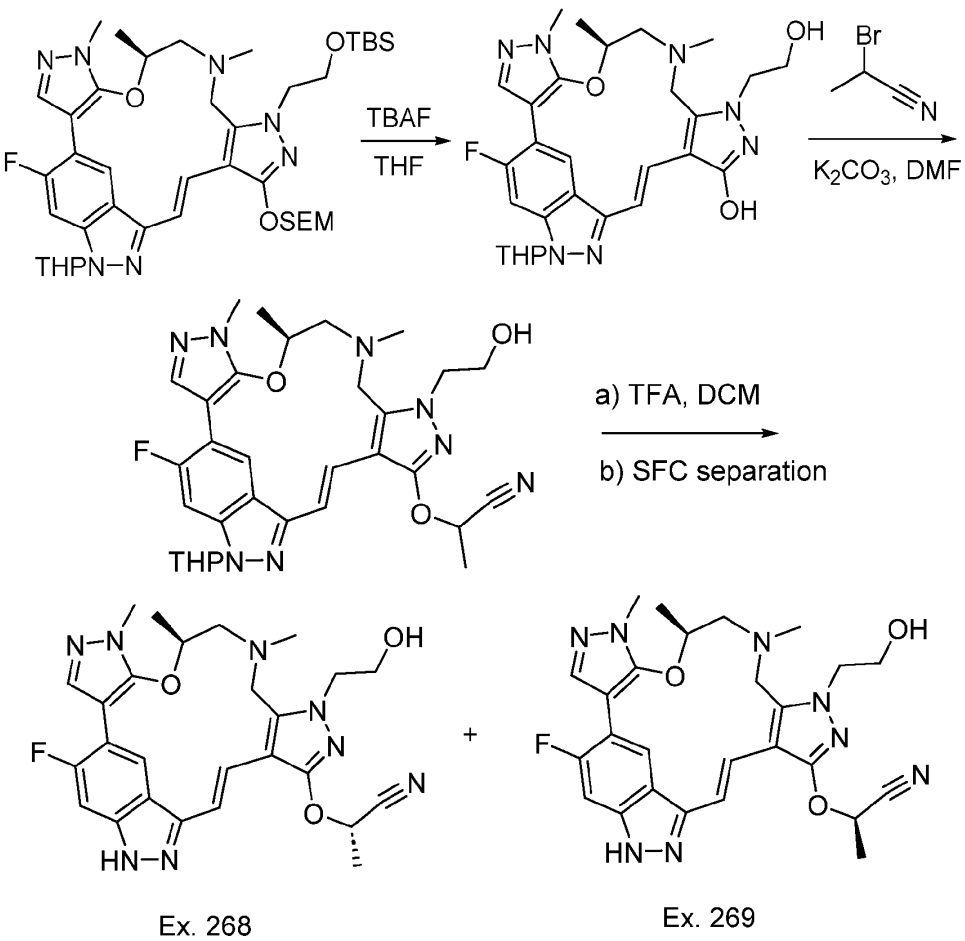
[01912] Step 3. To a solution of (2-chloro-6-ethoxy-3-pyridyl)methanol (2.85 g, 15.1 mmol, 1 *eq*) in DCM (30 mL) at 0 °C was added PBr_3 (4.93 g, 18.2 mmol, 1.2 *eq*). The

mixture was stirred at 25 °C for 16 h. On completion, the saturated sodium bicarbonate was quenched and the pH of the reaction solution was adjusted to 8 and extracted with DCM (3*100 mL). The combined organic layers were washed with brine (3*100mL), dried over Na_2SO_4 and concentrated to give 3-(bromomethyl)-2-chloro-6-ethoxy-pyridine (3.60 g, 14.3 mmol, 94% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.54 (s, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 249.9 (M+1)

[01913] The remaining steps were performed according to Ex. 151 from 3-(bromomethyl)-2-chloro-6-ethoxy-pyridine and 89-2 to give Ex. 267.

[01914] General Method X: Preparation of (2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile (Ex. 268) and (2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile (Ex. 269)





Ex. 268 Ex. 269

[01915] Steps 1 and 2 were performed in a similar manner to the synthesis of I-246.

[01916] Steps 3 and 4 were performed in a similar manner to steps 1 and 2 in General Method U.

[01917] Step 5. To a solution of tert-butyl-[2-[(8S,17E)-24-fluoro-5,8,10-trimethyl-21-tetrahy dropyran-2-yl-15-(2-trimethylsilylethoxymethoxy)-7-oxa-4,5,10,13,14,20,21-heptaza pentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26), 23-nonaen-13-yl]ethoxy]-dimethyl-silane (100 mg, 0.126 mmol, 1 *eq*) in THF (1 mL) was added TBAF (1 M, 754 μL, 6 *eq*), then the mixture was stirred at 70 °C for 3 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 dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM ether gradient @ 20 mL/min) to give (8S,17E)-24-fluoro-13-(2-hydroxyethyl)-5,8,10-trimethyl-21-

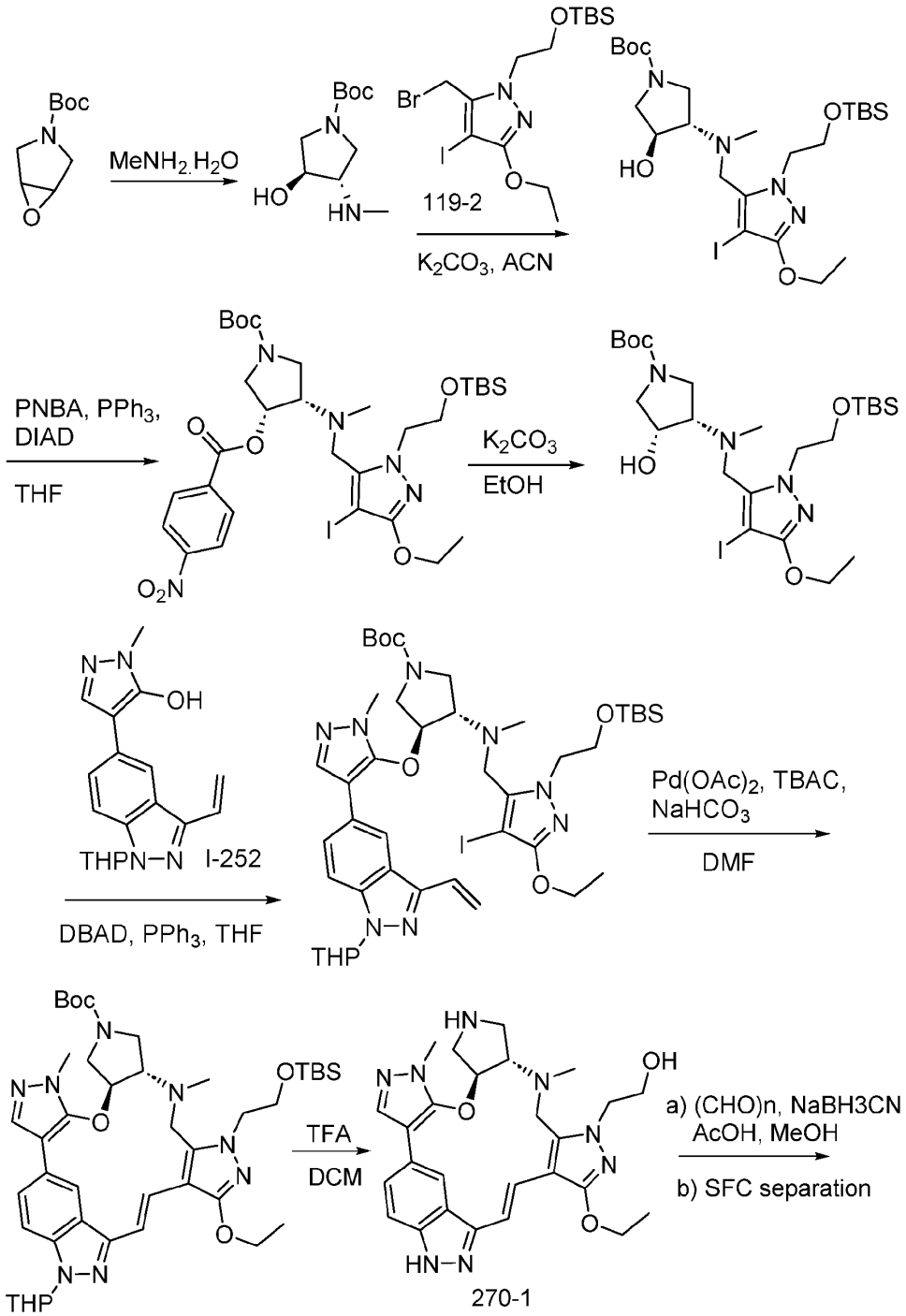
tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-ol (40.0 mg, 0.073 mmol, 58% yield) as a yellow oil. LCMS: *m/z* 552.2 (M+1).

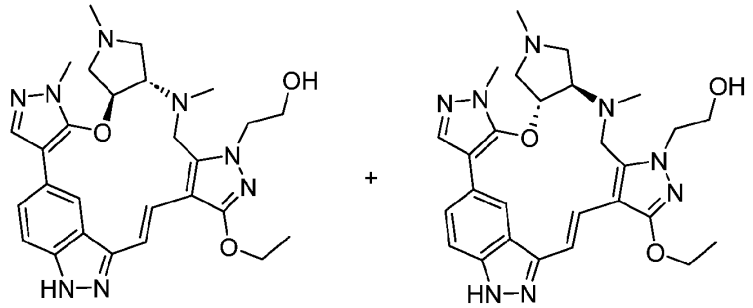
[01918] Step 6. To a solution of (8S,17E)-24-fluoro-13-(2-hydroxyethyl)-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012, 16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-ol (30.0 mg, 0.054 mmol, 1 *eq*) in DMF (1 mL) was added 2-bromopropanenitrile (10.9 mg, 0.082 mmol, 1.5 *eq*) and K_2CO_3 (22.6 mg, 0.163 mmol, 3 *eq*), then the mixture was stirred at 60 °C for 2 h. On completion, the reaction mixture was diluted with H_2O (3 mL) and extracted with EA (2mL * 3). The combined organic layers were washed with Brine (3 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-[[(8S,17E)-24-fluoro-13-(2-hydroxyethyl)-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]oxy]propanenitrile (40.0 mg, crude) as a yellow oil. LCMS: *m/z* 605.2 (M+1).

[01919] Step 7. To a solution of 2-[[(8S,17E)-24-fluoro-13-(2-hydroxyethyl)-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16. 022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-15-yl]oxy]propane nitrile (30.0 mg, 0.050 mmol, 1 *eq*) in DCM (0.5 mL) was added TFA (461 mg, 4.04 mmol, 81.4 *eq*), then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [water(NH_4HCO_3)-ACN];gradient:28%-58% B over 10 min) to give desired compound (30 mg) as a white solid, which was further separated by SFC (column: DAICEL CHIRALCEL OD(250mm*30mm,10um);mobile phase: [CO2-MeOH(0.1%NH3H2O)];B%:25%, isocratic elution mode) to give (2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile (1.31 mg, 0.003 mmol, 5 % yield) and (2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile (0.8 mg, 0.002 mmol, 3 % yield) as a white solid.

[01920] Preparation of 2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol (Ex. 270) and 2-[(4a*R*,7a*R*,13*E*)-12-

ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol (Ex. 271)





Ex. 270 Ex. 271

[01921] Step 1. A solution of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.00 g, 5.40 mmol, 1 *eq*) in methanamine (13.0 g, 125 mmol, 23.2 *eq*) was stirred at 50 °C for 12 h. On completion, the mixture was quenched with water (150 mL) and extracted with ethyl acetate (80 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl (3S,4S)-3-hydroxyl -4-(methylamino)pyrrolidine-1-carboxylate (1.00 g, 4.62 mmol, 85% yield) as off-white solid.

[01922] Step 2. A mixture of tert-butyl (3S,4S)-3-hydroxy-4-(methylamino)pyrrolidine-1-carboxylate (530 mg, 2.45 mmol, 1.2 *eq*) and 2-[5-(bromomethyl)-3-ethoxy-4-iodo -pyrazol-1-yl]ethoxy-tert-butyl-dimethyl-silane (1.00 g, 2.04 mmol, 1 *eq*) in ACN (10 mL) was added K_2CO_3 (847 mg, 6.13 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 h. On completion, the mixture was 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 (3S,4S)-3-[[2-[2-[tert-butyl(dimethyl) silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]-4-hydroxy-pyrrolidine-1-carboxylate (1.40 g, crude) as colorless oil. LCMS: *m/z* 625.2 (M+1).

[01923] Step 3. A solution of tert-butyl (3S,4S)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl] -5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]-4-hydroxy-pyrrolidine-1-carboxylate (1.30 g, 2.08 mmol, 1 *eq*), PPh_3 (1.09 g, 4.16 mmol, 2 *eq*) and 4-nitrobenzoic acid (521 mg, 3.12 mmol, 1.5 *eq*) in THF (19.5 mL) was stirred at 0 °C for 30 min. Then DIAD (841 mg, 4.16 mmol, 2 *eq*) was added to the mixture and stirred at 0 °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 4:1) to give tert-butyl (3S,4R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]-4-(4-nitrobenzoyl)oxy-pyrrolidine-1-carboxylate (1.44 g, 1.86 mmol, 89% yield) as yellow oil. LCMS: *m/z* 774.3 (M+1).

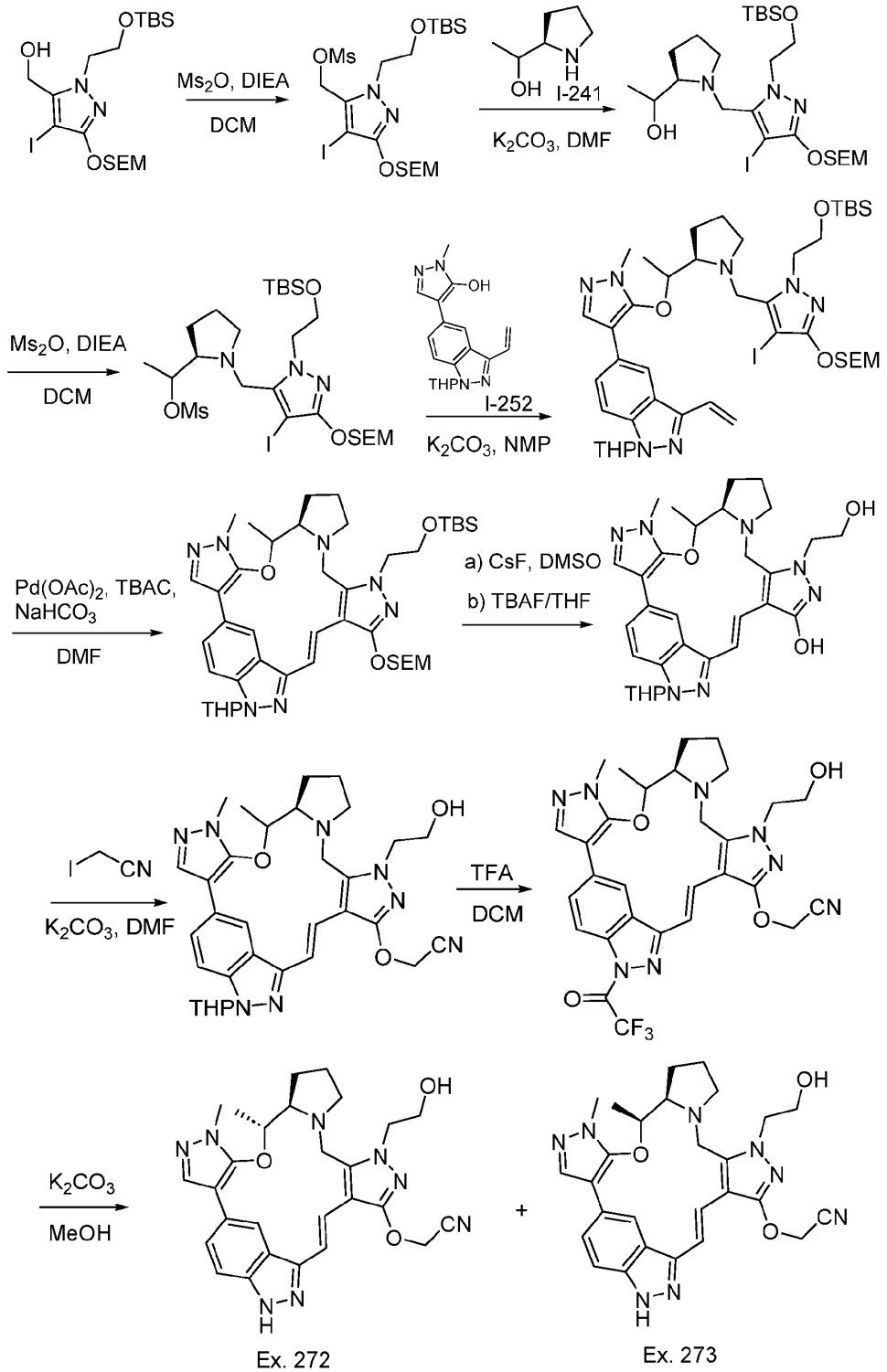
[01924] Step 4. To a solution of tert-butyl (3S,4R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl] -5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]-4-(4-

nitrobenzoyl)oxy-pyrrolidine-1-carboxylate (1.34 g, 1.73 mmol, 1 *eq*) in EtOH (14 mL) was added K_2CO_3 (47.8 mg, 0.346 mmol, 0.2 *eq*). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was 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 (3S,4R)-3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl-methyl-amino]-4-hydroxy-pyrrolidine-1-carboxylate (1.05 g, 1.68 mmol, 97% yield) as yellow oil. LCMS: *m/z* 625.1 (M+1).

[01925] Steps 5 through 7 were performed in a similar manner to steps 1 through 3 in General Method U to give racemic 270-1.

[01926] Step 8. The mixture of 2-[(8S,13R,20E)-18-ethoxy-5,13-dimethyl-7-oxa-4,5,10,13,16,17, 23,24-octazahexacyclo[20.5.2.$0^{2,6}$.$0^{8,12}$.$0^{15,19}$.$0^{25,29}$]nonacosa-1(28),2(6),3,15(19), 17,20,22,25(29),26-nonaen-16-yl]ethanol (400 mg, 0.792 mmol, 1 *eq*) and CHO (161 mg, 4.76 mmol, 6 *eq*) in MeOH (5 mL) was added AcOH (47.6 mg, 0.792 mmol, 1 *eq*) adjust pH=6, the mixture was stirred at 25 °C for 0.3 h, and then $NaBH_3CN$ (99.6 mg, 1.59 mmol, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 5 h. On completion, the mixture was quenched with water (0.5 mL) and concentrated to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um;mobile phase: [water(NH4HCO3)-ACN];gradient:17%-47% B over 10 min) to give desired compound (45.74 mg, 0.087 mmol, 11.0% yield, 99% purity) as white solid which was further separated by SFC (column: DAICEL CHIRALPAK IC(250mm*30mm,10um);mobile phase: [CO2-EtOH(0.1%NH3H2O)];B%:40%, isocratic elution mode) to give arbitrarily assigned 2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol (19.18 mg, 0.037 mmol, 48 % yield, 99% purity) as off-white solid and 2-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol (18.47 mg, 0.035 mmol, 46 % yield, 99.3% purity) as off-white solid..

[01927] Preparation of {[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4] oxazacyclopentadecin-1-yl]oxy}acetonitrile (Ex. 272) and {[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile (Ex. 273)


OTBS
OH
I
OSEM
Ms2O, DIEA
DCM
OMs
I-241
K2CO3, DMF
TBSO
OH
THPN–N
I-252
K2CO3, NMP
Pd(OAc)2, TBAC,
NaHCO3
DMF
a) CsF, DMSO
b) TBAF/THF
CN
TFA
CF3
K2CO3
MeOH
+

Ex. 272 Ex. 273

[01928] Step 1. To a solution of [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methanol (3.00 g, 5.68 mmol, 1 *eq*) from Ex. 186 in DCM (50 mL) was added methylsulfonyl methanesulfonate (1.48 g, 8.51 mmol, 1.5 *eq*) and DIEA (1.47 g, 11.3 mmol, 1.98 mL, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure to give [2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methyl methanesulfonate (6.40 g, crude) as brown solid. LCMS: *m/z* 607.0 (M+1).

[01929] Steps 2-5 were performed in a similar manner to steps 2-5 in General Method V.

[01930] Step 6. To a solution of tert-butyl-[2-[(9R,20E)-5,8-dimethyl-24-tetrahydropyran-2-yl-18-(2-trimethylsilylethoxymethoxy)-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo[20.5.2.02,

[01931] 6.09,13.015,19.025,29]nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-16-yl]ethoxy]-dimethyl-silane (900 mg, 1.12 mmol, 1 *eq*) in DMSO (10 mL) was added CsF (850 mg, 5.60 mmol, 5 *eq*). The mixture was stirred at 25 °C for 1h. On completion, the mixture was poured into H_2O (100 mL) and extracted with EA (50 mL*3), the combined organic phase was washed with H_2O (100 mL*2) and dried over anhydrous sodium sulfate, filtered and concentrated to give 2-[(9R,20E)-5,8-dimethyl-24-tetrahydropyran-2-yl-18-(2-trimethylsilylethoxymethoxy)-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo [20.5.2.02,6.09,13.015,19.025,29] nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-16-yl]ethanol (650 mg, crude) as yellow solid. LCMS: *m/z* 690.3 (M+1).

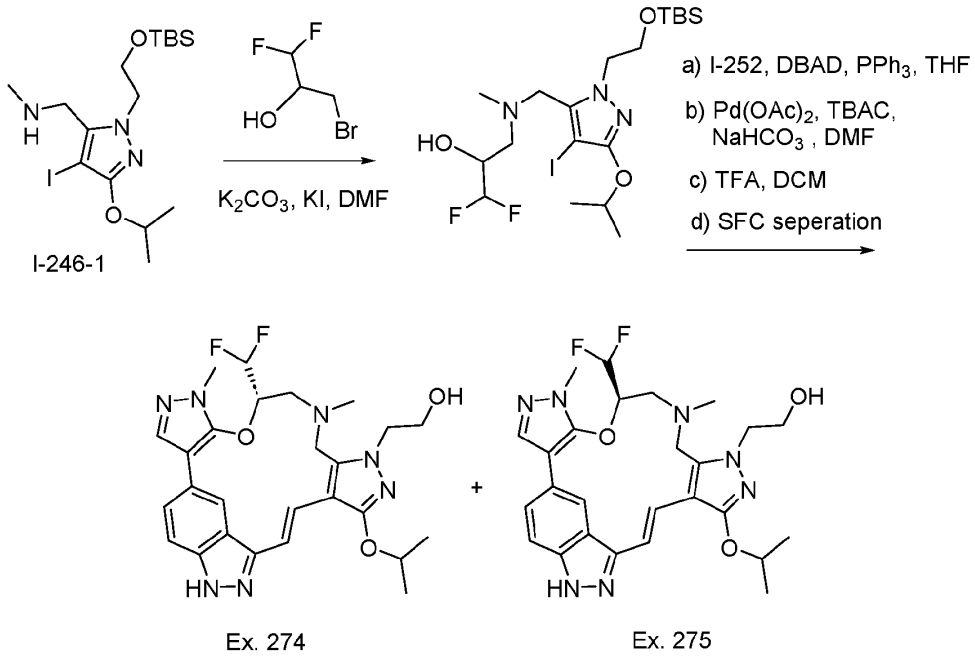
[01932] Step 7. To a solution of 2-[(9R,20E)-5,8-dimethyl-24-tetrahydropyran-2-yl-18-(2-trimethylsilylethoxymethoxy)-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo [20.5.2.02,6.09,13.015,19.025,29]nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-16-yl]ethanol (630 mg, 0.913 mmol, 1 *eq*) was added TBAF (4 M, 8 mL, 35 *eq*). The mixture was stirred at 70 °C for 12 h. On completion, the reaction mixture was diluted with water (50 mL) and was extracted with EA (30 mL*3). The combined organic layer was washed with brine (50 mL), dried over anh. Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=20:1 to 10:1) to give (9R,20E)-16-(2-hydroxyethyl)-5,8-dimethyl-24-tetrahydropyran-2-yl-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo [20.5.2.02,6.09,13.015,19.025,29] nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-18-ol (377 mg, 0.673 mmol, 73% yield) as yellow solid. LCMS: *m/z* 560.2 (M+1).

[01933] Step 8. To a solution of (9R,20E)-16-(2-hydroxyethyl)-5,8-dimethyl-24-tetrahydropyran-2-yl-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo[20.5.2.02,6.09,13.015,19.025,29]nonaco-sa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-18-ol (350 mg,0.625 mmol, 1 *eq*) in DMF (5 mL) was added 2-iodoacetonitrile (125 mg, 0.750 mmol, 1.2 *eq*) and K_2CO_3 (172 mg, 1.25 mmol, 2 *eq*). The mixture was stirred at 80 °C for 1 h. On completion, the mixture was poured into H_2O (50 mL) and extracted with EA (30 mL*3), the combined organic phase was washed with H_2O (20 mL*3) and dried over anhydrous sodium sulfate, filtered and concentrated to give 2-[[(9R,20E)-16-(2-hydroxyethyl)-5,8-dimethyl-24-tetrahydropyran-2-yl-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo[20.5.2.02,6.09,13.015,19.025,29]nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-18-yl]oxy]acetonitrile (350 mg, crude) as green solid. LCMS: *m/z* 599.2 (M+1).

[01934] Step 9 was performed in a similar manner to step 6 in General Method V.

[01935] Step 10. To a solution of 2-[[(9R,20E)-16-(2-hydroxyethyl)-5,8-dimethyl-24-(2,2,2-trifluoroacetyl)-7-oxa-4,5,13,16,17,23,24-heptazahexacyclo[20.5.2.02,6.09,13.015,19.025,29] nonacosa-1(28),2(6),3,15(19),17,20,22,25(29),26-nonaen-18-yl]oxy]acetonitrile (350 mg, 0.573 mmol, 1 *eq*) in MeOH (6 mL) was added K_2CO_3 (396 mg, 2.87 mmol, 5 *eq*). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was filtered and the filtrate was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC purification (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(TFA)-ACN];gradient:12%-42% B over min) to give arbitrarily assigned {[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile (32.3 mg, 0.063 mmol, 11 % yield, 99.7% purity) as yellow solid and {[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile (38.1 mg, 0.072 mmol, 13 % yield, 97 % purity) as yellow solid.

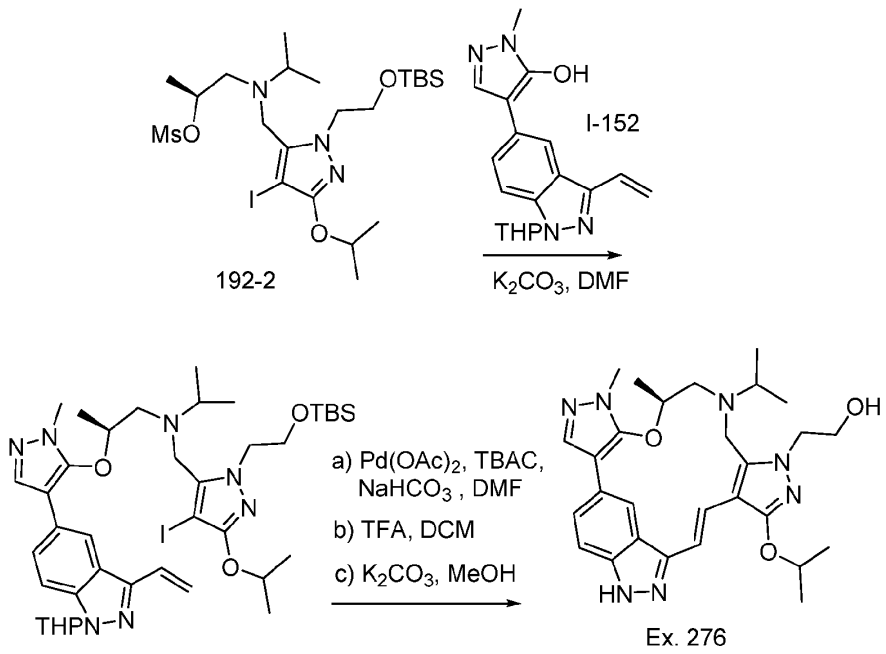
[01936] Preparation of 2-{(10*S*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 274) and 2-{(10*R*,17*E*)-10-(difluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex.275)



[01937] Step 1. To a solution of 1-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]-N-methylmethanamine (1.00 g, 2.21 mmol, 1 *eq*) in DMF (10 mL) was added KI (366 mg, 2.21 mmol, 1 *eq*) 3-bromo-1,1-difluoro-propan-2-ol (463 mg, 2.65 mmol, 1.2 *eq*) and K_2CO_3 (609 mg, 4.41 mmol, 2 *eq*). The mixture was stirred at 80 °C for 16 hours. On completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with EA (3 * 20 mL). The combined organic layers were washed with brine (2 * 20 mL), dried over by anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. And then the residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0.5/1) to give 3-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-methyl-amino]-1,1-difluoro-propan-2-ol (288 mg, 0.526 mmol, 24% yield) as yellow oil. LCMS: *m/z* 548.1 (M+1).

[01938] Steps 2-4 were performed in a similar manner to General Method U followed by SFC separation to provide arbitrarily assigned Ex. 274 and Ex. 275.

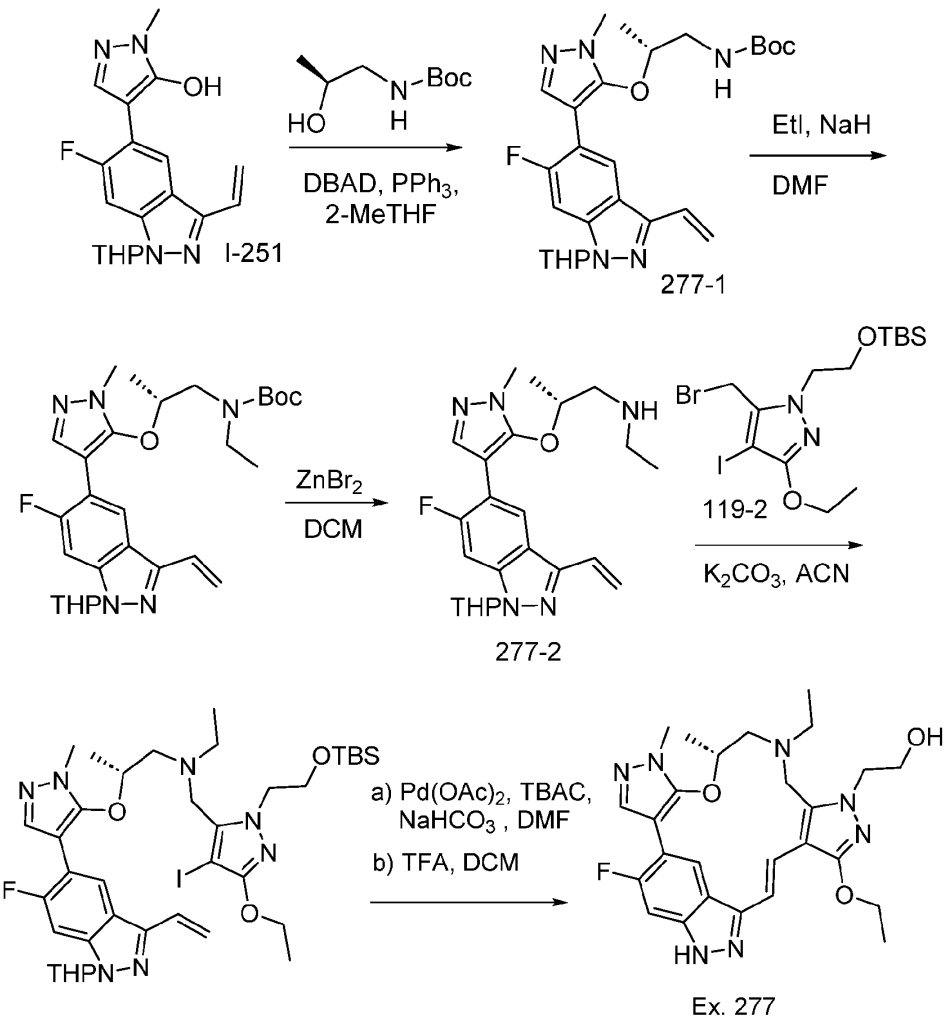
[01939] Preparation of 2-{(10*S*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol (Ex. 276)



[01940] Step 1. To a solution of 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (326 mg, 1.01 mmol, 1 *eq*) and [(1S)-2-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl-isopropyl-amino]-1-methyl-ethyl] methanesulfonate (745 mg, 1.21 mmol, 1.2 *eq*) in DMF (20 mL) was added K_2CO_3 (417 mg, 3.02 mmol, 3 *eq*). The mixture was stirred at 60 °C or 1 h. On completion, the mixture was quenched with water (40 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, PE:EA=1:0 to 2:1) to give 2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl]-N-isopropyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (543 mg, 0.642 mmol, 64% yield) as a yellow solid. LCMS: *m/z* 846.4 (M+1).

[01941] Steps 2-4 were performed in a similar manner to steps 5, 9, and 10 in Example 272 to give 276 (19.39 mg, 0.037 mmol, 38.3% yield) as a white solid.

[01942] General Method Y: Preparation of 2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 277)



[01943] Step 1. A mixture of 4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-ol (2.00 g, 5.84 mmol, 1 *eq*), tert-butyl N-[(2S)-2-hydroxypropyl]carbamate (2.05 g, 11.6 mmol, 2 *eq*), DBAD (2.96 g, 12.8 mmol, 2.2 *eq*), PPh_3 (3.37 g, 12.8 mmol, 2.2 eq) was degassed and purged with N_2 for 3 times, then added 2-MeTHF (20 mL) was degassed and purged with N_2 for 3 times again, and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. On completion, the reaction was concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1 to 1:1) to give tert-butyl N-[(2R)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (7.10 g, 5.68 mmol, 97% yield, 40% purity) as yellow solid. LCMS: *m/z* 500.1 (M+1).

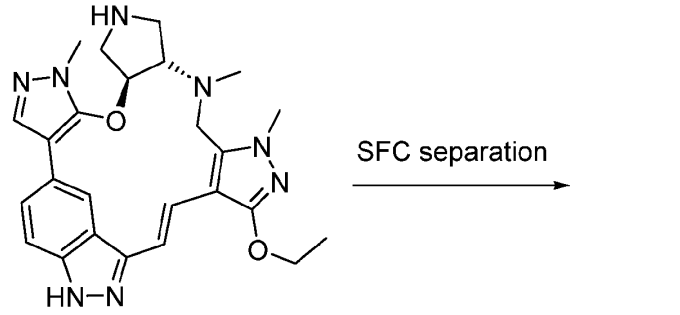
[01944] Step 2. To a solution of tert-butyl N-[(2R)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (6.60 g, 5.28 mmol, 1 *eq*) in DMF (20 mL) was added NaH (845 mg, 21.1 mmol, 60% purity, 4 *eq*) at 0 °C. The mixture was stirred at 25 °C for 0.5 h, then was added iodoethane (2.47 g, 15.8 mmol, 1.27 mL, 3 *eq*) at 25 °C, the mixture was stirred at 25 °C for 6 h. On completion, the mixture was poured into H_2O (200 mL) and extracted with EA (60 mL*3). The combined organic phase was washed with H_2O (100 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/Ethyl acetate=5:1 to 3:1) to give tert-butyl N-ethyl-N-[(2R)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (2.40 g, 4.55 mmol, 86% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.97 (dd, *J* = 2.0, 6.8 Hz, 1H), 7.58 (br s, 1H), 7.31 (br d, *J* = 10.4 Hz, 1H), 7.01 (dd, *J* = 11.6, 18.0 Hz, 1H), 6.08 (d, *J* = 18.0 Hz, 1H), 5.62 (dd, *J* = 2.4, 9.4 Hz, 1H), 5.55 (d, *J* = 11.6 Hz, 1H), 4.30 - 4.12 (m, 1H), 4.07 (br d, *J* = 11.2 Hz, 1H), 3.75 (s, 4H), 3.51 - 2.99 (m, 4H), 2.59 - 2.46 (m, 1H), 2.22 - 2.11 (m, 1H), 2.06 (br dd, *J* = 2.8, 13.2 Hz, 1H), 1.77 (br t, *J* = 8.4 Hz, 2H), 1.71 - 1.60 (m, 1H), 1.45 - 1.32 (m, 9H), 0.96 (br s, 6H); LCMS: *m/z* 528.1 (M+1).

[01945] Step 3. To a solution of tert-butyl N-ethyl-N-[(2R)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (2.00 g, 3.79 mmol, 1 *eq*) in DCM (20 mL) was added $ZnBr_2$ (2.56 g, 11.3 mmol, 3 *eq*). The mixture was stirred at 25 °C for 12 hr. On completion, the mixture was concentrated in vacuum to give (2R)-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl|oxy-propan-1-amine (4.20 g, 3.73 mmol, 98% yield, 38% purity) as white solid. LCMS: *m/z* 428.1 (M+1).

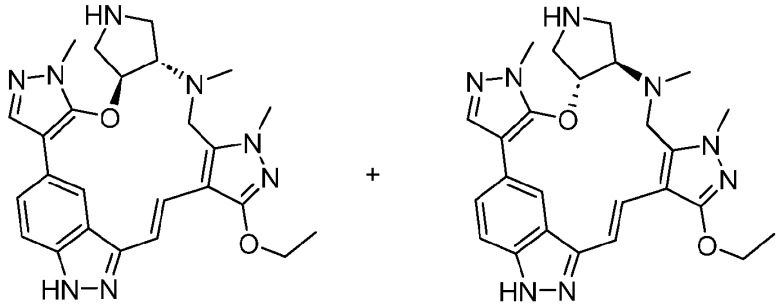
[01946] Step 4. To a solution of (2R)-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (500 mg, 1.17 mmol, 1 *eq*) in DMF (5 mL) was added K_2CO_3 (485 mg, 3.51 mmol, 3 *eq*) and 2-[5-(bromomethyl)-3-ethoxy-4-iodo-pyrazol-1-yl]ethoxy-tert-butyl-dimethyl-silane (763 mg, 1.17 mmol, 1 *eq*). On completion, the mixture was stirred at 80 °C for 1 h. The mixture was poured into H_2O (50 mL) and extracted with ethyl acetate (30 mL × 3), the combined organic phase was washed with H_2O (50 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=1/0 to 92/8) to give (2R)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl]methyl]-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (0.508 g, 0.608 mmol, 52% yield) as a light yellow oil. LCMS: *m/z* 836.1 (M+1).

[01947] Steps 5 and 6 were performed in a similar manner to steps 3 and 4 in General Method T.

[01948] Preparation of (4a*S*,7a*S*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine (Ex. 278) and (4a*R*,7a*R*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine (Ex.279)



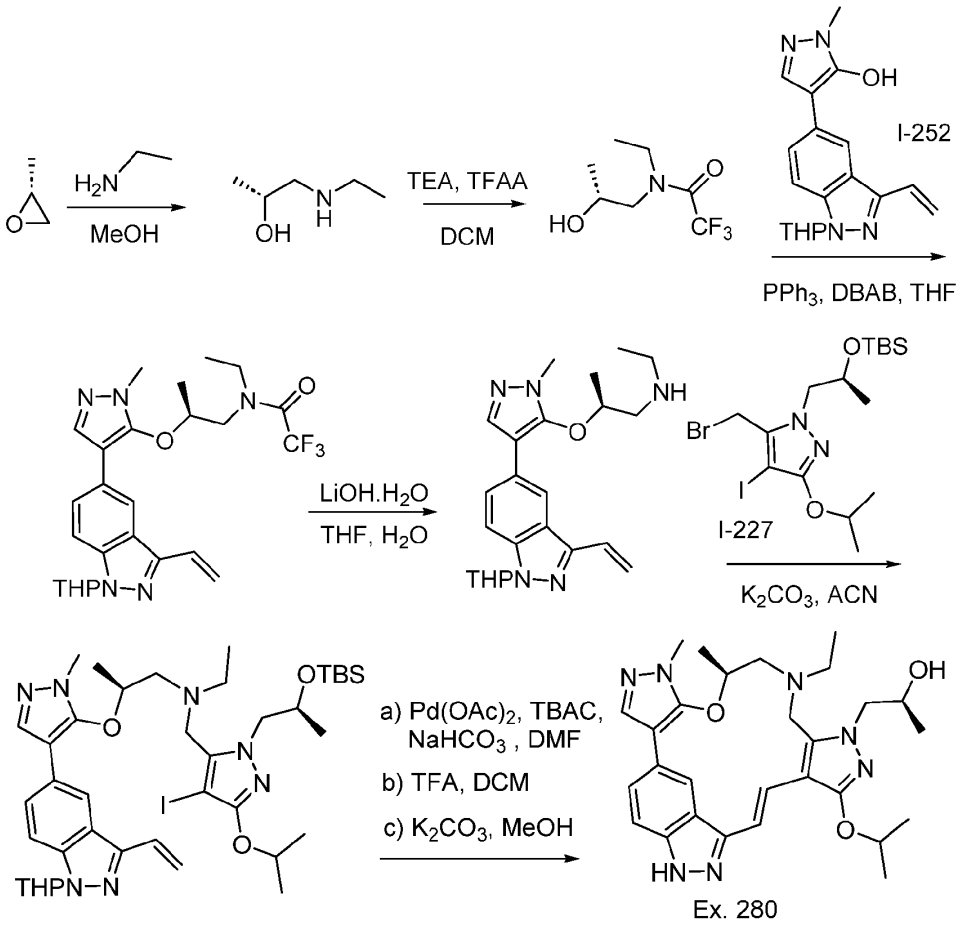
270-1



Ex. 278 Ex. 279

[01949] SFC separation of racemic 270-1 gave arbitrarily assigned Ex. 278 and Ex. 279.

[01950] Preparation of (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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol (Ex. 280)



Ex. 280

[01951] Step 1. To a solution of (2R)-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 (2R)-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).

[01952] Step 2. To a solution of (2R)-1-(ethylamino)propan-2-ol (8.13 g, 78.8 mmol, 1 *eq*) in DCM (80 mL) was added (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (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 1:1) to give N-ethyl-2,2,2-trifluoro-N-[(2R)-2-hydroxypropyl]acetamide (7.92 g, 39.8 mmol, 50% yield) as a white solid. LCMS: *m/z* 200.1 (M+1).

[01953] Step 3. A mixture of 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (700 mg, 2.16 mmol, 1 *eq*), N-ethyl-2,2,2-trifluoro-N-[(2R)-2-hydroxypropyl]acetamide (429 mg, 2.16 mmol, 1 *eq*), PPh_3 (1.13 g, 4.32 mmol, 2 *eq*) and DBAD (745 mg, 3.24 mmol, 1.5 *eq*) was degassed and purged with N_2 for 3 times, then THF (11 mL) was added. The mixture was stirred at 25 °C for 1 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 2:1) to give N-ethyl-2,2,2-trifluoro-N-[(2S)-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) pyrazol-3-yl]oxypropyl]acetamide (920 mg, 1.82 mmol, 84% yield) as a yellow oil. LCMS: *m/z* 506.0 (M+1).

[01954] Step 4. To a solution of N-ethyl-2,2,2-trifluoro-N-[(2S)-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxypropyl]acetamide (870 mg, 1.72 mmol, 1 *eq*) in THF (8.7 mL) and H_2O (1.74 mL) was added $LiOH.H_2O$ (361 mg, 8.60 mmol, 5 *eq*). The mixture was stirred at 25 °C for 12 h. On completion, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (15 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, Dichloromethane : Methanol=1:0 to 10:1) to give (2S)-N-ethyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (650 mg, 1.59 mmol, 92% yield) as a yellow oil. LCMS: *m/z* 410.2 (M+1).

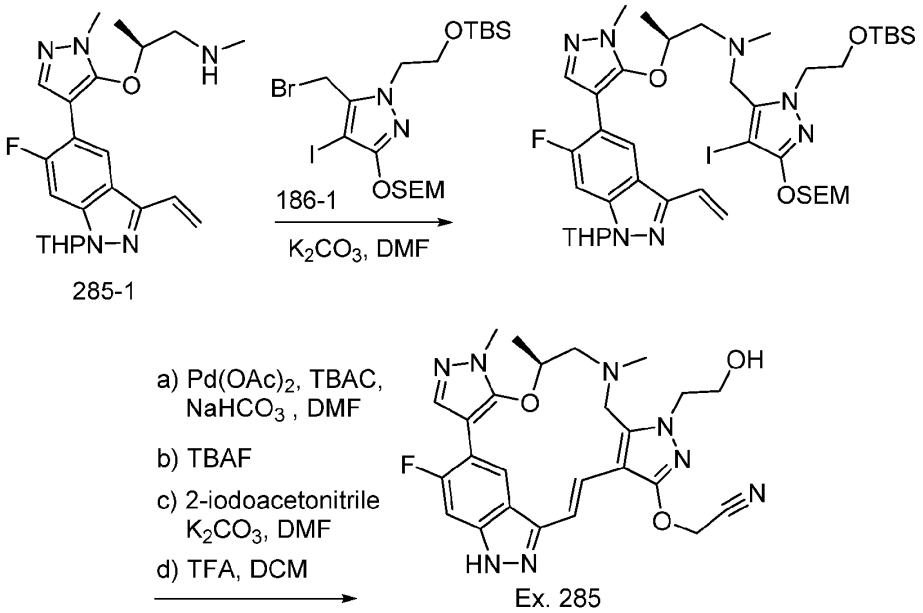
[01955] Step 5. To a solution of (2S)-N-ethyl-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (316 mg, 0.773 mmol, 1 *eq*) in ACN (3.5 mL) was added |(1S)-2-|5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl|-1-methyl-ethoxy]-tert-butyl-dimethyl-silane (400 mg, 0.773 mmol, 1 *eq*) and K_2CO_3 (320 mg, 2.32 mmol, 3 *eq*). The mixture was stirred at 60 °C for 2 h. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF=1:0 to 4:1) to give (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-indazol-5-yl)pyrazol-3-yl]oxy-propan-1-amine (520 mg, 0.614 mmol, 79% yield) as a colorless oil. LCMS: *m/z* 846.5 (M+1).

[01956] Steps 6-8 were performed in a similar manner to steps 5, 9, and 10 in Example 272 to give 280 (44.3 mg, 0.078 mmol, 48 % yield, 99% purity, FA) as a yellow solid.

[01957] Examples 281 and 282 were arbitrarily assigned from synthesis following General Method V.

[01958] Examples 283 and 284 were arbitrarily assigned from synthesis following General Method V.

[01959] Preparation of {[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile (Ex. 285)



[01960] Starting material 285-1 was made following the procedures of General Method Y steps 1 through 3.

[01961] Step 1. To a solution of (2S)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-N-methyl-propan-1-amine (830 mg, 2.01 mmol, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (832 mg, 6.02 mmol, 3 *eq*) and 2-[[5-(bromomethyl)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-pyrazol-3-yl]oxymethoxy]ethyl-trimethyl-silane (1.54 g, 2.61 mmol, 1.3 *eq*). The mixture was stirred at 80 °C for 16 h. On completion, the reaction mixture was diluted with H_2O (30 mL) and extracted with EA (20 mL * 3). The combined organic layers were washed with H_2O (40 mL * 3), 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 (2S)-N-[[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy)pyrazol-3-yl]methyl]-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-N-methyl-propan-1-amine (630 mg, 0.682 mmol, 34% yield) as colorless oil. LCMS: *m/z* 924.6 (M+1).

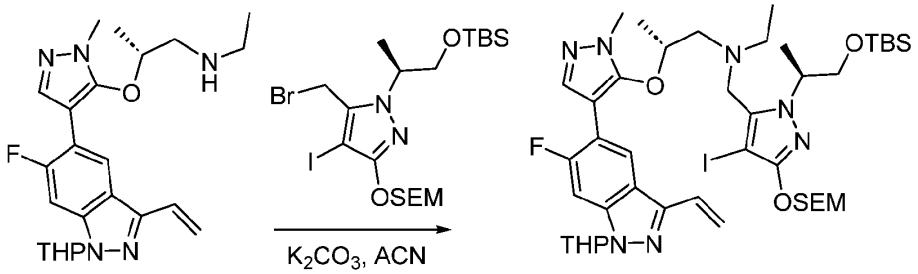
[01962] Steps 2 through 5 were performed in a similar manner to steps 4 through 7 in General Method X.

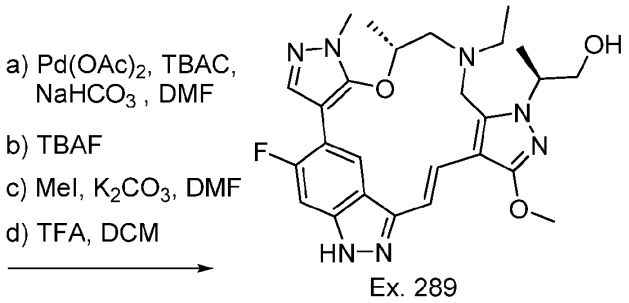
[01963] Example 286 was prepared using similar procedures to Example 285.

[01964] Example 287 was prepared using similar procedures to Example 280.

[01965] Example 288 was prepared using similar procedures to General Method Y.

[01966] Preparation of (2*S*)-2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol (Ex. 289)

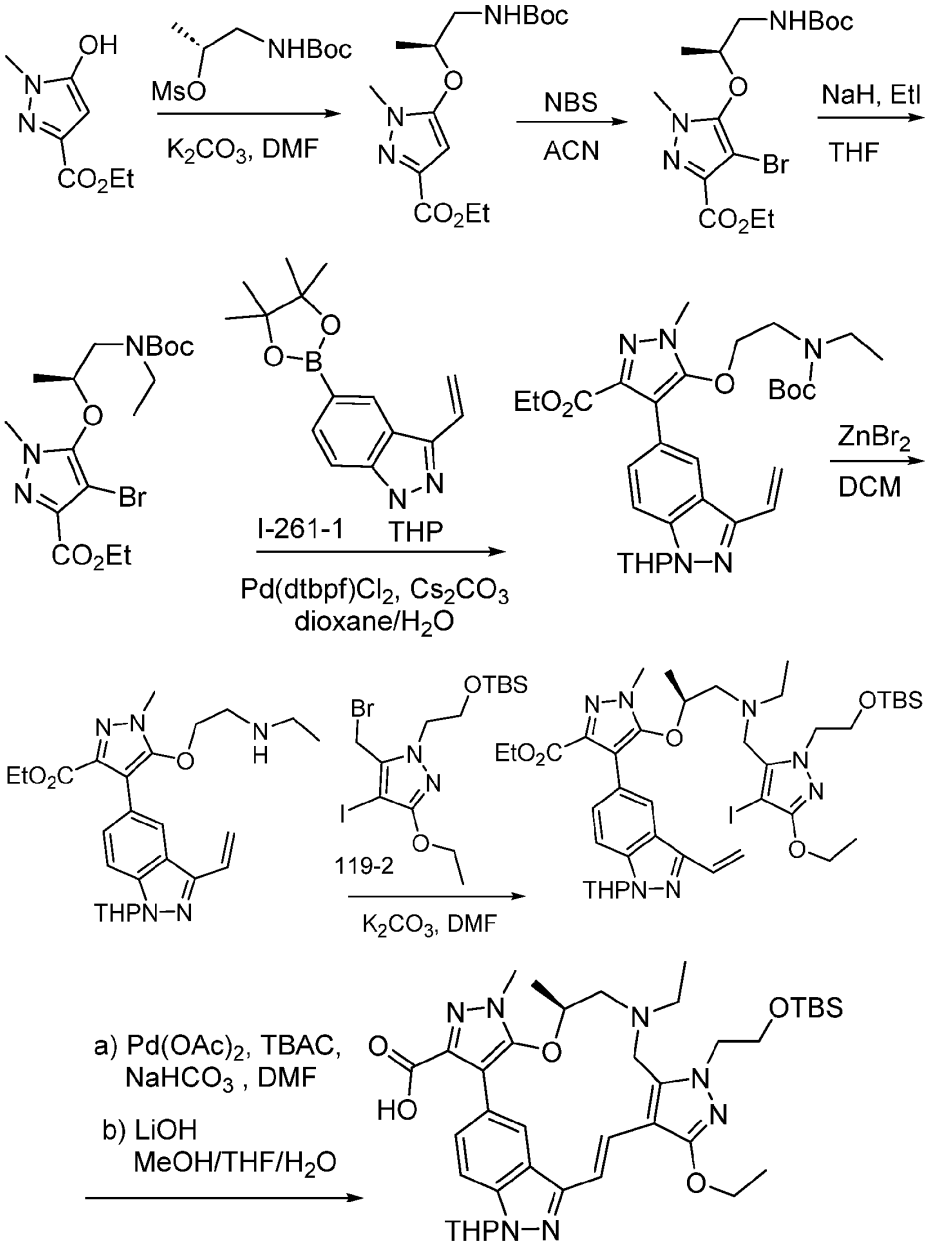


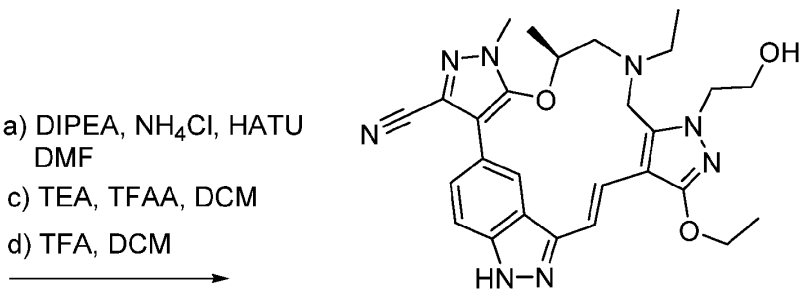


[01967] Step 1. A solution of (2S)-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (250 mg, 0.585 mmol, 1 *eq*), 2-[[5-(bromomethyl)-1-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-pyrazol-3-yl]oxymethoxy]ethyl-trimethyl-silane (425 mg, 0.702 mmol, 1.2 *eq*) from Ex. 214 and K_2CO_3 (242 mg, 1.75 mmol, 3 *eq*) in ACN (6 mL) was stirred at 60 °C for 2 h. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (4 g silica gel, EA in Petroleum ether from 0% to 100%) to give (2S)-N-[[2-[(1S)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl]-4-iodo-5-(2-trimethylsilylethoxymethoxy) pyrazol-3-yl]methyl]-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (400 mg, 0.298 mmol, 51% yield, 71% purity) as a yellow solid. LCMS: *m/z* 952.5 (M+1).

[01968] Steps 2 through 5 were performed in a similar manner to steps 4 through 7 in General Method X.

[01969] Preparation of (10*S*,17*E*)-16-ethoxy-12-ethyl-14-(2-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile (Ex. 290)





Ex. 290

[01970] Steps 1-3 were conducted according to General Method M steps 2-4.

[01971] Step 4. A mixture of ethyl 4-bromo-5-[(1S)-2-[tert-butoxycarbonyl(ethyl)amino]-1-methyl-ethoxy]-1-methyl-pyrazole-3-carboxylate(1.30 g, 2.99 mmol, 1 *eq*), 1-tetrahydropyran-2-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-vinyl-indazole (1.17 g, 3.29 mmol, 1.1 *eq*), ditert-butyl(cyclopentyl)phosphane; dichloropalladium; iron (195 mg, 0.299 mmol, 0.1 *eq*), Cs_2CO_3 (2.93 g, 8.98 mmol, 3 *eq*) in dioxane (15 mL) and H_2O (3 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 mixture was quenched with water (50 mL) and extracted with ethyl acetate (45 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 ethyl 5-[(1S)-2-[tert-butoxycarbonyl(ethyl)amino]-1-methyl-ethoxy]-1-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) pyrazole-3-carboxylate (700 mg, 1.20 mmol, 40% yield) as an orange solid. LCMS: *m/z* 582.3 (M+1).

[01972] Steps 5-6 were conducted according to General Method Q steps 5 and 6.

[01973] Step 7. A mixture of ethyl 5-[(1S)-2-[[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-5-ethoxy-4-iodo-pyrazol-3-yl] methyl-ethyl-amino]-1-methyl-ethoxy]-1-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) pyrazole-3-carboxylate (300 mg, 0.337 mmol, 1 *eq*), $Pd(OAc)_2$ (15.1 mg, 0.067 mmol, 0.2 *eq*), TBAC (93.6 mg, 0.337 mmol, 1 *eq*) and $NaHCO_3$ (70.8 mg, 0.842 mmol, 2.5 *eq*) in DMF (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 10 minutes under N_2 atmosphere. 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 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 ethyl (8S,17E)-13-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-15-ethoxy-10-ethyl-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13, 14,20,21- heptazapentacyclo

[17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3, 12(16),14,17,19,22(26),23-nonaene-3-carboxylate (200 mg, 0.262 mmol, 77% yield) as a white solid. LCMS: *m/z* 762.2 (M+1).

[01974] Step 8. To a solution of ethyl (8S,17E)-13-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-15-ethoxy-10-ethyl-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19, 22(26),23-nonaene-3-carboxylate (200 mg, 0.262 mmol, 1 *eq*) in MeOH (1.5 mL), H_2O (0.5 mL) and THF (1.5 mL) was added LiOH.H_2O (33.0 mg, 0.787 mmol, 3 *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 reversed-phase HPLC (Neutral condition) to give (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carboxylic acid (50.0 mg, 0.081 mmol, 31% yield) as a yellow solid. LCMS: *m/z* 620.1 (M+1).

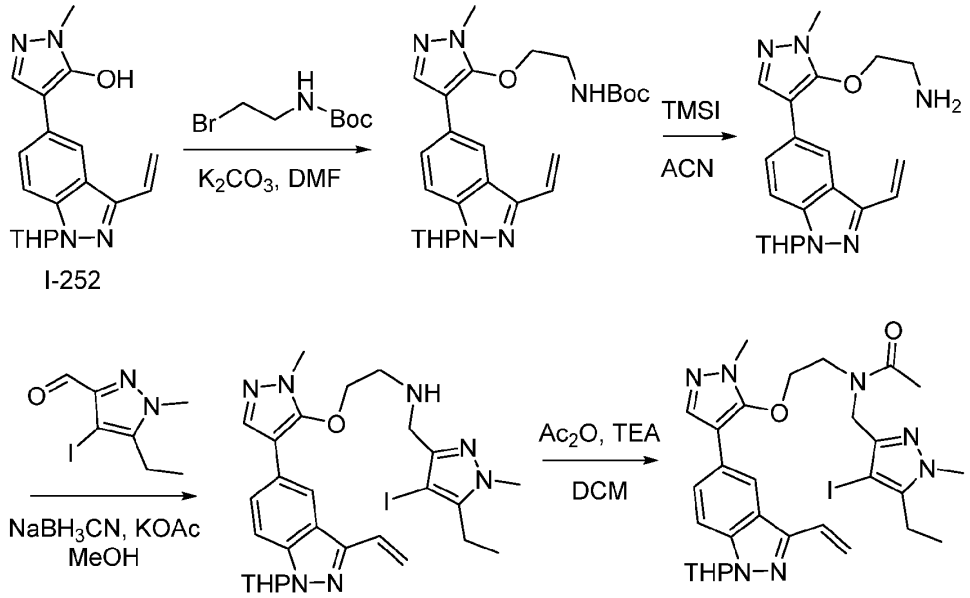
[01975] Step 9. To a solution of (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012, 16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carboxylic acid (30.0 mg, 0.048 mmol, 1 *eq*) and NH_4Cl (25.9 mg, 0.484 mmol, 10 *eq*) in DMF (0.5 mL) was added DIEA (31.2 mg, 0.242 mmol, 5 *eq*) and HATU (22.0 mg, 0.058 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 0.1 hour. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by reversed-phase HPLC (0.1% FA condition) to give (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carboxamide (15.0 mg, 0.024 mmol, 50% yield) as a white solid. LCMS: *m/z* 619.3 (M+1).

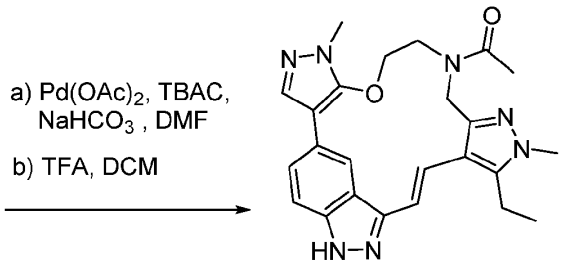
[01976] Step 10. To a solution of (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carboxamide (15.0 mg, 0.024 mmol, 1 *eq*) in $CHCl_3$ (0.5 mL) was added TEA (8.34 mg, 0.082 mmol, 3.4 *eq*) and TFAA (8.66 mg, 0.041 mmol, 1.7 *eq*). The mixture was stirred at 0 °C for 1 hour. On completion, the mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 mL * 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14, 20,21-heptazapentacyclo

[17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14, 17,19,22(26),23-nonaene-3-carbonitrile (14.0 mg, 0.023 mmol, 96% yield) as a yellow solid. LCMS: *m/z* 601.2 (M+1).

[01977] Step 11. To a solution of (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012, 16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carbonitrile (14.0 mg, 0.023 mmol, 1 *eq*) in DCM (0.5 mL) was added TFA (26.5 mg, 0.233 mmol, 10 *eq*). The mixture was stirred at 25 °C for 0.1 hours. On completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C_{18} 150*25mm*10um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient:26%-56% B over 10 min) to give (10*S*,17*E*)-16-ethoxy-12-ethyl-14-(2-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile (2.38 mg, 0.004 mmol, 19 % yield, 94 % purity) as a yellow solid.

[01978] Preparation of 1-[(17*E*)-16-ethyl-8,15-dimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one (Ex. 291)





Ex. 291

[01979] Step 1. To a solution of 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (4.00 g, 12.3 mmol, 1 *eq*) and tert-butyl N-(2-bromoethyl)carbamate (4.15 g, 18.5 mmol, 1.5 *eq*) in DMF (40 mL) was added K_2CO_3 (5.11 g, 36.9 mmol, 3 *eq*). The mixture was stirred at 80 °C for 1 hr. On completion, the mixture was diluted with water (60 mL) and extracted with ethyl acetate (60 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=1:1 to 1:1) to give tert-butyl N-[2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethyl]carbamate (3.70 g, 7.68 mmol, 62% yield, 97% purity) as a yellow oil. LCMS: *m/z* 468.1 (M+1).

[01980] Step 2. To a solution of tert-butyl N-[2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethyl]carbamate (3.20 g, 6.84 mmol, 1 *eq*) in ACN (32 mL) was added TMSI (1.78 g, 8.90 mmol, 1.3 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. On completion, the reaction mixture was quenched by addition sat. $NaHCO_3$ (30 mL) at 0 °C to adjust pH = 8, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (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, DCM/MeOH=1:1 to 1:1) to give 2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethanamine (1.90 g, 5.12 mmol, 75% yield, 99% purity) as a colorless liquid. LCMS: *m/z* 368.0 (M+1).

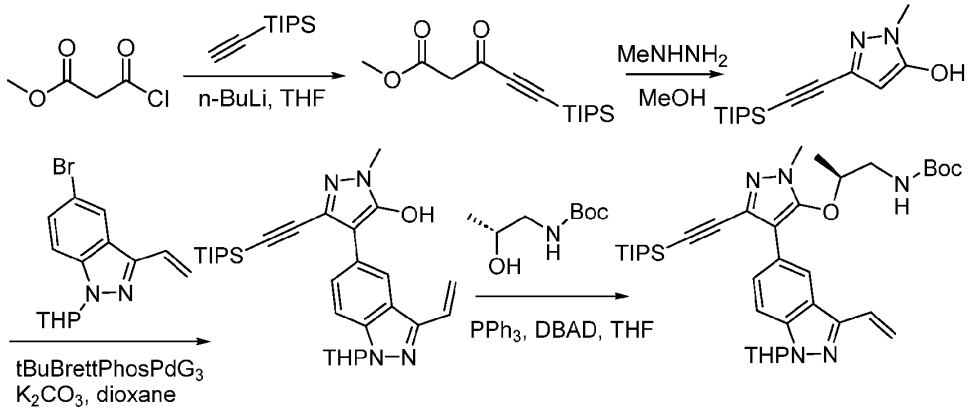
[01981] Step 3. To a solution of 2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethanamine (800 mg, 2.18 mmol, 1 *eq*) and 5-ethyl-4-iodo-1-methyl-pyrazole-3-carbaldehyde (344 mg, 1.31 mmol, 0.6 *eq*) in MeOH (10 mL) was added KOAc (1.07 g, 10.8 mmol, 5 *eq*). The mixture was stirred at 25 °C for 0.5 h. Then $NaBH_3CN$ (273 mg, 4.35 mmol, 2 *eq*) was added. The mixture was stirred at 25 °C for 1 h. On completion, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (25 mL× 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and

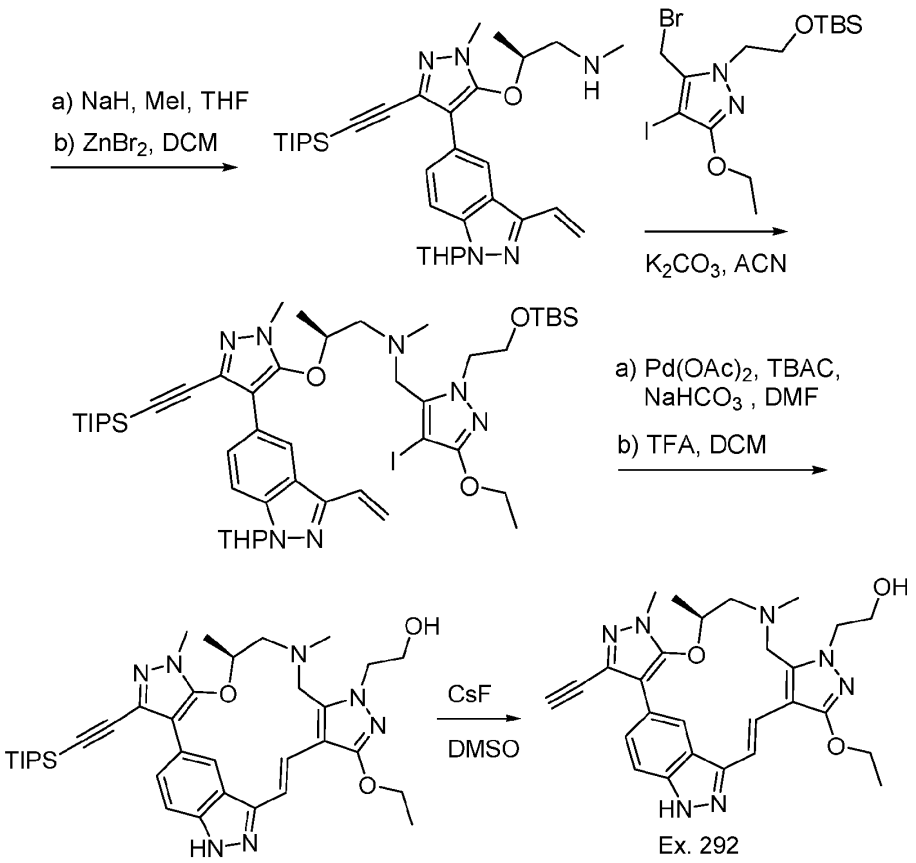
concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE: THF=1:0 to 1:2) to give N-[(5-ethyl-4-iodo-1-methyl-pyrazol-3-yl)methyl]-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-ethanamine (700 mg, 0.841 mmol, 39% yield, 74% purity) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 8.06 (s, 1H), 7.72 - 7.63 (m, 3H), 7.06 - 6.97 (m, 1H), 6.17 - 6.09 (m, 1H), 5.82 -5.73 (m, 1H), 5.55 - 5.48 (m, 2H), 4.10 - 4.03 (m, 2H), 4.02 - 3.98 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.66 (s, 2H), 2.91 (t, J = 5.6 Hz, 2H), 2.70 (q, J = 7.6 Hz, 2H), 2.55 - 2.43 (m, 1H), 2.22 (s, 4H), 1.90 - 1.74 (m, 2H), 1.16 - 1.09 (m, 3H); LCMS: m/z 615.9 (M+1).

[01982] Step 4. To a solution of N-[(5-ethyl-4-iodo-1-methyl-pyrazol-3-yl)methyl]-2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-ethanamine (650 mg, 1.06 mmol, 1 *eq*) in DCM (6.5 mL) was added Ac_2O (162 mg, 1.58 mmol, 1.5 *eq*) and TEA (321 mg, 3.17 mmol, 3 *eq*). The mixture was stirred at 25 °C for 2 h. On completion, the mixture was diluted with water (15 mL) and extracted with DCM (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, DCM/MeOH=10:1 to 1:1) to give N-[(5-ethyl-4-iodo-1-methyl-pyrazol-3-yl)methyl]-N-[2-[2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxyethyl]acetamide (360 mg, 0.515 mmol, 49% yield, 94% purity) as a colorless oil.

[01983] Steps 5 and 6 were performed in a similar manner to steps 3 and 4 in General Method T.

[01984] Preparation of 2-[(10*S*,17*E*)-16-ethoxy-6-ethynyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 292)





Ex. 292

[01985] Step 1. To a solution of ethynyl(triisopropyl)silane (33.4 g, 183 mmol, 41 mL, 2.5 *eq*) in THF (200 mL) at –78 °C was added n-BuLi (2.5 M, 88 mL, 3 *eq*) under N_2. The mixture was stirred at the -78 °C for 1 hr, and then $BF_3.Et_2O$ (26.0 g, 183 mmol, 23 mL, 2.5 *eq*) was added. After 0.2 hr, methyl 3-chloro-3-oxo-propanoate (10.0 g, 73.2 mmol, 7.82 mL, 1 *eq*) in THF (50 mL) was added. The mixture was stirred at -78 °C for 2 h. On completion, the mixture was quenched with sat. NH_4Cl (500 mL) and water (500 mL) and extracted with ethyl acetate (500 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (60.0 g, crude) as an orange oil. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1) to give methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (9.96 g, 35.3 mmol, 17% yield) as a red oil. ^1H NMR (400 MHz, $CDCl_3$-*d*) δ = 11.78 - 11.58 (m, 1H), 3.78 - 3.74 (m, 4H), 3.62 - 3.60 (m, 1H), 1.11 - 1.10 (m, 21H).

[01986] Step 2. To a solution of methyl 3-oxo-5-triisopropylsilyl-pent-4-ynoate (6.83 g, 24.2 mmol, 1 *eq*) in MeOH (70 mL) was added methylhydrazine (3.34 g, 29.0 mmol, 4 mL, 1.2 *eq*) at 0 °C. 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, DCM:MeOH=1:0 to 10:1) to give 2-methyl-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (3.15 g, 10.3 mmol, 43% yield, 91% purity) as a brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 11.46 - 11.02 (m, 1H), 5.48 (s, 1H), 3.50 (s, 3H), 1.07 (s, 21H); LCMS: *m/z* 279.2 (M+1).

