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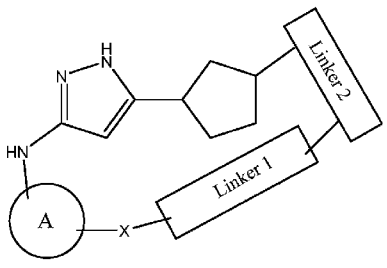

(I')

(57) Abstract: The present disclosure provides a compound represented by structural formula (I') or a pharmaceutically acceptable salt, or a stereoisomer thereof and their use in, e.g. treating a disease or disorder associated with CDK2. This disclosure also features compositions containing the same as well as methods of using and making the same.

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CDK2 INHIBITORS AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to International Patent Application No. PCT/CN2021/084358, filed on March 31, 2021. The entire contents of the aforementioned application are incorporated herein by reference.

BACKGROUND

Cyclin-Dependent Kinases (CDKs) are a family of protein kinases first discovered for their roles in regulating cell cycle. They have since been identified to play roles in regulating a number of other biological functions such as transcription, mRNA processing, and the differentiation of nerve cells.

CDKs are relatively small proteins with molecular weights between about 34-40 kDa. They contain little more than the kinase domain, and are essentially inactive when not in complex with a class of regulatory proteins called cyclins. CDK levels remain relatively constant throughout the cell cycle, and most regulation is post-translational, most prominently by binding to cyclins.

CDK2 is of particular interest because deregulation of CDK2 activity occurs frequently in a variety of human cancers. CDK2 plays a crucial role in promoting G1/S transition and S phase progression. In complex with cyclin E (CCNE), CDK2 phosphorylates retinoblastoma pocket protein family members (p107, p130, pRb), leading to de-repression of E2F transcription factors, expression of G1/S transition related genes and transition from G1 to S phase (Henley, S. A. and F. A. Dick, Cell Div, 2012, 7(1):10). This in turn enables activation of CDK2/cyclin A, which phosphorylates endogenous substrates that permit DNA synthesis, replication and centrosome duplication (Ekholm, S. V. and S. I. Reed, Curr Opin Cell Biol, 2000, 12(6):676-84). It has been reported that the CDK2 pathway influences tumorigenesis mainly through amplification and/or overexpression of CCNE1 and mutations that inactivate CDK2 endogenous inhibitors (*e.g.*, p27), respectively (Xu, X., *et al.*, Biochemistry, 1999, 38(27):8713-22).

CCNE1 copy-number gain and overexpression have been identified in ovarian, gastric, endometrial, breast and other cancers and been associated with poor outcomes in these tumors (Keyomarsi, K., *et al.*, N Engl J Med, 2002, 347(20):1566-75; Nakayama, N., *et al.*, Cancer, 2010, 116(11):2621-34; Au-Yeung, G., *et al.*, Clin Cancer Res, 2017, 23(7):1862-1874; Rosen, D. G., *et al.*, Cancer, 2006, 106(9):1925-32). Amplification and/or overexpression of CCNE1 also reportedly contribute to trastuzumab resistance in HER2+ breast cancer and resistance to CDK4/6 inhibitors in estrogen receptor-positive breast cancer (Scaltriti, M., *et al.*, Proc Natl Acad Sci USA, 2011, 108(9):3761-6; Herrera-Abreu, M. T., *et al.*, Cancer Res, 2016, 76(8):2301-13). Various approaches targeting CDK2 have been shown to induce cell cycle arrest and tumor growth inhibition (Chen, Y N., *et al.*, Proc Natl Acad Sci USA, 1999, 96(8):4325-9; Mendoza, N., *et al.*, Cancer Res, 2003, 63(5):1020-4). Inhibition of CDK2 also reportedly restores sensitivity to trastuzumab treatment in

resistant HER2+ breast tumors in a preclinical model (Scaltriti, supra).

These data provide a rationale for considering CDK2 as a potential target for new drug development in cancer associated with deregulated CDK2 activity. In the last decade there has been increasing interest in the development of CDK selective inhibitors. Despite significant efforts, there are no approved agents targeting CDK2 to date (Cicenas, J., *et al*., Cancers (Basel), 2014, 6(4):2224-42).

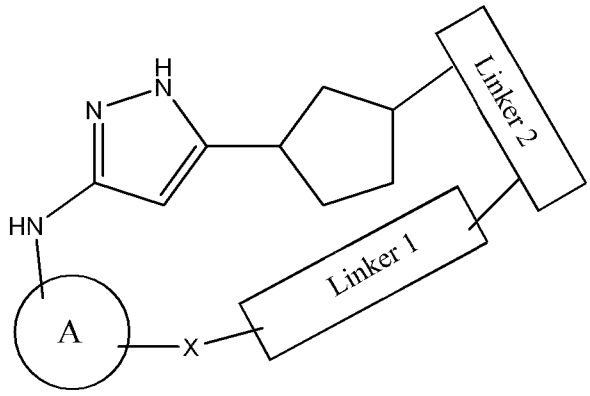
Identifying selective CDK2 inhibitors is very difficult, partly due to the extreme similarity between the active sites of CDK2 and other CDKs, especially CDK1, which is the only essential CDK in the cell cycle. Inhibition of CDK1 could lead to many unintended side effects.

Therefore, it remains a need to discover CDK inhibitors having novel activity profiles, in particular those specifically or selectively targeting CDK2.

SUMMARY

Described herein are compounds of Formula (I') or (I) that inhibit (*e.g.*, selectively inhibit) the activity of CDK2, and pharmaceutically acceptable salts, or stereoisomers thereof.

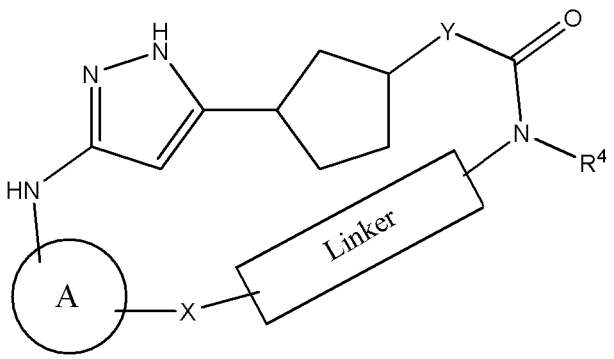
In one aspect, the present disclosure provides a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof:



(I'),

wherein ring A, linkers 1 and 2, X, and R^4 are as defined herein.

In another aspect, the present disclosure provides a compound of Formula (I), a pharmaceutically acceptable salt, or a stereoisomer thereof:



(I),

wherein ring A, linker, X, Y, and R^4 are as defined herein.

Also provided are pharmaceutical compositions comprising a compound of Formula (I') or (I), a pharmaceutically acceptable salt, or a stereoisomer thereof and a pharmaceutically acceptable carrier or excipient.

The present disclsoure further provides methods of inhibiting CDK2 in a patient, comprising administering to the patient a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, or a stereoisomer thereof.

The present disclsoure also provides methods of treating a disease or or condition modulated at least in part by CDK2 in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I') or (I), a pharmaceutically acceptable salt, or a stereoisomer thereof.

The present disclosure further provides a method of treating cancer in a patient in need thereof, comprising administering to the patient an effective amount of (1) a compound of Formula (I') or (I), a pharmaceutically acceptable salt, or a stereoisomer thereof; or (2) a pharmaceutically acceptable composition comprising a compound of Formula (I') or (I), a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the cancer is treatable by inhibiting (*e.g.*, selectively inhibiting) CDK2, such as a cancer selected from the group consisting of: ovarian cancer, breast cancer (such as hormone receptor positive, HER2/neu negative advanced or metastatic breast cancer, HER2 positive breast cancer and triple negative breast cancer), lung cancer, endometrial cancer, neuroblastoma, gastric cancer, colorectal cancer, prostate cancer, glioblastoma, melanoma, mantel cell lymphoma, chronic myeloid leukemia and acute myeloid leukemia. In certain embodiments, the cancer exhibits abnormally up-regulated CCNE1 / Cyclin E activity, through overexpression of Cyclin Eor duplication of the Cyclin E-coding CCNE1 gene. In certain embodiments, the cancer exhibits abnormally up-regulated Cyclin A2 activity.

In certain embodiments of the methods of the invention, the cancer can be treated by inhibiting (*e.g.*, selectively inhibiting) the activity of CDK2.

In certain embodiments of the methods of the invention, the compounds of the invention are

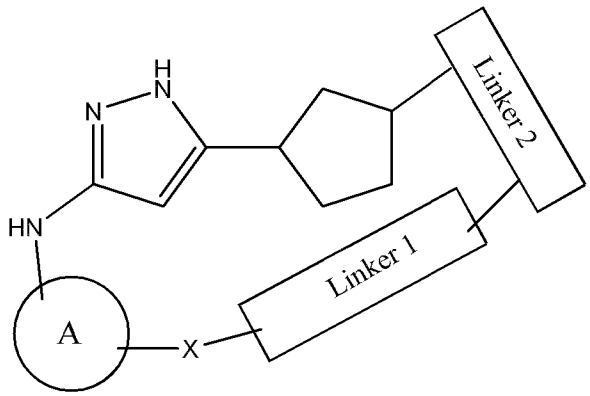
administered with any one of a second therapeutic agent as described herein that also treats the same cancer.

The present disclosure also provides a use of a compound of Formula (I') or (I), a pharmaceutically acceptable salt, or a stereoisomer thereof or a pharmaceutical composition comprising the same in any of the methods described herein. In one embodiment, provided is a compound of Formula (I') or (I) or a pharmaceutically acceptable salt or a stereoisomer thereof or a pharmaceutical composition comprising the same for use in any of the methods described herein. In another embodiment, provided is use of a compound of Formula (I') or (I) or a pharmaceutically acceptable salt or a stereoisomer thereof or a pharmaceutical composition comprising the same for the manufacture of a medicament for any of the methods described herein.

DETAILED DESCRIPTION

1. Compounds

In a first embodiment, the present disclosure provides a compound represented by Formula (I'):



(I'),

a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein:

ring A is 6-10 membered aryl or 5-10 memberaed heteroaryl; wherein said 6-10 membered aryl or 5-10 membered heteroaryl represented by ring A is optionally substituted by one or more R^1; wherein

R^1 is halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alknyl, C_{1-6}alkyleneamine, C_{1-6}alkylenehydroxyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-SR^{1a}$, $-NR^{1a}R^{1b}$, $-NR^{1a}C(O)R^{1b}$, $-NR^{1a}C(O)OR^{1b}$, $-NR^{1a}SO_2R^{1b}$, $-NR^{1a}SO_2NR^{1b}R^{1c}$, $-SO_2R^{1a}$, $-SO_2NR^{1a}R^{1b}$, or $-P(O)R^{1a}R^{1b}$, 3-6 membered carbocyclyl, 4-8 membered heterocyclyl, 6-10 membered aryl, 5-10 membered heteroaryl; wherein said C_{1-6}alkyleneamine, C_{1-6}alkylenehydroxyl, 3-6 membered carbocyclyl, 4-8 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl represented by R^1 is optionally substituted by one or more R^{10}, wherein

R^{10}, in each occurrence, is independently selected from the group consisting of halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, and 4-6 membered heterocyclyl;

R^{1a}, R^{1b}, and R^{1c} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and -C_{0-6}alkyl-4-6 membered heterocyclyl;

X is absent, ^-$(CH_2)_{0-1}$-O-^^, -NR^2-, ^-$(CH_2)_{0-1}$-C(O)-^^, ^-$(CH_2)_{0-1}$-NR^2C(O)-^^, ^-$(CH_2)_{0-1}$-C(O)NR^2-^^, ^-SO_2-^^, or ^-$C(R^2)$=N-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1; and

R^2, in each occurrence, is independently hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl;

Linker 1 is represented by formula

*-W-L-Z-**;

wherein *- represents the point which attaches to X; -** represents the point which attaches to Linker 2;

W is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by W is optionally substituted by one or more R^3;

L is absent, -O-, -NH-, 3-12 membered carbocyclyl, 3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-12 membered carbocyclyl,
3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl represented by L is optionally substituted by one or more R^3; and

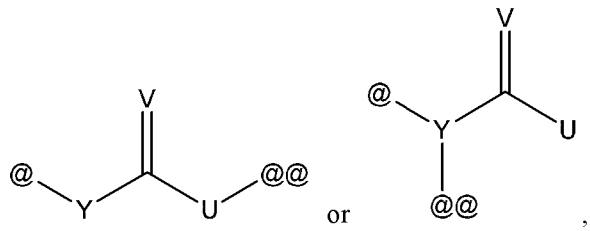
Z is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by Z is optionally substituted by one or more R^3; wherein

R^3, in each occurrence, is independently halogen, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, -OR^{3a}, -$C(=O)R^{3a}$, or -$NR^{3a}R^{3b}$; wherein

R^{3a} and R^{3b} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and 4-6 membered heterocyclyl;

wherein W, L, and Z are not absent simultaneously;

Linker 2 is represented by



wherein @- represents the point which attaches to the cyclopentyl shown in Formula (I'); -@@ represents the point which attaches to Linker1;

when U is connected with Linker1, Y is –O- or -NR^{22}-; and U is –O- or -NR^{4}-; wherein

R^{22} is hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl; and

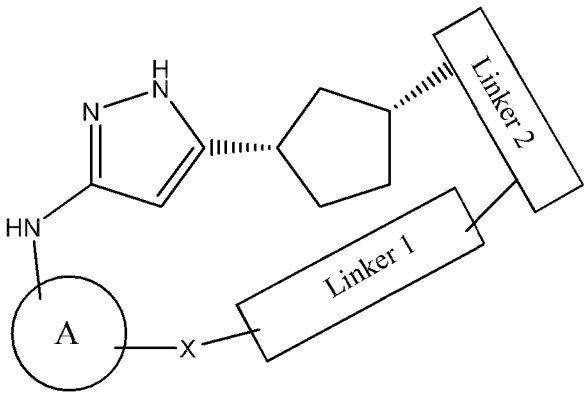
R^{4} is hydrogen or C_{1-6}alkyl; or

R^{4} and one R^{3} attached to Z together with the atoms to which they are attached form 4-8 membered heterocyclyl;

when Y is connected with Linker1, Y is N; and U is –$N(R^{5})_2$-; each R^{5} is independently hydrogen or C_{1-6}alkyl; and

V is O or S.

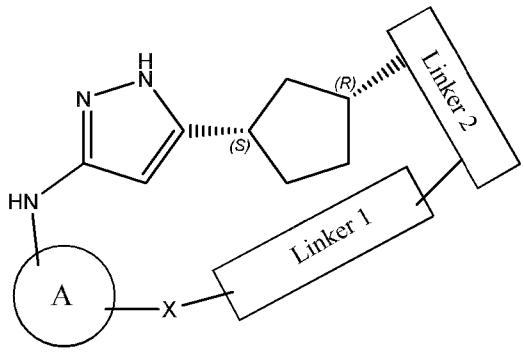
In a second embodiment, the present disclosure provides a compound according to the first embodiment, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is represented by Formula II':



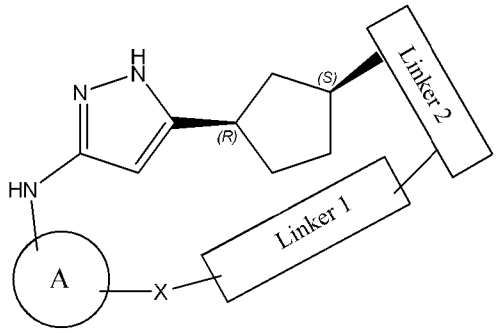
(II').

The definitions of the variables are provided in the first embodiment.

In a third embodiment, the present disclosure provides a compound according to the first or second embodiment, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is represented by Formula (II'A) or (II'B):



(II'A); or



(II'B).

The definitions of the remaining variables are provided in the first or second embodiment.

In a fourth embodiment, the present disclosure provides a compound according to any one of the first through third embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is phenyl or nitrogen containing 5-10 membered heteroaryl; wherein said phenyl or nitrogen containing 5-10 membered heteroaryl represented by ring A is optionally substituted by one to three R^1; wherein

R^1 is halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkyleneamine, C_{1-4}alkylenehydroxyl, -C(O)$NR^{1a}R^{1b}$, -OR^{1a}, -SR^{1a}, -SO_2R^{1a}, 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein said C_{1-4}alkyleneamine, C_{1-4}alkylenehydroxyl, 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl represented by R^1 is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, and 5-6 membered heterocyclyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and -C_{0-3}alkyl-4-6 membered heterocyclyl.

The definitions of the remaining variables are provided in the first through third embodiments.

In a fifth embodiment, the present disclosure provides a compound of any one of the first through fourth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is phenyl, nitrogen containing 5-6 membered heteroaryl, or nitrogen containing 9 membered bicyclic heteroaryl; wherein said phenyl, nitrogen containing 5-6 membered heteroaryl, or nitrogen containing 9 membered bicyclic heteroaryl represented by ring A is optionally substituted by one to two R^1; wherein

R^1 is halogen, -CN, C_{1-3}alkyl, C_{1-2}haloalkyl, C_{1-2}alkyleneamine, C_{1-2}alkylenehydroxyl, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-SR^{1a}$, $-SO_2R^{1a}$, 5-6 membered carbocyclyl, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein said C_{1-2}alkyleneamine, C_{1-2}alkylenehydroxyl, 5-6 membered carbocyclyl, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl represented by R^1 is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of F, Cl, -CN, C_{1-2}alkyl, C_{1-2}haloalkyl, C_{1-3}alkoxyl, and 5-6 membered heterocyclyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C_{1-2}alkyl, C_{1-2}haloalkyl, and $-C_{0-2}$alkyl-5 membered heterocyclyl.

The definitions of the remaining variables are provided in the first through fourth embodiments.

In a sixth embodiment, the present disclosure provides a compound of any one of first through fifth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from a group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, pyrrolopyridinyl, pyrazolopyrimidinyl, pyrazolopyrazinyl, thienopyridinyl, and imidazo[4,5-c]pyridinyl; wherein said phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, pyrrolopyridinyl, pyrazolopyrimidinyl, pyrazolopyrazinyl, thienopyridinyl, and imidazo[4,5-c]pyridinyl is optionally substituted by one to two R^1; wherein

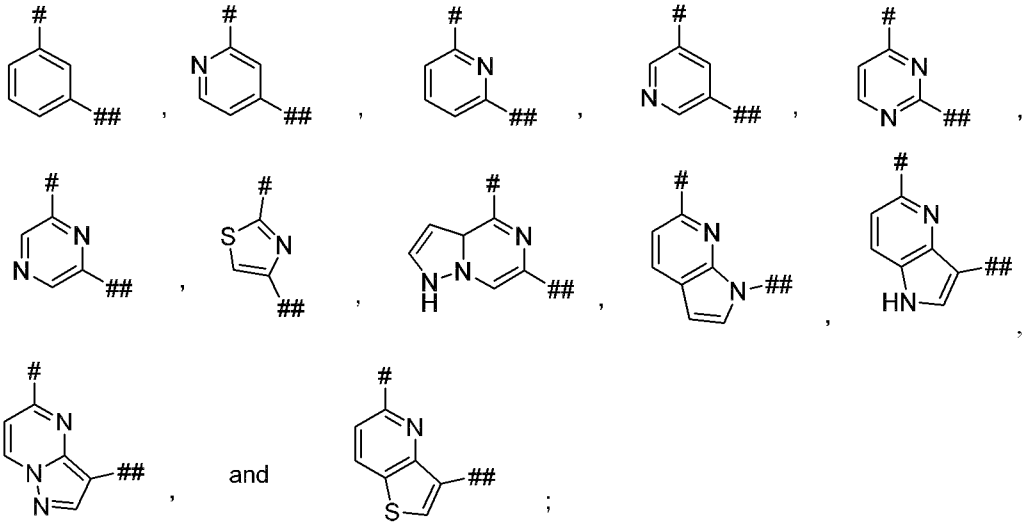
R^1 is F, Cl, Br, -CN, $-CH_3$, $-CH(CH_3)_2$, $-CF_3$, $-OR^{1a}$, $-SR^{1a}$, $-SO_2R^{1a}$, $-C(O)NR^{1a}R^{1b}$, $-CH_2NH_2$, $-CH_2OH$, cyclopentanyl, cyclohexanyl, cyclohexenyl, piperidinyl, tetrahydropyridinyl, 3,6-dihydro-2H-thiopyranyl, thiophenyl, pyrazolyl, phenyl, or pyridyl; wherein said $-CH_2NH_2$, $-CH_2OH$, cyclopentanyl, cyclohexanyl, cyclohexenyl, piperidinyl, tetrahydropyridinyl, 3,6-dihydro-2H-thiopyranyl, thiophenyl, pyrazolyl, phenyl, or pyridyl is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of F, Cl, -CN, $-CH_3$, $-CF_3$, $-CH_2CF_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, and morpholinyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, $-CH_3$, $-OCHF_2$, tetrahydrofuranyl, and $-(CH_2)_2$-pyrrolidinyl.

The definitions of the remaining variables are provided in the first through fifth embodiments.

In a seventh embodiment, the present disclosure provides a compound of any one of the first through sixth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from the group consisting of



wherein

each of them is optionally substituted by one to two R^1; and

represents the point which attaches to the moiety –NH-; ## represents the point which attaches to X.

The definitions of the remaining variables are provided in the first through the sixth embodiments.

In an eighth embodiment, the present disclosure provides a compound of any one of the first through the seventh embodiments, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, wherein ring A is pyridyl; wherein said pyridyl is optionally substituted by one R^1. The definitions of the remaining variables are provided in the first through the seventh embodiments.

In a ninth embodiment, the present disclosure provides a compound of any one of the first through the eighth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

X is absent, -O-, ^-CH_2-O-^^, ^-CH_2-C(O)-^^, ^-NR^2C(O)-^^, ^-CH_2-NR^2C(O)-^^, ^-C(O)NR^2-^^, ^-CH_2-C(O)NR^2-^^, ^-SO_2-^^, or ^-C(R^2)=N-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1;

R^2, in each occurrence, is independently hydrogen, C_{1-3}alkyl, or C_{1-3}haloalkyl.

The definitions of the remaining variables are provided in the first through the eighth embodiments.

In a tenth embodiment, the present disclosure provides a compound of any one of the first through the ninth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

X is absent, -O-, ^-CH_2-O-^^, ^-CH_2-C(O)-^^, ^-NHC(O)-^^, ^-CH_2-NHC(O)-^^, ^-C(O)NH-^^, ^-CH_2-C(O)NH-^^, ^-SO_2-^^, or ^-C(R^2)=N-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1; and

R^2, in each occurrence, is independently hydrogen, -CH_3, -CF_3, or isopropyl.

The definitions of the remaining variables are provided in the first through the ninth embodiments.

In an eleventh embodiment, the present disclosure provides a compound of any one of the first through the tenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein X is absent or ^-CH_2-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1.

The definitions of the remaining variables are provided in the first through the tenth embodiments.

In a twelfth embodiment, the present disclosure provides a compound of any one of the first through the eleventh embodiments, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein

W is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by W is optionally substituted by one to three R^3;

L is absent, -O-, -NH-, 3-8 membered carbocyclyl, 3-8 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-8 membered carbocyclyl, 3-6 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl represented by L is optionally substituted by one to three R^3; and

Z is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by Z is optionally substituted by one to three R^3; wherein

R^3, in each occurrence, is independently halogen, C_{1-4}alkyl, C_{1-4}haloalkyl, or -C(=O)R^{3a}; wherein

R^{3a} is hydrogen or C_{1-4}alkyl.

The definitions of the remaining variables are provided in the first through the eleventh embodiments.

In a thirteenth embodiment, the present disclosure provides a compound of any one of the first through the twelfth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by W is optionally substituted by one to two R^3;

L is absent, -O-, -NH-, 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic

heteroaryl; wherein said 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic heteroaryl represented by L is optionally substituted by one R^3; and

Z is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by Z is optionally substituted by one to two R^3; wherein

R^3, in each occurrence, is independently halogen, C_{1-3}alkyl, C_{1-2}haloalkyl, or - C(=O)CH_3.

The definitions of the remaining variables are provided in the first through the twelfth embodiments.

In a fourteenth embodiment, the present disclosure provides a compound of any one of the first through the thirteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene;

L is absent, -NH- or -O-; and

Z is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene.

The definitions of the remaining variables are provided in the first through the thirteenth embodiments.

In a fifteenth embodiment, the present disclosure provides a compound of any one of the first through the fourteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{3-4}alkylene, C_{3-4}haloalkylene, C_{3-4}alkenylene, or C_{3-4}alkynylene;

L is absent; and

Z is absent.

The definitions of the remaining variables are provided in the first through the fourteenth embodiments.

In a sixteenth embodiment, the present disclosure provides a compound of any one of the first through the fifteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-2}alkylene, or C_{1-2}haloalkylene;

L is 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, or 5-6 membered heteroaryl; and

Z is absent or methylene.

The definitions of the remaining variables are provided in the first through the fifteenth embodiments.

In a seventeenth embodiment, the present disclosure provides a compound of any one of the first through the sixteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -CH_2CH=CH-, or -CH_2C≡C-; wherein said -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -CH_2CH=CH-, or -CH_2C≡C- represented by W is optionally substituted by one to two R^3

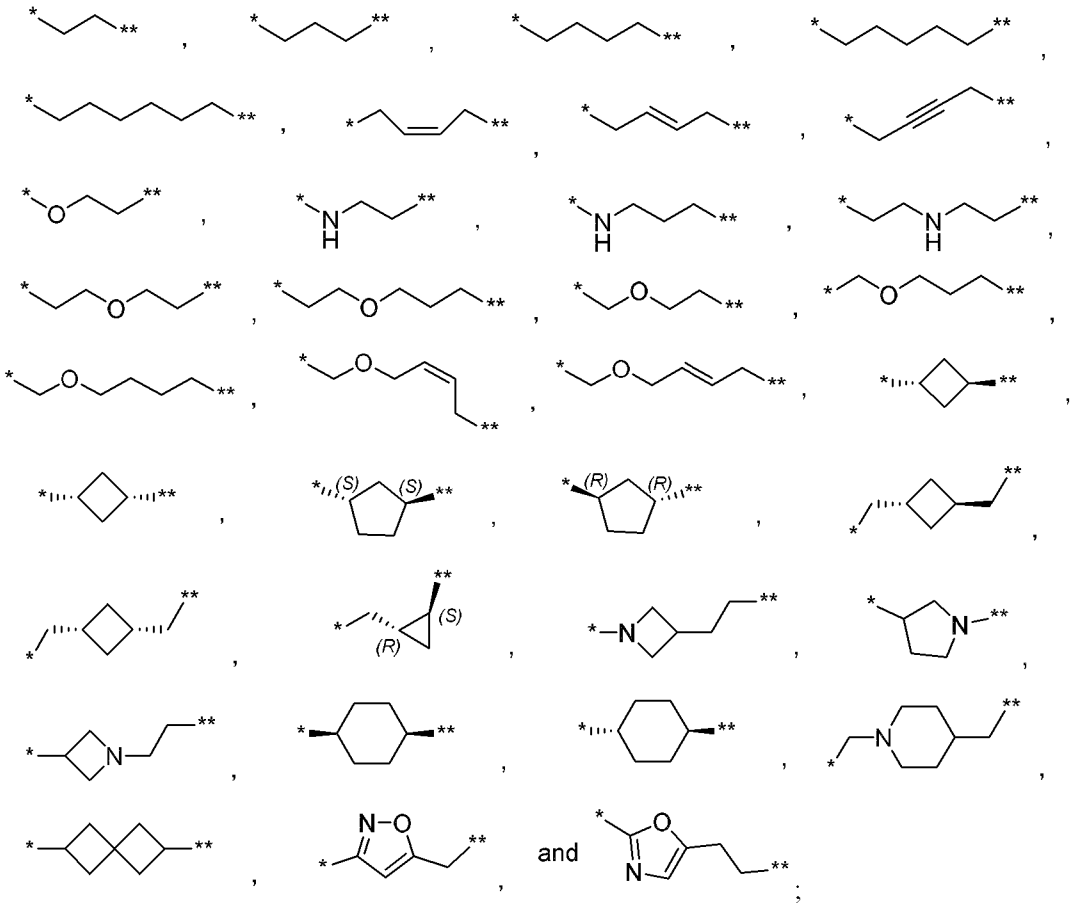
L is absent, -O-, -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, or thiozolyl; wherein said -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, or thiozolyl is optionally substituted by one R^3;

Z is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-CH=CHCH_2-$, or -C≡CCH-; wherein

R^3 is F, $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, or $-C(=O)CH_3$.

The definitions of the remaining variables are provided in the first through the sixteenth embodiments.

In an eighteenth embodiment, the present disclosure provides a compound of any one of the first through the thirteenth and seventeenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein *-W-L-Z-** is selected from the group consisting of



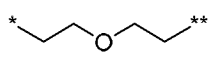
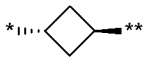
wherein each of them is optionally substituted by one to two R^3; wherein

*- represents the point which attaches to X; -** represents the point which attaches to

Linker 2.

The definitions of the remaining variables are provided in the first through the thirteenth and seventeenth embodiments.

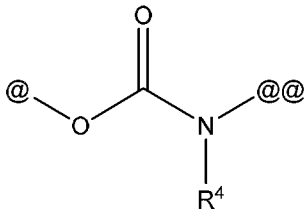
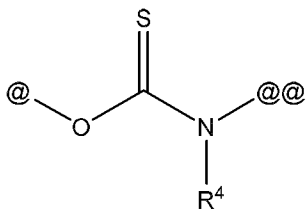
In a nineteenth embodiment, the present disclosure provides a compound of any one of the first through the thirteenth, seventeenth, and eighteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein *-W-L-Z-** is selected from the group consisting of

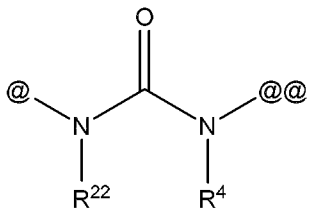
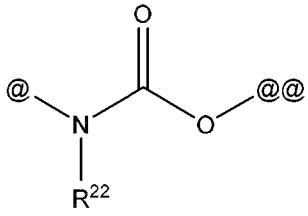
 and  ; wherein

*- represents the point which attaches to X; -** represents the point which attaches to Linker 2.

The definitions of the remaining variables are provided in the first through the thirteenth, seventeenth, and eighteenth embodiments.

In a twentieth embodiment, the present disclosure provides a compound of any one of the first through the nineteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is represented by Formula A, B, C, or D,

 (A),  (B)

 (C), or  (D)

wherein

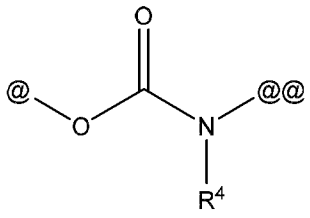
@- represents the point which attaches to the cyclopentyl shown in Formula (I'); -@@ represents the point which attaches to Linker1;

R^{22} is hydrogen, C_{1-4}alkyl, or C_{1-4}haloalkyl; and

R^4 is hydrogen or C_{1-4}alkyl; or R^4 and one R^3 attached to Z, together with the atoms to which they are attached, form 4-6 membered heterocyclyl.

The definitions of the remaining variables are provided in the first through the nineteenth embodiments.

In a twenty-first embodiment, the present disclosure provides a compound of the twentieth embodiment, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is



(A);

wherein

@- represents the point which attaches to the cyclopentyl shown in Formula (I');

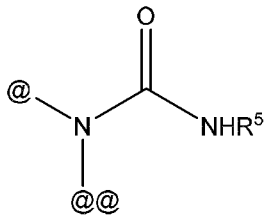
-@@ represents the point which attaches to Linker1; and

R^4 is hydrogen or $-CH_3$; or R^4 and one R^3 attached to Z together with the atoms to which they are attached, form azetidinyl or pyrrolidinyl.

The definitions of the remaining variables are provided in the twentieth embodiment.

In a twenty-second embodiment, the present disclosure provides a compound of the twenty-first embodiment, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R^4 is hydrogen. The definitions of the remaining variables are provided in the twenty-first embodiments.

In a twenty-third embodiment, the present disclosure provides a compound of any one of the first through the nineteenth embodiments, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is represented by Formula E:



(E);

wherein

@- represents the point which attaches to the cyclopentyl shown in Formula (I');

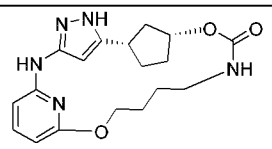
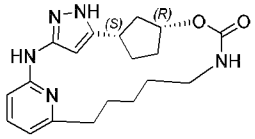
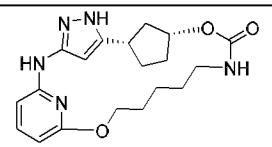
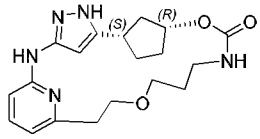
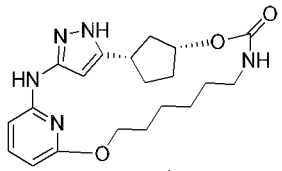
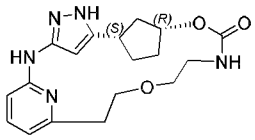
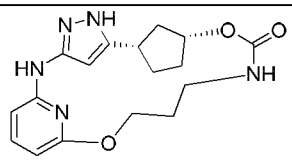
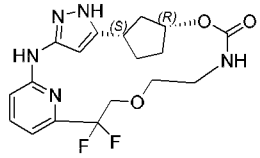
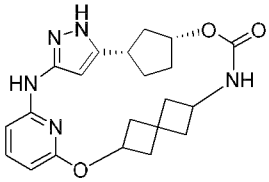
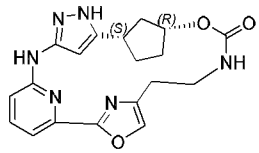
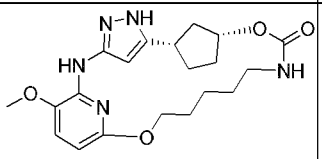
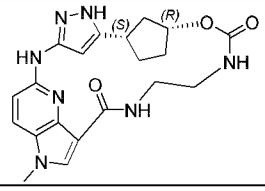
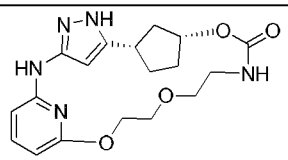
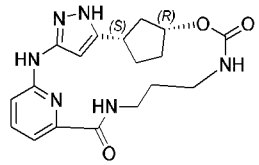
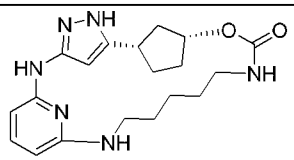
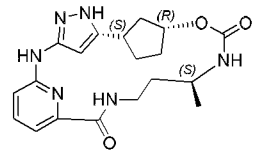
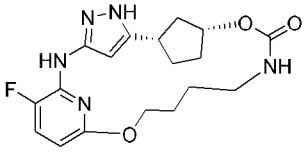
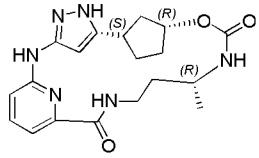
-@@ represents the point which attaches to Linker1; and

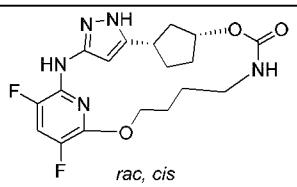
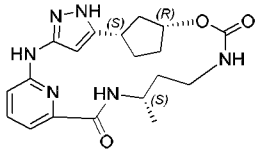
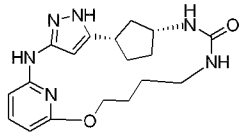
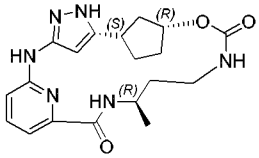
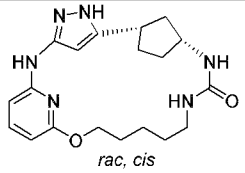
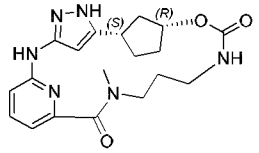
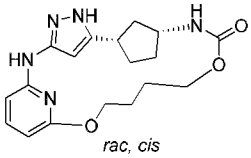
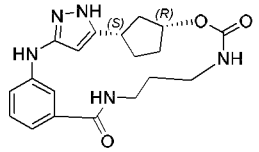
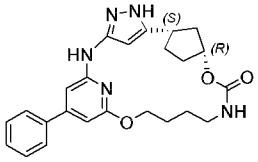
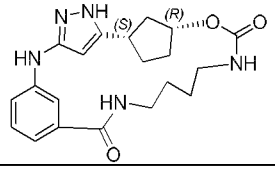
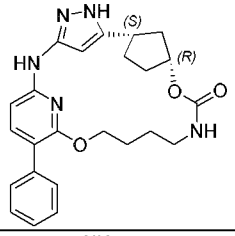
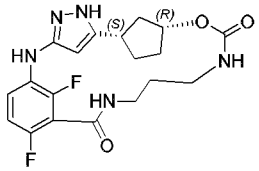
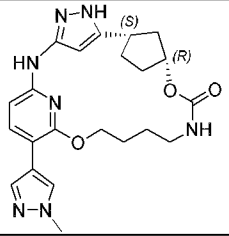
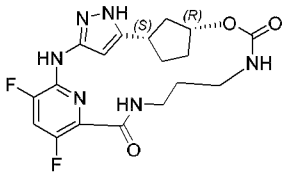
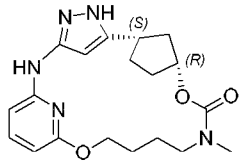
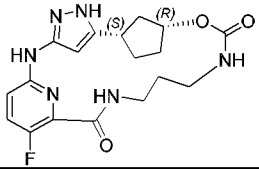
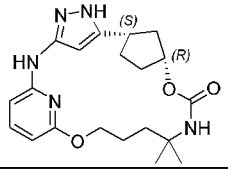
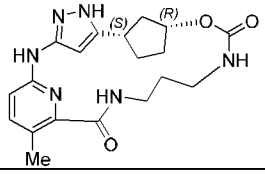
R^5 is hydrogen or isopropyl.

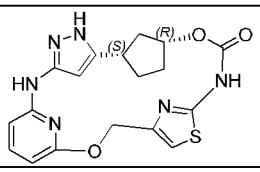
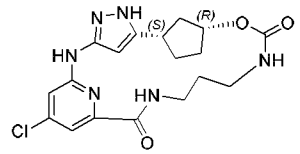
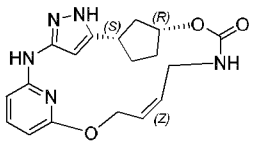
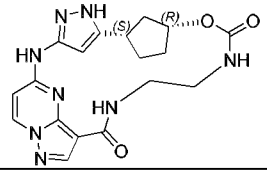
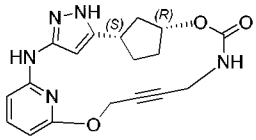
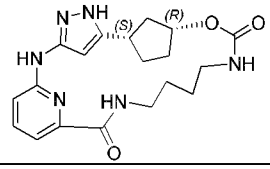
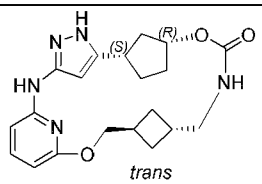
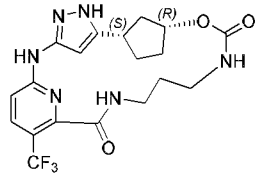
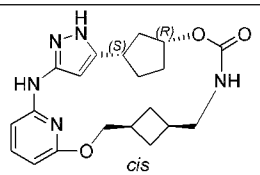
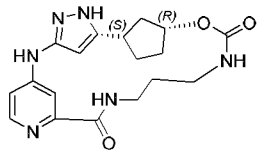
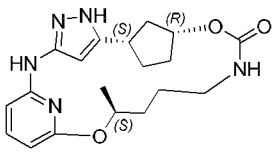
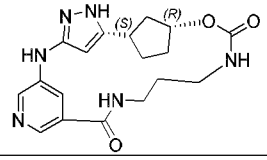
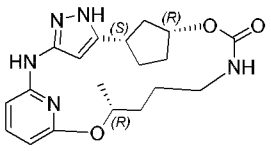
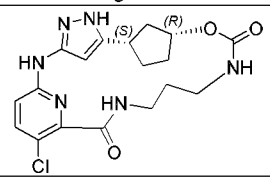
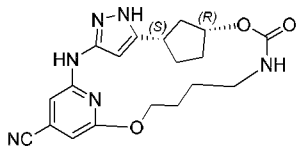
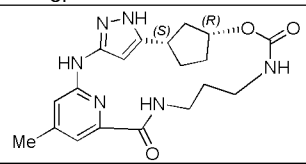
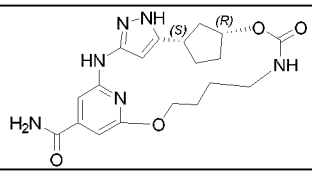
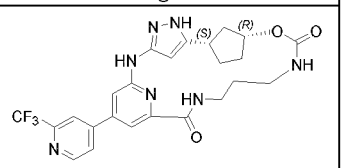
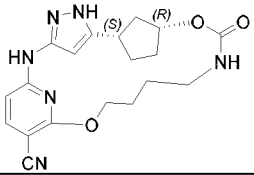
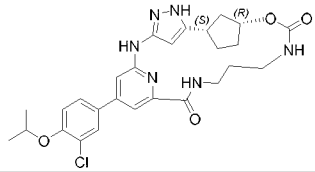
In one embodiment, the present disclosure provides a compound selected from the compounds disclosed in examples and Table 1, a pharmaceutically acceptable salt or a stereoisomer thereof.

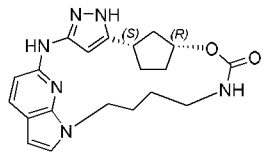
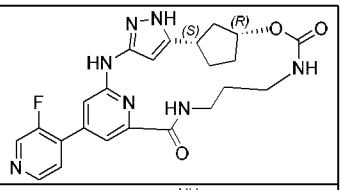
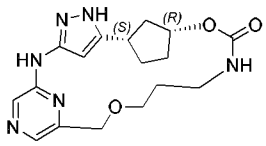
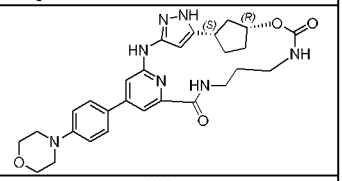
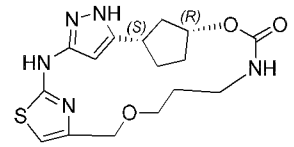
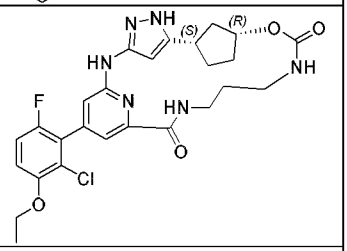
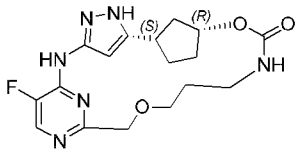
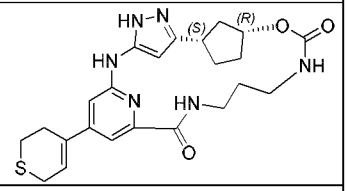
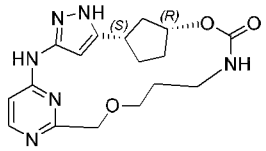
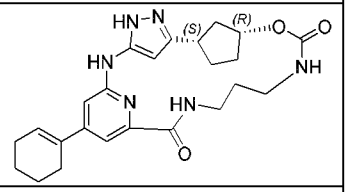
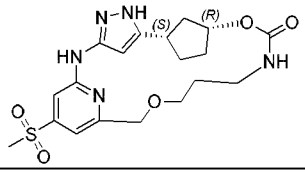
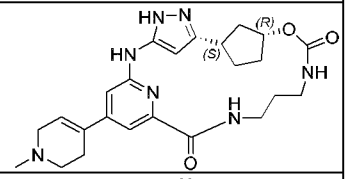
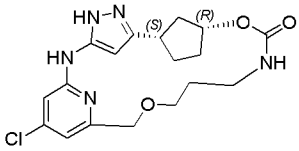
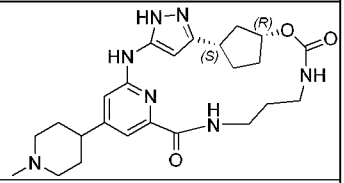
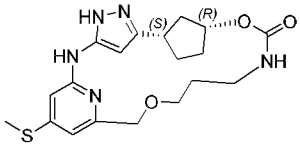
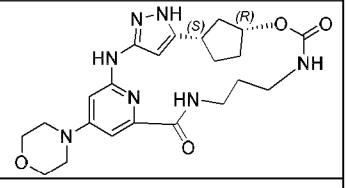
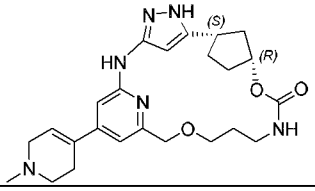
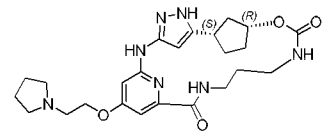
Table 1

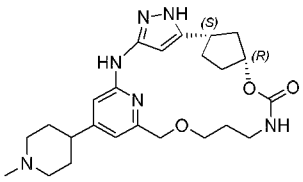
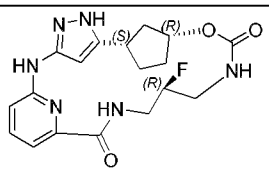
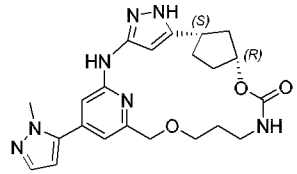
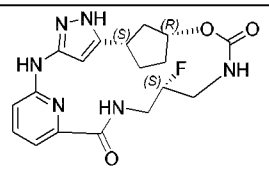
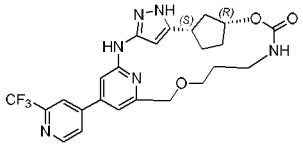
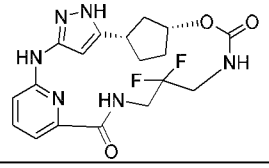
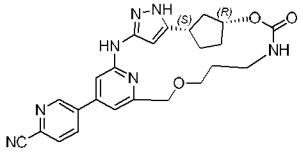
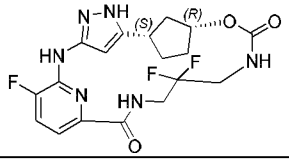
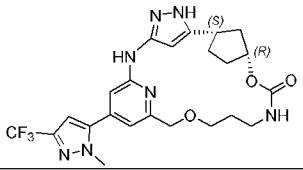
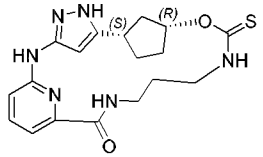
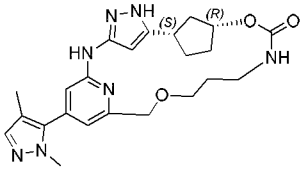
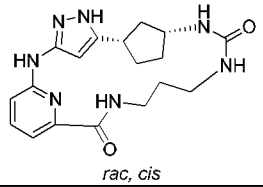
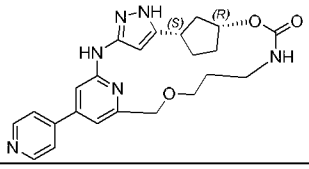
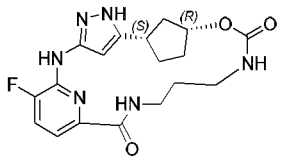
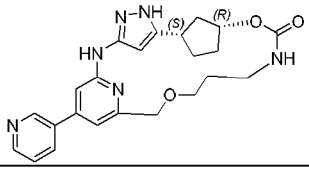
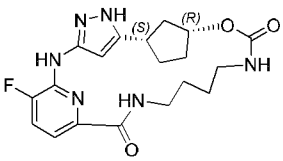
ID	Structure	ID	Structure

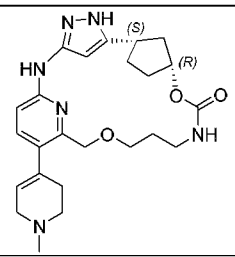
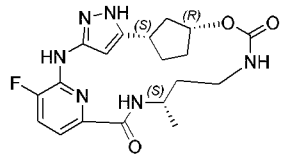
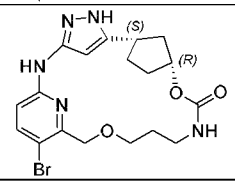
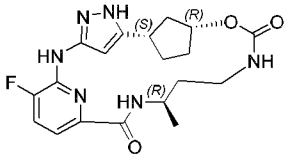
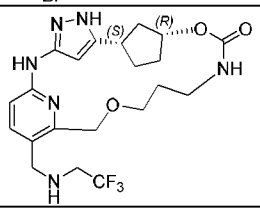
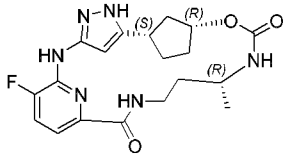
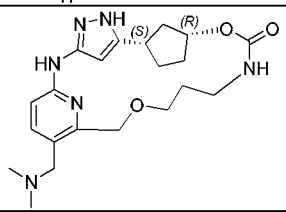
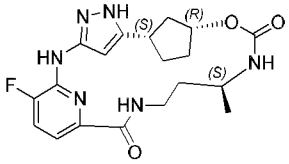
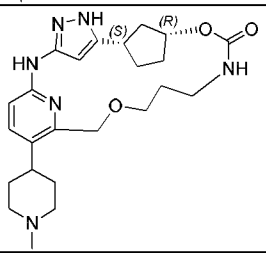
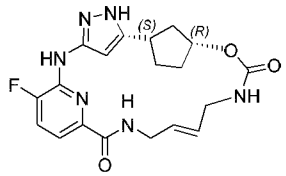
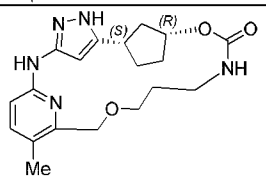
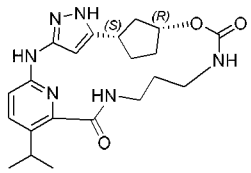
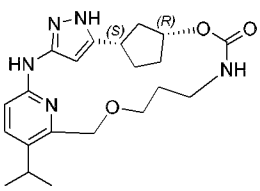
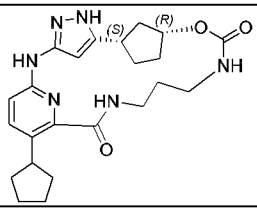
Compound **1**	 *rac, cis*	Compound **88**	
Compound **2**	 *rac, cis*	Compound **89**	
Compound **3**	 *rac, cis*	Compound **90**	
Compound **4**	 *rac, cis*	Compound **91**	
Compound **5**	 *rac, cis*	Compound **92**	
Compound **6**	 *rac, cis*	Compound **93**	
Compound **7**	 *rac, cis*	Compound **94**	
Compound **8**	 *rac, cis*	Compound **95**	
Compound **9**	 *rac, cis*	Compound **96**	

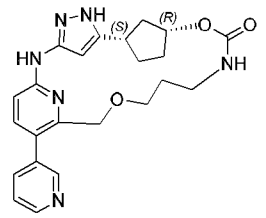
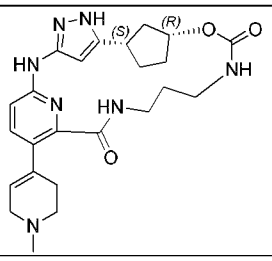
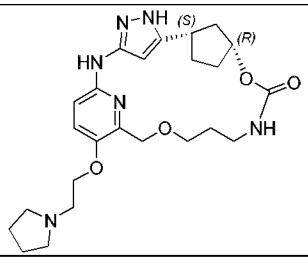
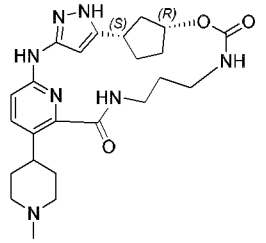
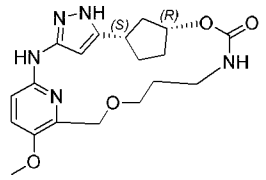
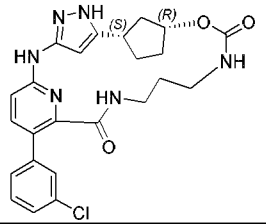
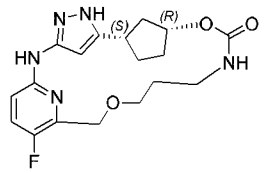
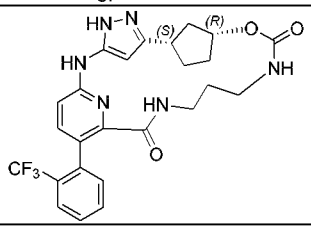
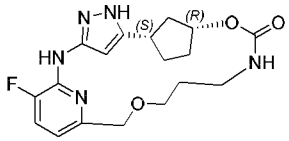
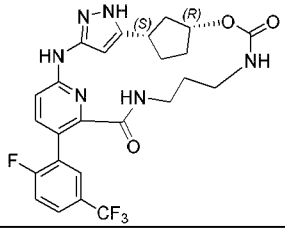
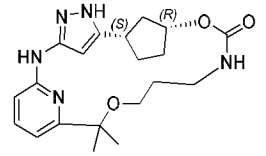
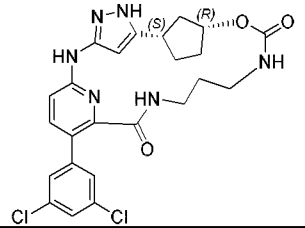
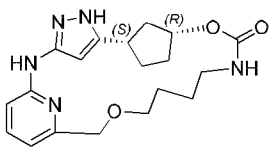
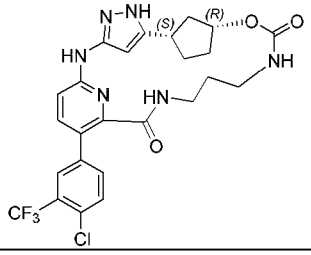
Compound **10**	 *rac, cis*	Compound **97**	
Compound **11**	 *rac, cis*	Compound **98**	
Compound **12**	 *rac, cis*	Compound **99**	
Compound **13**	 *rac, cis*	Compound **100**	
Compound **14**		Compound **101**	
Compound **15**		Compound **102**	
Compound **16**		Compound **103**	
Compound **17**		Compound **104**	
Compound **18**		Compound **105**	

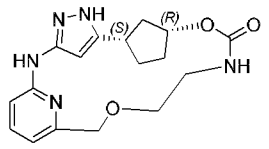
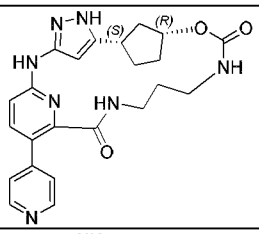
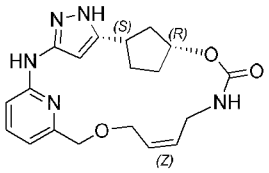
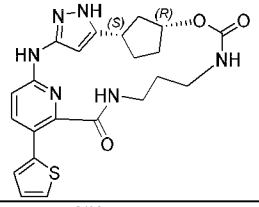
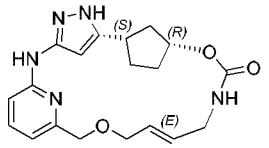
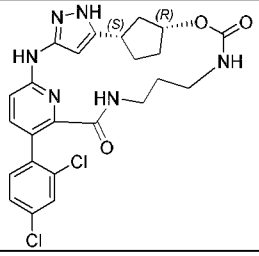
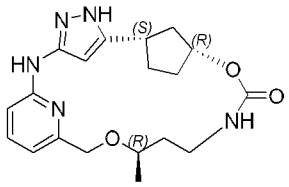
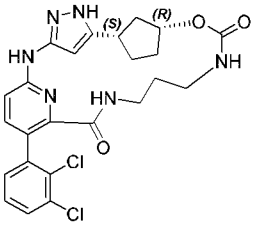
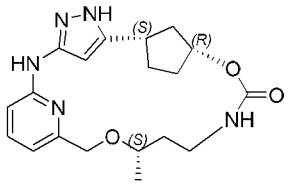
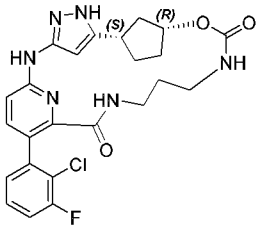
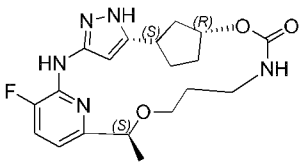
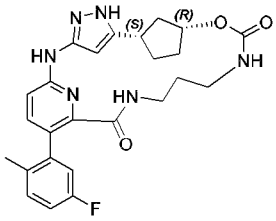
Compound **19**		Compound **106**	
Compound **20**		Compound **107**	
Compound **21**		Compound **108**	
Compound **22**		Compound **109**	
Compound **23**		Compound **110**	
Compound **24**		Compound **111**	
Compound **25**		Compound **112**	
Compound **26**		Compound **113**	
Compound **27**		Compound **114**	
Compound **28**		Compound **115**	

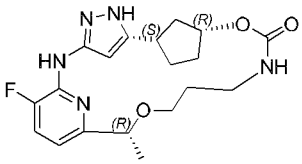
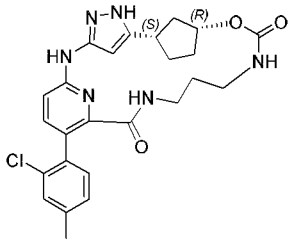
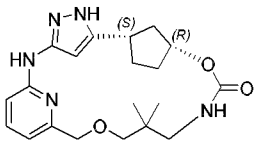
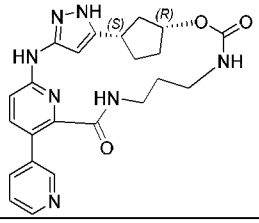
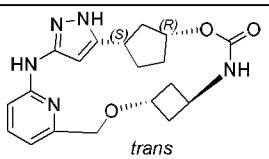
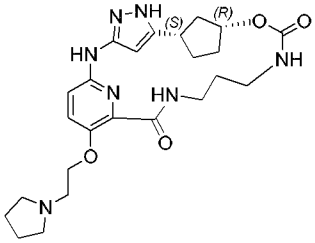
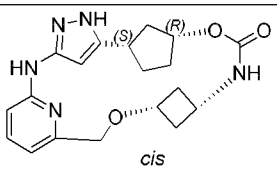
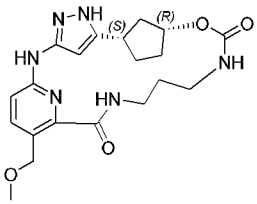
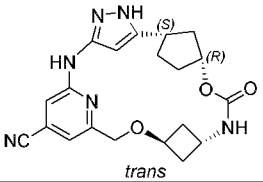
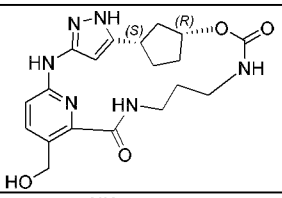
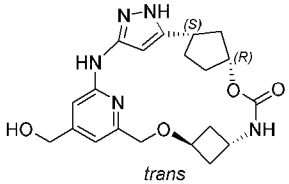
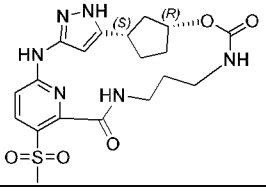
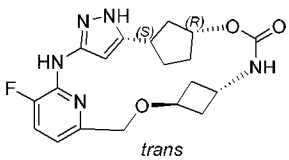
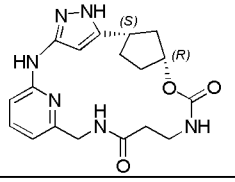
Compound **29**		Compound **116**	
Compound **30**		Compound **117**	
Compound **31**		Compound **118**	
Compound **32**		Compound **119**	
Compound **33**		Compound **120**	
Compound **34**		Compound **121**	
Compound **35**		Compound **122**	
Compound **36**		Compound **123**	
Compound **37**		Compound **124**	

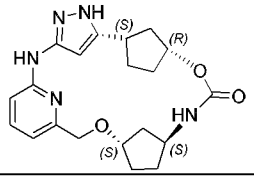
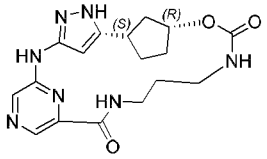
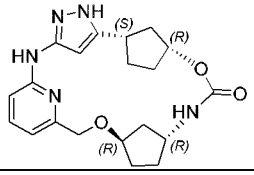
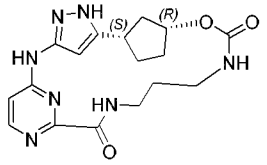
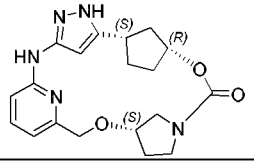
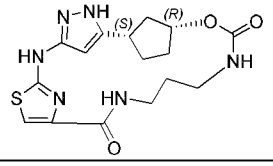
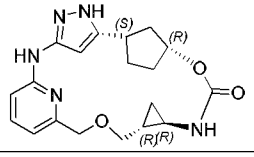
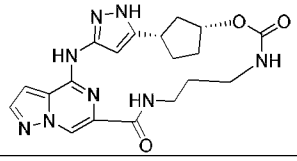
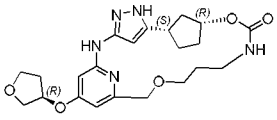
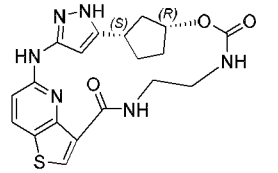
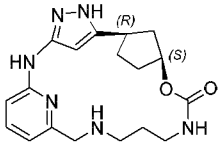
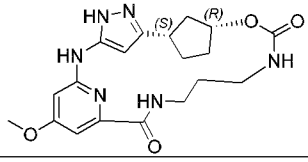
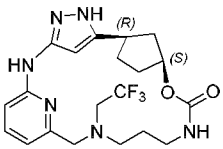
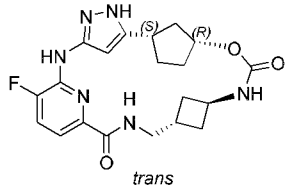
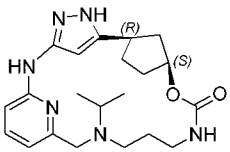
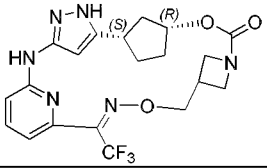
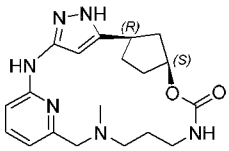
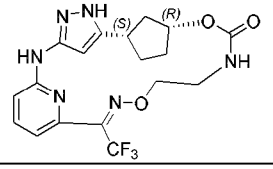
Compound **38**		Compound **125**	 separated by SFC absolute configuraton arbitrarily assigned retention time = 2.1 min
Compound **39**		Compound **126**	 separated by SFC absolute configuraton arbitrarily assigned retention time = 2.7 min
Compound **40**		Compound **127**	
Compound **41**		Compound **128**	
Compound **42**		Compound **129**	
Compound **43**		Compound **130**	 *rac, cis*
Compound **44**		Compound **131**	
Compound **45**		Compound **132**	

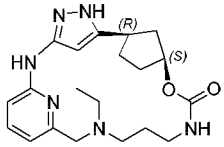
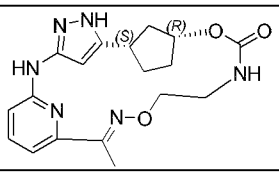
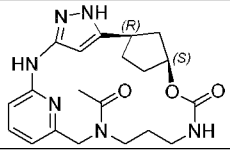
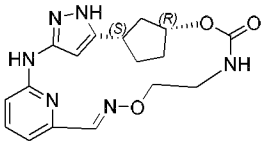
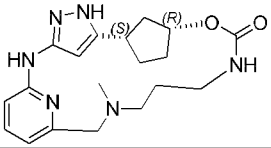
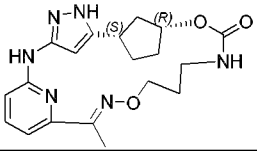
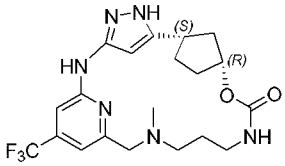
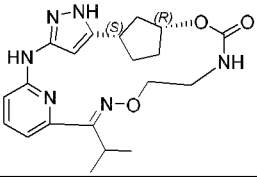
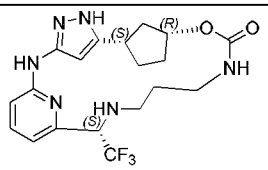
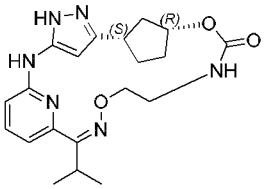
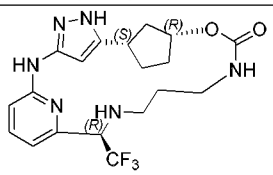
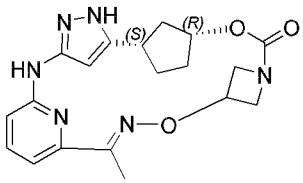
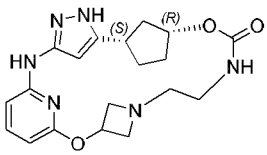
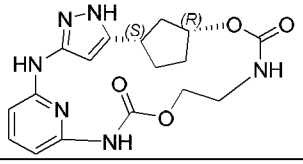
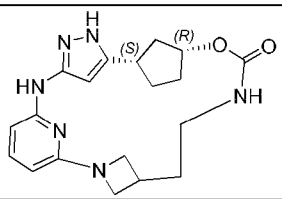
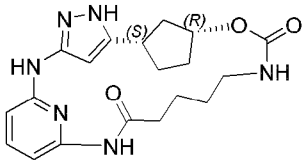
Compound **46**		Compound **133**	
Compound **47**		Compound **134**	
Compound **48**		Compound **135**	
Compound **49**		Compound **136**	
Compound **50**		Compound **137**	
Compound **51**		Compound **138**	
Compound **52**		Compound **139**	

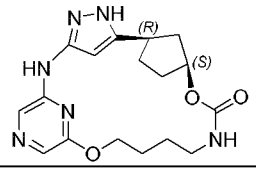
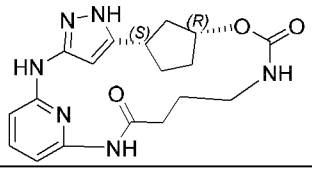
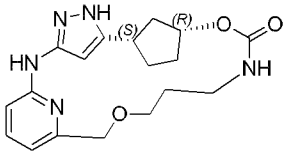
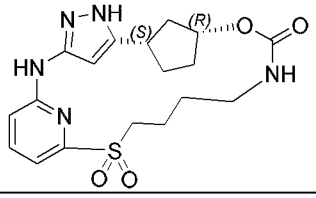
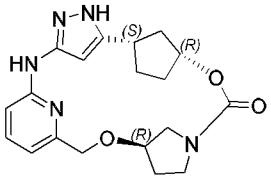
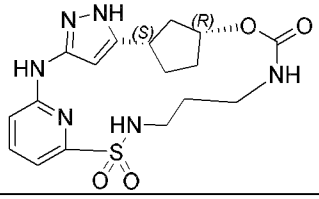
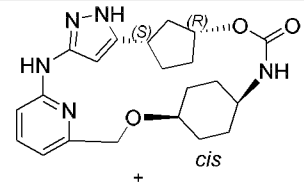
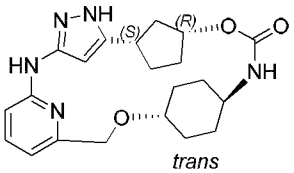
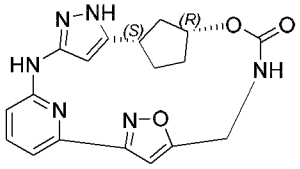
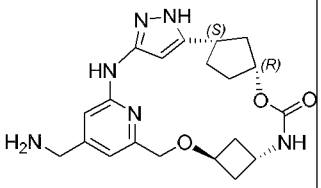
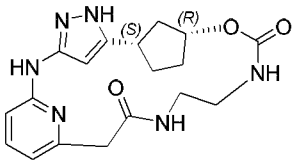
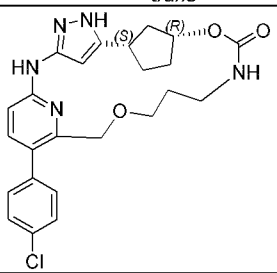
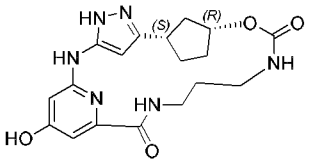
Compound **53**		Compound **140**	
Compound **54**		Compound **141**	
Compound **55**		Compound **142**	
Compound **56**		Compound **143**	
Compound **57**		Compound **144**	
Compound **58**		Compound **145**	
Compound **59**		Compound **146**	

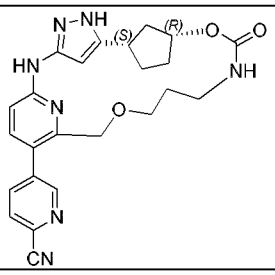
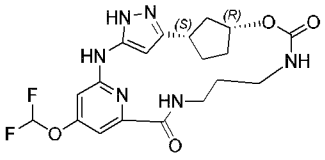
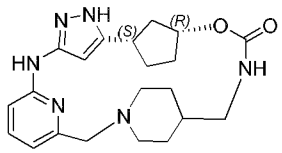
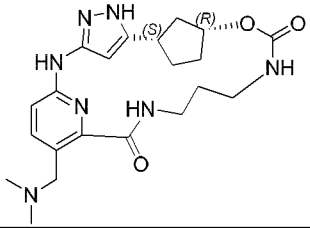
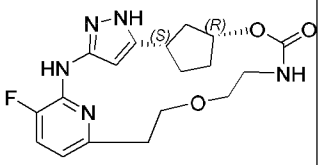
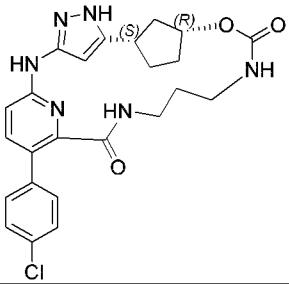
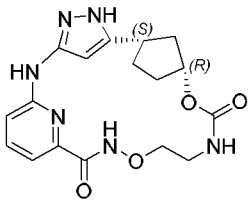
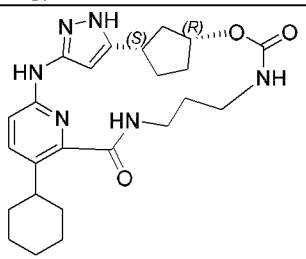
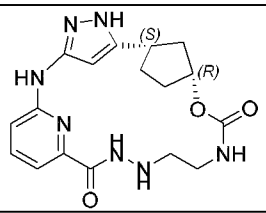
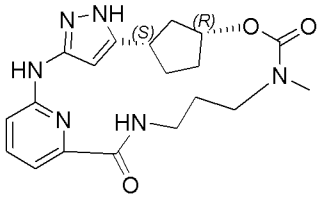
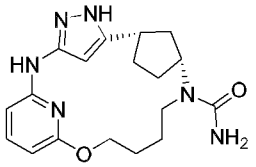
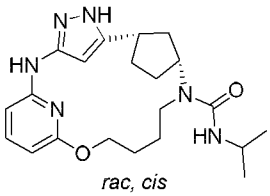
Compound **60**		Compound **147**	
Compound **61**		Compound **148**	
Compound **62**		Compound **149**	
Compound **63**	 separated by prep-HPLC retention time = 5.7 min absolute configuration arbitrarily assigned	Compound **150**	
Compound **64**	 separated by prep-HPLC retention time = 6.5 min absolute configuration arbitrarily assigned	Compound **151**	
Compound **65**	 separated by prep-HPLC retention time = 4.6 min absolute configuration arbitrarily assigned	Compound **152**	

Compound **66**	 separated by prep-HPLC retention time = 6.9 min absolute configuration arbitrarily assigned	Compound **153**	
Compound **67**		Compound **154**	
Compound **68**	 *trans* separated by SFC relative configuraton arbitrarily assigned retention time = 5.4 min	Compound **155**	
Compound **69**	 *cis* separated by SFC relative configuraton arbitrarily assigned retention time = 8.8 min	Compound **156**	
Compound **70**	 *trans*	Compound **157**	
Compound **71**	 *trans*	Compound **158**	
Compound **72**	 *trans*	Compound **159**	

Compound **73**		Compound **160**	
Compound **74**		Compound **161**	
Compound **75**		Compound **162**	
Compound **76**		Compound **163**	
Compound **77**		Compound **164**	
Compound **78**		Compound **165**	
Compound **79**		Compound **166**	 trans
Compound **80**		Compound **167**	
Compound **81**		Compound **168**	

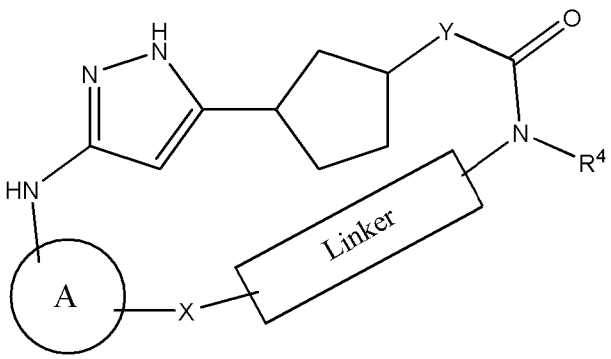
Compound **82**		Compound **169**	
Compound **83**		Compound **170**	
Compound **84**		Compound **171**	
Compound **85**		Compound **172**	
Compound **86**	 separated by prep-HPLC retention time = 8.5 min absolute configuration arbitrarily assigned	Compound **173**	
Compound **87**	 separated by prep-HPLC retention time = 10.9 min absolute configuration arbitrarily assigned	Compound **174**	
Compound **175**		Compound **189**	
Compound **176**		Compound **190**	

Compound **177**		Compound **191**	
Compound **178**		Compound **192**	
Compound **179**		Compound **193**	
Compound **180+181**	 *cis* +  *trans* unseparated mixture	Compound **194**	
Compound **182**	 *trans*	Compound **195**	
Compound **183**		Compound **196**	

Compound **184**		Compound **197**	
Compound **185**		Compound **198**	
Compound **186**		Compound **199**	
Compound **187**		Compound **200**	
Compound **188**		Compound **201**	
Compound 202	 *rac, cis*	Compound 203	 *rac, cis*

The present disclosure also provides other embodiments described in the text below.