[01987] Step 3. To a solution of 2-methyl-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (1.00 g, 3.59 mmol, 1 *eq*) in dioxane (10 mL) was added 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (1.21 g, 3.95 mmol, 1.1 *eq*) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (307 mg, 0.359 mmol, 0.1 *eq*) then the mixture was added K_2CO_3 (993 mg, 7.18 mmol, 2 *eq*) under N_2. The mixture was stirred at 100 °C for 3 hr. 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 10/1) to give 2-methyl-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-5-(2-triisopropylsilylethynyl)pyrazol-3-ol (960 mg, 1.77 mmol, 49% yield, 93% purity) as a brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 11.60 - 10.26 (m, 1H), 8.15 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 6.97 (dd, *J* = 11.4, 18.0 Hz,1H), 6.05 (d, *J* = 18.0 Hz, 1H), 5.84 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.50 (d, *J* = 12.4 Hz, 1H), 3.88 (br d, *J* = 11.2 Hz, 1H), 3.79 - 3.71 (m, 1H), 3.63 (s, 3H), 2.45 - 2.31 (m, 2H), 2.08 - 2.00 (m, 1H), 1.96 (br dd, *J* = 2.4, 13.1 Hz, 1H), 1.76 (td, *J* = 3.2, 6.3 Hz,2H), 1.59 (br d, *J* = 3.6 Hz, 3H), 1.05 - 1.01 (m, 18H); LCMS: *m/z* 505.2 (M+1).

[01988] Steps 4 through 9 were performed in a similar manner General Method Y to give 2-[(8S,17E)-15-ethoxy-5,8,10-trimethyl-3-(2-triisopropylsilylethynyl)-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]ethanol (300 mg, crude) as a brown oil. LCMS: *m/z* 658.3 (M+1).

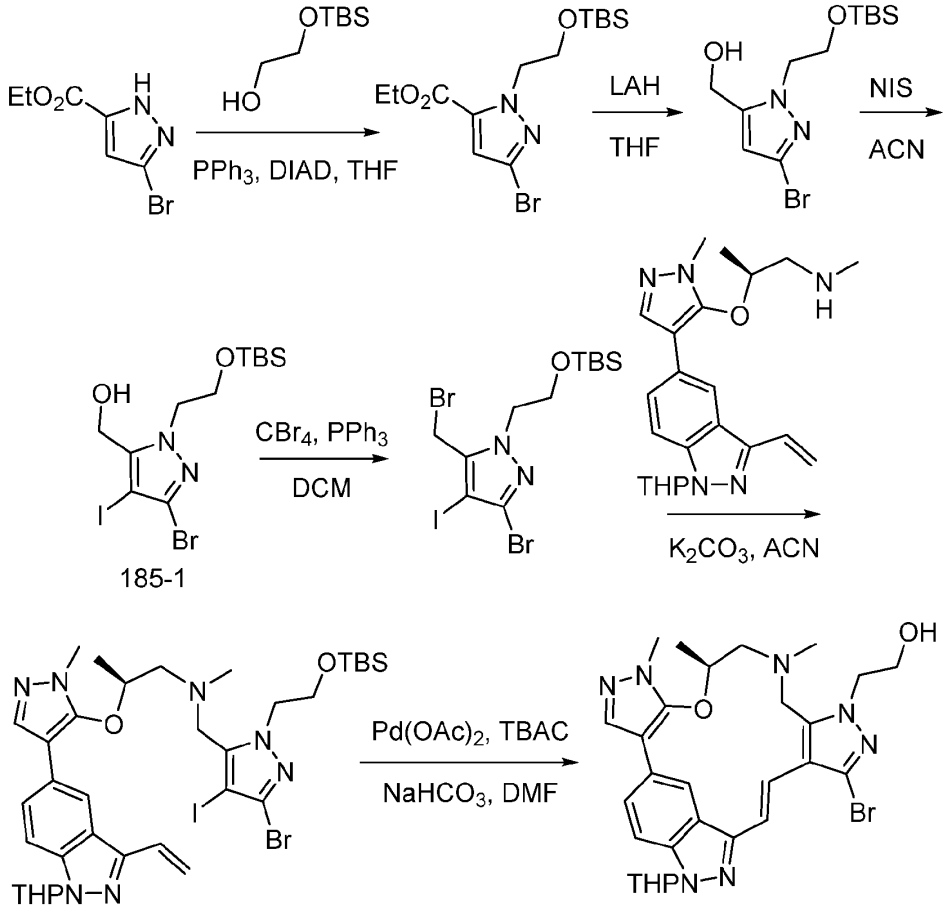
[01989] Step 10. To a solution of 2-[(8S,17E)-15-ethoxy-5,8,10-trimethyl-3-(2-triisopropylsilylethynyl)-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]ethanol (300 mg, 0.456 mmol, 1 *eq*) in DMSO (5 mL) was added CsF (416 mg, 2.74 mmol, 100 µL, 6 *eq*). The mixture was stirred at 25 °C for 5 hr. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:11%-41% B over 15 min) to give 2-[(10*S*,17*E*)-16-ethoxy-6-ethynyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-

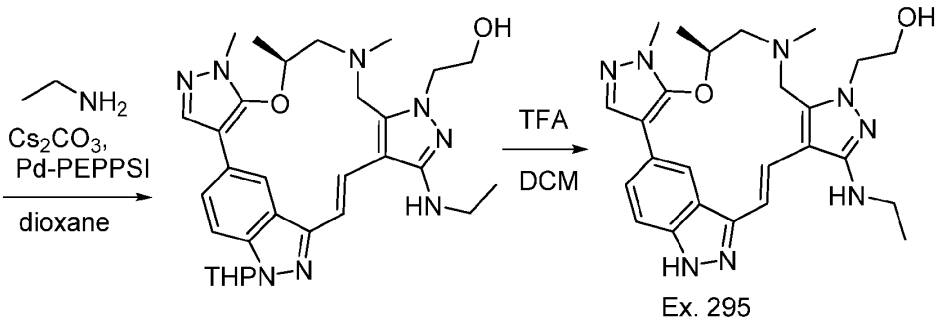
n][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (30.43 mg, 0.061 mmol, 13 % yield, 100% purity) as a white solid.

[01990] Example 293 was prepared using similar procedures to Example 285.

[01991] Example 294 was prepared using similar procedures to Example 291.

[01992] Preparation of 2-[(10*S*,17*E*)-16-(ethylamino)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 295)





Ex. 295

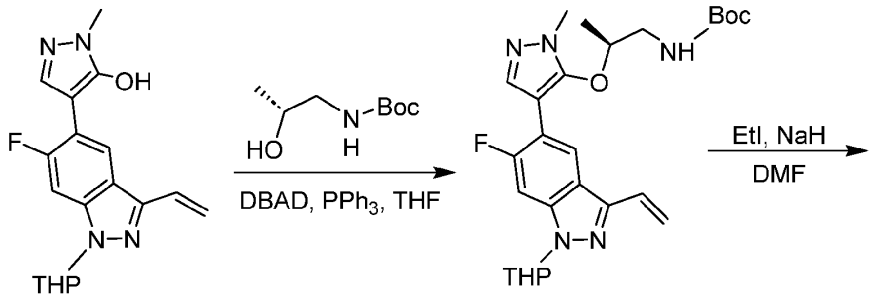
[01993] Steps 4 was conducted similarly to General Method O steps 5.

[01994] Steps 5-6 were conducted similarly to General Method Y steps 4-5.

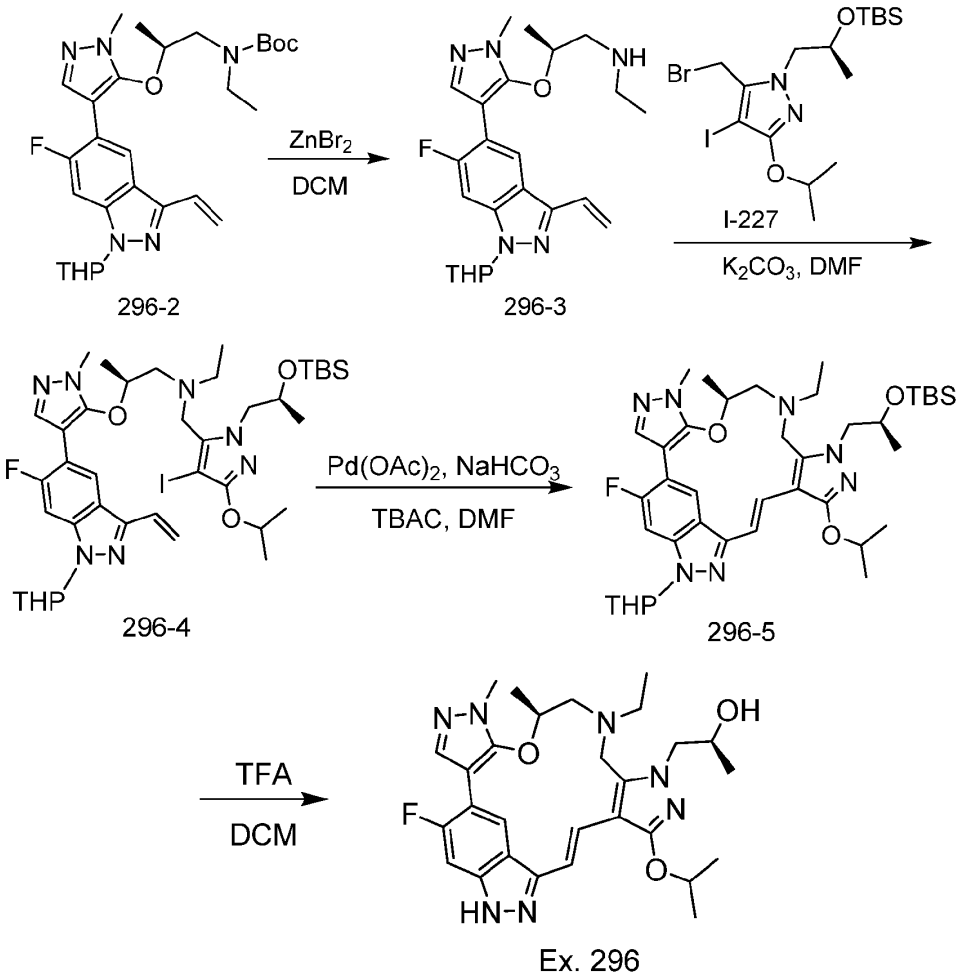
[01995] Step 7. A mixture of 2-[(8S,17E)-15-bromo-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6), 3,12(16),14,17,19,22(26),23-nonaen-13-yl]ethanol (200 mg, 0.017 mmol, 1 *eq*), ethanamine (2 M, 17.4 μL, 2 *eq*), Cs_2CO_3 (17.0 mg, 0.052 mmol, 3 *eq*), 1,3-bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-2H-imidazol-1-ium-2-ide;3-chloropyridine; dichloropalladium (1.70 mg, 0.002 mmol, 0.1 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 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, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give 2-[(8S,17E)-15-(ethylamino)-5,8,10-trimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3, 12(16),14,17,19, 22(26),23-nonaen-13-yl]ethanol (74.0 mg, crude) as a yellow solid. LCMS: *m/z* 561.1 (M+1).

[01996] Step 8 was performed in a similar manner to step 4 in General Method Y.

[01997] Example 296 was prepared using similar procedures to Example 280 using I-251 instead of I-252. Briefly, the synthesis of Example 296 was carried out as follows:



I-251 296-1



[01998] Preparation of (2*S*)-1-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol (Ex. 296)

[01999] Step 1: A mixture of 4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-ol (I-251; 8.90 g, 26.0 mmol, 1 *eq*), PPh_3 (15.0 g, 57.2 mmol, 2.2 *eq*), DBAD (13.2 g, 57.2 mmol, 2.2 *eq*) was degassed and purged with N_2 for 3 times, THF (90 mL) and tert-butyl N-[(2R)-2-hydroxypropyl]carbamate (9.11 g, 52.0 mmol, 2 *eq*) was added, then 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 tert-butyl N-[(2S)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-

methyl-pyrazol-3-yl]oxypropyl]carbamate (296-1; 22.0 g, 22.0 mmol, 85% yield, 50% purity) as red oil.

[02000] LCMS: (M+1) = 500.2.

[02001] Step 2: To a solution of tert-butyl N-[(2S)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (296-1; 11.0 g, 22.0 mmol, 1 *eq*) in DMF (110 mL) was added NaH (1.76 g, 44.0 mmol, 60% purity, 2 *eq*) at 0 °C and stirred at 25 °C for 30 min. EtI (5.15 g, 33.0 mmol, 2.64 mL, 1.5 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the reaction mixture was quenched by addition NH_4Cl (40 mL) at 0 °C, and then diluted with H_2O (20 mL) and extracted with EA (30 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 column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give tert-butyl N-ethyl-N-[(2S)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (296-2; 8.58 g, 16.3 mmol, 74% yield) as red oil.

[02002] LCMS: (M+1) = 528.2.

[02003] Step 3: To a solution of tert-butyl N-ethyl-N-[(2S)-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxypropyl]carbamate (296-2; 7.50 g, 14.2 mmol, 1 *eq*) in DCM (75 mL) was added $ZnBr_2$ (9.60 g, 42.6 mmol, 3 *eq*). The mixture was stirred at 25 °C for 16 hr. On completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give (2S)-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (296-3; 18.7 g, 13.1 mmol, 92% yield, 30% purity) as yellow solid.

[02004] LCMS: (M+1) = 428.1.

[02005] Step 4: To a solution of (2S)-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (296-3; 1.93 g, 4.51 mmol, 1 eq,), [(1S)-2-[5-(bromomethyl)-4-iodo-3-isopropoxy-pyrazol-1-yl]-1-methyl-ethoxy]-tert-butyl-dimethyl-silane (I-227; 1.40 g, 2.71 mmol, 0.6 *eq*) in DMF (20 mL) was added K_2CO_3 (1.87 g, 13.5 mmol, 3 *eq*) .The mixture was stirred at 60 °C for 16 h. On completion, the mixture was quenched by water (60 mL) at 0 °C and extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with water (100 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:THF=4:1) to give (2S)-N-[[2-[(2S)-2-[tert-butyl(dimethyl)silyl]oxypropyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl]-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (296-4; 850 mg, crude) as a yellow oil.

[02006] LCMS: (M+1) = 864.2

[02007] Step 5: To a solution of (2S)-N-[[2-[(2S)-2-[tert-butyl(dimethyl)silyl]oxypropyl]-4-iodo-5-isopropoxy-pyrazol-3-yl]methyl]-N-ethyl-2-[4-(6-fluoro-1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxy-propan-1-amine (296-4; 750 mg, 868 μmol, 1 ***eq***) in DMF (37 mL) was added $NaHCO_3$ (182 mg, 2.17 mmol, 2.5 ***eq***), $Pd(OAc)_2$ (39.0 mg, 174 μmol, 0.2 ***eq***) and TBAC (241 mg, 868 μmol, 1 ***eq***). The mixture was stirred at 130 °C for 1 h. On completion, the mixture was quenched by water (100 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic phase was washed with water (100 mL*2) and dried over Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE:EA=2:1) to give tert-butyl-[(1S)-2-[(8S,17E)-10-ethyl-24-fluoro-15-isopropoxy-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]-1-methyl-ethoxy]-dimethyl-silane (296-5; 445 mg, crude) as a yellow solid.

[02008] LCMS: (M+1) = 736.3.

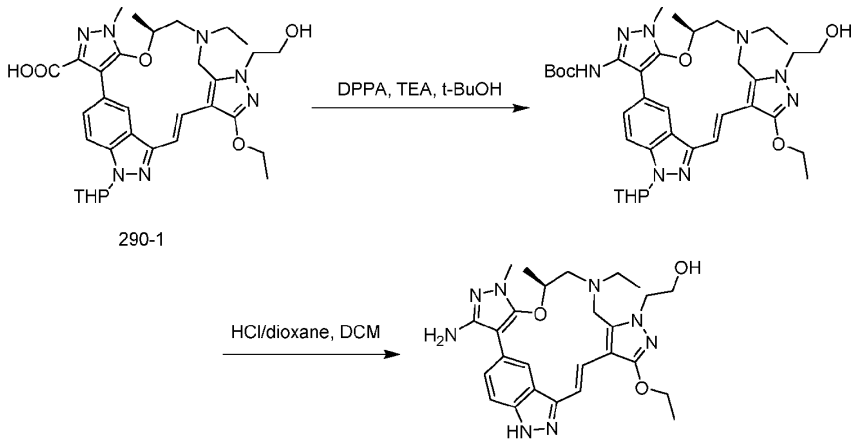
[02009] Step 6: To a solution of tert-butyl-[(1S)-2-[(8S,17E)-10-ethyl-24-fluoro-15-isopropoxy-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5. 2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]-1-methyl-ethoxy]-dimethyl-silane (296-5; 200 mg, 272 μmol, 1 ***eq***) in DCM (2 mL) was added TFA (9.42 mmol, 0.7 mL, 34.7 ***eq***). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (FA condition;column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:23%-43% B over 10 min) to give (2S)-1-[(8S,17E)-10-ethyl-24-fluoro-15-isopropoxy-5,8-dimethyl-7-oxa-4,5,10,13,14,20,21 -heptazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22 (26),23-nonaen-13-yl]propan-2-ol (ex. 296; 46.51 mg, 86.51 μmol, 31.84% yield) as an off-white solid.

[02010] ^{1}H NMR (400 MHz, MeOH-d_4) δ = 8.65 (br d, J = 7.2 Hz, 1H), 8.06 (d, J = 16.8 Hz, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.29 - 7.19 (m, 2H), 5.03 - 4.92 (m, 1H), 4.75 - 4.65 (m, 1H), 4.14 - 4.00 (m, 2H), 3.99 - 3.91 (m, 3H), 3.75 (s, 3H), 3.07 - 2.85 (m, 2H), 2.69 - 2.51 (m, 2H), 1.48 - 1.42 (m, 6H), 1.21 (d, J = 6.0Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H).

[02011] LCMS: (M+1) = 538.1.

[02012] Example 297

[02013] Preparation of 2-[(10*S*,17*E*)-6-amino-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol (Ex. 297)



Ex. 297

[02014] Step 1. A mixture of (8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16. 022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene-3-carboxylic acid (120 mg, 0.193 mmol, 1 *eq*), DPPA (106 mg, 0.387 mmol, 2 *eq*), TEA (39.1 mg, 0.387 mmol, 2 *eq*) in t-BuOH (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 0.5 hours under N_2 atmosphere. On completion, the mixture was filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=1:0 to 0:1) to give tert-butyl N-[(8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-3-yl] carbamate (52.0 mg, 0.075 mmol, 38% yield) as a yellow solid. LCMS: *m/z* 691.3 (M+1).

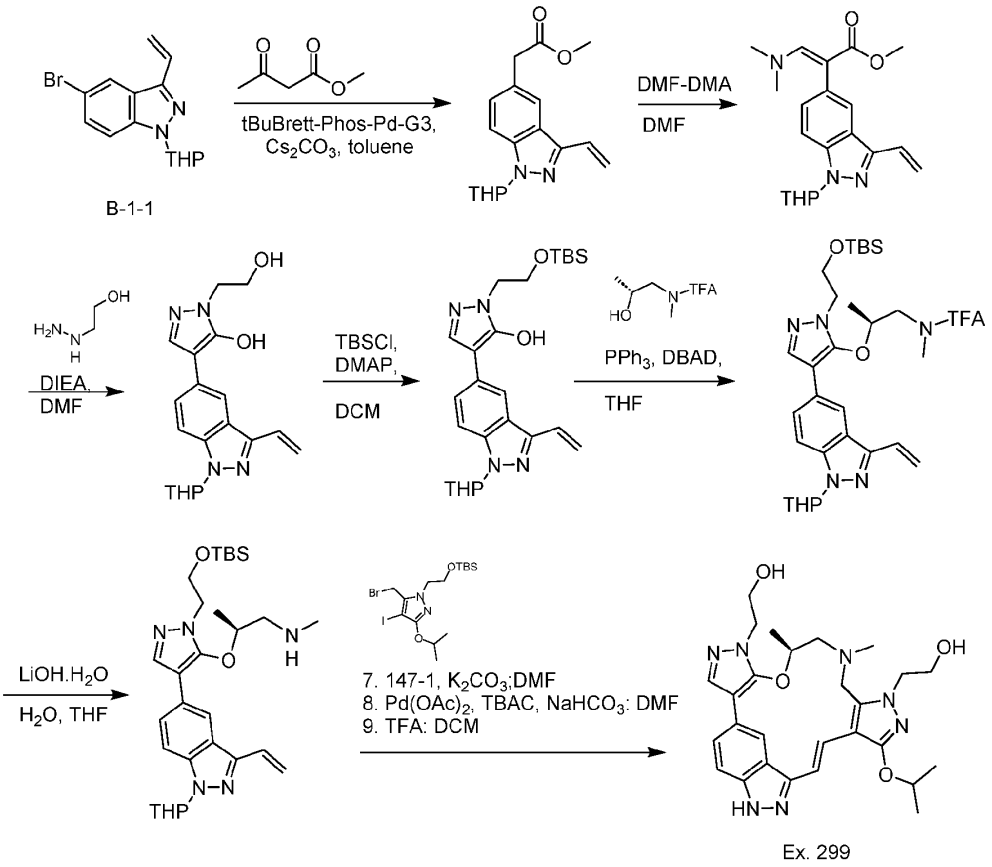
[02015] Step 2. To a solution of tert-butyl N-[(8S,17E)-15-ethoxy-10-ethyl-13-(2-hydroxyethyl)-5,8-dimethyl-21-tetrahydropyran-2-yl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-3-yl] carbamate (20.0 mg, 0.029 mmol, 1 *eq*) in DCM (0.5 mL) was added HCl/dioxane (4 M, 0.1 mL, 10 *eq*). The mixture was stirred at 25 °C for 0.1 hour. On completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Ultimate C18 150*25mm*5um; mobile

phase: [water(FA)-ACN]; gradient:5%-35% B over 10 min) to give 2-[(8S,17E)-3-amino-15-ethoxy-10-ethyl-5,8-dimethyl-7-oxa-4,5,10,13,14,20,21-heptazapentacyclo [17.5.2.02,6.012,16.022,26] hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl] ethanol (9.08 mg, 0.016 mmol, 57% yield, 100% purity, FA) as a brown solid.

[02016] Example 298 was prepared using similar procedures to Example 289.

[02017] Example 299

[02018] Preparation of 2,2'-[(10*S*,17*E*)-10,12-dimethyl-16-[(propan-2-yl)oxy]-10,11,12,13-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-8,14(2*H*)-diyl]di(ethan-1-ol) (Ex. 299)



[02019] Step 1. A solution of 5-bromo-1-tetrahydropyran-2-yl-3-vinyl-indazole (5.00 g, 16.3 mmol, 1 eq), methyl 3-oxobutanoate (2.83 g, 24.4 mmol, 1.5 eq), tBuBrett-Phos-Pd-G3 (695 mg, 0.814 mmol, 0.05 eq), Cs_2CO_3 (15.9 g, 48.8 mmol, 3 eq) in toluene (60 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for

12 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, PE: THF=3:1 to 3:1) to give methyl 2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) acetate (3.30 g, 11.0 mmol, 67% yield) as a yellow oil. LCMS: *m/z* 301.0 (M+1)

[02020] Step 2. To a solution of methyl 2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) acetate (3.00 g, 9.99 mmol, 1 eq) in DMF (20 mL) was added DMF-DMA (2.38 g, 19.9 mmol, 2 eq). The mixture was stirred at 60 °C for 12 h. On completion, the mixture was concentrated to give methyl (E)-3-(dimethylamino)-2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl) prop-2-enoate (3.80 g, crude) as a yellow oil. LCMS: *m/z* 329.0 (M+1-27)

[02021] Step 3. To a solution of methyl (E)-3-(dimethylamino)-2-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)prop-2-enoate (3.80 g, 10.7 mmol, 1 eq) in DMF (38 mL) was added DIEA (4.15 g, 32.1 mmol, 3 eq) and 2-hydrazinoethanol (1.22 g, 16.0 mmol, 1.5 eq). The mixture was stirred at 60 °C for 12 h. On completion, the mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH=10:1 to 10:1) to give 2-(2-hydroxyethyl)-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (2.00 g, 5.64 mmol, 53% yield) as a brown solid. LCMS: *m/z* 355.0 (M+1)

[02022] Step 4. To a solution of 2-(2-hydroxyethyl)-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (500 mg, 1.41 mmol, 1 eq) in DCM (5 mL) was added DMAP (689 mg, 5.64 mmol, 4 eq) and TBSCl (638 mg, 4.23 mmol 3 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was partitioned between DCM (5 mL × 3) and water (5 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, DCM:MeOH=10:1 to 10:1) to give 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol -3-ol (600 mg, 1.28 mmol, 91% yield) as a brown solid. LCMS: *m/z* 469.1 (M+1)

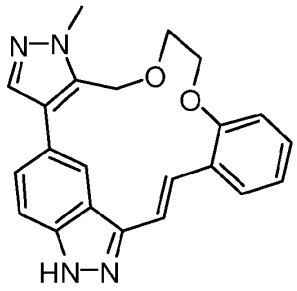
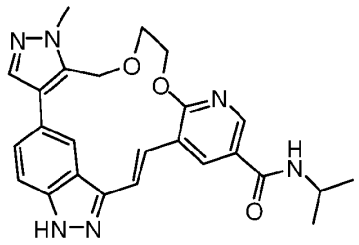
[02023] Step 5. To a solution of 2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-ol (510 mg, 1.09 mmol, 1 eq) in THF (5 mL) was added 2,2,2-trifluoro-N-[(2R)-2-hydroxypropyl]-N-methyl-acetamide (604 mg, 3.26 mmol, 3 eq), PPh_3 (571 mg, 2.18 mmol, 2 eq), and DBAD (376 mg, 1.63 mmol, 1.5 eq) under N_2. The mixture was stirred at 25 °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=4:1 to 4:1) to give N-[(2S)-2-[2-[2-[tert-butyl(dimethyl) silyl]oxyethyl] -4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxypropyl]-2,2,2-trifluoro-N-methyl-

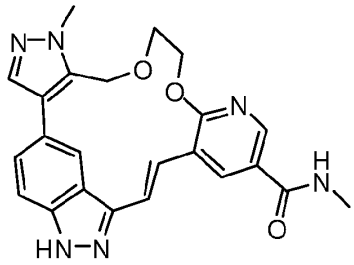
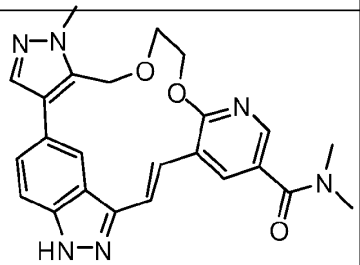
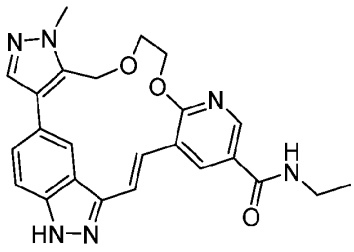
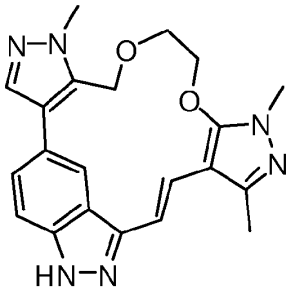
acetamide (530 mg, 0.325 mmol, 30% yield, 39% purity) as a brown oil. LCMS: *m/z* 636.3 (M+1)

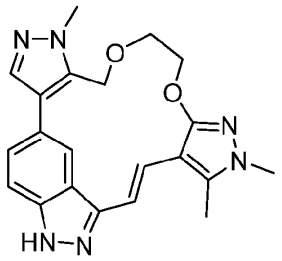
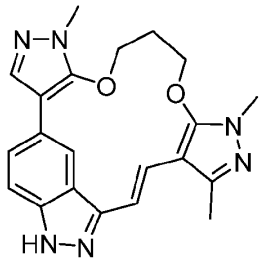
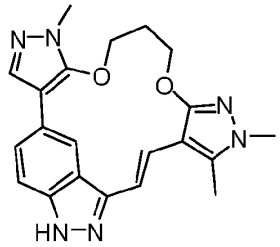
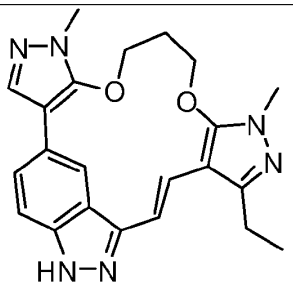
[02024] Step 6. To a solution of N-[(2S)-2-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-(1-tetrahydropy ran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxypropyl]-2,2,2-trifluoro-N-methyl-acetamide (480 mg, 0.754 mmol, 1 eq) in THF (5 mL) was added $LiOH.H_2O$ (126 mg, 3.02 mmol, 4 eq) and H_2O (1 mL). The mixture was stirred at 25 °C for 16 h. On completion, the reaction mixture was partitioned between EA (7 mL × 3) and water (7 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, DCM:MOH=10:1 to 10:1) to give (2S)-2-[2-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-4-(1-tetrahydropyran-2-yl-3-vinyl-indazol-5-yl)pyrazol-3-yl]oxy-N-methyl-propan-1-amine (102 mg, 0.189 mmol, 25% yield) as a yellow oil. LCMS: *m/z* 540.0 (M+1)

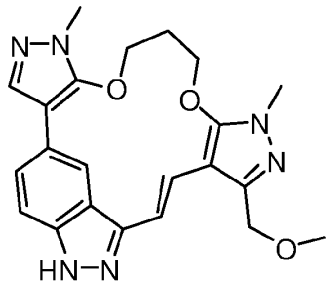
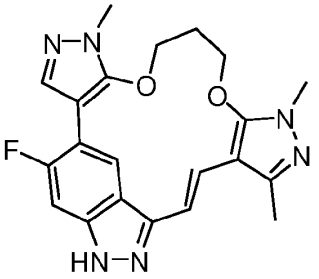
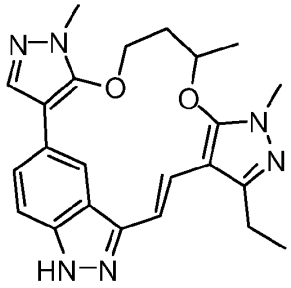
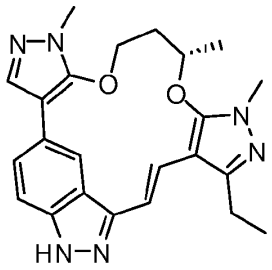
[02025] The remaining steps were performed according to those described in General Method Y to afford Ex. 299 as a white solid.

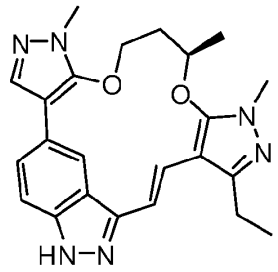
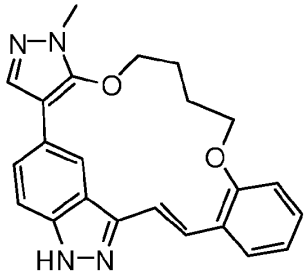
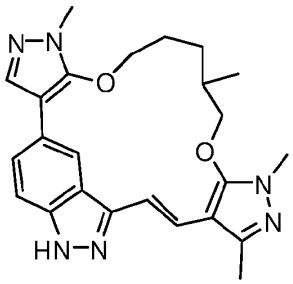
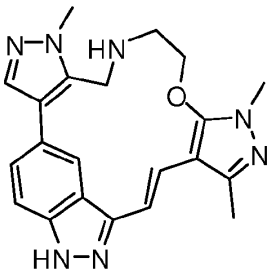
[02026]

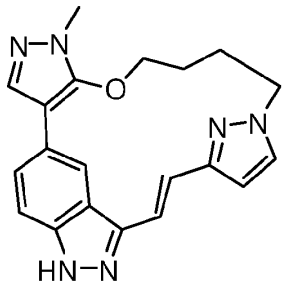
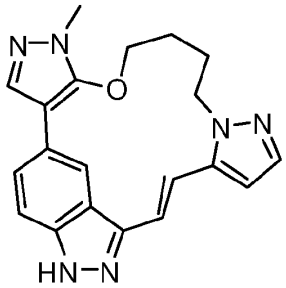
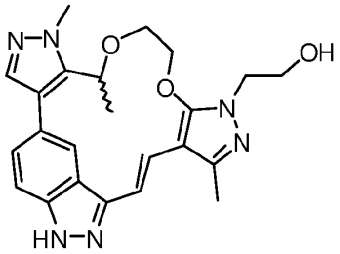
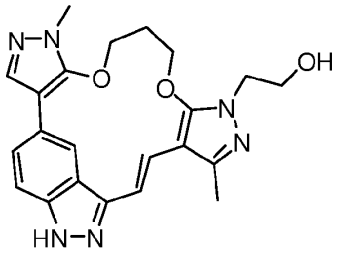
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
1		373.1	3.08 (s, 1H), 8.55 (s, 1H), 8.10 (d, *J* = 17.2 Hz, 1H), 7.91 - 7.85 (m, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 17.2 Hz, 1H), 7.34 - 7.27 (m, 1H), 7.26 - 7.20 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 4.48 (t, *J* = 6.0 Hz, 2H), 4.28 (t, *J* = 5.2 Hz, 2H), 3.74 (s, 3H), 2.40 (td, *J* = 5.2, 10.8 Hz, 2H
2		459.1	13.23 (s, 1H), 8.66 (d, *J* = 2.0 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.30 (s, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 17.6 Hz, 1H), 7.69 (s, 1H), 7.66 - 7.61 (m, 2H), 7.61 - 7.52 (m, 2H), 4.67 (s, 2H), 4.58 - 4.53 (m, 2H), 4.03 - 3.99 (m, 2H), 3.94 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 6H)

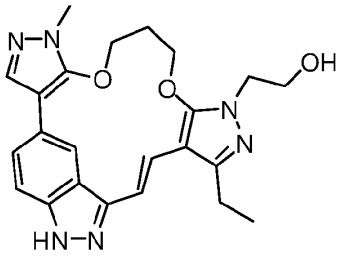
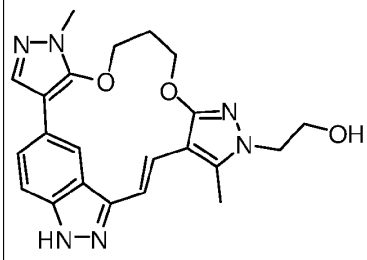
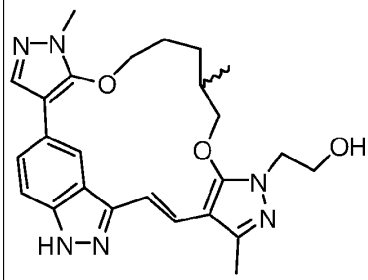
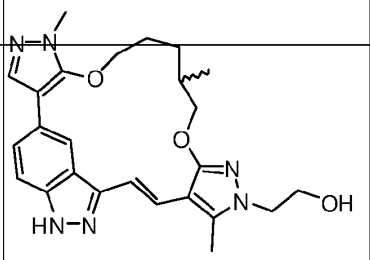
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
3		431.2	13.24 (s, 1H), 8.63 (d, *J* = 1.6 Hz, 1H), 8.57 - 8.50 (m, 2H), 8.30 (s, 1H), 8.05 (d, *J* = 17.2 Hz, 1H), 7.69 (s, 1H), 7.66 - 7.61 (m, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 4.66 (s, 2H), 4.55 (d, *J* = 2.8 Hz, 2H), 4.01 (d, *J* = 2.0 Hz, 2H), 3.93 (s, 3H), 2.82 (d, *J* = 4.4 Hz, 3H)
4		445.2	13.21 (s, 1H), 8.30 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 17.6 Hz, 1H), 7.69 (s, 1H), 7.64 - 7.58 (m, 2H), 7.56 - 7.53 (m, 1H), 4.66 (s, 2H), 4.56 - 4.53 (m, 2H), 4.02 - 4.01 (m, 2H), 3.93 (s, 3H), 3.01 (s, 6H)
5		445.2	13.22 (s, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 8.53 - 8.50 (m, 1H), 8.30 (s, 1H), 8.06 (d, *J* = 17.2 Hz, 1H), 7.69 (s, 1H), 7.65 - 7.59 (m, 2H), 7.57 - 7.54 (m, 1H), 4.67 (s, 2H), 4.58 - 4.55 (m, 2H), 4.02 - 4.00 (m, 2H), 3.93 (s, 3H), 3.31 - 3.28 (m, 2H), 1.17 (t, *J* = 7.6 Hz, 3H)
6		391.4	8.56 - 8.46 (m, 1H), 7.76 - 7.73 (m, 1H), 7.73 - 7.68 (m, 1H), 7.60 - 7.50 (m, 2H),7.13 - 7.07 (m, 1H), 4.67 - 4.60 (m, 2H), 4.43 (d, *J* = 3.6 Hz, 2H), 4.03 - 4.00 (m, 2H), 3.72 (s, 3H), 3.50 (s, 3H), 2.51 (s,3H)

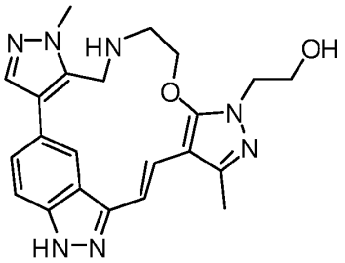
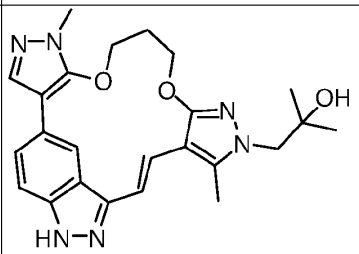
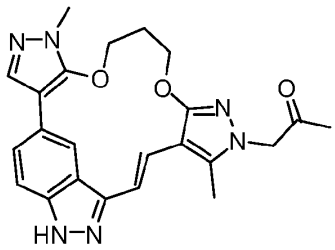
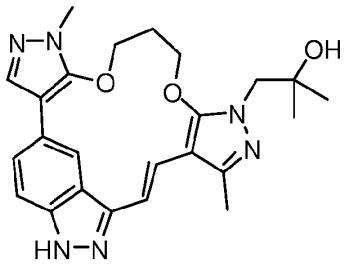
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
7		390.9	13.35 - 12.54 (m, 1H), 8.29 (s, 1H), 7.77 (s, 1H), 7.56 (s, 2H), 7.46 (d, J = 17.6 Hz, 1H), 6.98 (d, J = 17.6 Hz, 1H), 4.57 (s, 2H), 4.35 - 4.33 (m, 2H), 3.92 (s, 3H), 3.82 - 3.79 (m, 2H), 3.67 (s, 3H), 2.46 (s, 3H)
8		390.9	13.06 - 12.78 (m, 1H), 8.56 (s, 1H), 7.91 (s, 1H), 7.71 - 7.66 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 17.6 Hz, 1H), 6.91 (d, *J* = 17.2 Hz, 1H), 4.45 (t, *J* = 5.6 Hz, 2H), 4.34 (t, *J* = 4.8 Hz, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 2.43 - 2.38 (m, 2H), 2.37 (s, 3H)
9		390.8	12.90 (s, 1H), 8.47 (s, 1H), 7.90 (s, 1H), 7.68 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 17.6 Hz, 1H), 6.93 (d, *J* = 17.6 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.28 - 4.23 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.17 (s, 5H), 2.48 (s, 3H), 2.32 - 2.25 (m, 2H)
10		404.8	8.62 (s, 1H), 7.84 (s, 1H), 7.66 (dd, J = 1.2 , 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 6.94 (d, J = 17.0 Hz, 1H), 4.44 (t, J = 5.6 Hz, 2H), 4.36 (t, J = 5.0 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.83 (q, J = 7.6 Hz, 2H), 2.42 (quin, J = 5.2 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H)

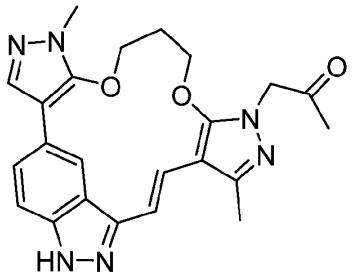
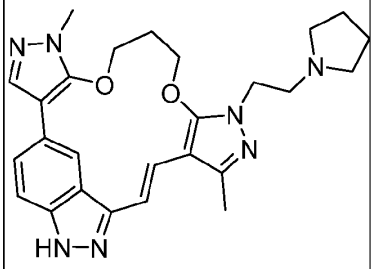
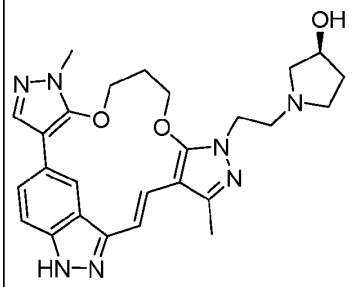
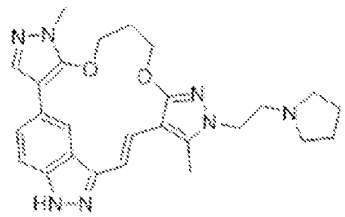
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
11		421.1	8.56 (s, 1H), 7.91 (s, 1H), 7.68 (dd, J = 1.2, 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 16.0 Hz, 1H), 7.04 (d, J = 16.0 Hz, 1H), 4.47 - 4.44 (m, 4H), 4.38 - 4.35 (m, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.32 (s, 3H), 2.44 - 2.37 (m, 2H)
12		408.8	13.16 - 12.82 (m, 1H), 8.64 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 5.2 Hz, 1H), 7.41 - 7.32 (m, 2H), 6.90 (d, J = 17.2 Hz, 1H), 4.49 (t, J = 5.6 Hz, 2H), 4.32 (t, J = 4.8 Hz, 1H), 4.38 - 4.26 (m, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 2.39 (br d, J = 5.2 Hz, 2H), 2.36 (s, 3H), 2.32 - 2.31 (m, 1H)
13		418.9	($CDCl_3$) δ = 8.67 (s, 1H), 7.85 (s, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 17.2 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 17.2 Hz, 1H), 5.01 - 4.90 (m, 1H), 4.81 - 4.72 (m, 1H), 4.26 - 4.18 (m, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 2.96 - 2.89 (m, 2H), 2.56 - 2.31 (m, 2H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.39 (t, *J* = 7.6 Hz, 3H)
14		419.0	12.92 (s, 1H), 8.55 (s, 1H), 7.90 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 17.2 Hz, 1H), 6.89 (d, *J* = 17.2 Hz, 1H), 4.81 - 4.58 (m, 2H), 4.36 - 4.28 (m, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.83 - 2.74 (m, 2H), 2.42 - 2.34 (m, 2H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H)

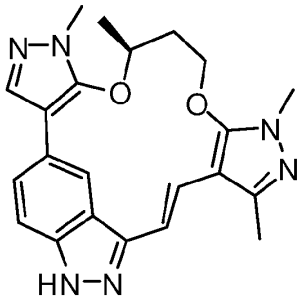
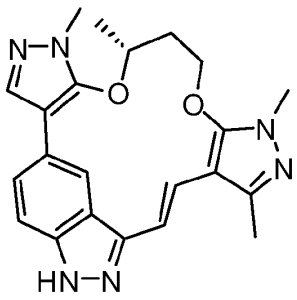
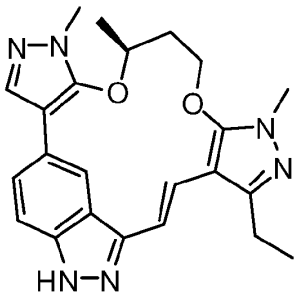
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
15		419.0	12.94 (s, 1H), 8.55 (s, 1H), 7.90 (s, 1H), 7.70 - 7.63 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 17.2 Hz, 1H), 6.89 (d, *J* = 17.2 Hz, 1H), 4.77 - 4.59 (m, 2H), 4.37 - 4.27 (m, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.81 - 2.75 (m, 2H), 2.41 - 2.35 (m, 2H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H)
16		387.1	13.86 - 12.04 (m, 1H), 8.48 (s, 1H), 7.89 - 7.84 (m, 2H), 7.82 - 7.79 (m, 1H), 7.71 - 7.68 (m, 1H), 7.56 (d, *J* = 4.0 Hz, 1H), 7.53 (d, *J* = 4.4 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 4.27 (t, *J* = 6.8 Hz, 2H), 4.16 (t, *J* = 5.2 Hz, 2H), 3.76 (s, 3H), 2.26 - 2.17 (m, 2H), 2.09 - 2.02 (m, 2H)
17		433.2	8.21 - 8.19 (m, 1H), 7.75 - 7.73 (m, 1H), 7.60 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.52 - 7.48 (m, 1H), 7.30 - 7.18 (m, 2H), 4.09 - 3.99 (m, 3H), 3.85 (dd, *J* = 6.2, 8.4 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.31 (s, 3H), 2.28 -2.19 (m, 1H), 2.09 - 1.96 (m, 2H), 1.88 - 1.73 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H)
18		390.0	13.21 - 12.83 (m, 1H), 9.83 - 9.42 (m, 1H), 8.28 - 8.12 (m, 1H), 7.95 - 7.85 (m, 1H), 7.58 (s, 2H), 7.54 (d, *J* = 18.0 Hz, 1H), 6.96 (d, *J* = 17.2 Hz, 1H), 4.68 - 4.56 (m, 2H), 4.55 - 4.43 (m, 2H), 4.03 (s, 3H), 3.67 (s, 3H), 2.72 (s, 2H), 2.37 (s, 3H)

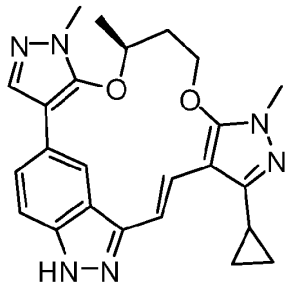
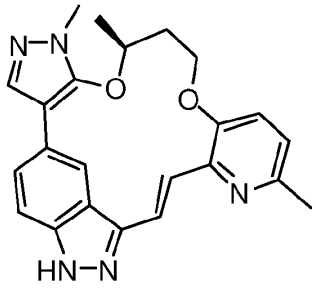
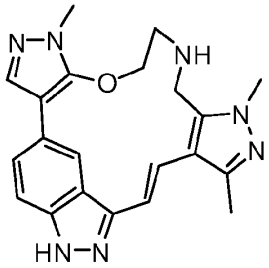
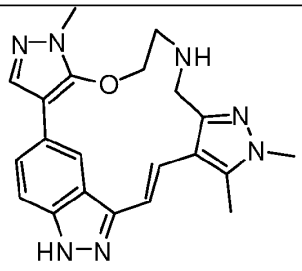
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
19		360.8	13.34 - 12.51 (m, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 2H), 6.64 (d, *J* = 2.0 Hz, 1H), 4.21 (d, *J* = 6.0 Hz, 4H), 3.70 (s, 3H), 1.92 - 1.78 (m, 4H)
20		360.9	13.45 - 12.79 (m, 1H), 8.53 (s, 1H), 7.94 (s, 1H), 7.76 - 7.71 (m, 1H), 7.60 - 7.52 (m, 2H),7.47 - 7.39 (m, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 4.44 - 4.34 (m, 4H), 3.73 (s, 3H), 2.02 (s, 4H)
21		435.0	13.02 - 12.71 (m, 1H), 9.02 - 8.80 (m, 1H), 7.64 - 7.58 (m, 2H), 7.49 (d, *J* = 1.8 Hz, 2H), 6.92 - 6.86 (m, 1H), 5.04 - 4.97 (m, 1H), 4.42 - 4.35 (m, 1H), 4.23 (t, *J* = 9.4 Hz, 1H), 4.06 (d, *J* = 9.4 Hz, 2H), 3.97 (s, 3H), 3.93 (d, *J* = 5.2 Hz, 3H), 3.71 (s, 2H), 2.39 - 2.35 (m, 3H), 1.32 (d, *J* = 6.4 Hz, 3H)
22		421.1	8.58 (s, 1H), 7.92 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 16.0 Hz, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 4.45 (t, *J* = 8.0, 2H), 4.40 (t, *J* = 8.0, 2H), 3.96 (t, *J* = 5.6 Hz, 2H), 3.76 (t, *J* = 5.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 1H), 2.41 (s, 2H), 2.39 (s, 3H)

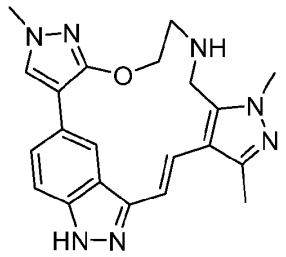
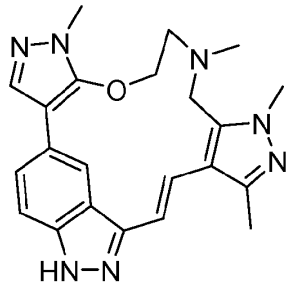
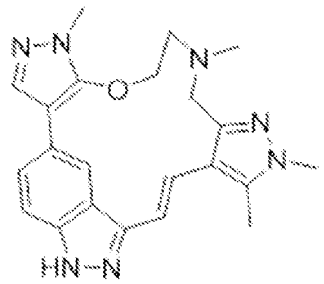
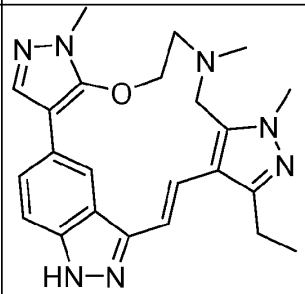
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
23		435.1	13.13 - 12.76 (m, 1H), 8.57 (s, 1H), 7.91 (s, 1H), 7.72 - 7.64 (m, 1H), 7.53 - 7.39 (m, 2H), 6.88 (d, J = 17.2 Hz, 1H), 4.45 (br t, J = 5.2 Hz, 2H), 4.40 (br t, J = 4.8 Hz, 2H), 3.97 (br t, J = 5.6 Hz, 2H), 3.78 - 3.75 (m, 3H), 3.75 (s, 3H), 2.82 - 2.75 (m, 2H), 2.40 (br d, J = 4.4 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H)
24		420.8	12.92 (s, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 7.71 - 7.65 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 17.6 Hz, 1H), 6.97 - 6.89 (d, *J* = 17.6 Hz, 1H), 4.91 (t, *J* = 5.6 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.27 (t, *J* = 5.2 Hz, 2H), 4.04 (t, *J* = 5.6 Hz, 2H), 3.73 (s, 3H), 3.72 - 3.66 (m, 2H), 2.50 (s, 3H), 2.32 - 2.26 (m, 2H)
25		463.0	8.12 (s, 1H), 7.80 - 7.76 (m, 1H), 7.60 - 7.56 (m, 1H), 7.53 - 7.49 (m, 1H), 7.23 - 7.11 (m, 2H), 4.06 (br dd, J = 2.3, 8.6 Hz, 1H), 4.02 (br d, J = 2.9 Hz, 1H), 3.99 (br s, 1H), 3.94 (br s, 1H), 3.88 (br d, J = 6.5 Hz, 1H), 3.86 (br d, J = 6.6 Hz, 1H), 3.76 (br s, 2H), 3.72 (s, 3H), 2.24 (s, 3H), 2.22 - 2.16 (m, 1H), 2.02 - 1.94 (m, 2H), 1.80 - 1.74 (m, 2H), 1.07 (d, J = 6.9 Hz, 3H)
26		463.1	8.15 - 8.05 (m, 1H), 7.91 - 7.79 (m, 1H), 7.69 - 7.58 (m, 1H), 7.53 - 7.36 (m, 2H), 7.15 (d, J = 16.1 Hz, 1H), 4.37 (dd, J = 4.1, 9.8 Hz, 1H), 4.15 - 4.09 (m, 1H), 4.06 - 4.01 (m, 1H), 3.97 - 3.94 (m, 2H), 3.93 (br d, J = 4.6 Hz, 1H), 3.71 (s, 3H), 3.67 - 3.66 (m, 2H), 2.30 (s, 3H), 2.28 - 2.22 (m, 1H), 2.07 - 1.95 (m, 2H), 1.82 - 1.75 (m,

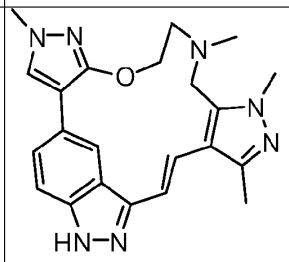
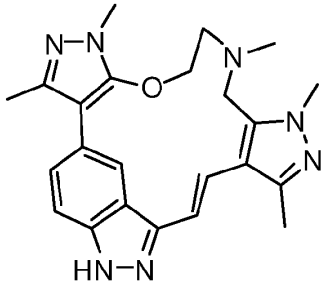
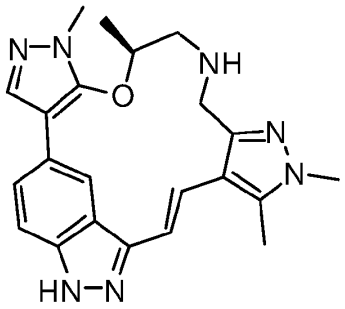
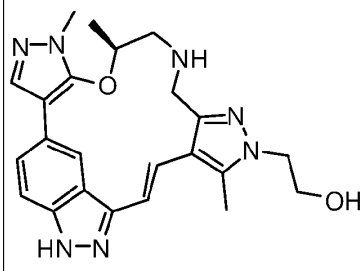
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
			1H), 1.74 - 1.65 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H)
27		419.9	13.05 (br s, 1H), 9.69 - 9.56 (m, 1H), 8.36 - 8.09 (m, 1H), 7.98 - 7.84 (m, 1H), 7.58 (br s, 2H), 7.55 (s, 1H), 7.01 - 6.93 (m, 1H), 5.07 - 4.85 (m, 1H), 4.73 - 4.48 (m, 4H), 4.02 (br d, J = 16.3 Hz, 5H), 3.80 - 3.75 (m, 2H), 3.71 - 3.60 (m, 2H), 2.40 (s, 3H)
28		449.3	8.48 (s, 1H), 7.89 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 17.6 Hz, 1H), 6.93 (d, *J* = 17.6 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.91 (s, 2H), 3.73 (s, 3H), 3.65 (s, 1H), 3.41 - 3.39 (m, 3H), 2.32 - 2.26 (m, 2H), 1.13 (s, 6H)
29		433.2	8.47 (s, 1H), 7.89 (s, 1H), 7.67 (d, *J* = 8.4, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 17.6 Hz, 1H), 6.94 (d, *J* = 17.6 Hz, 1H), 5.05 (s, 2H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.72 (s, 3H), 2.37 (s, 3H), 2.31 - 2.25 (m, 2H), 2.15 (s, 3H)
30		449.3	8.57 (s, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.52 - 7.42 (m, 2H), 6.93 (d, *J* = 16.8 Hz, 1H), 4.39 (d, *J* = 3.6 Hz, 4H), 3.90 (s, 2H), 3.73 (s, 3H), 2.44 (s, 3H), 2.41 - 2.35 (m, 2H), 1.23 (s, 6H)

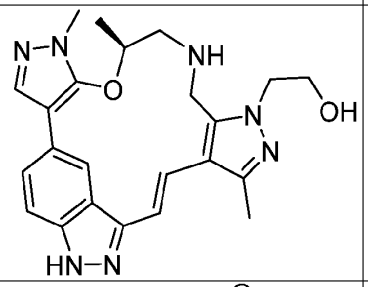
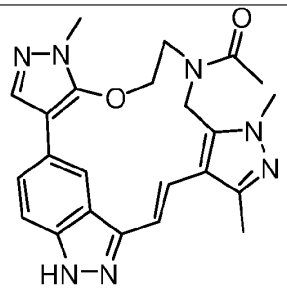
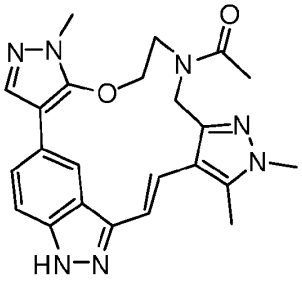
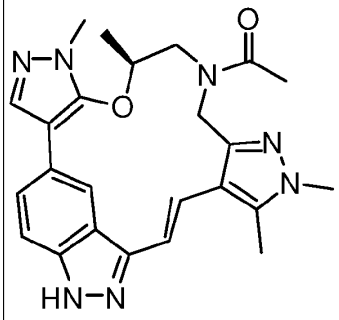
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
31		433.1	8.71 - 8.66 (s, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 7.61 - 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.49 (d, *J* = 8.0 Hz, 1H), 7.08 - 6.99 (d, *J* = 16.0 Hz, 1H), 4.62 (s, 2H), 4.53 - 4.46 (m, 2H), 4.45 - 4.38 (m, 2H), 3.81 - 3.77 (s, 3H), 2.49 - 2.46 (s, 3H), 2.22 (s, 2H), 1.95 - 1.90 (s, 3H)
32		474.0	13.03 (s, 1H), 9.74 - 9.63 (s, 1H), 8.60 - 8.56 (s, 1H), 7.95 - 7.91 (s, 1H), 7.74 - 7.67 (d, *J* = 7.2 Hz, 1H), 7.55 - 7.49 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 17.2 Hz, 1H), 7.02 - 6.95 (d, *J* = 17.2 Hz, 1H), 4.47 (t, *J* = 5.2 Hz, 2H), 4.43 (t, *J* = 5.2 Hz, 2H), 4.34 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 3.64 (d, *J* = 6.0 Hz, 4H), 3.60 (s, 2H), 3.14 - 3.04 (m, 2H), 2.43 (s, 3H), 2.06 - 1.98 (m, 2H), 1.92 - 1.83 (m, 2H)
33		504.2	13.13 - 12.84 (m, 1H), 8.59 - 8.55 (m, 1H), 7.93 (s, 1H), 7.72 - 7.67 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 17.2 Hz, 1H), 6.94 (d, J = 17.2 Hz, 1H), 4.51 - 4.33 (m, 8H), 3.76 (s, 3H), 3.46 (br d, J = 12.8 Hz, 2H), 3.21 - 3.10 (m, 2H), 3.09 - 2.99 (m, 1H), 2.85 - 2.79 (m, 2H), 2.45 - 2.41 (m, 2H), 2.29 - 2.21 (m, 1H), 2.02 - 1.79 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H)
34		474.6	9.77 (s, 1H), 8.48 (s, 1H), 7.90 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 17.2 Hz, 1H), 6.99 (d, *J* = 17.2 Hz, 1H), 4.42 - 4.39 (m, 4H), 4.31 (t, *J* = 5.2 Hz, 2H), 3.73 (s, 3H), 3.62 (d, *J* = 5.2 Hz, 4H), 3.12 - 3.00 (m, 2H), 2.55 (s, 3H), 2.32 (d,

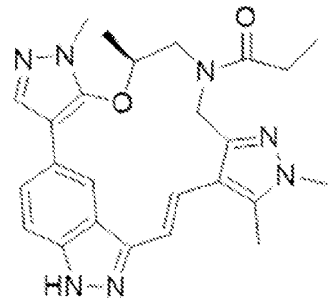
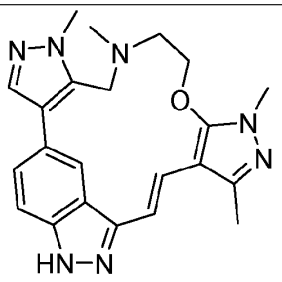
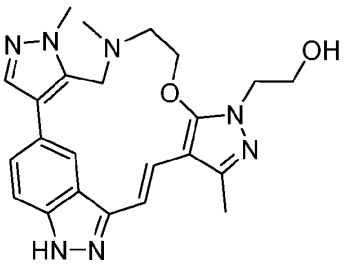
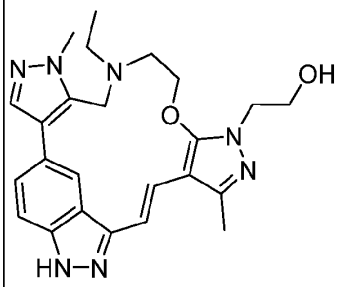
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			J = 5.6 Hz, 2H), 2.07 - 1.98 (m, 2H), 1.93 - 1.81 (m, 2H)
35		404.93	(500 MHz, DMSO-d6) δ = 13.02 - 12.77 (m, 1H), 8.40 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 17.2 Hz, 1H), 6.91 (d, J = 17.8 Hz, 1H), 4.98 - 4.92 (m, 1H), 4.43 - 4.34 (m, 1H), 4.30 - 4.24 (m, 1H), 3.67 (d, J = 5.7 Hz, 6H), 2.47 (s, 4H), 2.25 (q, J = 5.2 Hz, 2H), 1.28 - 1.19 (m, 5H)
36		405.0	(500 MHz, DMSO-d6) δ = 8.55 (s, 1H), 7.93 (s, 1H), 7.73 - 7.68 (m, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 17.8 Hz, 1H), 7.28 (br d, J = 4.0 Hz, 1H), 6.90 (d, J = 17.2 Hz, 1H), 6.68 (br d, J = 5.2 Hz, 1H), 6.55 (br s, 1H), 4.92 - 4.85 (m, 1H), 4.60 - 4.53 (m, 1H), 4.34 - 4.29 (m, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 2.41 - 2.35 (m, 5H), 1.30 (d, J = 6.3 Hz, 3H)
37		419.00	(500 MHz, DMSO-d6) δ = 13.05 - 12.78 (m, 1H), 8.55 (s, 1H), 7.93 (s, 1H), 7.70 (dd, J = 1.4, 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 17.2 Hz, 1H), 6.86 (d, J = 17.2 Hz, 1H), 4.93 - 4.84 (m, 1H), 4.57 (ddd, J = 3.3, 6.8, 9.9 Hz, 1H), 4.32 (ddd, J = 3.4, 6.2, 9.8 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 2.77 (q, J = 7.5 Hz, 2H), 2.41 - 2.35 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (t, J = 7.4 Hz, 3H)

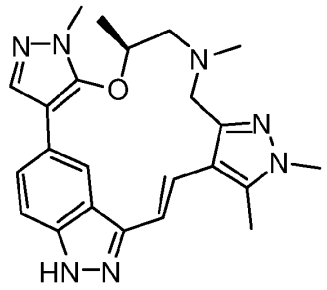
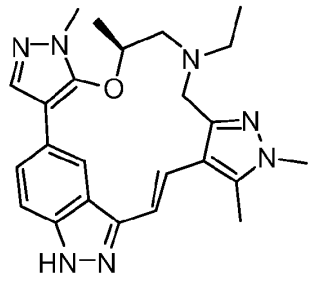
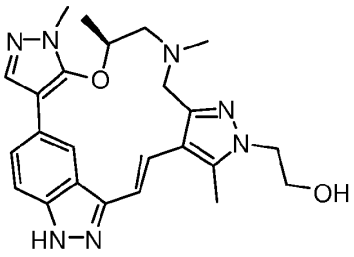
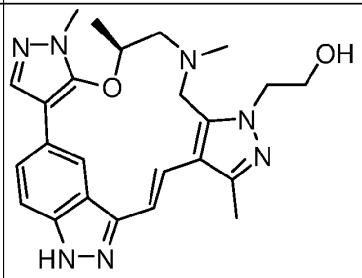
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
38		432.27	8.42 (s, 1H), 7.90 (s, 1H), 7.69 (dd, J = 1.1, 8.7 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 17.4 Hz, 1H), 7.09 (d, J = 17.2 Hz, 1H), 4.94 (q, J = 5.7 Hz, 1H), 4.43 - 4.36 (m, 1H), 4.28 - 4.21 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.25 (q, J = 5.2 Hz, 2H), 1.96 - 1.90 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H), 1.16 (dd, J = 1.4, 8.2 Hz, 2H), 0.80 - 0.73 (m, 2H)
39		401.6	8.48 (s, 1H), 8.06 (d, J = 16.7 Hz, 1H), 7.93 - 7.87 (m, 2H), 7.88 - 7.81 (m, 1H), 7.74 (dd, J = 1.1, 8.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.36 (br d, J = 7.7 Hz, 1H), 5.10 (qd, J = 5.9, 11.7 Hz, 1H), 4.51 (br s, 1H), 4.31 (br s, 1H), 3.69 (s, 3H), 2.56 (s, 3H), 2.38 - 2.31 (m, 2H), 1.20 (d, J = 6.3 Hz, 3H)
40		390.2	12.85 (s, 1H), 8.61 (s, 1H), 8.12 (d, *J* = 17.6 Hz, 1H), 7.91 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 17.6 Hz, 1H), 4.21 (s, 2H), 3.96 (s, 2H), 3.73 (s, 6H), 3.10 (d, *J* = 1.2 Hz, 2H), 2.39 (s, 3H)
41		389.9	13.12 - 12.90 (m, 1H), 9.41 (br d, J = 4.4 Hz, 1H), 8.61 (s, 1H), 7.95 (s, 1H), 7.76 - 7.68 (m, 1H), 7.58 - 7.50 (m, 2H), 7.03 (d, J = 17.2 Hz, 1H), 4.59 (br s, 2H), 4.44 (br s, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.62 (br s, 2H), 2.55 (s, 3H)

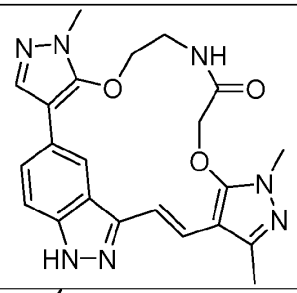
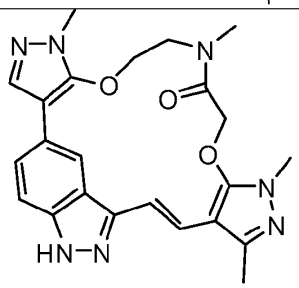
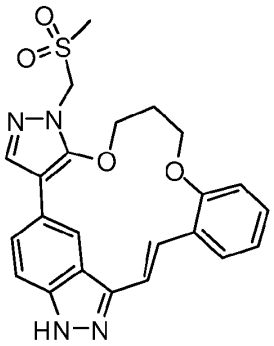
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
42		436.9	13.00 - 12.88 (m, 1H), 8.80 (s, 1H), 8.06 - 8.03 (m, 1H), 7.61 - 7.43 (m, 3H), 7.02 (d, J = 16.8 Hz, 1H), 4.62 (br s, 4H), 3.87 (s, 3H), 3.76 - 3.73 (m, 3H), 3.67 - 3.57 (m, 2H), 2.42 (s, 3H)
43		403.9	12.87 (s, 1H), 8.61 (s, 1H), 8.04 (d, *J* = 17.6 Hz, 1H), 7.95 - 7.87 (m, 1H), 7.71 - 7.65 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 17.6 Hz, 1H), 4.26 (t, *J* = 3.6 Hz, 2H), 3.82 (s, 2H), 3.74 (d, *J* = 2.8 Hz, 6H), 2.99 (t, *J* = 4.0 Hz, 2H), 2.39 (s, 3H), 2.19 (s, 3H)
44		403.9	8.78 (d, *J* = 11.2 Hz, 2H), 8.04 - 7.95 (m, 1H), 7.91 (s, 1H), 7.87 - 7.76 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 4.40 (t, *J* = 5.6 Hz, 2H), 4.33 - 4.23 (m, 2H), 3.77 (s, 3H), 2.67 (s, 3H), 2.49 - 2.37 (m, 2H)
45		418.1	8.69 (s, 1H), 7.88 (s, 1H), 7.74 - 7.66 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 17.2 Hz, 1H), 4.61 (br s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 3.81 - 3.80 (m, 1H), 3.31 - 3.29 (m, 3H), 2.93 (q, *J* = 7.6 Hz, 2H), 2.87 (s, 2H), 1.37 (t, *J* = 7.6 Hz, 3H)

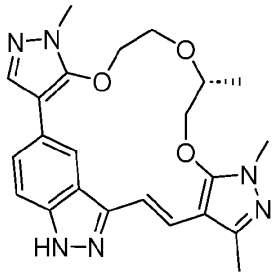
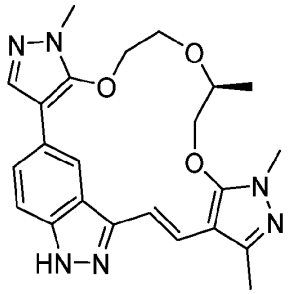
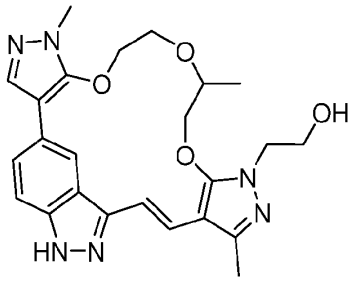
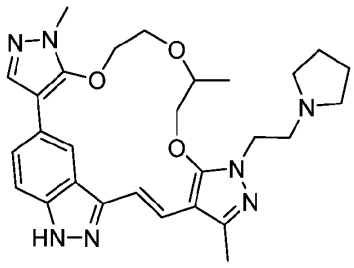
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
46		404.1	9.03 - 8.95 (m, 1H), 8.18 - 8.07 (m, 1H), 7.83 - 7.76 (m, 1H), 7.60 - 7.54 (m, 1H), 7.47 - 7.39 (m, 1H), 7.04 (d, J = 17.6 Hz, 1H), 4.41 - 4.33 (m, 2H), 3.82 (s, 3H), 3.80 - 3.77 (m, 3H), 3.76 (br s, 2H), 3.00 - 2.92 (m, 2H), 2.48 (s, 3H), 2.17 (s, 3H)
47		418.1	8.59 (s, 1H), 7.71 - 7.65 (m, 1H), 7.62 - 7.52 (m, 2H), 7.19 (d, J = 16.8 Hz, 1H), 4.84 (br s, 2H), 4.54 (br dd, J = 2.4, 6.0 Hz, 2H), 3.96 (s, 3H), 3.93 - 3.88 (m, 2H), 3.79 (s, 3H), 2.93 (s, 3H), 2.55 (s, 3H), 2.45 (s, 3H)
48		403.97	(500 MHz, DMSO-d6) δ = 13.01 (br s, 1H), 9.61 - 9.44 (m, 1H), 9.35 - 9.19 (m, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.68 (br dd, J = 1.4, 8.5 Hz, 1H), 7.59 - 7.39 (m, 2H), 7.06 - 6.87 (m, 1H), 5.20 - 5.07 (m, 1H), 4.67 - 4.51 (m, 1H), 4.37 - 4.24 (m, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.57 - 3.51 (m, 1H), 3.46 - 3.42 (m, 1H), 2.57 - 2.54 (m, 3H), 1.12 - 1.06 (m, 3H)
49		434.0	13.01 (br s, 1H), 9.71 - 9.47 (m, 1H), 9.39 - 9.11 (m, 1H), 8.51 (s, 1H), 8.03 - 7.83 (m, 1H), 7.68 (dd, J = 1.4, 8.8 Hz, 1H), 7.58 - 7.41 (m, 2H), 7.00 (d, J = 17.0 Hz, 1H), 5.24 - 5.07 (m, 1H), 5.04 - 4.84 (m, 1H), 4.65 - 4.53 (m, 1H), 4.39 - 4.26 (m, 1H), 4.26 - 4.06 (m, 2H), 3.76 (br t, J = 5.5 Hz, 2H), 3.72 (s, 3H), 2.89 (s, 1H), 2.77 - 2.72 (m, 2H), 2.56 (s, 2H), 1.09 (d, J = 6.3 Hz, 3H)