(1). A compound of formula I:



(I),

a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein:

ring A is 6-10 membered aryl or 5-10 membered heteroaryl; wherein said 6-10 membered aryl or 5-10 membered heteroaryl represented by ring A is optionally substituted by one or more R^1; wherein

R^1 is halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alknyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-NR^{1a}R^{1b}$, $-NR^{1a}C(O)R^{1b}$, $-NR^{1a}C(O)OR^{1b}$, $-NR^{1a}SO_2R^{1b}$, $-NR^{1a}SO_2NR^{1b}R^{1c}$, $-SO_2R^{1a}$, $-SO_2NR^{1a}R^{1b}$, or $-P(O)R^{1a}R^{1b}$; wherein

R^{1a}, R^{1b}, and R^{1c} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and 4-6 membered heterocyclyl;

X is absent, -O-, $-NR^2$-, -C(O)-, $-NR^2C(O)$-, or $-C(O)NR^2$-; wherein

R^2, in each occurrence, is independently hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl;

Y is –O- or NR^{22}-; wherein

R^{22} is hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl;

Linker is represented by formula

*-W-L-Z-**;

wherein *- represents the point which attaches to the variable X; -** represents the point which attaches to the moiety $-NR^4$-;

W is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by W is optionally substituted by one or more R^3;

L is absent, -O-, -NH-, 3-12 membered carbocyclyl, 3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-12 membered carbocyclyl, 3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl represented by L is optionally substituted by one or more R^3; and

Z is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by Z is optionally substituted by one or more R^3; wherein

R^3, in each occurrence, is independently halogen, CN, C_{1-6}alkyl, $-OR^{3a}$, or $-NR^{3a}R^{3b}$; wherein

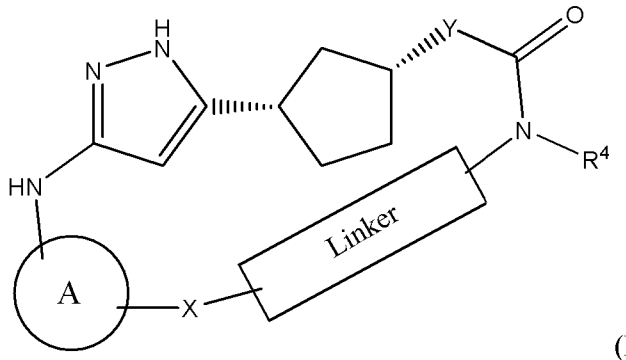
R^{3a} and R^{3b} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and 4-6 membered heterocyclyl;

R^4 is hydrogen or C_{1-6}alkyl; or one R^3 and R^4 together with the atoms to which they are attached form 4-8 membered heterocyclyl;

wherein W, L, and Z are not absent simultaneously; and

wherein said heterocyclyl comprises 1-3 heteroatoms selected from oxygen, nitrogen, and sulfur; and said heteroaryl comprises 1-4 heteroatoms selected from oxygen, nitrogen, and sulfur.

(2). The compound of embodiment (1) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is represented by Formula II:



(II).

(3). The compound of embodiment (1) or (2) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is phenyl or nitrogen containing 5-10 membered heteroaryl; wherein said phenyl or nitrogen containing 5-10 membered heteroaryl represented by ring A is optionally substituted by one to three R^1; wherein

R^1 is halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-NR^{1a}R^{1b}$, $-NR^{1a}C(O)R^{1b}$,

$-NR^{1a}C(O)OR^{1b}$, $-NR^{1a}SO_2R^{1b}$, $-NR^{1a}SO_2NR^{1b}R^{1c}$, $-SO_2R^{1a}$, $-SO_2NR^{1a}R^{1b}$, or $-P(O)R^{1a}R^{1b}$; wherein

R^{1a}, R^{1b}, and R^{1c} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, 4-6 membered cycloalkyl, and 4-6 membered heterocyclyl.

(4). The compound of any one of claims 1-3, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

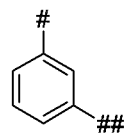
ring A is phenyl or nitrogen containing 5-6 membered heteroaryl; wherein said phenyl or nitrogen containing 5-6 membered heteroaryl represented by ring A is optionally substituted by one to two R^1;

R^1 is halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, $-OR^{1a}$, or $-NR^{1a}R^{1b}$; wherein

R^{1a} or R^{1b} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl.

(5). The compound of any one of embodiments (1) to (4) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from a group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, and imidazo[4,5-c]pyridinyl; wherein said phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, or imidazo[4,5-c]pyridinyl is optionally substituted by one to two R^1; wherein R^1 is halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, or $-OC_{1-4}$alkyl.

(6). The compound of any one of embodiments (1), (2), or (5) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from a group consisting of



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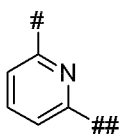

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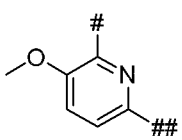

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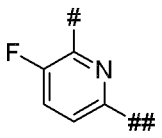

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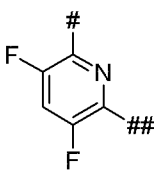

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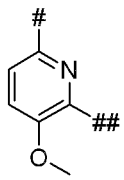

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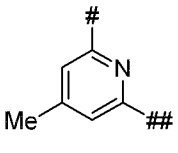

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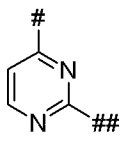

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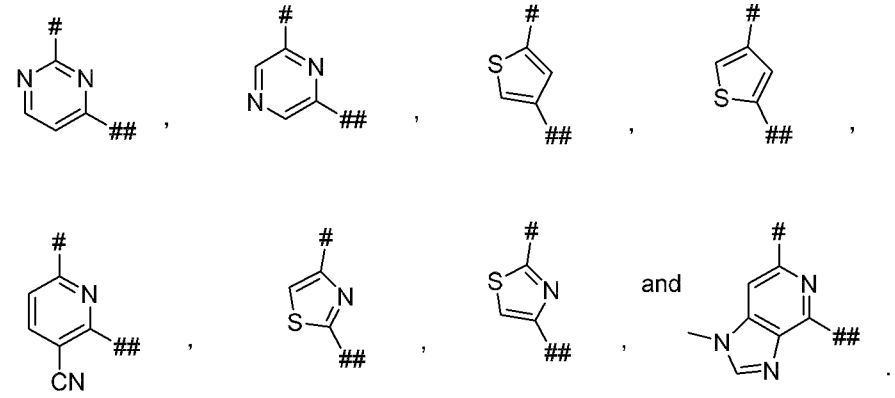
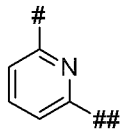


wherein # represents the point which attaches to the moiety –NH-; ## represents the point which attaches to variable X.

(7). The compound of any one of embodiments (1)-(5) above, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, wherein ring A is  optionally substituted by one to two R^1, wherein R^1 is F or $-OCH_3$; wherein # represents the point which attaches to the moiety –NH-; ## represents the point which attaches to variable X.

(8). The compound of any one of embodiments (1)-(7) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

X is absent, -O-, $-NR^2-$, -C(O)-, -NHC(O)-, or -C(O)NH-; wherein R^2 in each occurrence, is independently hydrogen, C_{1-4}alkyl, or C_{1-4}haloalkyl; and

Y is -O- or NR^{22}-; wherein R^{22} is hydrogen, C_{1-4}alkyl, or C_{1-4}haloalkyl.

(9). The compound of any one of embodiments (1)-(8) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein X is -O- or -NH- and Y is -O- or -NH-.

(10). The compound of any one of embodiments (1)-(9) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein X is -O- and Y is O.

(11). The compound of any one of embodiments (1)-(10) above, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein

W is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by W is optionally substituted by one to three R^3;

L is absent, -O-, -NH-, 3-8 membered carbocyclyl, 3-8 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-8 membered carbocyclyl, 3-6 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl represented by L is optionally substituted by one to three R^3; and

Z is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by Z is optionally substituted by one to three R^3; wherein R^3, in each occurrence, is independently halogen or C_{1-4}alkyl; and

R^4 is hydrogen, C_{1-4}alkyl, or C_{1-4}haloalkyl; or one R^3 and R^4 together with the atoms to which they are attached form 5-6 membered heterocyclyl.

(12). The compound of any one of embodiments (1)-(11) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by W is optionally substituted by one to two R^3;

L is absent, -O-, -NH-, 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic heteroaryl; wherein said 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic heteroaryl represented by L is optionally substituted by one R^3; and

Z is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by Z is optionally substituted by one R^3; wherein

R^3, in each occurrence, is independently halogen or C_{1-3}alkyl; and

R^4 is hydrogen, methyl, or $-CF_3$; or one R^3 and R^4 together with the atoms to which they are attached form 6 membered heterocyclyl.

(13). The compound of any one of embodiments (1)-(12) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene;

L is absent or -O-; and

Z is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene.

(14). The compound of any one of embodiments (1)-(12) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{3-4}alkylene, C_{3-4}haloalkylene, C_{3-4}alkenylene, or C_{3-4}alkynylene;

L is absent; and

Z is absent.

(15). The compound of any one of embodiments (1)-(12) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-2}alkylene, or C_{1-2}haloalkylene;

L is 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, or 5-6 membered heteroaryl; and

Z is absent or methylene.

(16). The compound of any one of embodiments (1)-(12) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH_2CH=CH-$, or $-CH_2C\equiv C-$;

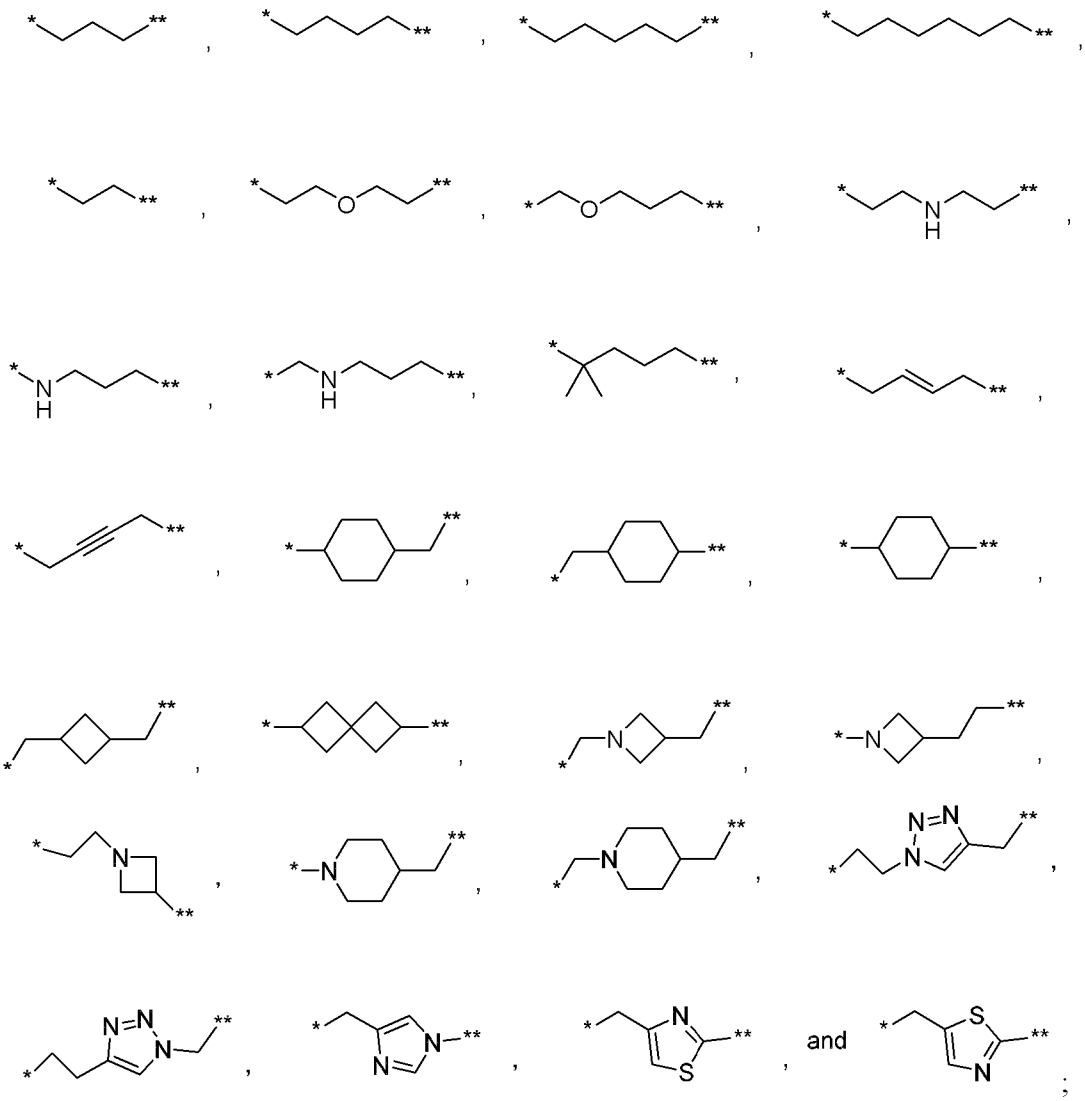
L is absent, -O-, -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, imidazolyl, triazolyl, or thiozolyl; wherein said -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, imidazolyl, triazolyl, or thiozolyl is optionally substituted by one R^3;

Z is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH=CHCH_2-$, or $-C\equiv CCH-$;

R^4 is hydrogen; or one R^3 and R^4 together with the atoms to which they are attached form a piperazinyl ring.

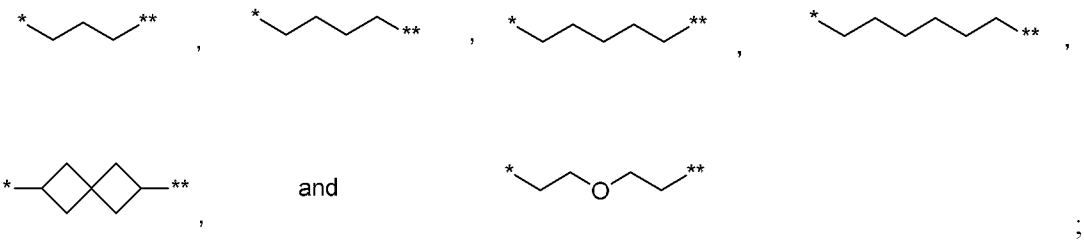
(17). The compound of any one of embodiments (1)-(16) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R^4 is hydrogen.

(18). The compound of any one of embodiments (1)-(12), (16), and (17) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker is selected from the group consisting of



wherein *- represents the point which attaches to variable X; -** represents the point which attaches to the moiety -NR^4-.

(19). The compound of embodiment (18) above, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker is selected from the group consisting of



wherein *- represents the point which attaches to variable X; -** represents the point which attaches to the moiety -NR^4-.

2. *Definitions*

The term "halogen," as used herein, refers to fluoride, chloride, bromide, or iodide.

The term "alkyl" used alone or as part of a larger moiety, such as "alkoxy" or "haloalkyl" and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical of formula -$C_nH_{(2n+1)}$. Unless otherwise specified, an alkyl group typically has 1-6 carbon atoms, *i.e.* C_{1-6}alkyl. As used herein, a "C_{1-6}alkyl" group means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, n-butyl, iso-butyl, *tert*- butyl, n-pentyl, isopentyl, hexyl, and the like.

The terms "haloalkyl" means alkyl, as the case may be, substituted with one or more halogen atoms. In one embodiment, the alkyl can be substituted by one to three halogens. Examples of haloalkyl, include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl and the like.

The term "alkylene" as used herein, means a straight or branched chain divalent hydrocarbon group of formula -C_nH_{2n}-. Non-limiting examples include ethylene, and propylene.

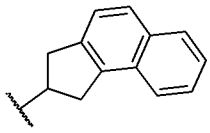
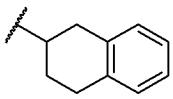
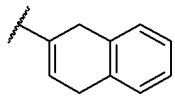
The terms "haloalkylene" means alkylene, as the case may be, substituted with one or more halogen atoms. In one embodiment, the alkylene can be substituted by one to three halogens.

The term "alkenyl" means an alkyl group in which one or more carbon/carbon single bond is replaced by a double bond.

The term "alkynyl" means an alkyl group in which one or more carbon/carbon single bond is replaced by a triple bond.

The term "carbocyclyl" refers to a 3-14 membered non-aromatic hydrocarbon ring system and may exist as a monocylic ring or a polycylic ring (*e.g.*, a bicyclic ring (including fused, spiro or bridged carbocyclic rings) or a tricyclic ring). In one embodiment, carbocyclyl is 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated. Any substitutable ring atom can be substituted (*e.g.*, by one or more substituents). Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl.

In one embodiment, carbocyclyl is intended to include, bridged, fused, and spirocyclic rings. In a spirocyclic carbocyclyl, one atom is common to two different rings. An example of a spirocyclic carbocyclyl is spiro[3.3]heptanyl. In a bridged carbocyclyl, the rings share at least two common non-adjacent atoms. Examples of bridged carbocyclyls include bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]hept-2-enyl, and adamantanyl. In a fused-ring carbocyclyl system, two or more rings may be fused together, such that two rings share one common bond. Examples of two- or three-fused ring carbocyclyls include naphthalenyl, tetrahydronaphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenanthrenyl, and decalinyl. The term "carbocyclyl" as used herein, includes groups in which a carbocyclyl ring is fused to one or more aryl, where the radical or point of attachment is on the carbocyclyl ring. Nonlimiting examples of such fused ring systems include:


, 
, and 
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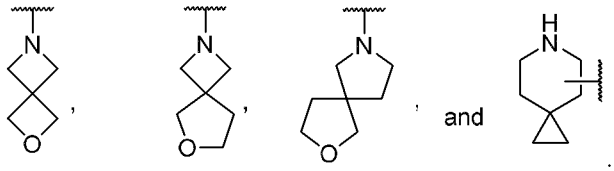
The term "cycloalkyl" refers to a cyclic, bicyclic, tricyclic, or polycyclic saturated hydrocarbon groups having 3 to 12 ring carbons. In one embodiment, cycloalkyl may have 3 to 7 ring cabons. Any substitutable ring atom can be substituted (*e.g.*, by one or more substituents). Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl include: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.0]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (*e.g.*, spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like.

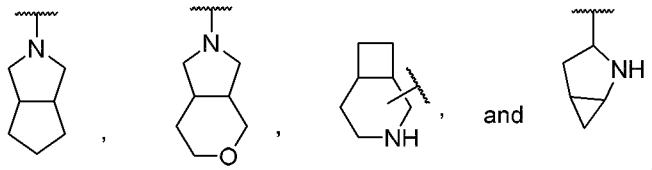
The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone ("3-12 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 3-7 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-7 membered heterocyclyl"). In some embodiments, a heterocyclyl group comprises 1-3 heteroatoms selected from oxygen, nitrogen, and sulfur. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a

bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl"); polycyclic ring systems include fused, bridged, or spiro ring systems). Exemplary monocyclic heterocyclyl groups include azetidinyl, oxetanyl, thietanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, piperazinyl, morpholinyl, azepanyl, oxepanyl, thiepanyl, tetrahydropyridinyl, and the like. Heterocyclyl polycyclic ring systems can include heteroatoms in one or more rings in the polycyclic ring system. Substituents may be present on one or more rings in the polycyclic ring system.

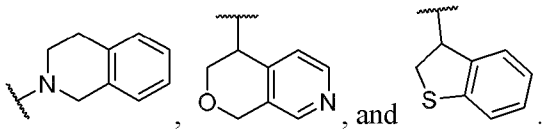
Spiro heterocyclyl refers to 5 to 12 membered polycyclic heterocyclyl with rings connected through one common carbon atom (called as spiro atom), wherein said rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone, the remaining ring atoms being C, wherein one or more rings may contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Representive examples of spiro heterocyclyl include, but are not limited to the following groups:



Fused heterocyclyl refers to a 5 to 12 membered polycyclic heterocyclyl group, wherein each ring in the group shares an adjacent pair of carbon atoms with another ring in the group, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated π-electron system, and wherein said rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone, the remaining ring atoms being C. Representive examples of fused heterocyclyl include, but are not limited to the following groups:

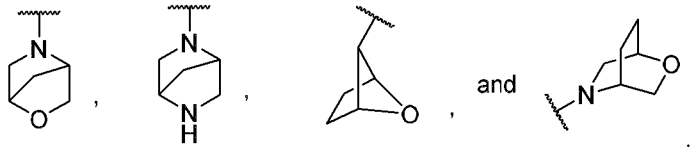


In some embodiments, a fused heterocyclyl include groups in which a heterocyclyl ring is fused to one or more aryl or heteroaryl, where the radical or point of attachment is on the heterocyclyl ring. Nonlimiting examples of such fused heterocyclyl ring systems include:



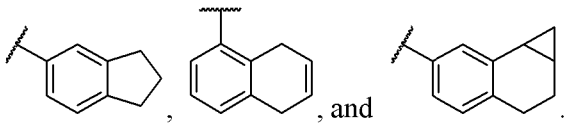
Bridged heterocyclyl refers to a 5 to 12 membered polycyclic heterocyclyl group, wherein any two rings in the group share two disconnected atoms, the rings can have one or more double

bonds but have no completely conjugated π-electron system, and the rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone as ring atoms, the remaining ring atoms being C. Representive examples of bridged heterocyclyl include, but are not limited to the following groups:



Generally, the carbocyclyl, the cycloalkyl, or the heterocyclyl may be unsubstituted, or be substituted with one or more substituents as valency allows, wherein the substituents can be independently selected from a number of groups such as oxo, -CN, halogen, alkyl and alkoxyl, opotionally, the alkyl substitution may be further substituted.

The term "aryl" refers to a 6 to 12 membered all-carbon monocyclic ring or a polycyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with other ring in the system) group, and has a completely conjugated π-electron system. The term "aryl" may be used interchangeably with the terms "aryl ring" "carbocyclic aromatic ring", "aryl group" and "carbocyclic aromatic group". Representive examples of aryl are phenyl and naphthyl. In some embodiments, two adjacent substituents on an aryl ring, taken together with the intervening ring atoms, form an optionally substituted fused 5- to 6-membered aromatic or 4- to 8-membered non-aromatic carbocyclyl ring. Thus, the term "aryl", as used herein, includes groups in which an aromatic ring is fused to one or more non-aromatic carbocyclyl ring, where the radical or point of attachment is on the aromatic ring. Nonlimiting examples of such fused ring systems include:



The term "heteroaryl," as used herein, refers to a monocyclic or multicyclic aromatic hydrocarbon in which at least one of the ring carbon atoms has been replaced with a heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl is based on a C_{5-10} aryl with one or more of its ring carbon atoms replaced by the heteroatom. In some embodiments, heteroaryl comprises 1-4 heteroatoms selected from oxygen, nitrogen, and sulfur. A heteroaryl group may be attached through a ring carbon atom or, where valency permits, through a ring nitrogen atom. Generally, the heteroaryl may be unsubstituted, or be substituted with one or more substituents as valency allows with the substituents being independently selected from halogen, OH, alkyl, alkoxyl, and amino (*e.g.*, NH_2, NHalkyl, $N(alkyl)_2$), optionally, the alkyl may be further substituted.

Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (*e.g.*, 2-furanyl, 3-furanyl), imidazolyl (*e.g.*, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (*e.g.*,

3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (*e.g.*, 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (*e.g.*, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (*e.g.*, 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (*e.g.*, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (*e.g.*, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (*e.g.*, 3-pyridazinyl), thiazolyl (*e.g.*, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (*e.g.*, 2-triazolyl, 5-triazolyl), tetrazolyl (*e.g.*, tetrazolyl), thienyl (*e.g.*, 2-thienyl, 3-thienyl), pyrimidinyl, pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzisoxazolyl. A "substituted heteroaryl group" is substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

As used herein, many moieties (*e.g.*, alkyl, alkylene, cycloalkyl, aryl, heteroaryl, or heterocyclyl) are referred to as being either "substituted" or "optionally substituted". When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted, which includes one or more substituents. Where if more than one substituent is present, then each substituent may be independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. The optional substituents can be any substituents that are suitable to attach to the moiety.

Where suitable substituents are not specifically enumerated, exemplary substituents include, but are not limited to: C_{1-5}alkyl, C_{1-5}hydroxyalkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy, C_{1-5} haloalkoxy, halogen, hydroxyl, cyano, amino, -CN, $-NO_2$, $-OR^{c1}$, $-NR^{a1}R^{b1}$, $-S(O)_iR^{a1}$, $-NR^{a1}S(O)_iR^{b1}$, $-S(O)_iNR^{a1}R^{b1}$, $-C(=O)OR^{a1}$, $-OC(=O)OR^{a1}$, $-C(=S)OR^{a1}$, $-O(C=S)R^{a1}$, $-C(=O)NR^{a1}R^{b1}$, | $-NR^{a1}C(=O)R^{b1}$, $-C(=S)NR^{a1}R^{b1}$, $-C(=O)R^{a1}$, $-C(=S)R^{a1}$, $NR^{a1}C(=S)R^{b1}$, $-O(C=O)NR^{a1}R^{b1}$, $-NR^{a1}(C=S)OR^{b1}$, $-O(C=S)NR^{a1}R^{b1}$, $-NR^{a1}(C=O)NR^{a1}R^{b1}$, $-NR^{a1}(C=S)NR^{a1}R^{b1}$, phenyl, or 5-6 membered heteroaryl. Each R^{a1} and each R^{b1} are independently selected from –H and C_{1-5}alkyl, optionally substituted with hydroxyl or C_{1-3}alkoxy; R^{c1} is –H, C_{1-5}haloalkyl or C_{1-5}alkyl, wherein the C_{1-5}alkyl is optionally substituted with hydroxyl or C_1-C_3alkoxy.

The symbol "  ," as used herein, refers to the point where the moiety attaches.

Pharmaceutically Acceptable Salts

The term "pharmaceutically-acceptable salt" refers to a pharmaceutical salt that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, and is commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are well known in the art. For example, S. M. Berge *et al.* describes pharmacologically acceptable salts in J. Pharm. Sci., 1977, 66, 1–19.

Pharmaceutically acceptable salts of the compounds of any one of the formulae described

above include acid addition and base salts.

Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. Compounds having basic groups can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as acetic, benzenesulfonic, benzoic, ethanesulfonic, methanesulfonic, and succinic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Pharmaceutically acceptable salts of compounds of any one of the formulae described above may be prepared by one or more of three methods:

(i) by reacting the compound of any one of the formulae described above with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of any one of the formulae described above or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of any one of the formulae described above to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of any one of the formulae described above, and pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms.

Stereoisomers and Other Variations

The compounds of any one of the formulae described above may exhibit one or more kinds of isomerism (*e.g.* optical, geometric or tautomeric isomerism). Such variation is implicit to the compounds of any one of the formulae described above defined as they are by reference to their structural features and therefore within the scope of the present disclosure.

Compounds having one or more chiral centers can exist in various stereoisomeric forms, *i.e.*, each chiral center can have an *R* or *S* configuration, or can be a mixture of both. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric and enantiomeric forms of a compound. Enantiomers are stereoisomers that are mirror images of each other. Diastereomers are stereoisomers having two or more chiral centers that are not identifcal and are not mirror images of each other.

When a compound is designated by its chemical name (*e.g.*, where the configuration is indicated in the chemical name by "*R*" or "*S*") or its structure (*e.g.*, the configuration is indicated by "wedge" bonds) that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as "enantiomerically pure"). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (*e.g.*, as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers is included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

When two stereoisomers are depicted by their chemical names or structures, and the chemical names or structures are connected by an "and", a mixture of the two stereoisomers is intended.

When two stereoisomers are depicted by their chemical names or structures, and the names or structures are connected by an "or", one or the other of the two stereoisomers is intended, but not both.

When a disclosed compound having a chiral center is depicted by a structure without showing a configuration at that chiral center, the structure is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center, or the compound with a mixture of the *R* and *S* configuration at that chiral center. When a disclosed compound having a chiral center is depicted by its chemical name without indicating a configuration at that chiral center with "*S*" or "*R*", the name is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center or the compound with a mixture of the *R* and *S* configuration at that chiral center.

Racemic mixture means 50% of one enantiomer and 50% of the corresponding enantiomer. When a compound with one chiral center is named or depicted without indicating the stereochemistry of the chiral center, it is understood that the name or structure encompasses both possible enantiomeric forms (*e.g.*, both enantiomerically-pure, enantiomerically-enriched or racemic) of the compound. When a compound with two or more chiral centers is named or depicted without indicating the stereochemistry of the chiral centers, it is understood that the name or structure encompasses all possible diasteriomeric forms (*e.g.*, diastereomerically pure, diastereomerically enriched and equimolar mixtures of one or more diastereomers (*e.g.*, racemic mixtures) of the compound.

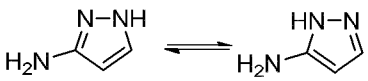
The term "geometric isomer" means isomers that differ in the orientation of substituent atoms

in relationship to a carbon-carbon double bond, to a carbocyclic ring, or to a bridged bicyclic system. Substituent atoms (other than hydrogen) on each side of a carbon-carbon double bond may be in an E or Z configuration according to the Cahn-Ingold-Prelog priority rules. In the "E" configuration, the substituents having the highest priorities are on opposite sides in relationship to the carbon-carbon double bond. In the "Z" configuration, the substituents having the highest priorities are oriented on the same side in relationship to the carbon-carbon double bond.

Substituents around a carbon-carbon double bond can also be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring, and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ("tautomerism") can occur. This can take the form of proton tautomerism in compounds of any one of the formulae described above containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

In certain instances tautomeric forms of the disclosed compounds exist, such as the tautomeric structures shown below:



When a geometric isomer is depicted by name or structure, it is to be understood that the named or depicted isomer exists to a greater degree than another isomer, that is that the geometric isomeric purity of the named or depicted geometric isomer is greater than 50%, such as at least 60%, 70%, 80%, 90%, 99%, or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of all of the geomeric isomers in the mixture.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers/ diastereomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of any one of the formulae described above contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by

chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Chiral compounds of any one of the formulae described above (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present disclosure are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series (1998), 75 (Supercritical Fluid Chromatography with Packed Columns), pp. 223-249 and references cited therein). Columns can be obtained from Chiral Technologies, Inc, West Chester, Pa., USA, a subsidiary of Daicel® Chemical Industries, Ltd., Tokyo, Japan.

It must be emphasized that the compounds of any one of the formulae described above have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the present disclosure.

3. Administration and Dosing

Typically, a compound of the present disclosure is administered in an amount effective to treat a condition as described herein. The compounds of the present disclosure can be administered as compound *per se*, or alternatively, as a pharmaceutically acceptable salt. For administration and dosing purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the present disclosure.

The compounds of the present disclosure are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the present disclosure may be administered orally, rectally, vaginally, parenterally, or topically.

The compounds of the present disclosure may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

In another embodiment, the compounds of the present disclosure may also be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

In another embodiment, the compounds of the present disclosure may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the present disclosure can also be administered intranasally or by inhalation. In another embodiment, the compounds of the present disclosure may be administered rectally or vaginally. In another embodiment, the compounds of the present disclosure may also be administered directly to the eye or ear.

The dosage regimen for the compounds of the present disclosure and/or compositions containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. In one embodiment, the total daily dose of a compound of the present disclosure is typically from about 0.001 to about 100 mg/kg (*i.e.*, mg compound of the present disclosure per kg body weight) for the treatment of the indicated conditions discussed herein.

For oral administration, the compositions may be provided in the form of tablets containing 0.1- 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient. Intravenously, doses may range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

Suitable subjects according to the present disclosure include mammalian subjects, including non-human mammal such as primates, rodents (mice, rats, hamsters, rabbits *etc*). In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

4. Pharmaceutical Compositions

In another embodiment, the present disclosure comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the present disclosure presented, a pharmaceutically acceptable salt, or a stereoisomer thereof with a pharmaceutically acceptable carrier or excipient. Other pharmacologically active substances can also be present.

As used herein, "pharmaceutically acceptable carrier or excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition. Pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

The compositions of present disclosure may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with antibodies in general. One mode of administration is parenteral (*e.g.* intravenous, subcutaneous, intraperitoneal, intramuscular). In another embodiment, the antibody is administered by intravenous infusion or injection. In yet another embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present disclosure. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of any one of the formulae described above are ordinarily combined with one or more adjuvants. Such capsules or tablets may contain a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

In another embodiment, the present disclosure comprises a parenteral dose form.

"Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*i.e.*, sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents.

In another embodiment, the present disclosure comprises a topical dose form.

"Topical administration" includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of present disclosure are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres,

bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, Finnin and Morgan, *J. Pharm. Sci.*, 88:955-958, 1999.

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of present disclosure is dissolved or suspended in a suitable carrier. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*i.e.*, absorbable gel sponges, collagen) and non-biodegradable (*i.e.*, silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methylcellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration or administration by inhalation, the compounds of the present disclosure are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present disclosure comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the present disclosure may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures.

The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., 1975; Liberman *et al.*, Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and Kibbe *et al.*, Eds., *Handbook of Pharmaceutical Excipients* (3rd Ed.), American

Pharmaceutical Association, Washington, 1999.

5. Method of Treatment

Compounds of the present disclosure can inhibit CDK2 and therefore are useful for treating diseases wherein the underlying pathology is, wholly or partially, mediated by CDK2. Such diseases include cancer and other diseases with proliferation disorder.

In some embodiments, the present disclosure provides treatment of an individual or a patient *in vivo* using a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, or a stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I') or (I) or of any of the formulae as described herein, or a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof, can be used to inhibit the growth of cancerous tumors with aberrations that activate the CDK2 kinase activity. These include, but not limited to, diseases (*e.g.*, cancers) that are characterized by amplification or overexpression of CCNE1 such as ovarian cancer, uterine carcinosarcoma and breast cancer and p27 inactivation such as breast cancer and melanomas. Accordingly, in some embodiments of the methods, the patient has been previously determined to have an amplification of the cyclin E1 (CCNE1) gene and/or an expression level of CCNE1 in a biological sample obtained from the human subject that is higher than a control expression level of CCNE1. Alternatively, a compound of Formula (I') or (I) or of any of the formulae as described herein, or a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof, can be used in conjunction with other agents or standard cancer treatments, as described below. In one embodiment, the present disclosure provides a method for inhibiting growth of tumor cells *in vitro*. The method includes contacting the tumor cells *in vitro* with a compound of Formula (I') or (I) or of any of the formulae as described herein, or of a compound as recited in any of the claims and described herein, or of a pharmaceutically acceptable salt or a stereoisomer thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor cells with CCNE1 amplification and overexpression in an individual or a patient. The method includes administering to the individual or patient in need thereof a therapeutically effective amount of a compound of Formula (I') or (I) or of any of the formulae as described herein, or of a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

In certain embodiments, compounds of the present disclosure selectively inhibit CDK2 over CDK1, with a ratio of IC_{50} values for the latter (CDK1) against the former (CDK2) of at least about 2, 5, 10, 15, 20, 40, 50, 60, 80, 100 or more.

In some embodiments, provided herein is a method of inhibiting CDK2, comprising contacting the CDK2 with a compound of Formula (I') or (I) or any of the formulae as described

herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt, or a stereoisomer thereof. In some embodiments, provided herein is a method of inhibiting CDK2 in a patient, comprising administering to the patient a compound of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, provided herein is a method for treating cancer. The method includes administering to a patient (in need thereof), a therapeutically effective amount of a compound of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof. In another embodiment, the cancer is characterized by amplification or overexpression of CCNE1. In some embodiments, the cancer is characterized by inactivation of a CDK2 inhibitor, such as p21Cip1 or p27Kip1. In some embodiments, the cancer is ovarian cancer or breast cancer, characterized by amplification or overexpression of CCNE1.

In certain embodiments, the patient has been diagnosed with a cancer characterized by amplification or overexpression of CCNE1, and/or loss of function of p21Cip1 or p27Kip1.

In certain embodiments, the method further comprises determining the status of expression of CCNE1, p21Cip1 and/or p27Kip1.

In certain embodiments, the method further comprises selecting patients characterized by amplification or overexpression of CCNE1, and/or loss of function of p21Cip1 or p27Kip1 for treatment.

In some embodiments, provided herein is a method of treating a disease or disorder associated with CDK2 in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the disease or disorder associated with CDK2 is associated with an amplification of the cyclin E1 (CCNE1) gene and/or overexpression of CCNE1.

In some embodiments, the disease or disorder associated with CDK2 is N-myc amplified neuroblastoma cells (See Molenaar *et al.*, Proc Natl Acad Sci USA, 106(31):12968-12973), K-Ras mutant lung cancers (see Hu, S., *et al.*, Mol Cancer Ther, 2015, 14(11):2576-85, and cancers with FBW7 mutation and CCNE1 overexpression (see Takada, *et al.*, Cancer Res, 2017, 77(18):4881-4893).

In some embodiments, the disease or disorder associated with CDK2 is breast, lung, colorectal, gastric, or bone cancer, leukemia or lymphoma.

In some embodiments, the disease or disorder associated with CDK2 is lung squamous cell

carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, breast invasive carcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, bladder urothelial carcinoma, mesothelioma, or sarcoma.

In some embodiments, the disease or disorder associated with CDK2 is lung adenocarcinoma, breast invasive carcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma, or stomach adenocarcinoma.

In some embodiments, the disease or disorder associated with CDK2 is an adenocarcinoma, carcinoma, or cystadenocarcinoma.

In some embodiments, the disease or disorder associated with CDK2 is uterine cancer, ovarian cancer, stomach cancer, esophageal cancer, lung cancer, bladder cancer, pancreatic cancer, or breast cancer.

In some embodiments, the disease or disorder associated with CDK2 is a cancer.

In some embodiments, the cancer is characterized by amplification or overexpression of CCNE1.

In some embodiments, the cancer is ovarian cancer or breast cancer, characterized by amplification or overexpression of CCNE1.

In some embodiments, the breast cancer is chemotherapy or radiotherapy resistant breast cancer, endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/6 inhibition.

In some embodiments, the breast cancer is advanced or metastatic breast cancer. Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of

metastatic cancers.

In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (*e.g.*, metastatic malignant melanoma, BRAF and HSP90 inhibition- resistant melanoma), renal cancer (*e.g.*, clear cell carcinoma), prostate cancer (*e.g.*, hormone refractory prostate adenocarcinoma), breast cancer, colon cancer, lung cancer (*e.g.*, non-small cell lung cancer and small cell lung cancer), squamous cell head and neck cancer, urothelial cancer (*e.g.*, bladder) and cancers with high microsatellite instability (MSI^{high}). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (*e.g.*, prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, cholangiocarcinoma, bile duct cancer, triple negative breast cancer, rhabdomyosarcoma, small cell lung cancer, leiomyosarcoma, hepatocellular carcinoma, Ewing's sarcoma, brain cancer, brain tumor, astrocytoma, neuroblastoma, neurofibroma, basal cell carcinoma, chondrosarcoma, epithelioid sarcoma, eye cancer, Fallopian tube cancer, gastrointestinal cancer, gastrointestinal stromal tumors, hairy cell leukemia, intestinal cancer, islet cell cancer, oral cancer, mouth cancer, throat cancer, laryngeal cancer, lip cancer, mesothelioma, neck cancer, nasal cavity cancer, ocular cancer, ocular melanoma, pelvic cancer, rectal cancer, renal cell carcinoma, salivary gland cancer, sinus cancer, spinal cancer, tongue cancer, tubular carcinoma, urethral cancer, and ureteral cancer. In some embodiments, the compounds of the present disclosure can be used to treat sickle cell disease and sickle cell anemia.

In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or

refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (*e.g.*, primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL) and multiple myeloma (MM).

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, harmatoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), bronchogenic carcinoma, squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma, alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors.

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre -tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, Merkel cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids. In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to, sickle cell disease (*e.g.*, sickle cell anemia), triple-negative breast cancer (TNBC), myelodysplastic syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

It is believed that compounds of Formula (I') or (I), or any of the embodiments thereof, may possess satisfactory pharmacological profile and promising biopharmaceutical properties, such as toxicological profile, metabolism and pharmacokinetic properties, solubility, and permeability. It will be understood that determination of appropriate biopharmaceutical properties is within the knowledge of a person skilled in the art, *e.g.*, determination of cytotoxicity in cells or inhibition of certain targets or channels to determine potential toxicity.

The terms “individual” or “patient,” used interchangeably, refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed (*i.e.*, therapeutic treatment). In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*i.e.*, prophylactic treatment) (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

The terms “condition,” “disease,” and “disorder” are used interchangeably.

The term “administer,” “administering,” or “administration” refers to methods introducing a compound disclosed herein, or a composition thereof, in or on a patient. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described

herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

Generally, an effective amount of a compound taught herein varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present teachings may be readily determined by one of ordinary skill by routine methods known in the art.

The term "therapeutically effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be an amount effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular anticancer agent, its mode of administration, combination treatment with other therapies, and the like.

6. Combination Therapies

I. Cancer Therapies

Cancer cell growth and survival can be impacted by dysfunction in multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, and/or reduce the toxicity of treatment.

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-estrogen agents, anti-inflammatory agents, steroids, immunosuppressants, immune-oncology agents, metabolic enzyme inhibitors, chemokine receptor inhibitors, and phosphatase inhibitors, as well as targeted therapies such as Bcr-Abl, Flt-3, EGFR, HER2, JAK, c-MET, VEGFR, PDGFR, c-Kit, IGF-1R, RAF, FAK, and CDK4/6 kinase inhibitors such as, for example, those described in WO 2006/056399 can be used in combination with the compounds of the present disclosure for treatment of CDK2-associated diseases, disorders or conditions. Other agents such as therapeutic antibodies can be used in combination with the compounds of the present disclosure for treatment of CDK2-

associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

In some embodiments, the CDK2 inhibitor is administered or used in combination with an anti-estrogen agent or a CDK4/6 inhibitor or a mTOR inhibitor or a BCL2 inhibitor or a chemotherapy.

The compounds as disclosed herein can be used in combination with one or more other enzyme/protein/receptor inhibitors therapies for the treatment of diseases, such as cancer and other diseases or disorders described herein. Examples of diseases and indications treatable with combination therapies include those as described herein. Examples of cancers include solid tumors and non-solid tumors, such as liquid tumors, blood cancers. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, BCL2, CDK4/6, TGF-DR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IDH2, IGF-1R, IR-R, PDGFαR, PDGF βR, PI3K (alpha, beta, gamma, delta, and multiple or selective), CSF1R, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, PARP, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following inhibitors for the treatment of cancer or infections. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancer and infections include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, *e.g.*, pemigatinib (INCB54828), INCB62079), an EGFR inhibitor (also known as ErB-1 or HER-1; *e.g.*, erlotinib, gefitinib, vandetanib, orsimertinib, cetuximab, necitumumab, or panitumumab), a VEGFR inhibitor or pathway blocker (*e.g.*, bevacizumab, pazopanib, sunitinib, sorafenib, axitinib, regorafenib, ponatinib, cabozantinib, vandetanib, ramucirumab, lenvatinib, ziv-aflibercept), a PARP inhibitor (*e.g.*, olaparib, rucaparib, veliparib or niraparib), a JAK inhibitor (JAK1 and/or JAK2, *e.g.*, ruxolitinib or baricitinib; JAK1, *e.g.*, itacitinib (INCB39110), INCB052793, or INCB054707), an IDO inhibitor (*e.g.*, epacadostat, NLG919, or BMS-986205, MK7162), an LSD1 inhibitor (*e.g.*, GSK2979552, INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (*e.g.*, parsaclisib (INCB50465) or INCB50797), a PI3K-gamma inhibitor such as PI3K-gamma selective inhibitor, a Pim inhibitor (*e.g.*, INCB53914), a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer; *e.g.*, INCB081776), an adenosine receptor antagonist (*e.g.*, A2a/A2b receptor antagonist), an HPK1 inhibitor, a chemokine receptor inhibitor (*e.g.*, CCR2 or CCR5 inhibitor), a SHP1/2 phosphatase inhibitor, a histone deacetylase inhibitor (HDAC) such as an HDAC8 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for

example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), c- MET inhibitors (*e.g.*, capmatinib), an anti-CD19 antibody (*e.g.*, tafasitamab), an ALK2 inhibitor (*e.g.*, INCB00928); or combinations thereof.

In some embodiments, the compound or salt described herein is administered with a PI3K6 inhibitor. In some embodiments, the compound or salt described herein is administered with a JAK inhibitor. In some embodiments, the compound or salt described herein is administered with a JAK1 or JAK2 inhibitor (*e.g.*, baricitinib or ruxolitinib). In some embodiments, the compound or salt described herein is administered with a JAK1 inhibitor. In some embodiments, the compound or salt described herein is administered with a JAK1 inhibitor, which is selective over JAK2. Example antibodies for use in combination therapy include, but are not limited to, trastuzumab (*e.g.*, anti-HER2), ranibizumab (*e.g.*, anti-VEGF-A), bevacizumab (AVASTINTM , *e.g.*, anti-VEGF), panitumumab (*e.g.*, anti-EGFR), cetuximab (*e.g.*, anti-EGFR), rituxan (*e.g.*, anti-CD20), and antibodies directed to c-MET. One or more of the following agents may be used in combination with the compounds of the present disclosure and are presented as a non-limiting list: a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptosar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, IRESSATM (gefitinib), TARCEVATM (erlotinib), antibodies to EGFR, intron, ara-C, adriamycin, cytoxan, gemcitabine, uracil mustard, chlormethine, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™ (oxaliplatin), pentostatine, vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mithramycin, deoxycoformycin, mitomycin-C, L- asparaginase, teniposide 17.alpha.-ethinylestradiol, diethylstilbestrol, testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, testolactone, megestrolacetate, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrazole, letrazole, capecitabine, reloxafine, droloxafine, hexamethylmelamine, avastin, HERCEPTIN™ (trastuzumab), BEXXAR™ (tositumomab), VELCADE™ (bortezomib), ZEVALIN™ (ibritumomab tiuxetan), TRISENOX™ (arsenic trioxide), XELODA™ (capecitabine), vinorelbine, porfimer, ERBITUX™ (cetuximab), thiotepa, altretamine, melphalan, trastuzumab, lerozole, fulvestrant, exemestane, ifosfomide, rituximab, C225 (cetuximab), Campath (alemtuzumab), clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (*e.g.*, interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, bispecific or multi-specific antibody, antibody drug conjugate, adoptive T cell transfer, Toll receptor agonists, RIG-I agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor, PI3Kd inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutic agent. Examples of chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, mecloretharnine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, and zoledronate.

Additional examples of chemotherapeutics include proteasome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include corticosteroids such as dexamethasone or prednisone. Example Bcr-Abl inhibitors include imatinib mesylate (GLEEVAC™), nilotinib, dasatinib, bosutinib, and ponatinib, and pharmaceutically acceptable salts. Other example suitable Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No.5,521,184, WO 04/005281, and U.S. Ser. No.60/578,491.

Example suitable Flt-3 inhibitors include midostaurin, lestaurtinib, linifanib, sunitinib, sunitinib, maleate, sorafenib, quizartinib, crenolanib, pacritinib, tandutinib, PLX3397 and ASP2215,

and their pharmaceutically acceptable salts. Other example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include dabrafenib, sorafenib, and vemurafenib, and their pharmaceutically acceptable salts. Other example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

Example suitable FAK inhibitors include VS-4718, VS-5095, VS-6062, VS- 6063, BI853520, and GSK2256098,and their pharmaceutically acceptable salts. Other example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

Example suitable CDK4/6 inhibitors include palbociclib, ribociclib, trilaciclib, lerociclib, and abemaciclib, and their pharmaceutically acceptable salts. Other example suitable CDK4/6 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 09/085185, WO 12/129344, WO 11/101409, WO 03/062236, WO 10/075074, and WO 12/061156.

In some embodiments, the compounds of the disclosure can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the compounds of the disclosure can be used in combination with a chemotherapeutic in the treatment of cancer, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. In some embodiments, the compounds of the disclosure can be used in combination with a chemotherapeutic provided herein. For example, additional pharmaceutical agents used in the treatment of multiple myeloma, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM). Additive or synergistic effects are desirable outcomes of combining a CDK2 inhibitor of the present disclosure with an additional agent.

The agents can be combined with the present compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

The compounds of the present disclosure can be used in combination with one or more other inhibitors or one or more therapies for the treatment of infections. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the compounds of the disclosure where the dexamethasone is administered intermittently as opposed to continuously.

The compounds of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non- limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the compounds of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The compounds of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

In some further embodiments, combinations of the compounds of the disclosure with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

The compounds of Formula (I') or (I) or any of the formulae as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C),

Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

Viruses causing infections treatable by methods of the present disclosure include, but are not limit to human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, Ebola virus, measles virus, herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Pathogenic bacteria causing infections treatable by methods of the disclosure include, but are not limited to, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

Pathogenic fungi causing infections treatable by methods of the disclosure include, but are not limited to, Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Pathogenic parasites causing infections treatable by methods of the disclosure include, but are not limited to, Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (*e.g.*, for more than two agents).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, *e.g.*, 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

II. Immune-checkpoint therapies

Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors for the treatment of diseases, such as cancer or infections. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CBL-B, CD20,

CD28, CD40, CD122, CD96, CD73, CD47, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, HPK1, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, TIGIT, CD112R, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, TIGIT, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the compounds provided herein can be used in combination with one or more agonists of immune checkpoint molecules, *e.g.*, OX40, CD27, GITR, and CD137 (also known as 4-1B).

In some embodiments, the inhibitor of an immune checkpoint molecule is anti- PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, *e.g.*, an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK- 3475), pidilizumab, SHR-1210, PDR001, MGA012, PDR001, AB122, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 monoclonal antibody is MGA012. In some embodiments, the anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics such as 4-1BB (*e.g.*, urelumab, utomilumab).

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, *e.g.*, an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1 and PD-L1, *e.g.*, an anti-PD-1/PD-L1 bispecific antibody. In some embodiments, the anti-PD-1/PD-L1 is MCLA-136. In some embodiments, the inhibitor is MCLA-145.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, *e.g.*, an anti-CTLA-4 antibody. In some embodiments, the anti- CTLA-4 antibody is ipilimumab, tremelimumab, AGEN1884, or CP-675,206.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, *e.g.*, an anti-LAG3 antibody. In some embodiments, the anti- LAG3 antibody is BMS-986016, LAG525, or INCAGN2385.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of

TIM3, *e.g.*, an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, *e.g.*, an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, or MEDI1873.

In some embodiments, the inhibitor of an immune checkpoint molecule is an agonist of OX40, *e.g.*, OX40 agonist antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562, MOXR-0916, PF-04518600, GSK3174998, or BMS-986178. In some embodiments, the OX40L fusion protein is MEDI6383.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD20, *e.g.*, an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is obinutuzumab or rituximab. The compounds of the present disclosure can be used in combination with bispecific antibodies.

In some embodiments, one of the domains of the bispecific antibody targets PD-1, PD-L1, CTLA-4, GITR, OX40, TIM3, LAG3, CD137, ICOS, CD3 or TGFb receptor.

In some embodiments, the compounds of the disclosure can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include epacadostat, NLG919, BMS-986205, PF-06840003, IOM2983, RG-70099 and LY338196.

As provided throughout, the additional compounds, inhibitors, agents, etc. can be combined with the present compound in a single or continuous dosage form, or they can be administered simultaneously or sequentially as separate dosage forms.

7. Treatment Kits

One aspect of the present invention relates to a kit for conveniently and effectively carrying out the methods or uses in accordance with the present invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following representative examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof. These examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit its scope. Indeed, various modifications of the invention, and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art upon review of this document, including the examples which follow and the references to the scientific and patent literature cited herein.

The contents of the cited references are incorporated herein by reference to help illustrate the state of the art.

In addition, for purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "Organic Chemistry," Morrison & Boyd (3d Ed), the entire contents of both of which are incorporated herein by reference.

8. Preparation

The compounds of any one of the formulae described above, may be prepared by the general and specific methods described below, using the common general knowledge of one skilled in the art of synthetic organic chemistry. Such common general knowledge can be found in standard reference books such as *Comprehensive Organic Chemistry*, Ed. Barton and Ollis, Elsevier; *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Larock, John Wiley and Sons; and *Compendium of Organic Synthetic Methods*, Vol. I-XII (published by Wiley-Interscience). The starting materials used herein are commercially available or may be prepared by routine methods known in the art.

In the preparation of the compounds of any one of the formulae described above, it is noted that some of the preparation methods described herein may require protection of remote functionality (*e.g.*, primary amine, secondary amine, carboxyl in any one of the formulae described above precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

For example, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a

subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethylenoxycarbonyl (Fmoc) for amines, and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the any one of the formulae described above compounds.

The Schemes described below are intended to provide a general description of the methodology employed in the preparation of the compounds of the present disclosure. Some of the compounds of the present present disclosure may contain single or multiple chiral centers with the stereochemical designation (*R*) or (*S*). It will be apparent to one skilled in the art that all of the synthetic transformations can be conducted in a similar manner whether the materials are enantioenriched or racemic. Moreover, the resolution to the desired optically active material may take place at any desired point in the sequence using well known methods such as described herein and in the chemistry literature.

EXAMPLES

Abbreviations

ATP	Adenosine triphosphate
ACN	Acetonitrile
AcOH	Acetic acid
BSA	Bovine serum albumin
CDI	1,1'-Carbonyldiimidazole
DCE	1,2-Dichloromethane
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DTT	Dithiothreitol
EDCI	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOH	Ethanol
EDTA	Ethylenediaminetetraacetic acid
EtOAc	Ethyl acetate
FA	Formic acid
FBS	Fetal bovine serum
FCC	Flash column chromatrography

HATU	N-[(Dimethylamino)-lH-l,2,3-triazolo-[4,5-b]pyridin-l-ylmethylene]-N methylmethanaminium hexafluorophosphate N-oxide
HOBT	1-Hydroxybenzotriazole
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	High performance liquid chromatography
Prep-HPLC	Preparative High-performance liquid chromatography
LC-MS	Liquid chromatography - mass spectrometry
MeOH	Methanol
NBS	N-bromosuccinimide
NMM	N-Methylmorpholine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
$Pd(dppf)Cl_2$	Dichloro[l, l'-bis(diphenylphosphino)ferrocene]palladium
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
PE	Petroleum ether
rac	Racemic
SFC	Supercritical fluid chromatography
TEA	Triethyl amine
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
wt. %	Weight percentage

General Equipment Description

^{1}H NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

The analytical low-resolution mass spectra (MS) were recorded on Waters ACQUITY UPLC with SQ Detectors using a Waters CORTECS C18+, 2.7 μm 4.6×30 mm using a gradient elution method.

Solvent A: 0.1% formic acid (FA) in water

Solvent B: 0.1% FA in acetonitrile

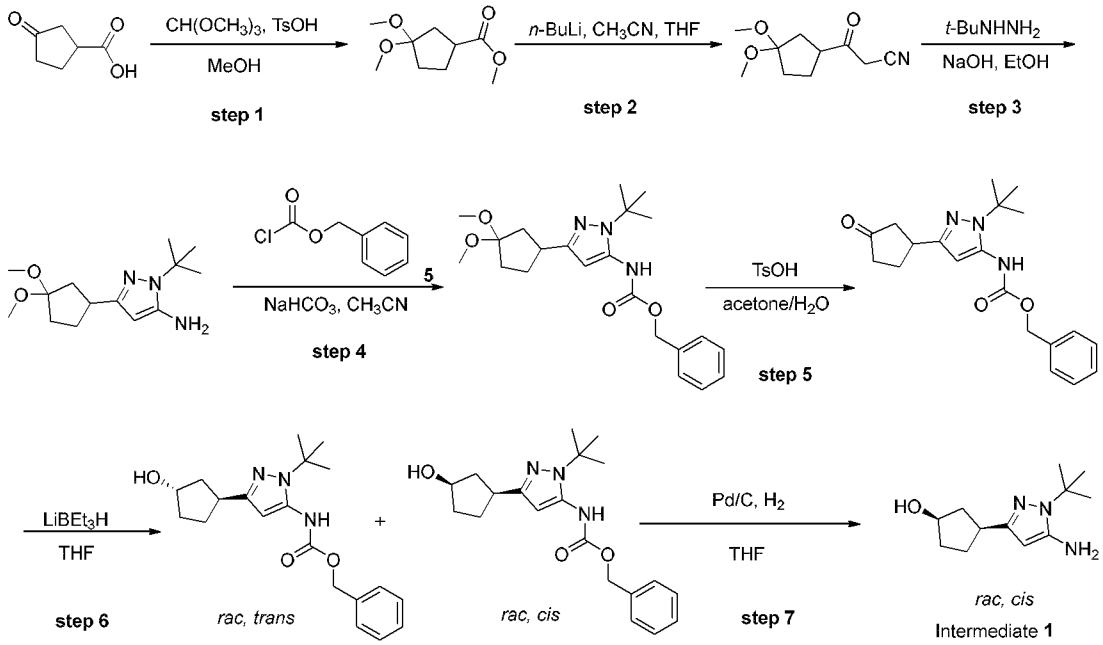
5% ACN to 95% ACN in 1.0 min, hold 1.0 min,

Total 2.5 min; Flow rate: 1.8 mL/min; Column Temp 40 degree.

Benzyl (1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)carbamate, Benzyl (1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)carbamate and (*trans, rac*)-3-(5-(((benzyloxy)carbonyl)amino)-1-(tert-butyl)-1H-pyrazol-3-yl)cyclopentyl methanesulfonate were

purchased from PharmaBlock.

Intermediate **1**



Step 1: methyl 3,3-dimethoxycyclopentane-1-carboxylate

To a solution of 3-oxocyclopentanecarboxylic acid (15 g, 117.1 mmol) in MeOH (30 mL) was added trimethoxymethane (74.5 g, 702.4 mmol, 77.0 mL) and p-Toluenesulfonic acid monohydrate (445.4 mg, 2.3 mmol, 359.2 μL) at 0 °C. The mixture was stirred at 20 °C for 16 hours. The mixture was quenched with NaHCO3 aq. (2x50 mL), extracted with EtOAc (40 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give methyl 3,3-dimethoxycyclopentanecarboxylate (19 g, crude) as a yellow oil.

Step 2: 3-(3,3-dimethoxycyclopentyl)-3-oxopropanenitrile

To a solution of n-BuLi (2.4 M, 84.1 mL) in THF (30 mL) was added acetonitrile (8.3 g, 201.9 mmol, 10.5 mL) at -78 °C. The mixture was stirred at -78 °C under N_2 for 1 hour. Then methyl 3,3-dimethoxycyclopentanecarboxylate (19 g, 100.9 mmol) was added and stirred for 1.5 hours. The mixture was quenched with water, adjusted pH to 7 by HCl (1 M), extracted with EtOAc (50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give 3-(3,3-dimethoxycyclopentyl)-3-oxo-propanenitrile (18.9 g, crude) as a red oil.

Step 3: 1-(*tert*-butyl)-3-(3,3-dimethoxycyclopentyl)-1H-pyrazol-5-amine

To a solution of *tert*-butylhydrazine·hydrochloride (14.33 g, 114.99 mmol) in EtOH (25 mL) was added NaOH (4.6 g, 114.9 mmol) at 0 °C and stirred for 1 hours. Then 3-(3,3-dimethoxycyclopentyl)-3-oxo-propanenitrile (18.9 g, 95.8 mmol) was added and stirred at 75 °C for 16 hours. LCMS showed the

desired mass peak was found. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by FCC (120 g silica gel, 0~20%~50% EtOAc in PE) to give 2-*tert*-butyl-5-(3,3-dimethoxycyclopentyl)pyrazol-3-amine (8.8 g, 32.8 mmol, 34% yield) as a red oil and 2-*tert*-butyl-5-[(3Z)-3-(*tert*-butylhydrazono)cyclopentyl]pyrazol-3-amine (2.0 g, 6.9 mmol, 7% yield) as a red oil. LC-MS: m/z 222 $[M+H]^+$.

Step 4: benzyl (1-(*tert*-butyl)-3-(3,3-dimethoxycyclopentyl)-1H-pyrazol-5-yl)carbamate

To a solution of 2-*tert*-butyl-5-(3,3-dimethoxycyclopentyl)pyrazol-3-amine (8.8 g, 32.8 mmol) in CH_3CN (30 mL) was added benzyl carbonochloridate (11.2 g, 65.7 mmol, 9.3 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hours. Then Sodium bicarbonate (8.8 g, 105.1 mmol) was added and stirred at 20 °C for 16 hours. LCMS showed the desired mass peak was found. The mixture was filtered, concentrated under reduced pressure. The residue was extracted with EtOAc (40 mL), washed with water (2x50 mL). The organic phase was concentrated under reduced pressure to give benzyl N-[2-*tert*-butyl-5-(3,3-dimethoxycyclopentyl)pyrazol-3-yl]carbamate (17.9 g, crude) as a red oil. The crude product was used to the next step directly. LC-MS: m/z 402 $[M+H]^+$.

Step 5: benzyl (1-(*tert*-butyl)-3-(3-oxocyclopentyl)-1H-pyrazol-5-yl)carbamate

A solution of benzyl N-[2-*tert*-butyl-5-(3,3-dimethoxycyclopentyl)pyrazol-3-yl]carbamate (17.9 g, 44.8 mmol) and p-Toluenesulfonic acid monohydrate (1.1 g, 5.8 mmol) in acetone (30 mL) and H_2O (30 mL) was stirred at 60 °C for 16 hours. LCMS showed the reaction was completed. The mixture was extracted with EtOAc (45 mL), washed with water (2x55 mL). The organic phase was concentrated under reduced pressure. The residue was purified by FCC (120 g silica gel, 0~35% EtOAc in PE) to give benzyl N-[2-*tert*-butyl-5-(3-oxocyclopentyl)pyrazol-3-yl]carbamate (8.0 g, 22.7 mmol, 50% yield) as a yellow solid. LC-MS: m/z 356 $[M+H]^+$.

Step 6: (*rac, cis*)-benzyl (1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)carbamate

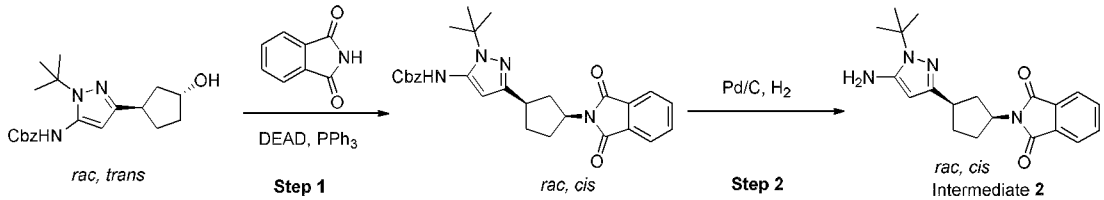
To a solution of benzyl N-[2-*tert*-butyl-5-(3-oxocyclopentyl)pyrazol-3-yl]carbamate (8.0 g, 22.7 mmol) in THF (25 mL) was added Lithium triethylborohydride (1.0 M, 45.4 mL) at -65 °C dropwise. The mixture was stirred at -65 °C under N_2 for 1.5 hours. LCMS showed the desired mass peak was found. The mixture was quenched with $NaHCO_3$ aq. at -40 °C, extracted with EtOAc (35 mL). The organic phase was concentrated under reduced pressure. The residue was purified by FCC (120 g silica gel, 0~50% DCM in EtOAc) to give (*rac, cis*)-benzyl (1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)carbamate (5.6 g, 15.7 mmol, 69% yield) as a white solid. And (*rac, trans*)-benzyl (1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)carbamate (2.0 g, 5.6 mmol, 24% yield) as a light yellow solid. LC-MS: m/z 358 $[M+H]^+$.

Step 7: (*rac, cis*)-3-(5-amino-1-(*tert*-butyl)-1H-pyrazol-3-yl)cyclopentan-1-ol

To a solution of (*rac, cis*)-benzyl N-[2-*tert*-butyl-5-[3-hydroxycyclopentyl]pyrazol-3-yl]carbamate (2.8 g, 6.4 mmol) in THF (18 mL) was added Pd/C (300 mg) at 20 °C. The mixture was stirred at 20 °C for

4 hours under H_2. LCMS showed the reaction was completed. The mixture was filtered, concentrated to give (*rac, cis*)-3-(5-amino-1-(*tert*-butyl)-1H-pyrazol-3-yl)cyclopentan-1-ol (1.7 g, 5.7 mmol, 88% yield) as a yellow oil. LC-MS: m/z 224 $[M+H]^+$.

Intermediate **2**



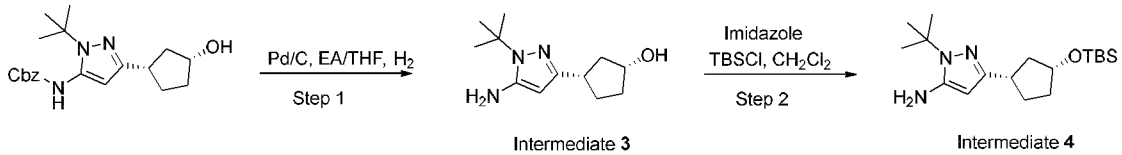
Step 1: (*rac, cis*)-benzyl (1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1H-pyrazol-5-yl)carbamate:

To a stirred solution of (*rac, trans*)-benzyl N-[1-*tert*-butyl-3-[3-hydroxycyclopentyl]pyrazol-5-yl]carbamate (400 mg, 1.12 mmol) in THF (10 mL) were sequentially added isoindoline-1,3-dione (247 mg, 1.68 mmol), triphenyl phosphate (730 mg, 2.24 mmol) and diethyl azodicarboxylate (292 mg, 275 μL, 1.68 mmol) at 0 °C. The resulting mixture was warmed to 25 °C and stirred at that temperature for 3 h. The mixture was quenched with saturated aq. $NaHCO_3$ (0.1 mL) and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 75% in 20 min to give (*rac, cis*)-benzyl N-[1-*tert*-butyl-3-[-3-(1,3-dioxoisoindolin-2-yl)cyclopentyl]pyrazol-5-yl]carbamate (230 mg, 42% yield) as a colorless oil. LC-MS: m/z 487.8 $[M+H]^+$.

Step 2: (*rac, cis*)- 2-(3-(5-amino-1-(*tert*-butyl)-1H-pyrazol-3-yl)cyclopentyl)isoindoline-1,3-dione:

To a stirred solution of (*rac, cis*)-benzyl N-[1-*tert*-butyl-3-[-3-(1,3-dioxoisoindolin-2-yl)cyclopentyl]pyrazol-5-yl]carbamate (230 mg, 0.472 mmol) in Methanol (5.0 mL) was added Pd/C (50.3 mg, 5% wt., 0.0236 mmol). The reaction mixture was stirred under hydrogen atmosphere (balloon) at 25°C for 2 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford (*rac, cis*)-2-[3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentyl]isoindoline-1,3-dione (150 mg, 90% yield) as a brown oil which was used directly in the next step without further purification. LC-MS: m/z 353.8 $[M+H]^+$.

Intermediate **3** and **4**



Step 1: (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol

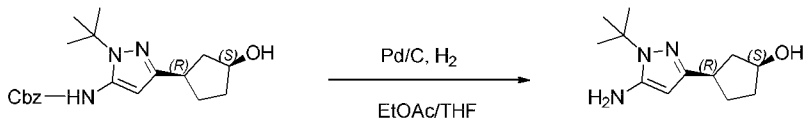
To a suspension of benzyl (1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)carbamate (20.0 g, 55.9 mmol) in THF (300 mL) was added Pd/C (10.0 g, 50 wt.%)

at 25°C and stirred at that temperature for 16 h under H_2. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (12.0 g, 96% yield) as a white solid. LC-MS: m/z [M+H]+ 224.2.