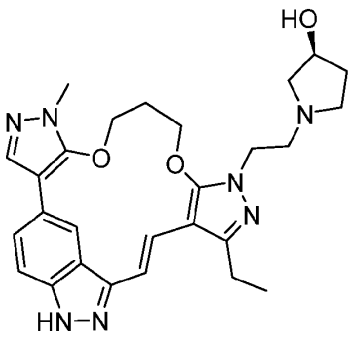
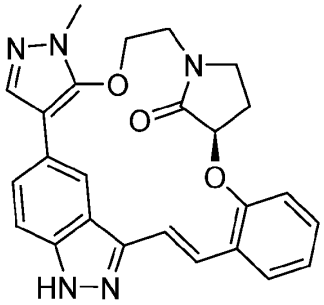
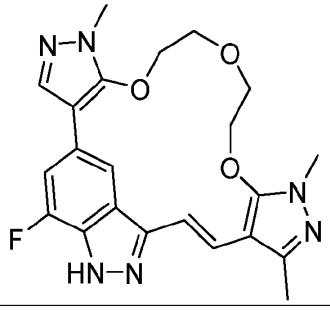
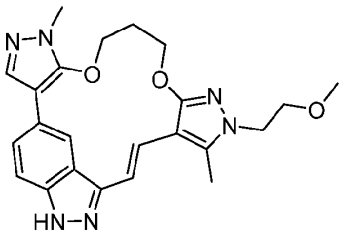
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
50		434.0	
51		432.1	12.95 (s, 1H), 8.40 (s, 1H), 7.92 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 16.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 16.8 Hz, 1H), 4.86 (s, 2H), 4.50 (t, *J* = 7.6 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 4H), 3.28 (s, 1H), 2.43 (s, 3H), 2.23 (s, 3H)
52		431.9	13.39 - 12.60 (m, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.68 - 7.61 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.05 (br d, J = 17.2 Hz, 1H), 4.63 (s, 2H), 4.33 (br t, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.77 (br s, 2H), 3.72 (s, 3H), 2.54 (s, 3H), 2.40 (s, 3H)
53		445.94	(500 MHz, DMSO-d_6) δ = 13.06 - 12.89 (m, 1H), 8.65 - 8.59 (m, 1H), 7.99 - 7.96 (m, 1H), 7.74 - 7.70 (m, 1H), 7.65 - 7.57 (m, 1H), 7.53 - 7.48 (m, 1H), 7.07 - 7.00 (m, 1H), 5.05 - 4.93 (m, 1H), 4.79 - 4.65 (m, 1H), 4.63 - 4.50 (m, 1H), 4.14 - 4.00 (m, 1H), 3.80 (s, 4H), 3.72 - 3.66 (m, 3H), 2.53 (s, 3H), 2.48 - 2.41 (m, 3H), 1.14 - 1.05 (m, 3H)

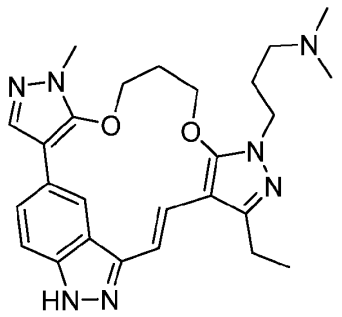
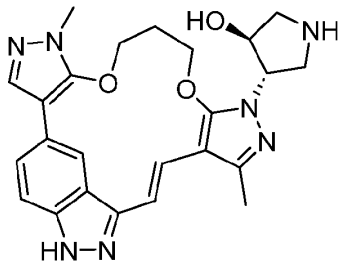
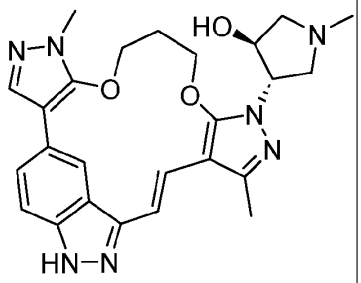
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
54		459.98	(499 MHz, DMSO-d_6) δ = 13.03 - 12.91 (m, 1H), 8.70 - 8.57 (m, 1H), 7.97 (s, 1H), 7.70 (s, 1H), 7.65 - 7.59 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 17.0 Hz, 1H), 5.03 - 4.95 (m, 1H), 4.76 - 4.69 (m, 1H), 4.60 - 4.50 (m, 1H), 4.44 - 4.36 (m, 1H), 4.10 - 4.03 (m, 1H), 3.82 - 3.78 (m, 3H), 3.70 - 3.66 (m, 3H), 3.04 - 2.90 (m, 1H), 2.88 - 2.76 (m, 1H), 2.55 - 2.53 (m, 3H), 1.25 - 1.19 (m, 2H), 1.10 - 1.08 (m, 3H), 1.03 - 0.98 (m, 1H)
55		403.8	13.55 - 12.31 (m, 1H), 8.67 - 8.32 (m, 1H), 8.02 - 7.88 (m, 1H), 7.65 - 7.59 (m, 1H), 7.58 - 7.52 (m, 1H), 7.48 (d, *J* = 17.2 Hz, 1H), 6.95 (d, *J* = 17.2 Hz, 1H), 4.75 - 4.23 (m, 4H), 3.98 (s, 3H), 3.64 (s, 3H), 2.67 (s, 2H), 2.50 (s, 3H), 2.36 (s, 3H)
56		434.1	13.35 - 12.65 (m, 1H), 8.89 - 8.62 (m, 1H), 8.00 - 7.75 (m, 1H), 7.65 - 7.52 (m, 2H), 7.49 (d, *J* = 17.6 Hz, 1H), 7.00 - 6.90 (m, 1H), 4.97 - 4.72 (m, 1H), 4.54 - 4.35 (m, 2H), 4.00 - 3.89 (m, 6H), 3.74 (s, 3H), 3.07 - 2.93 (m, 2H), 2.54 - 2.52 (m, 3H), 2.38 (s, 3H), 2.30 - 2.20 (m, 2H)
57		448.1	13.10 - 12.89 (m, 1H), 8.72 (br s, 1H), 7.95 - 7.76 (m, 1H), 7.65 - 7.58 (m, 1H), 7.56 - 7.49 (m, 2H), 6.98 - 6.92 (m, 1H), 4.52 - 4.36 (m, 2H), 4.07 - 3.88 (m, 9H), 3.78 - 3.69 (m, 3H), 2.38 (s, 3H), 1.38 - 1.14 (m, 2H), 1.10 - 0.92 (m, 3H)

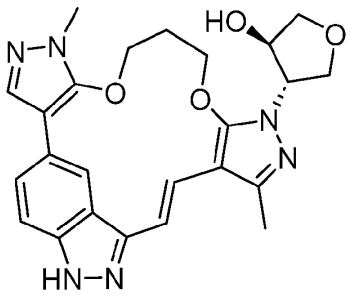
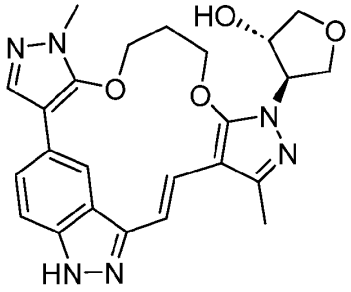
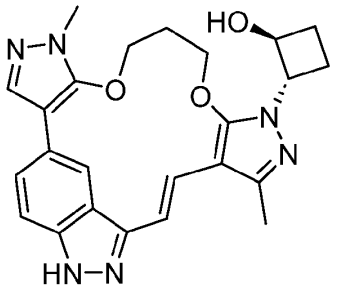
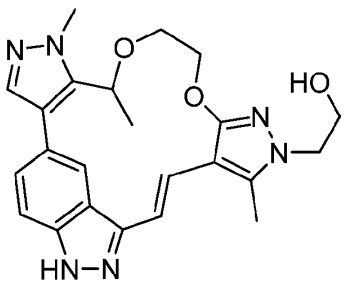
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
58		417.99	(500 MHz, DMSO-d_6) δ = 13.06 - 12.89 (m, 1H), 8.65 - 8.59 (m, 1H), 7.99 - 7.96 (m, 1H), 7.74 - 7.70 (m, 1H), 7.65 - 7.57 (m, 1H), 7.53 - 7.48 (m, 1H), 7.07 - 7.00 (m, 1H), 5.05 - 4.93 (m, 1H), 4.79 - 4.65 (m, 1H), 4.63 - 4.50 (m, 1H), 4.14 - 4.00 (m, 1H), 3.80 (s, 4H), 3.72 - 3.66 (m, 3H), 2.53 (s, 3H), 2.48 - 2.41 (m, 3H), 1.14 - 1.05 (m, 3H)
59		432.00	(500 MHz, DMSO-d_6) δ = 7.57 (s, 1H), 7.49 - 7.46 (m, 1H), 7.41 - 7.38 (m, 1H), 7.26 - 7.23 (m, 1H), 6.79 (d, J = 12.0 Hz, 1H), 6.62 - 6.58 (m, 1H), 4.26 - 4.19 (m, 1H), 4.17 - 4.12 (m, 1H), 3.84 - 3.79 (m, 1H), 3.70 - 3.67 (m, 1H), 3.66 (s, 3H), 3.44 - 3.42 (m, 3H), 1.82 - 1.66 (m, 3H), 1.57 - 1.47 (m, 1H), 1.43 (s, 3H), 1.27 - 1.23 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H)
60		448.0	(500 MHz, DMSO-d6) δ = 8.49 - 8.46 (m, 1H), 7.94 - 7.90 (m, 1H), 7.85 - 7.82 (m, 1H), 7.68 - 7.65 (m, 1H), 7.56 - 7.53 (m, 1H), 7.02 - 6.97 (m, 1H), 4.59 (s, 1H), 4.22 - 4.16 (m, 2H), 3.78 - 3.74 (m, 2H), 3.72 - 3.68 (m, 3H), 3.11 - 3.04 (m, 2H), 2.88 (s, 2H), 2.75 - 2.73 (m, 3H), 2.55 - 2.53 (m, 3H), 2.39 - 2.37 (m, 1H), 1.09 - 1.04 (m, 3H)
61		448.0	(500 MHz, DMSO-d6) δ = 8.55 - 8.42 (m, 1H), 7.87 - 7.78 (m, 1H), 7.74 - 7.68 (m, 1H), 7.68 - 7.63 (m, 1H), 7.58 - 7.53 (m, 1H), 7.04 - 6.97 (m, 1H), 5.18 - 5.04 (m, 1H), 4.66 - 4.51 (m, 1H), 4.41 - 4.28 (m, 1H), 4.25 - 4.14 (m, 2H), 3.68 (s, 5H), 3.54 - 3.46 (m, 1H), 3.44 - 3.36 (m, 1H), 2.74 - 2.66 (m,

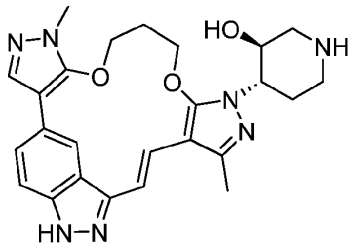
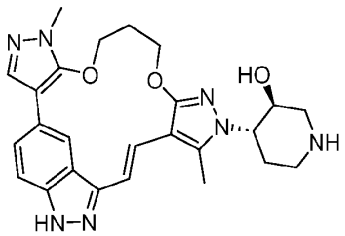
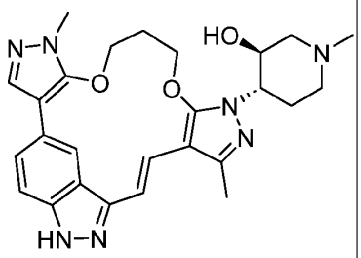
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			3H), 2.43 (s, 3H), 1.09 - 1.01 (m, 3H)
62		433.9	9.06 (t, J = 6.0 Hz, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.64 (dd, J = 1.2, 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.18 - 7.13 (m, 1H), 7.13 - 7.07 (m, 1H), 4.58 (s, 2H), 4.09 (t, J = 4.0 Hz, 2H), 3.74 (s, 5H), 3.66 (s, 3H), 2.23 (s, 3H)
63		447.9	8.32 - 7.86 (m, 1H), 7.73 (s, 1H), 7.60 - 7.55 (m, 1H), 7.54 - 7.44 (m, 1H), 7.34 - 7.07 (m, 1H), 7.03 - 6.86 (m, 1H), 5.15 - 4.95 (m, 2H), 4.23 - 4.15 (m, 2H), 3.89 - 3.83 (m, 2H), 3.78 - 3.71 (m, 3H), 3.65 (br s, 3H), 3.13 - 3.00 (m, 3H), 2.37 - 2.20 (m, 3H)
64		450.9	8.55 (s, 1H), 8.23 (d, *J* = 17.2 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.73 - 7.70 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 5.47 (s, 2H), 4.68 (t, *J* = 5.6 Hz, 2H), 4.34 (t, *J* = 5.6 Hz, 2H), 3.13 (s, 3H), 2.42 - 2.38 (m, 2H)

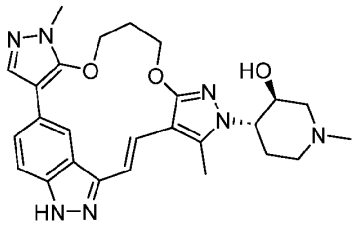
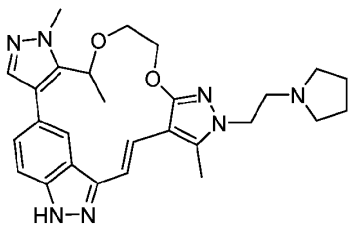
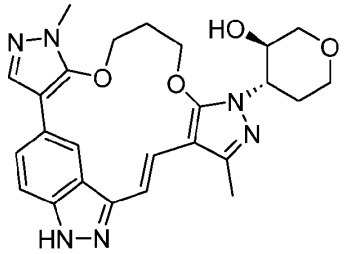
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
65		435.1	1H NMR (400 MHz, DMSO-d6) δ = 12.94 (s, 1H), 8.24 (s, 1H), 7.83 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.20 - 7.15 (m, 1H), 4.27 - 4.20 (m, 1H), 4.19 - 4.09 (m, 3H), 4.08 - 3.98 (m, 3H), 3.73 (s, 3H), 3.63 (s, 3H), 2.23 (s, 3H), 1.32 (br d, J = 6.0 Hz, 3H)
66		435.2	1H NMR (400 MHz, DMSO-d6) δ = 12.94 (s, 1H), 8.24 (s, 1H), 7.83 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.20 - 7.15 (m, 1H), 4.27 - 4.20 (m, 1H), 4.19 - 4.09 (m, 3H), 4.08 - 3.98 (m, 3H), 3.73 (s, 3H), 3.63 (s, 3H), 2.23 (s, 3H), 1.32 (br d, J = 6.0 Hz, 3H)
67		464.1	1H NMR (400 MHz, DMSO-d6) δ = 8.23 (s, 1H), 7.78 (s, 1H), 7.64 - 7.56 (m, 1H), 7.53 - 7.44 (m, 1H), 7.30 - 7.20 (m, 1H), 7.18 - 7.10 (m, 1H), 4.63 (br dd, J = 4.8, 10.0 Hz, 1H), 4.22 - 4.09 (m, 2H), 4.02 - 3.80 (m, 5H), 3.72 (s, 3H), 2.26 (s, 3H), 1.38 - 1.30 (m, 1H), 1.28 - 1.22 (m, 3H), 1.16 (d, J = 6.0 Hz, 3H)
68		518.4	1H NMR (400 MHz, DMSO-d6) δ = 13.84 - 11.86 (m, 1H), 8.28 - 8.18 (m, 1H), 7.86 - 7.75 (m, 1H), 7.66 - 7.57 (m, 1H), 7.54 - 7.47 (m, 1H), 7.30 - 7.22 (m, 1H), 7.21 - 7.14 (m, 1H), 4.66 (br t, J = 6.0 Hz, 1H), 4.37 - 4.05 (m, 6H), 4.02 - 3.93 (m, 2H), 3.73 (s, 3H), 3.67 - 3.62 (m, 4H), 3.08 (br d, J = 6.0 Hz, 2H), 2.33 - 2.27 (m, 3H), 2.03 (br s, 2H), 1.87 (br d, J = 6.0 Hz, 2H), 1.18 (d, J = 6.4 Hz, 3H)

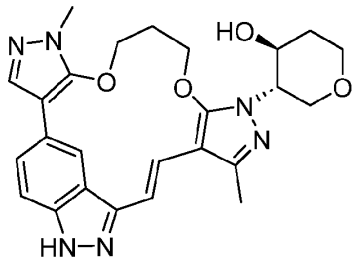
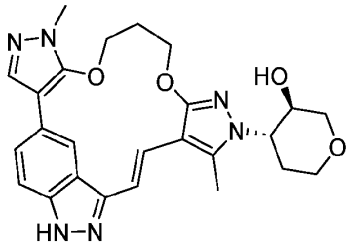
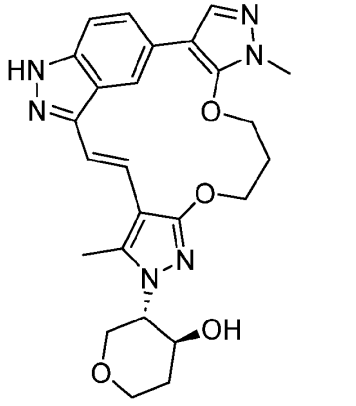
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
69		504.2	1H NMR (400 MHz, DMSO-d6) δ = 13.13 - 12.84 (m, 1H), 8.59 - 8.55 (m, 1H), 7.93 (s, 1H), 7.72 - 7.67 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 17.2 Hz, 1H), 6.94 (d, J = 17.2 Hz, 1H), 4.51 - 4.33 (m, 8H), 3.76 (s, 3H), 3.46 (br d, J = 12.8 Hz, 2H), 3.21 - 3.10 (m, 2H), 3.09 - 2.99 (m, 1H), 2.85 - 2.79 (m, 2H), 2.45 - 2.41 (m, 2H), 2.29 - 2.21 (m, 1H), 2.02 - 1.79 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H)
70		442.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.19 (s, 1H), 7.77 - 7.71 (m, 1H), 7.70 - 7.65 (m, 2H), 7.64 - 7.59 (m, 1H), 7.59 - 7.52 (m, 2H), 7.36 - 7.28 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 5.05 (br d, J = 5.9 Hz, 1H), 4.45 - 4.38 (m, 1H), 4.36 - 4.26 (m, 1H), 4.15 - 4.04 (m, 2H), 3.85 (s, 3H), 3.57 (br t, J = 8.8 Hz, 1H), 3.46 - 3.40 (m, 1H), 2.45 - 2.32 (m, 1H), 2.27 - 2.18 (m, 1H)
71		439.0	1H NMR (400 MHz, DMSO-d6) δ = 14.57 - 12.02 (m, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.53 (d, J = 12.8 Hz, 1H), 7.23 (s, 2H), 4.26 - 4.16 (m, 4H), 3.89 (br s, 4H), 3.73 (s, 3H), 3.63 (s, 3H), 2.22 (s, 3H)
72		435.1	1H NMR (400 MHz, DMSO-d6) δ = 12.95 - 12.85 (m, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 7.71 - 7.65 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 17.6 Hz, 1H), 6.93 (d, J = 17.2 Hz, 1H), 4.41 (br t, J = 6.0 Hz, 2H), 4.27 (t, J = 5.2 Hz, 2H), 4.15 (t, J = 5.6 Hz, 2H), 3.73 (s, 3H), 3.64 (t, J = 5.6 Hz, 2H),

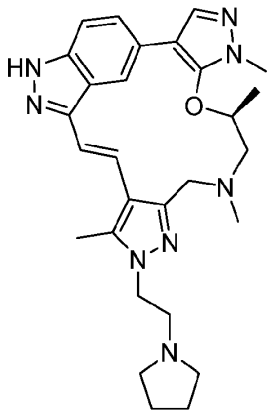
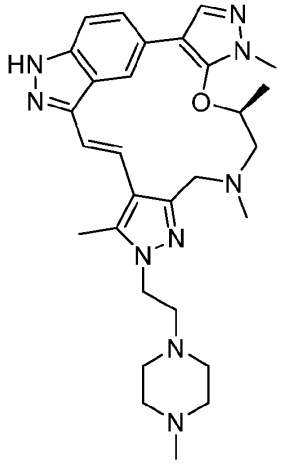
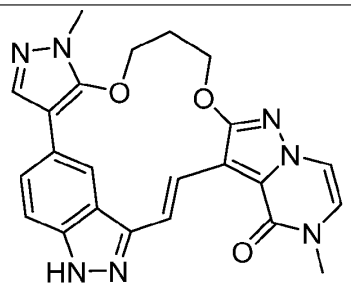
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			3.24 (s, 3H), 2.48 (br s, 3H), 2.32 - 2.26 (m, 2H)
73		476.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.12 (s, 1H), 7.72 (s, 2H), 7.68 - 7.66 (m, 1H), 7.62 - 7.58 (m, 1H), 7.56 - 7.52 (m, 1H), 7.28 (d, J = 16.4 Hz, 1H), 6.93 (d, J = 13.2 Hz, 1H), 4.07 (s, 4H), 4.05 - 3.95 (m, 4H), 3.79 (s, 3H), 2.91 - 2.89 (m, 6H), 2.85 - 2.78 (m, 2H), 2.34 - 2.24 (m, 2H), 2.22 - 2.12 (m, 1H), 1.32 (t, J = 7.6 Hz, 3H)
74		462.2	1H NMR (400 MHz, DMSO-d6) δ = 13.16 - 12.77 (m, 1H), 8.57 (s, 1H), 7.92 (s, 1H), 7.69 (dd, J = 1.3, 8.8 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 17.3 Hz, 1H), 6.98 (d, J = 17.3 Hz, 1H), 6.27 - 6.00 (m, 1H), 4.88 - 4.83 (m, 1H), 4.53 - 4.36 (m, 5H), 3.76 (s, 3H), 3.61 - 3.51 (m, 4H), 3.26 - 3.16 (m, 1H), 2.47 - 2.43 (m, 2H), 2.43 (s, 3H)
75		476.1	1H NMR (400 MHz, DMSO-d6) δ = 13.18 - 12.69 (m, 1H), 8.57 (s, 1H), 7.92 (s, 1H), 7.69 (dd, J = 1.0, 8.8 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 17.3 Hz, 1H), 6.99 (d, J = 17.3 Hz, 1H), 6.39 - 6.17 (m, 1H), 4.98 - 4.81 (m, 1H), 4.44 (br dd, J = 4.4, 11.1 Hz, 5H), 3.76 (s, 3H), 3.51 - 3.45 (m, 3H), 3.01 (br s, 4H), 2.44 (s, 3H), 2.43 - 2.40 (m, 2H)

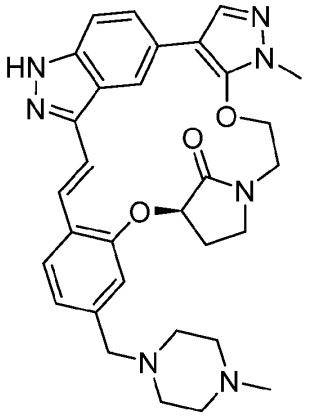
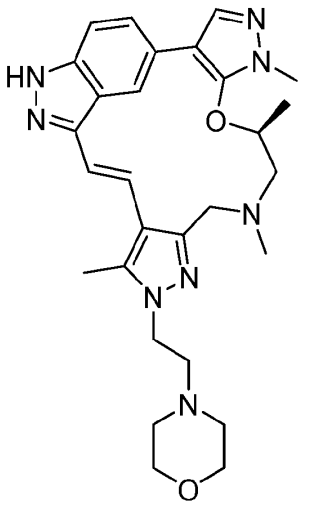
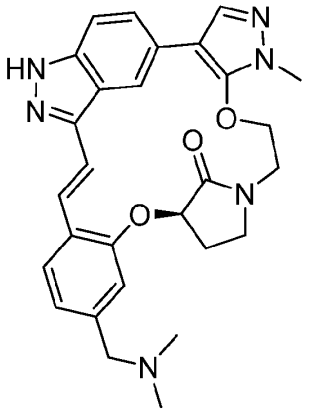
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
76		462.8	1H NMR (400 MHz, DMSO-d6) δ = 12.95 (s, 1H), 8.57 (s, 1H), 7.91 (s, 1H), 7.72 - 7.65 (m, 1H), 7.52 - 7.39 (m, 2H), 6.94 (d, J = 17.2 Hz, 1H), 5.59 (d, J = 4.8 Hz, 1H), 4.70 - 4.62 (m, 1H), 4.50 - 4.34 (m, 5H), 4.20 (br d, J = 1.2 Hz, 1H), 4.09 - 4.02 (m, 1H), 3.86 - 3.81 (m, 1H), 3.74 (s, 3H), 3.67 - 3.62 (m, 1H), 2.39 (s, 5H)
77		462.9	1H NMR (400 MHz, DMSO-d6) δ = 12.94 (br s, 1H), 8.57 (s, 1H), 7.91 (s, 1H), 7.70 - 7.66 (m, 1H), 7.52 - 7.41 (m, 2H), 6.94 (d, J = 17.2Hz, 1H), 5.59 (d, J = 4.8 Hz, 1H), 4.65 (br s, 1H), 4.46 - 4.35 (m, 5H), 4.23 - 4.17 (m, 1H), 4.08 - 4.01 (m, 1H), 3.86 - 3.81 (m, 1H), 3.74 (s, 3H), 3.66 - 3.62 (m, 1H), 2.39 (s, 5H)
78		447.3	1H NMR (400 MHz, DMSO-d6) δ = 13.30 - 12.47 (m, 1H), 8.56 (s, 1H), 7.91 (s, 1H), 7.68 (dd, J = 1.2, 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 17.2 Hz, 1H), 6.93 (d, J = 17.2 Hz, 1H), 4.83 - 4.76 (m, 1H), 4.52 - 4.46 (m, 1H), 4.43 - 4.37 (m, 2H), 4.31 (br dd, J = 4.8, 9.2 Hz, 2H), 3.74 (s, 3H), 2.42 (s, 3H), 2.37 (br s, 2H), 2.27 - 2.09 (m, 4H).
79		435.5	1H NMR (400 MHz, DMSO-d6) δ = 13.27 - 12.20 (m, 1H), 8.89 - 8.61 (m, 1H), 7.62 - 7.59 (m, 1H), 7.59 - 7.53 (m, 1H), 7.49 (br d, J = 7.8 Hz, 2H), 6.90 (d, J = 17.6 Hz, 1H), 5.13 - 4.96 (m, 1H), 4.30 - 4.20 (m, 2H), 4.03 - 4.00 (m, 2H), 3.96 (s, 3H), 3.93 - 3.91 (m, 2H), 3.69 - 3.65 (m, 2H), 2.47 (s, 3H), 1.34 (br d, J = 5.6 Hz, 3H)

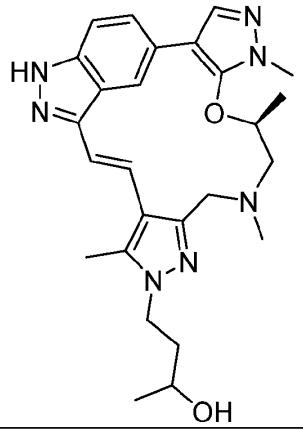
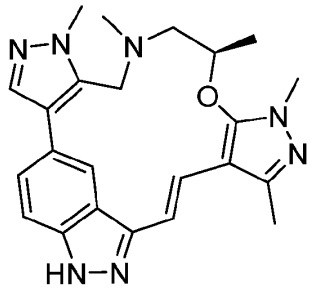
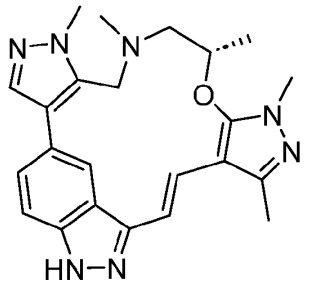
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
80		476.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.65 - 8.38 (m, 2H), 7.84 - 7.78 (m, 1H), 7.64 (br d, J = 8.9 Hz, 1H), 7.53 - 7.43 (m, 2H), 6.95 (dd, J = 2.4, 17.3 Hz, 1H), 4.50 (dt, J = 5.6, 9.3 Hz, 1H), 4.45 - 4.36 (m, 2H), 4.35 - 4.29 (m, 2H), 4.29 - 4.18 (m, 1H), 4.12 (dtd, J = 4.6, 9.6, 14.4 Hz, 1H), 3.77 - 3.72 (m, 3H), 3.55 - 3.44 (m, 2H), 3.42 - 3.34 (m, 1H), 3.16 - 3.06 (m, 1H), 2.97 - 2.86 (m, 1H), 2.59 - 2.46 (m, 3H), 2.41 (br s, 1H), 2.37 - 2.26 (m, 2H), 2.23 - 2.08 (m, 1H)
81		476.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.66 - 8.45 (m, 2H), 7.90 - 7.77 (m, 1H), 7.65 (br d, J = 8.8 Hz, 1H), 7.55 - 7.42 (m, 2H), 6.96 (dd, J = 3.6, 17.3 Hz, 1H), 4.55 - 4.49 (m, 1H), 4.47 - 4.37 (m, 2H), 4.36 - 4.29 (m, 2H), 4.24 (dt, J = 4.3, 10.3 Hz, 1H), 4.16 - 4.06 (m, 1H), 3.75 (d, J = 1.9 Hz, 3H), 3.55 - 3.44 (m, 2H), 3.41 - 3.33 (m, 1H), 3.15 - 3.04 (m, 1H), 2.95 - 2.86 (m, 1H), 2.60 - 2.47 (m, 3H), 2.43 (br s, 1H), 2.38 - 2.27 (m, 2H), 2.20 - 2.08 (m, 1H)
82		490.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.63 - 8.36 (m, 2H), 7.85 - 7.73 (m, 1H), 7.66 - 7.55 (m, 1H), 7.50 - 7.36 (m, 2H), 6.96 - 6.87 (m, 1H), 4.55 - 4.42 (m, 1H), 4.42 - 4.32 (m, 2H), 4.32 - 4.22 (m, 2H), 4.20 - 4.07 (m, 1H), 3.74 - 3.69 (m, 3H), 3.62 - 3.43 (m, 2H), 3.42 - 3.33 (m, 1H), 3.28 - 3.11 (m, 1H), 2.97 (br t, J = 11.4 Hz, 1H), 2.63 - 2.53 (m, 3H), 2.53 - 2.41 (m, 2H), 2.41 - 2.27 (m, 3H), 2.26 - 2.10 (m, 1H)

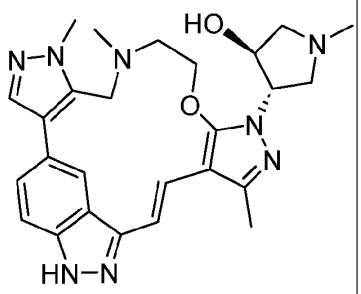
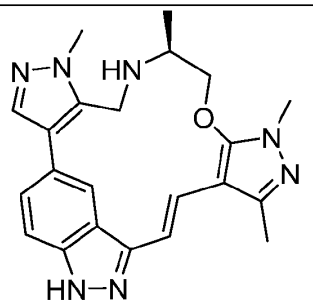
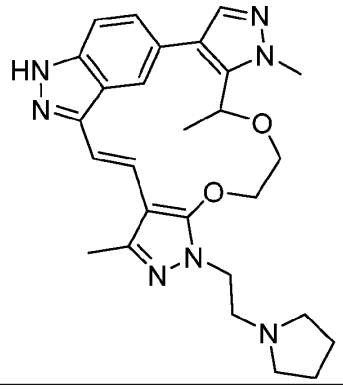
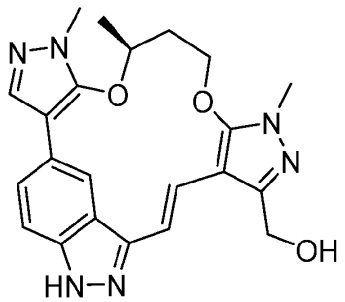
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
83		490.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.58 - 8.40 (m, 2H), 7.83 - 7.73 (m, 1H), 7.65 - 7.55 (m, 1H), 7.49 - 7.38 (m, 2H), 6.96 - 6.87 (m, 1H), 4.51 - 4.40 (m, 1H), 4.40 - 4.32 (m, 2H), 4.31 - 4.20 (m, 2H), 4.20 - 4.08 (m, 1H), 3.75 - 3.68 (m, 3H), 3.66 - 3.38 (m, 2H), 3.34 (br s, 1H), 3.27 - 3.12 (m, 1H), 2.97 (br t, J = 11.5 Hz, 1H), 2.62 - 2.53 (m, 3H), 2.45 (d, J = 7.6 Hz, 2H), 2.39 - 2.26 (m, 3H), 2.25 - 2.11 (m, 1H)
84		488.1	1H NMR (400 MHz, DMSO-d6) δ = 13.33 - 12.36 (m, 1H), 8.89 - 8.58 (m, 1H), 7.60 (s, 1H), 7.56 (br d, J = 17.8 Hz, 1H), 7.53 - 7.44 (m, 2H), 6.97 (d, J = 17.6 Hz, 1H), 5.11 - 4.97 (m, 1H), 4.36 (br t, J = 6.0 Hz, 2H), 4.26 (br s, 2H), 3.97 (s, 3H), 3.94 - 3.91 (m, 1H), 3.85 (br s, 1H), 3.59 (br s, 4H), 3.11 - 2.99 (m, 2H), 2.52 (s, 3H), 2.07 - 1.94 (m, 2H), 1.92 - 1.80 (m, 2H), 1.38 - 1.31 (m, 3H)
85		477.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 - 8.44 (m, 1H), 7.82 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 16.4 Hz, 1H), 6.64 - 6.56 (m, 1H), 5.73 - 5.60 (m, 1H), 5.26 - 5.18 (m, 2H), 5.10 (br d, J = 10.3 Hz, 1H), 4.12 - 4.07 (m, 1H), 4.00 - 3.91 (m, 3H), 3.52 - 3.45 (m, 2H), 3.20 - 3.16 (m, 1H), 2.82 (br d, J = 7.8 Hz, 2H), 2.18 - 2.15 (m, 3H), 2.14 - 2.02 (m, 2H), 1.87 - 1.80 (m, 1H), 1.30 - 1.27 (m, 1H)

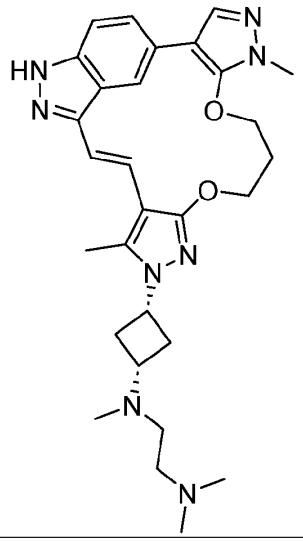
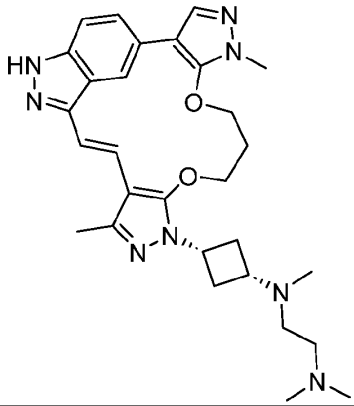
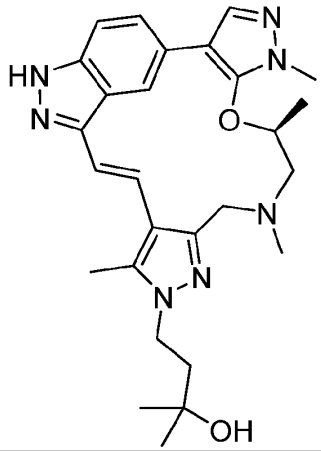
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
86		477.6	1H NMR (400 MHz, METHANOL-d4) δ = 8.52 - 8.43 (m, 1H), 7.86 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 16.5 Hz, 1H), 6.65 - 6.54 (m, 1H), 5.74 - 5.62 (m, 1H), 5.30 - 5.15 (m, 2H), 5.10 (br d, *J* = 10.5 Hz, 1H), 4.13 - 4.05 (m, 1H), 4.03 - 3.88 (m, 3H), 3.54 - 3.36 (m, 2H), 3.19 (t, *J* = 10.6 Hz, 1H), 2.82 (br d, *J* = 8.0 Hz, 2H), 2.19 - 2.14 (m, 3H), 2.04 (s, 2H), 1.88 - 1.80 (m, 1H), 1.32 - 1.26 (m, 1H)
87		477.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 - 8.40 (m, 1H), 7.83 - 7.72 (m, 2H), 7.49 - 7.41 (m, 1H), 6.94 (br d, J = 17.4 Hz, 1H), 6.59 (br d, J = 15.6 Hz, 1H), 5.51 - 5.48 (m, 1H), 5.20 (br d, J = 4.4 Hz, 2H), 5.09 (br s, 1H), 4.14 - 4.07 (m, 1H), 4.04 - 3.90 (m, 3H), 3.52 - 3.47 (m, 2H), 3.21 - 3.13 (m, 1H), 2.93 - 2.74 (m, 2H), 2.17 (br d, J = 2.1 Hz, 2H), 2.04 (d, J = 2.3 Hz, 3H), 1.78 - 1.71 (m, 1H), 1.30 - 1.28 (m, 1H)
88		476.9	1H NMR (400 MHz, METHANOL-d4) δ = 8.54 (br d, J = 2.9 Hz, 1H), 7.70 - 7.67 (m, 1H), 7.53 - 7.50 (m, 1H), 7.47 - 7.43 (m, 1H), 6.86 - 6.79 (m, 1H), 6.68 - 6.62 (m, 1H), 5.37 - 5.31 (m, 1H), 5.18 (br d, J = 7.9 Hz, 3H), 4.17 - 4.13 (m, 1H), 4.11 - 4.01 (m, 3H), 3.81 - 3.77 (m, 3H), 3.02 (br d, J = 7.3 Hz, 2H), 2.42 - 2.39 (m, 1H), 2.19 (br t, J = 7.9 Hz, 2H), 2.08 - 1.99 (m, 3H), 1.27 (br s, 1H)

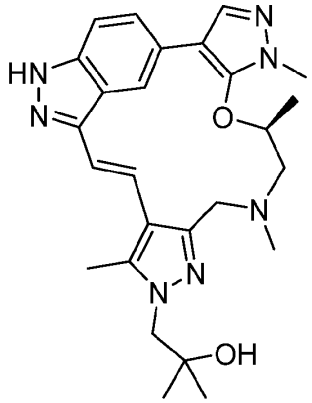
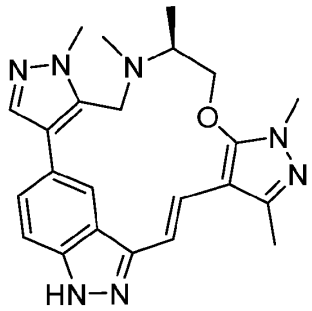
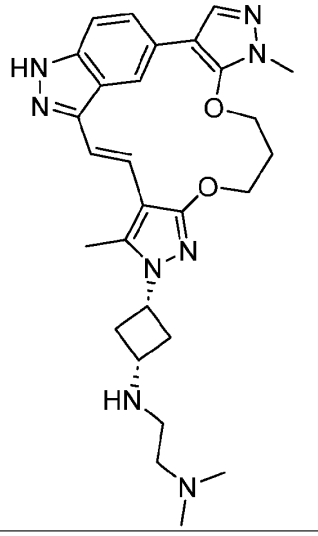
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
89		501.1	1H NMR (400 MHz, DMSO-d6) δ = 13.21 - 12.83 (m, 1H), 10.24 - 9.96 (m, 1H), 8.48 (s, 1H), 7.90 (br d, J = 1.4 Hz, 1H), 7.69 (br s, 1H), 7.54 (br d, J = 8.0 Hz, 1H), 7.52 - 7.40 (m, 1H), 7.10 - 6.96 (m, 1H), 5.51 - 5.00 (m, 1H), 4.92 - 4.67 (m, 1H), 4.63 - 4.40 (m, 3H), 4.07 - 3.84 (m, 2H), 3.73 (br s, 3H), 3.69 - 3.60 (m, 3H), 3.58 (br d, J = 1.3 Hz, 2H), 3.13 - 2.88 (m, 4H), 2.59 (br s, 2H), 2.03 (br s, 2H), 1.86 (br d, J = 5.8 Hz, 2H), 1.05 (br s, 3H)
90		530.1	1H NMR (600 MHz, DMSO-d6) δ = 13.01 - 12.78 (m, 1H), 9.54 - 9.35 (m, 1H), 8.48 (br s, 1H), 8.19 (br s, 1H), 7.86 (s, 1H), 7.68 (br d, J = 8.5 Hz, 1H), 7.50 (br d, J = 8.2 Hz, 1H), 6.91 (br d, J = 17.3 Hz, 1H), 4.88 - 4.71 (m, 1H), 4.17 (br d, J = 1.8 Hz, 1H), 3.90 (br d, J = 12.6 Hz, 1H), 3.68 (br s, 3H), 3.04 - 2.96 (m, 4H), 2.81 - 2.78 (m, 4H), 2.62 (br s, 1H), 2.57 - 2.55 (m, 8H), 2.39 (br s, 1H), 2.35 (br s, 1H), 2.26 (br s, 3H), 2.05 - 1.96 (m, 1H), 1.02 (br d, J = 4.7 Hz, 3H)
91		443.9	1H NMR (400 MHz, DMSO-d6) δ = 13.02 (s, 1H), 8.51 (s, 1H), 8.31 (d, J = 16.8 Hz, 1H), 7.90 (s, 1H), 7.73 - 7.67 (m, 1H), 7.63 (d, J = 5.9 Hz, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 7.16 (d, J = 5.9 Hz, 1H), 4.45 (t, J = 5.4 Hz, 4H), 3.73 (s, 3H), 3.47 (s, 3H), 2.42 - 2.34 (m, 2H)

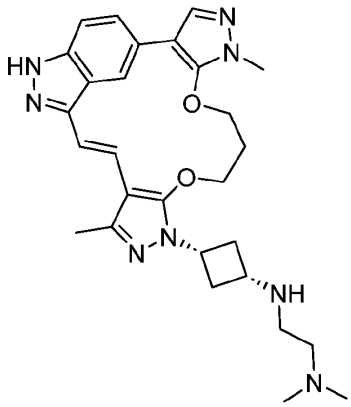
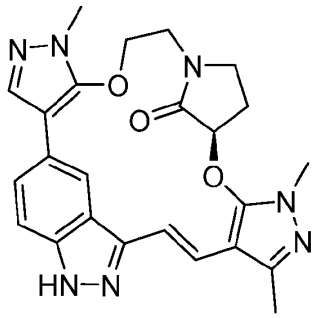
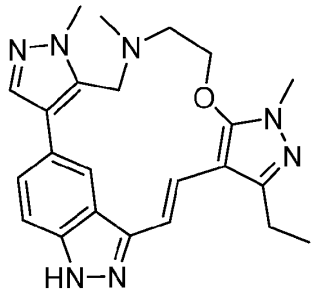
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
92		554.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.15 (s, 1H), 7.70 - 7.68 (m, 2H), 7.68 - 7.65 (m, 1H), 7.64 - 7.60 (m, 1H), 7.59 - 7.57 (m, 1H), 7.57 - 7.53 (m, 1H), 7.25 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 5.06 (br d, J = 5.6 Hz, 1H), 4.48 - 4.39 (m, 1H), 4.35 - 4.24 (m, 1H), 4.15 - 4.01 (m, 2H), 3.94 (s, 2H), 3.84 (s, 3H), 3.65 - 3.55 (m, 1H), 3.50 - 3.37 (m, 5H), 3.18 - 2.97 (m, 4H), 2.91 (s, 3H), 2.48 - 2.35 (m, 1H), 2.22 (br dd, J = 6.9, 14.3 Hz, 1H)
93		517.0	1H NMR (499 MHz, DMSO-d6) δ = 13.13 - 12.96 (m, 1H), 10.22 - 10.06 (m, 1H), 8.48 (s, 1H), 8.28 - 8.15 (m, 1H), 7.98 - 7.85 (m, 1H), 7.69 (br d, J = 3.3 Hz, 1H), 7.59 - 7.48 (m, 1H), 7.04 - 6.91 (m, 1H), 5.55 - 5.41 (m, 1H), 5.14 - 5.00 (m, 1H), 4.89 - 4.75 (m, 1H), 4.63 - 4.44 (m, 2H), 4.28 - 4.19 (m, 1H), 4.06 - 3.85 (m, 4H), 3.68 (br d, J = 4.4 Hz, 4H), 3.24 - 3.13 (m, 2H), 3.08 (br dd, J = 5.2, 7.4 Hz, 1H), 2.98 (br s, 1H), 2.93 - 2.86 (m, 1H), 2.75 (d, J = 4.9 Hz, 1H), 2.66 - 2.54 (m, 3H), 2.39 - 2.34 (m, 1H), 2.27 (br d, J = 2.7 Hz, 1H), 2.04 - 1.95 (m, 1H), 1.18 (br t, J = 7.4 Hz, 3H)
94		499.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.18 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.72 - 7.68 (m, 2H), 7.68 - 7.65 (m, 1H), 7.64 - 7.62 (m, 1H), 7.61 - 7.57 (m, 1H), 7.35 - 7.32 (m, 1H), 7.22 (d, J = 7.4 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.50 - 4.44 (m, 1H), 4.35 - 4.28 (m, 3H), 4.18 - 4.10 (m, 1H), 4.09 - 4.03 (m, 1H), 3.86 (s, 3H), 3.64 (br t, J = 8.6 Hz, 1H), 3.52 - 3.46 (m, 1H), 2.51 - 2.41

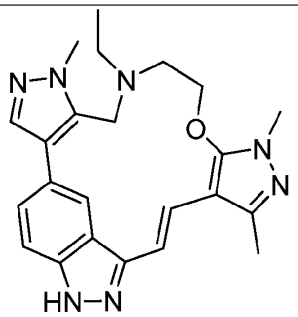
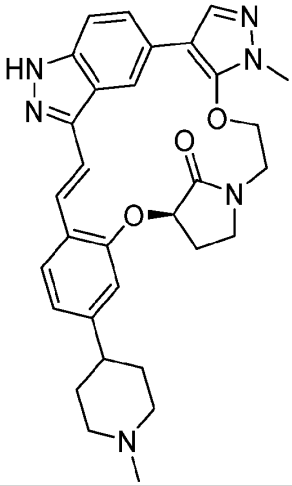
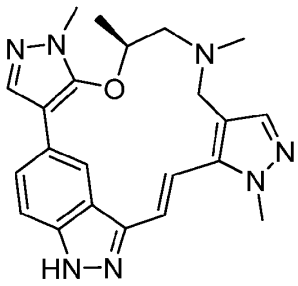
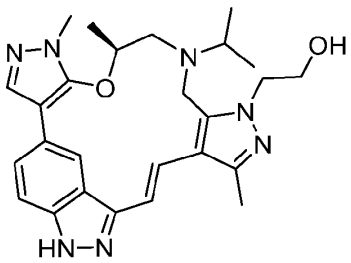
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			(m, 1H), 2.33 - 2.22 (m, 1H), 2.04 (s, 6H)
95		476.3	1H NMR (400 MHz, DMSO-d6) δ = 13.08 - 12.66 (m, 1H), 8.46 (s, 1H), 8.29 - 8.14 (m, 1H), 7.88 - 7.82 (m, 1H), 7.70 - 7.62 (m, 1H), 7.48 (d, J = 8 Hz, 1H), 6.96 - 6.83 (m, 1H), 4.85 - 4.69 (m, 1H), 4.32 - 4.12 (m, 3H), 3.56 (br s, 1H), 3.53 (br s, 1H), 2.54 - 2.52 (m, 3H), 1.04 - 0.98 (m, 3H)
96		418.0	1H NMR (400 MHz, METHANOL-d4) δ = 9.13 - 9.09 (m, 1H), 7.83 - 7.75 (m, 1H), 7.72 (s, 1H), 7.59 - 7.50 (m, 2H), 7.05 - 6.97 (m, 1H), 4.57 - 4.49 (m, 1H), 3.99 (s, 3H), 3.97 - 3.94 (m, 1H), 3.83 - 3.75 (m, 1H), 3.64 (s, 3H), 3.06 - 2.97 (m, 1H), 2.95 - 2.86 (m, 1H), 2.48 (s, 3H), 2.45 - 2.40 (m, 3H), 1.23 (d, J = 6.4 Hz, 3H)
97		417.23	1H NMR (400 MHz, METHANOL-d4) δ = 9.13 - 9.05 (m, 1H), 7.82 - 7.73 (m, 1H), 7.72 - 7.68 (m, 1H), 7.59 - 7.47 (m, 2H), 7.05 - 6.93 (m, 1H), 4.59 - 4.51 (m, 1H), 3.99 - 3.95 (m, 3H), 3.94 - 3.82 (m, 1H), 3.82 - 3.72 (m, 1H), 3.66 - 3.59 (m, 3H), 3.06 - 2.95 (m, 1H), 2.94 - 2.82 (m, 1H), 2.49 - 2.44 (m, 3H), 2.44 - 2.39 (m, 3H), 1.21 (br d, J = 6.0 Hz, 3H)

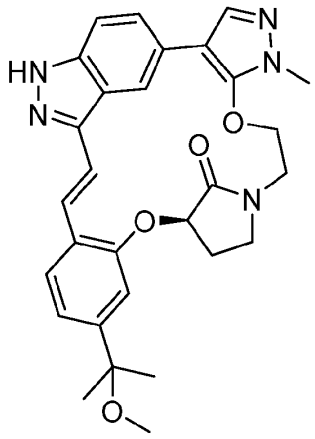
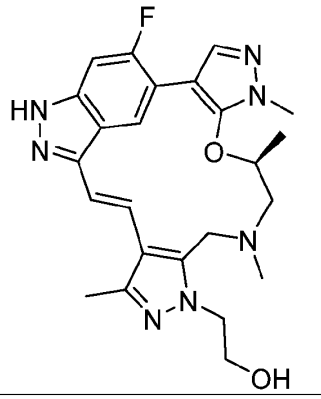
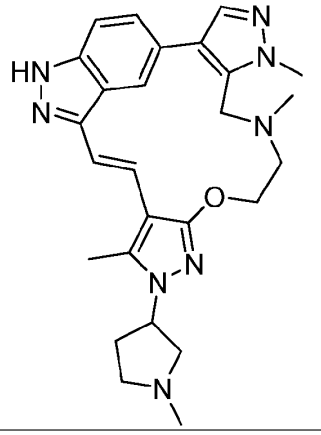
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
98		489.4	1H NMR (400 MHz, METHANOL-d4) δ = 7.88 (br d, J = 1.6 Hz, 1H), 7.19 (s, 1H), 6.92 (dd, J = 1.6, 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 6.78 - 6.67 (m, 1H), 6.64 - 6.56 (m, 1H), 4.30 - 4.26 (m, 2H), 3.86 (br s, 3H), 3.72 - 3.55 (m, 4H), 3.50 - 3.33 (m, 2H), 3.06 - 2.86 (m, 3H), 2.81 - 2.72 (m, 2H), 2.51 - 2.37 (m, 4H), 1.97 (br s, 3H), 1.78 (s, 3H)
99		403.9	1H NMR (400 MHz, DMSO-d6) δ = 13.14 - 12.93 (m, 1H), 8.34 - 8.14 (m, 1H), 7.89 (s, 1H), 7.59 - 7.50 (m, 3H), 6.94 (d, J = 16 Hz, 1H), 4.84 - 4.64 (m, 1H), 4.58 - 4.37 (m, 3H), 4.02 (s, 5H), 3.66 (s, 3H), 2.37 (s, 3H), 1.49 - 1.37 (m, 3H)
100		488.2	1H NMR (400 MHz, DMSO-d6) δ = 12.91 (s, 1H), 8.92 (br s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.49 (d, J = 2.8 Hz, 2H), 6.92 - 6.86 (m, 1H), 5.06 - 4.99 (m, 1H), 4.40 - 4.32 (m, 1H), 4.26 (br t, J = 9.2 Hz, 1H), 4.13 - 4.04 (m, 2H), 4.01 (br d, J = 4.8 Hz, 2H), 3.99 - 3.91 (m, 5H), 2.78 - 2.73 (m, 2H), 2.46 (br d, J = 4.8 Hz, 2H), 2.36 (s, 3H), 1.66 (br s, 4H), 1.34 - 1.30 (m, 3H)
101		421.0	1H NMR (400 MHz, DMSO-d6) δ = 8.56 (s, 1H), 7.93 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.24 - 7.16 (m, 1H), 5.20 (br s, 1H), 4.95 - 4.85 (m, 1H), 4.63 - 4.55 (m, 1H), 4.51 (br d, J = 3.4 Hz, 2H), 4.37 - 4.30 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.40 (br s, 2H), 1.31 (d, J = 6.2 Hz, 3H)

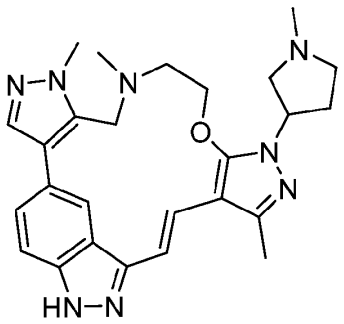
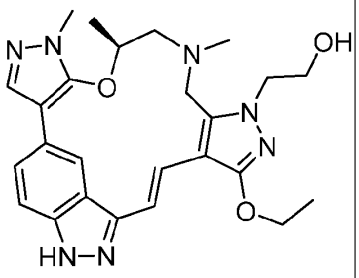
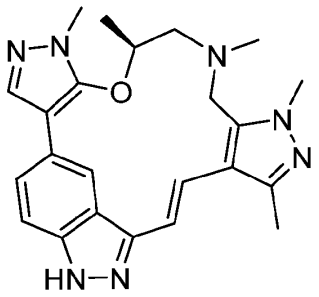
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
102		531.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.60 (s, 1H), 7.86 (s, 1H), 7.72 - 7.67 (m, 1H), 7.57 - 7.49 (m, 2H), 6.99 (d, J = 17.2 Hz, 1H), 4.74 - 4.66 (m, 2H), 4.49 (br t, J = 5.6 Hz, 2H), 4.44 - 4.37 (m, 2H), 3.79 (s, 3H), 3.04 (br t, J = 6.0 Hz, 2H), 2.98 - 2.93 (m, 6H), 2.88 (d, J = 2.0 Hz, 1H), 2.81 (br d, J = 5.6 Hz, 3H), 2.67 (s, 1H), 2.65 - 2.57 (m, 2H), 2.54 (s, 5H), 2.43 - 2.38 (m, 2H)
103		531.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.68 (s, 1H), 7.88 (s, 1H), 7.73 - 7.68 (m, 1H), 7.58 - 7.50 (m, 2H), 7.03 (d, J = 17.2 Hz, 1H), 4.69 - 4.63 (m, 2H), 4.51 (br t, J = 5.2 Hz, 2H), 4.40 (br t, J = 4.8 Hz, 2H), 3.80 (s, 3H), 3.09 - 3.00 (m, 1H), 2.94 (s, 6H), 2.86 - 2.79 (m, 2H), 2.79 - 2.67 (m, 3H), 2.58 - 2.53 (m, 1H), 2.51 (s, 4H), 2.49 (br d, J = 4.0 Hz, 2H), 2.39 (s, 3H)
104		490.5	1H NMR (400 MHz, DMSO-d6) δ = 12.95 - 12.83 (m, 1H), 8.49 - 8.44 (m, 1H), 8.23 - 8.14 (m, 1H), 7.85 (s, 1H), 7.68 - 7.64 (m, 1H), 7.51 - 7.46 (m, 1H), 6.92 - 6.84 (m, 1H), 4.83 - 4.72 (m, 1H), 4.29 - 4.06 (m, 2H), 3.66 (s, 3H), 3.59 (s, 1H), 3.53 (s, 2H), 2.94 - 2.87 (m, 2H), 2.78 - 2.68 (m, 2H), 2.54 (br s, 3H), 2.26 - 2.22 (m, 3H), 2.04 - 1.94 (m, 2H), 1.23 (br s, 3H), 1.14 (d, J = 2 Hz, 3H), 1.03 - 0.98 (m, 3H)

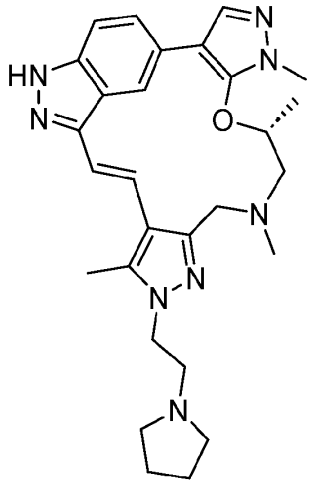
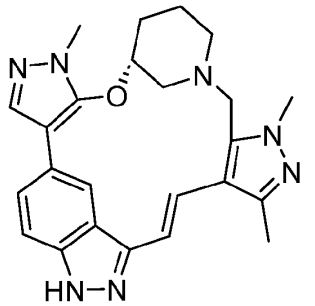
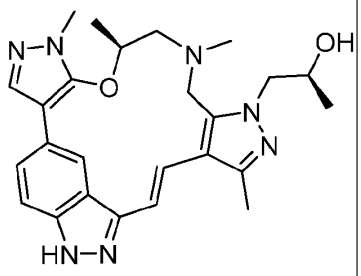
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
105		476.3	1H NMR (400 MHz, DMSO-d6) δ = 12.95 - 12.86 (m, 1H), 8.48 (s, 1H), 8.24 - 8.15 (m, 1H), 7.87 - 7.84 (m, 1H), 7.67 (br d, J = 8.8 Hz, 1H), 7.52 - 7.47 (m, 1H), 6.97 - 6.85 (m, 1H), 4.79 (br t, J = 6.0 Hz, 1H), 4.70 (s, 1H), 3.98 (s, 2H), 3.91 (br d, J = 12.9 Hz, 1H), 3.72 (s, 1H), 3.67 (s, 3H), 2.90 (br d, J = 13.3 Hz, 2H), 2.52 (br s, 3H), 2.26 (s, 3H), 1.12 (d, J = 5.0 Hz, 6H), 1.02 (d, J = 6.3 Hz, 3H)
106		418.2	1H NMR (400 MHz, DMSO-d6) δ = 12.96 (s, 1H), 8.59 (s, 1H), 7.83 (s, 1H), 7.61 - 7.56 (m, 1H), 7.55 - 7.50 (m, 1H), 7.38 (d, J = 17.2 Hz, 1H), 6.94 (d, J = 17.2 Hz, 1H), 4.39 - 4.30 (m, 2H), 3.91 (s, 4H), 3.79 (d, J = 13.2 Hz, 1H), 3.58 (s, 3H), 3.54 - 3.48 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H)
107		517.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.58 (s, 1H), 7.86 (s, 1H), 7.70 (dd, J = 1.2, 8.8 Hz, 1H), 7.56 - 7.48 (m, 2H), 6.98 (d, J = 17.6 Hz, 1H), 4.49 (t, J = 5.6 Hz, 2H), 4.41 (t, J = 5.2 Hz, 2H), 3.78 (s, 3H), 3.50 - 3.47 (m, 1H), 3.44 - 3.38 (m, 4H), 3.07 - 3.01 (m, 1H), 2.97 (s, 2H), 2.94 (s, 5H), 2.84 - 2.74 (m, 2H), 2.54 (s, 2H), 2.50 (s, 1H), 2.43 - 2.36 (m, 2H), 2.04 (s, 2H)

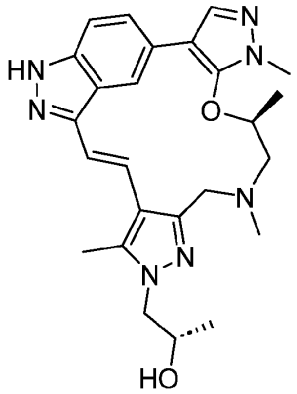
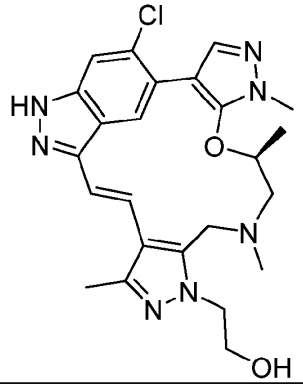
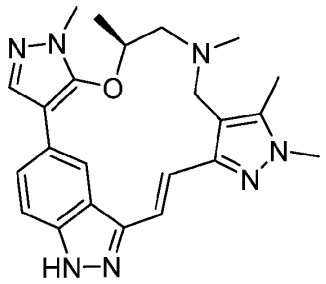
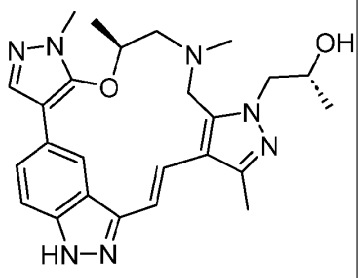
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
108		517.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.50 (br s, 1H), 7.81 - 7.75 (m, 1H), 7.60 (br d, J = 8.8 Hz, 1H), 7.46 - 7.41 (m, 1H), 7.37 (br d, J = 17.2 Hz, 1H), 6.89 (br d, J = 17.2 Hz, 1H), 4.77 - 4.66 (m, 2H), 4.30 (br d, J = 4.4 Hz, 2H), 4.16 (br d, J = 4.4 Hz, 2H), 3.83 - 3.75 (m, 1H), 3.68 (s, 3H), 3.61 - 3.44 (m, 4H), 3.01 - 2.98 (m, 6H), 2.97 - 2.88 (m, 2H), 2.86 - 2.73 (m, 2H), 2.46 - 2.40 (m, 3H), 2.28 (br d, J = 4.0 Hz, 2H)
109		460.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.06 (s, 1H), 7.74 - 7.67 (m, 1H), 7.63 - 7.59 (m, 1H), 7.57 - 7.52 (m, 1H), 7.30 - 7.24 (m, 1H), 7.20 (s, 1H), 4.97 (br dd, J = 4.0, 7.4 Hz, 1H), 4.45 - 4.35 (m, 1H), 4.23 (ddd, J = 2.1, 6.6, 14.6 Hz, 1H), 4.15 - 4.05 (m, 1H), 3.98 - 3.90 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.57 - 3.47 (m, 1H), 3.43 - 3.36 (m, 1H), 2.52 - 2.42 (m, 2H), 2.39 (s, 3H)
110		418.4	1H NMR (400 MHz, DMSO-d6) δ = 13.17 - 12.78 (m, 1H), 8.94 - 8.46 (m, 1H), 8.04 - 7.76 (m, 1H), 7.61 (br d, J = 7.9 Hz, 1H), 7.57 - 7.51 (m, 1H), 7.47 (d, J = 17.4 Hz, 1H), 6.91 (d, J = 17.3 Hz, 1H), 4.58 - 4.32 (m, 2H), 4.03 - 3.90 (m, 3H), 3.77 - 3.68 (m, 2H), 3.65 (br s, 2H), 3.06 - 2.90 (m, 2H), 2.77 (q, J = 7.3 Hz, 2H), 2.53 - 2.51 (m, 3H), 1.26 (t, J = 7.4 Hz, 3H)

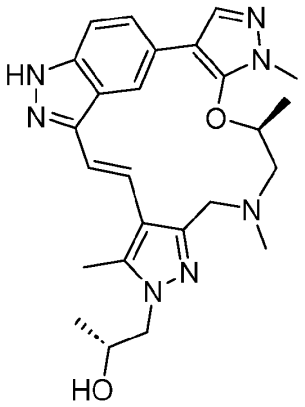
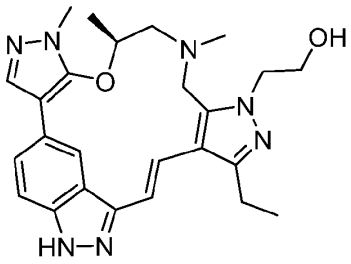
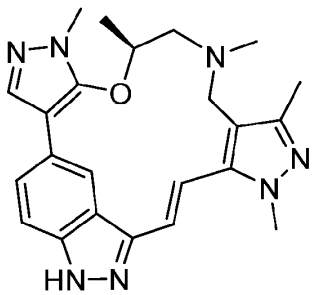
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
111		418.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 (br s, 1H), 7.95 (s, 1H), 7.62 (br d, J = 6.4 Hz, 3H), 7.05 (d, J = 17.3 Hz, 1H), 4.58 (br s, 4H), 4.06 (s, 3H), 3.71 (s, 5H), 3.29 - 3.19 (m, 2H), 2.44 (s, 3H), 1.32 (br t, J = 6.8 Hz, 3H)
112		539.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.18 (s, 1H), 7.68 (s, 3H), 7.61 (d, J = 1.2 Hz, 1H), 7.56 (s, 1H), 7.55 - 7.50 (m, 1H), 7.09 (s, 1H), 7.03 (dd, J = 1.3, 8.1 Hz, 1H), 5.10 (s, 1H), 4.40 - 4.32 (m, 2H), 4.12 - 4.05 (m, 2H), 3.85 (s, 3H), 3.62 - 3.51 (m, 2H), 3.49 - 3.43 (m, 2H), 2.98 - 2.82 (m, 3H), 2.78 (s, 3H), 2.41 - 2.32 (m, 1H), 2.20 (br dd, J = 6.8, 14.2 Hz, 1H), 2.10 (br d, J = 12.3 Hz, 2H), 2.02 - 1.88 (m, 2H)
113		404.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.58 (s, 1H), 7.88 (s, 1H), 7.77 - 7.67 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 5.54 - 5.37 (m, 1H), 4.20 (s, 3H), 4.15 - 4.00 (m, 1H), 3.92 - 3.80 (m, 2H), 3.79 (s, 3H), 3.64 (br dd, J = 2.0, 14.6 Hz, 1H), 3.05 (br s, 3H), 1.18 (d, J = 6.0 Hz, 3H)
114		476.3	1H NMR (400 MHz, DMSO-d6) δ = 12.86 (s, 1H), 8.64 - 8.59 (m, 1H), 8.04 (br d, J = 17.4 Hz, 1H), 7.87 (s, 1H), 7.67 - 7.63 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 17.4 Hz, 1H), 4.94 - 4.61 (m, 2H), 4.12 (t, J = 5.6 Hz, 2H), 4.01 - 3.90 (m, 2H), 3.69 (s, 5H), 2.91 - 2.74 (m, 2H), 2.71 - 2.64 (m, 1H), 2.41 (s, 3H), 1.06 (br

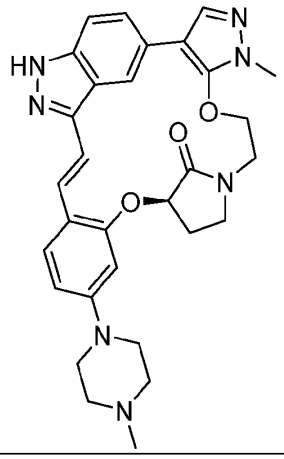
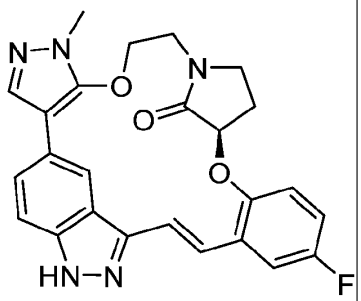
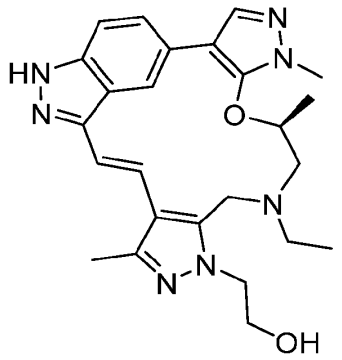
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			d, J = 6.4 Hz, 3H), 0.93 (br d, J = 6.4 Hz, 6H)
115		514.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.18 (s, 1H), 7.75 - 7.69 (m, 1H), 7.69 - 7.64 (m, 2H), 7.63 - 7.59 (m, 1H), 7.55 (br d, J = 4.0 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.15 (dd, J = 1.5, 8.1 Hz, 1H), 5.07 (br d, J = 6.0 Hz, 1H), 4.44 - 4.37 (m, 1H), 4.36 - 4.29 (m, 1H), 4.11 - 4.05 (m, 2H), 3.87 - 3.83 (m, 3H), 3.62 - 3.53 (m, 1H), 3.43 (td, J = 6.2, 8.2 Hz, 1H), 3.13 (s, 3H), 2.46 - 2.35 (m, 1H), 2.22 (br dd, J = 7.0, 14.4 Hz, 1H), 1.59 - 1.52 (m, 6H)
116		466.3	1H NMR (400 MHz, DMSO-d6) δ = 8.59 (d, J = 7.4 Hz, 1H), 8.10 - 7.96 (m, 1H), 7.75 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 12.0 Hz, 1H), 6.94 (d, J = 17.4 Hz, 1H), 4.90 - 4.80 (m, 1H), 4.20 - 4.12 (m, 3H), 4.11 - 4.04 (m, 1H), 3.77 (br s, 1H), 3.76 - 3.74 (m, 2H), 3.74 (s, 3H), 3.16 - 3.06 (m, 2H), 2.44 (s, 6H), 1.07 (d, J = 6.4 Hz, 3H)
117		473.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.98 (s, 1H), 8.53 (s, 1H), 7.84 - 7.72 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.20 - 7.12 (m, 1H), 4.42 (d, J = 2.4 Hz, 2H), 3.95 (d, J = 1.6 Hz, 3H), 3.73 (d, J = 4.0 Hz, 2H), 3.66 - 3.50 (m, 3H), 3.38 - 3.31 (m, 2H), 2.96 (s, 2H), 2.92 (s, 3H), 2.61 - 2.49 (m, 1H), 2.40 (s, 3H), 2.34 - 2.23 (m, 4H)