Step 2: 1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-amine

To a solution of (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (4.00 g, 17.9 mmol) and Imidazole (2.44 g, 35.8 mmol) in CH_2Cl_2 (100 mL) was added *tert*-butyl-chloro-dimethyl-silane (6.67 mL, 5.40 g, 35.8 mmol) at 25 °C. The mixture was stirred at that temperature for 16 h. The mixture was washed with water (100 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25 % in 25 min) to afford 1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-amine (6.00 g, 99% yield) as a yellow oil. LC-MS: m/z [M+H]+ 338.0.

Intermediate **5**

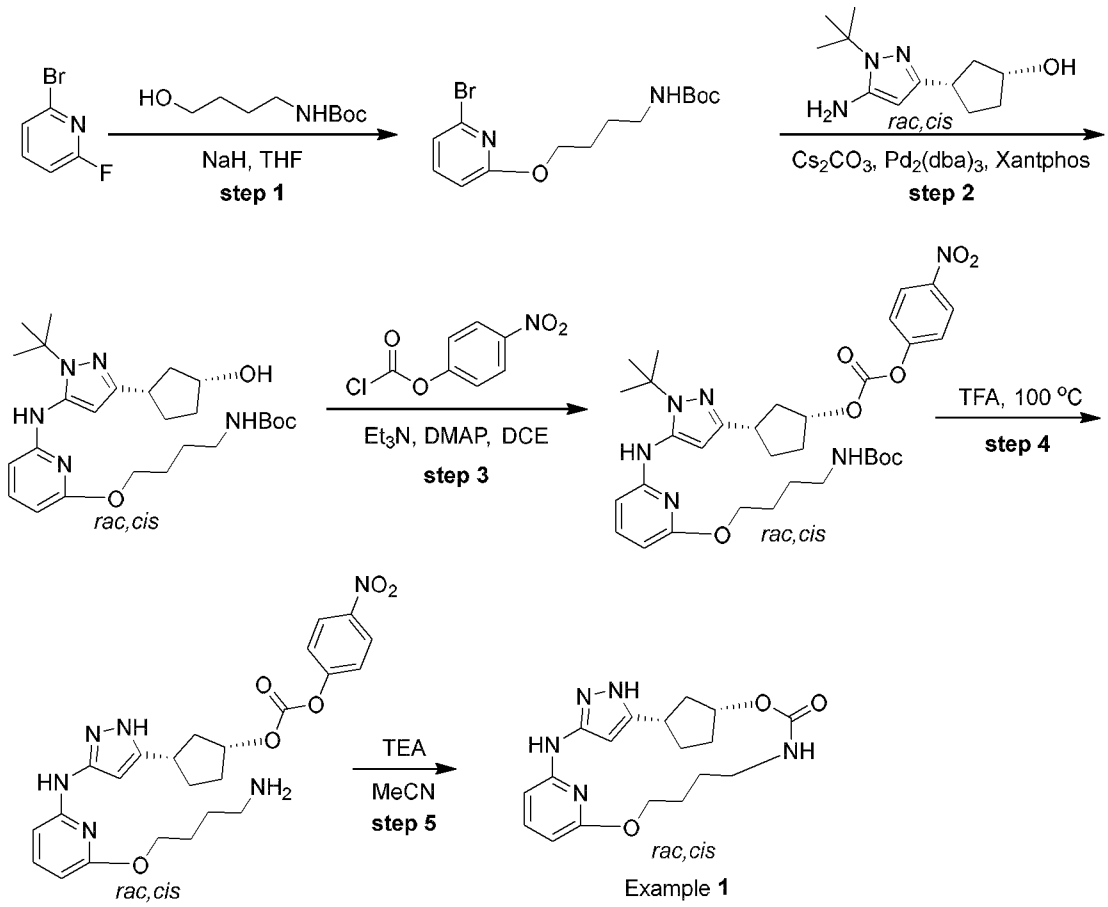


Intermediate **5**

A solution of benzyl (1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)carbamate (5.00 g, 14.0 mmol) in THF (20.0 mL) and EtOAc (20.0 mL) was stirred at 25 °C for 2 h under H_2 atmosphere (balloon) before it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give (1*S*,3*R*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (4.70 g, crude) as a white solid. LC-MS: m/z $[M+H]^+$224.2.

Synthetic Examples

Synthetic Example 1



Example **1**

Step 1: *tert*-butyl N-[4-[(6-bromo-2-pyridyl)oxy]butyl]carbamate

To a solution of *tert*-butyl N-(4-hydroxybutyl)carbamate (240 mg, 1.3 mmol) in THF (5 mL) was added sodium hydride (55 mg, 1.4 mmol, 60% purity) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 min and then 2-bromo-6-fluoro-pyridine (200 mg, 1.1 mmol) was added. The reaction was stirred at 0 °C for 2 hours. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-40% EtOAc in PE to afford *tert*-butyl N-[4-[(6-bromo-2-pyridyl)oxy]butyl]carbamate (295 mg, 75% yield) as colorless oil. LC-MS: m/z 344.7 $[M+H]^+$.

Step 2: (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate

To a mixture of *tert*-butyl N-[4-[(6-bromo-2-pyridyl)oxy]butyl]carbamate (150 mg, 434 μmol), *(rac, cis)*-3-(5-amino-2-*tert*-butyl-pyrazol-3-yl)cyclopentanol (110 mg, 492 μmol) and Cs_2CO_3 (290 mg, 890 μmol) in dioxane (5 mL) was added XantPhos (25 mg, 43 μmol) and $Pd_2(dba)_3$ (20 mg, 22 μmol) under

nitrogen. The reaction was stirred at 100 °C under nitrogen for 12 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-40% EtOAc in PE to afford (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (100 mg, 47% yield) as a light brown solid. LC-MS: m/z 487.9 $[M+H]^+$.

Step 3: (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate

A mixture of (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (100 mg, 205 μmol), 4-Nitrophenyl chloroformate (125 mg, 620 μmol), Et_3N (145 μL, 1.04 mmol) and DMAP (5 mg, 41 μmol) in DCE (5 mL) was stirred at 70 °C for 12 hours. The mixture was diluted with water (50 mL) and extracted with DCM (3x30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-30% EtOAc in PE to afford (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (85 mg, 63% yield) as a light brown solid. LC-MS: m/z 653.8 $[M+H]^+$.

Step 4: [(*rac, cis*)-3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl] (4-nitrophenyl) carbonate

A mixture of (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (85 mg, 130 μmol) in TFA (5 mL) was stirred at 100 °C for 5 hours. The solvent was evaporated to afford [(*rac, cis*)-3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl] (4-nitrophenyl) carbonate; 2,2,2-trifluoroacetic acid (80 mg, 100% yield) as colorless oil, which was used in the next step directly. LC-MS: m/z 496.8 $[M+H]^+$.

Step 5: (*rac, cis*)-2^{1}H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

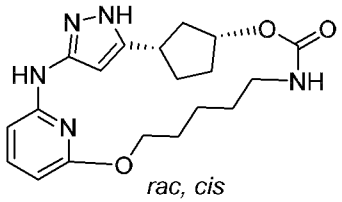
To a mixture of [(*rac, cis*)-3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl] (4-nitrophenyl) carbonate;2,2,2-trifluoroacetic acid (80 mg, 131 μmol) in MeCN (10 mL) was added Et_3N (100 μL, 717 μmol) at 15 °C. The reaction was stirred at 15 °C for 1 hour. The solvent was evaporated and the residue was purified by prep-HPLC (C18, 35-70% MeCN in 0.05% FA/water, 40 mL/min) to afford (*rac, cis*)-2^{1}H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-

cyclopentanacyclododecaphan-11-one (11.8 mg, 25% yield) as a white solid. LC-MS: m/z 357.9 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 11.82 (s, 1H), 9.34 - 9.10 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 6.0 Hz, 1H), 6.66 - 6.44 (m, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.12 - 4.94 (m, 1H), 4.49 – 3.94 (m, 2H), 3.24 – 2.70 (m, 3H), 2.08 – 1.43 (m, 10H).

The compounds in below table were prepared in accordance with the synthetic protocols set forth in **Example 1** using the appropriate starting materials.

Synthetic Example 2

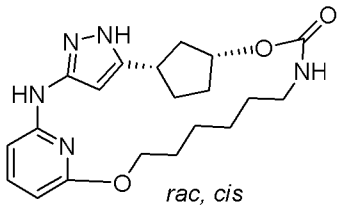


rac, cis

LC-MS: m/z 371.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 6.14 (d, *J* = 8.0 Hz, 2H), 5.26 - 5.06 (m, 1H), 4.77 - 4.60 (m, 1H), 4.49 – 4.22 (m, 2H), 4.16 - 4.06 (m, 1H), 3.62 -3.46 (m, 1H), 3.38 - 3.24 (m, 1H), 3.20 - 2.51 (m, 5H), 2.21 - 2.07 (m, 2H), 1.68 - 1.37 (m, 4H).

Synthetic Example 3

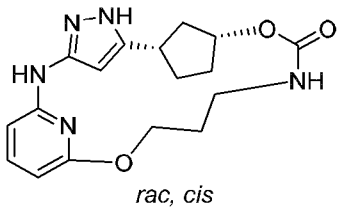


rac, cis

LC-MS: m/z 385.9 $[M+H]^+$.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.0 Hz, 1H), 6.96 - 6.63 (m, 1H), 6.17 (d, *J* = 8.0 Hz, 1H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.31 - 5.07 (m, 1H), 4.62 – 4.17 (m, 2H), 3.58 - 3.37 (m, 1H), 3.26 - 2.90 (m, 2H), 2.73 – 2.52 (m, 1H), 2.16 – 1.86 (m, 8H), 1.58 - 1.37 (m, 6H).

Synthetic Example 4

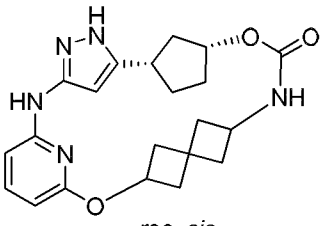


rac, cis

LC-MS: m/z 343.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 9.35 - 9.12 (m, 1H), 8.14 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 4.90 - 4.78 (m, 1H), 3.82 - 3.71 (m, 1H), 3.50 - 3.42 (m, 1H), 3.22 - 3.07 (m, 2H), 2.99 - 2.86 (m, 1H), 2.41 - 2.30 (m, 1H), 2.18 - 2.06 (m, 1H), 2.05 - 1.95 (m, 1H), 1.90 - 1.59 (m, 5H).

Synthetic Example 5

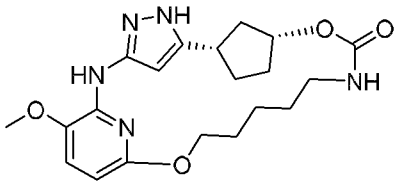


rac, cis

LC-MS: m/z 395.8 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.08 (d, *J* = 58.2 Hz, 1H), 7.84 – 6.71 (m, 1H), 6.62 – 6.14 (m, 2H), 5.97 (t, *J* = 8.0 Hz, 1H), 4.96 (d, *J* = 7.1 Hz, 1H), 4.70 (s, 1H), 3.62 (dt, *J* = 7.5, 3.5 Hz, 1H), 3.02 (s, 1H), 2.82 – 2.58 (m, 1H), 2.34 – 2.18 (m, 1H), 2.15 – 1.91 (m, 10H), 1.77 (d, *J* = 8.9 Hz, 2H).

Synthetic Example 6

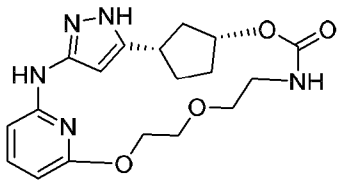


rac, cis

LC-MS: m/z 401.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 11.92 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 1H), 6.83 (brs, 1H), 6.60 - 6.43 (m, 1H), 6.04 (d, *J* = 8.4 Hz, 1H), 5.08 - 4.83 (m, 1H), 4.42 – 3.89 (m, 2H), 3.79 (s, 3H), 3.18 - 2.68 (m, 2H), 2.64 - 2.55 (m, 1H), 2.14 – 1.26 (m, 12H).

Synthetic Example 7

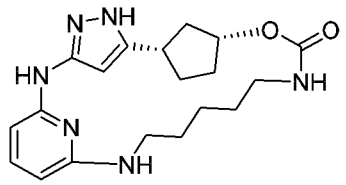


rac, cis

LC-MS: m/z 373.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, MeOD) δ 7.42 (t, *J* = 8.0 Hz, 1H), 6.67 (s, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 8.0 Hz, 1H), 5.15 - 5.02 (m, 1H), 4.55 - 4.40 (m, 1H), 4.25 - 4.14 (m, 1H), 3.92 - 3.73 (m, 2H), 3.70 - 3.45 (m, 3H), 3.23 - 2.99 (m, 2H), 2.66 - 2.53 (m, 1H), 2.16 - 1.97 (m, 2H), 1.97 - 1.73 (m, 3H).

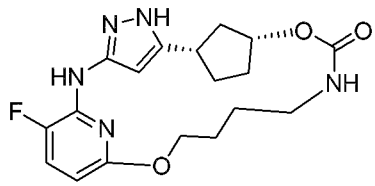
Synthetic Example 8



rac, cis

LC-MS: m/z 370.9 $[M+H]^+$.

Synthetic Example 9

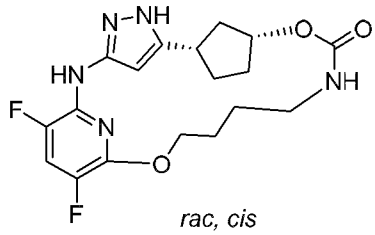


rac, cis

LC-MS: m/z 375.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 11.97 (s, 1H), 9.01 - 8.59 (m, 1H), 7.41 (t, *J* = 9.6 Hz, 1H), 6.92 - 6.79 (m, 1H), 6.67 - 6.44 (m, 1H), 6.01 (d, *J* = 8.4 Hz, 1H), 5.12 - 4.92 (m, 1H), 4.54 - 3.89 (m, 2H), 3.22 - 3.05 (m, 1H), 3.04 - 2.71 (m, 2H), 2.61 - 2.53 (m, 1H), 2.07 - 1.93 (m, 1H), 1.91 - 1.63 (m, 6H), 1.60 - 1.43 (m, 2H).

Synthetic Example 10

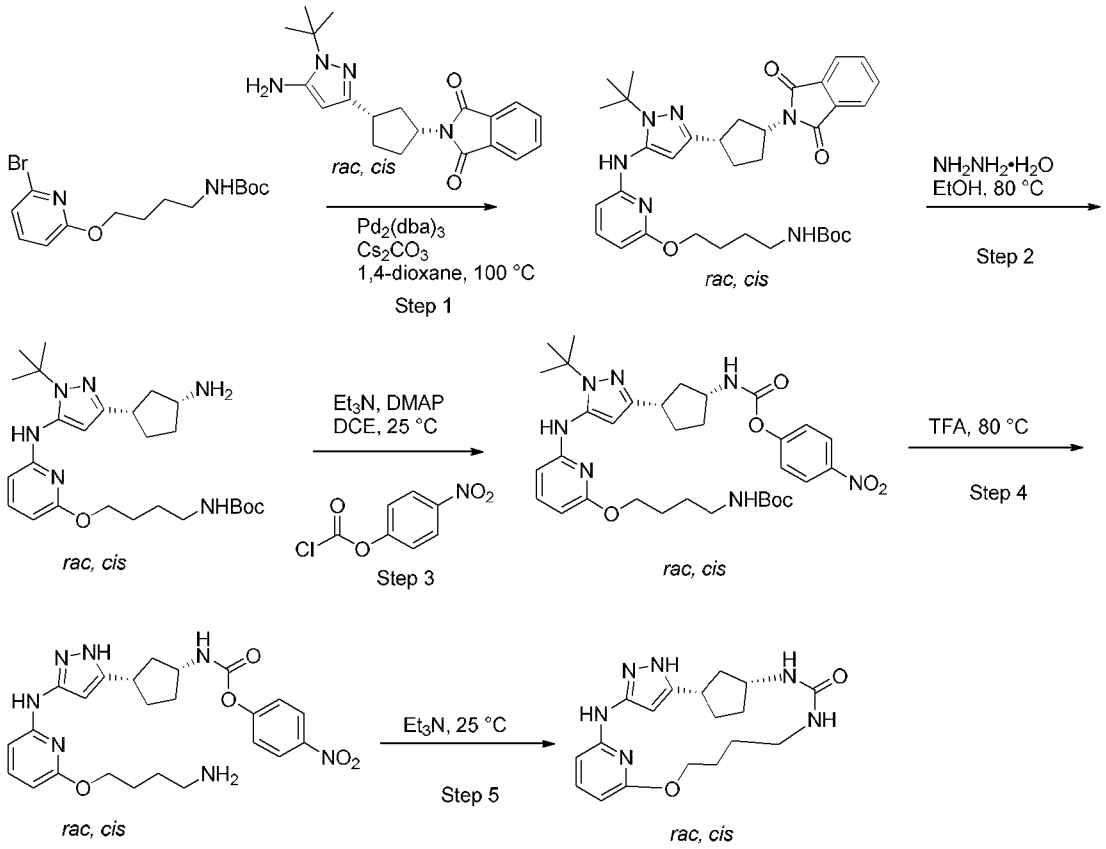


rac, cis

LC-MS: m/z 393.8 $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 11.97 (s, 1H), 9.14 - 8.62 (m, 1H), 7.74 (t, *J* = 9.6 Hz, 1H), 7.35 - 6.74 (m, 1H), 6.62 - 6.30 (m, 1H), 5.13 - 4.92 (m, 1H), 4.66 - 3.94 (m, 2H), 3.22 - 3.02 (m, 1H), 3.03 - 2.70 (m, 2H), 2.60 - 2.54 (m, 1H), 2.05 - 1.41 (m, 9H).

Synthetic Example 11



Step 1: (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of (*rac, cis*)-2-(3-(5-amino-1-(*tert*-butyl)-1H-pyrazol-3-yl)cyclopentyl)isoindoline-1,3-dione (100 mg, 0.284 mmol) in 1,4-dioxane (3.0 mL) were sequentially added *tert*-butyl N-[4-[(6-bromo-2-pyridyl)oxy]butyl]carbamate (108 mg, 0.312 mmol), 5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl-diphenyl-phosphane (16.4 mg, 0.0284 mmol), dicesium carbonate (185 mg, 0.567 mmol) and 1,5-diphenylpenta-1,4-dien-3-one palladium (13.0 mg, 0.142 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 8 h. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 50% in 20 min to give (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (100 mg, 57% yield) as a colorless oil. LC-MS: m/z 617.8 $[M+H]^+$.

Step 2: (*rac, cis*)-*tert*-butyl (4-((6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate

To a solution of (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (100 mg, 0.162 mmol) in Ethanol (4.0 mL) were sequentially added hydrazine hydrate (29.6 μL, 80% wt., 0.486 mmol) at 25 °C. The reaction

mixture was warmed to 80 °C and stirred at that temperature for 3 h. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 with MeOH from 0 to 20% in 20 min to give (*rac, cis*)-*tert*-butyl (4-((6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (60 mg, 76% yield) as a colorless oil. LC-MS: m/z 487.9 $[M+H]^+$.

Step 3: (rac, cis)-tert-butyl (4-((6-((1-(tert-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of (*rac, cis*)-*tert*-butyl (4-((6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (50 mg, 0.10 mmol) in dichloromethane (10 mL) were sequentially added (4-nitrophenyl) carbonochloridate (22.8 mg, 0.113 mmol), N,N-diethylethanamine (15.6 mg, 21.5 μL, 0.154 mmol) and N,N-dimethylpyridin-4-amine (1.3 mg, 0.010 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 8 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL). The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 75 % in 20 min to give (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (50 mg, 75% yield) as a colorless oil. LC-MS: m/z 652.7 $[M+H]^+$.

Step 4: (rac, cis)-(4-nitrophenyl) N-[3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl]carbamate

To a Biotage pressure tube were sequentially added (*rac, cis*)-*tert*-butyl (4-((6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl)carbamate (45 mg, 0.069 mmol) and trifluoroacetic acid (10 mL) at 25 °C. The mixture was sealed, warmed to 80 °C under microwave and stirred at that temperature for 30 min. The mixture was cooled to 25 °C and concentrated under reduced pressure to give (*rac, cis*)-(4-nitrophenyl) N-[3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl]carbamate (34 mg, 100% yield) as a colorless oil which was used directly in the next step without further purification. LC-MS: m/z 496.8 $[M+H]^+$.

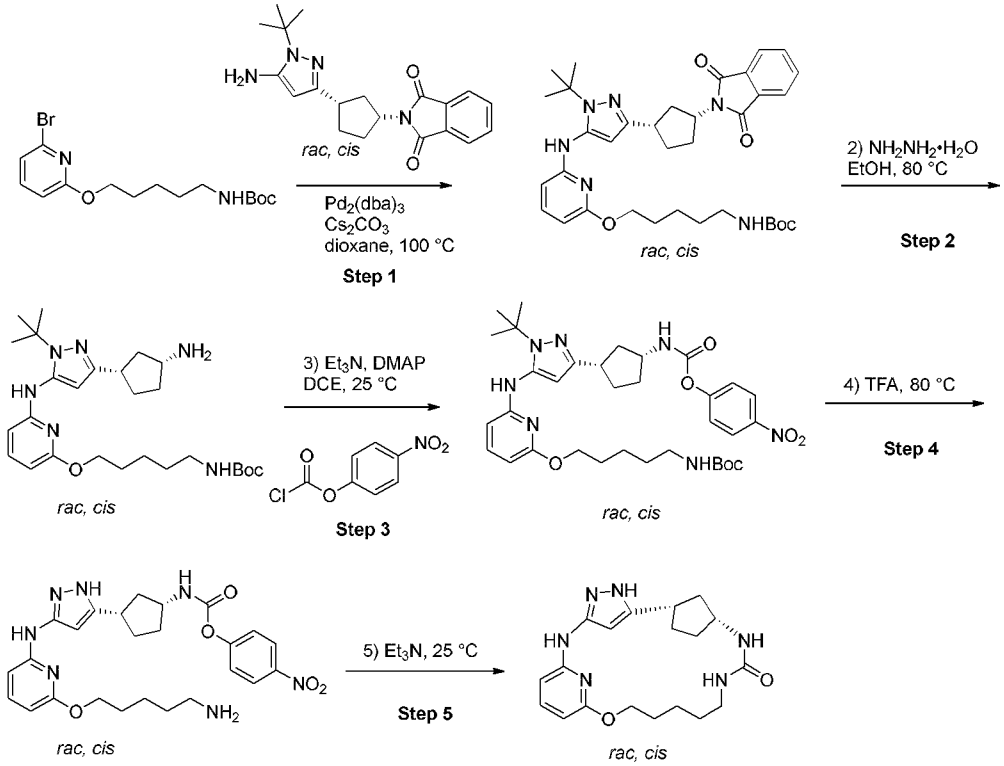
Step 5: (*rac, cis*)-2[1]H-5-oxa-3,10,12-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution of (*rac, cis*)-(4-nitrophenyl) N-[3-[3-[[6-(4-aminobutoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl]carbamate (35 mg, 0.071 mmol) in acetonitrile (10 mL) was added N,N-diethylethanamine (14.3 mg, 19.8 μL, 0.141 mmol) at 25 °C. The resulting mixture was stirred at that temperature for 2 h before it was concentrated under reduced pressure. The residue was purified by Pre-HPLC eluting with CH_3CN in water with CH_3CN from 5% to 95% in 9 min to give (*rac, cis*)-2[1]H-5-oxa-3,10,12-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (5.0 mg, 20% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.13 (s, 1H), 7.34 (t,

J = 7.9 Hz, 1H), 6.56 (s, 1H), 6.30 (d, *J* = 7.9 Hz, 1H), 5.98 (d, *J* = 7.7 Hz, 1H), 5.90 – 5.78 (m, 2H), 4.38 (d, *J* = 9.6 Hz, 1H), 4.14 – 4.03 (m, 1H), 4.01 – 3.88 (m, 1H), 3.13 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.82 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.37 – 2.23 (m, 1H), 1.97 – 1.87 (m, 1H), 1.86 – 1.64 (m, 5H), 1.60 – 1.47 (m, 3H). LC-MS: m/z 357.8 $[M+H]^+$.

Example 12

(*rac, cis*)- 2[1]H-5-oxa-3,11,13-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one



Step 1: (*rac, cis*)- tert-butyl (5-((6-((1-(tert-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)pentyl)carbamate

To a Biotage pressure tube were sequentially added tert-butyl N-[5-[(6-bromo-2-pyridyl)oxy]pentyl]carbamate (224 mg, 0.624 mmol), (*rac, cis*)-2-[3-(5-amino-2-tert-butyl-pyrazol-3-yl)cyclopentyl]isoindoline-1,3-dione (200 mg, 0.567 mmol), Cs_2CO_3 (370 mg, 1.13 mmol), $Pd_2(dba)_3$ (26.0 mg, 0.0284 mmol), Xantphos (32.8 mg, 0.0568 mmol) and 1,4-dioxane (6.0 mL) at 25 °C. The mixture was bubbled with N_2 for 10 mins before it was sealed and warmed to 100 °C and stirred at that temperature for 6 h. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 100% in 20 min to give (*rac, cis*)-tert-butyl N-[5-[[6-[[1-tert-butyl-5-[3-(1,3-dioxoisoindolin-2-yl)cyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]carbamate (310 mg, 87% yield) as a brown oil. LC-MS: m/z 631.8 $[M+H]^+$.

Step 2: (*rac, cis*)-tert-butyl (5-(((6-((3-(3-aminocyclopentyl)-1-(tert-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)pentyl)carbamate

To a stirred solution of (*rac, cis*)-tert-butyl N-[5-[[6-[[1-tert-butyl-5-[3-(1,3-dioxoisoindolin-2-yl)cyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]carbamate (300 mg, 0.476 mmol) in Ethanol (5.0 mL) was added hydrazine hydrate (89.3 mg, 86.7 μL, 1.43 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 3 h. The reaction mixture was cooled to 25 °C, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 with MeOH from 0 to 20% in 20 min to give (*rac, cis*)-tert-butyl N-[5-[[6-[[5-[3-aminocyclopentyl]-1-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]carbamate (220 mg, 92% yield) as a colorless oil. LC-MS: m/z 501.9 $[M+H]^+$.

Step 3: (*rac, cis*)- 4-nitrophenyl (3-(5-(((6-((5-((tert-butoxycarbonyl)amino)pentyl)oxy)pyridin-2-yl)amino)-1-(tert-butyl)-1H-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of (*rac, cis*)-tert-butyl N-[5-[[6-[[5-[3-aminocyclopentyl]-1-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]carbamate (108 mg, 0.216 mmol) in dichloromethane (10 mL) were sequentially added (4-nitrophenyl) carbonochloridate (65.2 mg, 0.324 mmol), Et_3N (65.5 mg, 90.2 μL, 0.647 mmol) and DMAP (65.5 mg, 0.647 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 8 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL). The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 75 % in 20 min to give (*rac, cis*)-(4-nitrophenyl) N-[3-[5-[[6-[5-(tert-butoxycarbonylamino)pentoxy]-2-pyridyl]amino]-2-tert-butyl-pyrazol-3-yl]cyclopentyl]carbamate (110 mg, 77% yield) as a color oil. LC-MS: m/z 666.8 $[M+H]^+$.

Step 4: (*rac, cis*)-4-nitrophenyl (3-(3-((6-((5-aminopentyl)oxy)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl)carbamate

To a Biotage pressure tube were sequentially added (*rac, cis*)-(4-nitrophenyl) N-[3-[5-[[6-[5-(tert-butoxycarbonylamino)pentoxy]-2-pyridyl]amino]-2-tert-butyl-pyrazol-3-yl]cyclopentyl]carbamate (110 mg, 0.165 mmol)and TFA (10 mL) at 25 °C. The mixture was sealed, warmed to 80 °C under microwave and stirred at that temperature for 30 min. The mixture was cooled to 25 °C and concentrated under reduced pressure to give (*rac, cis*)-(4-nitrophenyl) N-[3-[3-[[6-(5-aminopentoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl]carbamate (84.0 mg, 0.165 mmol, 99% yield) as a colorless oil which was used directly in the next step without further purification.LC-MS: m/z 510.8 $[M+H]^+$.

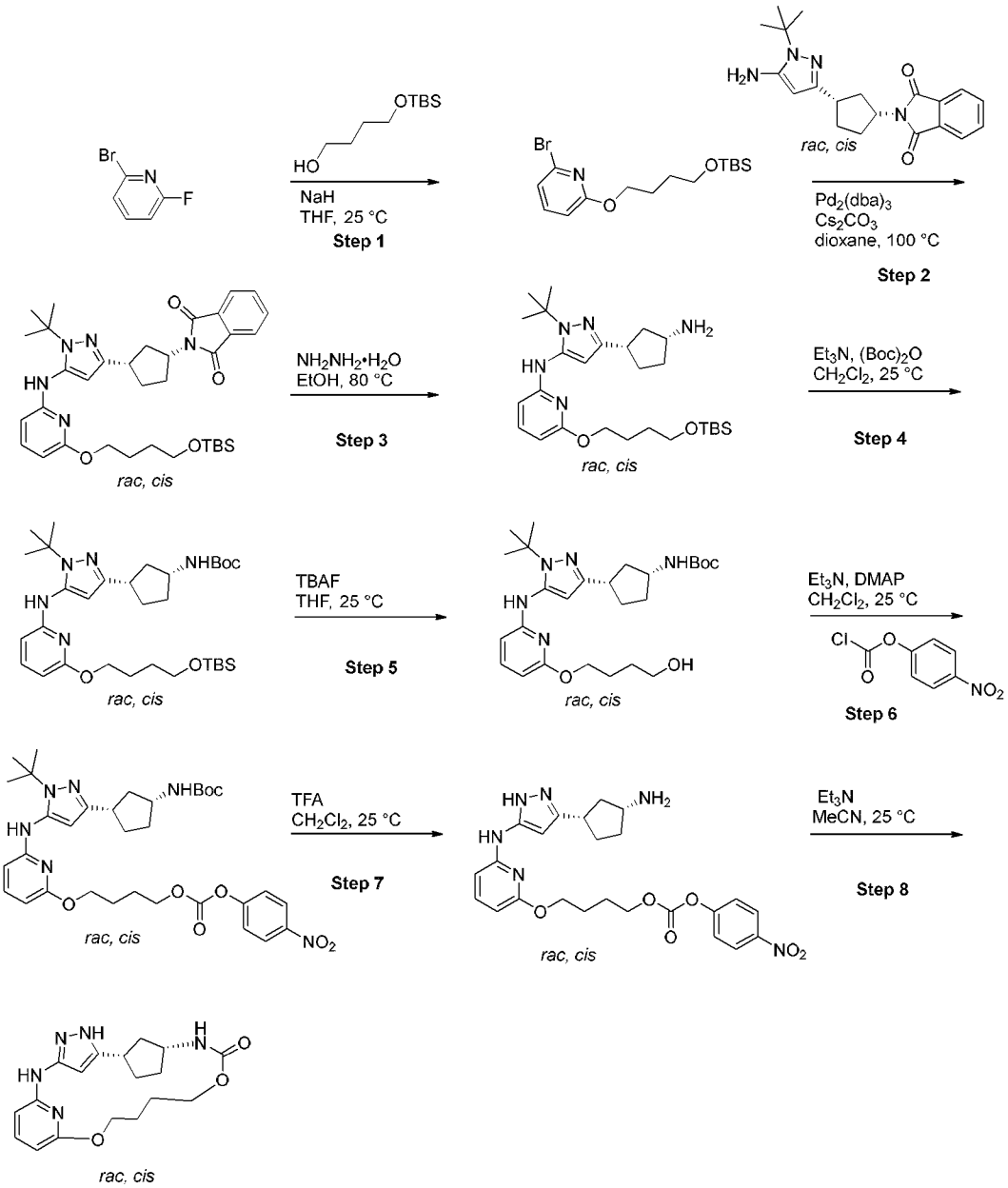
Step 5: (*rac, cis*)- 2^{1}H-5-oxa-3,11,13-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one

To a stirred solution of (*rac, cis*)- (4-nitrophenyl) N-[3-[3-[[6-(5-aminopentoxy)-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl]carbamate (84 mg, 0.165 mmol) in acetonitrile (10 mL) was added Et_3N (16.7 mg, 23.0 μL, 165 mmol) at 25 °C. The resulting mixture was stirred at that temperature for 2 h

before it was concentrated under reduced pressure. The residue was purified by Pre-HPLC eluting with CH_3CN in water with CH_3CN from 5% to 95% in 9 min to give (*rac, cis*)-2[1]H-5-oxa-3,11,13-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (18.5 mg, 30% yield) as a white solid. LC-MS: m/z 371.9 $[M+H]^+$.

Example 13

***(rac, cis)*- 2[1]H-5,10-dioxa-3,12-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one**



Step 1: 2-bromo-6-(4-((tert-butyldimethylsilyl)oxy)butoxy)pyridine

To a stirred solution of 4-[tert-butyl(dimethyl)silyl]oxybutan-1-ol (1.05 g, 5.14 mmol) in THF (20.0 mL) were sequentially added sodium hydride (256 mg, 6.68 mmol, 60% wt.) and 2-bromo-6-fluoro-pyridine (994 mg, 5.65 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 10 min before it was warmed to 50 °C and stirred at that temperature for 4 h. The reaction mixture was cooled to 25 °C, quenched with saturated aq. NH_4Cl (30 mL) and extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 50%) in 20 min to give 4-[(6-bromo-2-pyridyl)oxy]butoxy-tert-butyl-dimethyl-silane (1.51 g, 82% yield) as a yellow oil. LC-MS: m/z 359 .8 $[M+H]^+$.

Step 2: *(rac, cis)*-2-((1R,3S)-3-(1-(tert-butyl)-5-((6-(4-((tert-butyldimethylsilyl)oxy)butoxy)pyridin-2-yl)amino)-1H-pyrazol-3-yl)cyclopentyl)isoindoline-1,3-dione

To a Biotage pressure tube were sequentially added 4-[(6-bromo-2-pyridyl)oxy]butoxy-tert-butyl-dimethyl-silane (225 mg, 0.624 mmol), *(rac, cis)*-2-[3-(5-amino-1-tert-butyl-pyrazol-3-yl)cyclopentyl]isoindoline-1,3-dione (200 mg, 0.567 mmol), Cs_2CO_3 (370 mg, 1.13 mmol), $Pd_2(dba)_3$ (26.0 mg, 0.0284 mmol), Xantphos (32.8 mg, 0.0568 mmol) and 1,4-dioxane (6.0 mL) at 25 °C. The mixture was bubbled with N_2 for 10 min before it was sealed and warmed to 100 °C and stirred at that temperature for 6 h. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 100% in 20 min to give *(rac, cis)*-2-[3-[1-tert-butyl-5-[[6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]isoindoline-1,3-dione (285 mg, 79% yield) as a brown oil. LC-MS: m/z 632.8 $[M+H]^+$.

Step 3: (rac, cis)- N-(3-((3-aminocyclopentyl)-1-(tert-butyl)-1H-pyrazol-5-yl)-6-(4-((tert-butyldimethylsilyl)oxy)butoxy)pyridin-2-amine

To a stirred solution of *(rac, cis)*-2-[3-[1-tert-butyl-5-[[6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]isoindoline-1,3-dione (285 mg, 0.451 mmol) in Ethanol (10 mL) was added hydrazine hydrate (84.7 mg, 82.2 µL, 1.35 mmol) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 3 h before it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 containing 1% Et_3N (with MeOH from 1% to 10%) in 20 min to give *(rac, cis)*-N-[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]-6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]pyridin-2-amine (200 mg, 88% yield) as a colorless oil. LC-MS: m/z 502.9 $[M+H]^+$.

Step 4: *(rac, cis)*- tert-butyl (3-(1-(tert-butyl)-5-((6-(4-((tert-butyldimethylsilyl)oxy)butoxy)pyridin-2-yl)amino)-1H-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of *(rac, cis)*-N-[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]-6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]pyridin-2-amine (200 mg, 0.399 mmol) in CH_2Cl_2 (5.0 mL) were sequentially added Et_3N (121mg, 167 μL, 1.20 mmol), $(Boc)_2O$ (130mg, 137 μL, 598 mmol) at 25 °C. The mixture was stirred at that temperature for 3 h before it was quenched with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 100%) in 20 min to give *(rac, cis)*- tert-butyl N-[3-[1-tert-butyl-5-[[6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (220 mg, 92% yield) as a colorless oil. LC-MS: m/z 601.9 $[M+H]^+$.

Step 5: *(rac, cis)*-tert-butyl (3-(1-(tert-butyl)-5-((6-(4-hydroxybutoxy)pyridin-2-yl)amino)-1H-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of *(rac, cis)*-tert-butyl N-[3-[1-tert-butyl-5-[[6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (220 mg, 0.366 mmol) in THF (1.0 mL) was added TBAF (731 μL, 1.0 M, 0.731 mmol) at 25 °C. The mixture was stirred at that temperature for 2 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL) and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 100%) in 20 min to give *(rac, cis)*-tert-butyl N-[3-[1-tert-butyl-5-[[6-(4-hydroxybutoxy)-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (168 mg, 0.345 mmol, 94% yield) as a colorless oil. LC-MS: m/z 488.9 $[M+H]^+$.

Step 6: (rac, cis)- tert-butyl (3-(1-(tert-butyl)-5-((6-(4-(((4-nitrophenoxy)carbonyl)oxy)butoxy)pyridin-2-yl)amino)-1H-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of *(rac, cis)*-tert-butyl N-[3-[1-tert-butyl-5-[[6-(4-hydroxybutoxy)-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (100 mg, 0.205 mmol) were sequentially added (4-nitrophenyl) carbonochloridate (124 mg, 0.615 mmol), Et_3N (125 mg, 171 μL, 1.23 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 8 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL). The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 75 % in 20 min to give *(rac, cis)*-4-[[6-[[5-[3-(tert-butoxycarbonylamino)cyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl (4-nitrophenyl) carbonate (80.0 mg, 60% yield) as a color oil. LC-MS: m/z 653.8 $[M+H]^+$.

Step 7: (rac, cis)- 4-((6-((3-(3-aminocyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl (4-nitrophenyl) carbonate

To a Biotage pressure tube were sequentially added *(rac, cis)*-4-[[6-[[5-[3-(tert-butoxycarbonylamino)cyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl (4-nitrophenyl) carbonate (50.0 mg, 0.766 mmol) and TFA (5.0 mL) at 25 °C. The mixture was sealed,

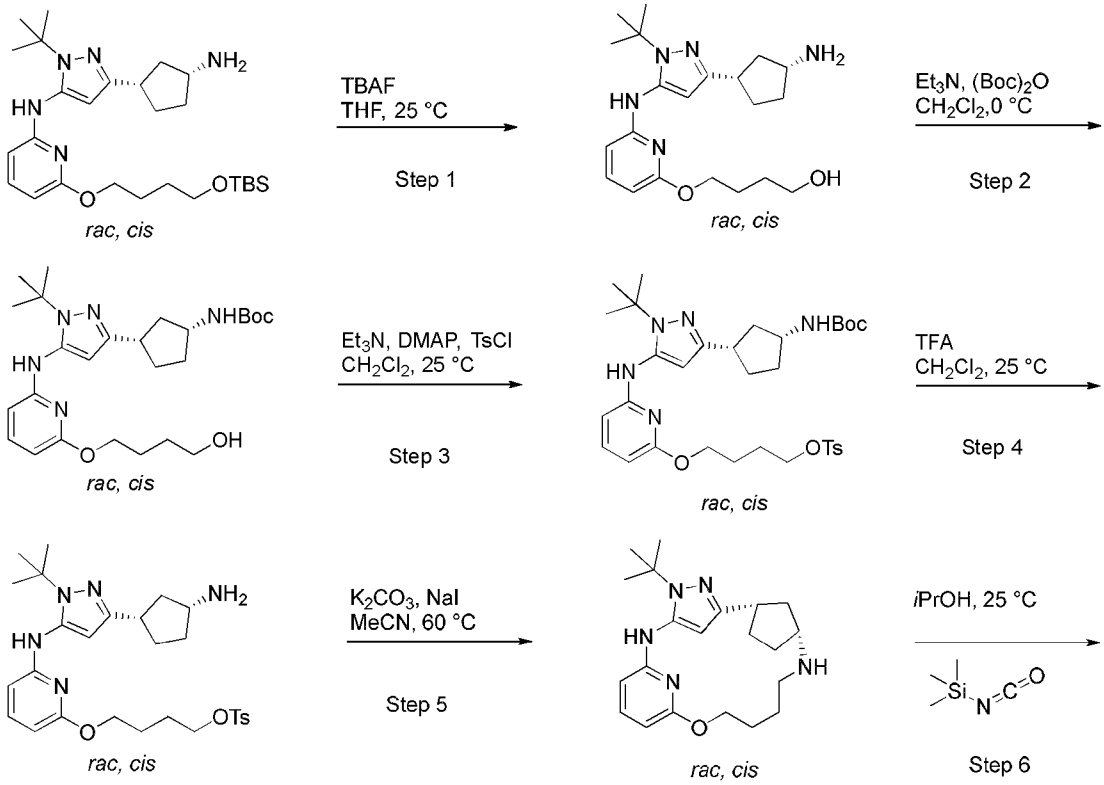
warmed to 80 °C under microwave and stirred at that temperature for 30 min. The mixture was cooled to 25 °C and concentrated under reduced pressure to give *(rac, cis)*-4-[[6-[[5-[3-aminocyclopentyl]-1H-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl (4-nitrophenyl) carbonate (37.0 mg, 97% yield) as a colorless oil which was used directly in the next step without further purification. LC-MS: m/z 497.8 $[M+H]^+$.

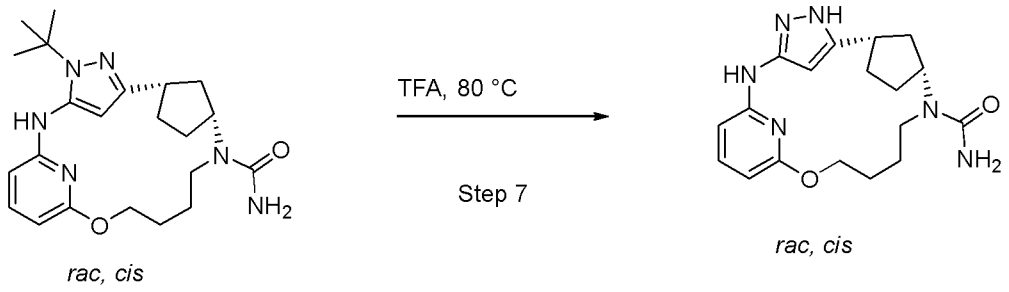
Step 8: *(rac, cis)*- 2[1]H-5,10-dioxa-3,12-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution of *(rac, cis)*-4-[[6-[[3-[3-aminocyclopentyl]-1H-pyrazol-5-yl]amino]-2-pyridyl]oxy]butyl (4-nitrophenyl) carbonate (37.0 mg, 0.0745 mmol) in acetonitrile (3.0 mL) was added Et_3N (75.4 mg, 104 μL, 0.745 mmol) at 25 °C. The resulting mixture was stirred at that temperature for 2 h before it was concentrated under reduced pressure. The residue was purified by Pre-HPLC eluting with CH_3CN in water with CH_3CN from 5% to 95% in 9 min to give *(rac, cis)* - 2[1]H-5,10-dioxa-3,12-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (3.5 mg,13% yield) as a white solid. LC-MS: m/z 358.9 $[M+H]^+$.

Example 202

(*rac, cis*) -2[1]H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamide





Step 1: (*rac, cis*)- 4-((6-((3-((3-aminocyclopentyl)-1-(tert-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butan-1-ol

To a stirred solution of (*rac, cis*)-N-[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]-6-[4-[tert-butyl(dimethyl)silyl]oxybutoxy]pyridin-2-amine (100 mg, 0.199 mmol) in THF (2.0 mL) was added TBAF (598 μL, 1.0 M in THF, 0.598 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with $MeOH/CH_2Cl_2$ containing 1% Et_3N (with MeOH from 0 to 10%) in 20 min to give to (*rac, cis*)-4-[[6-[[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butan-1-ol (65.0 mg, 84% yield) as a colorless oil. LC-MS: m/z 388.9 $[M+H]^+$.

Step 2: (rac, cis)-tert-butyl (3-(1-(tert-butyl)-5-((6-(4-hydroxybutoxy)pyridin-2-yl)amino)-1H-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of (*rac, cis*)-4-[[6-[[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butan-1-ol (55.0 mg, 0.142 mmol) in CH_2Cl_2 (3.0 mL) were sequentially added Et_3N (79 μL, 57.5 mg, 0.568 mmol), $(Boc)_2O$ (65 μL, 62.0 mg, 0.284 mmol) at 0 °C. The mixture was stirred at that temperature for 1 h before it was quenched with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 100%) in 20 min to give (*rac, cis*)-tert-butyl N-[3-[1-tert-butyl-5-[[6-(4-hydroxybutoxy)-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (61.0 mg, 88 yield) as a colorless oil. LC-MS: m/z 488.9 $[M+H]^+$.

Step 3: (rac, cis)-4-((6-((3-(3-((tert-butoxycarbonyl)amino)cyclopentyl)-1-(tert-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl 4-methylbenzenesulfonate

To a stirred solution of (*rac, cis*)-tert-butyl N-[3-[1-tert-butyl-5-[[6-(4-hydroxybutoxy)-2-pyridyl]amino]pyrazol-3-yl]cyclopentyl]carbamate (61.0 mg, 0.125 mmol) in CH_2Cl_2 (5.0 mL) were sequentially added Et_3N (52 μL, 38.0 mg, 0.375 mmol), TsCl (35.8 mg, 0.188 mmol) and DMAP (1.5 mg, 0.013 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 3 h before it was quenched with saturated aq. $NaHCO_3$ (0.1 mL) and concentrated under reduced pressure. The

residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 100%) in 20 min to (*rac, cis*)-4-[[6-[[5-[3-(tert-butoxycarbonylamino)cyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl 4-methylbenzenesulfonate (66.0 mg, 82 % yield) as a white solid. LC-MS: m/z 642.8 $[M+H]^+$.

Step 4: (rac, cis)- 4-((6-((3-(3-aminocyclopentyl)-1-(tert-butyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)oxy)butyl 4-methylbenzenesulfonate

To a stirred solution of (*rac, cis*)-4-[[6-[[5-[3-(tert-butoxycarbonylamino)cyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl 4-methylbenzenesulfonate (66.0 mg, 0.103 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (396 μL, 586 mg, 5.14 mmol) at 25 °C. The mixture was stirred at that temperature for 3 h before it was concentrated under reduced pressure to give (*rac, cis*)-4-[[6-[[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl 4-methylbenzenesulfonate (55.0 mg, 99 % yield) as a colorless oil which was used in the next step without further purification. LC-MS: m/z 542.8 $[M+H]^+$.

Step 5: (rac, cis)-tert-butyl-21H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane

To a stirred solution of (*rac, cis*)-4-[[6-[[5-[3-aminocyclopentyl]-2-tert-butyl-pyrazol-3-yl]amino]-2-pyridyl]oxy]butyl 4-methylbenzenesulfonate (50 mg, 92.30 umol) in MeCN (10 mL) were sequentially added K_2CO_3 (54.9 mg, 0.554 mmol) and NaI (4.2 mg, 0.028 mmol) at 25 °C. The reaction mixture was warmed to 60 °C and stirred at that temperature for 8 h. The reaction mixture was cooled to 25 °C, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 containing 1% Et_3N (with MeOH from 0 to 10%) in 20 min to give (*rac, cis*)-tert-butyl-2[1]H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane (30.0 mg, 88% yield) as a colorless oil. LC-MS: m/z 370.9 $[M+H]^+$.

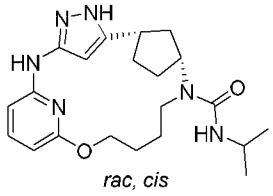
Step 6: (rac, cis)-21-(tert-butyl)-21H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamide

To a stirred solution of (*rac, cis*)-tert-butyl-2[1]H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane (30.0 mg, 0.0812 mmol) in *i*PrOH (3.0 mL) was added isocyanato(trimethyl)silane (55 μL, 46.8 mg, 0.406 mmol) at 25 °C. The mixture was stirred at that temperature for 12 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 100%) in 20 min to give (*rac, cis*)-21-(tert-butyl)-2[1]H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamid (31.0 mg, 93% yield) as a white solid. LC-MS: m/z 413.9 $[M+H]^+$.

Step 7: (rac, cis) -21H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamide

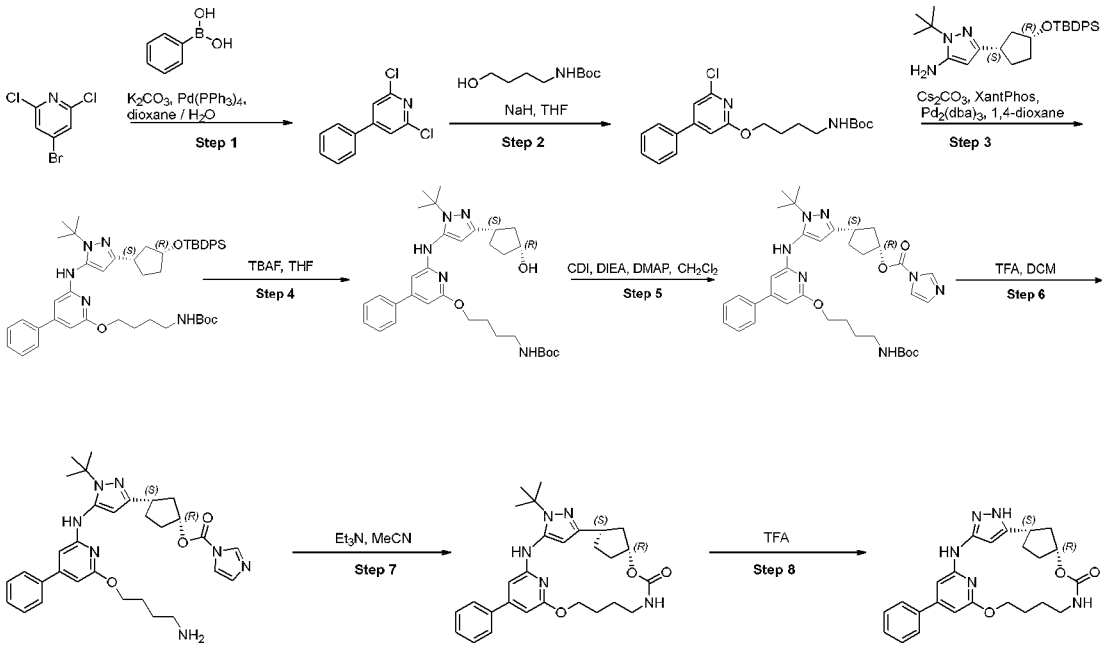
To a Biotage pressure tube were sequentially added (*rac, cis*)-2[1]-(tert-butyl)-21H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamid (31.0 mg, 0.0752 mmol) and TFA (3.0 mL) at 25 °C. The mixture was sealed and warmed to 80 °C by microwave radiation and stirred at that temperature for 30 min. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Pre-HPLC eluting with CH_3CN in water with CH_3CN from 5% to 95% in 10 min to give (*rac, cis*) -2[1]H-5-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphane-10-carboxamide (5.0 mg, 19% yield) as a white solid. LC-MS: m/z 357.9 $[M+H]^+$.

The following compounds were prepared using the similar procedure disclosed in synthetic example **202**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
203	 *rac, cis*	399.8

Example 14

(*1[1]S,1[3]R,Z*)-4[4]-phenyl-*2[1]H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 2,6-dichloro-4-phenyl-pyridine

To a stirred solution of 4-bromo-2,6-dichloro-pyridine (5.00 g, 22.04 mmol) in 1,4-dioxane (75.0 mL) and H_2O (15.0 mL) were sequentially added phenylboronic acid (2.96 g, 24.24 mmol), Pd $(PPh_3)_4$ (2.55 g, 2.20 mmol) and K_2CO_3 (4.57 g, 33.06 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 2 h before it was cooled to 25 °C and concentrated under reduced pressure. The reaction mixture was filtered through a pad of Celite with EtOAc (100 mL), and the combined organic phases were concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with DCM/PE (with DCM from 0 to 25% in 25 min) to give 2,6-dichloro-4-phenyl-pyridine (2.37 g, 48 % yield) as an off-white solid. LC-MS: m/z $[M+H]^+$ 224.1.

Step 2: *tert*-butyl (4-((6-chloro-4-phenylpyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of *tert*-butyl *N*-(4-hydroxybutyl)carbamate (802 mg, 4.24 mmol) in THF (15.0 mL) was added NaH (535 mg, 13.39 mmol, 60 wt.% in mineral oil) at 0 °C. The reaction mixture was stirred at that temperature for 30 min before 2,6-dichloro-4-phenyl-pyridine (1.00 g, 4.46 mmol) in THF (5.0 mL) was added at that temperature. The reaction mixture was warmed to 60 °C and stirred at that temperature for 2 h before it was concentrated under reduced pressure, purified by silica gel chromatography eluting with EtOAc /PE (with EtOAc from 0 to 25% in 25 min) to give *tert*-butyl (4-((6-chloro-4-phenylpyridin-2-yl)oxy)butyl)carbamate (700 mg, 42 % yield) as a colourless oil. LC-MS: m/z $[M+H]^+$ 377.2.

Step 3: *tert*-butyl (4-((6-((1-(tert-butyl)-3-((*1S,3R*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of *tert*-butyl (4-((6-chloro-4-phenylpyridin-2-yl)oxy)butyl)carbamate (100 mg, 265 μmol) were sequentially added 2-*tert*-butyl-5-[(*1S,3R*)-3-[*tert*-butyl(diphenyl)silyl]oxycyclopentyl]pyrazol-3-amine (98.0 mg, 212 μmol), XantPhos Pd G_3 (18.5 mg, 53.1 μmol) and Cs_2CO_3 (173 mg, 531 μmol) in 1,4-dioxane (4.0 mL) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 2 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with DCM /PE (with DCM from 0 to 15% in 15 min) to give *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-yl)oxy)butyl)carbamate (107 mg, 50 % yield) as a light yellow oil. LC-MS: m/z $[M+H]^+$ 801.7.

Step 4: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-

yl)oxy)butyl)carbamate (107 mg, 133.40 μmol) in THF (3.0 mL) was added TBAF (115 μL, 105 mg, 400 μmol, 1M in THF) at 25 °C. The resulting mixture was stirred at that temperature for 16 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 25 min) to give *tert*-butyl (4-((6-((1-(tert-butyl)-3-((*1S*,*3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-yl)oxy)butyl)carbamate (50 mg, 66 % yield) as a pale yellow solid. LC-MS: m/z $[M+H]^+$ 564.4.

Step 5: (*1R*,*3S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (4-((6-((1-(tert-butyl)-3-((*1S*,*3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-phenylpyridin-2-yl)oxy)butyl)carbamate (45.0 mg, 80 μmol) in DCM (1.0 mL) were sequentially added DMAP (5.0 mg, 40 μmol) , di(imidazol-1-yl)methanone (65.0 mg, 400 μmol) and *N*-ethyl-*N*-isopropyl-propan-2-amine (70 μL, 52.0 mg, 400 μmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/ DCM (with EtOAc from 0 to 30% in 20 min) to give (*1R*,*3S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (34 mg, 65 % yield) as a pale yellow solid. LC-MS: m/z $[M+H]^+$ 657.8.

Step 6: (*1R*,*3S*)-3-(5-((6-(4-aminobutoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a stirred solution of (*1R*,*3S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (34.0 mg, 52 μmol) in DCM (1.0 mL) was added TFA (39.8 μL, 58.9 mg, 517 μmol) at 25 °C. The reaction mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to afford (*1R*,*3S*)-3-(5-((6-(4-aminobutoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (28 mg, 97% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 558.3.

Step 7: (*1*^{1}*S*,*1*^{3}*R*,*Z*)-2^1-(*tert*-butyl)-4^4-phenyl-*2*^{1}*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

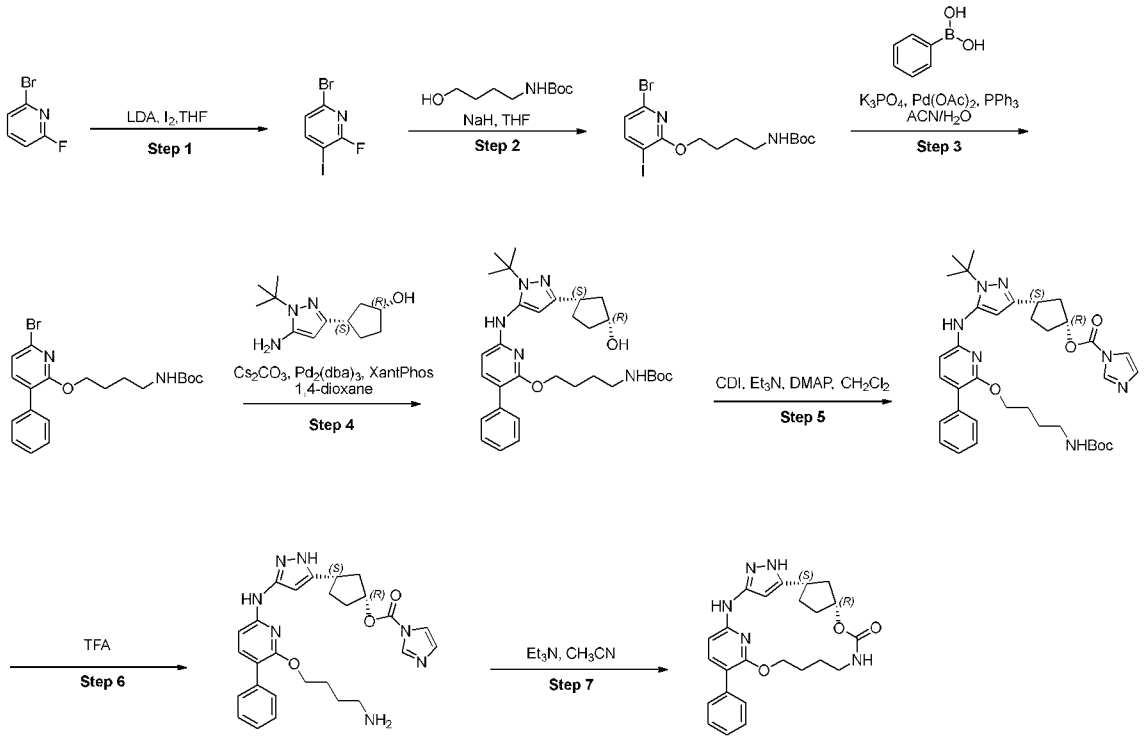
To a stirred solution of (*1R*,*3S*)-3-(5-((6-(4-aminobutoxy)-4-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (28.0 mg, 50.0 μmol) in CH_3CN (20.0 mL) was added Et_3N (7 μL, 5.0 mg, 50 μmol) at 25 °C. The reaction mixture was warmed to 70 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 20 min) to give (*1*^{1}*S*,*1*^{3}*R*,*Z*)-2^1-(*tert*-butyl)-4^4-phenyl-*2*^{1}*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (13 mg, 53% yield) as a light yellow solid. LC-MS: m/z $[M+H]^+$ 489.9.

Step 8: ($1^1S,1^3R,Z$)-4^4-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A stirred solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (13 mg, 27 μmol) in TFA (2.0 mL) was warmed to 70 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 60% in 50 min) to ($1^1S,1^3R,Z$)-4^4-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.3 mg, 10 μmol, 37 % yield) as a light pink solid. LC-MS: m/z $[M+H]^+$ 434.2.

Example 15

($1^1S,1^3R,Z$)-4^5-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 6-bromo-2-fluoro-3-iodopyridine

To a stirred solution of 2-bromo-6-fluoro-pyridine (10.0 g, 56.8 mmol, 5.86 mL) in THF (80.0 mL) was added LDA (31.3 mL, 6.70 g, 62.5 mmol, 2.0 M) slowly at -78 °C under N_2 atmosphere and the resulting mixture was stirred for 1 hours at that time before a solution of I_2 (14.4 g, 56.8 mmol) in THF (80.0 mL) was added slowly at - 78 °C. The reaction mixture was warmed to - 60 °C within 1.5 h before it was quenched with a saturated aqueous of $Na_2S_2O_3$ (100 mL) at - 60 °C. The reaction mixture was warmed to 25 °C and extracted with EtOAc (200 mL × 2). The combined organic layers

were washed with brine (200 mL) and dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 15 min) to afford 6-bromo-2-fluoro-3-iodopyridine (11.3 g, 66% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 302.3.

Step 2: *tert*-butyl (4-((6-bromo-3-iodopyridin-2-yl)oxy)butyl)carbamate

To a solution of *tert*-butyl *N*-(4-hydroxybutyl)carbamate (627 mg, 3.31 mmol) in THF (20.0 mL) was added NaH (265 mg, 60 wt.% in mineral oil, 6.63 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min before 6-bromo-2-fluoro-3-iodo-pyridine (1.0 g, 3.31 mmol) was added at 0 °C. The reaction mixture was warmed to 25 °C and stirred at that temperature for 16 h before it was poured into saturated aqueous of NH_4Cl (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15% in 20 min) to afford *tert*-butyl (4-((6-bromo-3-iodopyridin-2-yl)oxy)butyl)carbamate (900 mg, 58 % yield) as a white solid. LC-MS: m/z $[M+H]^+$ 414.5, 416.5.

Step 3: *tert*-butyl (4-((6-bromo-3-phenylpyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of *tert*-butyl (4-((6-bromo-3-iodopyridin-2-yl)oxy)butyl)carbamate (450 mg, 955 μmol) and phenylboronic acid (175 mg, 1.43 mmol) in CH_3CN (6.0 mL) and H_2O (1.0 mL) were sequentially added K_3PO_4 (405 mg, 1.91 mmol), PPh_3 (50.1 mg, 191 μmol) and $Pd(OAc)_2$ (21.4 mg, 95.5 μmol) at 25 °C. The mixture was warmed to 55 °C and stirred at that temperature for 16 h under N_2 before it was cooled to 25 °C. The reaction mixture was concentrated under reduced pressure and purified by flash silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10% in 15 min) to give *tert*-butyl (4-((6-bromo-3-phenylpyridin-2-yl)oxy)butyl) carbamate (230 mg, 57% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 421.9.

Step 4: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-phenylpyridin-2-yl)oxy)butyl)carbamate

To a stirred solution of *tert*-butyl (4-((6-bromo-3-phenylpyridin-2-yl)oxy)butyl) carbamate (396 mg, 940 μmol), (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (140 mg, 627 μmol) and Cs_2CO_3 (408 mg, 1.25 mmol) in 1,4 - dioxane (10.0 mL) were sequentially added $Pd_2(dba)_3$ (57.4 mg, 62.7 μmol) and XantPhos (36.3 mg, 62.7 μmol) at 25 °C. The reaction mixture was warmed up to 80 °C and stirred at that temperature for 16 h under N_2 before it was cooled to 25 °C, the mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 25 min) to afford *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-

hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-phenylpyridin-2-yl)oxy)butyl)carbamate (230 mg, 65% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 564.3.

Step 5: (1*R*,3*S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-5-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-phenylpyridin-2-yl)oxy)butyl)carbamate (200 mg, 355 μmol) in CH_2Cl_2 (3.0 mL) were sequentially added CDI (173 mg, 1.06 mmol), DMAP (4.33 mg, 35.5 μmol) and DIPEA (247 μL, 179 mg, 1.77 mmol) at 25 °C. The mixture was warmed to 35 °C and stirred at that temperature for 2 h before it was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to give (1*R*,3*S*)-3-(5-((6-(4-((tert-butoxycarbonyl)amino)butoxy)-5-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, 86% yield) as yellow oil which was directly used to the next step without any further purification. LC-MS: m/z $[M+H]^+$ 658.3.

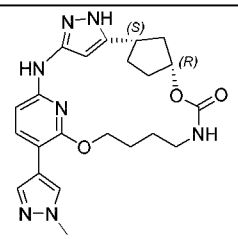
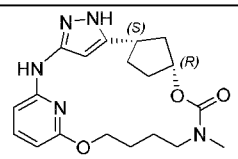
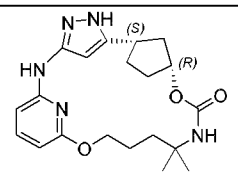
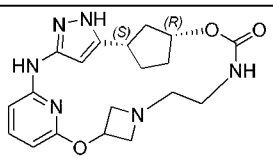
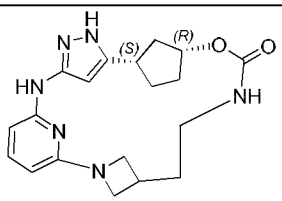
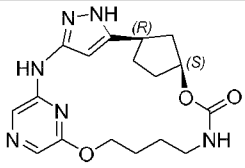
Step 6: (*1R,3S*)-3-(3-((6-(4-aminobutoxy)-5-phenylpyridin-2-yl)amino)-*1H*-pyrazol-5-yl)cyclopentyl *1H*-imidazole-1-carboxylate

A stirred solution of (1*R*,3*S*)-3-(5-((6-(4-((tert-butoxycarbonyl)amino)butoxy)-5-phenylpyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentyl *1H*-imidazole-1-carboxylate (200 mg, 304 μmol) in TFA (2.0 mL) was warmed to 70 °C and stirred at that temperature for 2 h before it was cooled to 25 °C. The mixture was concentrated under reduced pressure to give (1*R*,3*S*)-3-(3-((6-(4-aminobutoxy)-5-phenylpyridin-2-yl)amino)-*1H*-pyrazol-5-yl)cyclopentyl *1H*-imidazole-1-carboxylate (150 mg) as yellow oil which was directly used to the next step without any further purification. LC-MS: m/z $[M+H]^+$ 502.

Step 7: (1^1S,1^3R,*Z*)-4^5-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

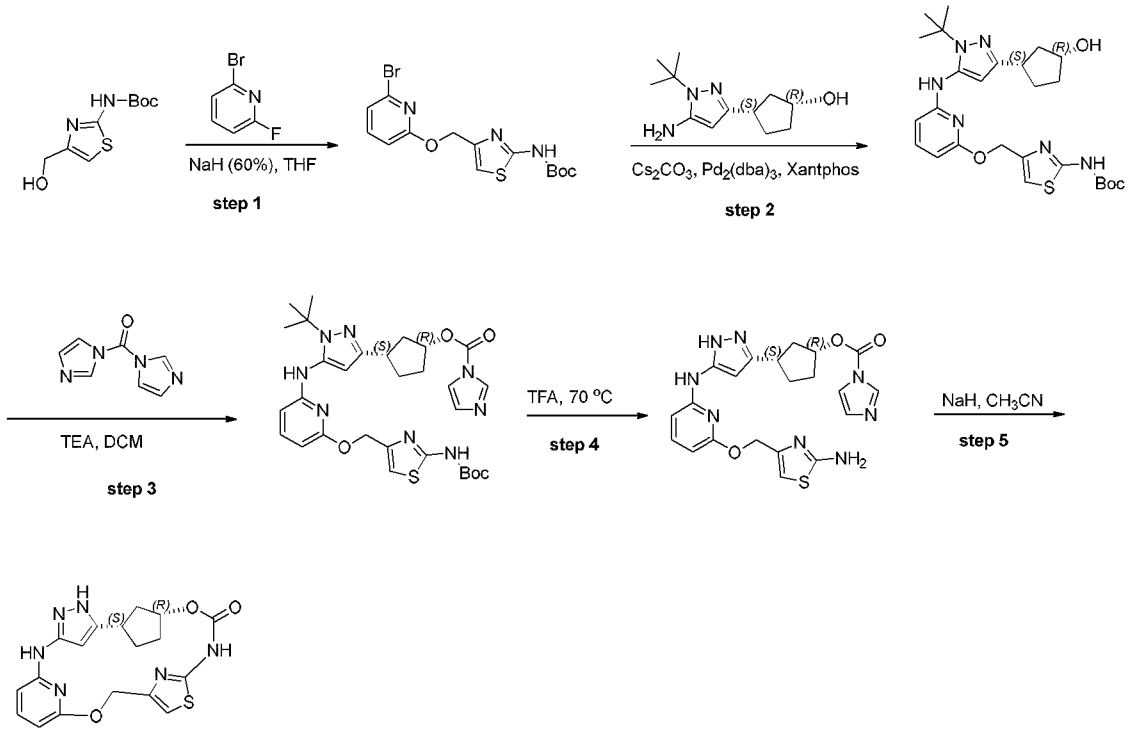
To a stirred solution of (1*R*,3*S*)-3-(3-((6-(4-aminobutoxy)-5-phenylpyridin-2-yl)amino)-1*H*-pyrazol-5-yl) cyclopentyl 1*H*-imidazole-1-carboxylate (150 mg, 299 μmol) in CH_3CN (1.0 mL) was added Et_3N (0.1 mL) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 5 h before it was cooled to 25 °C. The mixture was concentrated under reduced pressure and purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 40% in 40 min) to afford (1^1S,1^3R,*Z*)-4^5-phenyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (40.1 mg, 31% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 434.2.

The following compounds were prepared using the similar procedure disclosed in synthetic example **15**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
16		438.1
17		372.1
18		385.9
175		385.2
176		369.1
177		359.4

Example **19**

(1^1*S*,1^3*R*,2^4*Z*,7^2*Z*)-2$_1$H-5,10-dioxa-3,8-diaza-7(4,2)-thiazola-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphan-9-one



Step 1: *tert*-butyl (4-(((6-bromopyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate

To a solution of *tert*-butyl (4-(hydroxymethyl)thiazol-2-yl)carbamate (1.0 g, 4.34 mmol) in THF (20 mL) was added NaH (869 mg, 21.7 mmol, 60% purity) at 0 °C, the mixture was stirred at 0 °C for 30 min, 2-bromo-6-fluoro-pyridine (1.15 g, 6.51 mmol) was added, the mixture was warmed to 25 °C and stirred at this temperature for 16 h.

The mixture was quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 25 min) to afford tert-butyl (4-(((6-bromopyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate (1.46 g, 87% yield) as a colorless oil. LC-MS: (ESI) m/z 386.0 $[M+H]^+$.

Step 2: *tert*-butyl (4-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate

To a mixture of *tert*-butyl (4-(((6-bromopyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate (300 mg, 0.78 mmol) and (1*R*,3*S*)-3-(5-amino-1-tert-butyl-pyrazol-3-yl)cyclopentanol (173 mg, 0.78 mmol) in 1,4-dioxane (10 mL) was added Pd_2dba_3 (142 mg, 0.155 mmol), Xantphos (180 mg, 0.31 mmol) and Cs_2CO_3 (632 mg, 1.94 mmol) at 25 °C under nitrogen. The reaction was warmed to 90 °C and stirred at this temperature for 6 h. The mixture was cooled to 25 °C and was diluted with water (150 mL), the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60% in 25 min) to afford *tert*-butyl

(4-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate (310 mg, 75% yield) as a yellow oil. LC-MS: m/z 529.2 $[M+H]^+$.