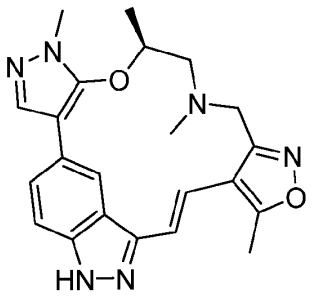
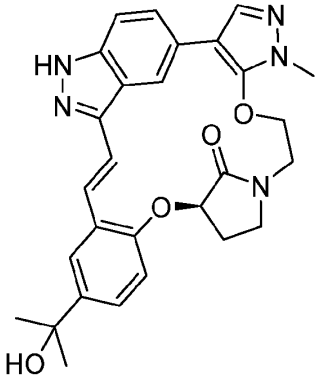
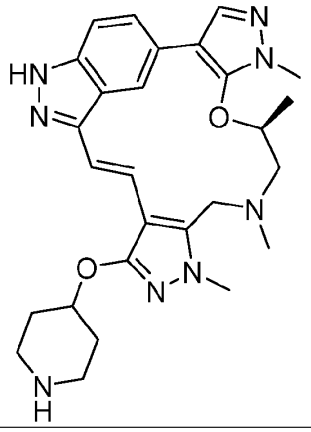
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
118		473.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.91 (s, 1H), 7.85 (s, 1H), 7.66 - 7.62 (m, 1H), 7.58 - 7.54 (m, 1H), 7.52 - 7.46 (m, 1H), 7.38 - 7.35 (m, 1H), 7.09 (br d, J = 17.2 Hz, 1H), 4.50 (br s, 4H), 3.99 (s, 3H), 3.79 (s, 2H), 3.71 - 3.51 (m, 3H), 3.11 (br s, 2H), 2.93 (br s, 2H), 2.70 - 2.58 (m, 1H), 2.50 (br s, 3H), 2.38 (s, 3H), 2.35 - 2.23 (m, 1H), 2.05 (s, 2H)
119		478.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.55 (s, 1H), 8.29 - 8.18 (m, 1H), 7.83 (s, 1H), 7.70 - 7.66 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 16.8 Hz, 1H), 4.35 (dd, J = 2.6, 6.8 Hz, 2H), 4.18 - 4.05 (m, 4H), 3.95 (br d, J = 11.8 Hz, 1H), 3.86 - 3.82 (m, 2H), 3.74 (s, 3H), 3.06 - 2.95 (m, 2H), 2.51 (br s, 3H), 1.49 (t, J = 7.0 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H)
120		418.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.54 (s, 1H), 8.35 (d, J = 17.6 Hz, 1H), 7.82 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 17.6 Hz, 1H), 4.93 - 4.91 (m, 1H), 4.01 - 3.93 (m, 1H), 3.87 - 3.81 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.95 - 2.87 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 1.09 (d, J = 6.0 Hz, 3H)

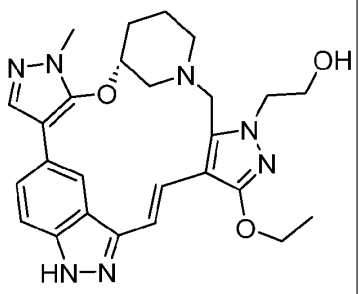
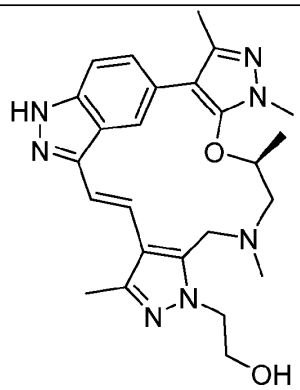
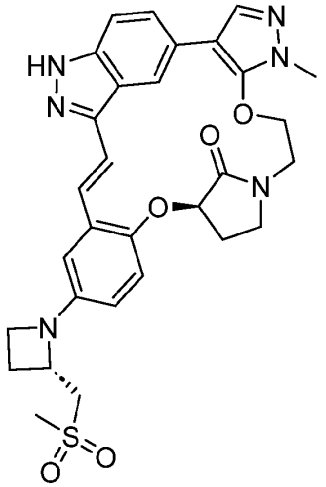
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
121		501.3	1H NMR (400 MHz, DMSO-d6) δ = 13.12 - 12.61 (m, 1H), 8.47 (s, 1H), 8.23 - 8.15 (m, 2H), 7.85 (s, 1H), 7.66 (dd, J = 1.3, 8.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 17.6 Hz, 1H), 4.78 (br t, J = 6.2 Hz, 1H), 4.20 - 4.13 (m, 2H), 3.89 (br d, J = 12.9 Hz, 1H), 3.66 (s, 3H), 3.56 (br s, 2H), 3.53 (br s, 2H), 2.93 - 2.86 (m, 1H), 2.82 (dt, J = 3.6, 6.8 Hz, 2H), 2.74 (br dd, J = 8.1, 14.4 Hz, 1H), 2.53 (br s, 3H), 2.25 (s, 3H), 1.72 - 1.65 (m, 4H), 1.01 (d, J = 6.3 Hz, 3H)
122		430.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.72 - 8.49 (m, 1H), 7.90 (s, 1H), 7.72 (dd, J = 1.2, 8.8 Hz, 1H), 7.52 (s, 2H), 7.22 - 7.08 (m, 1H), 4.99 (br s, 1H), 4.62 - 4.44 (m, 1H), 4.25 - 3.99 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.51 - 3.43 (m, 1H), 3.17 - 2.97 (m, 2H), 2.52 (s, 3H), 2.12 - 1.99 (m, 2H), 1.94 - 1.84 (m, 2H), 1.70 - 1.54 (m, 1H)
123		462.2	1H NMR (400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.47 - 8.44 (m, 1H), 8.28 (d, J = 17.6 Hz, 1H), 7.88 - 7.84 (m, 1H), 7.67 (dd, J = 1.1, 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 17.6 Hz, 1H), 4.87 (d, J = 5.2 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.01 - 3.89 (m, 4H), 3.86 - 3.80 (m, 1H), 3.67 (s, 3H), 2.97 - 2.89 (m, 1H), 2.80 (dd, J = 7.9, 14.4 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.09 (d, J = 6.0 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H)

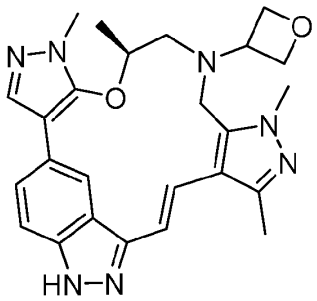
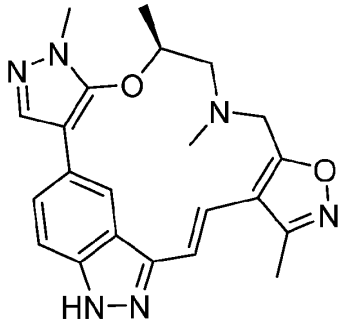
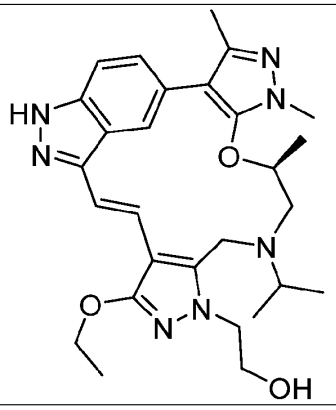
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
124		462.2	1H NMR (400 MHz, DMSO-d6) δ = 13.13 - 12.72 (m, 1H), 8.48 (s, 1H), 8.22 - 8.16 (m, 1H), 7.88 - 7.83 (m, 1H), 7.66 (dd, J = 1.4, 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 6.91 - 6.82 (m, 1H), 4.91 (br s, 1H), 4.78 (br t, J = 6.3 Hz, 1H), 4.04 - 3.83 (m, 4H), 3.66 (s, 3H), 3.60 - 3.51 (m, 2H), 2.95 - 2.85 (m, 1H), 2.75 (dd, J = 7.9, 14.4 Hz, 1H), 2.54 (s, 2H), 2.25 (s, 3H), 1.06 (br d, J = 5.8 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H)
125		482.2	1H NMR (400 MHz, DMSO-d6) δ = 13.43 - 12.75 (m, 1H), 8.42 (br s, 1H), 7.88 (br s, 1H), 7.71 (br s, 1H), 7.35 - 7.22 (m, 1H), 7.00 - 6.90 (m, 1H), 5.25 - 4.54 (m, 3H), 4.29 - 4.11 (m, 3H), 3.73 (br s, 6H), 2.91 - 2.53 (m, 4H), 2.43 (br s, 3H), 0.99 (br d, J = 3.6 Hz, 3H)
126		418.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.62 (s, 1H), 7.88 (s, 1H), 7.73 (br d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 1.6 Hz, 2H), 5.60 - 5.42 (m, 1H), 4.17 - 4.04 (m, 1H), 3.94 - 3.84 (m, 5H), 3.79 (s, 3H), 3.71 (br d, J = 14.0 Hz, 1H), 3.01 (br s, 3H), 2.45 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H)
127		462.2	1H NMR (400 MHz, DMSO-d6) δ = 12.86 (s, 1H), 8.52 - 8.45 (m, 1H), 8.32 (d, J = 17.6 Hz, 1H), 7.86 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 17.6 Hz, 1H), 4.90 (br d, J = 2.8 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.00 - 3.87 (m, 5H), 3.67 (s, 3H), 2.98 - 2.90 (m, 1H), 2.86 - 2.75 (m, 1H), 2.40 (s, 3H), 2.29 (s,

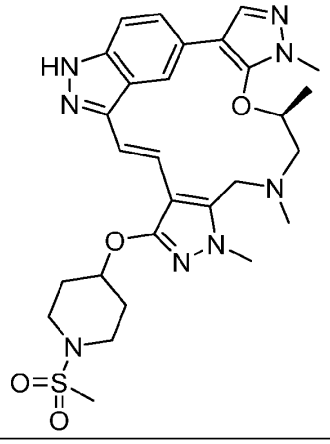
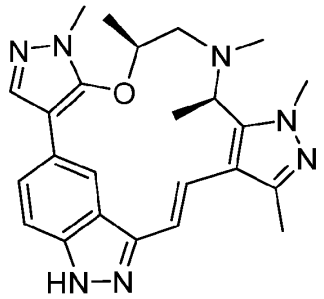
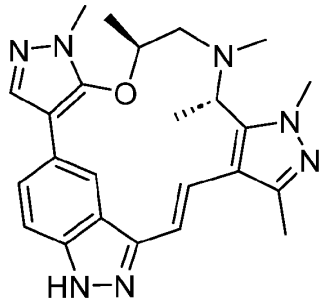
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			3H), 1.05 (br d, J = 6.0 Hz, 6H)
128		462.3	1H NMR (400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.47 (s, 1H), 8.20 (d, J = 17.6 Hz, 1H), 7.84 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 6.91 - 6.84 (m, 1H), 4.89 (d, J = 4.4 Hz, 1H), 4.83 - 4.74 (m, 1H), 4.01 - 3.86 (m, 4H), 3.69 - 3.65 (m, 3H), 3.54 (d, J = 12.8 Hz, 1H), 2.95 - 2.85 (m, 1H), 2.74 (dd, J = 8.0, 14.8 Hz, 1H), 2.49 - 2.47 (m, 3H), 2.26 (s, 3H), 1.07 (br d, J = 5.6 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H)
129			(400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.46 (s, 1H), 8.26 (d, J = 17.5 Hz, 1H), 7.85 (s, 1H), 7.69 - 7.64 (m, 1H), 7.48 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 17.6 Hz, 1H), 4.87 (br t, J = 5.1 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.16 - 4.10 (m, 2H), 3.98 - 3.93 (m, 1H), 3.87 - 3.82 (m, 1H), 3.71 - 3.68 (m, 1H), 3.67 (s, 3H), 3.64 (br d, J = 4.8 Hz, 1H), 2.96 - 2.90 (m, 1H), 2.85 - 2.82 (m, 1H), 2.81 - 2.77 (m, 2H), 2.29 (s, 3H), 1.28 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H
130		418.0	1H NMR (400 MHz, DMSO-d6) δ = 13.41 - 13.17 (m, 1H), 9.87 - 9.73 (m, 1H), 8.55 (s, 1H), 7.95 (s, 1H), 7.75 (br d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.36 - 7.29 (m, 1H), 5.53 - 5.43 (m, 1H), 4.05 (s, 3H), 3.94 - 3.87 (m, 2H), 3.75 (s, 3H), 3.64 - 3.53 (m, 2H), 2.87 (br d, J = 4.0 Hz, 3H), 2.24 (s, 3H), 1.07 (br d, J = 6.4 Hz, 3H).

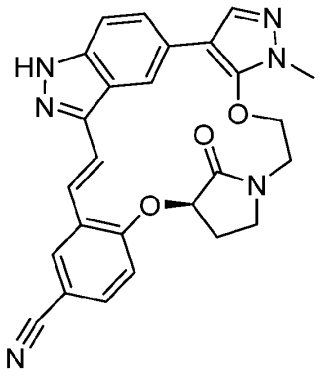
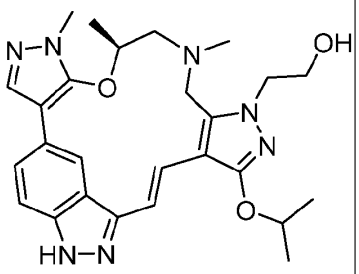
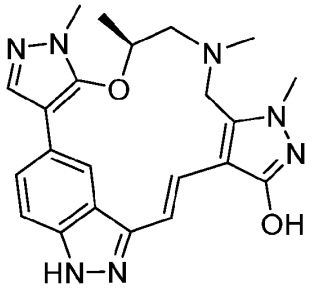
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
131		540.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.15 (s, 1H), 7.68 (s, 1H), 7.62 - 7.58 (m, 2H), 7.57 - 7.53 (m, 1H), 7.46 - 7.39 (m, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.84 - 6.75 (m, 2H), 6.49 (dd, J = 2.2, 8.4 Hz, 1H), 5.11 - 5.03 (m, 1H), 4.34 (s, 2H), 4.13 - 4.04 (m, 2H), 3.99 - 3.90 (m, 2H), 3.84 (s, 3H), 3.68 - 3.59 (m, 2H), 3.57 - 3.47 (m, 2H), 3.41 - 3.34 (m, 1H), 3.17 (br s, 2H), 3.00 - 2.95 (m, 3H), 2.42 - 2.28 (m, 1H), 2.23 - 2.14 (m, 1H)
132		460.0	1H NMR (400 MHz, DMSO-d6) δ = 13.25 (br s, 1H), 8.04 (s, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.64 - 7.58 (m, 3H), 7.52 - 7.46 (m, 1H), 7.27 (dd, J = 4.78, 9.6 Hz, 1H), 7.12 (dt, J = 3.2, 8.4 Hz, 1H), 5.00 (d, J = 6.0 Hz, 1H), 4.27 (br t, J = 8.0 Hz, 1H), 4.20 - 4.09 (m, 1H), 4.08 - 3.98 (m, 1H), 3.91 - 3.84 (m, 1H), 3.77 (s, 3H), 3.50 (br t, J = 8.4 Hz, 1H), 3.40 (br d, J = 8.4 Hz, 1H), 2.38 - 2.26 (m, 1H), 2.09 - 1.98 (m, 1H)
133		462.3	1H NMR (400 MHz, DMSO-d6) δ = 12.85 (s, 1H), 8.53 (s, 1H), 8.11 (d, J = 17.5 Hz, 1H), 7.84 (s, 1H), 7.64 (dd, J = 1.2, 8.7 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 17.5 Hz, 1H), 4.84 (t, J = 5.3 Hz, 1H), 4.75 - 4.66 (m, 1H), 4.14 - 4.05 (m, 2H), 3.98 - 3.86 (m, 2H), 3.65 (s, 5H), 2.95 - 2.89 (m, 1H), 2.88 - 2.80 (m, 1H), 2.59 - 2.51 (m, 2H), 2.38 (s, 3H), 1.02 (d, J = 6.3 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H)

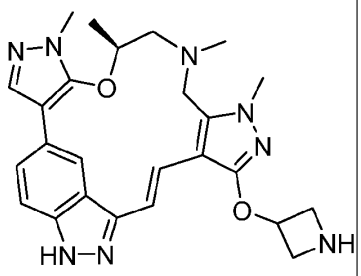
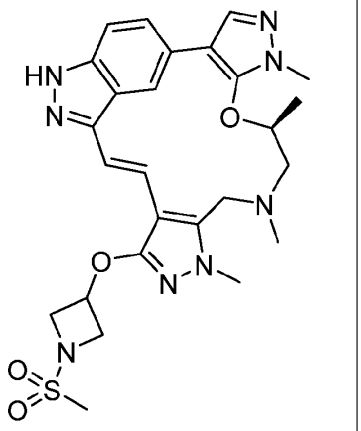
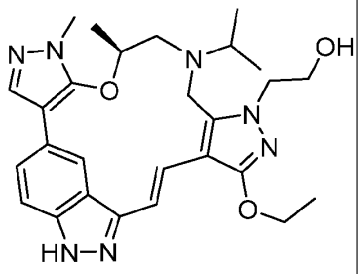
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
134		405.0	^{1}H NMR (500 MHz, DMSO-d6) δ = 13.06 (s, 1H), 8.45 (s, 1H), 8.03 (d, J = 17.5 Hz, 1H), 7.87 (s, 1H), 7.70 (dd, J = 1.4, 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 17.5 Hz, 1H), 4.81 (br t, J = 6.2 Hz, 1H), 3.99 (d, J = 13.4 Hz, 1H), 3.73 (d, J = 13.4 Hz, 1H), 3.67 (s, 3H), 2.98 - 2.91 (m, 1H), 2.80 (dd, J = 8.2, 14.5 Hz, 1H), 2.67 (s, 3H), 2.30 (s, 3H), 1.03 - 0.99 (m, 3H)
135		500.2	1H NMR (400 MHz, DMSO-d6) δ = 13.17 (s, 1H), 8.06 (s, 1H), 7.76 - 7.73 (m, 2H), 7.63 - 7.56 (m, 3H), 7.55 (s, 1H), 7.38 (dd, J = 2.4, 8.6 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 5.06 - 4.95 (m, 2H), 4.29 (t, J = 8.4 Hz, 1H), 4.19 - 4.11 (m, 1H), 4.03 (dt, J = 2.8, 5.2 Hz, 1H), 3.94 - 3.87 (m, 1H), 3.77 (s, 3H), 3.51 (t, J = 8.8 Hz, 1H), 3.44 - 3.39 (m, 1H), 2.32 (d, J = 8.0 Hz, 1H), 2.09 - 1.97 (m, 1H), 1.47 (s, 6H)
136		503.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.59 - 8.50 (m, 2H), 8.30 - 8.20 (m, 1H), 7.84 (s, 1H), 7.70 (br d, J = 8.8 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.29 - 7.21 (m, 1H), 4.00 - 3.91 (m, 1H), 3.81 (br d, J = 14.5 Hz, 1H), 3.73 (br d, J = 5.9 Hz, 6H), 3.52 - 3.40 (m, 2H), 3.00 - 2.83 (m, 2H), 2.42 (s, 3H), 2.28 - 2.17 (m, 4H), 1.12 (br d, J = 5.8 Hz, 3H)

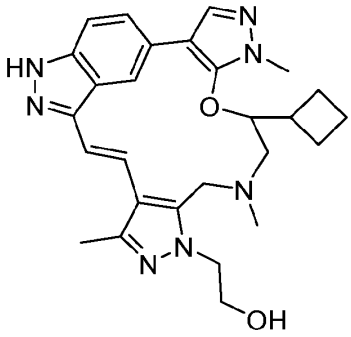
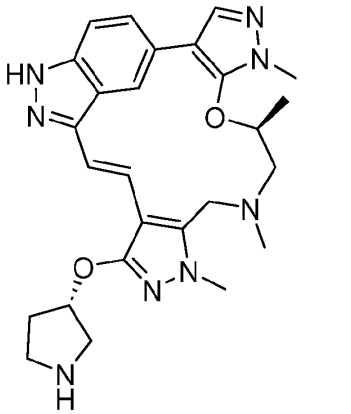
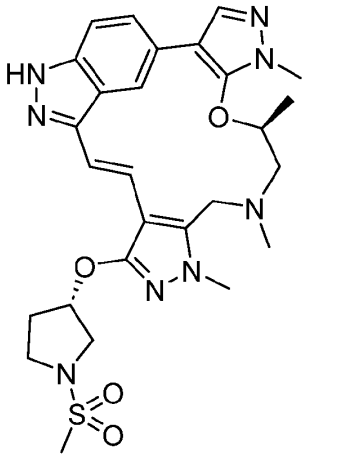
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
137		490.3	1H NMR (400 MHz, DMSO-d6) δ = 12.82 - 12.72 (m, 1H), 8.86 - 8.72 (m, 1H), 8.17 - 8.03 (m, 1H), 7.90 (s, 1H), 7.71 - 7.61 (m, 1H), 7.48 - 7.39 (m, 1H), 7.20 (s, 1H), 4.94 (br s, 1H), 4.32 - 4.24 (m, 2H), 4.06 - 3.92 (m, 4H), 3.78 (s, 3H), 3.69 - 3.57 (m, 4H), 2.85 - 2.64 (m, 2H), 1.67 - 1.52 (m, 2H), 1.41 (t, J = 7.2 Hz, 4H), 1.36 - 1.22 (m, 2H)
138		462.2	1H NMR (400 MHz, DMSO-d6) δ = 12.85 (br s, 1H), 8.36 (s, 1H), 8.21 - 8.11 (m, 1H), 7.63 - 7.44 (m, 2H), 6.87 (d, J = 16.0 Hz, 1H), 4.97 - 4.78 (m, 1H), 4.73 - 4.63 (m, 1H), 4.17 - 4.04 (m, 2H), 3.88 (s, 2H), 3.68 (br d, J = 4.0 Hz, 2H), 3.61 (s, 3H), 2.89 (br d, J = 16.0 Hz, 1H), 2.73 (br dd, J = 8.0, 14.4 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 0.95 (br d, J = 6.0 Hz, 3H)
139		589.3	1H NMR (400 MHz, DMSO-d6) δ = 13.78 - 12.78 (m, 1H), 8.05 (s, 1H), 7.77 - 7.69 (m, 1H), 7.61 - 7.54 (m, 2H), 7.53 - 7.44 (m, 2H), 7.25 - 7.09 (m, 1H), 7.07 - 6.96 (m, 1H), 6.08 - 5.91 (m, 1H), 5.76 (td, J = 7.2, 16.0 Hz, 1H), 4.82 (br d, J = 6.0 Hz, 1H), 4.27 - 4.11 (m, 2H), 4.11 - 4.04 (m, 1H), 3.91 (br d, J = 7.2 Hz, 2H), 3.87 - 3.74 (m, 6H), 3.00 - 2.92 (m, 2H), 2.87 (s, 3H), 2.22 - 2.14 (m, 1H), 2.07 (s, 2H), 2.00 - 1.93 (m, 1H)

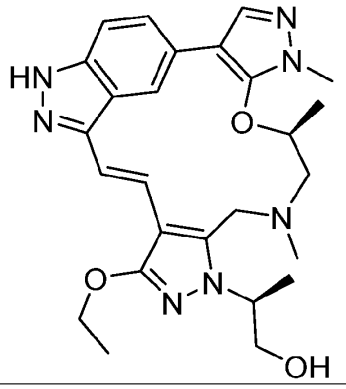
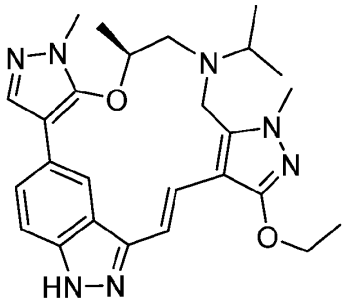
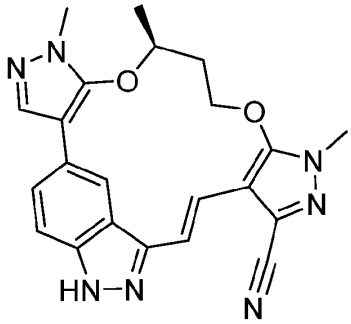
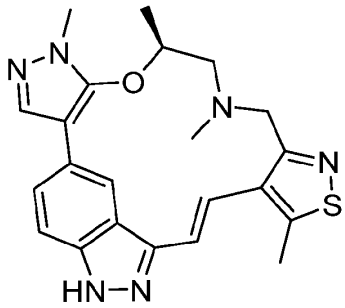
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
140		460.2	1H NMR (400 MHz, DMSO-d6) δ = 12.91 (s, 1H), 8.55 (s, 1H), 7.89 (s, 1H), 7.76 (d, J = 17.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 17.2 Hz, 1H), 4.96 - 4.81 (m, 1H), 4.68 - 4.48 (m, 2H), 4.27 - 4.21 (m, 1H), 4.17 - 4.06 (m, 2H), 3.90 - 3.83 (m, 1H), 3.73 (s, 3H), 3.70 - 3.64 (m, 4H), 3.10 - 2.99 (m, 1H), 2.91 - 2.80 (m, 1H), 2.38 (s, 3H), 1.07 - 1.03 (m, 3H)
141		405.1	1H NMR (499 MHz, DMSO-d6) δ = 13.06 (s, 1H), 8.47 (s, 1H), 8.19 (d, J = 17.5 Hz, 1H), 7.90 (s, 1H), 7.72 (dd, J = 1.4, 8.8 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 17.5 Hz, 1H), 4.74 (br t, J = 5.9 Hz, 1H), 4.15 (d, J = 15.3 Hz, 1H), 3.92 (br d, J = 15.3 Hz, 1H), 3.68 (s, 3H), 3.00 - 2.94 (m, 1H), 2.92 - 2.83 (m, 1H), 2.52 (s, 3H), 2.36 (s, 3H), 1.08 (d, J = 6.3 Hz, 3H)
142		520.3	1H NMR (400 MHz, DMSO-d6) δ = 12.77 (s, 1H), 8.47 (br s, 1H), 7.89 (br d, J = 16.0 Hz, 1H), 7.55 - 7.47 (m, 2H), 7.08 (br d, J = 16.0 Hz, 1H), 4.84 (br t, J = 6.0 Hz, 1H), 4.44 (br s, 1H), 4.28 (q, J = 8.0 Hz, 2H), 4.07 - 3.95 (m, 5H), 3.63 (s, 3H), 2.83 - 2.65 (m, 4H), 2.35 (s, 3H), 1.42 (t, J = 8.0 Hz, 3H), 0.94 (br d, J = 8.0 Hz, 3H), 0.85 (br t, J = 8.0 Hz, 6H)

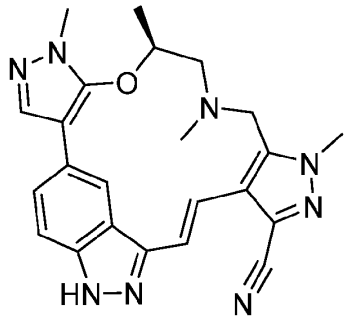
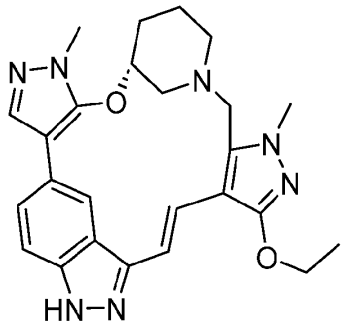
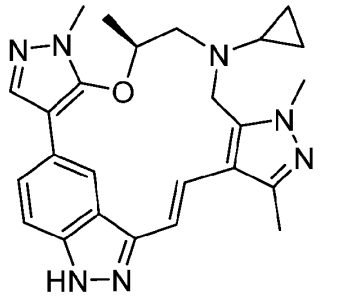
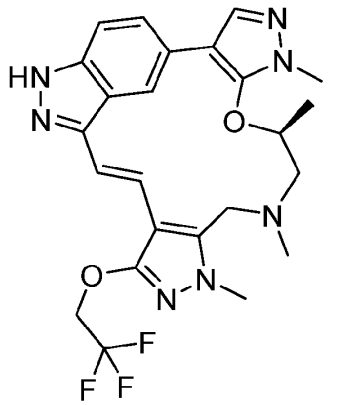
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
143		581.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 (s, 1H), 8.28 - 8.20 (m, 1H), 7.85 - 7.82 (m, 1H), 7.71 - 7.66 (m, 1H), 7.49 (d, J = 9.1 Hz, 1H), 7.29 (d, J = 17.1 Hz, 1H), 4.99 - 4.95 (m, 2H), 4.59 - 4.55 (m, 1H), 4.00 - 3.94 (m, 1H), 3.82 (br d, J = 14.5 Hz, 1H), 3.74 (d, J = 7.0 Hz, 6H), 3.47 (br dd, J = 5.6, 10.3 Hz, 2H), 3.02 - 2.90 (m, 2H), 2.88 (s, 3H), 2.44 (s, 3H), 2.07 (br s, 4H), 1.45 - 1.41 (m, 1H), 1.13 (d, J = 6.1 Hz, 3H)
144		432.2	1H NMR (400 MHz, DMSO-d6) δ = 12.86 (br s, 1H), 8.59 - 8.43 (m, 2H), 7.86 (s, 1H), 7.67 (br d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 17.6 Hz, 1H), 4.61 (br d, J = 6.0 Hz, 1H), 3.84 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.63 - 2.52 (m, 2H), 2.41 - 2.33 (m, 6H), 1.37 (br d, J = 6.4 Hz, 3H), 1.05 (br d, J = 6.0 Hz, 3H)
145		432.2	1H NMR (400 MHz, DMSO-d6) δ = 13.16 - 12.59 (m, 1H), 8.70 (s, 1H), 8.47 (br d, J = 17.6 Hz, 1H), 7.90 (s, 1H), 7.69 (br d, J = 8.4 Hz, 1H), 7.46 (br d, J = 8.4 Hz, 1H), 6.90 (br d, J = 17.6 Hz, 1H), 4.45 (br s, 1H), 3.90 - 3.82 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.28 - 3.23 (m, 1H), 2.68 (br d, J = 13.2 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 1.41 (br d, J = 6.0 Hz, 3H), 1.18 (br d, J = 6.0 Hz, 3H)

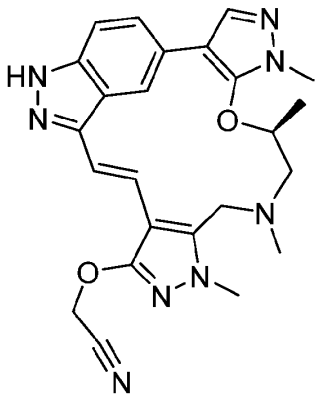
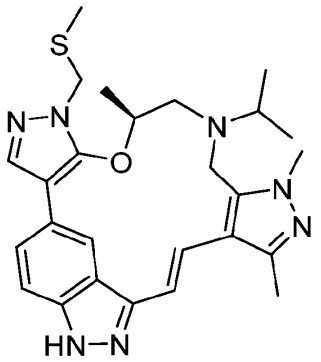
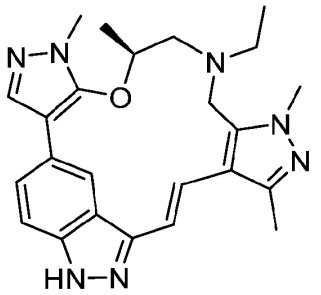
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
146		467.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.15 (s, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.71 - 7.69 (m, 1H), 7.65 (br d, J = 2.4 Hz, 1H), 7.62 (s, 1H), 7.59 - 7.55 (m, 1H), 7.49 - 7.46 (m, 1H), 7.36 - 7.31 (m, 2H), 5.17 (br d, J = 6.4 Hz, 1H), 4.27 - 4.15 (m, 2H), 4.00 (td, J = 3.2, 6.8 Hz, 1H), 3.85 (s, 3H), 3.71 - 3.65 (m, 1H), 3.61 - 3.50 (m, 2H), 2.54 (dt, J = 8.0, 14.4 Hz, 1H), 2.32 - 2.21 (m, 1H)
147		492.2	1H NMR (400 MHz, DMSO-d6) δ = 12.77 (br s, 1H), 8.49 - 8.39 (m, 1H), 8.12 (d, J = 17.1 Hz, 1H), 7.86 (s, 1H), 7.65 (dd, J = 1.1, 8.8 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 17.1 Hz, 1H), 4.95 - 4.86 (m, 1H), 4.86 - 4.79 (m, 1H), 4.74 (br dd, J = 5.5, 6.5 Hz, 1H), 4.08 - 3.96 (m, 2H), 3.96 - 3.88 (m, 1H), 3.86 - 3.77 (m, 1H), 3.67 (s, 3H), 3.65 - 3.62 (m, 2H), 3.01 - 2.89 (m, 1H), 2.80 (br dd, J = 7.0, 14.6 Hz, 1H), 2.36 - 2.31 (m, 3H), 1.38 (dd, J = 6.3, 8.0 Hz, 6H), 1.05 (d, J = 6.4 Hz, 3H)
148		420.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.52 (s, 1H), 8.12 (br d, J = 16.8 Hz, 1H), 7.80 (s, 1H), 7.67 - 7.62 (m, 1H), 7.49 - 7.44 (m, 1H), 7.31 (d, J = 16.8 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.63 - 3.58 (m, 1H), 2.96 - 2.88 (m, 2H), 2.42 (br s, 3H), 1.86 (td, J = 3.2, 6.8 Hz, 2H), 1.11 - 1.07 (m, 3H)

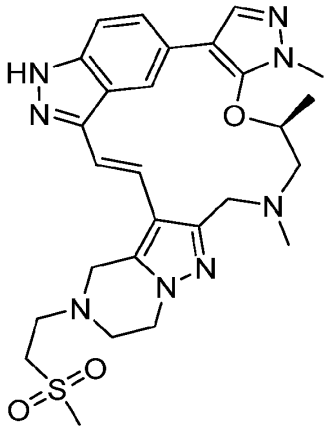
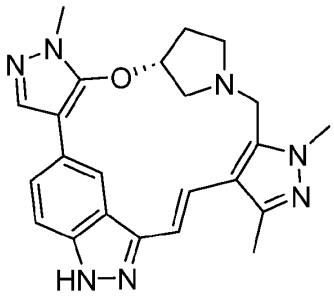
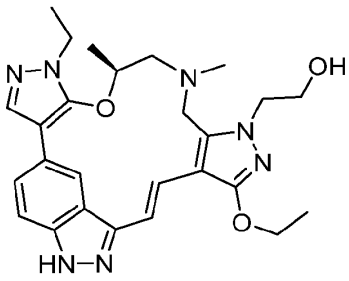
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
149		475.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.57 - 8.55 (m, 1H), 8.26 (d, J = 17.2 Hz, 1H), 7.85 (s, 1H), 7.71 (dd, J = 0.8, 8.8 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.32 - 7.25 (d, J = 17.2 Hz, 1H), 5.44 - 5.34 (m, 1H), 4.56 (br d, J = 11.6 Hz, 3H), 4.31 - 4.25 (m, 2H), 4.00 - 3.94 (m, 1H), 3.83 (br d, J = 14.4 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.01 - 2.88 (m, 2H), 2.43 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H)
150		553.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 - 8.52 (s, 1H), 8.26 - 8.18 (d, J = 12.8 Hz, 1H), 7.85 - 7.82 (s, 1H), 7.72 - 7.66 (m, 1H), 7.52 - 7.47 (m, 1H), 7.30 - 7.23 (d, J = 12.8 Hz, 1H), 5.30 - 5.22 (m, 1H), 4.91 - 4.88 (m, 1H), 4.40 - 4.33 (m, 2H), 4.12 (dd, J = 4.8, 9.6 Hz, 2H), 3.96 - 3.77 (m, 2H), 3.73 (s, 3H), 3.71 - 3.68 (m, 3H), 3.05 - 3.01 (m, 3H), 2.98 - 2.84 (m, 2H), 2.44 - 2.39 (m, 3H), 1.11 (d, J = 6.4 Hz, 3H)
151		506.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.70 (s, 1H), 8.12 - 8.04 (d, J = 16.8 Hz, 1H), 7.84 - 7.81 (m, 1H), 7.69 - 7.63 (m, 1H), 7.51 - 7.46 (m, 1H), 7.33 - 7.26 (d, J = 16.8 Hz, 1H), 4.79 - 4.72 (m, 1H), 4.57 (br s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 4.19 - 4.11 (m, 2H), 4.06 - 4.00 (m, 2H), 3.88 - 3.82 (m, 2H), 3.76 (s, 3H), 2.91 - 2.84 (m, 2H), 1.50 (t, J = 7.2 Hz, 3H), 1.15 - 1.11 (m, 3H), 1.03 (br d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H)

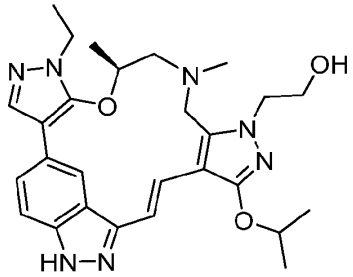
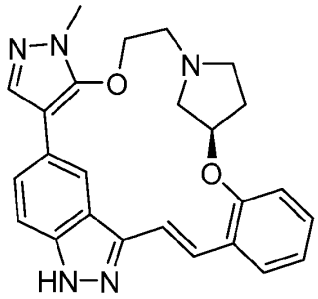
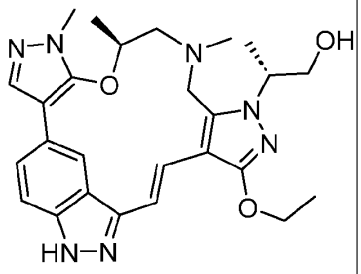
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
152		488.4	1H NMR (400 MHz, DMSO-d6) δ = 12.88 (s, 1H), 8.57 - 8.41 (m, 1H), 8.29 (br d, J = 17.6 Hz, 1H), 7.77 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 17.6 Hz, 1H), 4.86 (br s, 1H), 4.70 - 4.50 (m, 1H), 4.09 (br d, J = 4.8 Hz, 2H), 3.95 (br d, J = 14.0 Hz, 1H), 3.86 - 3.75 (m, 1H), 3.70 (s, 3H), 3.67 (br s, 2H), 2.79 - 2.68 (m, 2H), 2.40 (s, 3H), 2.26 (br s, 3H), 1.82 (br d, J = 2.4 Hz, 1H), 1.76 - 1.60 (m, 2H), 1.52 - 1.37 (m, 2H), 1.32 - 1.20 (m, 2H)
153		488.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.57 (s, 1H), 7.86 (s, 1H), 7.79 - 7.69 (m, 2H), 7.53 (d, J = 9.2 Hz, 1H), 7.33 - 7.25 (m, 1H), 5.51 (br s, 1H), 5.24 - 5.17 (m, 2H), 4.64 - 4.55 (m, 1H), 4.33 - 4.23 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.68 - 3.53 (m, 4H), 3.50 - 3.40 (m, 2H), 2.83 (s, 3H), 2.57 - 2.47 (m, 1H), 2.45 - 2.35 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H)
154		567.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 (s, 1H), 8.22 (d, J = 17.2 Hz, 1H), 7.83 (s, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 17.2 Hz, 1H), 5.36 (s, 2H), 3.98 (d, J = 14.4 Hz, 1H), 3.82 (d, J = 14.4 Hz, 1H), 3.69 - 3.67 (m, 2H), 3.49 - 3.46 (m, 1H), 3.14 - 3.11 (m, 1H), 3.02 (q, J = 7.2 Hz, 5H), 2.97 - 2.94 (m, 1H), 2.93 - 2.90 (m, 1H), 2.88 (s, 3H), 2.67 (s, 3H), 2.43 (s, 3H), 1.12 (d, J = 6.0 Hz, 3H)

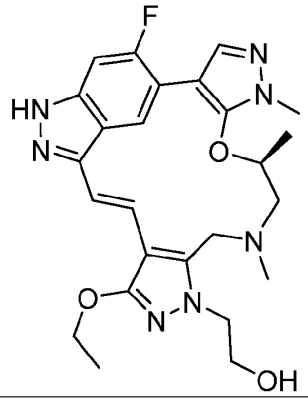
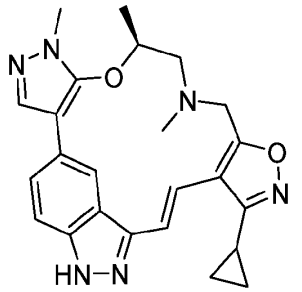
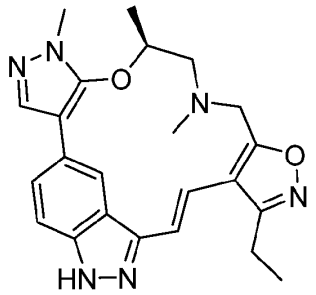
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
155		492.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.63 - 8.54 (m, 1H), 7.89 - 7.82 (m, 1H), 7.73 - 7.67 (m, 1H), 7.59 - 7.49 (m, 2H), 7.42 - 7.34 (m, 1H), 5.44 - 5.30 (m, 1H), 4.61 - 4.48 (m, 2H), 4.42 (dd, J = 1.6, 7.2 Hz, 2H), 3.85 - 3.58 (m, 8H), 3.02 (s, 3H), 1.54 - 1.45 (m, 6H), 1.19 (d, J = 6.4 Hz, 3H)
156		476.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.77 - 8.61 (m, 1H), 7.98 (d, J = 17.0 Hz, 1H), 7.83 (s, 1H), 7.69 - 7.64 (m, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.32 - 7.25 (m, 1H), 4.80 - 4.72 (m, 1H), 4.61 - 4.51 (m, 1H), 4.36 - 4.29 (m, 2H), 3.98 (s, 2H), 3.76 (d, J = 2.0 Hz, 6H), 2.89 - 2.78 (m, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.16 - 1.09 (m, 3H), 1.07 - 0.99 (m, 6H)
157		416.0	1H NMR (499 MHz, DMSO-d6) δ = 13.16 (s, 1H), 8.53 (s, 1H), 7.96 (s, 1H), 7.74 (dd, J = 1.4, 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 7.38 - 7.33 (m, 1H), 4.90 - 4.85 (m, 1H), 4.75 - 4.68 (m, 1H), 4.51 (td, J = 5.4, 10.3 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.52 (d, J = 1.9 Hz, 1H), 2.44 (d, J = 5.2 Hz, 1H), 1.30 (d, J = 6.6 Hz, 3H)
158		421.0	1H NMR (499 MHz, DMSO-d6) δ = 13.12 (s, 1H), 8.47 (s, 1H), 8.44 (d, J = 17.5 Hz, 1H), 7.85 (s, 1H), 7.68 (dd, J = 1.4, 8.8 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 17.5 Hz, 1H), 4.90 - 4.84 (m, 1H), 4.06 (d, J = 12.9 Hz, 1H), 3.75 (d, J = 12.9 Hz, 1H), 3.67 (s, 3H), 2.87 (dd, J = 2.2, 14.5 Hz, 1H), 2.78 - 2.71 (m, 4H), 2.23 (s, 3H), 0.97 (d, J = 6.3 Hz, 3H)

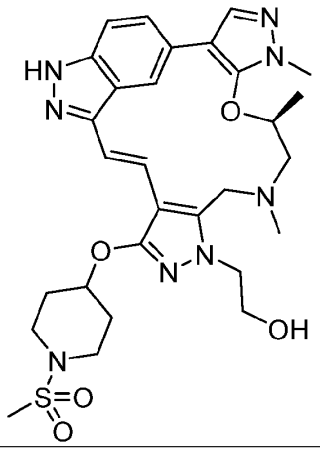
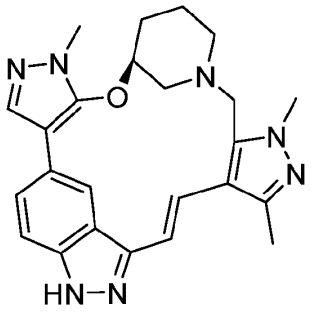
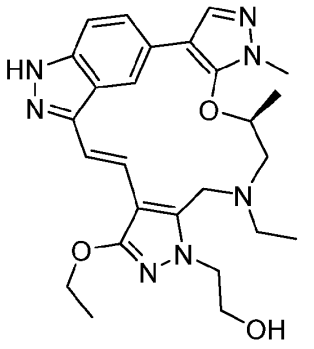
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
159		429.0	1H NMR (400 MHz, DMSO-d6) δ = 8.47 (s, 1H), 8.25 (d, J = 17.4 Hz, 1H), 7.90 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 17.6 Hz, 1H), 4.77 (br t, J = 6.1 Hz, 1H), 4.10 - 4.03 (m, 1H), 3.97 - 3.89 (m, 4H), 3.68 (s, 3H), 3.00 - 2.93 (m, 1H), 2.91 - 2.84 (m, 1H), 2.33 (s, 3H), 1.06 (d, J = 6.2 Hz, 3H
160		460.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.90 - 8.77 (m, 1H), 8.24 - 8.11 (m, 1H), 7.86 (s, 1H), 7.68 (dd, J = 1.4, 8.8 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.44 - 7.39 (m, 1H), 4.58 (s, 1H), 4.35 - 4.29 (m, 2H), 3.99 (d, J = 15.6 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.58 - 3.53 (m, 1H), 2.91 - 2.78 (m, 2H), 2.09 - 1.94 (m, 2H), 1.77 - 1.56 (m, 4H), 1.50 (t, J = 7.2 Hz, 3H)
161		444.3	1H NMR (400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.50 - 8.31 (m, 1H), 7.97 - 7.79 (m, 1H), 7.68 - 7.54 (m, 2H), 7.47 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 17.2 Hz, 1H), 4.82 - 4.64 (m, 1H), 4.09 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.19 - 3.12 (m, 2H), 2.39 (s, 3H), 2.07 (s, 2H), 0.99 (d, J = 6.4 Hz, 3H), 0.38 - 0.29 (m, 2H), 0.28 - -0.14 (m, 2H)
162		502.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 - 8.50 (s, 1H), 8.25 - 8.16 (d, J = 16.0 Hz, 1H), 7.82 (s, 1H), 7.72 - 7.65 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.25 - 7.16 (d, J = 16.0 Hz, 1H), 4.91 - 4.90 (m, 1H), 4.83 - 4.73 (m, 2H), 3.99 - 3.78 (m, 2H), 3.73 (s, 6H), 3.01 - 2.83 (m, 2H), 2.48 - 2.40 (s, 3H), 1.14 - 1.07 (m, 3H)

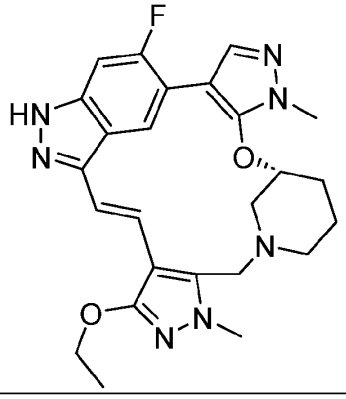
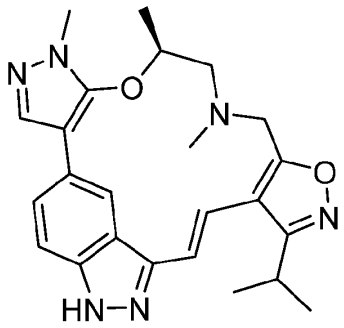
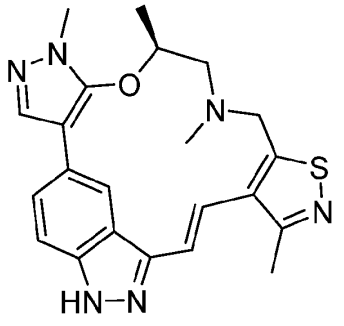
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
163		459.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 - 8.50 (m, 1H), 8.26 - 8.18 (m, 1H), 7.83 (s, 1H), 7.68 (br d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.22 - 7.15 (m, 1H), 5.15 - 5.11 (m, 2H), 4.61 - 4.56 (m, 1H), 3.99 - 3.80 (m, 2H), 3.74 (d, J = 6.4 Hz, 5H), 3.00 - 2.86 (m, 2H), 2.43 (s, 2H), 2.06 - 2.01 (m, 2H), 1.15 - 1.08 (m, 3H)
164		492.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.66 (s, 1H), 8.13 (d, J = 17.4 Hz, 1H), 7.89 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 17.5 Hz, 1H), 5.26 (br d, J = 14.0 Hz, 1H), 5.08 (br d, J = 13.6 Hz, 1H), 4.59 (s, 1H), 4.02 (s, 2H), 3.85 (s, 3H), 3.04 - 2.91 (m, 1H), 2.87 - 2.66 (m, 2H), 2.49 (s, 3H), 2.25 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.03 (br d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H)
165		432.3	1H NMR (400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.55 (s, 1H), 8.05 (d, J = 17.6 Hz, 1H), 7.86 (s, 1H), 7.71 - 7.61 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 17.6 Hz, 1H), 4.81 - 4.66 (m, 1H), 4.01 - 3.81 (m, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 3.02 - 2.80 (m, 2H), 2.60 - 2.53 (m, 2H), 2.39 (s, 3H), 1.04 (d, J = 6.4 Hz, 3H), 0.99 - 0.89 (m, 3H)

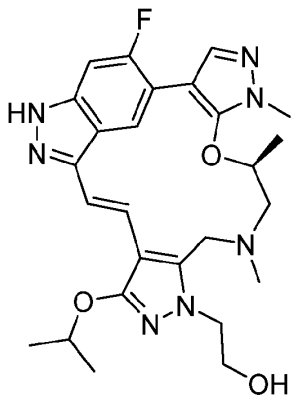
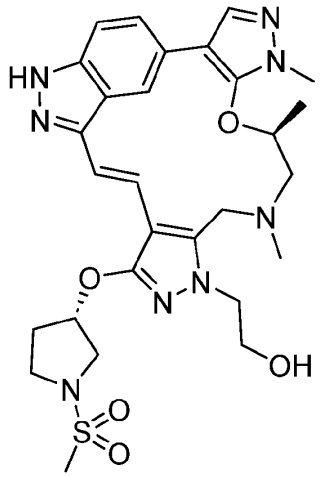
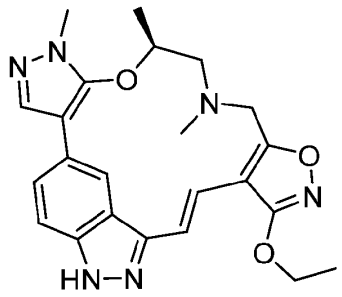
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
166		551.1	1H NMR (400 MHz, DMSO-d6) δ = 12.90 (br s, 1H), 8.46 (s, 1H), 8.20 (d, J = 17.6 Hz, 1H), 7.85 (s, 1H), 7.67 (dd, J = 1.3, 8.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 17.5 Hz, 1H), 4.78 (br t, J = 6.2 Hz, 1H), 4.12 - 4.06 (m, 2H), 4.03 (s, 1H), 3.95 (br d, J = 7.1 Hz, 1H), 3.92 (br d, J = 4.6 Hz, 1H), 3.67 (s, 3H), 3.60 (br d, J = 12.9 Hz, 1H), 3.50 (br t, J = 6.9 Hz, 2H), 3.09 (br t, J = 7.1 Hz, 3H), 3.04 (s, 3H), 2.99 - 2.94 (m, 1H), 2.94 - 2.89 (m, 1H), 2.76 (dd, J = 7.9, 14.5 Hz, 1H), 2.28 (s, 3H), 1.02 (d, J = 6.3 Hz, 3H)
167		416.3	1H NMR (400 MHz, DMSO-d6) δ = 12.02 (s, 1H), 7.85 (s, 1H), 7.42 (d, J = 17.6 Hz, 1H), 7.05 (s, 1H), 6.81 (dd, J = 1.2, 8.7 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.09 (d, J = 17.6 Hz, 1H), 4.40 (br t, J = 5.2 Hz, 1H), 3.37 (d, J = 15.2 Hz, 1H), 2.97 (s, 3H), 2.89 (s, 3H), 2.81 - 2.68 (m, 3H), 2.37 - 2.29 (m, 1H), 1.56 (s, 3H), 1.44 - 1.35 (m, 1H), 1.27 - 1.20 (m, 2H)
168		492.1	1H NMR (400 MHz, DMSO-d6) δ = 12.88 - 12.66 (m, 1H), 8.42 (s, 1H), 8.21 - 8.09 (m, 1H), 7.87 (s, 1H), 7.68 - 7.63 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 17.2 Hz, 1H), 4.83 (t, J = 5.6 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.27 (ttd, J = 3.2, 7.0, 10.4 Hz, 2H), 4.07 - 3.97 (m, 4H), 3.97 - 3.91 (m, 1H), 3.85 - 3.78 (m, 1H), 3.69 - 3.59 (m, 2H), 2.99 - 2.91 (m, 1H), 2.85 - 2.74 (m, 1H), 2.35 (s, 3H), 1.44 - 1.38 (m, 3H), 1.38 - 1.32 (m, 3H), 1.05 (d, J = 6.2 Hz, 3H)

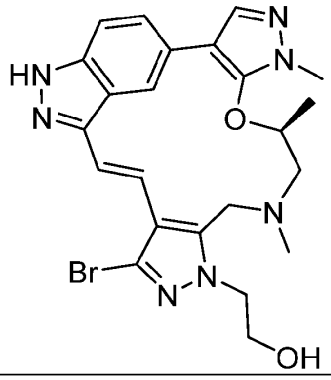
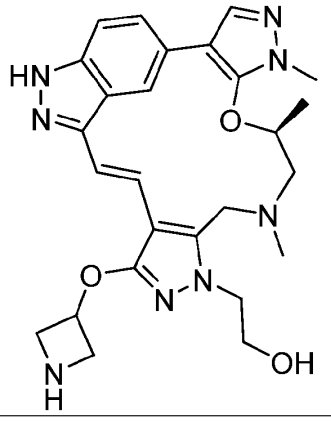
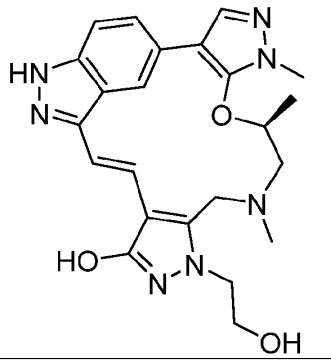
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
169		506.2	1H NMR (400 MHz, DMSO-d6) δ = 12.78 (s, 1H), 8.42 (s, 1H), 8.13 (d, J = 17.2 Hz, 1H), 7.87 (s, 1H), 7.69 - 7.58 (m, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 17.2 Hz, 1H), 4.95 - 4.87 (m, 1H), 4.84 (t, J = 5.2 Hz, 1H), 4.80 - 4.72 (m, 1H), 4.07 - 3.97 (m, 4H), 3.95 - 3.77 (m, 2H), 3.69 - 3.60 (m, 2H), 2.98 - 2.91 (m, 1H), 2.78 (dd, J = 7.6, 14.0 Hz, 1H), 2.35 (s, 3H), 1.40 (d, J = 6.0 Hz, 3H), 1.38 - 1.32 (m, 6H), 1.04 (d, J = 6.4Hz, 3H)
170		428.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.48 - 8.31 (m, 1H), 7.88 - 7.73 (m, 2H), 7.70 (s, 1H), 7.61 - 7.53 (m, 2H), 7.48 - 7.37 (m, 1H), 7.36 - 7.30 (m, 1H), 7.13 - 7.01 (m, 2H), 5.43 - 5.25 (m, 1H), 4.56 - 4.38 (m, 2H), 4.30 - 4.07 (m, 2H), 4.02 - 3.88 (m, 2H), 3.85 (s, 3H), 3.78 - 3.58 (m, 2H), 2.66 - 2.36 (m, 2H)
171		492.2	1H NMR (400 MHz, DMSO-d6) δ = 12.80 - 12.77 (m, 1H), 8.50 - 8.46 (m, 1H), 8.20 - 8.12 (d, J = 17.2 Hz, 1H), 7.89 - 7.86 (m, 1H), 7.70 - 7.65 (m, 1H), 7.49 - 7.44 (m, 1H), 7.19 - 7.13 (d, J = 17.2 Hz, 1H), 4.86 - 4.70 (m, 2H), 4.41 - 4.34 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.95 - 3.83 (m, 2H), 3.69 - 3.67 (m, 3H), 3.67 - 3.53 (m, 2H), 2.99 - 2.93 (m, 1H), 2.82 (dd, J = 7.2, 14.4 Hz, 1H), 2.35 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.10 - 1.05 (m, 3H)

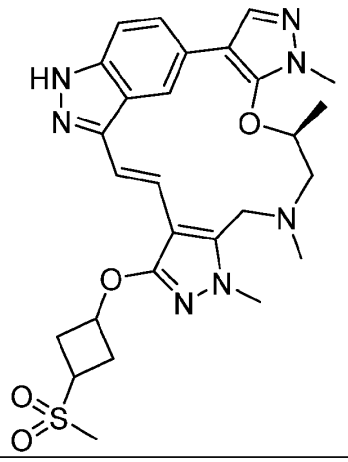
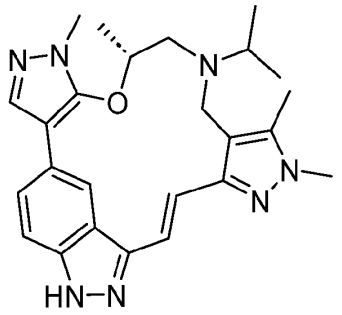
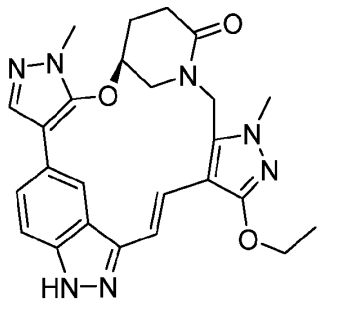
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
172		496.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.66 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 4.8 Hz, 1H), 7.74 - 7.49 (m, 1H), 7.36 (d, J = 16.4 Hz, 1H), 7.30 (d, J = 11.6 Hz, 1H), 5.32 - 5.11 (m, 1H), 4.43 - 4.36 (m, 2H), 4.22 (t, J = 5.2 Hz, 2H), 3.96 - 3.86 (m, 2H), 3.80 (s, 3H), 3.61 - 3.46 (m, 2H), 3.34 - 3.32 (m, 3H), 3.01 - 2.88 (m, 2H), 1.50 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H)
173		431.0	1H NMR (400 MHz, DMSO-d6) δ = 8.49 (s, 1H), 8.21 (d, J = 17.6 Hz, 1H), 7.91 (s, 1H), 7.72 (dd, J = 0.9, 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 17.4 Hz, 1H), 4.74 (br t, J = 5.6 Hz, 1H), 4.14 (br d, J = 15.1 Hz, 1H), 3.90 (br d, J = 15.1 Hz, 1H), 3.68 (s, 3H), 3.00 - 2.84 (m, 2H), 2.36 (s, 3H), 2.23 - 2.14 (m, 1H), 1.14 - 1.05 (m, 5H), 1.02 - 0.94 (m, 1H), 0.92 - 0.85 (m, 1H
174		418.8	H NMR (400 MHz, DMSO-d6) δ = 8.47 (s, 1H), 8.18 (d, J = 17.8 Hz, 1H), 7.90 (s, 1H), 7.75 - 7.69 (m, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 17.6 Hz, 1H), 4.74 (br t, J = 5.6 Hz, 1H), 4.16 (d, J = 15.3 Hz, 1H), 3.92 (br d, J = 15.1 Hz, 1H), 3.68 (s, 3H), 3.01 - 2.84 (m, 4H), 2.35 (s, 3H), 1.33 (t, J = 7.4 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H

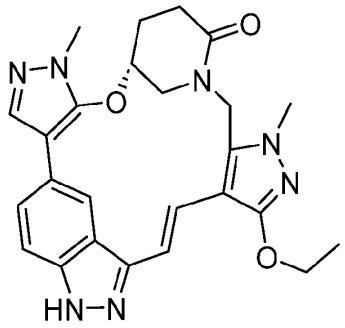
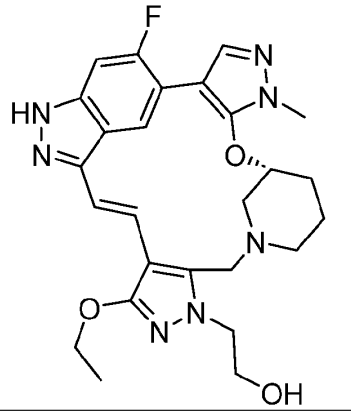
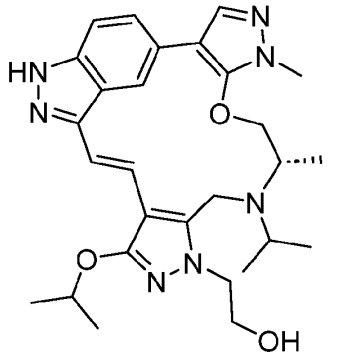
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
175		611.5	1H NMR (400 MHz, DMSO-d6) δ = 12.79 (s, 1H), 8.46 (s, 1H), 8.16 (d, J = 17.6 Hz, 1H), 7.87 (s, 1H), 7.72 - 7.59 (m, 1H), 7.52 - 7.41 (m, 1H), 7.18 (d, J = 17.2 Hz, 1H), 4.94 - 4.80 (m, 2H), 4.79 - 4.70 (m, 1H), 4.10 - 3.98 (m, 2H), 3.97 - 3.79 (m, 2H), 3.67 (s, 3H), 3.65 - 3.58 (m, 2H), 3.27 - 3.18 (m, 4H), 2.91 (s, 3H), 2.87 - 2.76 (m, 2H), 2.39 - 2.31 (m, 3H), 2.18 - 2.06 (m, 2H), 1.97 - 1.86 (m, 2H), 1.06 (br d, J = 6.4 Hz, 3H)
176		430.1	1H NMR (400 MHz, DMSO-d6) δ = 12.90 - 12.82 (m, 1H), 8.83 - 8.71 (m, 1H), 8.20 - 8.07 (m, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 17.2 Hz, 1H), 4.97 - 4.90 (m, 1H), 4.06 (d, J = 15.2 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.55 (d, J = 15.2 Hz, 1H), 2.40 (s, 3H), 2.15 - 1.93 (m, 2H), 1.88 - 1.69 (m, 2H), 1.68 - 1.56 (m, 2H), 1.41 - 1.23 (m, 2H)
177		492.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.62 (s, 1H), 7.86 (s, 1H), 7.75 - 7.67 (m, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.50 - 7.37 (m, 2H), 5.44 (br s, 1H), 5.03 - 4.89 (m, 3H), 4.62 (br d, J = 15.2 Hz, 1H), 4.47 - 4.36 (m, 2H), 4.31 - 4.14 (m, 2H), 4.06 - 3.83 (m, 4H), 3.60 (br d, J = 5.6 Hz, 1H), 3.50 (br d, J = 14.0 Hz, 1H), 3.39 (br d, J = 5.2 Hz, 1H), 1.56 - 1.46 (m, 6H), 1.21 (d, J = 6.4 Hz, 3H)

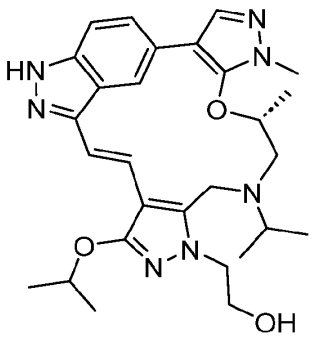
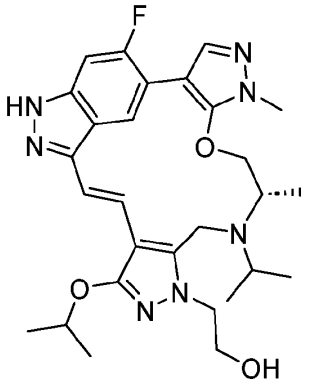
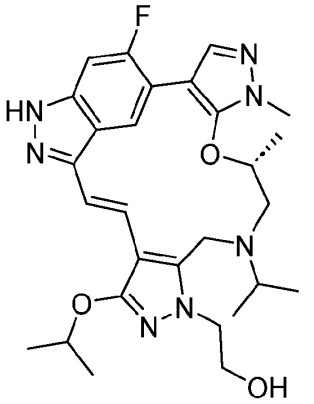
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
178		478.1	1H NMR (400 MHz, METHANOL-d4) δ = 9.01 - 8.90 (m, 1H), 8.30 - 8.19 (m, 1H), 7.88 - 7.83 (m, 1H), 7.45 - 7.37 (m, 1H), 7.23 - 7.17 (m, 1H), 4.89 - 4.88 (m, 1H), 4.32 (d, J = 7.2 Hz, 2H), 3.98 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.58 (d, J = 15.6 Hz, 1H), 2.94 - 2.75 (m, 2H), 2.11 - 1.87 (m, 2H), 1.75 - 1.55 (m, 2H), 1.50 (t, J = 7.2 Hz, 3H), 1.30 (br s, 2H)
179		433.0	1H NMR (499 MHz, DMSO-d6) δ = 13.08 (s, 1H), 8.46 (s, 1H), 8.15 (d, J = 17.8 Hz, 1H), 7.89 (s, 1H), 7.72 (dd, J = 1.4, 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 17.8 Hz, 1H), 4.73 (br t, J = 5.7 Hz, 1H), 4.15 (d, J = 15.3 Hz, 1H), 3.90 (br d, J = 15.1 Hz, 1H), 3.68 (s, 3H), 3.41 (td, J = 6.8, 13.5 Hz, 1H), 2.98 - 2.83 (m, 2H), 2.34 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H)
180		420.7	1H NMR (499 MHz, DMSO-d6) δ = 13.14 (s, 1H), 8.48 (s, 1H), 8.39 (d, J = 17.8 Hz, 1H), 7.86 (s, 1H), 7.70 (dd, J = 1.4, 8.8 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 17.5 Hz, 1H), 4.83 (br t, J = 6.3 Hz, 1H), 4.16 (d, J = 14.0 Hz, 1H), 3.86 (d, J = 13.7 Hz, 1H), 3.67 (s, 3H), 2.93 - 2.87 (m, 1H), 2.78 (dd, J = 8.5, 14.5 Hz, 1H), 2.69 (s, 3H), 2.30 (s, 3H), 1.00 (d, J = 6.3 Hz, 3H)

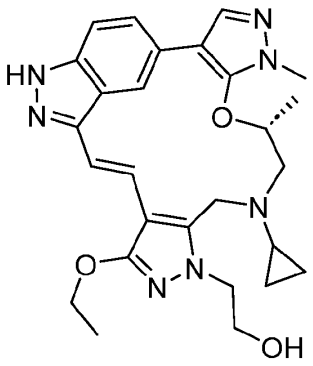
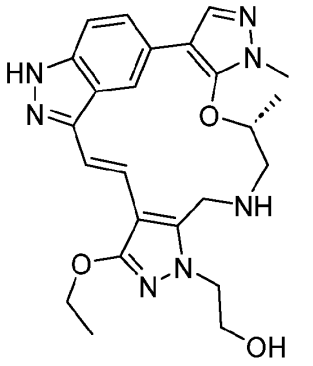
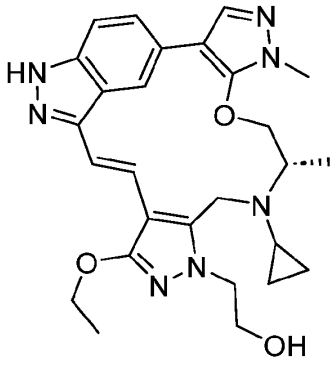
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
181		510.2	1H NMR (400 MHz, DMSO-d6) δ = 8.54 (br d, J = 6.4 Hz, 1H), 8.06 (d, J = 17.2 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.34 (d, J = 12.0 Hz, 1H), 7.12 (d, J = 17.2 Hz, 1H), 4.95 - 4.87 (m, 1H), 4.85 (br t, J = 4.0 Hz, 1H), 4.73 - 4.64 (m, 1H), 4.11 - 3.98 (m, 2H), 3.97 - 3.90 (m, 1H), 3.87 - 3.78 (m, 1H), 3.70 (s, 3H), 3.65 (br s, 2H), 2.99 (br d, J = 14.0 Hz, 1H), 2.79 (br dd, J = 6.8, 15.2 Hz, 2H), 2.30 (s, 3H), 1.38 (t, J = 6.4 Hz, 6H), 1.04 (d, J = 6.4 Hz, 3H)
182		597.5	1H NMR (400 MHz, METHANOL-d4) δ = 8.58 (s, 1H), 7.87 (s, 1H), 7.75 - 7.68 (m, 1H), 7.61 - 7.49 (m, 2H), 7.35 (d, J = 16.4 Hz, 1H), 5.45 - 5.40 (m, 1H), 5.35 (br d, J = 6.0 Hz, 1H), 4.91 - 4.89 (m, 1H), 4.55 (br d, J = 14.0 Hz, 1H), 4.26 (t, J = 4.8 Hz, 2H), 4.02 - 3.86 (m, 2H), 3.81 - 3.57 (m, 9H), 3.06 (s, 3H), 2.91 (s, 3H), 2.49 - 2.28 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H)
183		434.9	1H NMR (499 MHz, DMSO-d6) δ = 13.03 (s, 1H), 8.47 (s, 1H), 8.12 (d, J = 17.2 Hz, 1H), 7.91 (s, 1H), 7.72 (dd, J = 1.4, 8.8 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 17.2 Hz, 1H), 4.78 - 4.69 (m, 1H), 4.42 - 4.34 (m, 2H), 4.10 (br d, J = 15.6 Hz, 1H), 3.87 (br d, J = 15.3 Hz, 1H), 3.68 (s, 3H), 3.04 - 2.97 (m, 1H), 2.88 (dd, J = 6.7, 14.4 Hz, 1H), 2.40 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H), 1.09 (d, J = 6.3 Hz, 3H

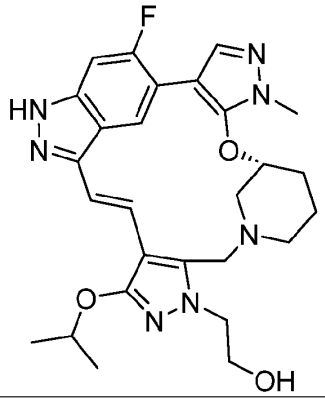
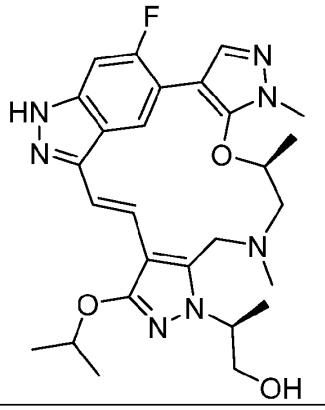
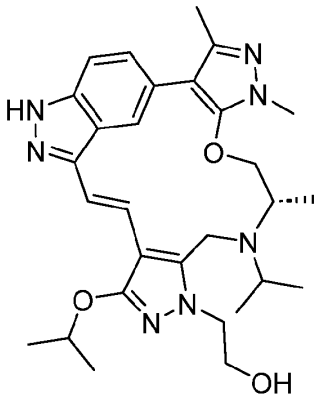
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
184		514.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.57 (s, 1H), 7.92 - 7.83 (m, 2H), 7.79 - 7.73 (m, 1H), 7.73 - 7.69 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 5.22 (br s, 1H), 4.72 - 4.60 (m, 1H), 4.45 (br d, J = 14.4 Hz, 1H), 4.35 (t, J = 5.2 Hz, 2H), 4.02 - 3.87 (m, 2H), 3.77 (s, 3H), 3.54 - 3.38 (m, 2H), 2.85 (br s, 3H), 1.15 (d, J = 6.4 Hz, 3H)
185		505.2	1H NMR (400 MHz, DMSO-d6) δ = 13.34 - 12.49 (m, 1H), 8.92 - 8.75 (m, 1H), 8.46 (br s, 1H), 7.89 (s, 1H), 7.69 (br d, J = 8.8 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.22 (br d, J = 16.8 Hz, 1H), 5.43 - 5.22 (m, 2H), 4.87 - 4.67 (m, 2H), 4.51 - 4.34 (m, 3H), 4.23 - 3.97 (m, 6H), 3.81 - 3.59 (m, 6H), 3.09 - 2.75 (m, 2H), 2.43 - 2.34 (m, 1H), 1.07 (br d, J = 6.0 Hz, 3H)
186		450.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.56 (s, 1H), 8.30 (d, J = 17.2 Hz, 1H), 7.83 (s, 1H), 7.70 - 7.63 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.37 - 7.30 (m, 1H), 4.11 - 4.03 (m, 2H), 4.01 - 3.94 (m, 1H), 3.91 - 3.86 (m, 1H), 3.81 (t, J = 5.6 Hz, 2H), 3.74 (s, 3H), 3.43 - 3.38 (m, 1H), 3.01 - 2.86 (m, 2H), 2.51 - 2.45 (m, 3H), 1.14 - 1.10 (m, 3H)