Step 3: (1*R*,3*S*)-3-(5-((6-((2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (4-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)thiazol-2-yl)carbamate (50.0 mg, 94.6 μmol) in DCM (3.0 mL) was added Et_3N (47.8 mg, 473 μmol) and CDI (46.1 mg, 284 μmol) at 25 °C, the mixture was warmed to 35 °C and stirred at this temperature for 1 h. The mixture was cooled to 25 °C and diluted with water (50 mL), the aqueous layer was extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford (1*R*,3*S*)-3-(5-((6-((2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (50 mg, crude) as yellow oil. LC-MS: m/z 623.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(5-((6-((2-aminothiazol-4-yl)methoxy)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

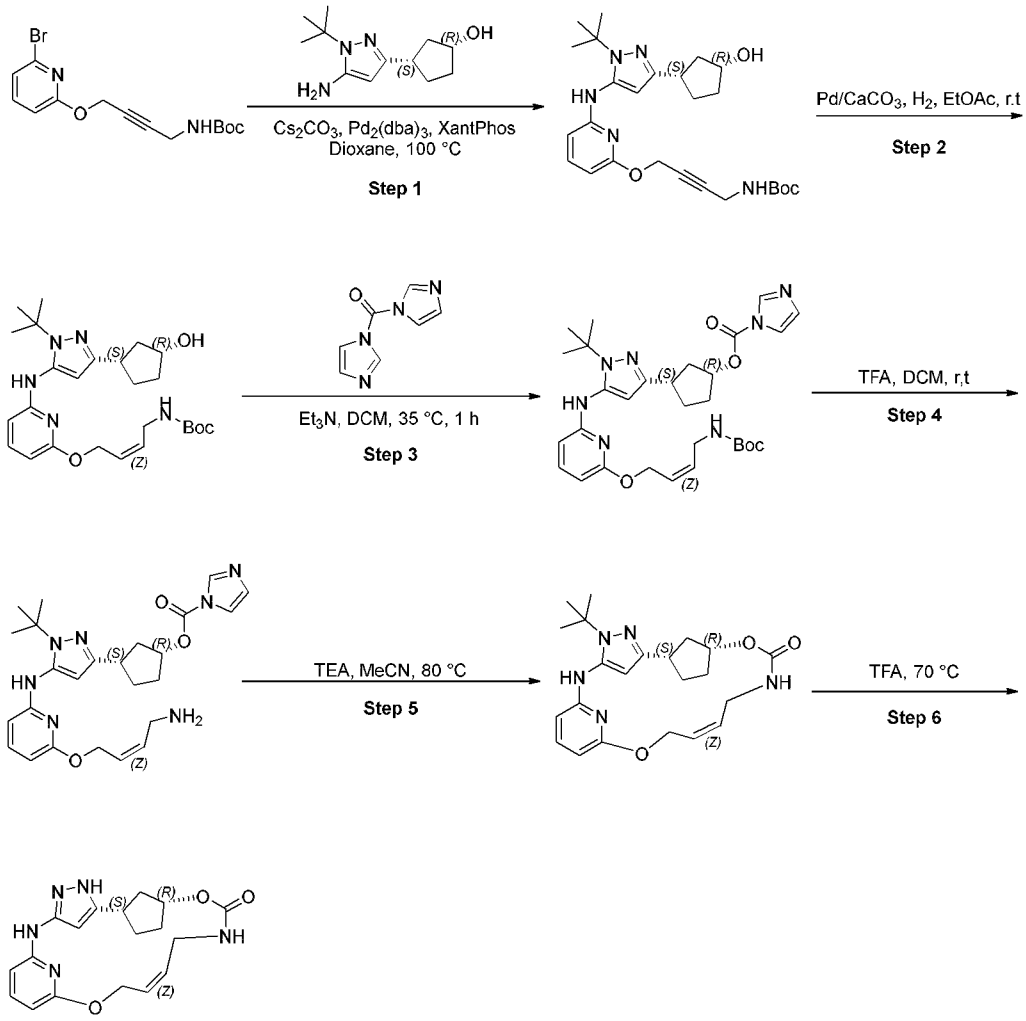
The mixture of (1*R*,3*S*)-3-(5-((6-((2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (50.0 mg, 94.7 μmol) in TFA (2.0 mL) was warmed to 70 °C and stirred at this temperature for 4 h. The mixture was cooled to 25 °C and was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((2-aminothiazol-4-yl)methoxy)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (40 mg, crude) as a yellow oil, which was used in the next step directly. LC-MS: m/z 467.1 $[M+H]^+$.

Step 5: (1^1S,1^3R,2^4Z,7^2Z)-2^1H-5,10-dioxa-3,8-diaza-7(4,2)-thiazola-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphan-9-one

To a solution of (1*R*,3*S*)-3-(5-((6-((2-aminothiazol-4-yl)methoxy)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (30.0 mg, 64.3 μmol) in ACN (3.0 mL) was added Et_3N (65.1 mg, 643 μmol) and NaH (25.7 mg, 643 μmol, 60% purity) at 25 °C, after addition, the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (with CH_3CN from 22% to 32% in 12 min) to afford (1^1S,1^3R,2^4Z,7^2Z)-2^1H-5,10-dioxa-3,8-diaza-7(4,2)-thiazola-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclodecaphan-9-one (0.5 mg, 2% yield) as a white solid. LC-MS: m/z 399.1 $[M+H]^+$.

Example **20**

(1¹*S*,1³*R*,2⁴*Z*,7*Z*)-2¹*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one



Step 1: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-yn-1-yl)carbamate

To a solution of *tert*-butyl (4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (160 mg, 469 μmol) and (1*R*,3*S*)-3-(5-amino-1-tert-butyl-pyrazol-3-yl)cyclopentanol (105 mg, 469 μmol) in dioxane (5.0 mL) was added $Pd_2(dba)_3$ (42.9 mg, 46.9 μmol), XantPhos (54.3 mg, 93.8 μmol) and Cs_2CO_3 (458 mg, 1.41 mmol) under the atmosphere of N_2. Then the reaction mixture was heated to 100 °C and stirred at 100 °C under the atmosphere of N_2 for 3 hours. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0~60%) in 20 min to afford the product *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (134 mg, 59% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 484.2.

Step 2: *tert*-butyl ((*Z*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-en-1-yl)carbamate

To a solution of *tert*-butyl *N*-[4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]but-2-ynyl]carbamate (110 mg, 227 μmol) in EtOAc (5.0 mL) was added $Pd/CaCO_3$ (40 .0 mg, 18.8 μmol, 5% purity). Then the reaction mixture was degassed with H_2 (balloon) for 3 times. Then the reaction mixture was stirred at 20 °C under the atmosphere of H_2 for 15 h. The mixture was filtered and concentrated under reduced pressure, the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0~50%) in 20 min to afford the product *tert*-butyl *N*-[(*Z*)-4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl] pyrazol-3-yl] amino]-2-pyridyl]oxy]but-2-enyl]carbamate (61.0 mg, 55% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 486.2.

Step 3: (1*R*,3*S*)-3-(5-((6-(((*Z*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl *N*-[(*Z*)-4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]but-2-enyl]carbamate (61.0 mg, 126 μmol) in DCM (5.0 mL) was added Et_3N (63.6 mg, 628 μmol, 87.5 μL) at 20 °C, then di(imidazol-1-yl)methanone (40.7 mg, 251 μmol) was added to the reaction mixture. The mixture was stirred at 35 °C for 5 h. The mixture was quenched with ice water (80 mL), then the mixture was extracted with EtOAc (100 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtAOc in PE (with EtOAc from 0~60%) in 15 min to afford the product [(1*R*,3*S*)-3-[5-[[6-[(*Z*)-4-(*tert*-butoxycarbonylamino)but-2-enoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (60.0 mg, 82% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 580.2.

Step 4: (1*R*,3*S*)-3-(5-((6-(((*Z*)-4-aminobut-2-en-1-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of [(1*R*,3*S*)-3-[5-[[6-[(*Z*)-4-(*tert*-butoxycarbonylamino)but-2-enoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (60.0 mg, 103 μmol) in DCM (5.0 mL) was added TFA (740mg, 6.49 mmol, 0.5 mL) . Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford the product [(1*R*,3*S*)-3-[5-[[6-[(*Z*)-4-aminobut-2-enoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (60.0 mg, crude, TFA) as a yellow oil. LC-MS: (ESI) m/z $[M+H]^+$ 480.2.

Step 5: (1^1S,1^3R,2^4Z,7*Z*)-2^1-(tert-butyl)-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one

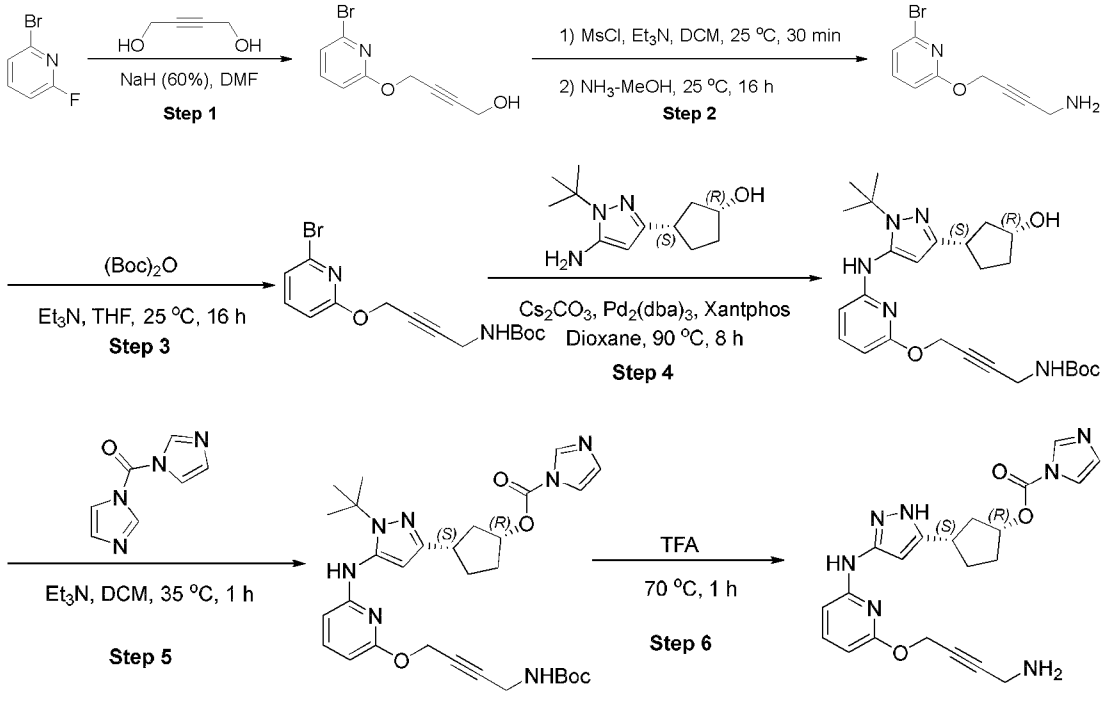
To a solution of [(1*R*,3*S*)-3-[5-[[6-[(*Z*)-4-aminobut-2-enoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (60.0 mg, 101 μmol, TFA) in ACN (12 mL) was added Et_3N (10.2 mg, 101 μmol, 14.1 μL) . Then the reaction mixture was heated to 80 °C and stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column eluting with EtAOc in PE (with EtOAc from 0~50%) in 15 min to afford the product (1^1S,1^3R,2^4Z,7*Z*)-2^1-(*tert*-butyl)-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one (12.0 mg, 29% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 412.1.

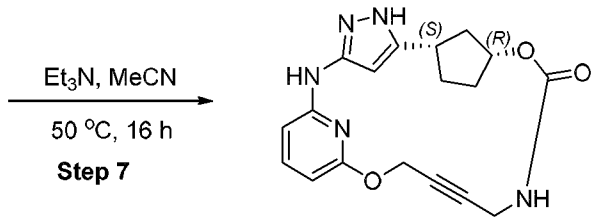
Step 6: (1^1S,1^3R,2^4Z,7*Z*)-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one

The solution of (1^1S,1^3R,2^4Z,7*Z*)-2^1-(*tert*-butyl)-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one (12.0 mg, 29.2 μmol) in TFA (5.0 mL) was heated to 70 °C and stirred at 70 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was sent to purified by prep-HPLC (with CH_3CN from 25% to 55% in 8 min) to afford the product (1^1S,1^3R,2^4Z,7*Z*)-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-7-en-11-one (3.00 mg, 29% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 356.1.

Example **21**

(*7S,10R*)-11,18-dioxa-2,4,5,13,23-pentaazatetracyclo[17.3.1.$1^{3,6}$.$1^{7,10}$]pentacosa-1(23),3,6(25),19,21-pentaen-15-yn-12-one





Step 1: 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-ol

To a solution of but-2-yne-1,4-diol (500 mg, 5.81 mmol) in DMF (10 mL) was added Sodium hydride (278 mg, 11.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. Then the mixture was added 2-bromo-6-fluoro-pyridine (1.02 g, 5.81 mmol, 598 μL) at 25 °C and stirred at 25 °C for 1 h. The mixture was added H_2O (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtAOc in PE (with EtOAc from 0~40%) in 15 min to afford 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-ol (1.26 g, 90% yield) as a colorless oil. LC-MS: m/z 242.0 $[M+H]^+$.

Step 2: 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-amine

To a mixture of 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-ol (1.26 g, 5.22 mmol) and Et_3N (1.06 g, 10.4 mmol, 1.45 mL) in DCM (15 mL) was added MsCl (717 mg, 6.26 mmol, 485 μL) dropwise at 0 °C. The mixture was stirred at 25 °C for 0.5 h. Then the mixture was quenched with H_2O (5.0 mL) and extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was added NH_3-MeOH (70 mmol, 10 mL, 7 mol/L in MeOH) at 25 °C and stirred at 25 °C for 6 h. The mixture was concentrated under reduced pressure to afford 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-amine (800 mg, crude) as a yellow oil, which was used directly into the next step without further treatment. LC-MS: m/z 241.1 $[M+H]^+$.

Step 3: *tert*-butyl (4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-yl)carbamate

To a mixture of 4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-amine (800 mg, 3.32 mmol) and $(Boc)_2O$ (1.09 g, 4.98 mmol, 1.14 mL) in THF (10 mL) was added Et_3N (1.01 g, 9.96 mmol, 1.39 mL) at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was added H_2O (10 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtAOc in PE (with EtOAc from 0~25%) in 15 min to afford the desired product *tert*-butyl (4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (326 mg, 29% yield) as a yellow solid. LC-MS: m/z 363.0 $[M+Na]^+$.

Step 4: *tert*-butyl (4-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-yn-1-yl)carbamate

To a mixture of *tert*-butyl (4-((6-bromopyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (150 mg, 439 μmol) and (1*R*,3*S*)-3-(5-amino-1-tert-butyl-pyrazol-3-yl)cyclopentanol (98.1 mg, 439 μmol) in dioxane (5.0 mL) was added $Pd_2(dba)_3$ (80.5 mg, 87.9 μmol) , Xantphos (101 mg, 175 μmol) and Cs_2CO_3 (429 mg, 1.32 mmol) at 25 °C. The mixture was heated to 95 °C and stirred at 95 °C for 6 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtAOc in PE (with EtOAc from 0~80%) in 25 min to afford *tert*-butyl (4-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (171 mg, 80% yield) as a yellow oil. LC-MS: m/z 484.2 $[M+H]^+$.

Step 5: (1*R*,3*S*)-3-(5-((6-((4-((tert-butoxycarbonyl)amino)but-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a mixture of *tert*-butyl (4-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)but-2-yn-1-yl)carbamate (151 mg, 312 μmol) and 1,1'-Carbonyldiimidazole (253 mg, 1.56 mmol) in DCM (5.0 mL) was added Et_3N (157 mg, 1.56 mmol, 217.60 μL) at 25 °C. The mixture was stirred at 35 °C for 16 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((4-((*tert*-butoxycarbonyl)amino)but-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (175 mg, crude) as a brown oil. LC-MS: m/z 578.3 $[M+H]^+$.

Step 6: (1*R*,3*S*)-3-(3-((6-((4-aminobut-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

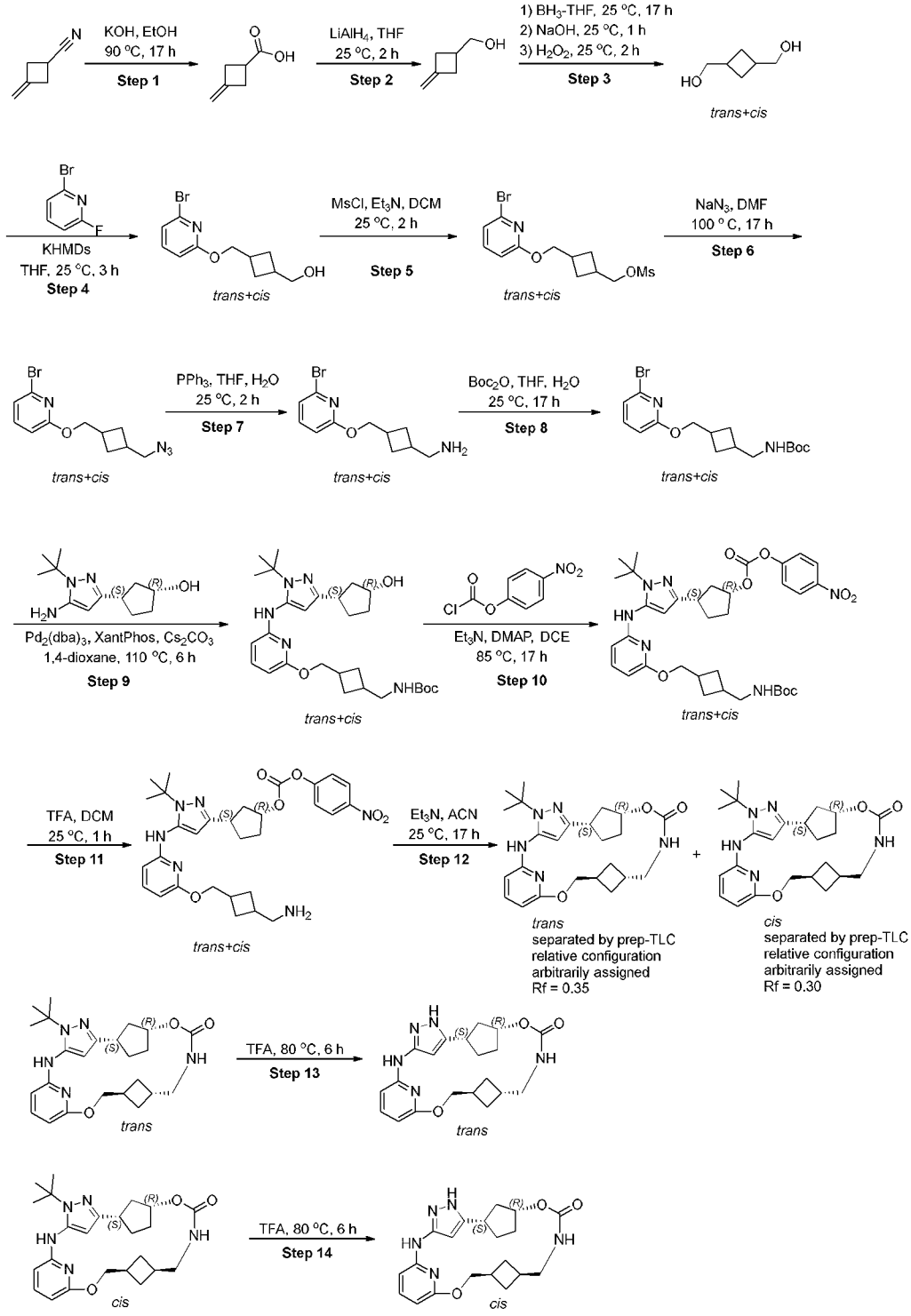
A solution of (1*R*,3*S*)-3-(5-((6-((4-((*tert*-butoxycarbonyl)amino)but-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (175 mg, 302 μmol) in TFA (2.96 g, 25.9 mmol, 2.0 mL) was heated to 70 °C and stirred at 70 °C for 1 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(3-((6-((4-aminobut-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (125 mg, crude) as a brown oil. LC-MS: m/z 422.1 $[M+H]^+$.

Step 7: (*7S,10R*)-11,18-dioxa-2,4,5,13,23-pentaazatetracyclo[17.3.1.1^{3,6}.1^{7,10}]pentacosa-1(23),3,6(25),19,21-pentaen-15-yn-12-one

To a solution of (1*R*,3*S*)-3-(3-((6-((4-aminobut-2-yn-1-yl)oxy)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (65.0 mg, 154.23 μmol) in Acetonitrile (5.0 mL) was added Et_3N (726.00 mg, 7.17 mmol, 1.0 mL) at 25 °C. The mixture was heated to 50 °C and stirred at 50 °C for 16 h. The mixture was purified by Prep-TLC (DCM/MeOH=15:1) to afford RGT002-940-102-01 (1.10 mg, 2% yield) as a white solid. LC-MS: m/z 354.2 $[M+H]^+$.

Example **22** and **23**

(1^{1}S,1^{3}R,7^{1}R,7^{3}S,Z)-2^1*H*-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one and (1^{1}S,1^{3}R,7^{1}S,7^{3}R,Z)-2^1*H*-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one



Step 1: 3-methylenecyclobutane-1-carboxylic acid

The mixture of 3-methylenecyclobutanecarbonitrile (1.00 g, 10.7 mmol) and potassium hydroxide (2.41 g, 42.9 mmol) in EtOH (5.0 mL) and H_2O (5.0 mL) was heated to 90 °C and stirred at 90 °C for 17 h. The mixture was concentrated under reduced pressure. To the residue was added H_2O (10 mL), and the pH value of the aqueous layer was adjusted to 1 by adding conc. HCl. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give 3-methylenecyclobutanecarboxylic acid (800 mg, 66% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (brs, 1H), 4.82 (q, *J* = 2.4 Hz, 2H), 3.17-3.15 (m, 1H), 3.08-3.00 (m, 2H), 2.98-2.90 (m, 2H).

Step 2: (3-methylenecyclobutyl)methanol

To a stirred solution of 3-methylenecyclobutanecarboxylic acid (1.23 g, 10.9 mmol) in THF (10 mL) at 0 °C was added a solution of lithium aluminium hydride in THF (13.1 mL, 13.1 mmol) slowly. After addition, the mixture was stirred at 25 °C for 2 h. The mixture was cooled down to 0 °C and was quenched with ice-water (50 mL). THF was removed under reduced pressure and the aqueous layer was extracted with EtOAc (15 mL × 3), the combined organic layer was dried over Na_2SO_4, filtered and concentrated to give (3-methylenecyclobutyl)methanol (800 mg, 74% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (q, *J* = 2.4 Hz, 2H), 3.66 (d, *J* = 6.8 Hz, 2H), 2.77-2.74 (m, 2H), 2.51-2.47 (m, 1H), 2.43-2.38 (m, 2H).

Step 3: cyclobutane-1,3-diyldimethanol

To a stirring solution of (3-methylenecyclobutyl)methanol (6.20 g, 63.1 mmol) in THF (50 mL) at 0 °C was added BH_3-THF (1.0 M, 94.7 mL) slowly. After addition, the mixture was stirred at 25 °C for 17 h. The mixture was cooled down to 0 °C. The aqueous potassium hydroxide (3.0 M, 42.1 mL) solution was added to the above mixture slowly. After addition, the mixture was stirred at 25 °C for 1 h. 30% hydrogen peroxide (13.0 mL, 126 mmol) was added to the mixture. The mixture was stirred for further 2 h. To the mixture was added H_2O (100 mL), the aqueous layer was extracted with EtOAc (80 mL × 4). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 50%) in 25 mins to give (*trans*+*cis*)-cyclobutane-1,3-diyldimethanol (3.20 g, 44% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, *J* = 6.8 Hz, 2H), 3.56 (d, *J* = 6.0 Hz, 2H), 2.51-2.38 (m, 2H), 2.16-2.09 (m, 1H), 1.87 (t, *J* = 7.2 Hz, 2H), 1.60-1.54 (m, 1H).

Step 4: (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methanol

To a stirring solution of cyclobutane-1,3-diyldimethanol (99.01 mg, 852.34 μmol) in THF (5.0 mL) at 0 °C was added KHMDs in THF (1.0 M, 511.40 μL) portionwise. After addition, the mixture was stirred at 25 °C for 30 min. To the mixture was added 2-bromo-6-fluoro-pyridine (75.0 mg, 426 μmol). The mixture was stirred at 25 °C for 3 h. The mixture was quenched with aqueous NH_4Cl

solution (10 mL). The aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum ether (with EtOAc from 0 to 25 %) in 20 min to give (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methanol (40.0 mg, 34% yield) as a colorless oil. LC-MS: m/z 272.0 $[M+H]^+$.

Step 5: (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl methanesulfonate

To a stirring solution of (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methanol (130 mg, 477 μmol) and Et_3N (133 μL, 955 μmol,) in DCM (15 mL) at 0 °C was added methanesulfonyl chloride (71.1 mg, 621 μmol). After addition, the mixture was stirred at 25 °C for 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and the aqueous layer was extracted with DCM (10 mL × 2). The combined organic layer was dried, filtered. The residue was concentrated to give (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl methanesulfonate (160 mg, 96% yield) as a yellow oil, which was used directly into the next step without further purification. LC-MS: m/z 350.0 $[M+H]^+$

Step 6: 2-((3-(azidomethyl)cyclobutyl)methoxy)-6-bromopyridine

The mixture of (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl methanesulfonate (150 mg, 428 μmol) and sodium azide (55.6 mg, 856 μmol) in DMF (8.0 mL) was heated to 100 °C and stirred at 100 °C for 17 h. After cooled down to room temperature, the mixture was poured into ice-water (30 mL). The aqueous layer was extracted with EtOAc (10 mL × 2), the combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum ether (with EtOAc from 0 to 20%) in 20 min to give 2-((3-(azidomethyl)cyclobutyl)methoxy)-6-bromopyridine (70.0 mg, 55% yield) as a colorless oil. LC-MS: m/z 297.0 $[M+H]^+$.

Step 7: (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methanamine

The mixture of 2-((3-(azidomethyl)cyclobutyl)methoxy)-6-bromopyridine (70.0 mg, 235 μmol) and triphenylphosphane (185 mg, 706 μmol) in THF (2.0 mL) and H_2O (2.0 mL) was stirred at 25 °C for 2 h. The solution was used directly in the next step without further purification. LC-MS: m/z 271.0 $[M+H]^+$.

Step 8: *tert*-butyl ((3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate

To a stirred mixture of (3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methanamine (100 mg, 368 μmol) and sodium carbonate (390 mg, 3.69 mmol) in THF (5.0 mL) and H_2O (5.0 mL) was added Boc_2O (241 mg, 1.11 mmol). The mixture was stirred at 25 °C for 17 h. The aqueous layer was extracted with EtOAc (5.0 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum

ether (with EtOAc from 0 to 20%) in 20 minutes to give *tert*-butyl ((3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (35.0 mg, 26% yield) as a colorless oil. LC-MS: m/z 393.0 $[M+Na]^+$.

Step 9: *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate

The mixture of *tert*-butyl ((3-(((6-bromopyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (300 mg, 808 μmol), (*1R,3S*)-3-(5-amino-1-tert-butyl-pyrazol-3-yl)cyclopentanol (180 mg, 808 μmol), Cs_2CO_3 (789 mg, 2.42 mmol), $Pd_2(dba)_3$ (73.9 mg, 80.8 μmol) and XantPhos (93.4 mg, 161 μmol) in 1,4-dioxane (10 mL) was heated to 110 °C and stirred at 100 °C for 6 h under N_2. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with EtOAc in petroleum ether (with EtOAc from 0 to 50%) in 25 minutes to give *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (280 mg, 67% yield) as a yellow solid. LC-MS: m/z 514.3 $[M+H]^+$.

Step 10: *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate

The mixture of *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (280 mg, 545 μmol), (4-nitrophenyl) carbonochloridate (329 mg, 1.64 mmol), Et_3N (275 mg, 2.73 mmol) and DMAP (13.3 mg, 109 μmol) in DCE (9.8 mL) was heated to 85 °C and stirred at 85 °C for 17 h. The mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (EtOAc/PE = 1/1) to give *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (150 mg, 41% yield) as a yellow oil. LC-MS: m/z 679.3 $[M+H]^+$.

Step 11: (1*R*,3*S*)-3-(5-((6-((3-(aminomethyl)cyclobutyl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

The mixture of *tert*-butyl ((3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)methyl)cyclobutyl)methyl)carbamate (150 mg, 221 μmol) in DCM (3.0 mL) and trifluoroacetic acid (3.0 mL) was stirred at 25 °C for 1 h. The mixture was concentrated in vacuo to give (1*R*,3*S*)-3-(5-((6-((3-(aminomethyl)cyclobutyl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (150 mg, 70% yield) as a brown oil, which was used directly into the next step without further purification. LC-MS: m/z 579.2 $[M+H]^+$.

Step 12: (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one and (1^1S,1^3R,7^1S,7^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one

The mixture of (1*R*,3*S*)-3-(5-((6-((3-(aminomethyl)cyclobutyl)methoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (150 mg, 259 μmol) and Et_3N (524 mg, 5.18 mmol) in acetonitrile (70 mL) was stirred at 25 °C for 17 h. The mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (EtOAc/PE= 1/1) to give (1^1S,1^3R,7^1S,7^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (relative configuration arbitrarily assigned, 46.0 mg, Rf = 0.35, 40% yield) as a yellow oil and (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (relative configuration arbitrarily assigned, 29.0 mg, Rf = 0.3, 25% yield) as a yellow oil. LC-MS: m/z 440.2 $[M+H]^+$.

Step 13: (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one

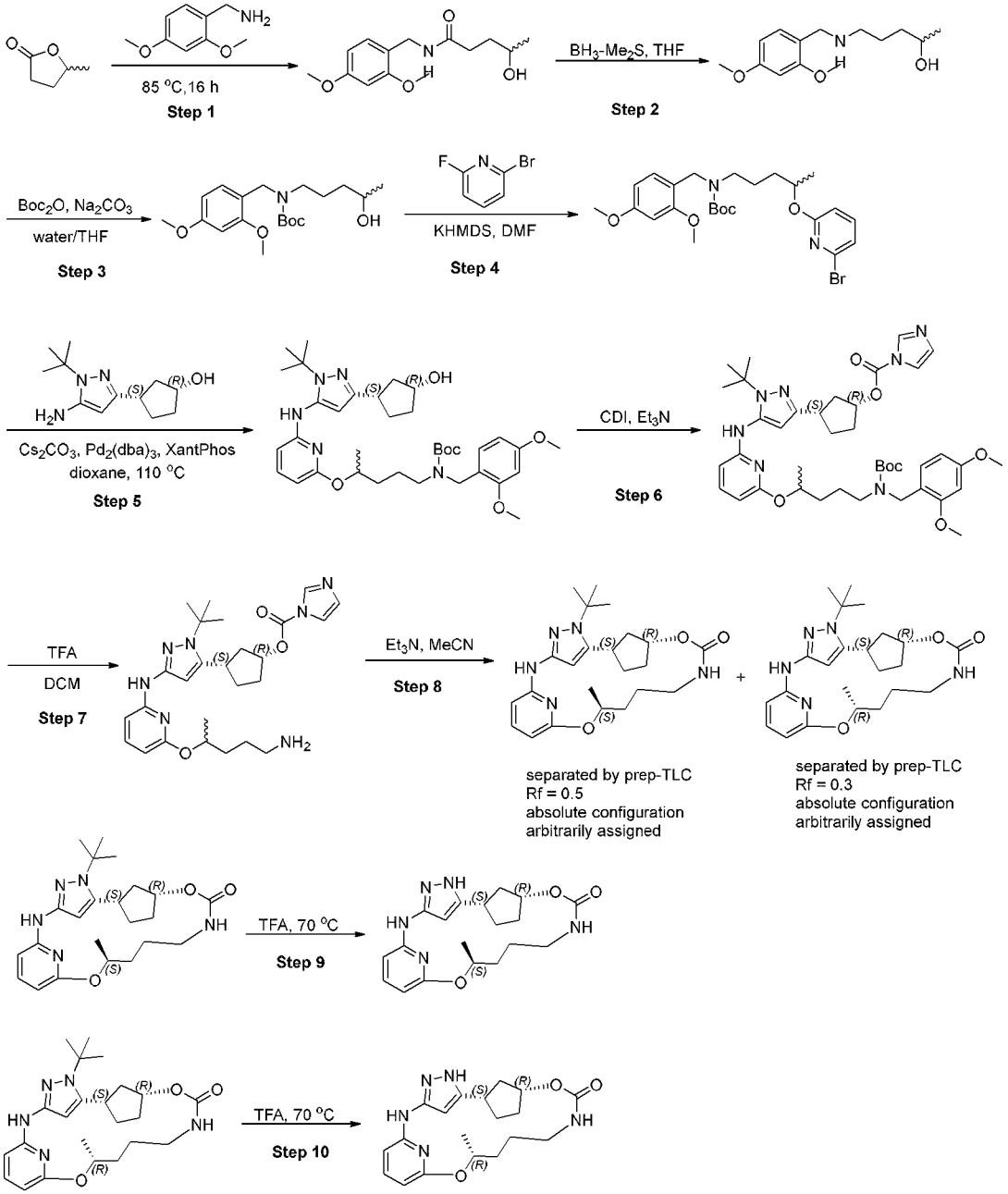
The mixture of (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (29.0 mg, 65.9 μmol) in trifluoroacetic acid (5.0 mL) was heated to 80 °C and stirred at 80 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified Prep-HPLC (with CH_3CN from 50% to 80% in 20 min) to give (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (8.6 mg, 36% yield) as a white solid. LC-MS: m/z 384.2 $[M+H]^+$.

Step 14: (1^1S,1^3R,7^1S,7^3R,*Z*)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one

The mixture of (1^1S,1^3R,7^1S,7^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (46 mg, 104.65 μmol) in trifluoroacetic acid (5 mL) was heated 80 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified Prep-HPLC eluting with CH_3CN in water with CH_3CN from 50% to 80% in 20 min to give (1^1S,1^3R,7^1S,7^3R,*Z*)-2^1H-5,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacycloundecaphan-10-one (20.4 mg, 51% yield) as a white solid. LC-MS: m/z 384.2 $[M+H]^+$.

Example **24** and **25**

(1^1*S*,1^3*R*,6*S*,*Z*)-6-methyl-2^1*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1*S*,1^3*R*,6*R*,*Z*)-6-methyl-2^1*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *N*-(2,4-dimethoxybenzyl)-4-hydroxypentanamide

The mixture of 5-methyltetrahydrofuran-2-one (1.00 g, 9.99 mmol, 950 μL) and (2,4-dimethoxyphenyl)methanamine (1.84 g, 10.9 mmol) was heated to 85 °C and stirred at 85 °C for 16 h. The reaction was diluted with water (20 mL) and then extracted with EA (50 mL × 3). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash

chromatography eluting with MeOH in DCM (with MeOH from 0 to 5%) in 15 min to give *N*-[(2,4-dimethoxyphenyl)methyl]-4-hydroxy-pentanamide (1.90 g, 71% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 268.2.