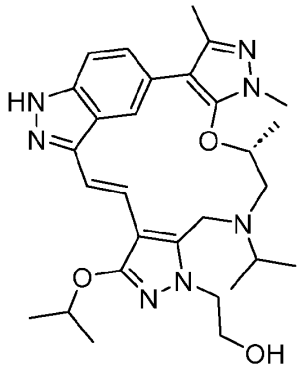
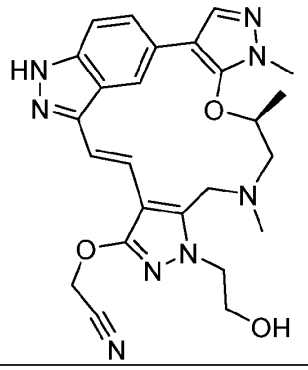
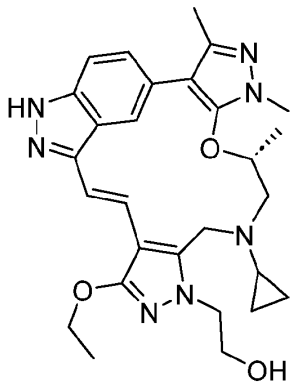
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
187		552.1	^{1}H NMR (400 MHz, MeOH-d_4) δ = 8.57 - 8.53 (m, 1H), 8.22 (br d, *J* = 16.8 Hz, 1H), 7.83 (s, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.49 (br d, *J* = 9.2 Hz, 1H), 7.31 - 7.22 (br d, *J* = 16.8 Hz, 1H), 4.62 - 4.56 (m, 2H), 3.96 (br d, *J* = 14.4 Hz, 1H), 3.83 - 3.79 (m, 1H), 3.73 (d, *J* = 10.4 Hz, 6H), 2.94 - 2.89 (m, 6H), 2.69 - 2.61 (m, 2H), 2.43 (s, 3H), 1.30 (br s, 2H), 1.17 - 1.11 (m, 3H).
188		445.26	1H NMR (400 MHz, DMSO-d6) δ = 13.31 - 12.85 (m, 1H), 8.60 (s, 1H), 7.88 (s, 1H), 7.73 - 7.66 (m, 1H), 7.54 (br d, J = 8.8 Hz, 1H), 7.48 (br d, J = 16.4 Hz, 1H), 7.34 - 7.26 (m, 1H), 5.49 (br d, J = 7.6 Hz, 1H), 4.81 - 4.71 (m, 1H), 4.33 - 4.21 (m, 1H), 3.93 - 3.85 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.14 - 3.05 (m, 1H), 2.34 (s, 3H), 1.46 (br t, J = 5.2 Hz, 6H), 1.06 (br d, J = 6.0 Hz, 3H)
189		474.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.34 (s, 1H), 7.83 - 7.74 (m, 1H), 7.66 - 7.59 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 16.4 Hz, 1H), 7.19 - 7.11 (m, 1H), 5.07 - 4.95 (m, 2H), 4.35 - 4.26 (m, 3H), 4.16 - 3.96 (m, 2H), 3.82 (d, J = 2.8 Hz, 6H), 2.54 - 2.37 (m, 2H), 2.35 - 2.22 (m, 1H), 2.22 - 2.09 (m, 1H), 1.46 (t, J = 7.2 Hz, 3H)

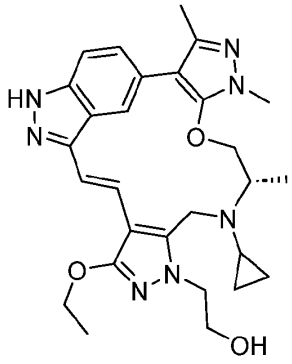
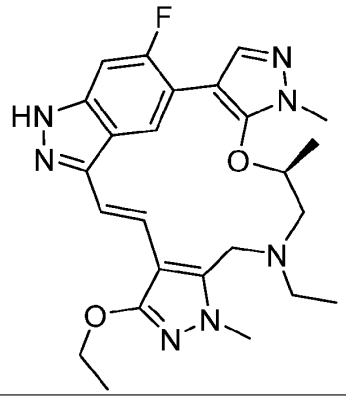
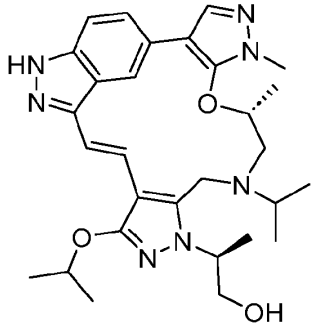
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
190		474.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.33 (s, 1H), 7.79 (s, 1H), 7.66 - 7.59 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 16.4 Hz, 1H), 7.20 - 7.08 (m, 1H), 5.07 - 4.95 (m, 2H), 4.38 - 4.25 (m, 3H), 4.15 - 3.96 (m, 2H), 3.82 (d, J = 3.6 Hz, 6H), 2.57 - 2.35 (m, 2H), 2.33 - 2.24 (m, 1H), 2.21 - 2.09 (m, 1H), 1.46 (t, J = 7.2 Hz, 3H)
191		508.1	1H NMR (400 MHz, DMSO-d6) δ = 12.80 (s, 1H), 8.99 - 8.80 (m, 1H), 8.25 - 8.06 (m, 1H), 7.86 - 7.74 (m, 1H), 7.38 - 7.20 (m, 2H), 4.91 (s, 2H), 4.28 (d, J = 7.2 Hz, 2H), 4.08 - 3.92 (m, 3H), 3.82 (s, 3H), 3.71 - 3.59 (m, 3H), 2.06 - 1.88 (m, 2H), 1.85 - 1.68 (m, 2H), 1.65 - 1.52 (m, 2H), 1.42 (t, J = 6.8 Hz, 3H), 1.24 (d, J = 1.6 Hz, 2H)
192		520.4	1H NMR (499 MHz, METHANOL-d4) δ ppm 8.65 (s, 1 H), 7.86 (s, 1 H), 7.68 (dd, J=8.76, 1.37 Hz, 1 H), 7.58 - 7.65 (m, 1 H), 7.48 (d, J=8.76 Hz, 1 H), 7.35 (d, J=16.70 Hz, 1 H), 5.00 (dt, J=12.25, 6.06 Hz, 1 H), 4.54 (br d, J=8.49 Hz, 1 H), 4.28 - 4.35 (m, 1 H), 4.10 (dt, J=14.30, 4.89 Hz, 1 H), 3.95 (s, 2 H), 3.84 - 3.94 (m, 4 H), 3.79 (s, 3 H), 3.41 (br dd, J=12.05, 5.75 Hz, 1 H), 3.11 - 3.18 (m, 1 H), 1.46 (dd, J=6.02, 1.64 Hz, 6 H), 1.42 (d, J=7.12 Hz, 3 H), 1.19 (br d, J=6.30 Hz, 3 H), 1.04 (d, J=6.84 Hz, 3 H)

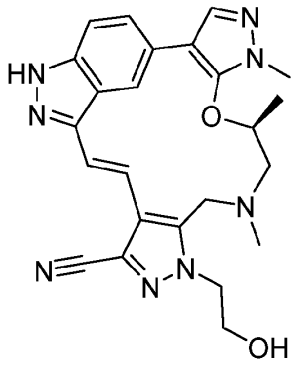
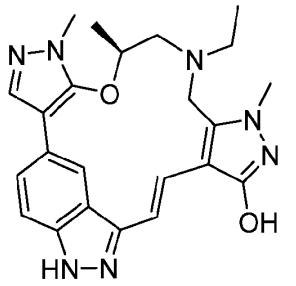
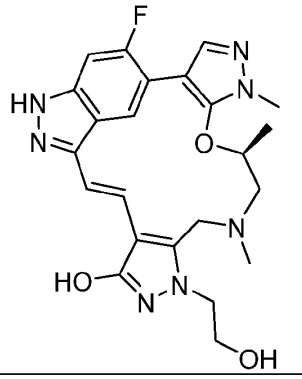
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
193		520.4	1H NMR (499 MHz, METHANOL-d4) δ ppm 8.70 (br s, 1 H), 8.07 (br d, J=16.70 Hz, 1 H), 7.83 (s, 1 H), 7.66 (dd, J=8.76, 1.37 Hz, 1 H), 7.48 (d, J=8.76 Hz, 1 H), 7.31 (d, J=16.97 Hz, 1 H), 4.99 (dt, J=12.25, 6.06 Hz, 1 H), 4.76 (br s, 1 H), 4.10 - 4.21 (m, 2 H), 3.98 - 4.08 (m, 2 H), 3.85 (t, J=5.61 Hz, 2 H), 3.76 (s, 3 H), 2.89 (td, J=13.00, 6.30 Hz, 3 H), 1.45 (dd, J=6.02, 4.38 Hz, 6 H), 1.13 (d, J=6.30 Hz, 3 H), 1.03 (d, J=6.57 Hz, 3 H), 0.99 (d, J=6.57 Hz, 3 H)
194		538.4	1H NMR (400 MHz, DMSO-d6) δ = 12.89 (s, 1H), 8.64 (br d, J = 7.2 Hz, 1H), 7.78 (d, J = 4.8 Hz, 1H), 7.52 - 7.43 (m, 1H), 7.34 (d, J = 12.4 Hz, 1H), 7.17 (d, J = 16.8 Hz, 1H), 4.96 - 4.90 (m, 1H), 4.89 (br t, J = 5.2 Hz, 1H), 4.57 (br dd, J = 2.8, 5.2 Hz, 1H), 4.21 - 4.12 (m, 1H), 4.06 - 3.98 (m, 1H), 3.94 - 3.81 (m, 3H), 3.77 (s, 3H), 3.74 - 3.68 (m, 2H), 3.25 (br s, 1H), 3.17 - 2.98 (m, 1H), 1.40 (t, J = 5.6 Hz, 6H), 1.31 (d, J = 6.8 Hz, 3H), 1.12 (br d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H)
195		538.4	1H NMR (400 MHz, DMSO-d6) δ = 12.87 (s, 1H), 8.84 - 8.60 (m, 1H), 7.87 (br d, J = 16.4 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.33 (d, J = 11.6 Hz, 1H), 7.12 (d, J = 17.2 Hz, 1H), 4.97 - 4.90 (m, 1H), 4.89 - 4.84 (m, 1H), 4.63 - 4.46 (m, 1H), 4.05 (br t, J = 5.2 Hz, 2H), 4.01 - 3.90 (m, 2H), 3.73 (s, 3H), 3.70 - 3.63 (m, 3H), 2.83 - 2.73 (m, 2H), 1.40 (dd, J = 4.0, 6.0 Hz, 6H), 1.06 (br d, J = 6.0 Hz, 3H), 0.93 (br d, J = 4.4 Hz, 6H)

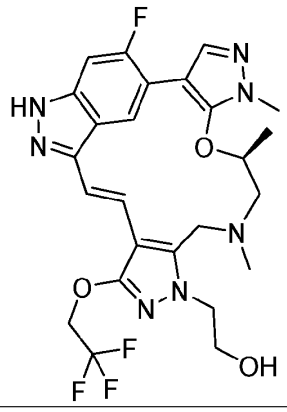
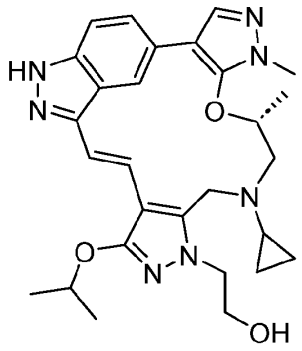
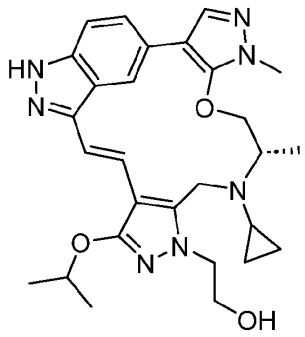
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
196		504.2	1H NMR (400 MHz, DMSO-d6) δ = 12.80 (s, 1H), 8.43 (s, 1H), 7.88 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 10.0 Hz, 1H), 7.44 (s, 1H), 7.12 (d, J = 16.8 Hz, 1H), 4.89 - 4.68 (m, 2H), 4.33 - 4.23 (m, 4H), 4.10 - 3.96 (m, 3H), 3.94 - 3.84 (m, 1H), 3.70 (d, J = 4.8 Hz, 2H), 3.68 (s, 3H), 2.10 - 2.00 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.42 - 0.28 (m, 3H), 0.12 - 0.02 (m, 1H)
197		464.2	1H NMR (400 MHz, DMSO-d6) δ = 13.11 - 12.76 (m, 1H), 8.47 (s, 1H), 7.90 (s, 1H), 7.73 - 7.62 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.46 - 7.28 (m, 1H), 7.16 (d, J = 16.4 Hz, 1H), 5.31 - 5.11 (m, 1H), 4.78 - 4.43 (m, 2H), 4.38 - 4.28 (m, 2H), 4.27 - 4.09 (m, 2H), 3.72 (s, 3H), 3.69 (t, J = 4.8 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.05 (t, J = 7.2 Hz, 2H)
198		504.1	1H NMR (400 MHz, DMSO-d6) δ = 12.82 (s, 1H), 8.49 (s, 1H), 7.88 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 16.8 Hz, 1H), 7.15 (d, J = 16.8 Hz, 1H), 4.91 - 4.83 (m, 1H), 4.64 - 4.55 (m, 1H), 4.32 - 4.25 (m, 2H), 4.22 - 4.13 (m, 1H), 4.11 - 4.04 (m, 1H), 4.03 - 3.96 (m, 2H), 3.88 - 3.80 (m, 1H), 3.74 (s, 3H), 3.72 - 3.67 (m, 2H), 2.15 - 2.08 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.27 - 1.20 (m, 1H), 0.53 - 0.11 (m, 4H)

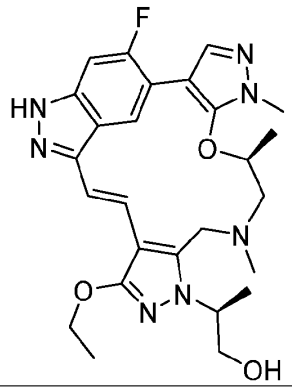
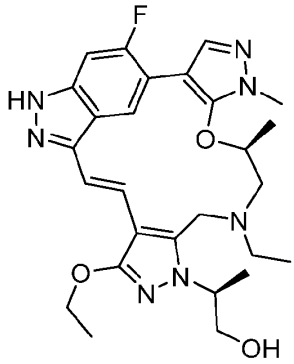
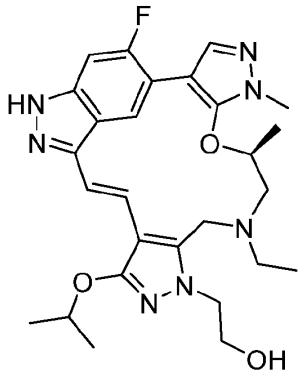
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
199		522.2	1H NMR (400 MHz, METHANOL-d4) δ = 9.04 - 8.90 (m, 1H), 8.37 - 8.14 (m, 1H), 7.92 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 17.2 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 5.02 - 4.99 (m, 1H), 4.11 - 4.04 (m, 3H), 3.88 - 3.84 (m, 5H), 3.72 (d, J = 15.2 Hz, 1H), 3.52 - 3.49 (m, 1H), 3.01 - 2.81 (m, 2H), 1.98 - 1.59 (m, 4H), 1.47 (d, J = 6.0 Hz, 6H), 1.38 - 1.31 (m, 2H)
200		524.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.63 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 4.8 Hz, 1H), 7.53 - 7.42 (m, 1H), 7.41 - 7.34 (m, 1H), 7.31 (d, J = 12.0 Hz, 1H), 5.31 (d, J = 1.6 Hz, 1H), 5.13 - 5.04 (m, 1H), 4.85 - 4.80 (m, 2H), 4.61 - 4.48 (m, 2H), 3.80 (s, 3H), 3.78 - 3.59 (m, 4H), 3.02 (s, 3H), 1.53 - 1.48 (m, 3H), 1.48 - 1.43 (m, 6H), 1.19 (d, J = 6.4 Hz, 3H)
201		533.31	1H NMR (400 MHz, DMSO-d6) δ = 12.79 (br s, 1H), 8.51 (s, 1H), 7.62 - 7.54 (m, 2H), 7.52 - 7.47 (m, 1H), 7.17 (d, J = 16.8 Hz, 1H), 4.95 - 4.88 (m, 1H), 4.40 - 4.31 (m, 1H), 4.17 - 4.07 (m, 1H), 4.05 - 3.96 (m, 1H), 3.95 - 3.84 (m, 3H), 3.72 - 3.68 (m, 2H), 3.67 (s, 3H), 3.28 - 3.20 (m, 2H), 3.00 - 2.90 (m, 1H), 2.39 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H), 1.32 (d, J = 6.8 Hz, 3H), 1.05 (br d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H)

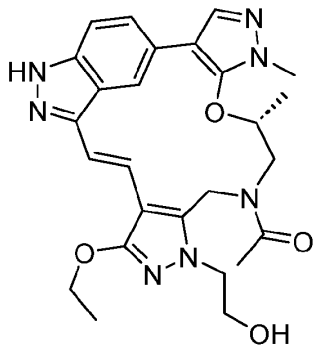
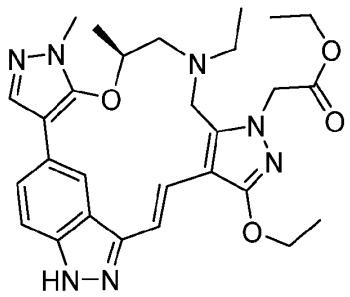
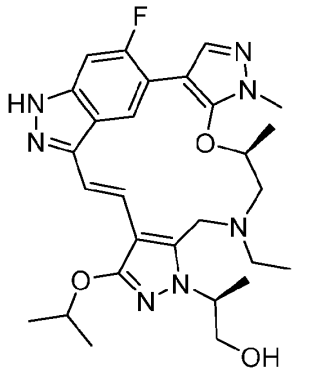
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
202		534.4	1H NMR (400 MHz, DMSO-d6) δ = 12.77 (br s, 1H), 8.46 (s, 1H), 7.87 (br d, J = 17.2 Hz, 1H), 7.55 - 7.51 (m, 1H), 7.51 - 7.47 (m, 1H), 7.09 (d, J = 17.2 Hz, 1H), 4.95 - 4.85 (m, 1H), 4.44 (br s, 1H), 4.03 (br t, J = 5.6 Hz, 2H), 3.98 (s, 2H), 3.66 (br t, J = 5.6 Hz, 2H), 3.63 (s, 3H), 2.85 - 2.62 (m, 4H), 2.34 (s, 3H), 1.41 - 1.37 (m, 6H), 0.94 (br d, J = 6.4 Hz, 3H), 0.85 (br t, J = 6.8 Hz, 6H
203		489.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.55 (s, 1H), 8.37 - 8.30 (m, 1H), 7.88 - 7.81 (m, 1H), 7.72 - 7.66 (m, 1H), 7.53 - 7.47 (m, 1H), 7.21 (d, J = 17.2 Hz, 1H), 5.18 - 5.13 (m, 2H), 4.95 - 4.92 (m, 1H), 4.23 - 4.07 (m, 2H), 4.03 - 3.92 (m, 2H), 3.91 - 3.85 (m, 2H), 3.74 (s, 3H), 3.02 - 2.86 (m, 2H), 2.50 - 2.44 (m, 3H), 1.17 - 1.07 (m, 3H)
204		518.3	1H NMR (400 MHz, DMSO-d6) δ = 12.79 (s, 1H), 8.38 (s, 1H), 7.55 - 7.48 (m, 2H), 7.47 - 7.42 (m, 1H), 7.06 (d, J = 16.8 Hz, 1H), 4.86 (br s, 1H), 4.57 - 4.50 (m, 1H), 4.32 - 4.21 (m, 3H), 4.09 - 3.95 (m, 3H), 3.73 - 3.68 (m, 2H), 3.63 (s, 3H), 3.12 - 3.06 (m, 1H), 3.05 - 2.98 (m, 1H), 2.35 (s, 3H), 2.03 - 1.98 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.31 - 0.23 (m, 2H), 0.18 (br d, J = 11.6 Hz, 1H), -0.03 (br d, J = 6.0 Hz, 1H)

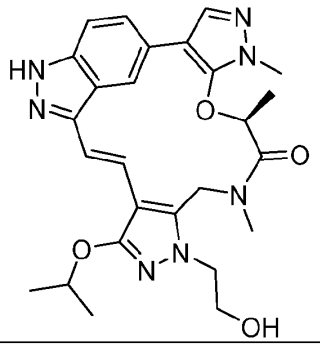
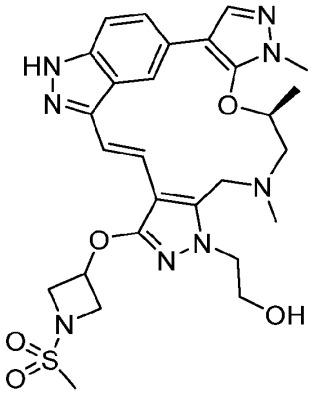
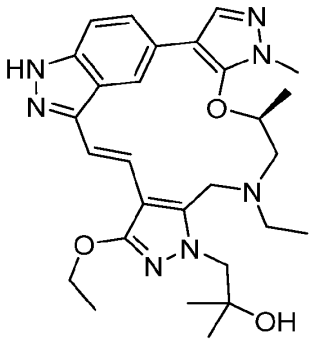
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
205		518.4	1H NMR (400 MHz, DMSO-d6) δ = 12.83 (s, 1H), 8.37 (s, 1H), 7.56 - 7.48 (m, 2H), 7.34 (d, J = 16.8 Hz, 1H), 7.12 (d, J = 16.8 Hz, 1H), 4.89 - 4.84 (m, 1H), 4.41 - 4.35 (m, 1H), 4.31 - 4.25 (m, 2H), 4.20 - 3.97 (m, 5H), 3.84 (br d, J = 14.4 Hz, 1H), 3.72 - 3.70 (m, 1H), 3.68 (s, 3H), 3.37 (br d, J = 5.6 Hz, 1H), 2.35 (s, 3H), 2.13 - 2.06 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H), 0.41 - 0.29 (m, 2H), 0.20 - 0.04 (m, 2H)
206		480.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.71 (br d, J = 7.2 Hz, 1H), 8.03 (d, J = 17.2 Hz, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.27 (s, 1H), 7.23 (d, J = 3.6 Hz, 1H), 4.37 - 4.27 (m, 2H), 4.04 - 3.90 (m, 2H), 3.78 (br s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.06 - 2.95 (m, 2H), 2.68 - 2.55 (m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H)
207		534.3	1H NMR (400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.47 (s, 1H), 7.64 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 5.80 (s, 1H), 4.99 (s, 1H), 4.95 - 4.81 (m, 2H), 4.35 - 4.29 (m, 1H), 3.88 - 3.76 (m, 3H), 3.65 (s, 3H), 3.10 - 2.99 (m, 1H), 2.82 (dd, J = 5.2, 15.2 Hz, 1H), 2.65 - 2.55 (m, 2H), 1.32 (d, J = 6.4 Hz, 6H), 1.19 (d, J = 5.6 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H), 0.92 - 0.86 (m, 3H), 0.51 - 0.21 (m, 3H)

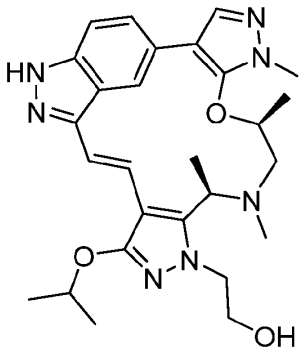
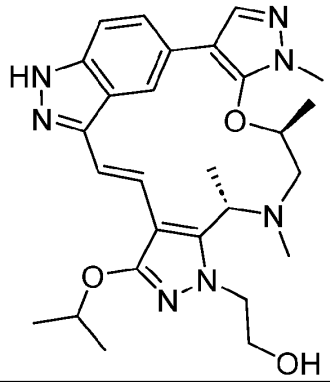
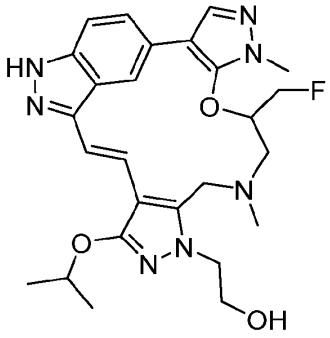
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
208		459.3	1H NMR (400 MHz, DMSO-d6) δ = 13.23 - 13.01 (m, 1H), 8.47 (s, 1H), 8.33 (br d, J = 17.2 Hz, 1H), 7.90 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 17.6 Hz, 1H), 4.85 - 4.72 (m, 1H), 4.31 (br d, J = 3.6 Hz, 2H), 4.04 (br d, J = 14.4 Hz, 3H), 3.74 (br d, J = 4.4 Hz, 2H), 3.68 (s, 3H), 3.02 - 2.80 (m, 2H), 2.34 (br s, 3H), 1.06 (br d, J = 6.4 Hz, 3H)
209		434.1	1H NMR (400 MHz, DMSO-d6) δ = 12.82 - 12.67 (m, 1H), 10.33 (d, J = 4.4 Hz, 1H), 8.56 (s, 1H), 7.97 - 7.85 (m, 2H), 7.69 - 7.61 (m, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.22 - 7.09 (m, 1H), 4.80 - 4.69 (m, 1H), 3.97 - 3.89 (m, 1H), 3.84 - 3.78 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 2.95 - 2.90 (m, 2H), 2.63 - 2.59 (m, 2H), 1.08 (d, J = 6.0 Hz, 3H), 0.99 - 0.92 (m, 3H)
210		468.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.68 - 8.63 (m, 1H), 8.18 - 8.09 (m, 1H), 7.87 - 7.83 (m, 1H), 7.28 (s, 1H), 7.27 - 7.23 (m, 1H), 4.82 - 4.73 (m, 1H), 4.38 - 4.33 (m, 2H), 4.01 - 3.95 (m, 3H), 3.77 - 3.75 (m, 3H), 3.70 (s, 1H), 3.06 - 2.98 (m, 1H), 2.90 - 2.82 (m, 1H), 2.41 - 2.36 (m, 3H), 1.16 - 1.11 (m, 3H)

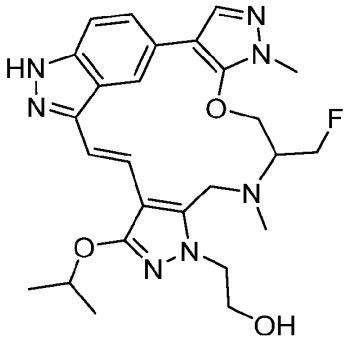
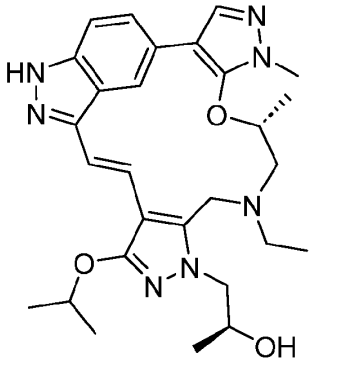
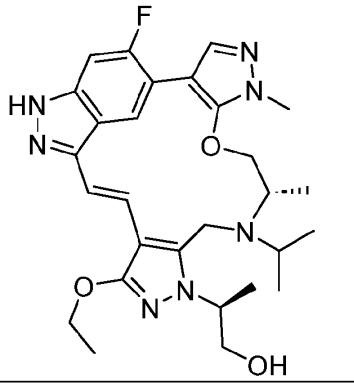
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
211		550.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.68 (br d, J = 7.2 Hz, 1H), 8.52 (br s, 1H), 8.17 (d, J = 17.2 Hz, 1H), 7.86 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 11.6 Hz, 1H), 7.29 (d, J = 17.2 Hz, 1H), 5.15 - 5.07 (m, 2H), 4.59 (s, 2H), 4.38 - 4.33 (m, 2H), 4.02 - 3.95 (m, 3H), 3.77 (s, 3H), 3.05 - 2.99 (m, 1H), 2.89 - 2.81 (m, 1H), 2.38 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H)
212		518.1	1H NMR (400 MHz, DMSO-d6) δ = 12.80 (s, 1H), 8.43 (s, 1H), 7.87 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.12 (d, J = 16.8 Hz, 1H), 4.96 - 4.89 (m, 1H), 4.85 (t, J = 5.2 Hz, 1H), 4.77 - 4.69 (m, 1H), 4.31 - 4.22 (m, 1H), 4.08 - 3.99 (m, 2H), 3.94 - 3.84 (m, 1H), 3.72 - 3.68 (m, 2H), 3.68 (s, 3H), 3.19 - 3.12 (m, 1H), 3.06 - 2.97 (m, 1H), 1.39 (t, J = 6.0 Hz, 6H), 1.02 (d, J = 6.4 Hz, 3H), 0.41 - 0.27 (m, 3H), 0.13 - 0.02 (m, 1H)
213		518.2	1H NMR (400 MHz, DMSO-d6) δ = 12.83 (s, 1H), 8.49 (s, 1H), 7.89 (s, 1H), 7.70 - 7.63 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 16.4 Hz, 1H), 7.22 - 7.12 (m, 1H), 4.98 - 4.91 (m, 1H), 4.90 - 4.87 (m, 1H), 4.70 - 4.49 (m, 1H), 4.24 - 4.13 (m, 1H), 4.12 - 3.91 (m, 4H), 3.75 (s, 3H), 3.72 - 3.68 (m, 2H), 2.16 - 2.08 (m, 2H), 1.39 (dd, J = 4.4, 6.0 Hz, 6H), 1.33 (br d, J = 6.8 Hz, 3H), 0.53 - 0.29 (m, 4H)

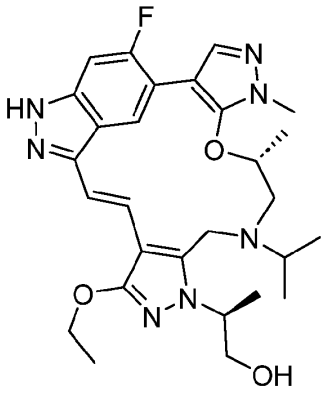
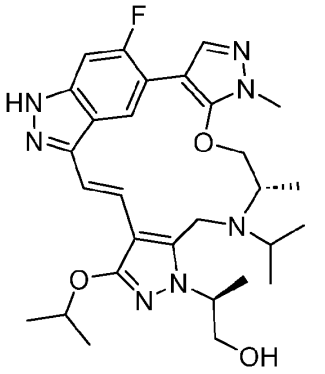
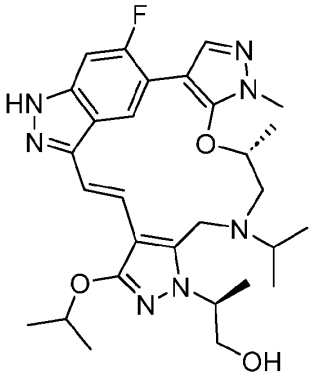
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
214		510.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.63 (d, J = 7.4 Hz, 1H), 7.91 - 7.83 (m, 1H), 7.68 - 7.51 (m, 1H), 7.40 - 7.26 (m, 2H), 5.34 - 5.14 (m, 1H), 5.02 (t, J = 5.1 Hz, 1H), 4.84 - 4.61 (m, 1H), 4.56 - 4.49 (m, 1H), 4.45 - 4.38 (m, 2H), 3.80 (s, 3H), 3.73 - 3.67 (m, 1H), 3.55 (br t, J = 6.4 Hz, 1H), 2.92 (br s, 2H), 1.53 - 1.45 (m, 6H), 1.19 - 1.17 (m, 6H)
215		524.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.74 - 8.68 (m, 1H), 8.06 (d, J = 17.0 Hz, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.29 - 7.25 (m, 1H), 7.23 (s, 1H), 4.78 - 4.72 (m, 1H), 4.50 (br dd, J = 7.1, 12.0 Hz, 1H), 4.39 - 4.33 (m, 2H), 4.00 (s, 2H), 3.87 - 3.80 (m, 1H), 3.77 (s, 3H), 3.68 (dd, J = 4.7, 11.3 Hz, 1H), 3.08 - 3.02 (m, 1H), 2.96 - 2.91 (m, 1H), 2.71 - 2.61 (m, 2H), 1.48 (t, J = 7.1 Hz, 3H), 1.42 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H)
216		524.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.82 - 8.67 (m, 1H), 8.20 - 8.06 (m, 1H), 7.90 - 7.81 (m, 1H), 7.36 - 7.19 (m, 2H), 4.62 (br s, 2H), 4.15 (br dd, J = 6.1, 11.7 Hz, 2H), 4.01 (br s, 2H), 3.86 - 3.82 (m, 2H), 3.77 (s, 3H), 3.04 - 2.96 (m, 2H), 2.69 - 2.61 (m, 2H), 1.51 - 1.43 (m, 6H), 1.12 (br d, J = 6.1 Hz, 3H), 1.04 - 0.96 (m, 3H)

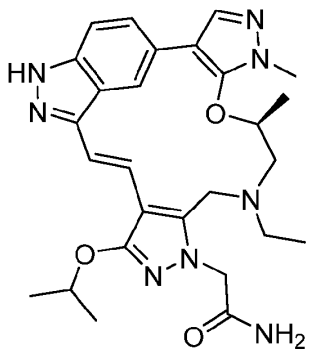
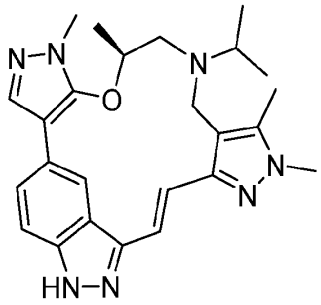
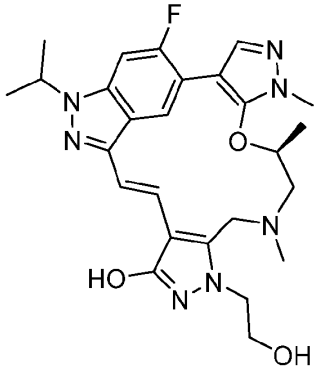
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
217		506.3	1H NMR (499 MHz, DMSO-d6) δ ppm 12.74 - 13.11 (m, 1 H) 8.44 - 8.61 (m, 1 H) 7.98 (s, 1 H) 7.70 (d, J=9.03 Hz, 1 H) 7.46 - 7.50 (m, 1 H) 7.38 - 7.45 (m, 1 H) 7.22 - 7.29 (m, 1 H) 5.24 - 5.40 (m, 1 H) 5.23 - 5.39 (m, 1 H) 5.12 - 5.23 (m, 1 H) 5.12 - 5.21 (m, 1 H) 4.26 - 4.36 (m, 3 H) 4.19 - 4.25 (m, 1 H) 4.01 - 4.02 (m, 1 H) 4.00 - 4.09 (m, 1 H) 3.73 (br s, 10 H) 2.22 (s, 3 H) 1.42 (t, J=7.12 Hz, 3 H) 1.19 - 1.29 (m, 3 H) 1.09 - 1.18 (m, 3 H)
218		534.3	1H NMR (400 MHz, DMSO-d6) δ = 12.86 - 12.81 (m, 1H), 8.60 - 8.54 (m, 1H), 8.10 - 8.03 (m, 1H), 7.88 (s, 1H), 7.70 - 7.63 (m, 1H), 7.49 - 7.44 (m, 1H), 7.23 - 7.14 (m, 1H), 4.95 (s, 2H), 4.76 - 4.68 (m, 1H), 4.29 - 4.22 (m, 2H), 4.18 - 4.12 (m, 2H), 3.94 - 3.80 (m, 2H), 3.68 (s, 2H), 2.95 - 2.88 (m, 2H), 2.71 - 2.61 (m, 3H), 1.41 (s, 3H), 1.22 (s, 3H), 1.10 - 1.05 (m, 3H), 0.93 (s, 3H)
219		538.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.69 (br d, J = 7.2 Hz, 1H), 8.03 (d, J = 16.8 Hz, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.27 (d, J = 11.0 Hz, 1H), 7.23 (d, J = 6.0 Hz, 1H), 5.05 - 4.98 (m, 1H), 4.59 (s, 1H), 4.53 - 4.43 (m, 1H), 3.99 (s, 2H), 3.78 - 3.76 (m, 3H), 3.71 - 3.66 (m, 1H), 3.08 - 3.00 (m, 1H), 2.95 - 2.87 (m, 1H), 2.71 - 2.58 (m, 2H), 2.03 (s, 2H), 1.46 - 1.40 (m, 9H), 1.10 (d, J = 6.4 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H)

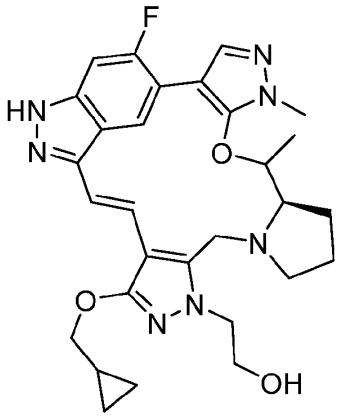
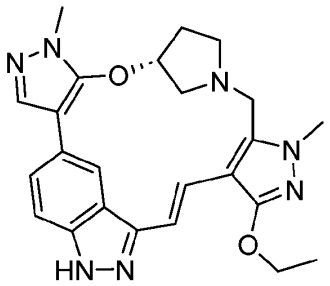
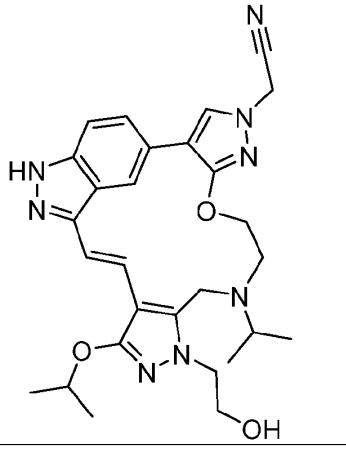
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
220		506.2	1H NMR (400 MHz, DMSO-d6) δ = 12.91 (s, 1H), 8.03 - 7.82 (m, 2H), 7.67 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.34 - 7.17 (m, 1H), 6.92 (d, J = 16.8 Hz, 1H), 5.01 - 4.83 (m, 2H), 4.06 (s, 2H), 3.76 (s, 3H), 3.69 (s, 2H), 3.33 - 3.32 (m, 3H), 3.08 (s, 2H), 1.44 (s, 3H), 1.41 - 1.36 (m, 6H)
221		583.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.60 - 8.51 (m, 1H), 8.40 - 8.23 (m, 1H), 7.93 - 7.77 (m, 1H), 7.75 - 7.64 (m, 1H), 7.50 (br dd, J = 4.0, 8.7 Hz, 1H), 7.36 - 7.23 (m, 1H), 5.40 - 5.20 (m, 1H), 4.66 - 4.53 (m, 1H), 4.37 (br d, J = 4.0 Hz, 2H), 4.20 - 4.04 (m, 4H), 4.01 - 3.88 (m, 2H), 3.87 - 3.79 (m, 2H), 3.78 - 3.68 (m, 3H), 3.07 - 2.99 (m, 3H), 2.98 - 2.84 (m, 2H), 2.45 (br d, J = 4.0 Hz, 3H), 1.21 - 1.03 (m, 3H)
222		520.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.67 - 8.63 (m, 1H), 8.23 (d, J = 17.0 Hz, 1H), 7.84 (s, 1H), 7.67 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 17.0 Hz, 1H), 4.96 - 4.90 (m, 6H), 4.36 - 4.29 (m, 2H), 3.92 (s, 3H), 3.76 (d, J = 10.9 Hz, 6H), 3.08 - 3.00 (m, 1H), 2.94 - 2.87 (m, 1H), 2.77 - 2.67 (m, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H)

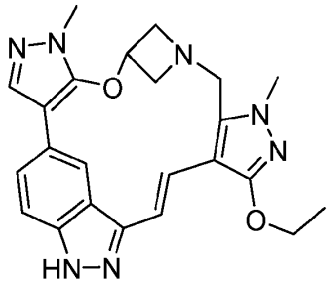
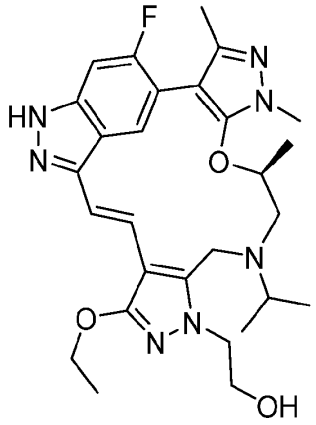
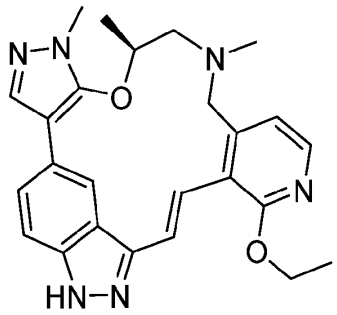
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
223		506.4	1H NMR (400 MHz, DMSO-d6) δ = 12.76 (s, 1H), 8.69 (s, 1H), 8.35 (d, J = 17.2 Hz, 1H), 7.89 (s, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.50 - 7.39 (m, 1H), 7.24 - 7.08 (m, 1H), 4.82 (s, 2H), 4.51 - 4.36 (m, 1H), 4.09 (s, 2H), 3.92 - 3.84 (m, 1H), 3.70 (s, 3H), 3.25 - 3.15 (m, 3H), 2.77 - 2.69 (m, 1H), 2.35 (s, 3H), 1.43 (d, J = 6.4 Hz, 3H), 1.39 (t, J = 6.4 Hz, 6H), 1.20 (d, J = 6.4 Hz, 3H)
224		506.2	1H NMR (400 MHz, DMSO-d6) δ = 12.78 (s, 1H), 8.61 - 8.41 (m, 1H), 8.31 (d, J = 17.2 Hz, 1H), 7.86 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 17.2 Hz, 1H), 4.95 - 4.82 (m, 2H), 4.66 - 4.54 (m, 1H), 4.14 - 3.92 (m, 2H), 3.89 - 3.81 (m, 1H), 3.67 (s, 3H), 2.56 (d, J = 7.6 Hz, 4H), 2.41 (s, 3H), 1.44 - 1.34 (m, 9H), 1.06 (d, J = 6.4 Hz, 3H)
225		510.2	1H NMR (400 MHz, DMSO-d6) δ = 12.81 (s, 1H), 8.32 (s, 1H), 8.09 (d, J = 17.2 Hz, 1H), 7.87 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 17.2 Hz, 1H), 4.94 - 4.87 (m, 1H), 4.84 (t, J = 5.6 Hz, 1H), 4.54 - 4.29 (m, 2H), 4.08 - 3.98 (m, 2H), 3.96 - 3.83 (m, 2H), 3.72 - 3.68 (m, 3H), 3.67 - 3.62 (m, 2H), 3.10 - 2.99 (m, 2H), 2.33 (s, 3H), 1.41 - 1.36 (m, 6H)

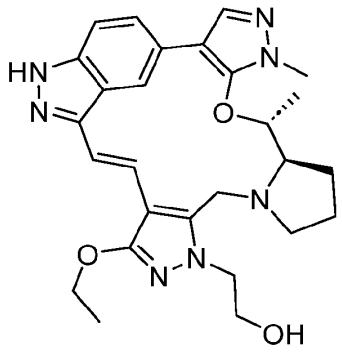
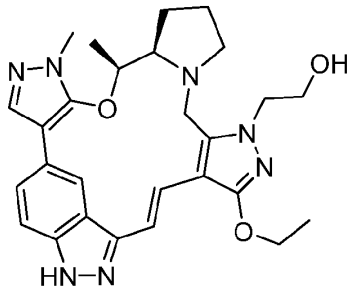
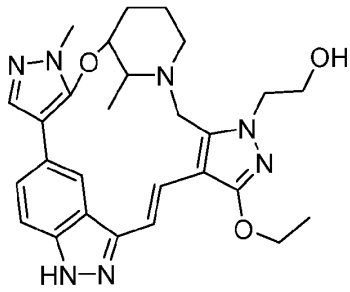
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
226		510.1	1H NMR (400 MHz, DMSO-d6) δ = 12.83 (s, 1H), 8.44 (s, 1H), 7.92 (s, 1H), 7.76 (d, J = 16.8 Hz, 1H), 7.72 - 7.64 (m, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 16.8 Hz, 1H), 5.16 - 4.75 (m, 5H), 4.40 - 4.32 (m, 2H), 4.17 (d, J = 14.8 Hz, 1H), 4.06 - 3.99 (m, 2H), 3.95 (d, J = 14.8 Hz, 1H), 3.72 (s, 3H), 3.68 (t, J = 5.6 Hz, 2H), 2.43 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H)
227		520.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.64 (br s, 1H), 7.87 (s, 1H), 7.71 (br d, J = 8.4 Hz, 1H), 7.54 (br d, J = 8.8 Hz, 1H), 7.51 - 7.44 (m, 2H), 5.46 - 5.38 (m, 1H), 5.13 - 5.03 (m, 1H), 4.71 - 4.60 (m, 2H), 4.40 - 4.28 (m, 1H), 4.12 - 4.05 (m, 2H), 4.00 - 3.87 (m, 2H), 3.79 (s, 3H), 3.50 (br d, J = 14.8 Hz, 2H), 1.53 (br d, J = 6.4 Hz, 3H), 1.47 (br t, J = 6.4 Hz, 6H), 1.21 (br d, J = 6.4 Hz, 6H)
228		538.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.77 (d, J = 7.2 Hz, 1H), 7.94 - 7.84 (m, 1H), 7.70 - 7.49 (m, 1H), 7.44 - 7.12 (m, 2H), 4.65 - 4.54 (m, 6H), 4.41 - 4.35 (m, 2H), 4.13 - 4.07 (m, 1H), 3.97 - 3.94 (m, 2H), 3.94 - 3.90 (m, 1H), 3.90 - 3.85 (m, 1H), 3.82 (s, 3H), 3.67 - 3.65 (m, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.42 (dd, J = 2.4, 6.8 Hz, 6H), 1.04 (d, J = 5.6 Hz, 3H)

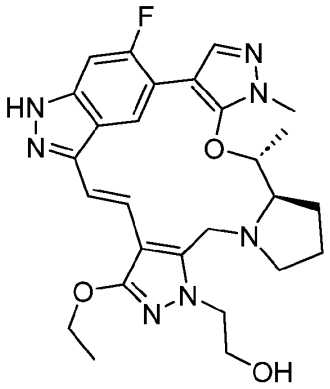
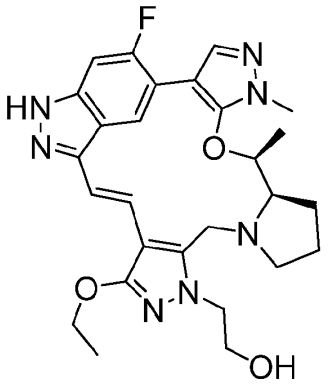
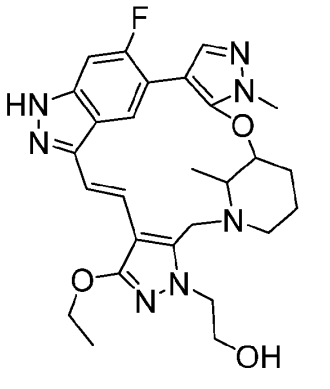
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
229		538.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.66 (br d, J = 7.2 Hz, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.42 - 7.35 (m, 1H), 7.31 (d, J = 11.6 Hz, 1H), 5.46 - 5.25 (m, 1H), 4.77 - 4.73 (m, 1H), 4.60 (br d, J = 14.8 Hz, 2H), 4.48 - 4.33 (m, 4H), 4.27 - 4.15 (m, 1H), 3.84 (br d, J = 3.2 Hz, 1H), 3.79 (s, 3H), 3.29 - 3.22 (m, 1H), 1.49 (br t, J = 7.2 Hz, 9H), 1.30 (br d, J = 6.0 Hz, 3H), 1.20 (br d, J = 6.0 Hz, 3H)
230		552.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.76 (br d, J = 7.6 Hz, 1H), 7.87 (br d, J = 4.4 Hz, 1H), 7.57 - 7.46 (m, 1H), 7.41 - 7.31 (m, 1H), 7.26 (br d, J = 12.0 Hz, 1H), 5.11 - 5.00 (m, 1H), 4.65 - 4.44 (m, 2H), 4.16 - 4.05 (m, 1H), 3.99 - 3.92 (m, 1H), 3.83 (s, 3H), 3.73 (br t, J = 6.0 Hz, 3H), 3.70 - 3.65 (m, 1H), 3.23 - 3.11 (m, 1H), 1.45 (br dd, J = 6.4, 8.0 Hz, 12H), 1.35 - 1.25 (m, 6H)
231		552.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.66 (br d, J = 7.2 Hz, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.66 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 7.31 (d, J = 11.6 Hz, 1H), 5.57 - 5.32 (m, 1H), 5.13 - 5.04 (m, 1H), 4.81 - 4.70 (m, 1H), 4.65 - 4.53 (m, 1H), 4.46 - 4.30 (m, 2H), 4.26 - 4.12 (m, 1H), 3.85 - 3.81 (m, 1H), 3.79 (s, 3H), 3.76 - 3.70 (m, 1H), 3.28 - 3.21 (m, 1H), 1.45 (dd, J = 6.0, 9.6 Hz, 12H), 1.30 (br d, J = 5.6 Hz, 3H), 1.19 (br d, J = 6.0 Hz, 3H

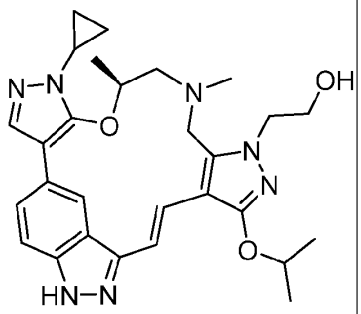
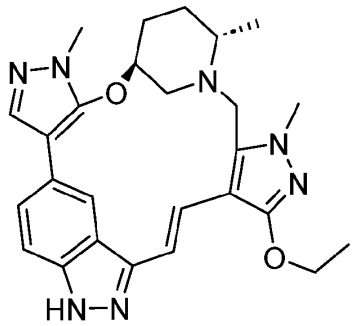
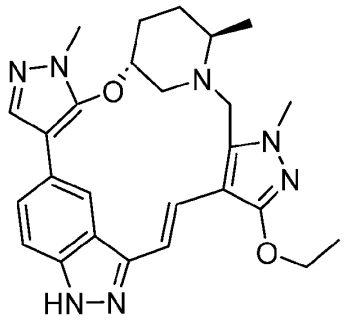
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
232		519.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.65 (br s, 1H), 8.19 (br d, J = 16.8 Hz, 1H), 7.83 (s, 1H), 7.68 (br d, J = 8.8 Hz, 1H), 7.49 (br d, J = 8.4 Hz, 1H), 7.38 - 7.32 (m, 1H), 5.05 - 4.97 (m, 1H), 4.78 - 4.75 (m, 2H), 4.63 - 4.56 (m, 1H), 3.93 (s, 2H), 3.74 (s, 3H), 3.08 - 3.00 (m, 1H), 2.94 - 2.86 (m, 1H), 2.80 - 2.68 (m, 2H), 1.45 (br t, J = 5.2 Hz, 6H), 1.13 (br d, J = 6.0 Hz, 3H), 1.01 (br t, J = 6.8 Hz, 3H)
233		446.1	1H NMR (400 MHz, DMSO-d6) δ = 13.22 - 12.90 (m, 1H), 8.60 (s, 1H), 7.91 - 7.85 (m, 1H), 7.69 (br d, J = 8.8 Hz, 1H), 7.55 (br d, J = 8.8 Hz, 1H), 7.48 (br d, J = 16.6 Hz, 1H), 7.34 - 7.25 (m, 1H), 5.58 - 5.39 (m, 1H), 4.77 (br d, J = 15.2 Hz, 1H), 4.33 - 4.21 (m, 1H), 3.94 - 3.86 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.15 - 3.03 (m, 1H), 2.35 (s, 3H), 1.50 - 1.41 (m, 6H), 1.06 (br d, J = 6.0 Hz, 3H)
234		510.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.65 (br d, J = 7.2 Hz, 1H), 8.10 (d, J = 17.2 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 12.4 Hz, 1H), 7.33 (d, J = 17.2 Hz, 1H), 4.85 - 4.81 (m, 1H), 4.81 - 4.76 (m, 1H), 4.38 - 4.33 (m, 2H), 4.01 - 3.95 (m, 3H), 3.76 (s, 3H), 3.74 - 3.69 (m, 1H), 3.06 - 2.99 (m, 1H), 2.86 (dd, J = 7.2, 14.7 Hz, 1H), 2.38 (s, 3H), 1.55 (d, J = 6.8 Hz, 6H), 1.13 (d, J = 6.4 Hz, 3H)

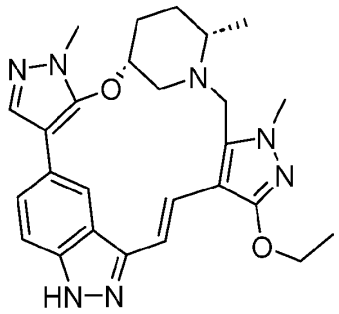
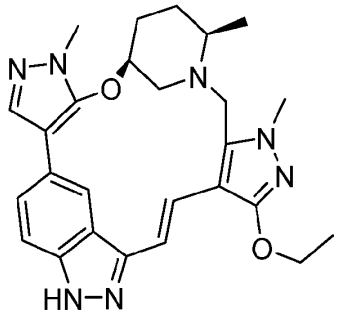
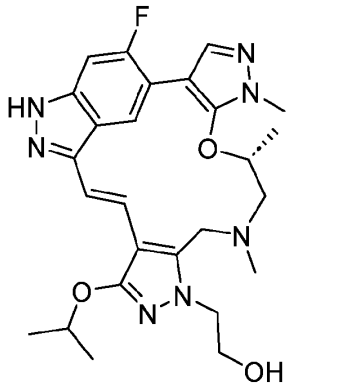
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
235		548.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.91 (br d, J = 1.2 Hz, 1H), 8.32 (d, J = 17.2 Hz, 1H), 7.87 (d, J = 4.4 Hz, 1H), 7.32 (br d, J = 17.2 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.51 - 4.42 (m, 1H), 4.33 - 4.24 (m, 1H), 4.23 - 4.03 (m, 5H), 3.96 (d, J = 14.4 Hz, 1H), 3.83 (br s, 2H), 3.81 (s, 3H), 3.08 (td, J = 4.4, 8.8 Hz, 1H), 3.03 - 2.95 (m, 1H), 2.53 - 2.43 (m, 1H), 2.26 - 2.09 (m, 1H), 1.91 - 1.74 (m, 2H), 1.44 - 1.36 (m, 1H), 1.33 (br d, J = 4.8 Hz, 3H), 0.71 - 0.62 (m, 2H), 0.42 (q, J = 4.8 Hz, 2H)
236		446.1	1H NMR (400 MHz, DMSO-d6) δ = 8.65 (s, 1H), 8.16 (d, J = 17.2 Hz, 1H), 7.88 (s, 1H), 7.67 - 7.61 (m, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 17.2 Hz, 1H), 5.21 (t, J = 5.6 Hz, 1H), 4.31 - 4.20 (m, 3H), 3.79 (s, 3H), 3.63 (s, 3H), 3.59 - 3.53 (m, 2H), 3.25 - 3.16 (m, 1H), 2.56 (dd, J = 4.8, 10.8 Hz, 2H), 2.10 - 1.98 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H)
237		531.1	1H NMR (400 MHz, METHANOL-d4) δ = 9.28 (s, 1H), 8.30 (d, J = 17.2 Hz, 1H), 7.91 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.43 (br d, J = 9.2 Hz, 1H), 7.39 (d, J = 17.2 Hz, 1H), 5.16 (s, 2H), 5.04 - 4.94 (m, 1H), 4.58 - 4.52 (m, 2H), 4.14 (t, J = 5.2 Hz, 2H), 3.95 (s, 2H), 3.84 (t, J = 5.2 Hz, 2H), 3.07 - 3.01 (m, 1H), 3.00 - 2.96 (m, 2H), 1.45 (d, J = 6.0 Hz, 6H), 0.98 (d, J = 6.4 Hz, 6H)

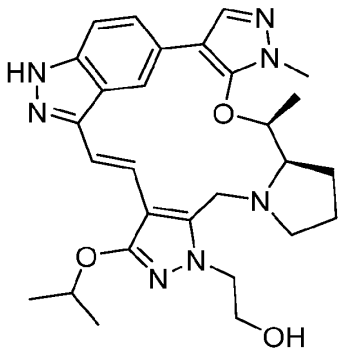
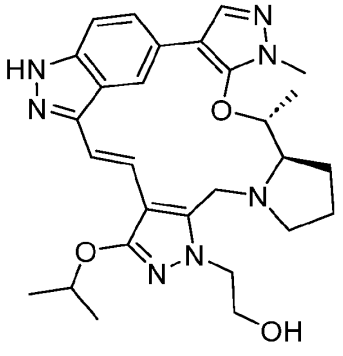
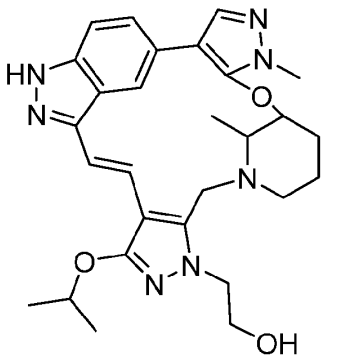
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
238		432.0	1H NMR (400 MHz, DMSO-d6) δ = 12.74 (s, 1H), 8.97 (s, 1H), 8.29 (d, J = 17.2 Hz, 1H), 7.82 (s, 1H), 7.56 (dd, J = 1.2, 8.8 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.00 (d, J = 17.2 Hz, 1H), 5.38 (t, J = 5.2 Hz, 1H), 4.25 (d, J = 7.2 Hz, 2H), 3.87 (s, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 3.52 (s, 2H), 3.46 - 3.43 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H)
239		538.3	1H NMR (400 MHz, DMSO-d6) δ = 12.87 - 12.80 (m, 1H), 8.27 - 8.17 (m, 1H), 7.90 - 7.78 (d, J = 16.8 Hz, 1H), 7.36 - 7.29 (m, 1H), 7.03 - 6.95 (d, J = 16.8 Hz, 1H), 4.88 - 4.82 (m, 1H), 4.36 - 4.30 (m, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.03 - 3.99 (m, 3H), 3.68 - 3.64 (m, 2H), 3.64 (s, 3H), 3.48 - 3.42 (m, 1H), 2.83 - 2.71 (m, 1H), 2.63 (br d, J = 6.4 Hz, 1H), 2.14 - 2.12 (m, 2H), 1.43 - 1.38 (m, 3H), 1.20 - 1.17 (m, 2H), 0.88 (br d, J = 6.0 Hz, 3H), 0.80 - 0.71 (m, 6H)
240		445.0	1H NMR (400 MHz, DMSO-d6) δ = 13.09 (s, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 7.99 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 17.2 Hz, 1H), 7.80 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 4.8 Hz, 1H), 4.88 (t, J = 6.4 Hz, 1H), 4.52 (s, 2H), 4.01 (d, J = 12.0 Hz, 1H), 3.66 (s, 3H), 3.58 (d, J = 12.0 Hz, 1H), 2.87 - 2.80 (m, 1H), 2.74 - 2.67 (m, 1H), 2.20 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.42 - 1.42 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H)

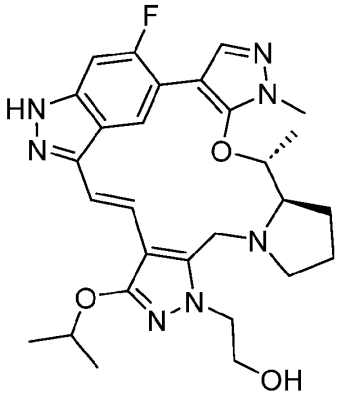
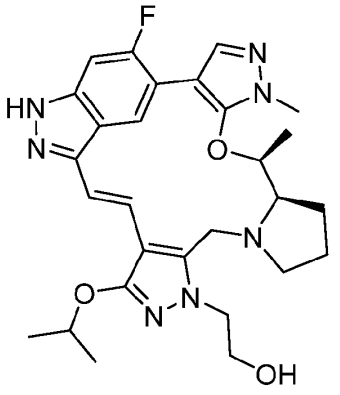
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
241		504.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.85 - 8.35 (m, 1H), 7.96 (br d, J = 16.6 Hz, 1H), 7.81 (s, 1H), 7.64 (br d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 16.9 Hz, 1H), 4.44 - 4.21 (m, 5H), 4.18 - 4.05 (m, 2H), 3.97 - 3.82 (m, 4H), 3.81 - 3.76 (m, 3H), 2.99 - 2.81 (m, 1H), 2.59 - 2.50 (m, 1H), 2.22 - 2.11 (m, 1H), 1.91 - 1.73 (m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.05 (br d, J = 6.4 Hz, 3H)
241		504.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.88 - 8.70 (m, 1H), 7.89 - 7.80 (m, 1H), 7.77 - 7.61 (m, 2H), 7.57 - 7.48 (m, 1H), 7.43 - 7.31 (m, 1H), 5.11 - 4.91 (m, 1H), 4.79 (br s, 2H), 4.44 - 4.36 (m, 2H), 4.30 - 4.20 (m, 2H), 4.02 - 3.86 (m, 3H), 3.84 (s, 3H), 3.60 - 3.47 (m, 1H), 3.43 - 3.31 (m, 2H), 2.49 - 2.31 (m, 1H), 2.07 (br s, 2H), 1.50 (dt, J = 1.8, 7.2 Hz, 3H), 1.41 - 1.26 (m, 3H)
242		504.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.24 - 8.21 (m, 1H), 8.05 - 8.02 (m, 1H), 7.79 (dd, J = 1.4, 8.8 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.37 - 7.31 (m, 1H), 5.50 - 5.40 (m, 1H), 5.20 (br d, J = 15.6 Hz, 1H), 4.47 - 4.37 (m, 4H), 4.18 - 4.09 (m, 2H), 4.03 - 3.93 (m, 3H), 3.79 - 3.76 (m, 3H), 2.30 - 2.16 (m, 2H), 2.11 - 1.95 (m, 4H), 1.65 (d, J = 6.8 Hz, 3H), 1.55 - 1.50 (m, 3H)

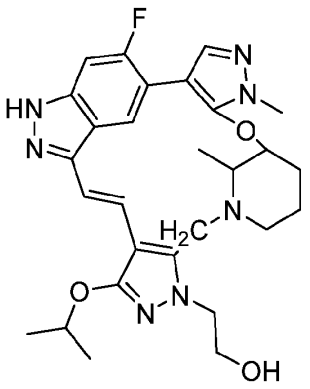
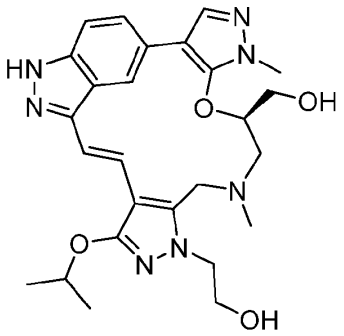
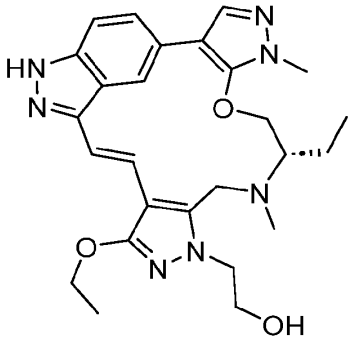
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
243		522.1	1H NMR (400 MHz, METHANOL-d4) δ = 9.03 - 8.62 (m, 1H), 7.92 (br d, J = 17.6 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.28 - 7.18 (m, 2H), 4.58 (br s, 2H), 4.38 - 4.32 (m, 3H), 4.11 (td, J = 4.4, 14.4 Hz, 2H), 3.88 (br s, 2H), 3.86 (br d, J = 5.2 Hz, 2H), 3.81 (s, 3H), 2.88 - 2.79 (m, 1H), 2.56 - 2.48 (m, 1H), 2.22 - 2.15 (m, 1H), 1.79 - 1.74 (m, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.35 - 1.27 (m, 3H), 1.03 (br d, J = 6.4 Hz, 3H)
244		522.0	1H NMR (400 MHz, METHANOL-d4) δ = 9.02 - 8.88 (m, 1H), 8.35 (br d, J = 17.2 Hz, 1H), 7.94 - 7.84 (m, 1H), 7.31 (br d, J = 16.4 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 4.54 - 4.46 (m, 1H), 4.40 - 4.33 (m, 2H), 4.24 - 4.17 (m, 1H), 4.15 - 4.08 (m, 1H), 3.99 (br d, J = 14.4 Hz, 1H), 3.88 - 3.85 (m, 2H), 3.84 (s, 3H), 3.14 - 3.08 (m, 1H), 3.06 - 2.98 (m, 1H), 2.56 - 2.44 (m, 1H), 2.30 - 2.12 (m, 2H), 1.94 - 1.79 (m, 2H), 1.52 (t, J = 7.2 Hz, 3H), 1.41 - 1.28 (m, 6H)
245		522.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.99 - 8.91 (m, 1H), 8.45 - 8.22 (m, 1H), 7.92 - 7.84 (m, 1H), 7.41 - 7.26 (m, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.49 (br s, 1H), 4.36 - 4.34 (m, 2H), 4.18 (br d, J = 2.0 Hz, 1H), 4.12 (br t, J = 4.8 Hz, 1H), 4.00 (s, 1H), 3.85 (br s, 2H), 3.83 (s, 3H), 3.11 - 3.08 (m, 1H), 3.02 - 2.99 (m, 1H), 2.52 - 2.48 (m, 1H), 1.89 - 1.82 (m, 2H), 1.61 (ddd, J = 3.2, 6.4, 11.2 Hz, 2H), 1.50 (t, J = 7.2 Hz, 3H), 1.34 (br s, 3H), 1.29 (br s, 3H)

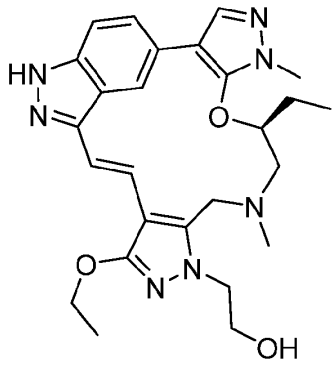
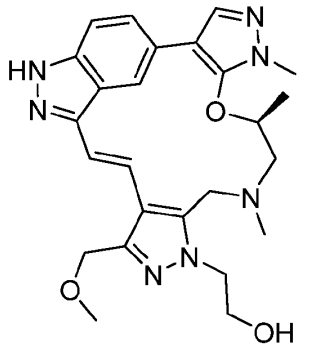
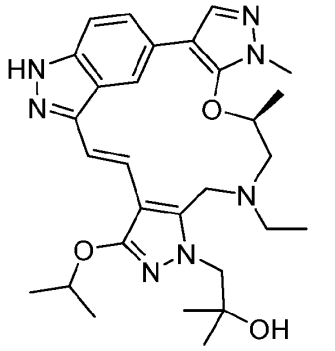
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
246		518.2	1H NMR (400 MHz, DMSO-d6) δ = 12.78 (s, 1H), 8.53 (s, 1H), 8.13 (d, J = 17.2 Hz, 1H), 7.82 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 17.2 Hz, 1H), 4.91 (quin, J = 6.0 Hz, 1H), 4.87 - 4.78 (m, 2H), 4.09 - 3.97 (m, 2H), 3.96 - 3.90 (m, 1H), 3.87 - 3.80 (m, 1H), 3.70 - 3.60 (m, 3H), 3.00 (d, J = 13.6 Hz, 1H), 2.82 (dd, J = 6.8, 14.4 Hz, 1H), 2.35 (s, 3H), 1.39 (t, J = 6.4 Hz, 6H), 1.15 - 1.07 (m, 4H), 1.07 - 1.03 (m, 1H), 0.99 (d, J = 7.2 Hz, 2H)
247		474.2	1H NMR (400 MHz, DMSO-d6) δ 12.90 - 12.64 (m, 1H), 8.49 - 8.39 (m, 1H), 7.66 - 7.51 (m, 1H), 7.39 - 7.25 (m, 2H), 7.16 - 7.05 (m, 1H), 7.01 - 6.85 (m, 1H), 4.38 - 4.27 (m, 2H), 4.21 - 4.04 (m, 1H), 3.77 - 3.55 (m, 2H), 3.40 (br d, J = 2.8 Hz, 6H), 3.20 - 3.06 (m, 2H), 2.79 - 2.72 (m, 2H), 1.46 - 1.41 (m, 3H), 1.19 - 1.10 (m, 2H), 1.06 - 0.97 (m, 3H), 0.55 - 0.36 (m, 1H)
248		474.3	1H NMR (400 MHz, DMSO-d6) δ 13.01 - 12.58 (m, 1H), 8.48 - 8.38 (m, 1H), 7.66 - 7.49 (m, 1H), 7.41 - 7.23 (m, 2H), 7.20 - 7.04 (m, 1H), 7.03 - 6.78 (m, 1H), 4.32 (td, J = 7.2, 14.4 Hz, 2H), 4.22 - 4.00 (m, 1H), 3.64 (br s, 2H), 3.55 - 3.42 (m, 6H), 3.16 - 3.00 (m, 2H), 2.75 (br s, 2H), 1.42 (br t, J = 6.4 Hz, 3H), 1.25 - 1.11 (m, 2H), 1.07 - 0.92 (m, 3H), 0.57 - 0.35 (m, 1H)

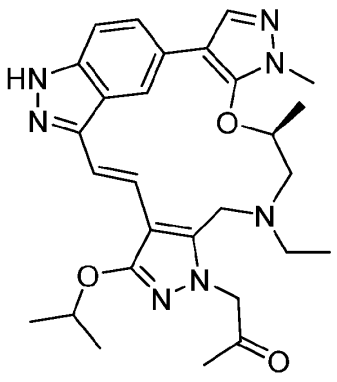
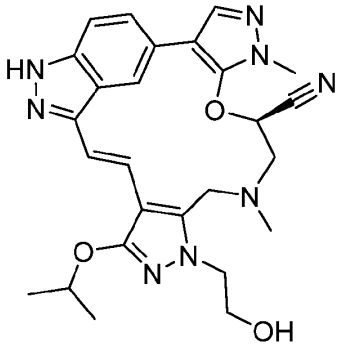
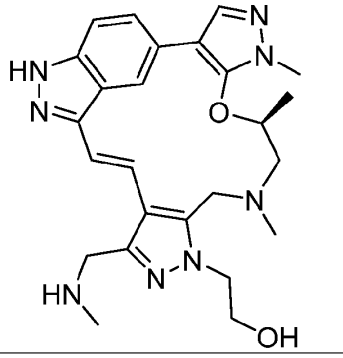
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
249		474.1	1H NMR (400 MHz, DMSO-d6) δ 12.81 (s, 1H), 7.96 (s, 1H), 7.74 - 7.68 (m, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 16.8 Hz, 1H), 4.98 - 4.85 (m, 1H), 4.31 - 4.23 (m, 2H), 4.13 (br d, J = 15.6 Hz, 1H), 3.74 (s, 2H), 3.64 (s, 3H), 3.31 (s, 3H), 3.15 - 3.05 (m, 1H), 2.95 - 2.79 (m, 2H), 1.93 - 1.80 (m, 1H), 1.75 - 1.61 (m, 2H), 1.49 (dt, J = 3.6, 6.0 Hz, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.14 (br d, J = 6.4 Hz, 3H)
250		474.1	1H NMR (400 MHz, DMSO-d6) δ 12.96 - 12.68 (m, 1H), 7.96 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 16.8 Hz, 1H), 4.99 - 4.86 (m, 1H), 4.32 - 4.23 (m, 2H), 4.13 (br d, J = 15.6 Hz, 1H), 3.74 (s, 2H), 3.64 (s, 3H), 3.31 (br s, 3H), 3.16 - 3.03 (m, 1H), 2.87 (br d, J = 9.6 Hz, 2H), 1.93 - 1.81 (m, 1H), 1.76 - 1.62 (m, 2H), 1.54 - 1.45 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.14 (br d, J = 6.4 Hz, 3H)
251		510.1	1H NMR (400 MHz, DMSO-d6) δ = 13.44 - 12.41 (m, 1H), 8.57 - 8.51 (m, 1H), 8.05 (d, J = 17.2 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.35 (br d, J = 12.0 Hz, 1H), 7.12 (d, J = 17.2 Hz, 1H), 4.90 (s, 2H), 4.73 - 4.63 (m, 1H), 4.09 - 3.98 (m, 2H), 3.94 - 3.81 (m, 2H), 3.73 - 3.68 (m, 3H), 3.66 - 3.60 (m, 2H), 3.02 - 2.92 (m, 1H), 2.85 - 2.74 (m, 1H), 2.30 (s, 3H), 1.38 (t, J = 6.4 Hz, 6H), 1.04 (br d, J = 6.0 Hz, 3H)

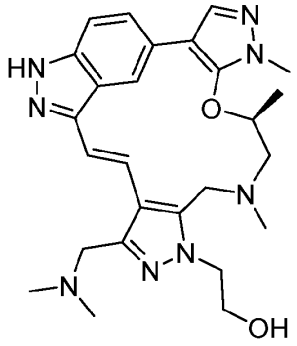
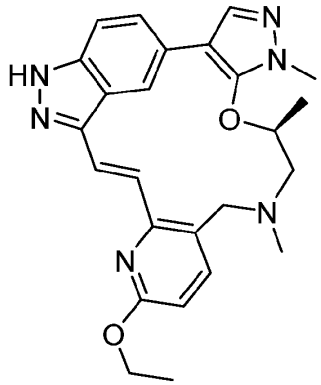
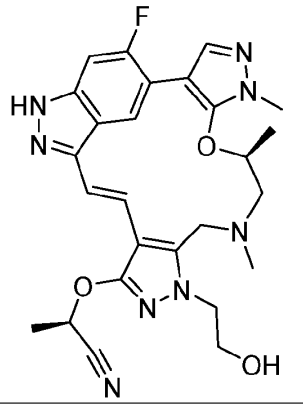
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
252		518.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.51 (br s, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.47 - 7.40 (m, 1H), 7.40 - 7.31 (m, 1H), 5.62 (br d, J = 2.4 Hz, 1H), 5.17 - 5.05 (m, 2H), 4.72 - 4.64 (m, 1H), 4.33 - 4.21 (m, 2H), 4.01 (td, J = 4.0, 11.4 Hz, 2H), 3.91 (td, J = 5.5, 11.3 Hz, 1H), 3.82 (s, 3H), 3.80 - 3.74 (m, 1H), 3.66 - 3.51 (m, 1H), 2.71 - 2.57 (m, 1H), 2.57 - 2.45 (m, 1H), 2.43 - 2.32 (m, 1H), 2.21 (br dd, J = 4.3, 5.9 Hz, 1H), 1.47 (dd, J = 6.1, 17.6 Hz, 6H), 1.23 (br d, J = 6.4 Hz, 3H)
253		518.2	1H NMR (499 MHz, METHANOL-d4) δ ppm 8.84 - 8.99 (m, 1 H), 8.20 - 8.40 (m, 1 H), 7.87 (s, 1 H), 7.69 (d, J=8.76 Hz, 1 H), 7.47 (d, J=8.76 Hz, 1 H), 7.38 (br d, J=16.97 Hz, 1 H), 4.99 (dt, J=12.11, 6.13 Hz, 1 H), 4.48 - 4.58 (m, 1 H), 4.07 - 4.31 (m, 3 H), 3.92 - 4.06 (m, 1 H), 3.82 - 3.89 (m, 2 H), 3.81 (s, 3 H), 2.97 - 3.20 (m, 2 H), 2.44 - 2.62 (m, 1 H), 2.07 - 2.31 (m, 2 H), 1.95 (br d, J=5.48 Hz, 1 H), 1.85 (br s, 1 H), 1.46 (dd, J=6.30, 1.37 Hz, 6 H), 1.35 - 1.43 (m, 3 H)
254		518.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.21 (s, 1H), 8.03 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.61 - 7.55 (m, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.32 (d, J = 16.3 Hz, 1H), 5.48 - 5.40 (m, 1H), 5.20 (br d, J = 15.3 Hz, 1H), 5.08 (td, J = 6.1, 12.2 Hz, 1H), 4.43 - 4.33 (m, 2H), 4.32 - 4.25 (m, 1H), 4.18 - 4.09 (m, 1H), 3.97 (br d, J = 5.9 Hz, 2H), 3.77 (s, 3H), 3.70 - 3.62 (m, 2H), 2.25 (br dd, J = 4.6, 11.6 Hz, 1H), 2.10 - 1.97 (m, 3H), 1.66 (d, J = 6.9 Hz,

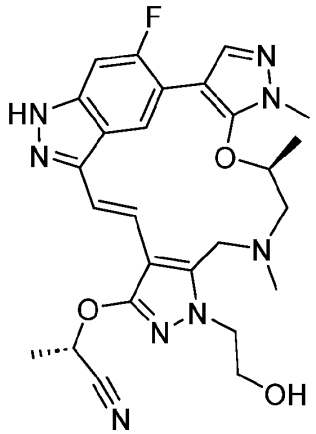
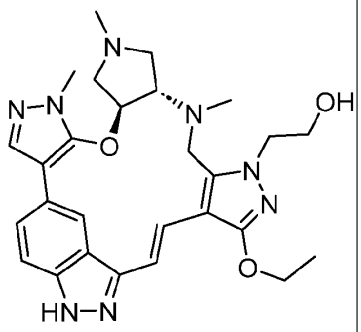
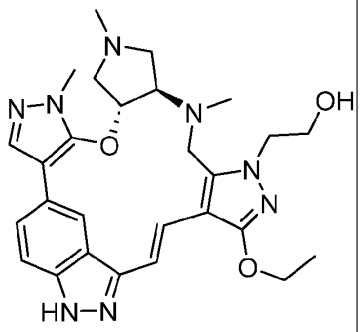
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
			3H), 1.49 (dd, J = 3.1, 6.1 Hz, 6H)518.1
255		536.4	1H NMR (400 MHz, METHANOL-d4) δ = 8.92 (br d, J = 2.8 Hz, 1H), 8.30 (br d, J = 16.8 Hz, 1H), 7.93 - 7.80 (m, 1H), 7.37 - 7.26 (m, 1H), 7.22 (d, J = 12.1 Hz, 1H), 5.03 - 4.93 (m, 1H), 4.56 - 4.41 (m, 1H), 4.35 - 4.24 (m, 1H), 4.24 - 4.15 (m, 1H), 4.14 - 4.05 (m, 1H), 3.96 (br d, J = 14.0 Hz, 1H), 3.86 - 3.83 (m, 2H), 3.81 (s, 3H), 3.08 (td, J = 4.4, 8.8 Hz, 1H), 3.04 - 2.95 (m, 1H), 2.57 - 2.40 (m, 1H), 2.26 - 2.12 (m, 1H), 2.11 - 1.94 (m, 1H), 1.92 - 1.72 (m, 2H), 1.45 (d, J = 6.0 Hz, 6H), 1.33 (br d, J = 4.0 Hz, 3H)
256		536.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.70 - 8.32 (m, 1H), 7.81 (d, J = 5.0 Hz, 1H), 7.43 - 7.23 (m, 3H), 5.69 - 5.32 (m, 1H), 5.06 (td, J = 6.0, 12.0 Hz, 2H), 4.73 - 4.47 (m, 1H), 4.24 (br s, 2H), 3.97 (br d, J = 11.2 Hz, 2H), 3.88 (td, J = 5.6, 11.2 Hz, 1H), 3.82 (s, 3H), 3.76 - 3.64 (m, 1H), 3.62 - 3.38 (m, 1H), 2.70 - 2.50 (m, 1H), 2.50 - 2.24 (m, 2H), 2.24 - 2.00 (m, 1H), 1.45 (dd, J = 6.0, 14.8 Hz, 6H), 1.18 (br d, J = 2.0 Hz, 3H)

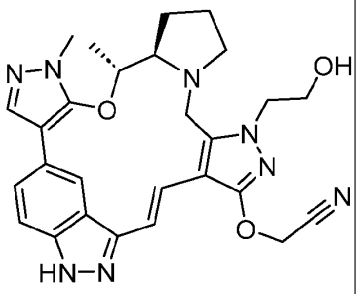
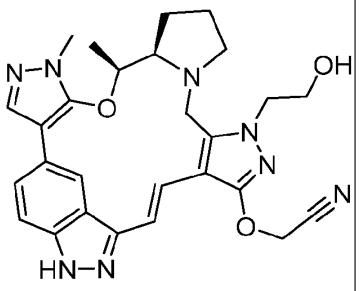
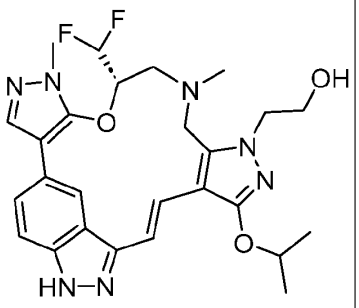
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
257		536.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.32 (d, J = 7.2 Hz, 1H), 8.05 (d, J = 4.7 Hz, 1H), 7.55 (d, J = 16.4 Hz, 1H), 7.33 - 7.24 (m, 2H), 5.49 - 5.40 (m, 1H), 5.16 (br d, J = 15.4 Hz, 1H), 5.08 (td, J = 6.0, 12.4 Hz, 1H), 4.44 - 4.33 (m, 2H), 4.33 - 4.23 (m, 1H), 4.10 (quin, J = 6.4 Hz, 1H), 3.97 (br d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 3.71 - 3.55 (m, 2H), 2.31 - 2.17 (m, 1H), 2.03 (br s, 2H), 2.00 - 1.92 (m, 1H), 1.66 (d, J = 6.8 Hz, 3H), 1.48 (dd, J = 2.4, 6.0 Hz, 6H)
258		508.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.47 (s, 1H), 8.28 (d, J = 16.0 Hz, 1H), 7.80 (s, 1H), 7.66 (dd, J = 4.4, 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 16.0 Hz, 1H), 4.97 (td, J = 6.0, 12.0 Hz, 1H), 4.72 (br s, 1H), 4.16 - 4.07 (m, 2H), 3.99 - 3.88 (m, 2H), 3.83 (t, J = 6.0 Hz, 2H), 3.78 (s, 3H), 3.66 - 3.58 (m, 1H), 3.47 (dd, J = 2.0, 12.0 Hz, 1H), 3.11 - 3.05 (m, 2H), 2.44 (s, 3H), 1.45 (t, J = 6.0 Hz, 6H)
259		492.1	1H NMR (400 MHz, DMSO-d6) δ = 12.83 (s, 1H), 8.49 (s, 1H), 7.92 (s, 1H), 7.73 - 7.62 (m, 2H), 7.47 (d, J = 9.4 Hz, 1H), 7.20 (d, J = 17.4 Hz, 1H), 4.92 - 4.85 (m, 1H), 4.47 - 4.38 (m, 1H), 4.33 - 4.24 (m, 2H), 4.17 - 4.06 (m, 3H), 4.03 - 3.93 (m, 1H), 3.89 - 3.80 (m, 1H), 3.74 (s, 3H), 3.72 - 3.67 (m, 2H), 2.90 - 2.83 (m, 1H), 2.33 (s, 3H), 1.76 - 1.67 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H), 0.95 - 0.88 (m, 3H)

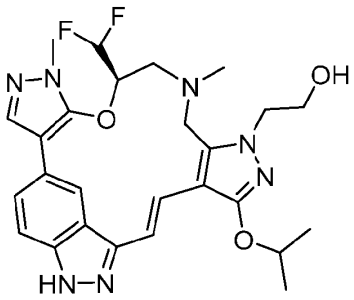
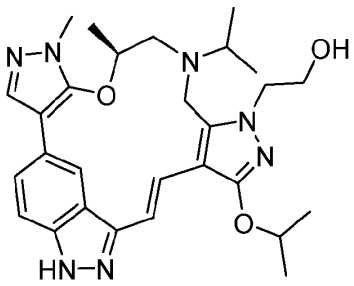
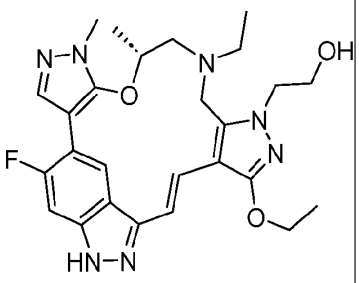
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
260		492.1	1H NMR (400 MHz, DMSO-d6) δ = 12.80 (s, 1H), 8.52 - 8.42 (m, 1H), 8.17 (d, J = 17.2 Hz, 1H), 7.86 (s, 1H), 7.71 - 7.62 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 17.4 Hz, 1H), 4.86 (t, J = 5.4 Hz, 1H), 4.54 - 4.40 (m, 1H), 4.32 - 4.25 (m, 2H), 4.08 - 4.00 (m, 2H), 3.99 - 3.93 (m, 1H), 3.90 - 3.80 (m, 1H), 3.68 (s, 3H), 3.65 (br d, J = 5.6 Hz, 2H), 3.01 (br d, J = 14.8 Hz, 1H), 2.88 - 2.81 (m, 1H), 2.35 (br s, 3H), 1.76 - 1.57 (m, 1H), 1.42 (t, J = 7.0 Hz, 4H), 0.72 (br t, J = 7.4 Hz, 3H)
261		478.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 (s, 1H), 8.41 (d, J = 17.2 Hz, 1H), 7.80 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 17.2 Hz, 1H), 4.95 - 4.90 (m, 1H), 4.65 - 4.53 (m, 2H), 4.33 - 4.16 (m, 2H), 4.04 - 3.92 (m, 2H), 3.91 - 3.82 (m, 2H), 3.72 (s, 3H), 3.48 (s, 3H), 2.95 - 2.79 (m, 2H), 2.37 (s, 3H), 1.07 (d, J = 6.2 Hz, 3H)
262		534.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.67 (s, 1H), 8.22 (d, J = 17.2 Hz, 1H), 7.85 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.40 - 7.29 (m, 1H), 5.02 - 4.98 (m, 1H), 4.62 (br s, 1H), 4.16 - 3.94 (m, 4H), 3.76 (s, 3H), 3.15 - 2.97 (m, 1H), 2.93 (br d, J = 14.8 Hz, 1H), 2.82 - 2.58 (m, 2H), 1.53 - 1.43 (m, 6H), 1.23 (d, J = 3.6 Hz, 6H), 1.14 (br d, J = 6.4 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H)

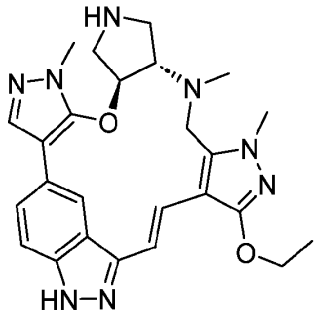
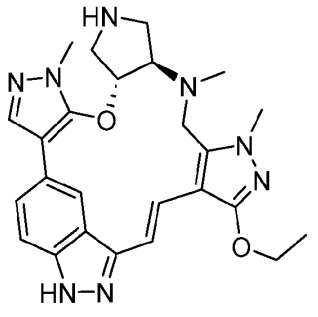
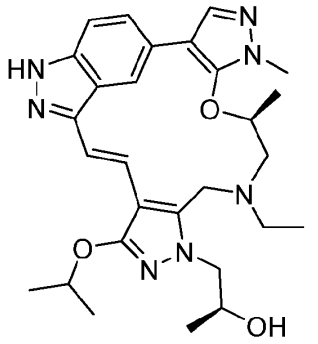
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
263		518.5	1H NMR (400 MHz, METHANOL-d4) δ = 8.65 (s, 1H), 8.20 (d, J = 16.8 Hz, 1H), 7.83 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 17.2 Hz, 1H), 4.97 (s, 2H), 4.96 - 4.92 (m, 1H), 4.60 (s, 2H), 3.92 - 3.77 (m, 2H), 3.74 (s, 3H), 3.08 - 2.98 (m, 1H), 2.88 (br d, J = 15.6 Hz, 1H), 2.77 - 2.63 (m, 2H), 2.23 - 2.15 (m, 3H), 1.47 - 1.42 (m, 6H), 1.12 (br d, J = 6.4 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H)
264		503.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.54 (s, 1H), 8.18 (d, J = 16.0 Hz, 1H), 7.92 (s, 1H), 7.75 (dd, J = 1.2, 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 16.0 Hz, 1H), 5.48 (dd, J = 4.0, 8.0 Hz, 1H), 4.99 (td, J = 6.0, 12.0 Hz, 1H), 4.16 - 4.08 (m, 2H), 4.04 (d, J = 4.0 Hz, 2H), 3.85 (s, 3H), 3.84 - 3.80 (m, 2H), 3.38 - 3.32 (m, 2H), 2.47 (s, 3H), 1.45 (dd, J = 4.0, 6.0 Hz, 6H)
265		477.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 - 8.45 (m, 2H), 7.86 (s, 1H), 7.74 - 7.69 (m, 1H), 7.56 - 7.51 (m, 1H), 6.89 - 6.82 (m, 1H), 4.61 - 4.59 (m, 1H), 4.53 - 4.49 (m, 2H), 4.32 (td, J = 2.9, 6.3 Hz, 2H), 4.07 (s, 2H), 3.91 (br s, 2H), 3.77 - 3.73 (m, 3H), 2.96 - 2.92 (m, 2H), 2.89 (s, 3H), 2.44 - 2.39 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H)

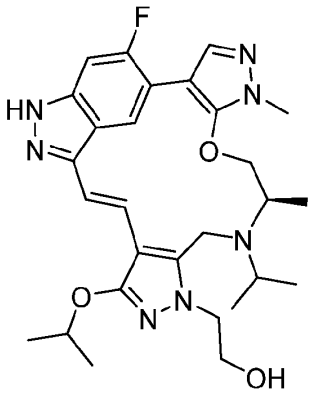
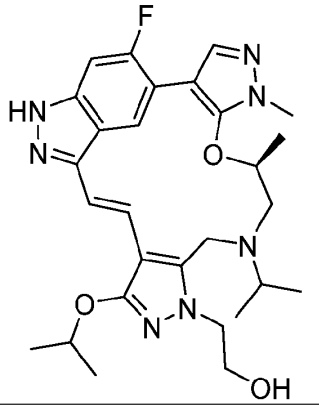
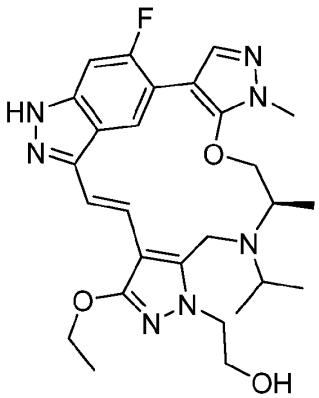
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
266		491.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.60 - 8.54 (m, 1H), 8.48 - 8.41 (m, 1H), 7.86 - 7.81 (m, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.57 - 7.49 (m, 1H), 7.02 (d, J = 17.6 Hz, 1H), 4.61 (br s, 1H), 4.34 - 4.27 (m, 4H), 4.01 (br d, J = 11.6 Hz, 2H), 3.93 - 3.88 (m, 2H), 3.75 (s, 3H), 2.96 - 2.90 (m, 2H), 2.81 (s, 6H), 2.41 (s, 3H), 1.10 (d, J = 6.1 Hz, 3H)
267		445.0	1H NMR (400 MHz, DMSO-d6) δ = 13.19 (s, 1H), 8.54 (s, 1H), 8.50 (d, J = 16.0 Hz, 1H), 7.91 - 7.86 (m, 2H), 7.71 (dd, J = 1.2, 8.8 Hz, 1H), 7.54 (dd, J = 2.0, 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 1H), 4.90 (t, J = 6.4 Hz, 1H), 4.44 (dq, J = 3.2, 7.2 Hz, 2H), 4.06 (br d, J = 12.5 Hz, 1H), 3.67 (s, 3H), 3.40 (br d, J = 12.4 Hz, 1H), 2.93 - 2.85 (m, 1H), 2.84 - 2.75 (m, 1H), 2.22 (s, 3H), 1.40 (d, J = 2.8 Hz, 1H), 1.39 - 1.36 (m, 2H), 1.01 (d, J = 6.0 Hz, 3H)
268		521.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.61 (br d, J = 7.2 Hz, 1H), 8.24 (br d, J = 17.2 Hz, 1H), 7.84 (d, J = 5.2 Hz, 1H), 7.31 - 7.13 (m, 2H), 5.59 - 5.47 (m, 1H), 4.60 (br d, J = 2.8 Hz, 1H), 4.22 - 4.07 (m, 2H), 4.03 - 3.92 (m, 2H), 3.90 - 3.81 (m, 2H), 3.76 (s, 3H), 3.06 - 2.95 (m, 1H), 2.94 - 2.80 (m, 1H), 2.42 (s, 3H), 1.84 (d, J = 6.8 Hz, 3H), 1.12 (br d, J = 6.4 Hz, 3H)

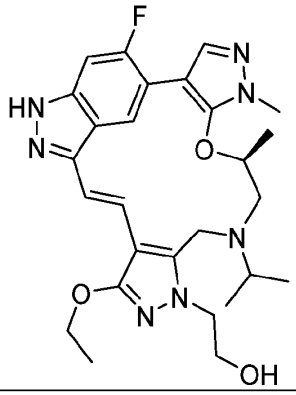
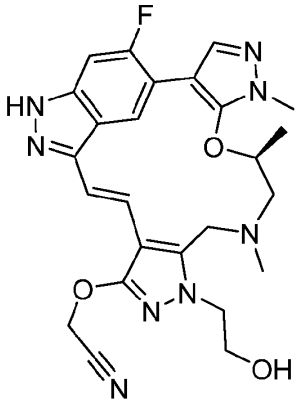
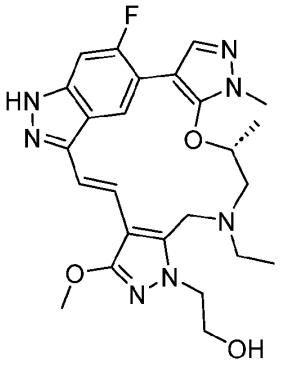
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
269		521.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.64 (br d, J = 6.8 Hz, 1H), 8.26 (d, J = 17.2 Hz, 1H), 7.84 (d, J = 5.2 Hz, 1H), 7.32 - 7.10 (m, 2H), 5.59 - 5.49 (m, 1H), 4.59 (s, 1H), 4.23 - 4.10 (m, 2H), 4.01 - 3.92 (m, 2H), 3.91 - 3.83 (m, 2H), 3.76 (s, 3H), 3.03 - 2.98 (m, 1H), 2.92 - 2.86 (m, 1H), 2.42 (s, 3H), 1.91 - 1.82 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H)
270		519.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.19 - 8.15 (m, 1H), 8.07 (br d, J = 16.8 Hz, 1H), 7.75 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 17.2 Hz, 1H), 4.86 - 4.82 (m, 1H), 4.34 - 4.26 (m, 2H), 4.09 - 4.03 (m, 1H), 3.99 (br t, J = 5.2 Hz, 2H), 3.85 - 3.80 (m, 3H), 3.75 (s, 4H), 3.02 (br t, J = 8.4 Hz, 1H), 2.69 (br d, J = 12.0 Hz, 1H), 2.34 (br t, J = 9.2 Hz, 1H), 2.27 (s, 3H), 2.06 (s, 3H), 2.04 - 1.99 (m, 1H), 1.49 (t, J = 7.2 Hz, 3H).
271		519.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.17 (br s, 1H), 8.07 (br d, J = 17.2 Hz, 1H), 7.75 (s, 1H), 7.57 (br d, J = 8.8 Hz, 1H), 7.39 (br d, J = 8.8 Hz, 1H), 7.33 (br d, J = 17.2 Hz, 1H), 4.85 - 4.82 (m, 1H), 4.34 - 4.27 (m, 2H), 4.06 (br d, J = 14.0 Hz, 1H), 3.98 (br d, J = 4.4 Hz, 2H), 3.86 - 3.79 (m, 3H), 3.74 (s, 4H), 3.02 (br t, J = 8.0 Hz, 1H), 2.69 (br d, J = 12.0Hz, 1H), 2.33 (br t, J = 8.8 Hz, 1H), 2.27 (s, 3H), 2.09 - 1.98 (m, 4H), 1.49 (br t, J = 6.8 Hz, 3H).

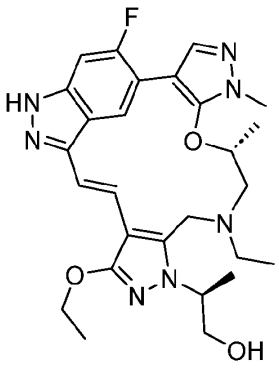
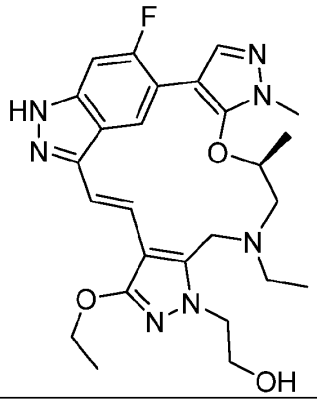
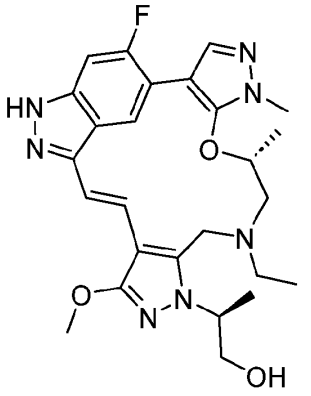
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
272		515.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.51 (br s, 1H), 7.83 (s, 1H), 7.76 - 7.69 (m, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.44 - 7.29 (m, 2H), 5.62 (br s, 1H), 5.24 (d, J = 0.9 Hz, 2H), 5.14 (br d, J = 15.1 Hz, 1H), 4.79 - 4.69 (m, 1H), 4.38 - 4.27 (m, 2H), 4.05 (td, J = 4.1, 11.3 Hz, 2H), 3.99 - 3.91 (m, 1H), 3.83 (s, 3H), 3.81 - 3.73 (m, 1H), 3.67 - 3.53 (m, 1H), 2.62 (br d, J = 2.6 Hz, 1H), 2.56 - 2.46 (m, 1H), 2.38 (br s, 1H), 2.30 - 2.12 (m, 1H), 1.23 (d, J = 6.4 Hz, 3H)
273		515.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.87 - 8.56 (m, 1H), 7.91 - 7.78 (m, 1H), 7.64 (br d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 1H), 7.26 (br d, J = 16.6 Hz, 1H), 5.21 (s, 2H), 4.83 - 4.64 (m, 3H), 4.35 - 4.27 (m, 2H), 4.04 - 3.93 (m, 3H), 3.83 (s, 3H), 3.55 (br d, J = 4.8 Hz, 1H), 3.45 - 3.33 (m, 1H), 2.48 - 2.31 (m, 1H), 2.14 - 1.93 (m, 3H), 1.37 - 1.20 (m, 3H)
274		528.2	1H NMR (400 MHz, DMSO-d6) δ = 12.84 (s, 1H), 8.24 (s, 1H), 8.09 (d, J = 17.2 Hz, 1H), 7.79 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 17.2 Hz, 1H), 6.35 - 5.95 (m, 1H), 4.94 - 4.86 (m, 2H), 4.84 (t, J = 5.2 Hz, 1H), 4.07 - 3.99 (m, 2H), 3.99 - 3.94 (m, 1H), 3.89 - 3.84 (m, 1H), 3.71 (s, 3H), 3.67 - 3.62 (m, 2H), 3.11 (br d, J = 14.4 Hz, 1H), 2.99 - 2.90 (m, 1H), 2.34 (s, 3H), 1.41 - 1.37 (m, 6H)

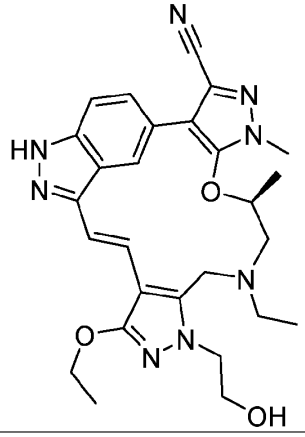
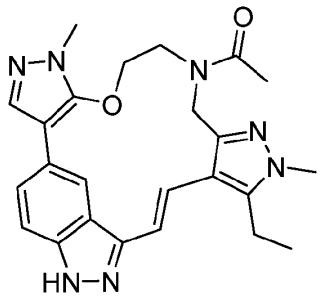
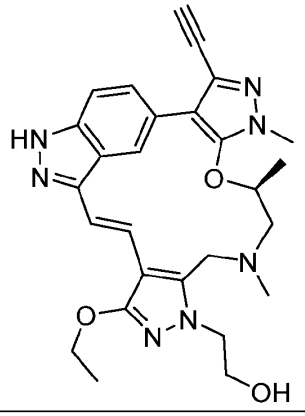
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
275		528.2	1H NMR (400 MHz, DMSO-d6) δ = 12.84 (s, 1H), 8.24 (s, 1H), 8.09 (d, J = 17.2 Hz, 1H), 7.79 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 17.2 Hz, 1H), 6.30 - 5.97 (m, 1H), 4.94 - 4.87 (m, 2H), 4.86 - 4.83 (m, 1H), 4.07 - 3.99 (m, 2H), 3.98 - 3.94 (m, 1H), 3.89 - 3.84 (m, 1H), 3.71 (s, 3H), 3.66 - 3.61 (m, 2H), 3.14 - 3.08 (m, 1H), 2.98 - 2.90 (m, 1H), 2.34 (s, 3H), 1.41 - 1.37 (m, 6H)
276		520.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.70 (s, 1H), 8.07 (br d, J = 16.8 Hz, 1H), 7.83 (s, 1H), 7.69 - 7.64 (m, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 16.8 Hz, 1H), 5.03 - 4.95 (m, 1H), 4.76 (br s, 1H), 4.19 - 4.13 (m, 2H), 4.08 - 3.97 (m, 2H), 3.85 (t, J = 5.6 Hz, 2H), 3.76 (s, 3H), 2.95 - 2.84 (m, 3H), 1.48 - 1.44 (m, 6H), 1.13 (br d, J = 6.4 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H)
277		510.0	1H NMR (400 MHz, METHANOL-d4) δ = 8.75 - 8.67 (m, 1H), 8.17 - 8.08 (m, 1H), 7.86 - 7.81 (m, 1H), 7.31 - 7.21 (m, 2H), 4.73 (br d, J = 1.9 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 4.19 - 4.09 (m, 2H), 4.01 (br s, 2H), 3.84 (t, J = 5.3 Hz, 2H), 3.77 (s, 3H), 3.04 - 2.93 (m, 2H), 2.68 - 2.59 (m, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.12 (br d, J = 6.1 Hz, 3H), 0.98 (br t, J = 7.1 Hz, 3H)

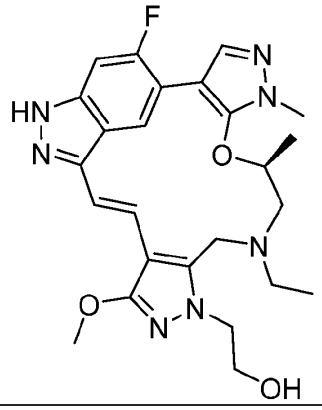
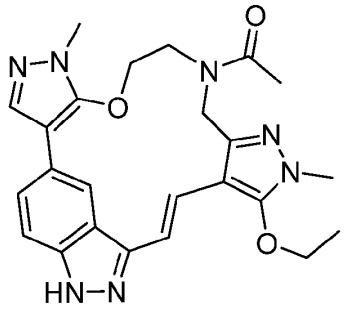
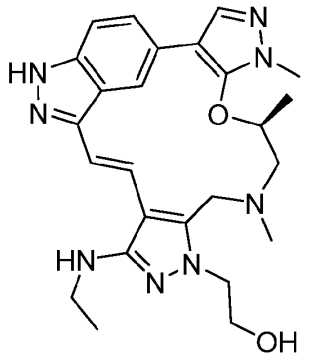
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
278		475.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.08 (s, 1H), 7.97 (d, J = 17.2 Hz, 1H), 7.66 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 17.2 Hz, 1H), 4.94 - 4.92 (m, 1H), 4.30 - 4.21 (m, 2H), 3.97 (br d, J = 14.8 Hz, 1H), 3.69 (s, 3H), 3.67 - 3.60 (m, 2H), 3.58 (s, 3H), 3.21 - 3.12 (m, 1H), 2.88 - 2.74 (m, 2H), 2.63 - 2.55 (m, 1H), 2.04 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H)
279		475.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.18 (s, 1H), 8.06 (d, J = 17.2 Hz, 1H), 7.76 (s, 1H), 7.63 - 7.58 (m, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 17.2 Hz, 1H), 5.07 (br d, J = 2.8 Hz, 1H), 4.34 - 4.25 (m, 2H), 4.12 (d, J = 14.8 Hz, 1H), 3.82 - 3.73 (m, 5H), 3.65 (s, 3H), 3.34 (s, 1H), 3.04 - 2.92 (m, 2H), 2.82 - 2.74 (m, 1H), 2.14 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H)
280		520.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.60 (s, 1H), 8.12 (d, J = 16.8 Hz, 1H), 7.81 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 16.8 Hz, 1H), 4.99 - 4.92 (m, 1H), 4.84 (br s, 1H), 4.09 - 3.92 (m, 5H), 3.72 (s, 3H), 3.09 - 3.01 (m, 1H), 2.85 (br d, J = 14.8 Hz, 1H), 2.78 - 2.61 (m, 2H), 1.43 (t, J = 5.6 Hz, 6H), 1.19 (d, J = 6.0 Hz, 3H), 1.09 (br d, J = 6.4 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H)

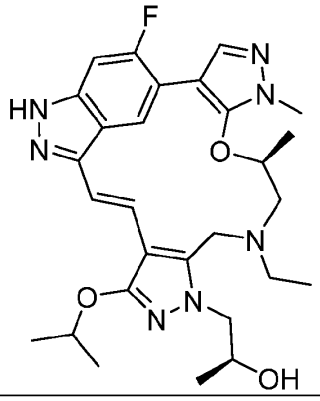
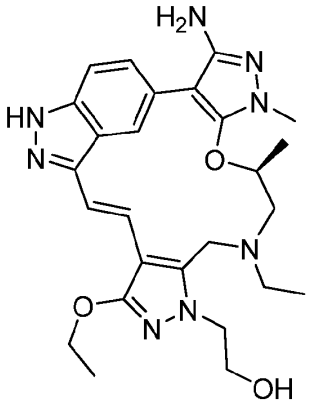
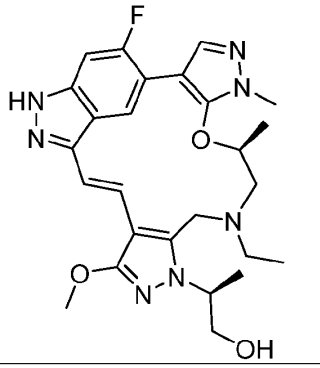
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
281		538.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.71 (br d, J = 7.2 Hz, 1H), 7.87 - 7.82 (m, 1H), 7.66 - 7.55 (m, 1H), 7.32 (d, J = 16.8 Hz, 1H), 7.21 (d, J = 12.0 Hz, 1H), 5.00 (td, J = 6.0, 12.3 Hz, 1H), 4.50 - 4.41 (m, 1H), 4.32 - 4.23 (m, 1H), 4.12 - 4.05 (m, 1H), 3.96 - 3.83 (m, 5H), 3.80 (s, 3H), 3.78 - 3.75 (m, 1H), 3.42 - 3.35 (m, 1H), 1.48 - 1.40 (m, 9H), 1.16 (br d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H)
282		538.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.71 (br d, J = 6.4 Hz, 1H), 8.02 (br d, J = 16.8 Hz, 1H), 7.80 (d, J = 4.4 Hz, 1H), 7.28 - 7.20 (m, 2H), 4.98 (td, J = 6.0, 12.2 Hz, 1H), 4.61 (br s, 1H), 4.18 - 4.11 (m, 2H), 4.08 - 4.01 (m, 2H), 3.85 (t, J = 5.2 Hz, 2H), 3.77 (s, 3H), 2.93 (br s, 3H), 1.45 (dd, J = 3.2, 6.1 Hz, 6H), 1.09 (br d, J = 6.4 Hz, 3H), 0.97 (br dd, J = 6.4, 10.1 Hz, 6H)
283		524.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.63 (br s, 1H), 7.80 (br d, J = 4.0 Hz, 1H), 7.55 (br d, J = 16.0 Hz, 1H), 7.33 - 7.24 (m, 1H), 7.17 (br d, J = 12.4 Hz, 1H), 4.43 - 4.30 (m, 3H), 4.29 - 4.19 (m, 1H), 4.08 (td, J = 4.4, 14.0 Hz, 1H), 3.96 - 3.82 (m, 6H), 3.81 - 3.74 (m, 3H), 3.35 (br s, 1H), 3.03 (br s, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.43 - 1.36 (m, 3H), 1.13 (br d, J = 6.0 Hz, 3H), 1.01 - 0.95 (m, 3H)

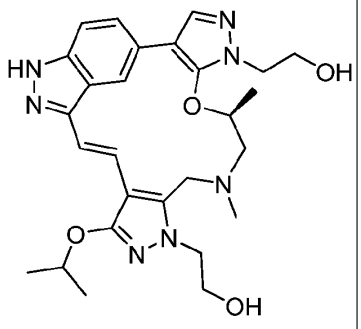
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
284		524.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.76 - 8.62 (m, 1H), 8.00 (br d, J = 17.2 Hz, 1H), 7.78 (br d, J = 4.4 Hz, 1H), 7.23 (br d, J = 6.8 Hz, 1H), 7.19 (s, 1H), 4.60 (br s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.21 - 4.09 (m, 2H), 4.09 - 3.98 (m, 2H), 3.86 (br t, J = 5.2 Hz, 2H), 3.76 (s, 3H), 2.96 - 2.76 (m, 3H), 1.49 (t, J = 7.0 Hz, 3H), 1.08 (br d, J = 6.1 Hz, 3H), 1.02 - 0.89 (m, 6H)
285		507.2	1H NMR (400 MHz, DMSO-d6) δ = 12.99 - 12.85 (m, 1H), 8.64 - 8.47 (m, 1H), 8.16 - 8.05 (d, J = 17.2 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.42 - 7.30 (m, 1H), 7.11 - 6.99 (d, J = 17.2 Hz, 1H), 5.27 - 5.17 (m, 2H), 4.95 - 4.65 (m, 2H), 4.12 - 4.04 (m, 2H), 3.74 - 3.62 (m, 6H), 3.00 (br d, J = 14.8 Hz, 1H), 2.86 - 2.77 (m, 1H), 2.69 - 2.64 (m, 1H), 2.54 - 2.53 (m, 1H), 2.33 - 2.30 (m, 3H), 1.07 - 1.03 (m, 2H)
286		496.0	1H NMR (400 MHz, DMSO-d6) δ = 13.00 - 12.73 (m, 1H), 8.65 (br d, J = 6.8 Hz, 1H), 8.04 - 7.89 (m, 1H), 7.79 - 7.72 (m, 1H), 7.34 (br d, J = 11.6 Hz, 1H), 7.16 - 7.05 (m, 1H), 4.70 - 4.56 (m, 1H), 4.22 - 4.02 (m, 3H), 3.99 (br s, 2H), 3.94 (br s, 3H), 3.72 (s, 3H), 3.66 (br s, 2H), 3.37 - 3.30 (m, 2H), 3.04 - 2.84 (m, 2H), 1.06 (br d, J = 6.0 Hz, 3H), 0.91 (br t, J = 6.4 Hz, 3H)

Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
287		524.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.78 - 8.70 (m, 1H), 8.19 - 8.11 (m, 1H), 7.86 - 7.81 (m, 1H), 7.29 - 7.25 (m, 1H), 7.25 - 7.20 (m, 1H), 4.75 - 4.70 (m, 1H), 4.61 (s, 1H), 4.52 - 4.46 (m, 1H), 4.36 (q, J = 7.0 Hz, 2H), 4.06 - 3.99 (m, 2H), 3.92 (dd, J = 8.1, 11.3 Hz, 1H), 3.77 (s, 3H), 3.76 - 3.72 (m, 1H), 2.99 (br d, J = 2.9 Hz, 2H), 2.70 - 2.60 (m, 2H), 1.48 (t, J = 7.1 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.13 (br d, J = 6.4 Hz, 3H), 0.99 (t, J = 7.1 Hz, 3H)
288		510.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.69 (br d, J = 7.2 Hz, 1H), 8.22 - 7.94 (m, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.30 - 7.22 (m, 2H), 4.81 - 4.66 (m, 1H), 4.42 - 4.29 (m, 2H), 4.21 - 4.11 (m, 2H), 4.10 - 3.92 (m, 2H), 3.85 (br t, J = 5.2 Hz, 2H), 3.77 (s, 3H), 3.11 - 2.86 (m, 2H), 2.84 - 2.47 (m, 2H), 1.49 (t, J = 7.0 Hz, 3H), 1.22 - 0.84 (m, 6H)
289		510.3	1H NMR (400 MHz, METHANOL-d4) δ = 8.72 (br d, J = 7.2 Hz, 1H), 8.13 (d, J = 17.2 Hz, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.26 - 7.16 (m, 2H), 4.77 - 4.67 (m, 1H), 4.54 - 4.43 (m, 1H), 4.04 - 4.02 (m, 3H), 4.02 - 3.90 (m, 3H), 3.78 - 3.76 (m, 3H), 3.76 - 3.72 (m, 1H), 2.99 (br d, J = 4.0 Hz, 2H), 2.72 - 2.56 (m, 2H), 1.37 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H)

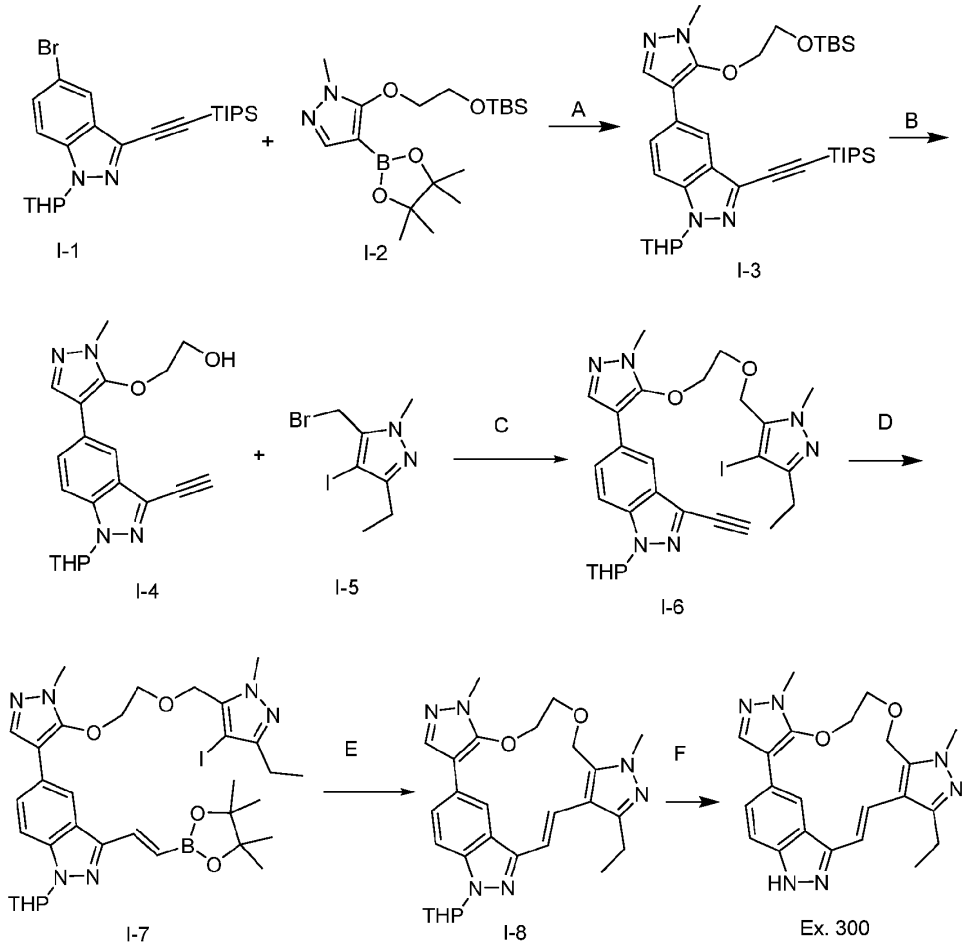
Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
290		517.2	1H NMR (400 MHz, DMSO-d6) δ = 13.00 (s, 1H), 8.56 (s, 1H), 7.95 (d, J = 17.2 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 16.8 Hz, 1H), 4.89 - 4.81 (m, 1H), 4.77 - 4.67 (m, 1H), 4.33 - 4.22 (m, 2H), 4.11 - 3.99 (m, 2H), 3.97 - 3.89 (m, 2H), 3.83 (s, 3H), 3.68 - 3.61 (m, 2H), 2.92 (s, 2H), 2.59 - 2.53 (m, 2H), 1.45 - 1.38 (m, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.92 - 0.83 (m, 3H)
291		446.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.75 - 8.69 (m, 1H), 7.94 (s, 1H), 7.78 - 7.66 (m, 2H), 7.60 - 7.46 (m, 1H), 7.17 - 7.07 (m, 1H), 4.60 (s, 2H), 4.36 (br t, J = 6.8 Hz, 2H), 3.92 - 3.84 (m, 5H), 3.80 (s, 3H), 2.99 (s, 1H), 2.54 - 2.47 (m, 3H), 1.40 - 1.32 (m, 3H)
292		502.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 (s, 1H), 8.28 (dd, J = 1.2, 8.8 Hz, 1H), 8.22 - 8.08 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 16.8 Hz, 1H), 4.82 (br d, J = 1.6 Hz, 1H), 4.35 (dq, J = 2.8, 7.2 Hz, 2H), 4.19 - 4.08 (m, 2H), 3.98 (br dd, J = 2.4, 4.2 Hz, 2H), 3.87 - 3.82 (m, 2H), 3.80 (s, 1H), 3.76 (s, 3H), 3.09 - 2.81 (m, 2H), 2.45 (br s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H)

Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
293		496.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.70 (br d, J = 7.2 Hz, 1H), 8.20 - 7.95 (m, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.28 - 7.18 (m, 2H), 4.82 - 4.64 (m, 1H), 4.23 - 4.11 (m, 2H), 4.03 (s, 3H), 3.86 (br t, J = 5.2 Hz, 2H), 3.77 (s, 3H), 3.30 (br s, 2H), 3.11 - 2.86 (m, 2H), 2.85 - 2.49 (m, 2H), 1.13 (br d, J = 6.4 Hz, 3H), 1.09 - 0.81 (m, 3H)
294		462.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.62 (s, 1H), 7.86 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.60 - 7.47 (m, 2H), 7.25 (d, J = 16.8 Hz, 1H), 4.67 (br s, 2H), 4.36 (br t, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.90 (br t, J = 7.6 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.48 (s, 3H), 1.54 (t, J = 7.2 Hz, 3H)
295		477.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.53 (s, 1H), 8.38 (d, J = 17.6 Hz, 1H), 7.80 (s, 1H), 7.66 (dd, J = 1.6, 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 17.6 Hz, 1H), 4.95 - 4.90 (m, 1H), 4.20 - 4.07 (m, 2H), 3.98 - 3.86 (m, 2H), 3.85 - 3.80 (m, 2H), 3.75 - 3.71 (m, 3H), 3.38 - 3.32 (m, 2H), 2.95 - 2.86 (m, 2H), 2.44 - 2.40 (m, 3H), 1.31 (t, J = 7.6 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H)

Ex #	Structure	MS *m/z* $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm
296		538.1	1H NMR (400 MHz, METHANOL-d4) δ = 8.65 (br d, J = 7.2 Hz, 1H), 8.06 (d, J = 16.8 Hz, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.29 - 7.19 (m, 2H), 5.03 - 4.92 (m, 1H), 4.75 - 4.65 (m, 1H), 4.14 - 4.00 (m, 2H), 3.99 - 3.91 (m, 3H), 3.75 (s, 3H), 3.07 - 2.85 (m, 2H), 2.69 - 2.51 (m, 2H), 1.48 - 1.42 (m, 6H), 1.21 (d, J = 6.0Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H)
297		507.2	1H NMR (400 MHz, DMSO-d6) δ = 12.72 (s, 1H), 8.39 (s, 1H), 7.95 (d, J = 17.2 Hz, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 17.2 Hz, 1H), 4.92 - 4.75 (m, 1H), 4.55 (s, 2H), 4.54 - 4.49 (m, 1H), 4.32 - 4.21 (m, 2H), 4.11 - 3.97 (m, 2H), 3.92 (s, 2H), 3.65 (s, 2H), 3.48 (s, 3H), 2.86 (s, 2H), 2.49 - 2.43 (m, 2H), 1.47 - 1.35 (m, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.92 - 0.82 (m, 3H)
298		510.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.67 (br d, J = 7.2 Hz, 1H), 8.04 - 7.87 (m, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.28 - 7.18 (m, 2H), 4.56 - 4.43 (m, 1H), 4.20 - 4.06 (m, 2H), 4.03 (s, 3H), 3.88 - 3.78 (m, 2H), 3.77 (s, 3H), 3.72 - 3.66 (m, 1H), 3.16 - 2.91 (m, 2H), 2.89 - 2.62 (m, 2H), 1.44 (br d, J = 6.4 Hz, 3H), 1.11 (br d, J = 6.2 Hz, 6H)

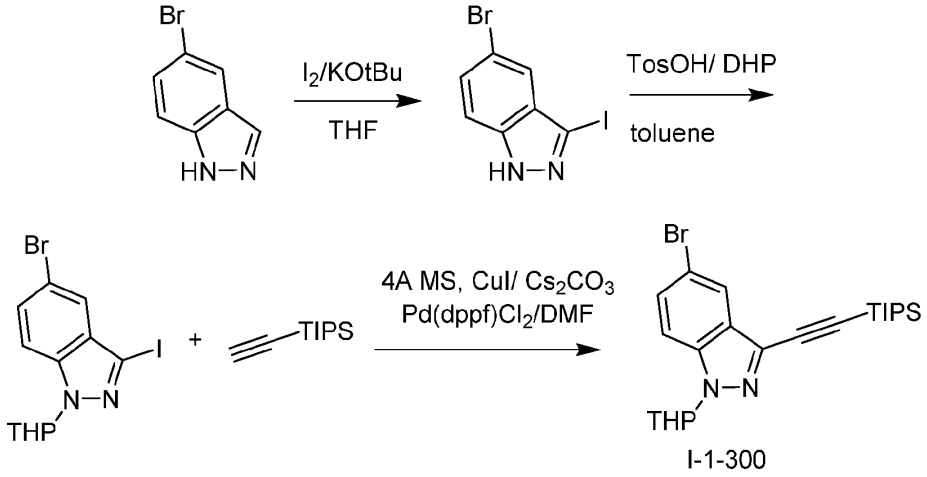
Ex #	Structure	MS *m/z* $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ ppm
299		522.2	1H NMR (400 MHz, METHANOL-d4) δ = 8.54 (s, 1H), 8.30 (d, J = 17.2 Hz, 1H), 7.85 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 17.2 Hz, 1H), 5.02 - 4.94 (m, 2H), 4.31 - 4.18 (m, 1H), 4.17 - 4.04 (m, 3H), 4.00 - 3.88 (m, 4H), 3.87 - 3.78 (m, 2H), 3.01 - 2.81 (m, 2H), 2.46 (s, 3H), 1.44 (t, J = 6.0 Hz, 6H), 1.12 (d, J = 6.0 Hz, 3H)

[02027] General Scheme I



[02028] General Scheme I is using Example 300 as an illustration. Compounds I-1 and I-2 are prepared via conventional chemistry from commercially available materials. Under palladium catalyzed coupling condition A, compounds I-1 and I-2 are converted to a product, I-3, which is then deprotected under condition B to generate I-4. I-4 is alkylated with I-5 under condition C to produce a product, e. g. I-6. A boronic ester I-7 is produced under Condition D followed by palladium-catalyzed Suzuki reaction under Condition E to generate the macrocyclic product, e. g. I-8. After deprotection, I-8 is converted to the final product, e. g. Ex.300.

[02029] Preparation of 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-1-300)



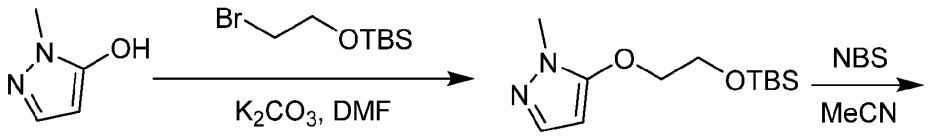
I-1-300

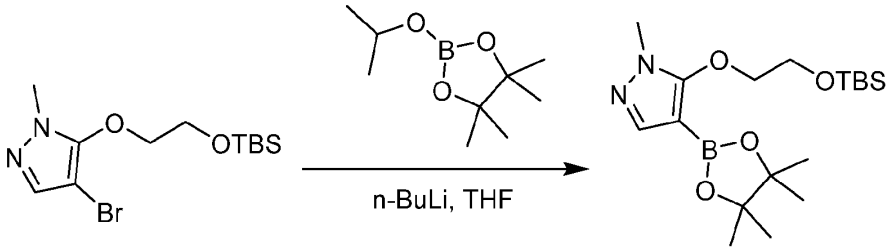
[02030] Step 1. A solution of 5-bromo-1H-indazole (21.0 g, 107 mmol, 1 *eq*) in THF (250 mL) was cooled down on an ice bath and KOtBu (35.9 g, 320 mmol, 3 *eq*) was added portion wise. The resulting slurry was stirred at 0 °C and a solution of I_2 (54.1 g, 213 mmol, 42.9 mL, 2 *eq*) in THF (250 mL) was added dropwise. The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1H-indazole (120 g, 350 mmol, 82% yield, 94% purity) as a white solid. LCMS: 324.7 (M+1).

[02031] Step 2. To a mixture of 5-bromo-3-iodo-1H-indazole (25.0 g, 77.4 mmol, 1 *eq*) and 3,4-dihydro-2H-pyran (13.0 g, 155 mmol, 2 *eq*) in toluene (250 mL) was added 4-methylbenzenesulfonic acid (2.67 g, 15.5 mmol, 0.2 *eq*). The mixture was stirred at 90 °C for 12 hours. On completion, the reaction was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (24.0 g, 58.9 mmol, 76% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 1.6 Hz, 1H), 7.54 - 7.44 (m, 2H), 5.68 (dd, *J* = 3.2, 9.1 Hz, 1H), 4.04 - 3.95 (m, 1H), 3.79 - 3.66 (m, 1H), 2.58 - 2.46 (m, 1H), 2.20 - 2.03 (m, 2H), 1.87 - 1.54 (m, 3H).

[02032] Step 3. To a mixture of 5-bromo-3-iodo-1-tetrahydropyran-2-yl-indazole (23.0 g, 56.5 mmol, 1 *eq*) and ethynyl(triisopropyl)silane (11.3 g, 62.2 mmol, 1.1 *eq*) in DMF (250 mL) was added Cs_2CO_3 (55.2 g, 170 mmol, 3 *eq*), Pd(dppf)Cl_2 (2.48 g, 3.39 mmol, 0.06 *eq*) and CuI (646 mg, 3.39 mmol, 0.06 *eq*) under N_2. The mixture was stirred at 25 °C for 3 hours. On completion, the reaction was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to afford compound 2-(5-bromo-1-tetrahydropyran-2-yl-indazol-3-yl)ethynyl-triisopropyl-silane (I-1-300, 38.0 g, 79.9 mmol, 70% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.57 - 7.43 (m, 2H), 5.70 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.02 (bd, *J* = 11.2 Hz, 1H), 3.80 - 3.65 (m, 1H), 2.59 - 2.41 (m, 1H), 2.14 (d, *J* = 3.2 Hz, 1H), 2.08 (s, 1H), 1.79 - 1.70 (m, 2H), 1.67 (s, 1H), 1.22 - 1.18 (m, 18H), 1.18 - 1.14 (m, 3H).

[02033] Preparation of tert-butyl-dimethyl-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazol-3-yl]oxyethoxy]silane (I-2-300)





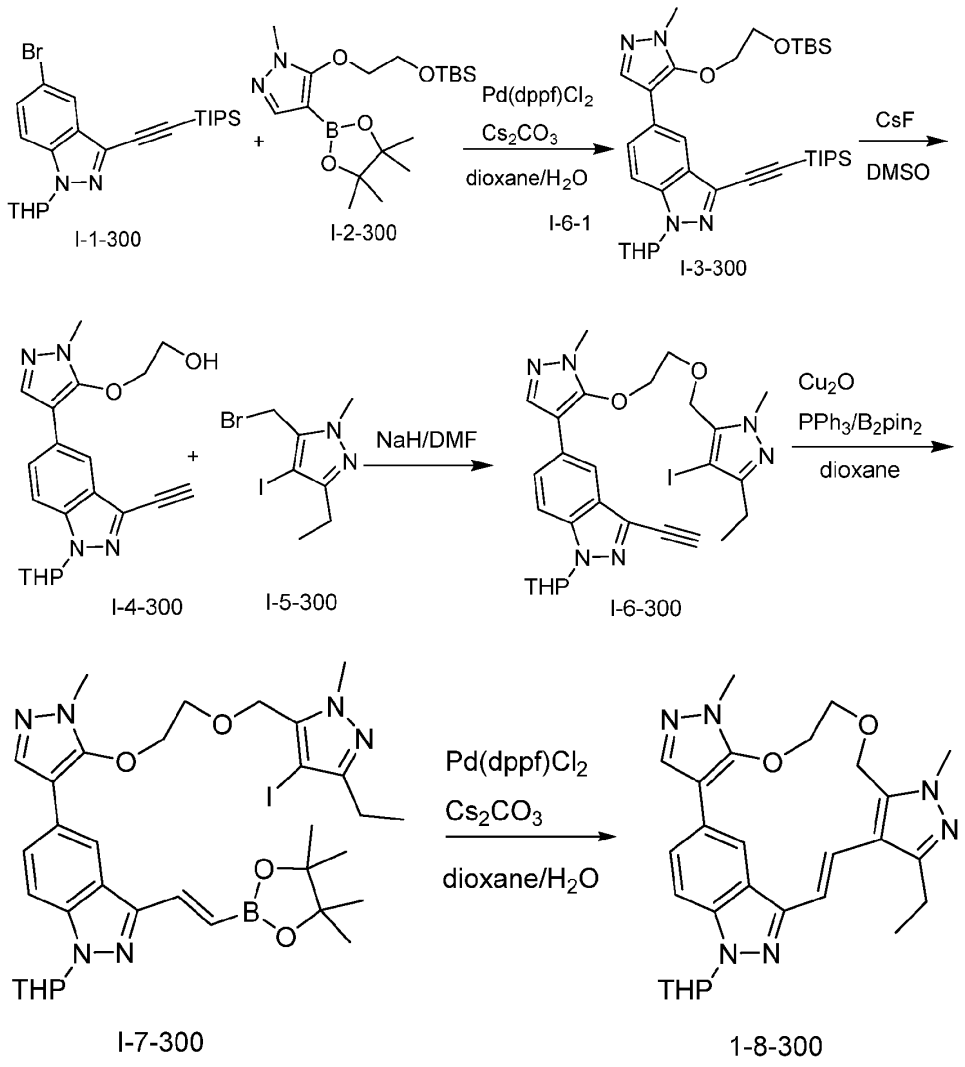
I-2-300

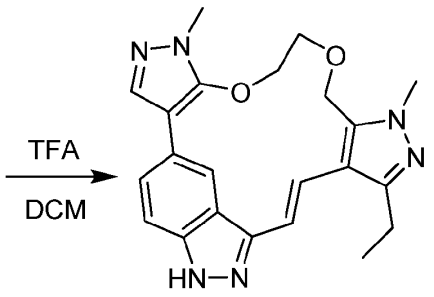
[02034] Step 1. To a mixture of 2-methylpyrazol-3-ol (15.0 g, 152 mmol, 1 eq) in DMF (150 mL) was added 2-bromoethoxy-tert-butyl-dimethyl-silane (40.2 g, 168 mmol, 1.1 eq) and K_2CO_3 (63.4 g, 458 mmol, 3 eq), the reaction mixture was stirred at 30°C for 12 hours. On completion, the reaction mixture was diluted with water (150 mL) and extracted with EA (2 X 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford tert- butyl- dimethyl- [2-(2- methylpyrazol -3-yl) oxyethoxy]silane (9.00 g, 35.1 mmol, 22% yield) as colorless oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.19 (d, J = 2.0 Hz, 1H), 5.62 (d, J = 2.0 Hz, 1H), 4.10 - 4.07 (m, 2H), 3.91 - 3.88 (m, 2H), 3.53 (s, 3H), 0.86 (s, 9H), 0.08 - 0.02 (m, 6H).

[02035] Step 2. To a mixture of tert-butyl-dimethyl-[2-(2-methylpyrazol-3-yl)oxyethoxy]silane (8.00 g, 31.2 mmol, 1 *eq*) in ACN (70 mL) at 0°C and then the reaction mixture was added NBS (6.11 g, 34.3 mmol, 1.1 *eq*), the reaction mixture was stirred at 25°C for 2 hours. On completion, the reaction mixture was diluted with water (100 mL) and extracted with EA (2 X 100 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethanol (9.00 g, 90% yield) as yellow oil. LCMS: $[M+H]^+$ *m/z* = 220.9

[02036] Step 3. To a mixture of 2-(4-bromo-2-methyl-pyrazol-3-yl)oxyethoxy-tert-butyl-dimethyl-silane (18.0 g, 53.6 mmol, 1 *eq*) in THF (180 mL) was added n-BuLi (2.5 M, 64.4 mL, 3 *eq*), the reaction mixture was stirred at -60°C for 0.5 hours, and then 2-isopropoxy-4,4,5,5-tetramethyl -1,3,2-dioxaborolane (29.9 g, 161 mmol, 32.8 mL, 3 *eq*) was added, the reaction mixture was stirred at -60°C for 2 hours. On completion, the reaction mixture was quenched with aq.NH_4Cl (300 mL) under stirring, and then the residue was diluted with water (200 mL) and extracted with EA (2 X 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford tert-butyl-dimethyl-[2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazol-3-yl]oxyethoxy]silane (14.2 g, 37.3 mmol, 69% yield) as yellow oil. LCMS: $[M+H]^+$ *m/z* = 383.4

[02037] General Method Z. Preparation of (17*E*)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 300)





Ex. 300

[02038] Step 1. To a mixture of I-2-300 (5.19 g, 13.5 mmol, 1.1 *eq*) in dioxane (60 mL) and H_2O (12 mL) was added I-1-300 (5.70 g, 12.3 mmol, 1 *eq*), Cs_2CO_3 (12.0 g, 37.0 mmol, 3 *eq*) and Pd(dppf)Cl_2 (451 mg, 0.617 mmol, 0.05 *eq*), the reaction mixture was stirred at 90°C for 12 hours. On completion, the reaction mixture was diluted with water (80 mL) and extracted with EA (2 X 80 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford I-3-300 (4.83 g, 7.58 mmol, 61% yield) as a yellow solid. LCMS: $[M+H]^+$ *m/z* = 638.0

[02039] Step 2. To a mixture of I-3-300 (4.00 g, 6.28 mmol, 1 *eq*) in DMSO (40 mL) was added CsF (2.86 g, 18.8 mmol, 3 *eq*), and the reaction mixture was stirred at 25°C for 12 hours. On completion, the reaction mixture was diluted with water (50 mL) and extracted with EA (2 X 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford I-4-300 (2.10 g, 5.73 mmol, 91.2% yield) as yellow oil. LCMS: $[M+H]^+$ *m/z* = 367.2

[02040] Step 3. To a mixture of I-4-300 (100 mg, 0.272 mmol, 1 *eq*) in DMF (3 mL) was added NaH (27.2 mg, 0.682 mmol, 60% purity, 2.5 *eq*) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hour, and then I-5-300 (89.7 mg, 0.272 mmol, 1 *eq*) was added to the reaction mixture. The reaction mixture was stirred at 25°C for 12 hours. On completion, the reaction mixture was quenched with water (0.5 mL), and then the residue was diluted with water (5 mL) and extracted with EA (2 X 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford I-6-300 (50.0 mg, 0.081 mmol, 29% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.79 (s, 1H), 7.74 (s, 2H), 5.87 (dd, *J* = 2.4, 9.6 Hz, 1H), 4.58 (s, 1H), 4.56 (s, 2H), 4.10 - 4.06 (m, 2H), 3.89 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.79 - 3.72 (m, 1H), 3.68 (s, 3H), 3.66 (s, 2H), 2.47 - 2.44 (m, 1H), 2.36 - 2.29 (m, 1H), 2.18

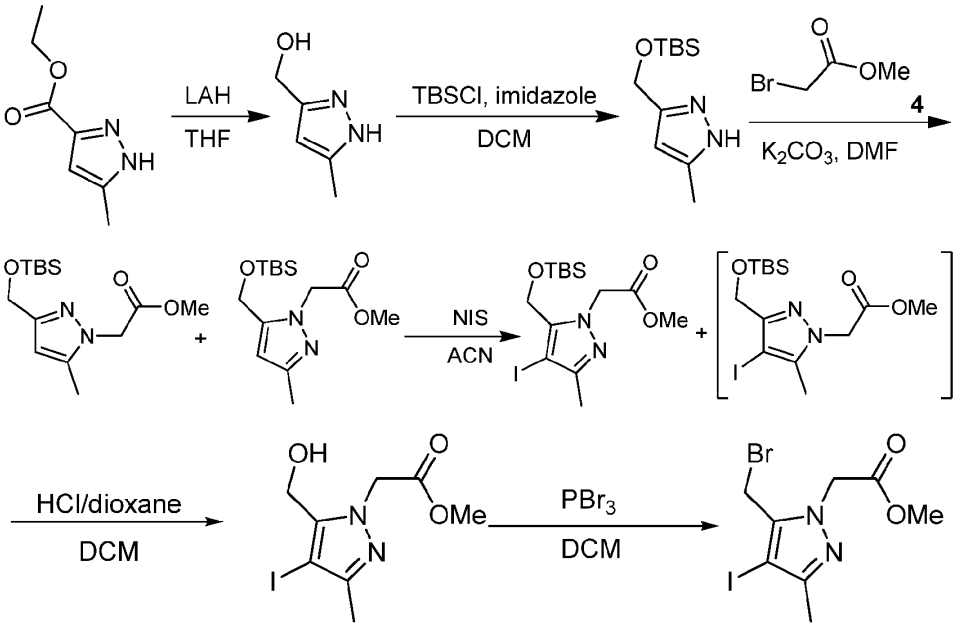
(s, 1H), 2.08 - 1.99 (m, 2H), 1.82 - 1.70 (m, 1H), 1.60 (d, *J* = 3.6 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H).

[02041] Step 4. To a mixture of I-6-300 (430 mg, 0.699 mmol, 1 *eq*) in dioxane (5 mL) was added Cu_2O (50.0 mg, 0.349 mmol, 0.5 *eq*), PPh_3 (201 mg, 0.769 mmol, 1.1 *eq*) and 4,4,5,5-tetramethyl -2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1,3,2- dioxaborolane (355 mg, 1.40 mmol, 2 *eq*). The reaction mixture was stirred at 80°C for 12 hours. On completion, the residue was diluted with water (10 mL) and extracted with EA (2 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford I-7-300 (384 mg, 0.517 mmol, 73% yield) as yellow oil. LCMS: $[M+H]^+$ *m/z* = 742.8

[02042] Step 5. To a mixture of I-7-300 (350 mg, 0.471 mmol, 1 *eq*) in dioxane (5 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (34.4 mg, 0.047 mmol, 0.1 *eq*) and Cs_2CO_3 (460 mg, 1.41 mmol, 3 *eq*). The reaction mixture was stirred at 90°C for 12 hours. On completion, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford I-8-300 (188 mg, 0.384 mmol, 81% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.05 (d, *J* = 17.6 Hz, 1H), 7.95 (s, 1H), 7.79 - 7.76 (m, 1H), 7.72 - 7.69 (m, 1H), 6.88 (s, 1H), 5.81 (dd, *J* = 2.4, 9.6 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H), 4.04 - 4.00 (m, 2H), 3.94 - 3.88 (m, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.94 - 1.86 (m, 4H), 1.58 (d, *J* = 3.6 Hz, 2H), 1.27 (s, 3H).

[02043] Step 6. To a mixture of I-8-300 (168 mg, 0.343 mmol, 1 *eq*) in DCM (1 mL) was added TFA (12.9 g, 113 mmol, 8.40 mL, 329 *eq*), the reaction mixture was stirred at 25°C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo*. The residue was triturated with EA (3 mL), filtered and concentrated in vacuo to afford Ex. 3001 (38.7 mg, 0.956 mmol, 27% yield) as brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.02 (d, *J* = 17.6 Hz, 1H), 7.92 (s, 1H), 7.70 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 17.6 Hz, 1H), 4.87 (s, 2H), 4.30 (dd, *J* = 2.4, 4.4 Hz, 2H), 4.05 - 3.99 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.80 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). LCMS: $[M+H]^+$ *m/z* = 404.8.

[02044] Preparation of methyl 2-[5-(bromomethyl)-4-iodo-3-methyl-pyrazol-1-yl]acetate (I-1-301)



I-1-301

[02045] Step 1. To a mixture of ethyl 5-methyl-1H-pyrazole-3-carboxylate (10.0 g, 64.8 mmol, 1 eq) in THF (100 mL) was added LAH (2.95 g, 77.8 mmol, 1.2 eq), the reaction mixture was stirred at 0°C for 2 hours. On completion, the mixture was slowly added to water (3 ml), saturated sodium hydroxide (3 ml) and water (9 ml) to quench. The reaction mixture was filtered and concentrated under reduced pressure to afford (5-methyl-1H-pyrazol-3-yl)methanol (3.40 g, 30.3 mmol, 46% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.89 (s, 1H), 4.36 (s, 2H), 2.16 (s, 3H)

[02046] Step 2. To a mixture of (5-methyl-1H-pyrazol-3-yl)methanol (25.0 g, 222 mmol, 1 eq) in DCM (300 mL) was added imidazole (30.3 g, 445 mmol, 2 eq) and TBSCl (50.4 g, 334 mmol, 40.9 mL, 1.5 eq) at 0 °C, the reaction mixture was stirred at 25 °C for 12 hours. On completion, the residue was diluted with water (300 mL) and extracted with DCM (2 X 300 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to afford tert-butyl-dimethyl-[(5-methyl-1H-pyrazol-3-yl)methoxy]silane (65.0 g, 90% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.34 - 12.09 (m, 1H), 5.90 (s, 1H), 4.55 (s, 2H), 2.17 (s, 3H), 0.86 (s, 9H), 0.05 - 0.02 (m, 6H).

[02047] Step 3. A mixture of methyl 2-bromoacetate (40.5 g, 265 mmol, 25.0 mL, 2 eq), tert-butyl-dimethyl-[(5-methyl-1H-pyrazol-3-yl)methoxy]silane (30.0 g, 132 mmol, 1 eq), K_2CO_3 (54.9 g, 397 mmol, 3 eq) was combined in DMF (300 mL). The mixture was

stirred at 80 °C for 16 hours. On completion, the reaction mixture was filtered and then the residue was diluted with water (500 mL) and extracted with EA (2 X 500 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography to afford methyl 2-[3-[[tert-butyl(dimethyl)silyl] oxymethyl] -5- methyl-pyrazol-1-yl]acetate and methyl 2-[5- [[tert-butyl (dimethyl)silyl]oxymethyl]-3- methyl-pyrazol-1-yl]acetate (21.2 g, 35.5 mmol, 52% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 5.98 (s, 1H), 4.94 (s, 2H), 4.91 (s, 2H), 3.65 (s, 3H), 2.17 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H).

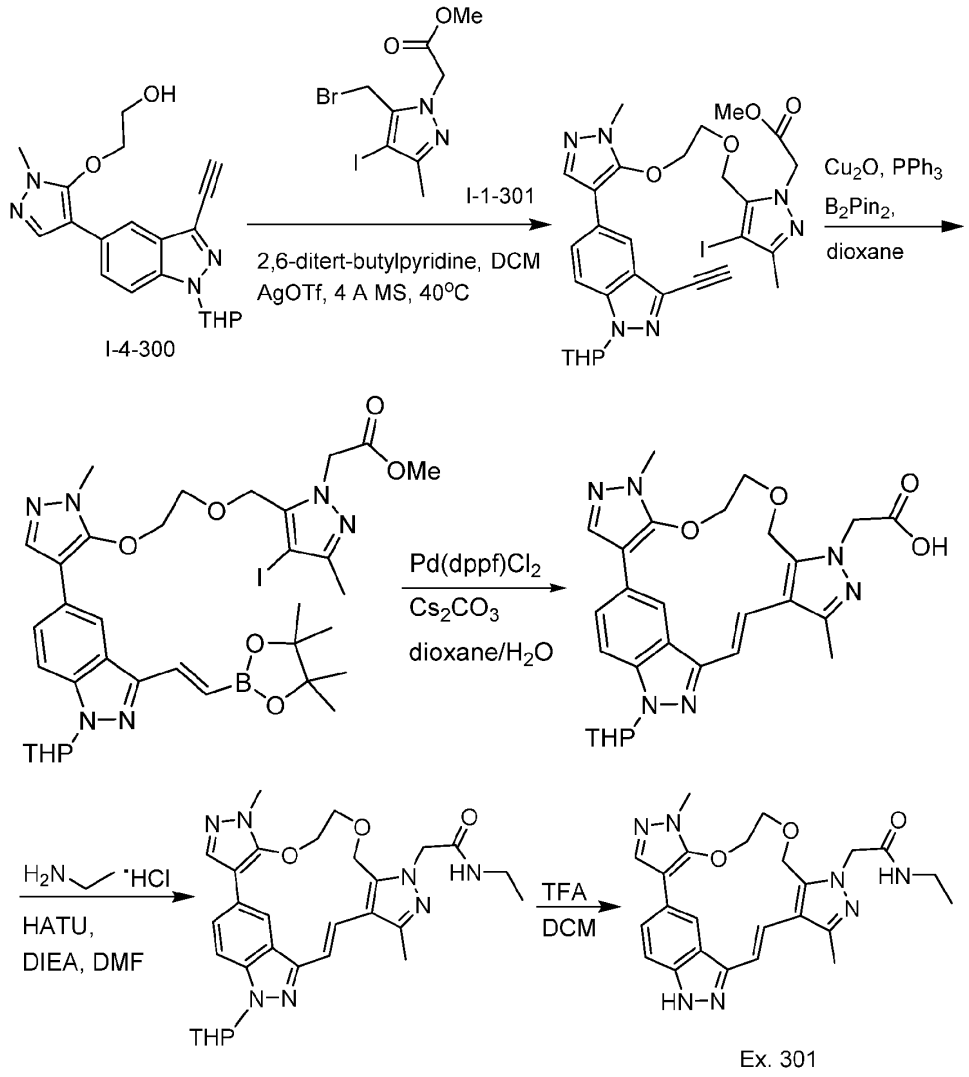
[02048] Step 4. To a mixture of methyl 2-[5-[[tert-butyl(dimethyl)silyl] oxymethyl]-3-methyl -pyrazol-1-yl] acetate and methyl 2-[3-[[tert-butyl (dimethyl) silyl] oxymethyl] -5-methyl-pyrazol-1-yl]acetate (21.2 g, 35.5 mmol, 1 eq) in ACN (200 mL) was added NIS (7.99 g, 35.5 mmol, 1 eq), the reaction mixture was stirred at 25°C for 12 hours. On completion, the residue was diluted with water (200 mL) and extracted with EA (2 X 200 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography to afford methyl 2-[3-[[tert-butyl(dimethyl) silyl]oxymethyl] -4-iodo-5- methyl-pyrazol -1-yl] acetate (6.19 g, 14.5 mmol, 41% yield) as yellow solid and afford methyl 2-[5-[[tert-butyl (dimethyl) silyl]oxymethyl] -4-iodo-3-methyl -pyrazol-1-yl]acetate (13.0 g, 30.6 mmol, 86% yield) yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 5.09 (s, 2H), 4.48 (s, 2H), 3.68 (s, 3H), 2.20 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H). and 1H NMR (400 MHz, DMSO-d6) δ 5.03 (s, 2H), 4.64 (s, 2H), 3.65 (s, 3H), 2.11 (s, 3H), 0.85 (s, 9H), 0.06 (s, 6H).

[02049] Step 5. To a mixture of methyl 2-[5-[[tert-butyl(dimethyl)silyl] oxymethyl] -4-iodo- 3-methyl –pyrazol -1-yl]acetate (10.0 g, 23.5 mmol, 1 eq) in DCM (100 mL) was added HCl/dioxane (4 M, 10.0 mL, 1.70 eq), the reaction mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was concentrated in vacuo, and then the residue was diluted with water (100 mL) and extracted with DCM (2 X 100 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to afford methyl 2-[5-(hydroxymethyl) -4-iodo-3-methyl - pyrazol-1-yl]acetate (9.78 g, 92% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 5.07 - 5.03 (m, 2H), 4.43 - 4.41 (m, 2H), 3.67 - 3.65 (m, 3H), 2.11 - 2.09 (m, 3H), 0.84 (s, 5H), -0.04 (s, 4H)

[02050] Step 6. To a solution of methyl 2-[5-(hydroxymethyl)-4-iodo-3-methyl-pyrazol-1-yl]acetate (5.00 g, 16.1 mmol, 1 eq) in DCM (90 mL). Then PBr_3 (4.36 g, 16.1 mmol, 1 eq) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the residue was diluted with water (100 mL) and extracted with DCM (2 X 100 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo

to give a residue. The residue was purified by column chromatography and then purified by reverse phase (0.1 % FA condition) to afford I-1-301 (4.50g, 12.0 mmol, 74% yield) as white solid. 1H NMR (400 MHz, DMSO-d6) δ 5.13 (s, 2H), 4.70 (s, 2H), 3.67 (s, 3H), 2.11 (s, 3H).

[02051] General Method B. Preparation of 2-[(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(8*H*)-yl]-*N*-ethylacetamide (Ex. 301)



[02052] Step 1. To a mixture of I-4-300 (2.70 g, 7.37 mmol, 1 eq) in DCM (10 mL) was added I-1-2 (2.02 g, 5.42 mmol, 7.36^{e-1} eq), AgOTf (3.79 g, 14.7 mmol, 2 eq), 4A MS (7.37 mmol, 1 eq) and 2,6-ditert-butylpyridine (8.46 g, 44.2 mmol, 6 eq), the reaction mixture was stirred at 40 °C for 12 hours. On completion, the residue was diluted with water

(10 mL) and extracted with DCM (2 X 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by flash column chromatography to afford methyl 2-[5-[2-[4- (3-ethynyl-1- tetrahydropyran-2-yl-indazol-5-yl) -2-methyl-pyrazol-3-yl] oxyethoxymethyl]-4-iodo-3-methyl-pyrazol-1-yl]acetate (700 mg, 1.06 mmol, 14% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.82 - 7.77 (m, 2H), 7.76 - 7.71 (m, 1H), 5.91 - 5.85 (m, 1H), 5.78 - 5.74 (m, 1H), 5.05 - 5.01 (m, 2H), 4.56 (s, 2H), 4.15 - 4.08 (m, 1H), 4.04 - 4.00 (m, 1H), 3.92 - 3.85 (m, 1H), 3.69 - 3.66 (m, 3H), 3.65 - 3.61 (m, 2H), 3.60 - 3.56 (m, 2H), 3.51 - 3.46 (m, 3H), 2.43 - 2.29 (m, 2H), 2.12 (s, 3H), 2.05 - 1.96 (m, 2H), 1.60 (s, 2H).

[02053] Step 2. To a mixture of methyl 2-[5-[2-[4- (3-ethynyl-1- tetrahydropyran-2-yl-indazol-5-yl) -2-methyl-pyrazol-3-yl] oxyethoxymethyl]-4-iodo-3-methyl-pyrazol-1-yl]acetate (700 mg, 1.06 mmol, 1 eq) in dioxane (4 mL) was added Cu_2O (76.0 mg, 531 umol, 0.5 eq), PPh_3 (278 mg, 1.06 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 (404 mg, 1.59 mmol, 1.5 eq), the reaction mixture was stirred at 80 °C for 12 hours. On completion, the residue was diluted with water (10 mL) and extracted with EA (2 X 10 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by flash column chromatography and then purified by reverse phase to afford 2-[4-iodo-3-methyl-5- [2-[2-methyl-4- [1-tetrahydropyran -2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethoxymethyl]pyrazol-1-yl]acetate (120 mg, 152 umol, 14% yield) as white solid. LCMS: $[M+H]^+$ *m/z*= 787.0

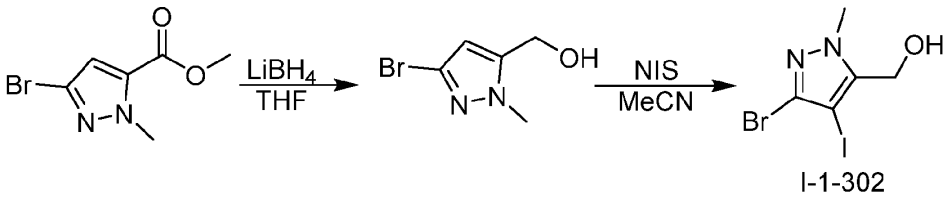
[02054] Step 3. To a mixture of 2-|4-iodo-3-methyl-5- |2-|2-methyl-4- |1-tetrahydropyran -2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazol-5-yl]pyrazol-3-yl]oxyethoxymethyl]pyrazol-1-yl]acetate (120 mg, 152 umol, 1 eq) in H_2O (0.2 mL) and 1,4-dioxane (1 mL) was added $Pd(dppf)Cl_2$ (11.1 mg, 15.2 umol, 0.1 eq) and Cs_2CO_3 (149 mg, 457 umol, 3 eq), the reaction mixture was stirred at 90°C for 8 hours. On completion, the residue was diluted with water (5 mL) and extracted with EA (2 X 5 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by prep-HPLC to afford 2-[(17E)-5,15-dimethyl- 21-tetrahydropyran-2-yl- 7,10 – dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetic acid (32.0 mg, 30% yield) as white solid. LCMS: $[M+H]^+$ *m/z* =519.3

[02055] Step 4. To a mixture of 2-[(17E)-5,15-dimethyl- 21-tetrahydropyran-2- yl-7,10 – dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]acetic acid (27.0 mg, 52.0 umol, 1 eq)

in DMF (2 mL) was added HATU (23.7 mg, 62.4 umol, 1.2 eq) and DIEA (20.1 mg, 156 umol, 27.2 uL, 3 eq), the reaction mixture was stirred at 25°C for 0.5 hour, and then the reaction mixture was added ethanamine;hydrochloride (27.0 mg, 228 umol, 4.39 eq) , the reaction mixture was stirred at 25 °C for 2 hours. On completion, the residue was diluted with water (5 mL) and extracted with EA (2 X 5 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated in vacuo to afford 2-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,10-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]-N-ethyl-acetamide (23.0 mg, 42.1 umol, 80% yield) as colourless gum. LCMS: $[M+H]^+$ *m/z*= 546.3

[02056] Step 5. To a mixture of 2-[(17E)-5,15-dimethyl-21-tetrahydropyran-2-yl-7,10-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$.$0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaen-13-yl]-N-ethyl-acetamide (21.0 mg, 38.4 umol, 1 eq) in DCM (1 mL) was added TFA (16.1 g, 141 mmol, 10.5 mL, 3684 eq), the reaction mixture was stirred at 25 °C for 1 hour. On completion, the residue was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC to afford Ex. 301 (3.74 mg, 5.85 umol, 15% yield, 90% purity, TFA) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 13.12 - 12.70 (m, 1H), 8.54 (s, 1H), 8.16 (t, J = 5.4 Hz, 1H), 8.10 (d, J = 17.5 Hz, 1H), 7.92 (s, 1H), 7.70 (dd, J = 1.3, 8.8 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 17.6 Hz, 1H), 4.84 (s, 2H), 4.69 (s, 2H), 4.28 (br dd, J = 2.2, 4.3 Hz, 2H), 3.99 (br s, 2H), 3.74 (s, 3H), 3.14 - 3.08 (m, 2H), 2.39 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H). LCMS: $[M+H]^+$ *m/z* =461.9

[02057] Preparation of (5-bromo-4-iodo-2-methyl-pyrazol-3-yl)methanol (I-1-302)

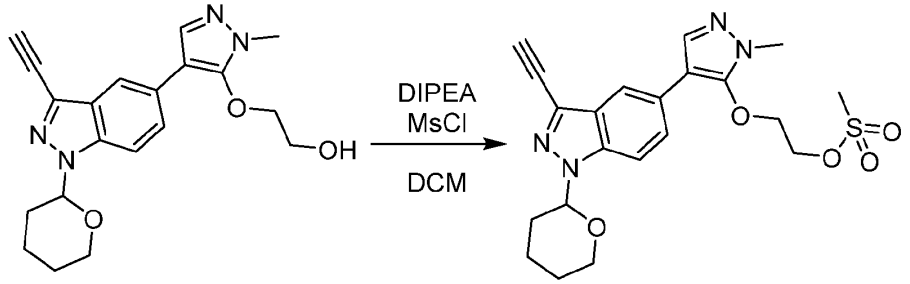


I-1-302

[02058] Step 1. To methyl 5-bromo-2-methyl-pyrazole-3-carboxylate (500 mg, 2.28 mmol) in THF (11.4 mL) at 0 °C was added, $LiBH_4$ (120 mg, 5.44 mmol). Stirred as temperature increase to RT over 18 hr. Reaction was quenched with water at 0 °C and the reaction was worked up with DCM and water (30 mL). The aqueous layer was extracted with DCM (2x 20mL). The combined organic layer was washed with brine and dried over sodium sulfate. The filtrate was concentrated and residue was crystallized with EA (10mL) and Hexanes (30 mL) to afford (5-bromo-2-methyl-pyrazol-3-yl)methanol (333 mg, 1.74 mmol, 76.37% yield). LCMS: $[M/M+2]^+$ *m/z*= 190.9/192.9

[02059] Step 2. To (5-bromo-2-methyl-pyrazol-3-yl)methanol (333 mg, 1.74 mmol) in Acetonitrile (8.72 mL) was added NIS (470.64 mg, 2.09 mmol). Stir at 22 °C for 18 hr. Quenched with water (5mL) and worked up with DCM and water (30 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Filtrate was concentrated after filtration. Resulting residue was crystallized with EA and Hexanes to afford I-1-302 (488 mg, 1.54 mmol, 88.33% yield) as a beige solid. Further dried on house vacuum overnight. LCMS: $[M/M+2]^+$ *m/z*= 316.2/318.2

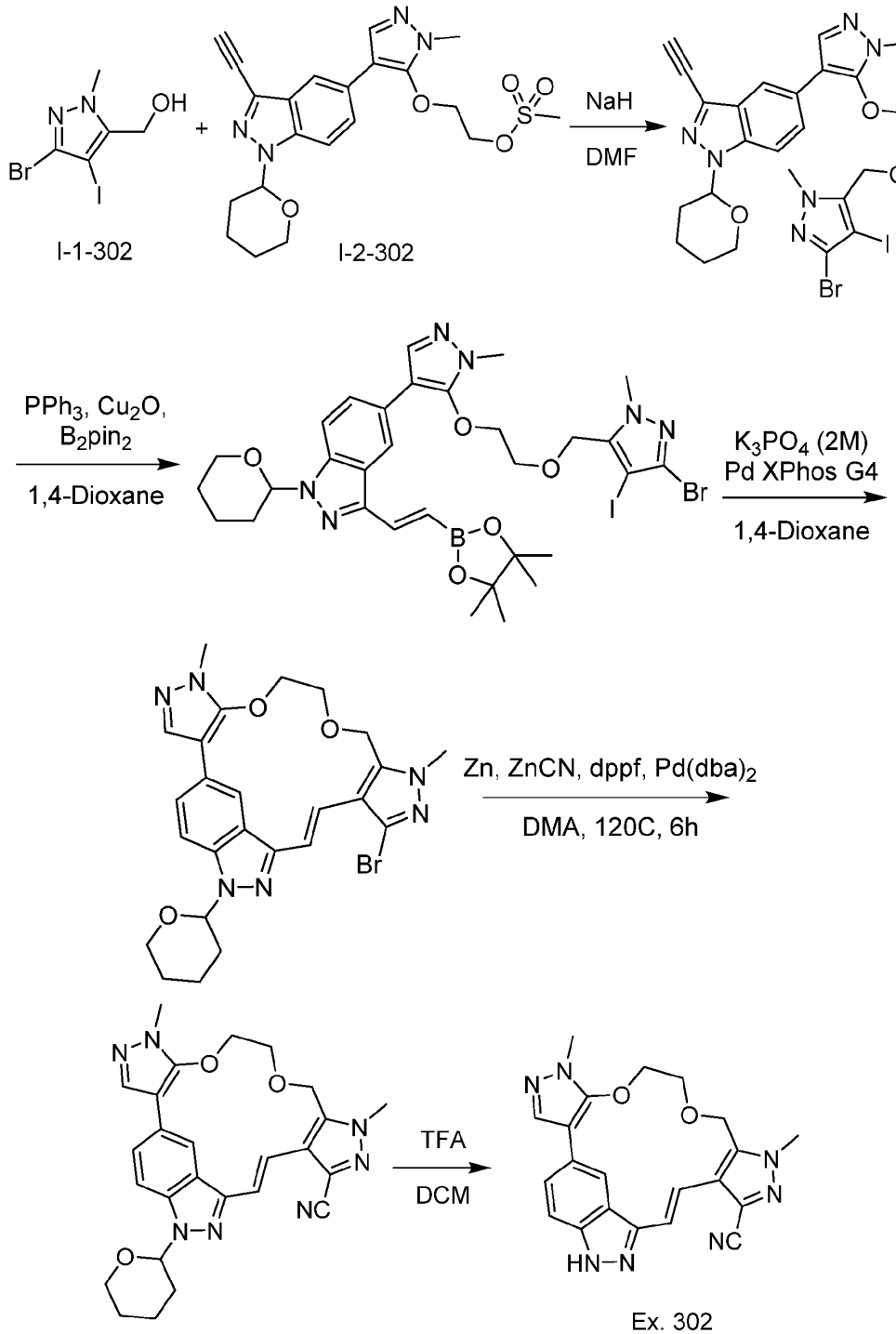
[02060] Preparation of 2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethyl methanesulfonate (I-2-302)



I-4 I-2-302

[02061] Step 1. To 2-[4-(3-ethynyl-1-tetrahydropyran-2-yl-indazol-5-yl)-2-methyl-pyrazol-3-yl]oxyethanol, I-4, (204 mg, 556.8 µmol) in DCM (3 mL) was added base, DIPEA (1.67 mmol, 290 µL) followed by methanesulfonyl chloride (668.10 µmol, 52 µL). Stirred at 0 °C as temperature warmed for 18 hr. Reaction was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 40-100% EA in Hexanes) provided I-2-302 (175 mg, 393.70 µmol, 70.71% yield). LCMS: $[M+H]^+$ *m/z*= 444.9

[02062] General Method C. Preparation of (17E)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c"]tripyrazole-16-carbonitrile (Ex. 302)



[02063] Step 1. To I-1-302 (107 mg, 337.5 μmol) in anhydrous DMF (1.1 mL) was added sodium hydride (13.50 mg, 337.5 μmol, 60% in mineral oil) at 0 °C under argon.

Stirred as temperature increases to RT over 1 h. Cooled again and a solution of I-2-302 (100 mg, 224.97 μmol) in DMF (1 mL) was added dropwise over 5 minutes. Stir as temperature increased to RT overnight. Cooled to 0 °C and quenched with saturated NH_4Cl (aq) (2 mL). Reaction mixture was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 20-80% EA in Hexanes) twice provided I-3-302 (21.49 mg, 32.30 μmol, 14.36% yield). LCMS: $[M/M+2]^+$ *m/z*= 664.8/666.8

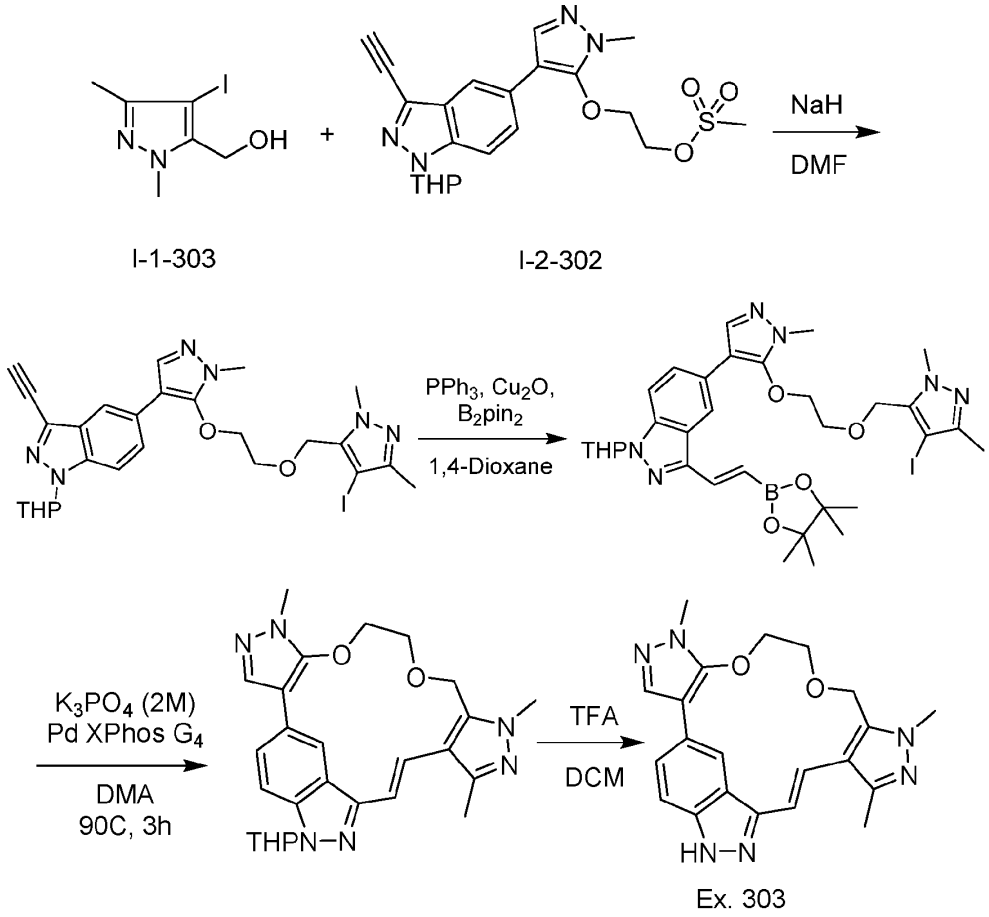
[02064] Step 2 was performed in a similar manner to step 4 in General Method A to provided I-4-302 (19.96 mg, 25.16 μmol, 77.90% yield). LCMS: $[M/M+2]^+$ *m/z*= 792.8/794.8

[02065] Step 3. To I-4-302 (66.8 mg, 81.45 μmol) in solvent, 1,4-Dioxane (1.88 mL) was added K_3PO_4 (2 M, 122 μL). Stir as argon bubbled through and catalyst, Pd Xphos G4 (7.00 mg, 8.15 μmol) was added. Vessel sealed and heated to 85 °C for 1.5 hr. Reaction was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-10% MeOH in DCM) followed by preparative HPLC (C18, 10-100% acetonitrile in water with 0.035% TFA) afforded I-5-302 (9.76 mg, 17.23 μmol, 21.15% yield). LCMS: $[M/M+2]^+$ *m/z* =538.9/540.9

[02066] Step 4. To I-5-302 (9.76 mg, 17.23 μmol) in DMA (1 mL) was added zinc (2.3 mg, 34.46 μmol) and zinc cyanide (22.3 mg, 189.52 μmol), argon was bubbled through as dppf (5.7 mg, 10.34 μmol) was added followed by $Pd(dba)_2$ (3 mg, 5.2 μmol). Stir under argon for about 5 minutes. Vessel was closed and heated to 120 °C and stirred for 6 hr. Reaction was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography twice (automated system, 12g silica, 0-10% MeOH in DCM, then 0-10% MeOH/DCM (1/3) in EA) provided I-6-302 (3.85 mg, 7.51 μmol, 43.59% yield). LCMS: $[M+H]^+$ *m/z* =486.0

[02067] Step 5 was performed in a similar manner to step 6 in General Method A to provided Ex. 302 (1.77 mg, 4.30 μmol, 68.74% yield, 97.61% purity). 1H NMR (400 MHz, DMSO-d6) δ = 8.53 (s, 1H), 8.10 (d, J = 17.6 Hz, 1H), 7.96 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 17.4 Hz, 1H), 5.01 (s, 2H), 4.33 - 4.28 (m, 2H), 4.08 - 4.02 (m, 2H), 3.87 (s, 3H), 3.75 (s, 3H). LCMS: $[M+H]^+$ *m/z* =401.96

[02068] General Method D. Preparation of (17E)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-c:15,14-c':6,7-c'']tripyrazole (Ex. 303)



[02069] Intermediate I-1-303 was prepared similarly to I-1-302 starting from appropriate alcohol in step 2.

[02070] Step 1. To I-1-303 (56.70 mg, 224.97 μmol) in DMF (1 mL) was added base, sodium hydride (8.1 mg, 202.47 μmol, 60% in mineral oil) followed by I-2-3 (50 mg, 112.49 μmol). Stirred at 22 °C for 18 hr. Reaction was cooled and quenched with 1 mL of saturated NH_4Cl(aq), diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 40-100% EA in Hexanes) provided 3-ethynyl-5-[5-[2-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methoxy]ethoxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazole (18.11 mg, 30.16 μmol, 26.81% yield). LCMS: $[M+H]^+$ *m/z* =601.1

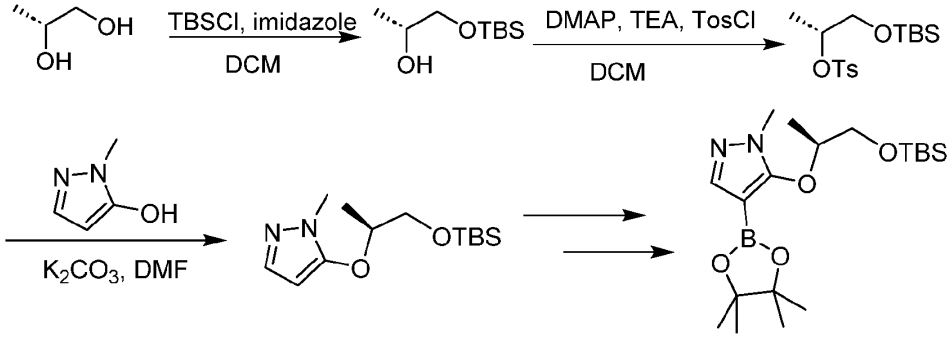
[02071] Step 2. To 3-ethynyl-5-[5-[2-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methoxy]ethoxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-indazole (18.11 mg, 30.16 μmol) in solvent, 1,4-Dioxane (1 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (11.5 mg, 45 μmol) and triphenylphosphine (11.9 mg, 45.2 μmol). Stir as argon was bubbled through and catalyst, copper(I) oxide (4.3 mg, 30.2 μmol) was added. Vessel sealed and heated to 80 °C for 1 hr. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 3 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 40-100% EA in Hexanes) provided 5-[5-[2-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methoxy]ethoxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazole (21.97 mg, 30.16 μmol, 100.00% yield). Taken forward without additional purification. LCMS: $[M+H]^+$ *m/z* =729.2

[02072] Step 3. To 5-[5-[2-[(4-iodo-2,5-dimethyl-pyrazol-3-yl)methoxy]ethoxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazole (21.97 mg, 30.16 μmol) in solvent, DMA (0.5 mL) was added aqueous K_3PO_4 (2 M, 45 μL). Stir as argon was bubbled through and catalyst, Pd Xphos G4 (2.6 mg, 3.02 μmol) was added. Vessel sealed and heated to 90 °C for 3 hr. Reaction was diluted with DCM and water (5 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system, 12g silica, 0-10% methanol in DCM) provided (14E)-16,29,30-trimethyl-31-tetrahydropyran-2-yl-32,33-dioxa-26,27,28,29,30,31-hexazapentacyclohexacosa-3,5(17),6(26),14,16(27),18,20(24),21,23(28)-nonaene (2.04 mg, 4.30 μmol, 14.25% yield). LCMS: $[M+H]^+$ *m/z* =475.1

[02073] Step 4. To (14E)-16,29,30-trimethyl-31-tetrahydropyran-2-yl-32,33-dioxa-26,27,28,29,30,31-hexazapentacyclohexacosa-3,5(17),6(26),14,16(27),18,20(24),21,23(28)-nonaene (2.04 mg, 4.30 μmol) in DCM (1 mL) was added trifluoroacetic acid (2.60 mmol, 0.2 mL). Stirred at 22 °C for 18 hr. Volatiles were removed under reduced pressure and residue was purified by preparative HPLC (C18, 21 x100mm, acetonitrile in water with 0.035% TFA) twice to afford Ex. 303 (1.09 mg, 2.12 μmol, 49.25% yield, 97.99% purity) as a TFA salt. 1H NMR (500 MHz, DMSO-d6) δ = 12.90 (br s, 1H), 8.54 (br s, 1H), 8.06 (dd, J = 2.6, 17.5 Hz, 1H), 7.92 (d, J = 3.4 Hz, 1H), 7.70 (br d, J = 6.9 Hz, 1H), 7.49 (dd, J = 2.6, 8.3 Hz, 1H), 6.92 (dd, J = 2.9, 17.8 Hz, 1H), 4.87 (d, J = 2.3 Hz, 2H), 4.30 (br d, J = 3.4 Hz,

2H), 4.02 (br d, J = 3.4 Hz, 2H), 3.74 (d, J = 2.9 Hz, 3H), 3.70 (d, J = 2.9 Hz, 3H), 2.39 (d, J = 2.3 Hz, 3H). LCMS: $[M+H]^+$ *m/z* =391.0

[02074] Preparation of tert-butyl-dimethyl-[(2S)-2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]oxypropoxy]silane (I-1-319)



I-1-319

[02075] Step 1: To a solution of (2R)-propane-1,2-diol (10.0 g, 131 mmol, 1 *eq*) in DCM (100 mL) was added imidazole (8.95 g, 131 mmol, 1 eq) and TBSCl (19.8 g, 131 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 2 h. On completion, the mixture was quenched with water (200 mL) and extracted with DCM (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 5-bromo-6-chloro-3-iodo-1H-indazole (7.70 g, 99% yield) as a red solid.

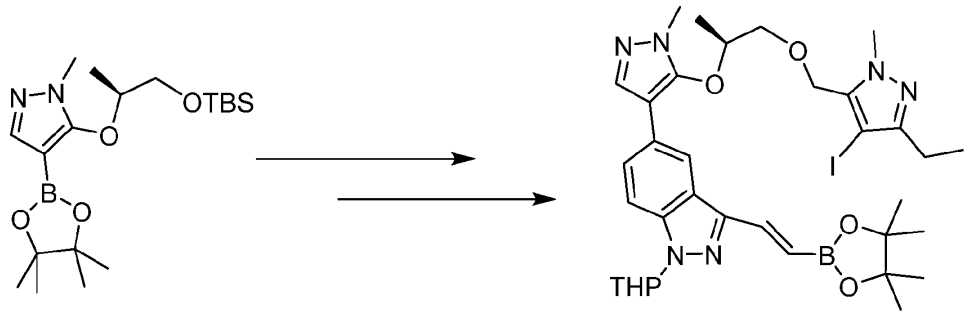
[02076] Step 2. To a solution of (2R)-1-[tert-butyl(dimethyl)silyl]oxypropan-2-ol (24.0 g, 126 mmol, 1 eq) and TosCl (36.0 g, 189 mmol, 1.5 eq) in DCM (300 mL) was added DMAP (2.31 g, 18.9 mmol, 0.15 eq) and TEA (38.2 g, 378 mmol, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 12 h. On completion, the mixture was quenched with water (200 mL) and extracted with DCM (250 mL × 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give [(1R)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl] 4-methylbenzenesulfonate (40.0 g, 116 mmol, 92% yield) as a yellow oil.

[02077] Step 3. To a solution of 2-methylpyrazol-3-ol (8.00 g, 81.5 mmol, 1 *eq*) and [(1R)-2-[tert-butyl(dimethyl)silyl]oxy-1-methyl-ethyl] 4-methylbenzenesulfonate (33.7 g, 97.8 mmol, 1.2 *eq*) in DMF (200 mL) was added K_2CO_3 (33.8 g, 244 mmol, 3 *eq*). The mixture was stirred at 80 °C for 4 h. On completion, the mixture was quenched with water (400 mL) and extracted with EA (500 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/EA=10:1 to 5:1) to give tert-butyl-dimethyl-

[(2S)-2-(2-methylpyrazol-3-yl)oxypropoxy]silane (10.0 g, 36.9 mmol, 45% yield) as a yellow oil. LCMS: $[M+H]^+$ *m/z* =271.7

[02078] Step 4. tert-butyl-dimethyl-[(2S)-2-(2-methylpyrazol-3-yl)oxypropoxy]silane was converted to I-1-319 in a similar manner to method to make I-2-1. LCMS: $[M+H]^+$ *m/z*= 397.2

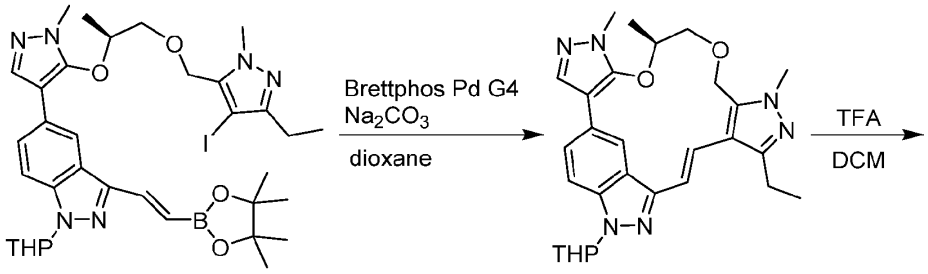
[02079] Preparation of 5-[5-[(1S)-2-[(5-ethyl-4-iodo-2-methyl-pyrazol-3-yl)methoxy]-1-methyl-ethoxy]-1-methyl-pyrazol-4-yl]-1-tetrahydropyran-2-yl-3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]indazole (I-2-319)



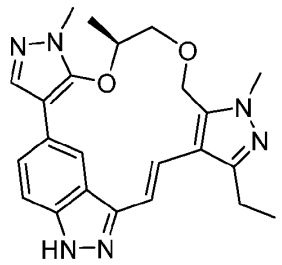
I-1-319 I-2-319

[02080] I-1-319 was converted to I-2-319 in a manner similar to those described in General Method A. LCMS: $[M+H]^+$ *m/z*= 757.2

[02081] Preparation of (10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole (Ex. 319)



I-2-319



Ex. 319

[02082] Step 1. To a solution of I-2-319 (500 mg, 660 umol, 1 eq) in dioxane (10 mL) was added Na_2CO_3 (1.5 M, 1.32 mL, 3 eq) and dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+), Brettphos Pd G4 (60.8 mg, 66.1 umol, 0.1 eq). The mixture was stirred at 80 °C for 2 h under N_2. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/THF=5:1 to 3:1) to give (8S,17E)-15-ethyl-5,8,13-trimethyl-21-tetrahydropyran-2-yl-7,10-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.$0^{2,6}$.$0^{12,16}$. $0^{22,26}$]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (230 mg, 320 umol, 48% yield, 70% purity) as a white solid. LCMS: $[M+H]^+$ *m/z* =503.3

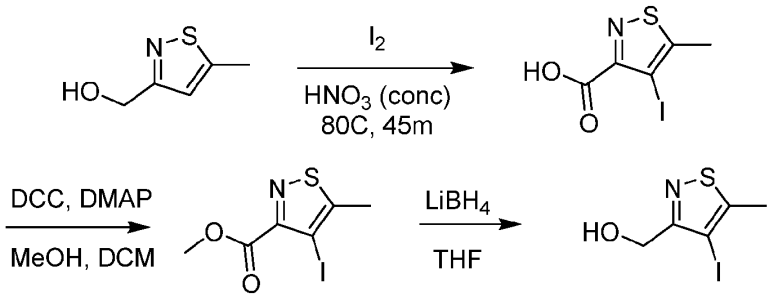
[02083] Step 2. To a solution of (8S,17E)-15-ethyl-5,8,13-trimethyl-21-tetrahydropyran-2-yl-7,10-dioxa-4,5,13,14,20,21-hexazapentacyclo[17.5.2.02,6.012,16.022,26]hexacosa-1(25),2(6),3,12(16),14,17,19,22(26),23-nonaene (150 mg, 298 umol, 1 eq) in DCM (1 mL) was added TFA (4.62 g, 40.5 mmol, 135 eq). The mixture was stirred at 25 °C for 1 h. On completion, the mixture was concentrated to give a residue. The crude product was triturated with ACN (5 mL) at 25 °C for 5 minutes to give Example 319 (38.7 mg, 92.5 umol, 31.0% yield) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 8.51 (s, 1H), 8.15 (d, J = 16.0 Hz, 1H), 7.79 (s, 1H), 7.64 (dd, J = 1.2, 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 16.0 Hz, 1H), 4.78 (br d, J = 16.0 Hz, 3H), 3.90 - 3.80 (m, 2H), 3.71 (s, 6H), 2.83 (dq, J = 1.2, 8.0 Hz, 2H), 1.31 (t, J = 8.0 Hz, 3H), 1.10 (d, J = 6.0 Hz, 3H). $[M+H]^+$ *m/z* =419.3

[02084] Ex. 320 was prepared in a manner similar to Method D. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.55 (s, 1H), 7.93 (s, 1H), 7.81 - 7.68 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 17.4 Hz, 1H), 4.84 (s, 2H), 4.33 - 4.27 (m, 2H), 4.08 - 4.02 (m, 2H), 3.74 (s, 3H), 2.68 (s, 3H). LCMS: $[M+H]^+$ *m/z* =378.2

[02085] Ex. 321 was prepared in a manner similar to Method D. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.53 (s, 1H), 8.08 (d, J = 17.6 Hz, 1H), 7.95 (s, 1H), 7.74 (br d, J = 8.7 Hz,

1H), 7.66 - 7.58 (m, 1H), 7.52 (br d, J = 8.7 Hz, 1H), 7.12 (br d, J = 17.6 Hz, 1H), 5.02 (s, 2H), 4.28 (br s, 2H), 4.05 (br d, J = 2.5 Hz, 2H), 3.74 (s, 3H), 2.53 (br s, 3H). LCMS: $[M+H]^+$ *m/z* =378.2

[02086] Preparation of (4-iodo-5-methyl-isothiazol-3-yl)methanol (I-1-322)



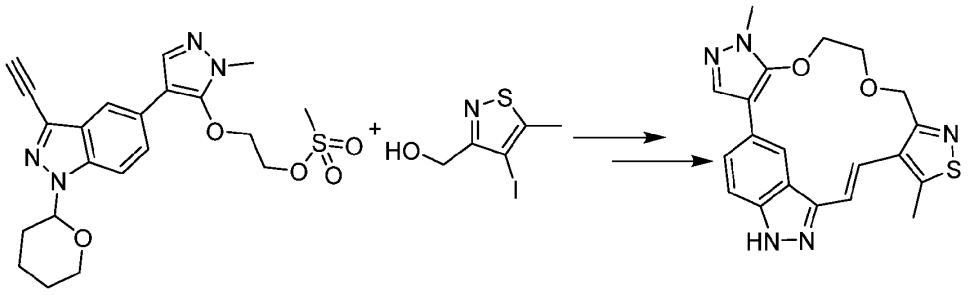
I-1-322

[02087] Step 1. To (5-methylisothiazol-3-yl)methanol (100 mg, 774 μmol) in a vial was added nitric acid (774 μmol, 3 mL, 70% purity) followed by Iodine (196 mg, 774 μmol). The mixture was stirred and heated for 1hr at 80 °C. Reaction was cooled and carefully quenched with 1M sodium bisulfite(aq) (3 mL). The mixture was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The filtrate was concentrated and triturated with hexanes to give 4-iodo-5-methyl-isothiazole-3-carboxylic acid (169 mg, 628 μmol, 81.14% yield). LCMS: $[M+H]^+$ *m/z* =269.8

[02088] Step 2. To 4-iodo-5-methyl-isothiazole-3-carboxylic acid (167 mg, 620.7 μmol) in Methanol (1 mL) and DCM (1 mL) was added DCC (141 mg, 683 μmol), followed by DMAP (7.6 mg, 62 μmol). Stir at 22 °C for 18 hr. Reaction was diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography (automated system with ELSD, 12g silica, 0-60% EA in Hexanes) provided methyl 4-iodo-5-methyl-isothiazole-3-carboxylate (118.7 mg, 419.31 μmol, 67.56% yield). LCMS: $[M+H]^+$ *m/z* =283.8

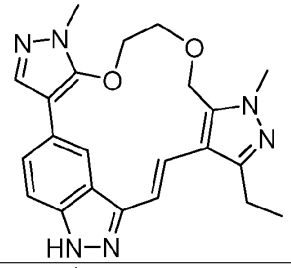
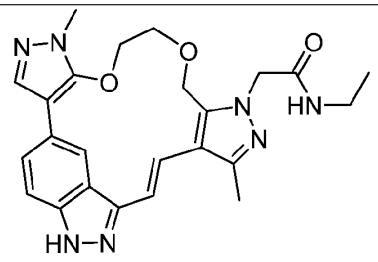
[02089] Step 3. To methyl 4-iodo-5-methyl-isothiazole-3-carboxylate (118.7 mg, 419.31 μmol) in THF (2 mL) was added lithium borohydride (18.27 mg, 838.61 μmol). Stirred as temperature increased over 1 hr. Reaction was cooled and quenched with water (5 mL) carefully and then diluted with DCM and water (10 mL) and the layers were separated. The aqueous layer was extracted again with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Flash column chromatography

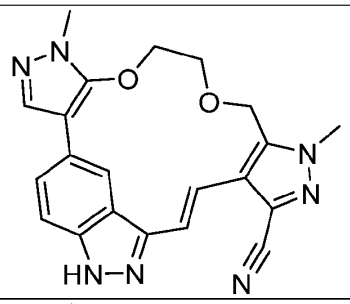
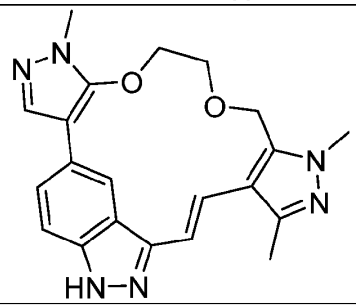
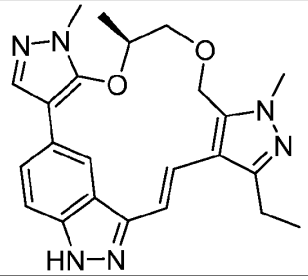
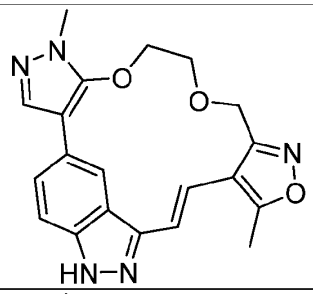
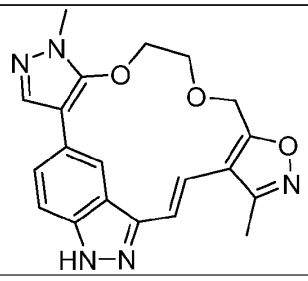
(automated system, 12g silica, 0-60% EA in Hexanes) provided I-1-322 (82 mg, 321.47 µmol, 76.67% yield). LCMS: $[M+H]^+$ *m/z* =255.8

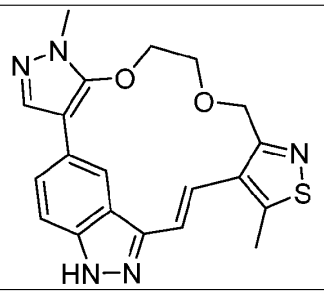


I-2-302 I-1-322 Ex. 322

[02090] Ex. 322 was prepared in a manner similar to Method D from the appropriate intermediates: I-2-302 and I-1-322. ^{1}H NMR (500 MHz, DMSO-d6) δ = 13.13 (s, 1H), 8.62 (s, 1H), 8.04 (d, J = 17.5 Hz, 1H), 7.92 (s, 1H), 7.72 (dd, J = 1.4, 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 17.2 Hz, 1H), 4.82 (s, 2H), 4.31 (br dd, J = 2.9, 4.5 Hz, 2H), 4.07 - 4.00 (m, 2H), 3.74 (s, 3H), 2.77 (s, 3H). LCMS: $[M+H]^+$ *m/z* =393.9

Ex #	Structure	LC	NMR (400 MHz, DMSO-d6)
300		404.8	δ = 8.54 (s, 1H), 8.02 (d, J = 17.5 Hz, 1H), 7.92 (s, 1H), 7.70 (dd, J = 1.1, 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 17.5 Hz, 1H), 4.87 (s, 2H), 4.30 (dd, J = 2.4, 4.4 Hz, 2H), 4.05 - 3.99 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.80 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H)
301		461.9	δ = 13.12 - 12.70 (m, 1H), 8.54 (s, 1H), 8.16 (t, J = 5.4 Hz, 1H), 8.10 (d, J = 17.5 Hz, 1H), 7.92 (s, 1H), 7.70 (dd, J = 1.3, 8.8 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 17.6 Hz, 1H), 4.84 (s, 2H), 4.69 (s, 2H), 4.28 (br dd, J = 2.2, 4.3 Hz, 2H), 3.99 (br s, 2H), 3.74 (s, 3H), 3.14 - 3.08 (m, 2H), 2.39 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H)

Ex #	Structure	LC	NMR (400 MHz, DMSO-d6)
302		402.2	δ = 8.53 (s, 1H), 8.10 (d, J = 17.6 Hz, 1H), 7.96 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 17.4 Hz, 1H), 5.01 (s, 2H), 4.33 - 4.28 (m, 2H), 4.08 - 4.02 (m, 2H), 3.87 (s, 3H), 3.75 (s, 3H
303		391.0	(500 MHz, DMSO-d6) δ = 12.90 (br s, 1H), 8.54 (br s, 1H), 8.06 (dd, J = 2.6, 17.5 Hz, 1H), 7.92 (d, J = 3.4 Hz, 1H), 7.70 (br d, J = 6.9 Hz, 1H), 7.49 (dd, J = 2.6, 8.3 Hz, 1H), 6.92 (dd, J = 2.9, 17.8 Hz, 1H), 4.87 (d, J = 2.3 Hz, 2H), 4.30 (br d, J = 3.4 Hz, 2H), 4.02 (br d, J = 3.4 Hz, 2H), 3.74 (d, J = 2.9 Hz, 3H), 3.70 (d, J = 2.9 Hz, 3H), 2.39 (d, J = 2.3 Hz, 3H)
319		419.3	(400 MHz, METHANOL-d4) δ = 8.51 (s, 1H), 8.15 (d, J = 16.0 Hz, 1H), 7.79 (s, 1H), 7.64 (dd, J = 1.2, 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 16.0 Hz, 1H), 4.78 (br d, J = 16.0 Hz, 3H), 3.90 - 3.80 (m, 2H), 3.71 (s, 6H), 2.83 (dq, J = 1.2, 8.0 Hz, 2H), 1.31 (t, J = 8.0 Hz, 3H), 1.10 (d, J = 6.0 Hz, 3H)
320		378.2	δ = 8.55 (s, 1H), 7.93 (s, 1H), 7.81 - 7.68 (m, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 17.4 Hz, 1H), 4.84 (s, 2H), 4.33 - 4.27 (m, 2H), 4.08 - 4.02 (m, 2H), 3.74 (s, 3H), 2.68 (s, 3H
321		378.3	δ = 8.53 (s, 1H), 8.08 (d, *J* = 17.6 Hz, 1H), 7.95 (s, 1H), 7.74 (br d, *J* = 8.7 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.52 (br d, *J* = 8.7 Hz, 1H), 7.12 (br d, *J* = 17.6 Hz, 1H), 5.02 (s, 2H), 4.28 (br s, 2H), 4.05 (br d, *J* = 2.5 Hz, 2H), 3.74 (s, 3H), 2.53 (br s, 3H)

Ex #	Structure	LC	NMR (400 MHz, DMSO-d6)
322		393.9	(500 MHz, DMSO-d6) δ = 13.13 (s, 1H), 8.62 (s, 1H), 8.04 (d, J = 17.5 Hz, 1H), 7.92 (s, 1H), 7.72 (dd, J = 1.4, 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 17.2 Hz, 1H), 4.82 (s, 2H), 4.31 (br dd, J = 2.9, 4.5 Hz, 2H), 4.07 - 4.00 (m, 2H), 3.74 (s, 3H), 2.77 (s, 3H)

Screen assays

[02091] Biochemical Assays for inhibition of wild-type and mutant EGFRs

[02092] The inhibitory activities against EGFR WT, EGFR (D770_N771insNPG), EGFR Δ746-750 mutant, EGFR Δ746-750/C797S mutant, EGFR L858R mutant, EGFR L858R/T790M mutant, EGFR L858R/T790M/C797S mutant and ALK were evaluated at Reaction Biology Corporation (See, www.reactionbiology.com) using HotSpot assay platform, a radiometric assay based on conventional filter-binding assays, that directly measures kinase catalytic activity toward a specific substrate (Anastassiadis T, et al. Comprehensive Assay of Kinase Catalytic Activity Reveals Features of Kinase Inhibitor Selectivity. *Nat Biotechnol.* 2011, 29:1039-45). Briefly, specific kinase / substrate pairs along with required cofactors were prepared in reaction buffer; 20 mM Hepes pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, 1% DMSO. Compounds were delivered into the reaction, followed ~ 20 minutes later by addition of a mixture of ATP (Sigma, St. Louis MO) and ^{33}P ATP (Perkin Elmer, Waltham MA) to a final concentration of 10 μM. Reactions were carried out at room temperature for 120 min, followed by spotting of the reactions onto P81 ion exchange filter paper (Whatman Inc., Piscataway, NJ). Unbound phosphate was removed by extensive washing of filters in 0.75% phosphoric acid. After subtraction of background derived from control reactions containing inactive enzyme, kinase activity data was expressed as the percent remaining kinase activity in test samples compared to vehicle (dimethyl sulfoxide) reactions. IC_{50} values and curve fits were obtained using Prism (GraphPad Software).

Table 1. Inhibition of WT and mutant EGFR kinase activities.

Ex. #	EGFR (L858R) IC_{50}, nM	EGFR (L858R, T790M) IC_{50}, nM	EGFR (L858R/T790M/C797S) IC_{50}, nM	EGFR (Δ746-750) IC_{50}, nM	EGFR (Δ746-750/C797S) IC_{50}, nM	EGFR (Δ770_N771insNPG) IC_{50}, nM	EGFR wt IC_{50}, nM
1	848.20	250.60	258.90	68.37	176.90	>1000	>1000
2	>1000		>1000	>1000		>1000	>1000
3			862.90				
7	687.40		201.60	898.20		2117.00	>1000
8	103.60		24.34	44.83		376.90	884.10
9	348.60		27.22	284.20		945.40	1167.00
10	181.20		42.18	74.29		712.60	972.60
11	1585.00	153.30	218.30	850.00	797.90	>1000	>1000
14	63.83		19.50	124.10	34.70	311.70	339.10
15	104.80		26.43	138.70	27.51	286.00	419.40
16	49.23		48.35	131.50		520.80	522.90
22	4.49	1.87	0.54	3.84	5.10	94.78	158.20
23	96.58	13.05	22.51	29.34	44.48	362.50	290.40
24	>1000		315.20	755.40		1772.00	>1000
28	1001.00		578.20	819.20		>1000	>1000
30	267.50		36.82	216.50		983.10	1304.00
31	67.69		4.93	58.75		731.50	927.00
32	242.20		37.34	155.00		456.70	1262.00
33	121.00	14.86	25.60	93.04	92.40	305.80	404.90
34	113.90		40.90	153.50		190.50	326.10
35	135.00		30.85	101.20	99.63	1041.00	584.10
37	41.82		17.33	64.04	49.91	211.70	156.80
39	221.60		35.26	176.10		1442.00	1073.00
43	144.30	13.46	34.53	74.81	133.10	541.30	543.30
44	285.10		26.97	111.70	130.10	>1000	1465.00
47	821.80	79.32	169.50	488.00	943.70	>1000	>1000
49	861.80	126.30	84.42	617.10	1040.00	>1000	>1000
55	35.16		4.10	33.36	8.93	78.28	100.80
56	22.23	1.22	1.12	14.99	8.48	50.05	42.66
58	9.29		1.57	11.10	7.29	221.80	49.17
59	7.63	0.70	1.02	18.63	2.42	126.80	44.11
60	100.70	6.86	3.27	89.69	89.43	677.90	580.60
61	1.23	0.29	0.17	1.08	1.96	9.21	6.19
63	827.80	43.34	33.49	295.70	227.60	>1000	781.70
69	121.00	14.86	25.60	93.04	92.40	305.80	404.90
70	70.09	3.81	3.68	32.29	27.11	73.59	98.74
74	36.13	12.47	15.83	74.10	39.78	108.80	85.97
75	55.93	17.54	21.22	59.70	28.53	84.27	295.10
76	155.70	42.93	63.42	147.00	90.75	232.90	538.30
77	2084.00	427.00	453.40	749.40	803.30	1882.00	>1000
78	688.40	205.60	295.80	211.60	774.60	909.90	>1000
79	526.10	57.06	67.67	596.20	284.40	951.00	1908.00

Ex. #	EGFR (L858R) IC_{50}, nM	EGFR (L858R, T790M) IC_{50}, nM	EGFR (L858R/T790M/C797S) IC_{50}, nM	EGFR (Δ746-750) IC_{50}, nM	EGFR (Δ746-750/C797S) IC_{50}, nM	EGFR (Δ770_N771insNPG) IC_{50}, nM	EGFR wt IC_{50}, nM
80	24.72	4.37	11.22	38.72	39.20	59.11	50.81
81	16.76	1.70	7.42	29.63	33.37	40.28	43.76
82	15.26	1.24	5.77	27.87	29.84	56.75	67.83
83	19.04	1.48	5.29	34.62	31.28	55.41	61.47
84	284.80	30.78	28.23	380.60	130.00	551.30	1076.00
85	>1000	>1000	>1000	>1000	>1000	>1000	>1000
86	>1000	>1000	>1000	>1000	>1000	>1000	>1000
87	>1000	>1000	>1000	>1000	>1000	>1000	>1000
89	4.66	0.06	0.45	19.71	6.67	191.00	63.97
90	1.02	0.06	0.81	11.61	4.65	81.82	17.06
91	>1000	400.40	>1000	>1000	>1000	>1000	>1000
92	4.10	0.41	3.26	7.95	6.65	6.34	14.49
93	11.45	0.86	5.02	49.16	16.68	138.10	69.15
94	9.99	0.82	5.75	17.65	14.09	17.23	44.12
95	30.13	1.95	4.93	121.00	23.03	524.30	167.10
96	74.89	5.29	9.45	284.70	94.14	195.80	242.50
97	131.80	10.80	28.47	221.00	100.80	304.10	412.60
98	41.06	3.56	12.12	84.93	26.96	148.10	119.10
100	87.71	10.40	19.21	197.90	91.04	250.30	289.50
102	25.41	4.10	13.05	48.12	44.74	94.54	62.40
103	103.10	11.48	40.43	104.80	170.80	343.50	358.00
106	34.81	2.49	10.83	57.63	68.51	111.50	107.20
107	13.63	2.28	11.33	34.14	42.18	66.47	41.90
108	26.18	3.86	11.92	30.85	49.20	103.00	101.40
109	164.90	15.93	47.10	38.01	152.10	298.10	855.60
110	30.44	4.99	8.54	14.41	28.51	112.20	150.40
111	8.04	0.39	1.91	3.29	9.18	16.84	63.29
112	1.31	0.21	0.98	0.61	2.75	1.12	8.28
113	96.80	8.66	9.91	69.87	67.41	727.50	488.50
114	0.10	0.11	0.98	0.17	0.92	0.91	0.38
115	37.28	1.60	14.02	12.94	60.07	32.30	147.00
116	0.58	0.38	2.71	1.06	2.85	18.47	3.98
117	19.99	2.20	6.18	6.91	8.36	53.45	70.12
118	34.38	4.65	8.42	21.10	31.66	65.70	130.40
119	0.61	0.26	2.12	0.63	1.25	8.50	2.34
120	7.91	0.33	2.62	7.76	5.80	99.75	41.30
121	94.13	6.14	13.00	40.68	41.33	283.10	295.50
122	11.95	1.46	2.09	7.45	6.79	58.02	94.18
123	1.50	0.33	0.75	1.30	0.80	10.10	11.44
124	18.29	3.32	2.32	18.34	13.88	139.90	168.30
125	11.91	43.58	7.49	20.58	4.99	175.10	137.70
126	18.64	2.07	2.80	16.09	19.84	132.80	164.40

Ex. #	EGFR (L858R) IC_{50}, nM	EGFR (L858R, T790M) IC_{50}, nM	EGFR (L858R/T790M/C797S) IC_{50}, nM	EGFR (Δ746-750) IC_{50}, nM	EGFR (Δ746-750/C797S) IC_{50}, nM	EGFR (Δ770_N771insNPG) IC_{50}, nM	EGFR wt IC_{50}, nM
127	1.81	0.15	0.43	2.82	0.85	25.56	11.11
128	21.89	0.77	1.01	33.74	15.22	382.90	263.80
129	0.47	0.09	0.33	0.58	0.40	6.50	3.02
130	84.34	7.32	5.66	81.06	38.40	850.60	456.80
131	4.02	0.57	1.90	1.65	4.09	6.79	17.67
132	157.00	20.08	35.32	39.37	67.03	283.60	720.60
133	0.09	0.07	0.24	0.12	0.35	1.62	0.54
134	182.40	24.01	12.64	173.30	90.75	>1000	1210.00
135	128.10	19.96	38.61	48.27	97.70	802.40	828.60
136	14.56	0.80	1.54	15.19	12.12	334.20	103.00
137	7.80	0.60	1.02	6.59	4.80	129.10	55.30
138	3.50	0.61	0.55	3.64	1.40	85.17	23.76
140	11.55	1.19	1.30	9.35	6.14	185.60	84.82
142	0.90	1.29	1.83	1.11	1.32	16.69	2.14
143	39.61	1.58	4.63	39.44	41.25	1626.00	320.50
144	1.47	0.41	0.70	1.88	1.93	24.47	8.81
147	0.44	0.11	0.19	0.59	0.39	9.08	3.16
148	42.36	4.25	2.77	35.05	23.65	402.90	372.10
150	2.31	0.45	0.37	3.21	2.58	33.43	6.36
151	0.22	0.48	0.46	0.30	0.72	2.55	0.87
152	20.66	0.58	0.62	61.53	86.39	94.50	112.00
155	0.34	0.45	0.62	0.62	0.86	6.36	1.74
156	4.34	0.88	1.04	1.77	3.62	64.89	19.26
159	34.67	1.54	0.74	26.96	14.06	116.10	160.50
160	34.40	1.42	1.08	13.59	19.46	245.80	62.97
161	47.11	3.10	1.40	20.00	13.45	190.50	170.80
162	47.37	1.40	0.90	30.55	33.55	523.40	237.60
163	8.20	0.85	0.86	7.33	4.72	51.96	29.56
164	16.67	3.23	1.76	33.40	20.17	95.26	219.70
165	6.08	0.47	0.44	4.84	2.33	19.02	28.54
166	12.78	0.72	0.55	15.00	8.10	45.59	99.82
167	35.69	3.42	8.89	23.83	13.62	47.09	123.30
168	1.88	0.72	2.72	5.96	1.38	13.89	16.61
169	2.01	0.48	1.26	3.24	1.60	36.06	19.28
170	309.90	36.59	25.92	115.90	30.21	328.70	907.50
171	7.50	0.50	1.32	38.30	8.74	86.01	67.17
172	0.60	0.48	1.34	2.10	0.69	6.61	1.84
173	512.60	45.50	27.41	532.90	127.00	>1000	>1000
174	127.10	10.87	4.88	133.00	27.19	996.20	752.40
175	42.59	2.06	3.39	67.82	8.97	713.20	175.50
176	55.47	6.94	13.13	24.86	35.17	83.42	152.20
177	0.38	0.60	1.78	0.56	0.75	1.56	0.67

Ex. #	EGFR (L858R) IC_{50}, nM	EGFR (L858R, T790M) IC_{50}, nM	EGFR (L858R/T790M/C797S) IC_{50}, nM	EGFR (Δ746-750) IC_{50}, nM	EGFR (Δ746-750/C797S) IC_{50}, nM	EGFR (Δ770_N771insNPG) IC_{50}, nM	EGFR wt IC_{50}, nM
178	8.73	4.35	19.33	6.90	5.25	231.60	22.20
179	>1000	1014.00	507.00	>1000	>1000	>1000	>1000
181	1.80	1.29	2.50	2.23	1.68	84.37	12.50
182	24.74	0.54	1.37	23.96	6.60	299.90	139.00
183	61.48	0.65	1.05	53.81	17.74	533.89	194.71
186	14.60	1.48	0.46	12.87	3.06	59.07	43.84
187	6.88	0.47	0.33	8.88	7.84	74.65	25.88
191	5.61	4.23	2.63	9.04	4.19	102.00	19.80
193	36.59	2.42	1.05	10.21	5.92	77.34	90.07
195	39.89	6.18	3.67	18.61	8.68	156.20	99.74
197	95.23	4.58	2.18	62.01	29.75	217.20	194.30
198	13.11	0.89	0.26	5.84	1.96	47.05	36.79
199	87.79	64.39	43.94	146.80	42.51	>1000	1284.00
200	2.01	1.41	0.69	4.08	1.93	59.87	6.46
202	98.75	3.38	2.00	45.04	20.72	423.40	179.20
203	0.12	0.17	0.78	0.11	0.23	0.65	0.23
204	5.50	1.77	2.53	1.85	1.93	20.07	5.49
205	16.34	1.00	1.13	5.17	1.42	136.90	58.29
206	1.69	0.52	1.46	0.76	0.74	43.54	3.33
207	>1000	>1000	>1000	>1000	>1000	>1000	>1000
211	400.00	>1000	>1000	>1000	2872.00	>1000	>1000
212	52.34	0.57	0.42	16.91	3.87	138.80	153.70
213	82.57	0.42	0.20	21.06	5.07	431.00	295.90
214	0.35	0.20	0.17	0.22	0.48	8.31	0.77
215	1.70	1.49	0.89	0.69	1.93	3.75	1.71
216	2.22	0.44	0.37	0.47	0.63	28.91	2.43
217	37.06	0.69	1.42	3.61	1.94	107.10	71.68
218	28.76	1.99	2.04	8.48	16.64	161.10	118.90
219	4.73	5.30	3.84	3.02	5.13	21.23	7.25
220	515.10	23.09	27.49	398.10	474.80	574.50	1441.00
221	0.97	0.21	0.14	0.55	0.35	10.35	4.14
222	4.75	0.31	0.18	1.77	2.17	57.78	27.76
223	7.07	0.61	0.34	4.07	3.12	102.20	42.59
225	12.20	0.57	0.21	5.39	1.44	65.44	51.81
226	50.74	1.19	0.60	8.98	6.43	222.30	120.60
227	60.13	0.84	0.36	9.86	6.82	166.80	251.10
228	25.24	25.87	10.57	12.21	44.39	481.50	52.72
229	7.10	4.07	1.24	1.94	4.05	38.61	24.80
232	0.22	0.13	0.11	0.08	0.55	1.39	0.41
233	41.48	1.32	1.61	10.68	25.00	256.20	150.90
236	11.97	0.80	1.06	5.11	11.52	68.91	26.84
238	73.01	10.22	11.72	17.51	41.29	219.50	203.20

Ex. #	EGFR (L858R) IC_{50}, nM	EGFR (L858R, T790M) IC_{50}, nM	EGFR (L858R/T790M/C797S) IC_{50}, nM	EGFR (Δ746-750) IC_{50}, nM	EGFR (Δ746-750/C797S) IC_{50}, nM	EGFR (Δ770_N771insNPG) IC_{50}, nM	EGFR wt IC_{50}, nM
239	30.52	36.35	8.44	18.30	9.44	527.50	62.08
240	775.40	5.92	10.53	825.60	652.90	>1000	>1000
241	0.30	0.30	0.28	0.13	0.31	0.18	0.40
241	0.27	0.19	0.18	0.15	0.23	0.73	0.52
242	124.10	9.27	4.93	55.52	40.31	303.90	380.70
246	5.14	1.71	4.42	8.71	3.18	39.52	23.31
252	2.38	1.91	5.35	1.31	2.29	15.66	4.74
253	1.66	2.55	5.27	0.75	1.98	3.21	1.63
255	1.18	3.01	6.62	0.95	1.98	4.05	1.43
258	1.56	0.48	2.17	1.22	1.26	15.76	5.72
259	66.50	9.39	21.80	40.05	22.87	499.50	329.30
260	4.55	0.90	3.19	3.50	3.74	25.31	13.63
261	21.55	1.92	5.10	23.50	5.93	230.40	93.69
262	40.06	4.98	1.67	8.48	7.12	98.35	94.55
263	3.97	0.75	0.50	1.28	1.79	18.24	6.94
264	491.30	18.00	8.63	162.40	70.01	826.50	814.60
266	>1000	282.50	60.43	971.30	577.30	>1000	>1000
267	240.60	8.31	5.42	116.90	106.90	1234.00	769.40
268	4.35	1.04	0.52	2.01	1.32	30.53	7.91
269	8.53	1.82	0.67	5.25	2.56	102.30	20.33
270	161.10	4.58	1.10	93.56	20.49	634.50	543.00
271	1580.00	56.74	31.62	471.60	421.90	>1000	>1000
319	181.9	24.72	60.47	217.9	425.1	1489	765.9

[02093] Table 2. Inhibition of ALK kinase activity

Ex. #	ALK IC_{50} (nM)	Ex. #	ALK IC_{50} (nM)
8	2.09	232	0.90
22	1.35	256	2.00
35	6.93	275	1.46
58	4.79	277	9.87
119	1.05	280	1.08
120	1.82	288	1.82
134	21.6	289	15.4
147	0.99	300	5.79

Ex. #	ALK IC_{50} (nM)	Ex. #	ALK IC_{50} (nM)
159	3.72	301	29.01
163	1.13	302	19.95
181	1.05	303	27.52
200	1.49	319	5.054
214	2.47	320	32.22
215	2.58	321	20.84
216	2.04	322	59.9
219	1.31		

[02094] Inhibition of CLK1, CLK2, CLK3 and CLK4 kinase acvtivity evaluated at Nanosyn

[02095] Kinase protein and substrate were pre-diluted in the HEPES assay buffer (100 mM HEPES, pH 7.5, 0.01% Triton X-100, 0.1% BSA, 5 mM $MgCl_2$, 1 mM DTT, 10 μM Sodium Orthovanadate, 10 μM Beta-Glycerophosphate) dispensed into 384 well plate (5 μL per well). Control samples (0%-inhibition in the absence of inhibitor, DMSO only) and 100%-inhibition (in the absence of enzyme) were assembled in replicates of six and were used to calculate %-inhibition in the presence of compounds. Test compounds were added to the protein samples by acoustic dispensing (Labcyte Echo550). Concentration of DMSO was equalized to 1% in all samples. Reactions were initiated by addition of ATP by acoustic dispensing (Labcyte Echo550) and incubated according to assay specific incubation time. After incubation, 5uL of Promega ADP-Glo reagent was added and incubated for 40 minutes. After 40 minutes, 10uL of Promega kinase detection reagent was added. After 10min of incubation with Kinase detection reagent, the luminescence was read on microplate reader (Biotek Synergy).

[02096] Table 3. Inhibition of CLK1, CLK2, CLK3 and CLK4 kinase activity

Ex. #	CLK1 IC_{50}, nM	CLK2 IC_{50}, nM	CLK3 IC_{50}, nM	CLK4 IC_{50}, nM
6	0.34	0.23	178.00	0.52
7	0.20	0.08	45.20	0.48
43	0.10	0.14	236.00	0.25
47	9.92	48.30	1000.00	2.70
52	0.24	0.19	148.00	0.56
55	0.09	0.13	185.00	0.58

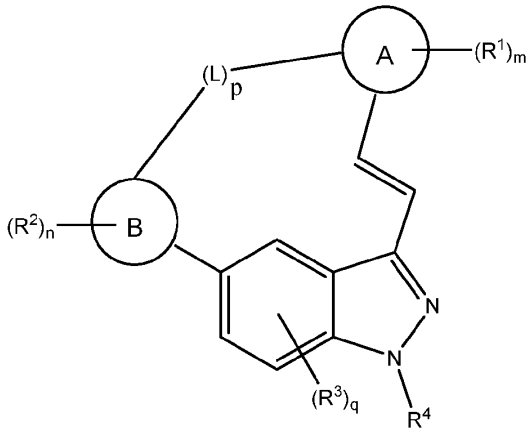
Ex. #	CLK1 IC_{50}, nM	CLK2 IC_{50}, nM	CLK3 IC_{50}, nM	CLK4 IC_{50}, nM
58	0.20	0.38	160.00	0.53
59	0.82	2.13	541.00	2.03
61	0.21	0.06	21.40	0.76
109	0.46	0.09	2.00	0.85
112	0.17	0.04	0.19	0.50
114	0.23	0.12	20.90	0.46
116	0.11	0.04	10.90	0.40
119	0.14	0.04	19.40	0.33
120	0.12	0.08	112.00	0.27
122	0.27	0.15	21.20	0.60
123	0.17	0.10	171.00	0.45
124	0.15	0.29	186.00	0.37
125	3.44	2.81	1000.00	4.31
126	0.32	0.12	188.00	0.49
132	0.19	0.02	0.28	0.30
134	0.29	0.19	230.00	0.61
137	1.37	2.13	79.20	1.55
141	0.11	0.03	41.90	0.13
142	11.90	13.90	1000.00	5.91
143	0.19	0.02	12.10	0.61
144	0.21	0.05	168.00	0.55
145	0.21	0.04	99.60	0.52
147	0.13	0.02	5.21	0.32
151	0.24	0.04	23.00	0.52
155	0.43	0.14	87.40	0.81
156	0.42	0.13	63.60	0.40
158	0.14	0.40	664.00	0.31
159	0.14	0.07	1000.00	0.38
160	0.22	0.30	38.20	0.41
161	0.27	0.14	164.00	0.57
162	0.11	0.07	784.00	0.25
163	0.28	0.06	215.00	0.63
164	0.39	0.75	1000.00	0.59
165	0.10	0.02	72.40	0.19
167	0.38	0.23	108.00	0.55
168	0.39	0.33	238.00	0.77
169	0.47	0.49	346.00	1.13
170	0.38	0.36	1000.00	0.43
171	0.85	0.62	977.00	0.57
172	0.32	0.08	64.70	0.59
173	0.70	0.89	1000.00	1.26
174	0.16	0.21	128.00	0.51
176	1.54	11.80	1000.00	1.44
177	0.47	0.23	59.10	1.08

Ex. #	CLK1 IC_{50}, nM	CLK2 IC_{50}, nM	CLK3 IC_{50}, nM	CLK4 IC_{50}, nM
178	1.08	2.38	61.80	1.56
179	2.75	9.57	1000.00	1.66
181	0.87	0.68	56.20	2.60
183	0.82	0.24	155.00	1.83
186	0.24	0.18	126.00	1.00
187	0.48	0.30	311.00	1.35
191	2.42	4.37	43.40	2.41
193	31.80	45.40	1000.00	21.00
195	36.60	53.50	435.00	22.30
197	1.16	3.06	78.60	1.59
198	0.76	1.61	1000.00	1.63
199	1.05	2.29	19.30	1.79
200	0.48	1.00	194.00	1.53
203	0.72	0.14	151.00	1.59
206	1.67	1.72	477.00	3.69
208	0.59	0.13	220.00	1.53
211	270.00	114.00	1.00	397.00
212	5.27	7.14	237.00	5.31
213	5.75	6.11	1.00	5.07
214	2.37	2.51	592.00	7.25
215	3.33	2.10	964.00	9.08
216	2.02	1.28	115.00	5.39
219	2.05	4.51	146.00	5.62
220	2.76	8.84	1.00	4.31
222	2.31	3.17	306.00	2.46
223	0.85	0.28	30.00	2.11
224	0.69	1.16	253.00	1.46
225	1.11	0.49	77.70	1.92
226	0.87	0.99	369.00	1.44
227	4.90	2.59	471.00	4.63
228	21.90	8.60	1000.00	34.00
229	131.00	59.60	1000.00	68.50
232	0.77	0.45	42.00	1.49
233	0.71	0.43	403.00	0.89
236	0.66	1.73	397.00	1.03
238	0.90	2.44	1000.00	1.07
240	1.12	12.50	1000.00	1.52
246	0.75	1.36	386.00	1.33
252	0.83	0.42	168.00	1.59
255	0.82	0.27	9.89	1.60
256	1.38	1.35	94.50	4.05
258	0.50	0.23	17.20	1.04
259	0.90	4.29	1000.00	1.30
260	4.90	5.21	361.00	3.15

Ex. #	CLK1 IC_{50}, nM	CLK2 IC_{50}, nM	CLK3 IC_{50}, nM	CLK4 IC_{50}, nM
261	0.20	0.33	209.00	0.44
262	0.82	0.49	104.00	1.50
263	0.64	0.71	32.70	1.31
264	1.06	3.08	519.00	1.59
268	0.57	0.18	45.10	1.22
269	0.94	0.32	238.00	1.76
275	0.80	1.03	241.00	2.25
277	4.28	2.99	51.10	2.77
280	0.52	0.24	242.00	1.96
288	0.32	0.24	131.00	1.31
290	69.40	102.00	1000.00	38.10
292	1.01	4.87	1000.00	1.36
294	1.27	3.25	1000.00	1.37
295	0.64	0.78	13.80	1.12
296	1.20	1.15	33.40	1.57
300	0.332	36.5	0.862	0.225
302	1.19	1000	1.23	1.33
320	0.324	69.7	0.2	0.155
321	1.35	418	1.92	0.847
322	1.04	34.9	0.322	0.636

WHAT IS CLAIMED IS:

1. A compound of the formula I



I

wherein

ring A is a 5- to 10-membered heteroarylene or C_6-C_{10} arylene;

ring B is a 5-membered heteroarylene;

each L is independently –O-, -S-, -S(O)-, -$S(O)_2$-, -$N(R^5)C(O)$-, -$C(O)N(R^5)$-, -$N(R^5)$-, -$N(R^5)S(O)$-, -$S(O)N(R^5)$-, -$N(R^5)S(O)_2$-, -$S(O)_2N(R^5)$-, or –$C(R^6)(R^7)$-, provided that $(L)_p$ does not comprise an O-O, S-O, or N-N bond;

each R^1, R^2, and R^3 when present, 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, 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, -$OC(O)R^c$, -$OC(O)NR^cR^d$, -$OC(=N)NR^cR^d$, -$OS(O)R^c$, -$OS(O)_2R^c$, -$OS(O)NR^cR^d$, -$OS(O)_2NR^cR^d$, -SR^c, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)NR^cR^d$, -$S(O)_2NR^cR^d$, -NR^cR^d, -$NR^cC(O)R^d$, -$N(C(O)R^c)(C(O)R^d)$, -$NR^cC(O)OR^d$, -$NR^cC(O)NR^cR^d$, -$NR^cC(=N)NR^cR^d$, -$NR^cS(O)R^d$, -$NR^cS(O)_2R^d$, -$NR^cS(O)NR^cR^d$, -$NR^cS(O)_2NR^cR^d$, -$C(O)R^c$, -$C(O)OR^c$, -$C(O)NR^cR^d$, -$C(=N)NR^cR^d$,

$-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

R^4 is H, deuterium, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-P(O)_2R^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)_2OR^c$, or $-S(O)_2OR^c$;

each R^5, when present, is independently 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, 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, or 5- to 10-membered heteroaryl is independently optionally substituted by $-OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^d$, $-OC(=N)NR^cR^d$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)NR^cR^d$, $-OS(O)_2NR^cR^d$, $-SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)NR^cR^d$, $-S(O)_2NR^cR^d$, $-NR^cR^d$, $-NR^cC(O)R^d$, $-N(C(O)R^c)(C(O)R^d)$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^d$, $-NR^cC(=N)NR^cR^d$, $-NR^cS(O)R^d$, $-NR^cS(O)_2R^d$, $-NR^cS(O)NR^cR^d$, $-NR^cS(O)_2NR^cR^d$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^d$, $-C(=N)NR^cR^d$, $-PR^cR^d$, $-P(O)R^cR^d$, $-P(O)_2R^cR^d$, $-P(O)NR^cR^d$, $-P(O)_2NR^cR^d$, $-P(O)OR^c$, $-P(O)_2OR^c$, -CN, or $-NO_2$;

each R^6 and R^7, 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, $-OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-OS(O)NR^aR^b$, $-OS(O)_2NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(O)NR^aR^b$, $-NR^aS(O)R^b$, $-NR^aS(O)_2R^b$, $-NR^aS(O)NR^aR^b$, $-NR^aS(O)_2NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-PR^aR^b$, $-P(O)R^aR^b$, $-P(O)_2R^aR^b$, $-P(O)NR^aR^b$, $-P(O)_2NR^aR^b$, $-P(O)OR^a$, $-P(O)_2OR^a$, -CN, or $-NO_2$, 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 $-NO_2$;

or two of R^5, R^6 and R^7, taken together with the atom or atoms 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^5, R^6 and R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$,

-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;

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, or 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;

m is 0, 1, 2, 3, or 4;

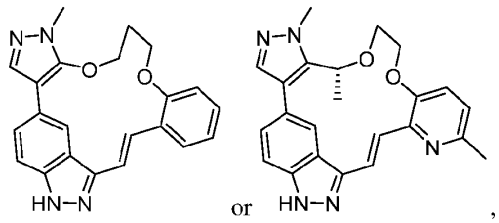
n is 0, 1, 2, or 3;

p is 4, 5, 6, 7, 8 or 9; and

q is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof;

provided that the compound is not of the formula



or a pharmaceutically acceptable salt thereof.

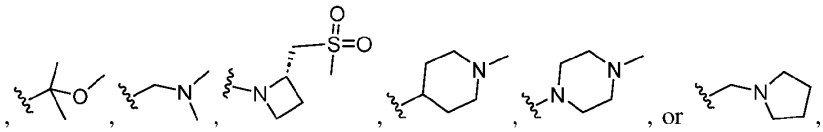
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $(L)_p$ does not comprise a $-NR^5C(O)-$ directly covalently attached to ring A.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ring A is a C_6-C_{10} arylene, and m is 0, 1, or 2.

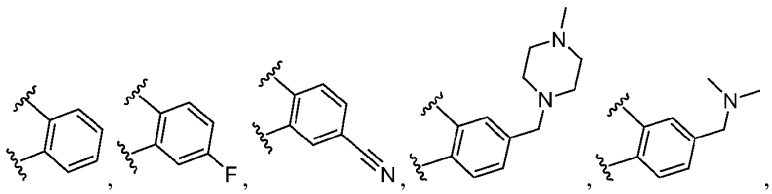
4. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, and m is 0, 1, or 2.

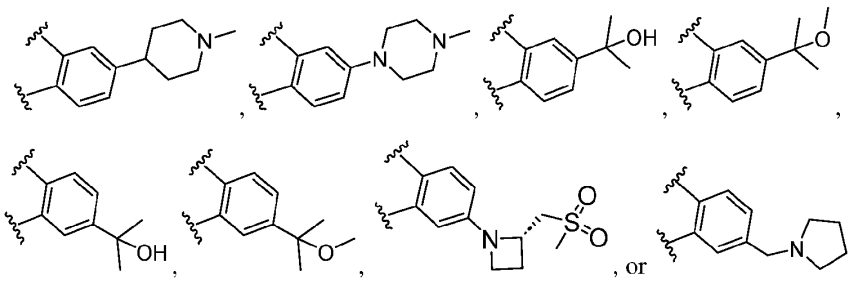
5. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, and m is 0 or 1.

6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a phenylene, m is 1, and R^1 is methyl, ethyl, F, Cl, Br, -CN, 


, or , 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



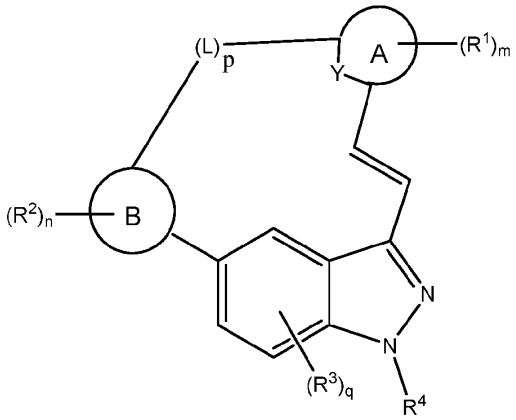


wherein each "〰" represents a point of covalent attachment.

8. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene, and m is 0, 1, 2, or 3.

9. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene, and m is 0, 1, or 2.

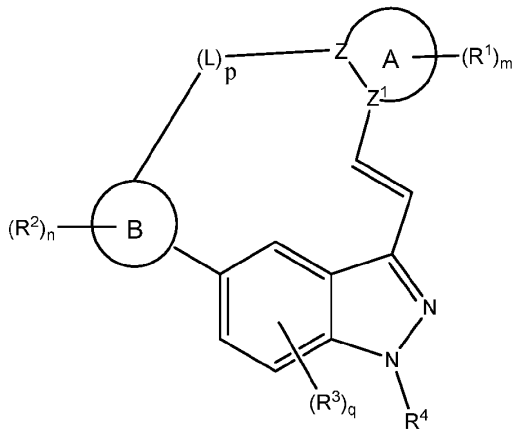
10. The compound of any one of the claims 1 to 3, or 9, or a pharmaceutically acceptable salt thereof, having the formula II



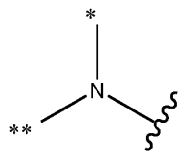
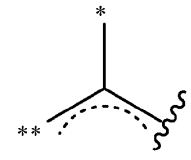
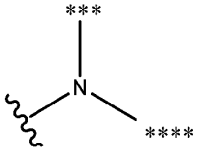
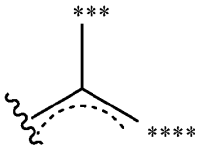
II

wherein Y is a single, a double bond, –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, and ring A is a 5- to 10-membered heteroarylene.

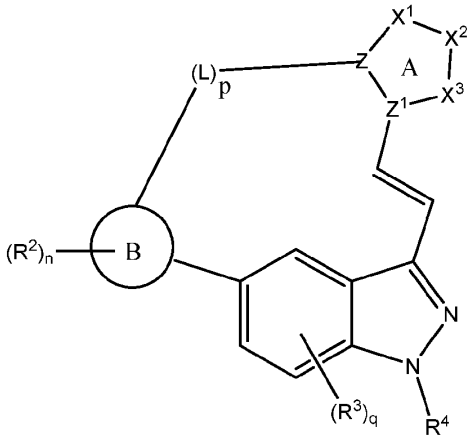
11. The compound of any one of claims 1 to 3, 9 or 10, or a pharmaceutically acceptable salt thereof, having the formula III



III

wherein Z is  or  , wherein * is a point of covalent attachment to $(L)_p$ provided that * is not an N-O or N-N bond, ** is a point of covalent attachment to Z^1, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋱" represents the condition that between the points of attachment ** and "〰", one bond is a single bond and one bond is a double bond; Z^1 is  or  wherein *** is a point of covalent attachment to "═", **** is a point of covalent attachment to Z, "〰" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋱" indicates the condition that between the points of attachment **** and "〰", one bond is a single bond and one bond is a double bond, provided that both Z and Z^1 are not a nitrogen atom; and ring A is a 5- to 10-membered heteroarylene.

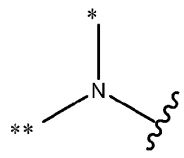
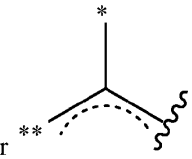
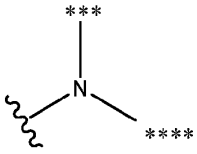
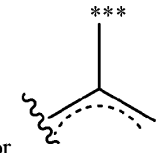
12. The compound of any one of claims 1 to 3, or 9 to 11, or a pharmaceutically acceptable salt thereof, having the formula IV



IV

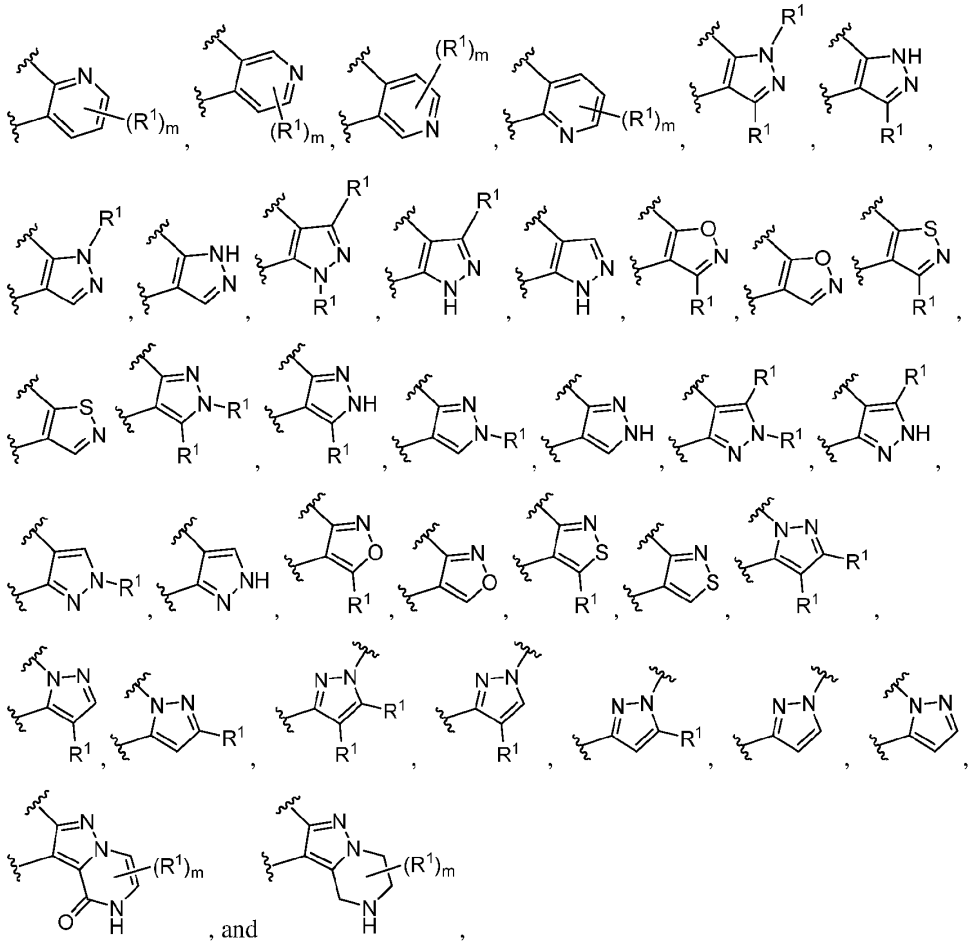
wherein

X^1, X^2, and X^3 are each independently –O-, -S-, =C(H)-, =C(R^1)-, -N(H)-, -N(R^1)- or =N-, provided that at least one of X^1, X^2, and X^3 is not =C(H)-, or =C(R^1)-;

Z is  or  , wherein * is a point of covalent attachment to $(L)_p$ provided that * is not an N-O or N-N bond, ** is a point of covalent attachment to Z^1, "∿∿∿" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋰⋰" represents the condition that between the points of attachment ** and "∿∿∿", one bond is a single bond and one bond is a double bond; Z^1 is  or  , wherein *** is a point of covalent attachment to "═══", **** is a point of covalent attachment to Z, "∿∿∿" represents a point of covalent attachment to a ring atom of ring A, and "⋰⋰⋰" indicates the condition that between the points of attachment **** and "∿∿∿", one bond is a single bond and one bond is a double bond, provided that both Z and Z^1 are not a nitrogen atom; and

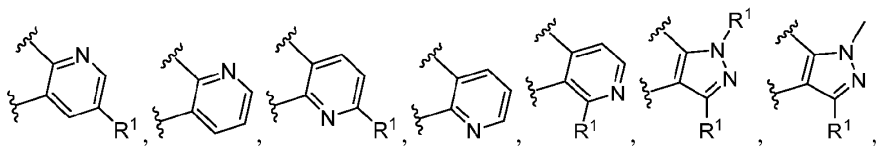
ring A is a 5- to 10-membered heteroarylene.

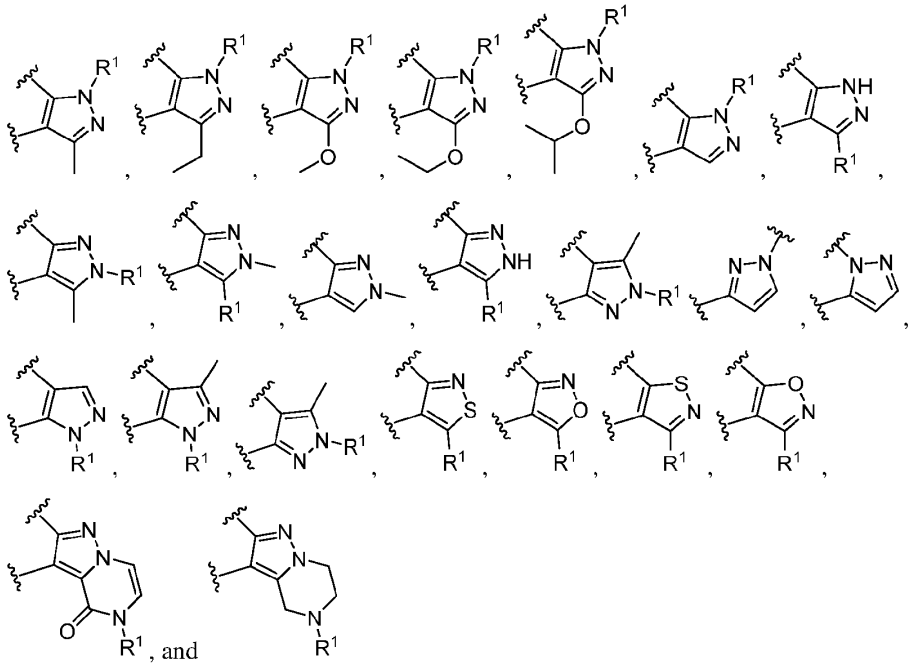
13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



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

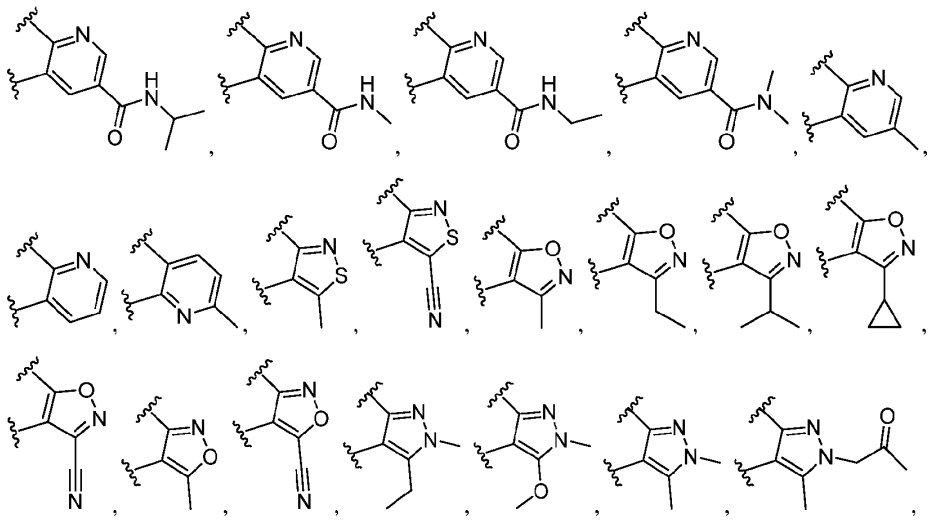
14. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of

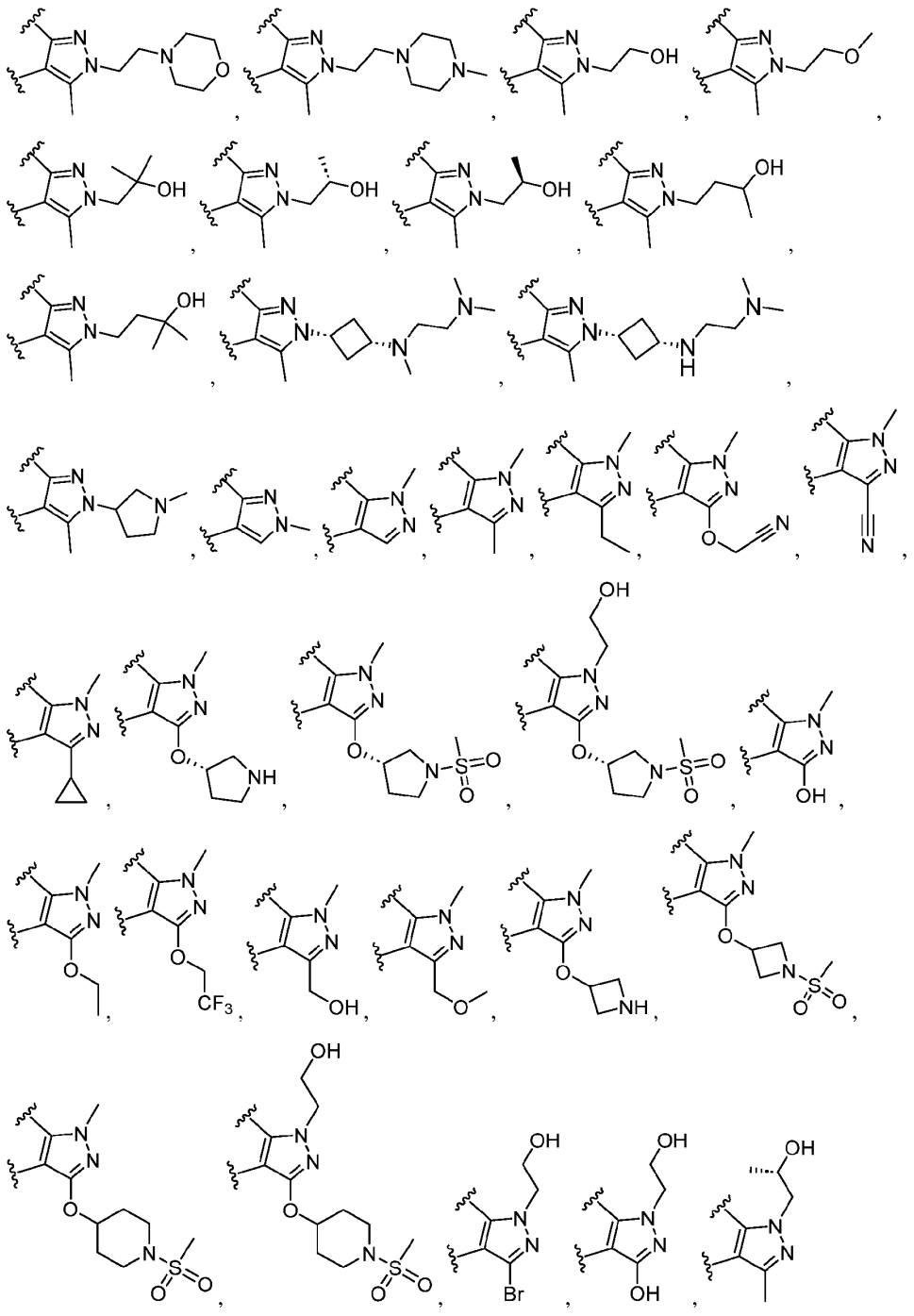


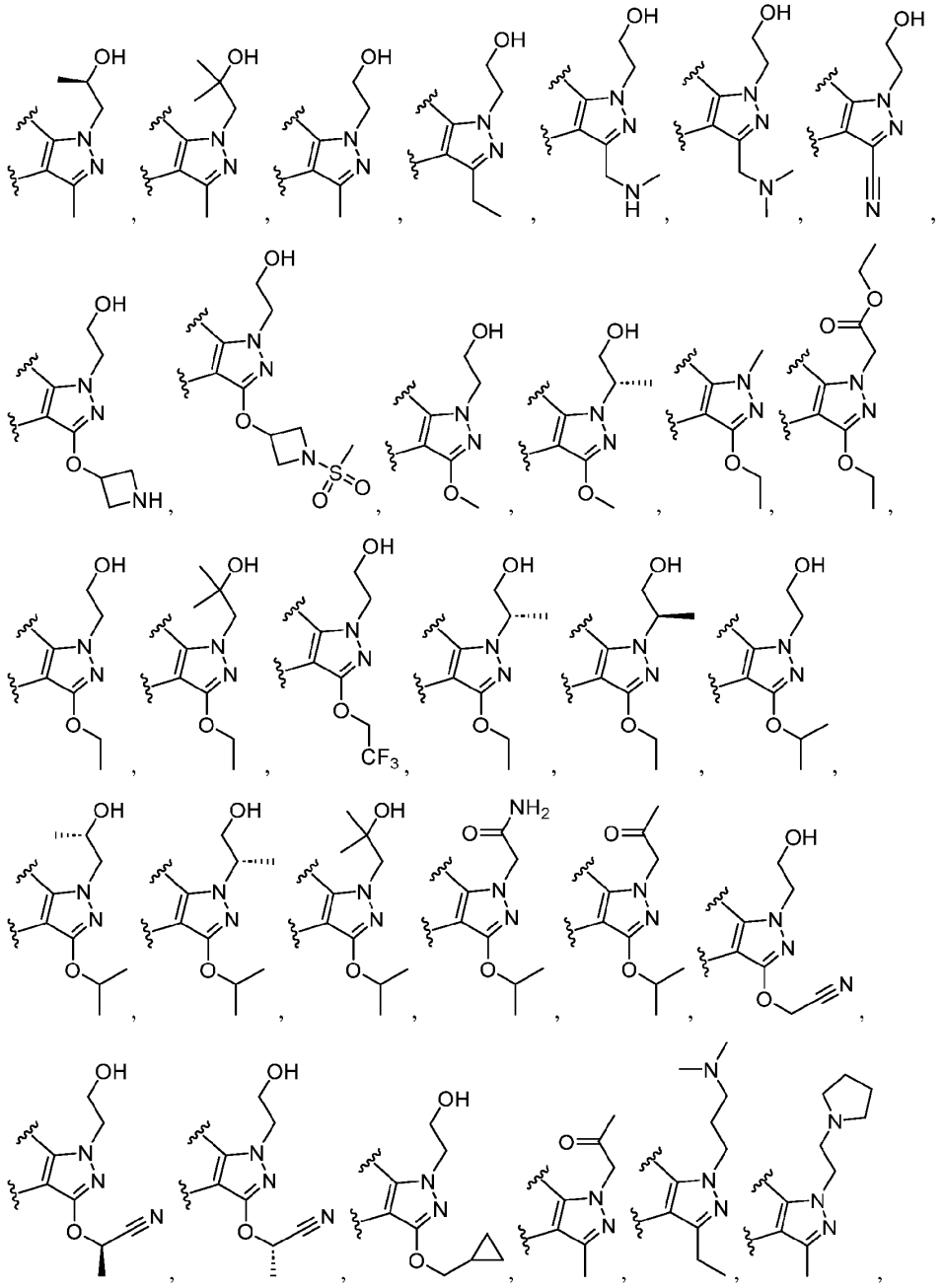


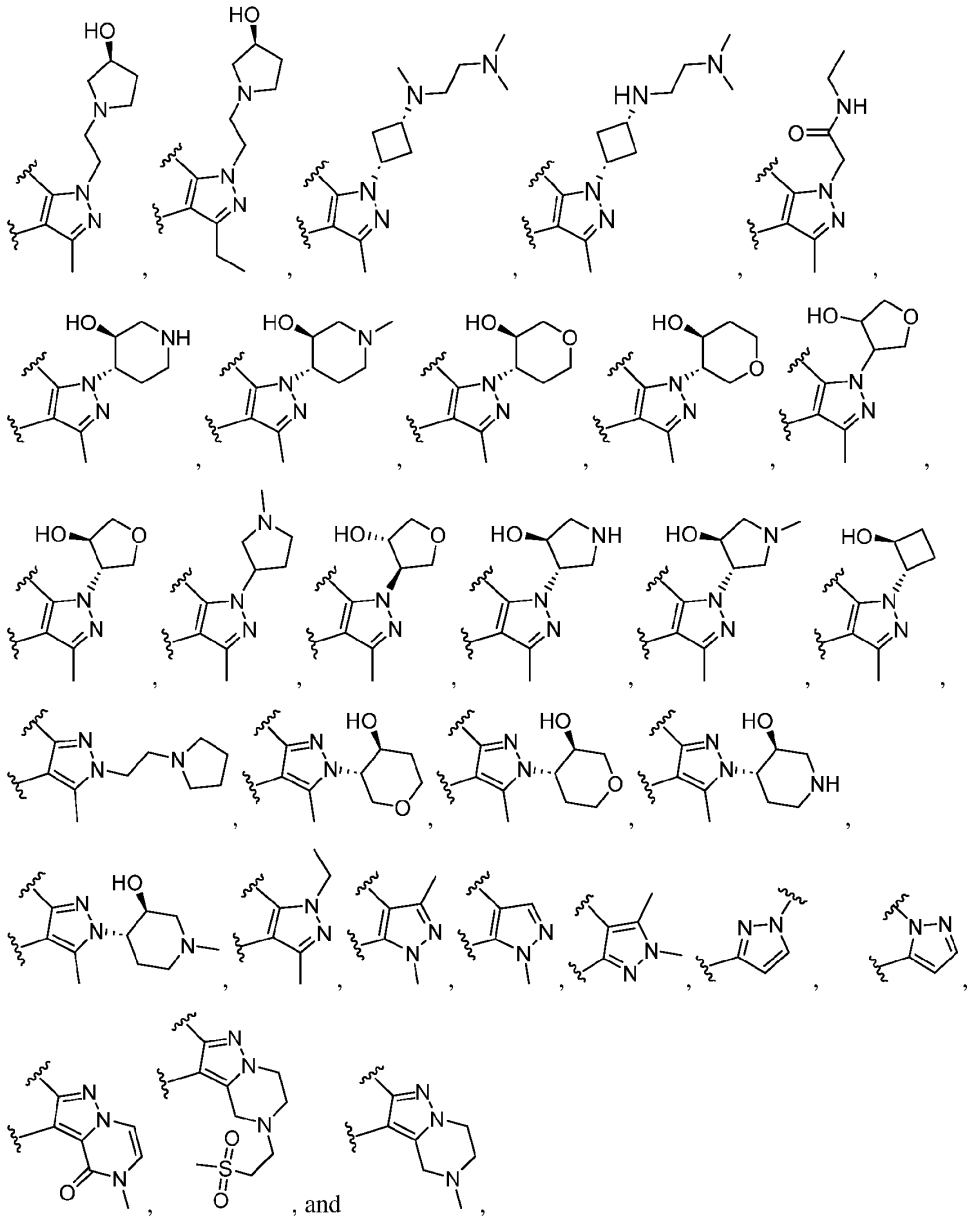
wherein each "〰" represents a point of covalent attachment.

15. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring A is a 5- to 10-membered heteroarylene selected from the group consisting of



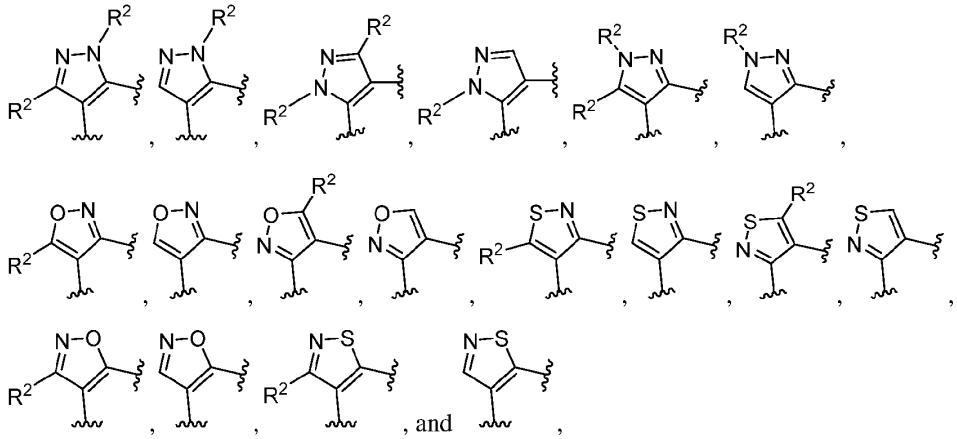






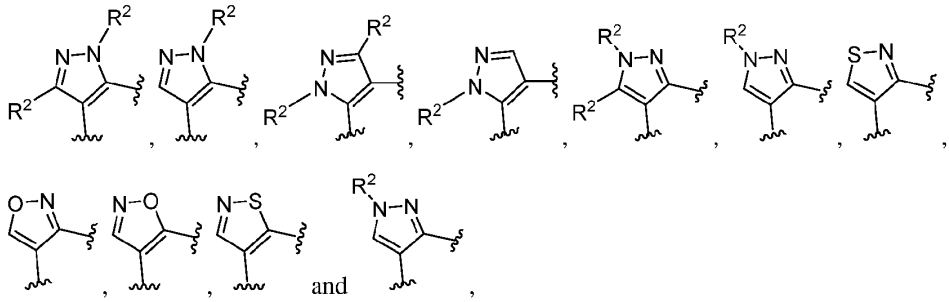
wherein each "〰" represents a point of covalent attachment.

16. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



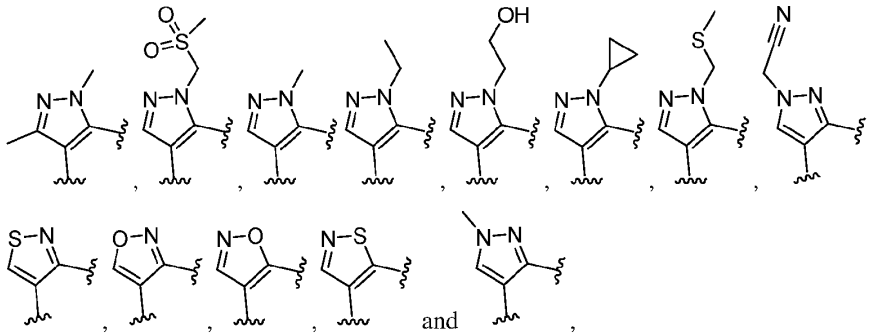
wherein each "〰" represents a point of covalent attachment.

17. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



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

18. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein ring B is a 5-membered heteroarylene selected from the group consisting of



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

19. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, q is 0, 1, or 2.

20. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, q is 0 or 1.

21. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^3 is F.

22. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^4 is H or methyl.

23. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each L is independently -$C(R^6)(R^7)$-, -C(O)-, -O-, or -$N(R^5)$-, provided that $(L)_p$ does not comprise a –O-O- or a –O-$N(R^5)$- bond, and the point of covalent attachment of $(L)_p$ to ring A does not form a –N-N- or a –O-N- bond.

24. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein -$(L)_p$- is -CR^6R^7-$O(CR^6R^7)_2O$-, -CR^6R^7-$O(CR^6R^7)_3O$-, -$(CR^6R^7)C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)N(R^5)C(O)$-$(CR^6R^7)_2$-, -$O(CR^6R^7)_2N(R^5)C(O)$-$(CR^6R^7)O$-, -$N(R^5)$-$C(O)(CR^6R^7)_2O(CR^6R^7)_2$-, -$CR^6R^7O(CR^6R^7)_2O$-$(CR^6R^7)_2$, -$O(CR^6R^7)_2O(CR^6R^7)_2O$-, -$CR^6R^7O$-$CR^6R^7$-$C(O)N(R^5)$-$(CR^6R^7)_2$-, -$(CR^6R^7)_3O(CR^6R^7)_2$-, -$(CR^6R^7)_2O(CR^6R^7)_3$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_4O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_2$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3O$-, -$CR^6R^7$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2O$-$CR^6R^7$-, -$O(CR^6R^7)_2O(CR^6R^7)_2$-, -$O(CR^6R^7)_2O(CR^6R^7)_3$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_3$-, -$O(CR^6R^7)_2$-$N(R^5)$-$CR^6R^7$-, -$(CR^6R^7)_2$-$N(R^5)$-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_2$-, -O-$(CR^6R^7)_3$-, -O-$(CR^6R^7)_4$-, -O-$(CR^6R^7)_5$-, -O-$(CR^6R^7)_2O$-, -O-$(CR^6R^7)_3O$-, -O-$(CR^6R^7)_4O$-, or -O-$(CR^6R^7)_5O$-.

25. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently H, methyl, ethyl, –$C(O)CH_3$, or –$C(O)CH_2CH_3$; or R^5, when present, and an R^6 or R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each

hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^5 and an R^6 or R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

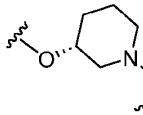
26. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein an R^6 and R^7, when present, taken together with the atom or atoms to which they are attached, combine to form a 3- to 7-membered heterocycloalkyl; wherein each hydrogen atom in the 3- to 7-membered heterocycloalkyl formed when R^6 and R^7 are taken together is independently optionally substituted by $-OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^f$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^eR^f$, $-OS(O)_2NR^eR^f$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-NR^eR^f$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^eR^f$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^eR^f$, $-NR^eS(O)_2NR^eR^f$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-PR^eR^f$, $-P(O)R^eR^f$, $-P(O)_2R^eR^f$, $-P(O)NR^eR^f$, $-P(O)_2NR^eR^f$, $-P(O)OR^e$, $-P(O)_2OR^e$, -CN, or $-NO_2$.

27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each R^6, that is not taken together with R^5 or an R^7, is independently H or C_1-C_6 alkyl.

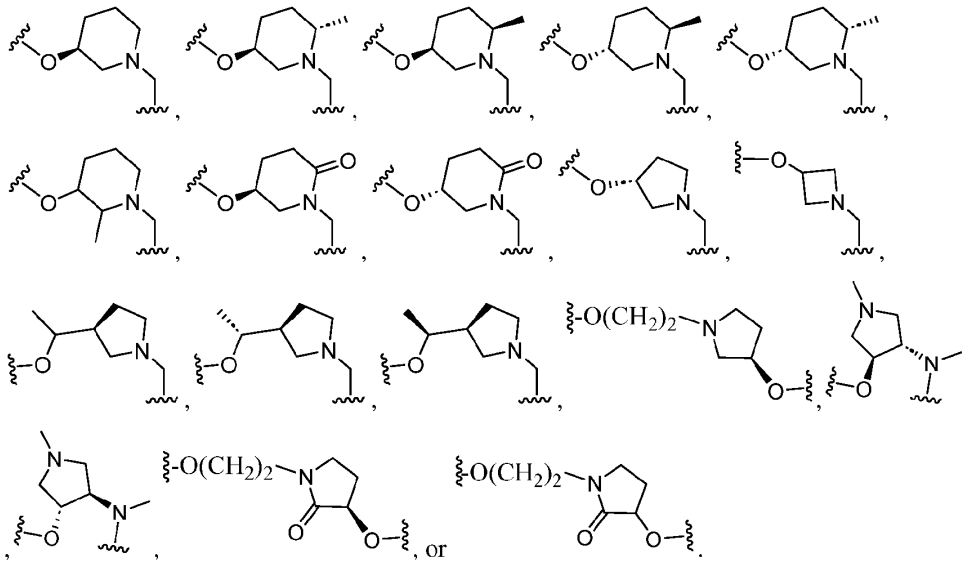
28. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein one R^6, that is not taken together with R^5 or an R^7, is methyl, and the remaining R^6 and R^7 are H.

29. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $-(L)_p-$ is $-O-(CH_2)_2O-CH_2-$, $-OC(H)(CH_3)-CH_2-O-CH_2-$, $-CH_2O-(CH_2)_2O-$, $-C(H)(CH_3)-O-(CH_2)_2O-$, $-CH_2N(H)-(CH_2)_2O-$, $-CH_2N(CH_3)-(CH_2)_2O-$, $-CH_2N(CH_2CH_3)-(CH_2)_2O-$, $-O(CH_2)_2N(H)CH_2-$, $-O(CH_2)_2N(CH_3)CH_2-$, $-OCH_2-C(H)(CH_3)-N(CH(CH_3)_2)CH_2-$, $-OCH_2-C(H)(CH_2F)-N(CH_3)CH_2-$, $-OCH_2-C(H)(CH_2CH_3)-N(CH_3)CH_2-$, $-O(CH_2)_2N(C(O)CH_3)CH_2-$, $-OC(H)(CH_3)CH_2N(H)CH_2-$, $-OC(H)(CH_3)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2CN)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2CH_3)CH_2N(CH_3)CH_2-$, $-OC(H)(CH_2F)CH_2N(CH_3)CH_2-$, $-OC(H)(CHF_2)CH_2N(CH_3)CH_2-$,

-OC(H)(CH_2OH)$CH_2N(CH_3)CH_2$-, -OC(H)(CH_3)C(O)N(CH_3)CH_2-,
-OC(H)(cyclobutyl)$CH_2N(CH_3)CH_2$-, -OC(H)(CH_3)$CH_2N(CH_2CH_3)CH_2$-,
-OC(H)(CH_3)$CH_2N(CH(CH_3)_2)$-CH_2-, -OC(H)(CH_3)$CH_2N(CH_3)$-C(H)(CH_3)-,
-OC(H)(CH_3)CH_2N(CH(oxetan-3-yl)-CH_2-, -OC(H)(CH_3)CH_2N(cyclopropyl)-CH_2-,
-OCH_2C(H)(CH_3)N(cyclopropyl)-CH_2-, -OC(H)(CH_3)$CH_2N(C(O)CH_3)CH_2$-,
-O(C(H)(CH_3))$CH_2N(C(O)CH_2CH_3)CH_2$-, -CH_2N(H)-$(CH_2)_2$(C(H)CH_3)CH_2O-,
-$CH_2N(CH_3)$-C(H)(CH_3)-CH_2O-, -$CH_2N(CH_3)$-$(CH_2)_2$(C(H)CH_3)CH_2O-,
-$CH_2N(CH_3)$-(CH_2)-(C(H)CH_3)O-, -O$(CH_2)_2$-, -O$(CH_2)_3$-, -O$(CH_2)_4$-, -O$(CH_2)_3$O-,
-O$(CH_2)_4$O-, -O$(CH_2)_5$O-, -O-(C(H)(CH_3)-$(CH_2)_2$O-, -O$(CH_2)_2$-C(H)(CH_3)-O-,
-O$(CH_2)_2$C(H)(CH_3)CH_2O-, -O$(CH_2)_3$C(H)(CH_3)CH_2O-, -O$(CH_2)_2$N(H)C(O)-(CH_2)O-,
-O$(CH_2)_2N(CH_3)$C(O)-(CH_2)O-, -O$(CH_2)_2O(CH_2)_2$O-, -OC(H)(CH_3)CH_2OCH_2-,



-O$(CH_2)_2OCH_2$C(H)(CH_3)O-, -O$(CH_2)_2$OC(H)(CH_3)-CH_2O-,



30. A compound selected from the group consisting of (11*E*)-1-methyl-1,18,19,21-tetrahydro-8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,4,12,13]benzodioxadiazacyclooctadecine;
(11*E*)-1-[(methanesulfonyl)methyl]-19,20-dihydro-1*H*,8*H*,18*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*f*][1,5,12,13]benzodioxadiazacyclooctadecine;
(11*E*)-1-methyl-18,19,20,21-tetrahydro-1*H*,8*H*-10,7,4-(ethan[1]yl[1,2]diylidene)pyrazolo[3,4-*g*][1,6,13,14]benzodioxadiazacyclononadecine;

(10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-3-methyl-13-[(4-methylpiperazin-1-yl)methyl]-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-13-[(dimethylamino)methyl]-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-3-methyl-13-(1-methylpiperidin-4-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-13-(2-methoxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-3-methyl-13-(4-methylpiperazin-1-yl)-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-14-fluoro-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-14-(2-hydroxypropan-2-yl)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-14-{(2*S*)-2-[(methanesulfonyl)methyl]azetidin-1-yl}-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecin-25-one;
(10*R*,16*E*)-3-methyl-25-oxo-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine-14-carbonitrile; and
(10*R*,16*E*)-3-methyl-3,5,6,9,10,19-hexahydro-8*H*-20,22-etheno-7,10-methanodipyrazolo[3,4-*i*:4',3'-*m*][1,8,5]benzodioxazacyclooctadecine;
or a pharmaceutically acceptable salt thereof.

31. A compound selected from the group consisting of (18*E*)-8-methyl-*N*-(propan-2-yl)-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;
(18*E*)-*N*,8-dimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;

(18*E*)-*N*,*N*,8-trimethyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;
(18*E*)-*N*-ethyl-8-methyl-8,9,11,12-tetrahydro-2*H*-3,5-ethenodipyrazolo[3',4':9,10;4",3":13,14][1,4]dioxacyclopentadecino[5,6-*b*]pyridine-16-carboxamide;
(10*S*,18*E*)-8,10,16-trimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,5]dioxacyclopentadecino[7,6-*b*]pyridine;
(10*S*,18*E*)-17-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[4,3-*f*][1,4]oxazacyclopentadecine; and
(10*S*,18*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*]pyrido[3,2-*f*][1,4]oxazacyclopentadecine;
or a pharmaceutically acceptable salt thereof.

32. A compound selected from the group consisting of (17*E*)-8,14,16-trimethyl-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(2*H*)-yl]ethan-1-ol;
(17*E*)-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
(17*E*)-19-fluoro-8,14,16-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
(17*E*)-16-ethyl-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-2-methylpropan-2-ol;
1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]propan-2-one;
2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethan-1-ol;
(17*E*)-8,16-dimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

(3*S*)-1-{2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

(17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(10*S*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(10*R*,17*E*)-8,10,14,16-tetramethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(12*S*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(12*R*,17*E*)-16-ethyl-8,12,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(10*S*,17*E*)-16-cyclopropyl-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(17*E*)-16-(methoxymethyl)-8,14-dimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c*':6,7-*c*'']tripyrazole;

(17*E*)-8,14,16-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

1-[(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

(17*E*)-8,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-6,8,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-16-ethyl-8,12,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-7,14,16-trimethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-7,12,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

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

(17*E*)-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-8,10,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

2-[(17*E*)-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

2-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

2-[(17*E*)-10-ethyl-8,16-dimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

(19*E*)-8,13,16,18-tetramethyl-2,11,12,13,14,16-hexahydro-8*H*,10*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,16*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-16-yl]ethan-1-ol;

(19*E*)-8,16,18-trimethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

(19*E*)-8,12,16,18-tetramethyl-2,11,12,16-tetrahydro-8*H*,10*H*-3,5-ethenotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,7,4]dioxazacycloheptadecin-13(14*H*)-one;

(13R,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

(13S,19E)-8,13,16,18-tetramethyl-2,10,11,13,14,16-hexahydro-8H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazole;

2-[(19E)-8,13,18-trimethyl-2,8,10,11,13,14-hexahydro-16H-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-c:17,16-c':8,9-c"]tripyrazol-16-yl]ethan-1-ol;

(19*E*)-8,13,18-trimethyl-16-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

(3*S*)-1-{2-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]ethyl}pyrrolidin-3-ol;

(19*E*)-22-fluoro-8,16,18-trimethyl-2,10,11,13,14,16-hexahydro-8*H*-3,5-etheno[1,4,7]trioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazole;

3-[(17*E*)-16-ethyl-8-methyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-*N*,*N*-dimethylpropan-1-amine;

(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]pyrrolidin-3-ol;
(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpyrrolidin-3-ol;
(3*R*,4*S*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;
(3*S*,4*R*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]oxolan-3-ol;
(*rac*)-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutan-1-ol;
(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]piperidin-3-ol;
(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-1-methylpiperidin-3-ol;
(*rac*)-1,5-anhydr-3o-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;
(*rac*)-1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]-L-*threo*-pentitol;
(12*R*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(12*S*,17*E*)-8,10,12,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(rac)-(3*S*,4*S*)-1-methyl-4-[(17*E*)-8,10,16-trimethyl-2,8,9,10,11,12-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]pyrrolidin-3-ol;
(11*S*,17*E*)-8,11,14,16-tetramethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(17*E*)-8,9,16-trimethyl-14-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
[(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-16-yl]methanol;
N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;

(11*S*,17*E*)-8,10,11,14,16-pentamethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,14*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14-yl]cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;

(10*R*,15*E*)-3,12,14-trimethyl-5,6,9,10,12,18-hexahydro-3*H*,8*H*-19,21-etheno-7,10-methanotripyrazolo[3,4-*i*:3',4'-*m*:4",3"-*q*][1,8,4]dioxazacyclooctadecin-24-one;

(17*E*)-16-ethyl-8,10,14-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(17*E*)-10-ethyl-8,14,16-trimethyl-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

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

2-[(10*S*,17*E*)-19-fluoro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

(17*E*)-8,10,16-trimethyl-14-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

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

(10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(10*R*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

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

2-[(10*S*,17*E*)-19-chloro-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

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

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

(10*S*,17*E*)-8,10,12,14-tetramethyl-16-[(piperidin-4-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

2-[(10*R*,19*E*)-18-ethoxy-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;
2-[(10*S*,17*E*)-6,8,10,12,16-pentamethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(10*S*,17*E*)-8,10,14,16-tetramethyl-12-(oxetan-3-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
2-[(10*S*,17*E*)-16-ethoxy-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,13*R*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,13*S*,17*E*)-8,10,12,13,14,16-hexamethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;
(10*S*,17*E*)-16-[(azetidin-3-yl)oxy]-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
2-[(10*S*,17*E*)-16-ethoxy-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(17*E*)-10-cyclobutyl-8,12,16-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(10*S*,17*E*)-8,10,12,14-tetramethyl-16-{[(3*S*)-pyrrolidin-3-yl]oxy}-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(2*S*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

(10*S*,17*E*)-16-ethoxy-8,10,14-trimethyl-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,14-trimethyl-2,11,12,14-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;
(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;
(10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;
(10*S*,17*E*)-12-cyclopropyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12,14-tetramethyl-16-(2,2,2-trifluoroethoxy)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
{[(10*S*,17*E*)-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
(10*S*,17*E*)-10,14,16-trimethyl-8-[(methylsulfanyl)methyl]-12-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-12-ethyl-8,10,14,16-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
2-[(10*S*,17*E*)-16-ethoxy-8-ethyl-10,12-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-{(10*S*,17*E*)-8-ethyl-10,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
(2*R*)-2-[(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)piperidin-4-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(10*S*,19*E*)-8,16,18-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;
2-[(10*S*,17*E*)-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

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

2-[(10*S*,17*E*)-16-{[(3*S*)-1-(methanesulfonyl)pyrrolidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

2-[(10*S*,17*E*)-16-bromo-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

(10*S*,17*E*)-16-{[3-(methanesulfonyl)cyclobutyl]oxy}-8,10,12,14-tetramethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(10*S*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

(10*R*,19*E*)-18-ethoxy-8,16-dimethyl-2,8,11,12,15,16-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-13(10*H*)-one;

2-[(10*R*,19*E*)-18-ethoxy-22-fluoro-8-methyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

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

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

2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(10*R*,17*E*)-16-ethoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-8,11-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(10*R*,19*E*)-22-fluoro-8-methyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;
(2*S*)-2-{(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;
2-{(11*S*,17*E*)-6,8,11-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
2-{(10*R*,17*E*)-6,8,10-trimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
{[(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;
2-[(10*R*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,10-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
2-[(11*S*,17*E*)-12-cyclopropyl-16-ethoxy-6,8,11-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;
(10*S*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(2*S*)-2-{(10*R*,17*E*)-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;
(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-16-carbonitrile;
(10*S*,17*E*)-12-ethyl-8,10,14-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;
(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;

2-[(10*S*,17*E*)-19-fluoro-8,10,12-trimethyl-16-(2,2,2-trifluoroethoxy)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

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

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

2-{(10*S*,17*E*)-12-ethyl-19-fluoro-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

1-[(10*R*,17*E*)-16-ethoxy-14-(2-hydroxyethyl)-8,10-dimethyl-2,8,10,11,13,14-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

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

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

(10*S*,17*E*)-14-(2-hydroxyethyl)-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,12,13,14-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-11(10*H*)-one;

2-[(10*S*,17*E*)-16-{[1-(methanesulfonyl)azetidin-3-yl]oxy}-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

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

2-{(10*S*,13*S*,17*E*)-8,10,12,13-tetramethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
2-{(17*E*)-10-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
2-{(17*E*)-11-(fluoromethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;
(2*S*)-1-{(10*R*,17*E*)-12-ethyl-8,10-dimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;
(2*S*)-2-[(11*S*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-[(10*R*,17*E*)-16-ethoxy-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;
(2*S*)-2-{(11*S*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;
(2*S*)-2-{(10*R*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-1-ol;
2-{(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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}acetamide;
(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2-(propan-2-yl)-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-ol;
2-[(8a*R*,19*E*)-1-(cyclopropylmethoxy)-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;
(10*R*,18*E*)-17-ethoxy-8,15-dimethyl-2,8,11,12,14,15-hexahydro-10*H*-3,5-etheno-10,13-methanotripyrazolo[3,4-*g*:3',4'-*k*:4",3"-*o*][1,5]oxazacyclohexadecine;

{(17*E*)-14-(2-hydroxyethyl)-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-7*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-7-yl}acetonitrile;

(17*E*)-16-ethoxy-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno-10,12-methanotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

2-[(10*S*,17*E*)-16-ethoxy-19-fluoro-6,8,10-trimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

2-[(8a*R*,9*R*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*S*,19*E*)-1-ethoxy-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(19*E*)-18-ethoxy-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*R*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*S*,19*E*)-1-ethoxy-22-fluoro-9,11-dimethyl-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(19*E*)-18-ethoxy-22-fluoro-8,21-dimethyl-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

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

(10*S*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

(10*R*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

(10*R*,13*S*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

(10*S*,13*R*,19*E*)-18-ethoxy-8,13,16-trimethyl-2,8,10,11,12,13,15,16-octahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecine;

2-{(10*R*,17*E*)-19-fluoro-8,10,12-trimethyl-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-[(8a*R*,9*S*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*R*,19*E*)-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(19*E*)-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*R*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(8a*R*,9*S*,19*E*)-22-fluoro-9,11-dimethyl-1-[(propan-2-yl)oxy]-7,8,8a,9,11,17-hexahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-3(4*H*)-yl]ethan-1-ol;

2-[(19*E*)-22-fluoro-8,21-dimethyl-18-[(propan-2-yl)oxy]-2,10,11,12,13,15-hexahydro-3,5-etheno-10,14-methanotripyrazolo[3,4-*h*:3',4'-*l*:4",3"-*p*][1,6]oxazacycloheptadecin-16(8*H*)-yl]ethan-1-ol;

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

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

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

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

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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}-2-methylpropan-2-ol;

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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-one;

(10*R*,17*E*)-14-(2-hydroxyethyl)-8,12-dimethyl-16-[(propan-2-yl)oxy]-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-10-carbonitrile;

2-{(10*S*,17*E*)-8,10,12-trimethyl-16-[(methylamino)methyl]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-{(10*S*,17*E*)-16-[(dimethylamino)methyl]-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol:

(2*R*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

(2*S*)-2-{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}propanenitrile;

2-[(4a*S*,7a*S*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

2-[(4a*R*,7a*R*,13*E*)-12-ethoxy-3,6,8-trimethyl-4a,5,6,7,7a,8,9,16-octahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecin-10(3*H*)-yl]ethan-1-ol;

{[(8a*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

{[(8a*R*,9*R*,19*E*)-3-(2-hydroxyethyl)-9,11-dimethyl-3,4,7,8,8a,9,11,17-octahydro-6*H*-14,16-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[2,1-*c*][1,4]oxazacyclopentadecin-1-yl]oxy}acetonitrile;

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

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

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

2-[(10*R*,17*E*)-16-ethoxy-12-ethyl-19-fluoro-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

(4a*S*,7a*S*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

(4a*R*,7a*R*,13*E*)-12-ethoxy-3,8,10-trimethyl-3,4a,5,6,7,7a,8,9,10,16-decahydro-17,19-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*]pyrrolo[3,4-*b*][1,4]oxazacyclopentadecine;

(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-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}propan-2-ol;

2-{(11*R*,17*E*)-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-{(10*S*,17*E*)-19-fluoro-8,10-dimethyl-12-(propan-2-yl)-16-[(propan-2-yl)oxy]-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl}ethan-1-ol;

2-[(11*R*,17*E*)-16-ethoxy-19-fluoro-8,11-dimethyl-12-(propan-2-yl)-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

{[(10*S*,17*E*)-19-fluoro-14-(2-hydroxyethyl)-8,10,12-trimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-16-yl]oxy}acetonitrile;

2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

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

(2*S*)-2-[(10*R*,17*E*)-12-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[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-hydroxyethyl)-8,10-dimethyl-2,10,11,12,13,14-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-6-carbonitrile;

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

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

2-[(10*S*,17*E*)-16-(ethylamino)-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]ethan-1-ol;

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

2-[(10*S*,17*E*)-6-amino-16-ethoxy-12-ethyl-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[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-ethyl-19-fluoro-16-methoxy-8,10-dimethyl-2,8,10,11,12,13-hexahydro-14*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-14-yl]propan-1-ol;

2,2'-[(10*S*,17*E*)-10,12-dimethyl-16-[(propan-2-yl)oxy]-10,11,12,13-tetrahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine-8,14(2*H*)-diyl]di(ethan-1-ol);

(17*E*)-16-ethyl-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

2-[(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-14(8*H*)-yl]-*N*-ethylacetamide;

(17*E*)-8,14-dimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

(17*E*)-8,14,16-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

(10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

(10*S*,17*E*)-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole-16-carbonitrile;

(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]oxazole-16-carbonitrile;
(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[6,5-*d*][1,2]thiazole-16-carbonitrile;
(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]oxazole-16-carbonitrile;
(10*S*,17*E*)-10,14-dimethyl-10,11,13,14-tetrahydro-2*H*-3,5-ethenodipyrazolo[4',3':13,14;4",3":9,10][1,4]dioxacyclopentadecino[5,6-*c*][1,2]thiazole-16-carbonitrile; and
(10*S*,17*E*)-16-ethyl-8,10,14-trimethyl-2,8,10,11,13,14-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
or a pharmaceutically acceptable salt thereof.

33. A compound selected from the group consisting of (17*E*)-8,15,16-trimethyl-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
(17*E*)-8,15,16-trimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]propan-2-one;
1-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-2-methylpropan-2-ol;
2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]ethan-1-ol;
(17*E*)-8,16-dimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;
(10*S*,17*E*)-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(17*E*)-8,15,16-trimethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

1-[(17*E*)-8,15,16-trimethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

(17*E*)-8,12,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]ethan-1-one;

(10*S*,17*E*)-8,10,12,15,16-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

2-[(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

2-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]ethan-1-ol;

(10*S*,17*E*)-12-ethyl-8,10,15,16-tetramethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

1-[(10*S*,17*E*)-8,10,15,16-tetramethyl-2,8,10,11,13,15-hexahydro-12*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-12-yl]propan-1-one;

2-[(19*E*)-8,13,18-trimethyl-2,8,11,12,13,14-hexahydro-10*H*,17*H*-3,5-etheno[1,7]dioxacycloheptadecino[12,13-*c*:17,16-*c'*:8,9-*c''*]tripyrazol-17-yl]ethan-1-ol;

(13*E*)-3-methyl-3,5,6,7,8,16-hexahydro-9,12-(azeno)-17,19-ethenodipyrazolo[3,4-*l*:4',3'-*p*][1,6]oxazacycloheptadecine;

(18*E*)-8-methyl-2,8,10,11,12,13-hexahydro-3,5-ethenotripyrazolo[1,5-*f*:3',4'-*j*:4",3"-*n*][1,6]oxazacyclopentadecine;

(17*E*)-15-(2-methoxyethyl)-8,16-dimethyl-2,11,12,15-tetrahydro-8*H*,10*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

2-[(17*E*)-8,9,16-trimethyl-8,9,11,12-tetrahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15(2*H*)-yl]ethan-1-ol;

(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]piperidin-3-ol;

(*rac*)-4-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-1-methylpiperidin-3-ol;

(17*E*)-8,9,16-trimethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,8,9,11,12,15-hexahydro-3,5-etheno[1,4]dioxacyclopentadecino[11,10-*c*:15,14-*c'*:6,7-*c''*]tripyrazole;

(*rac*)-1,5-anhydro-2,3-dideoxy-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;

1,5-anhydro-2,4-dideoxy-2-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]-L-*threo*-pentitol;
(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(4-methylpiperazin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(20*E*)-8,18-dimethyl-2,8,11,12-tetrahydro-10*H*-3,5-ethenodipyrazolo[3",4":10',11';4"',3"':14',15'][1,5]dioxacyclopentadecino[6',7':3,4]pyrazolo[1,5-*a*]pyrazin-19(18*H*)-one;
(10*S*,17*E*)-8,10,12,16-tetramethyl-15-[2-(morpholin-4-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;
N^1-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno[1,5]dioxacyclopentadecino[10,11-*c*:15,14-*c'*:6,7-*c''*]tripyrazol-15-yl]cyclobutyl}-N^1,N^2,N^2-trimethylethane-1,2-diamine;
2-methyl-4-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]butan-2-ol;
2-methyl-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;
N^2-{(1*s*,3*s*)-3-[(17*E*)-8,16-dimethyl-2,8,11,12-tetrahydro-10*H*,15*H*-3,5-etheno|1,5|dioxacyclopentadecino|10,11-*c*:15,14-*c'*:6,7-*c''*|tripyrazol-15-yl|cyclobutyl}-N^1,N^1-dimethylethane-1,2-diamine;
(17*E*)-8,10,16-trimethyl-15-(1-methylpyrrolidin-3-yl)-2,9,10,11,12,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:4',3'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*R*,17*E*)-8,10,12,16-tetramethyl-15-[2-(pyrrolidin-1-yl)ethyl]-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(2*S*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;
(10*S*,17*E*)-8,10,12,14,15-pentamethyl-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(2*R*)-1-[(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-15*H*-3,5-ethenotripyrazolo[3,4-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecin-15-yl]propan-2-ol;
(10*S*,17*E*)-8,10,12,14,16-pentamethyl-2,10,11,12,13,16-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;

(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12,16-tetramethyl-2,8,10,11,12,13-hexahydro-3,5-ethenodipyrazolo[3,4-*j*:4',3'-*n*][1,2]thiazolo[3,4-*f*][1,4]oxazacyclopentadecine;
(10*S*,20*E*)-18-[2-(methanesulfonyl)ethyl]-8,10,12-trimethyl-2,8,10,11,12,13,16,17,18,19-decahydro-3,5-ethenopyrazino[1',2':1,5]pyrazolo[3,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-16-cyclopropyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-16-ethyl-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,12-trimethyl-16-(propan-2-yl)-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-16-ethoxy-8,10,12-trimethyl-2,8,10,11,12,13-hexahydro-3,5-etheno[1,2]oxazolo[5,4-*f*]dipyrazolo[3,4-*j*:4',3'-*n*][1,4]oxazacyclopentadecine;
(10*R*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,14,15-tetramethyl-12-(propan-2-yl)-2,10,11,12,13,15-hexahydro-8*H*-3,5-ethenotripyrazolo[4,3-*f*:3',4'-*j*:4",3"-*n*][1,4]oxazacyclopentadecine;
(10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole;
(10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole-16-carbonitrile;
(10*S*,17*E*)-8,10,16-trimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole;
(10*S*,17*E*)-8,10-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]thiazole-16-carbonitrile;
(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;

(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;
(10*S*,17*E*)-8,10,16-trimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;
(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole-16-carbonitrile;
(10*S*,17*E*)-8,10-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole-16-carbonitrile;
(17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]oxazole;
(17*E*)-8,16-dimethyl-2,10,11,13-tetrahydro-8*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[7,6-*d*][1,2]oxazole; and
(17*E*)-8,16-dimethyl-2,8,10,11-tetrahydro-13*H*-3,5-ethenodipyrazolo[3',4':10,11;4",3":14,15][1,4]dioxacyclopentadecino[6,7-*c*][1,2]thiazole;
or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition comprising a compound of any one of the preceding claims, and optionally one or more excipients.

35. A method of treating disease in a subject comprising, administering a therapeutically effective amount of a compound of any one of claims 1 to 33, or a pharmaceutical composition of claim 35.

36. A compound according to any one of claims 1 to 33, for use in a method of treating disease in a subject.

37. Use of a compound according to any one of claims 1 to 33 in the manufacture of a medicament for the treatment of disease in a subject.