Step 2: 5-((2,4-dimethoxybenzyl)amino)pentan-2-ol

The mixture of *N*-[(2,4-dimethoxyphenyl)methyl]-4-hydroxy-pentanamide (1.70 g, 6.36 mmol) and borane;methylsulfanylmethane (966 mg, 12.7 mmol, 1.21 mL) in THF (20 mL) was heated to 70 °C and stirred at 70 °C for 3 h. The reaction was diluted with water (50 mL) and then extracted with EtOAc (50 mL × 3). The organic solution was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with MeOH in DCM (with MeOH from 0 to 10%) in 25 min to give 5-[(2,4-dimethoxyphenyl)methylamino]pentan-2-ol (400 mg, 24% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 254.2.

Step 3: *tert*-butyl (2,4-dimethoxybenzyl)(4-hydroxypentyl)carbamate

To a stirring solution of 5-[(2,4-dimethoxyphenyl)methylamino]pentan-2-ol (230 mg, 907 μmol) and Na_2CO_3 (288 mg, 2.72 mmol, 114 μL) in THF (2.5 mL) and water (5.0 mL) at 25 °C was added *tert*-butoxycarbonyl *tert*-butyl carbonate (396 mg, 1.82 mmol, 41 μL). After addition, the mixture was stirred at 25 °C for 16 h. The reaction was diluted with water (50 mL) and then extracted with EtOAc (50 mL × 3). The organic solution was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc in PE (with EtOAc from 0 to 10%) in 15 min to give *tert*-butyl *N*-[(2,4-dimethoxyphenyl)methyl]-*N*-(4-hydroxypentyl)carbamate (300 mg, 93% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 376.3.

Step 4: *tert*-butyl (4-((6-bromopyridin-2-yl)oxy)pentyl)(2,4-dimethoxybenzyl)carbamate

To a stirring solution of *tert*-butyl *N*-[(2,4-dimethoxyphenyl)methyl]-*N*-(4-hydroxypentyl)carbamate (300 mg, 848 μmol) and 2-bromo-6-fluoro-pyridine (179 mg, 1.02 mmol, 105 μL) in DMF (8.0 mL) at 0 °C was added KHMDS (253 mg, 1.27 mmol, 288 μL). After addition, the mixture was stirred at 25 °C for 2 h. The reaction was diluted with water (50 mL) and then extracted with EtOAc (50 mL × 3). The organic solution was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc in PE (with EtOAc from 0 to 30%) in 20 min to give *tert*-butyl *N*-[4-[(6-bromo-2-pyridyl)oxy]pentyl]-*N*-[(2,4-dimethoxyphenyl)methyl]carbamate (300 mg, 69% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 531.1.

Step 5: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxy)pentyl)(2,4-dimethoxybenzyl)carbamate

The mixture of *tert*-butyl *N*-[4-[(6-bromo-2-pyridyl)oxy]pentyl]-*N*-[(2,4-dimethoxyphenyl)methyl]carbamate (350 mg, 687 μmol), (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (138 mg, 618 μmol), dicesium;carbonate (671 mg, 2.06 mmol), (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one;palladium (62.9 mg, 68.7 μmol) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (79.5 mg, 137 μmol) in dioxane (8.0 mL) was heated to 100 °C and stirred at 100 °C for 3 h. The reaction was diluted with water (50 mL) and then

extracted with EtOAc (50 mL × 3). The organic solution was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc in PE (with EtOAc from 0 to 50%) in 20 min to give *tert*-butyl *N*-[4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]-*N*-[(2,4-dimethoxyphenyl)methyl]carbamate (250 mg, 55% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 652.3.

Step 6: (1*R*,3*S*)-3-(5-((6-((5-((*tert*-butoxycarbonyl)(2,4-dimethoxybenzyl)amino)pentan-2-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirring solution of *tert*-butyl *N*-[4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]oxy]pentyl]-*N*-[(2,4-dimethoxyphenyl)methyl]carbamate (300 mg, 460 μmol) and Et_3N (232 mg, 2.30 mmol, 320 μL) in DCM (8.0 mL) at 25 °C was added CDI (198 mg, 1.38 mmol). After addition, the mixture was stirred at 35 °C for 2 h. The reaction was diluted with water (30 mL) and then extracted with DCM (40 mL × 3). The organic solution was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc in PE (with EtOAc from 0 to 50%) in 20 min to give [(1*R*,3*S*)-3-[5-[[6-[4-[*tert*-butoxycarbonyl-[(2,4-dimethoxyphenyl)methyl]amino]-1-methyl-butoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (250 mg, 72% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 746.3.

Step 7: (1*R*,3*S*)-3-(3-((6-((5-aminopentan-2-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

The mixture of [(1*R*,3*S*)-3-[5-[[6-[4-[*tert*-butoxycarbonyl-[(2,4-dimethoxyphenyl)methyl]amino]-1-methyl-butoxy]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, 268.13 μmol) in TFA (5.0 mL) was stirred at 25 °C for 16 h. The reaction was concentrated to give [(1*R*,3*S*)-3-[5-[[6-(4-amino-1-methyl-butoxy)-2-pyridyl]amino]-1-tert-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (100 mg, 75% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 496.3.

Step 8: (1^1S,1^3R,6*S*,*Z*)-21-(*tert*-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one &(1^1S,1^3R,6*R*,*Z*)-21-(tert-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirring solution of [(1*R*,3*S*)-3-[5-[[6-(4-amino-1-methyl-butoxy)-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (75.0 mg, 151 μmol) in MeCN (2.0 mL) at 25 °C was added Et_3N (15.3 mg, 151 μmol, 21.0 μL). After addition, the mixture was heated to 60 °C and stirred at 60 °C for 17 h. The reaction was concentrated. The residue was purified by prep-TLC (petroleum ether/EtOAc = 1:1) to give (1^1S,1^3R,6*S*,*Z*)-21-(*tert*-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (absolute

configuration is arbitrarily assigned, 25.0 mg, Rf = 0.5, 38% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 428.3. And (1^1S,1^3R,6*R*,*Z*)-2^1-(*tert*-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (absolute configuration is arbitrarily assigned, 25.0 mg, Rf = 0.3, 38% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 428.3.

Step 9: (1^1S,1^3R,6*S*,*Z*)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

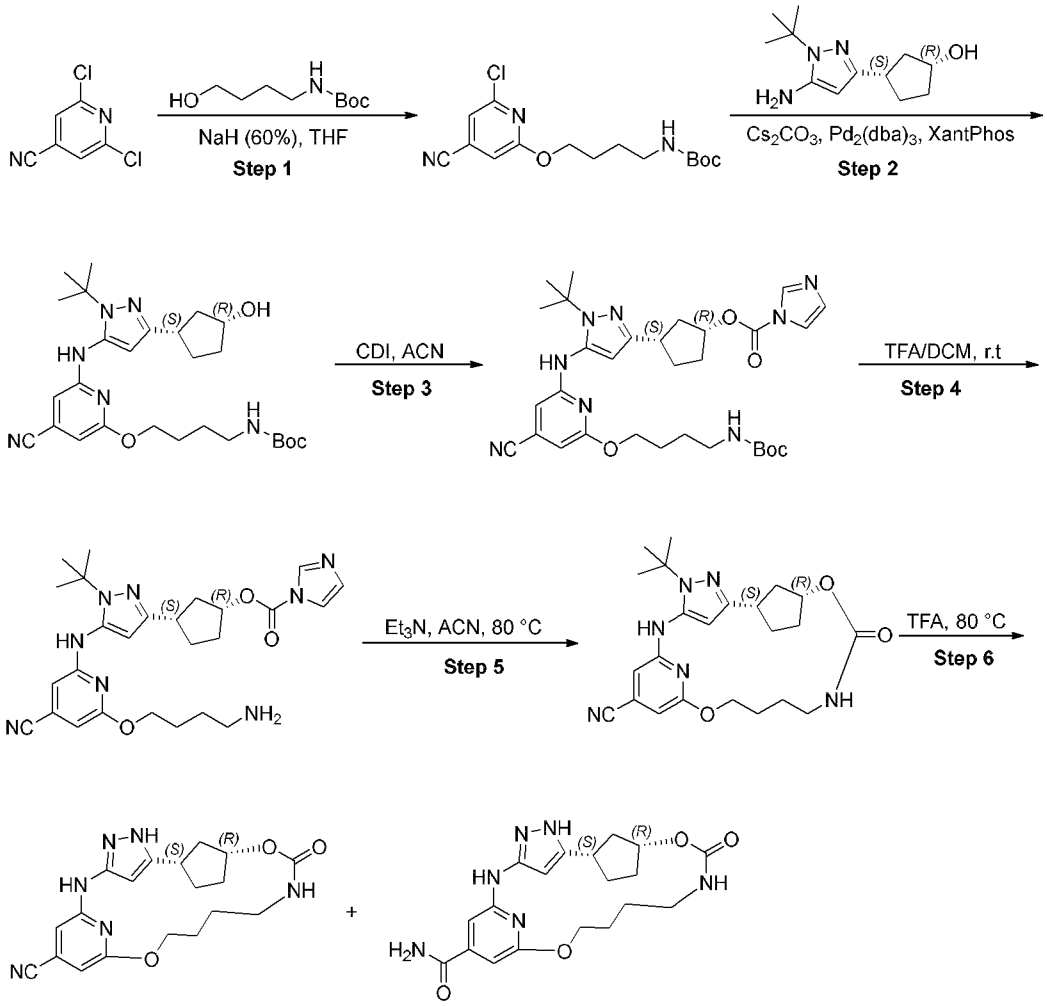
The mixture of (1^1S,1^3R,6*S*,*Z*)-21-(*tert*-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (21.5 mg, 50.4 μmol) in TFA (3.0 mL) was heated to 60 °C and stirred at 60 °C for 17 h. The reaction was concentrated. The residue was purified by prep-HPLC (with CH_3CN from 25% to 55% in 8 min) to give (1^1S,1^3R,6*S*,*Z*)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.00 mg, 21% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 372.1.

Step 10: (1^1S,1^3R,6*R*,*Z*)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The mixture of (1^1S,1^3R,6*S*,*Z*)-2^1-(*tert*-butyl)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (21.5 mg, 50.4 μmol) in TFA (3 mL) was heated to 60 °C and stirred at 60 °C for 17 h. The reaction was concentrated. The residue was purified by prep-HPLC (with CH_3CN from 25% to 55% in 8 min) to give (1^1S,1^3R,6*R*,*Z*)-6-methyl-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.20 mg, 21% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 372.1.

Example **26** and **27**

(1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile and **(1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carboxamide**



Step 1: *tert*-butyl (4-((6-chloro-4-cyanopyridin-2-yl)oxy)butyl)carbamate

To a solution of *tert*-butyl N-(4-hydroxybutyl)carbamate (1.31 g, 6.94 mmol) in THF (10 mL) was added NaH (1.16 g, 28.9 mmol, 60% purity) at 0 °C, then the reaction mixture was stirred at 0 °C for 30 minutes. Then 2,6-dichloropyridine-4-carbonitrile (1.00 g, 5.78 mmol) was added to the reaction mixture. The mixture was stirred at 20 °C for 3 h. The mixture was not quenched (the reaction mixture cannot contact with water and MeOH) and the mixture was filtered and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0-80%) in 25 min to afford the product *tert*-butyl (4-((6-chloro-4-cyanopyridin-2-yl)oxy)butyl)carbamate (1.40 g, 74% yield) as a colorless oil. LC-MS: (ESI) m/z $[M+Na]^+$ 348.0.

Step 2: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-cyanopyridin-2-yl)oxy)butyl)carbamate

To a solution of *tert*-butyl N-[4-[(6-chloro-4-cyano-2-pyridyl)oxy]butyl]carbamate (230 mg, 705 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (150 mg, 671 μmol) in dioxane (5.0 mL) was added $Pd_2(dba)_3$ (61.5 mg, 67.2 μmol), XantPhos (77.7 mg, 134 μmol) and

Cs_2CO_3 (656 mg, 2.02 mmol) under the atmosphere of N_2. Then the reaction mixture was heated to 100 °C and stirred at 100 °C under the atmosphere of N_2 for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0-60%) in 15 min to afford *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-cyanopyridin-2-yl)oxy)butyl)carbamate (253 mg, 73% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 513.2.

Step 3: (1*R*,3*S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-cyanopyridin-2-yl)oxy)butyl)carbamate (230 mg, 449 μmol) in DCM (5.0 mL) was added Et_3N (227 mg, 2.24 mmol, 312 μL) at 20 °C. Then di(imidazol-1-yl)methanone (145 mg, 897 μmol) was added to the reaction mixture. The mixture was stirred at 35 °C for 12 h. The mixture was quenched with ice water (80 mL), then the mixture was extracted with EtOAc (100 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0-60%) in 15 min to afford the product [(1*R*,3*S*)-3-[5-[[6-[4-(*tert*-butoxycarbonylamino)butoxy]-4-cyano-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (260 mg, 96% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 607.2.

Step 4: (1*R*,3*S*)-3-(5-((6-(4-aminobutoxy)-4-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of [(1*R*,3*S*)-3-[5-[[6-[4-(*tert*-butoxycarbonylamino)butoxy]-4-cyano-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (190 mg, 313 μmol) in DCM (5.0 mL) was added TFA (178 mg, 1.57 mmol, 121 μL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford the product (1*R*,3*S*)-3-(5-((6-(4-aminobutoxy)-4-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 507.2.

Step 5: (1^1*S*, 1^3*R*, *Z*)-2^1-(*tert*-butyl)-11-oxo-2^1*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile

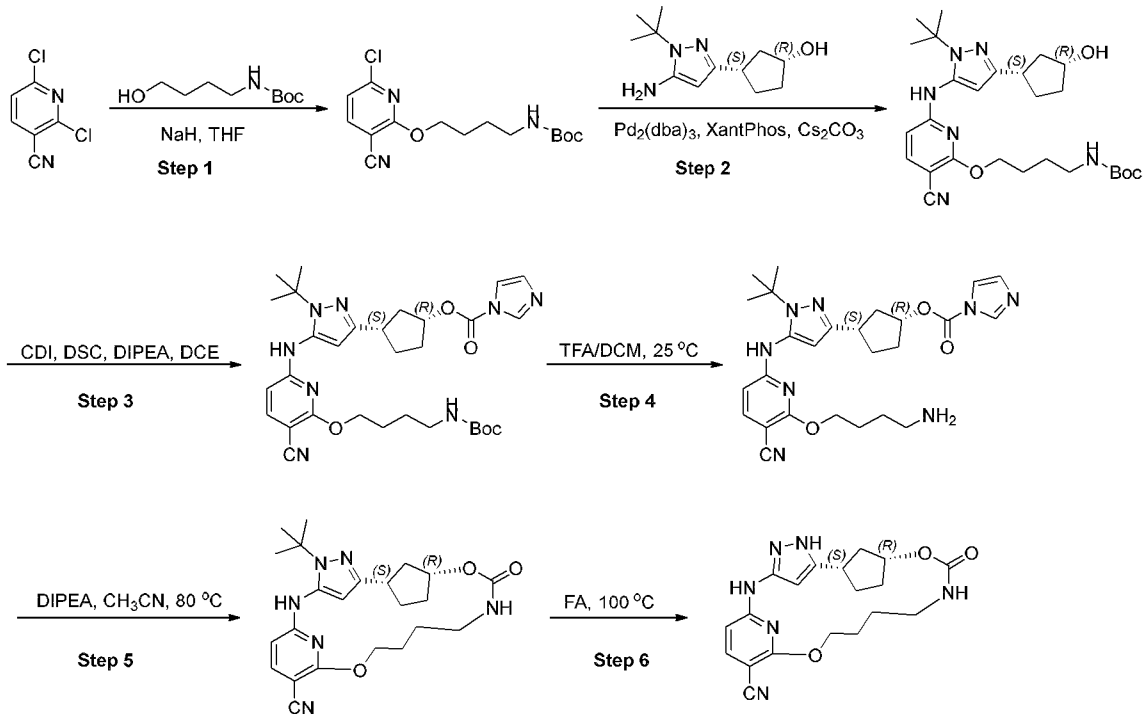
To a solution of (1*R*,3*S*)-3-(5-((6-(4-aminobutoxy)-4-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, 322 μmol) in CH_3CN (8.0 mL) was added Et_3N (1.09 g, 10.8 mmol, 1.50 mL). Then the reaction mixture was heated to 80 °C and stirred at 80 °C for 15 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc in PE (with EtOAc from 0-50%) in 15 min to afford (1^1*S*, 1^3*R*, *Z*)-2^1-(*tert*-butyl)-11-oxo-2^1*H*-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile (78.0 mg, 55% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 439.2

Step 6: (1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile and (1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carboxamide

The solution of (1^1S, 1^3R, *Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile (78.0 mg, 178 μmol) in TFA (5.0 mL) was heated to 70 °C and stirred at 70 °C for 32 h. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC (with CH_3CN from 30% to 60% in 10 min) to afford (1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carbonitrile (23.0 mg, 34% yield) as a pale yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 383.1. And to afford (1^1S, 1^3R, *Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^4-carboxamide (18.0 mg, 25% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 401.2.

Example **28**

(1^1S,1^3R,*Z*)-1^1-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbonitrile



Step 1: *tert*-butyl (4-((6-chloro-3-cyanopyridin-2-yl)oxy)butyl)carbamate

To a solution of *tert*-butyl (4-hydroxybutyl) carbamate (457 mg, 2.64 mmol) in THF (10 mL) was added sodium hydride (211 mg, 5.28 mmol, 60% purity) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 minutes and then 2,6-dichloronicotinonitrile (500 mg, 2.64 mmol) was added.

The reaction was stirred at 25 °C for 2 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with EtOAc in PE (with EtOAc from 0 to 40%) in 15 min to afford *tert*-butyl (4-((6-chloro-3-cyanopyridin-2-yl)oxy)butyl)carbamate (285 mg, 33% yield) as colorless oil. LC-MS: m/z 348.1 $[M+H]^+$.

Step 2: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-cyanopyridin-2-yl)oxy)butyl)carbamate

To a mixture of (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (150 mg, 671 μmol), *tert*-butyl (4-((6-chloro-3-cyanopyridin-2-yl)oxy)butyl)carbamate (243 mg, 746 μmol) and Cs_2CO_3 (730 mg, 2.24 mmol) in dioxane (15 mL) was added XantPhos (173 mg, 298 μmol) and $Pd_2(dba)_3$ (137 mg, 149 μmol) under nitrogen. The reaction was heated to 95 °C and stirred at 95 °C under nitrogen for 16 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with EtOAc in PE (with EtOAc from 0-50%) in 20 min to afford *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-cyanopyridin-2-yl)oxy)butyl)carbamate (136 mg, 36% yield) as a light yellow solid. LC-MS: m/z 513.3 $[M+H]^+$.

Step 3: (1*R*,3*S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-5-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A mixture of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-cyanopyridin-2-yl)oxy)butyl)carbamate (130 mg, 254 μmol), CDI (822 mg, 5.07 mmol), DIPEA (164 mg, 1.27 mmol) and DSC (649 mg, 2.54 mmol) in DCE (10 mL) was heated to 70 °C and stirred at 70 °C for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with EtOAc in PE (with EtOAc from 0-100%) in 15 min to afford (1*R*,3*S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-5-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (89 mg, 58% yield) as a yellow solid. LC-MS: m/z 607.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(5-((6-(4-aminobutoxy)-5-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A solution of (1*R*,3*S*)-3-(5-((6-(4-((*tert*-butoxycarbonyl)amino)butoxy)-5-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (89 mg, 146 μmol) in TFA (3.0 mL) and DCM (10 mL) was stirred at 25 °C for 1 h. The solvent was evaporated to afford

(1*R*,3*S*)-3-(5-((6-(4-aminobutoxy)-5-cyanopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (74 mg, 100% yield) as light brown oil, which was used in the next step directly. LC-MS: m/z 507.2 $[M+H]^+$.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbonitrile

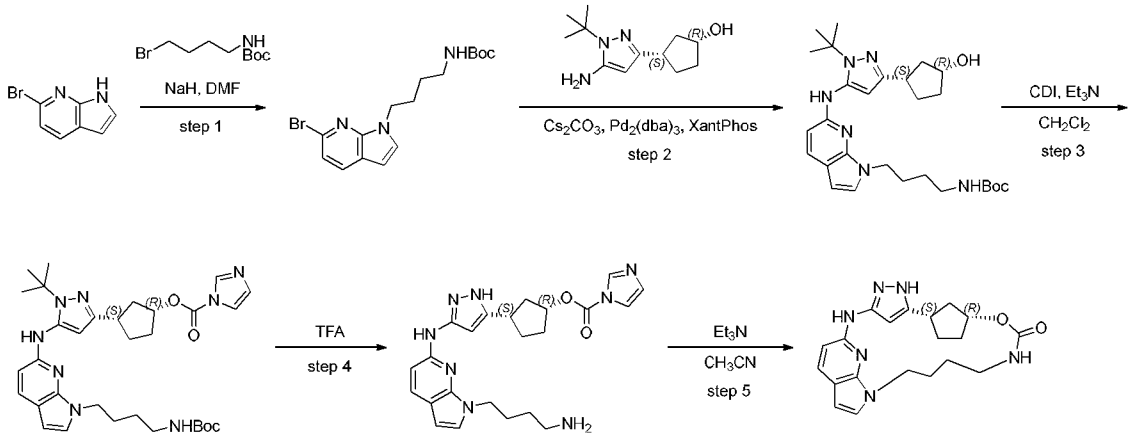
To a solution of [(1*R*,3*S*)-3-[5-[[6-(4-aminobutoxy)-5-cyano-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (140 mg, 276 μmol) in CH_3CN (6.0 mL) was added *N*,*N*-Diisopropylethylamine (107 mg, 829 μmol, 144 μL). The mixture was heated to 80 °C and stirred at 80 °C for 12 h. LCMS showed the starting material was consumed and desired product was formed. The mixture was concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic layer was washed by brine (50 mL) and dried over Na_2SO_4, filtered and concentrated .The residue was purified by flash chromatography eluting with MeOH in DCM (with MeOH from 0 to 5%) in 15 min to provide the (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-45-carbonitrile (20 mg, 16% yield) as a white solid. LC-MS: m/z 439.3 $[M+H]^+$.

Step 6: (1^1S,1^3R,*Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbonitrile

The mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbonitrile (15.0 mg, 34.2 μmol) in FA (3.0 mL) was heated to 100 °C and stirred at 100 °C for 12 h in a Schlenk tube. LCMS showed the starting material was consumed and desired product was formed. The residue was purified by prep-HPLC (with CH_3CN from 10% to 40% in 8 min) to provide (1^1S,1^3R,*Z*)-11-oxo-2^1H-5,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbonitrile (1.00 mg, 7% yield) as a colorless solid. LC-MS: m/z 383.1 $[M+H]^+$.

Example 29

(1^1S,1^3R,*Z*)-2^1H,4^1H-11-oxa-3,9-diaza-4(6,1)-pyrrolo[2,3-b]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one



Step 1: *tert*-butyl *N*-[4-(6-bromopyrrolo[2,3-b]pyridin-1-yl)butyl]carbamate

To a suspension of 6-bromo-1*H*-pyrrolo[2,3-b]pyridine (300 mg, 1.52 mmol) in DMF (12.0 mL) was added slowly NaH (91.3 mg, 60 wt.% in mineral oil, 2.28 mmol) at 0 °C and stirred for 30 min under N_2. Then *tert*-butyl *N*-(4-bromobutyl)carbamate (575 mg, 2.28 mmol) was added at 0 °C. The reaction was stirred at 25 °C for 24 h. Then it was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25% in 25 min) to afford *tert*-butyl *N*-[4-(6-bromopyrrolo[2,3-b]pyridin-1-yl)butyl]carbamate (410 mg, 73% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 367.9.

Step 2: *tert*-butyl *N*-[4-[6-[[1-*tert*-butyl-5-[(*1S,3R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]pyrrolo[2,3-b]pyridin-1-yl]butyl]carbamate

To a suspension of *tert*-butyl *N*-[4-(6-bromopyrrolo[2,3-b]pyridin-1-yl)butyl]carbamate (250 mg, 0.678 mmol) in toluene (10.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-2-*tert*-butyl-pyrazol-3-yl)cyclopentanol (151 mg, 0.678 mmol), $Pd_2(dba)_3$ (62.2 mg, 0.067 mmol), XantPhos (78 mg, 0.135 mmol) and Cs_2CO_3 (663 mg, 2.04 mmol). The reaction was warmed to 80 °C and stirred at that temperature for 16 h under N_2. Then it was concentrated under reduced pressure and purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 25 min) to afford *tert*-butyl *N*-[4-[6-[[1-*tert*-butyl-5-[(*1S,3R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]pyrrolo[2,3-b]pyridin-1-yl]butyl]carbamate (110 mg, 31% yield) as a brown oil. LC-MS: m/z $[M+H]^+$ 511.0.

Step 3: [(*1R,3S*)-3-[5-[[1-[4-(*tert*-butoxycarbonylamino)butyl]pyrrolo[2,3-b]pyridin-6-yl]amino]-2-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[4-[6-[[1-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]pyrrolo[2,3-b]pyridin-1-yl]butyl]carbamate (100 mg, 0.195 mmol) in CH_2Cl_2 (5.0 mL) was added CDI (84.6 mg, 0.587 mmol) and Et_3N (136 μL, 99.0 mg, 0.979 mmol) at 35 °C and stirred for 16 h. Then the reaction mixture was quenched with ice-cold water (10 mL) and extracted with CH_2Cl_2

(3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product [(1*R*,3*S*)-3-[5-[[1-[4-(*tert*-butoxycarbonylamino)butyl]pyrrolo[2,3-b]pyridin-6-yl]amino]-2-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 605.0.

Step 4: [(1*R*,3*S*)-3-[3-[[1-(4-aminobutyl)pyrrolo[2,3-b]pyridin-6-yl]amino]-1*H*-pyrazol-5-yl]cyclopentyl] imidazole-1-carboxylate

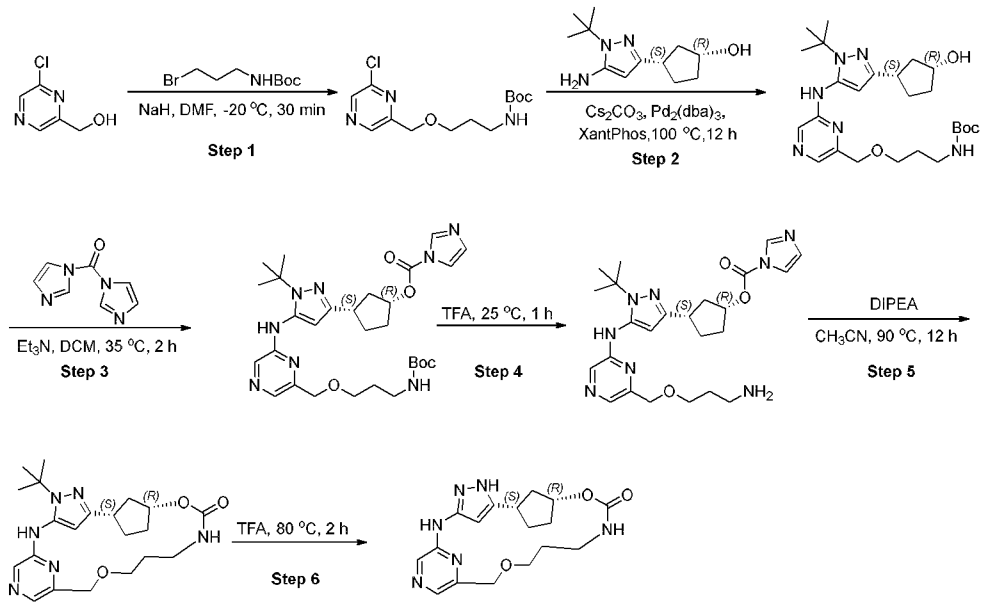
A mixture of [(1*R*,3*S*)-3-[5-[[1-[4-(*tert*-butoxycarbonylamino)butyl]pyrrolo[2,3-b]pyridin-6-yl]amino]-2-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in TFA (5.0 mL) was stirred for 16 h at 70 °C. Then it was concentrated to give crude [(1*R*,3*S*)-3-[3-[[1-(4-aminobutyl)pyrrolo[2,3-b]pyridin-6-yl]amino]-1*H*-pyrazol-5-yl]cyclopentyl]imidazole-1-carboxylate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 448.9.

Step 5: (1^1S,1^3R,*Z*)-2^1H,4^1H-11-oxa-3,9-diaza-4(6,1)-pyrrolo[2,3-b]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one

To a suspension of [(*1R,3S*)-3-[3-[[1-(4-aminobutyl)pyrrolo[2,3-b]pyridin-6-yl]amino]-1*H*-pyrazol-5-yl]cyclopentyl] imidazole-1-carboxylate in CH_3CN (5.0 mL) was added Et_3N (0.27 mL, 196 mg, 1.94 mmol) at room temperature. The mixture was stirred at 80 °C for 5 h in a sealed tube. Then it was concentrated and purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 55% in 10 min (0.1% HCO_2H condition)) to afford (1^1S,1^3R,*Z*)-2^1H,4^1H-11-oxa-3,9-diaza-4(6,1)-pyrrolo[2,3-b]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one (13.2 mg, 17% yield) as an off-white solid. LC-MS: m/z $[M+H]^+$ 380.8.

Example **30**

(1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-((6-chloropyrazin-2-yl)methoxy)propyl)carbamate

To a solution of NaH (110 mg, 2.77 mmol, 60% purity) in DMF (15 mL) was added (6-chloropyrazin-2-yl)methanol (200 mg, 1.38 mmol) in DMF (1.0 mL). The mixture was stirred for 10 min at -20 °C under N_2. Then *tert*-butyl *N*-(3-bromopropyl)carbamate (362 mg, 1.52 mmol) in DMF (1.0 mL) was added to this mixture, then it was stirred at -20°C for 20 min. LCMS showed the starting material was consumed and desired product was detected. The reaction was quenched with addition of saturation water (50 mL), extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50% to give *tert*-butyl (3-((6-chloropyrazin-2-yl)methoxy)propyl)carbamate (160 mg, 38% yield) as yellow oil. LC-MS: m/z $[M\text{-Boc+H}]^+$ 202.1.

Step 2: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazin-2-yl)methoxy)propyl)carbamate

To a suspension of *tert*-butyl (3-((6-chloropyrazin-2-yl)methoxy)propyl)carbamate (140 mg, 464 μmol) in dioxane (20 mL) was added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (103 mg, 464μmol), $Pd_2(dba)_3$ (84.9 mg, 92.7 μmol), XantPhos (107 mg, 185 μmol) and K_2CO_3 (192 mg, 1.39 mmol) at 25 °C. Then the reaction mixture was stirred at 100 °C for 3 h under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH/DCM (with MeOH from 0 to 5% in 20 min) to give *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazin-2-yl)methoxy)propyl)carbamate (87.0 mg, 38% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 489.3.

Step 3: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyrazin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazin-2-yl)methoxy)propyl)carbamate (67.0 mg, 137 μmol) in DCM (3.0 mL) was added Et_3N (138 mg, 1.37 mmol, 191 μL) and di(imidazol-1-yl)methanone (66.7 mg, 411 μmol). The mixture was stirred at 40 °C for 2 h under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH/DCM (MeOH from 0 to 5% in 15 min) to give (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyrazin-2-yl)amino)-1-(*ter*t-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (70.0 mg, 88% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 583.3.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)pyrazin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyrazin-2-yl)amino)-1-(*ter*t-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (60.0 mg, 102 μmol) in DCM (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at 25 °C for 0.5 h under N_2. LCMS showed the starting material was consumed and desired product was detected. The crude product was used immediately in the next step without purification. LC-MS: m/z $[M+H]^+$ 483.2.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

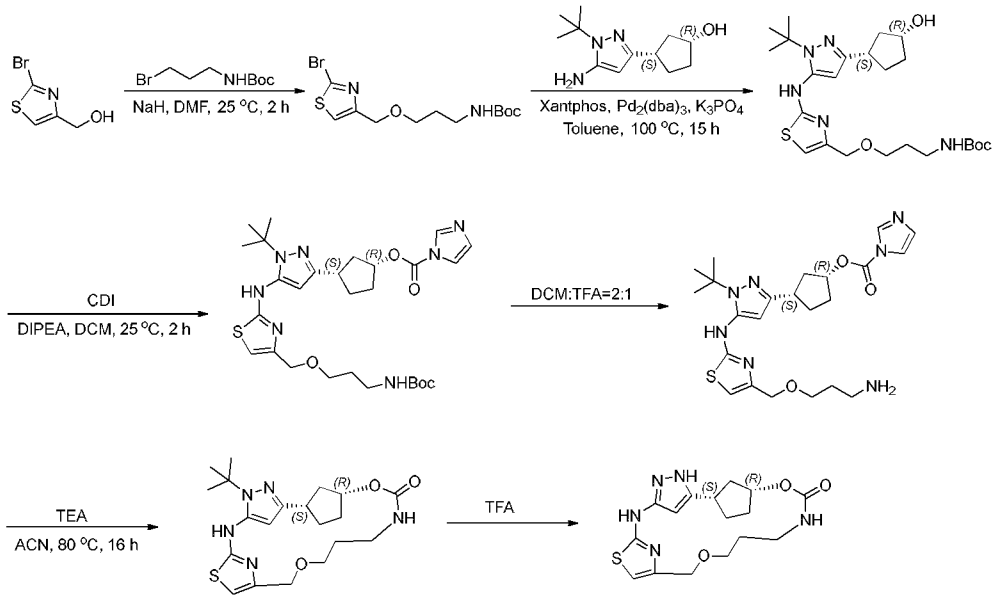
To a solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)pyrazin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (60.0 mg, 124 μmol) in CH_3CN (30 mL) was added DIPEA (5.0 mL). The mixture was heated to 90 °C and stirred at 90 °C for 12 h under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH/DCM (with MeOH from 0 to 5% in 15 min) to give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 58% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 415.2.

Step 6: (1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A suspension of give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 72.3 μmol) in TFA (5.0 mL). The mixture was heated to 80 °C and stirred at 80 °C for 20 h under N_2. LCMS showed the starting material was consumed and desired product was detected. The crude product was purified by prep-HPLC (with CH_3CN from 14% to 44% in 9 min) to give (1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.90 mg, 19% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 359.1.

Example **31**

(1^1S,1^3R,2^4Z,4^2Z)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-((2-bromothiazol-4-yl)methoxy)propyl)carbamate

To a solution of (2-bromothiazol-4-yl)methanol (350 mg, 1.80 mmol) and *tert*-butyl (3-bromopropyl)carbamate (859 mg, 3.61 mmol) in DMF (10 mL) was added NaH (216 mg, 9.02 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was diluted with H_2O (20 ml), and extrated with EtOAc (20 mL × 2). Organic layers were combined and dired over Na_2SO_4, filtered and concentrated to get a residue, which was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 12 min) to afford the product *tert*-butyl (3-((2-bromothiazol-4-yl)methoxy)propyl)carbamate (600 mg, 95% yield) as a white gum. LC-MS: m/z 372.9 $[M+Na]^+$.

Step 2: *tert*-butyl (3-((2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazol-4-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl *N*-[3-[(2-bromothiazol-4-yl)methoxy]propyl]carbamate (200 mg, 569 μmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (150 mg, 672 μmol) in toluene (2.0 mL) was added XantPhos (132 mg, 228 μmol), $Pd_2(dba)_3$ (104 mg, 114 μmol) and K_3PO_4 (363 mg, 1.71 mmol). The mixture was heated to 100 °C and stirred at 100 °C for 15 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/ PE (with EtOAc from 0 to 100% in 15 min) to afford *tert*-butyl (3-((2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazol-4-yl)methoxy)propyl)carbamate (90.0 mg, 32% yield) as a brown liquid. LC-MS: m/z 494.3 $[M+H]^+$.

Step 3: (1*R*,3*S*)-3-(5-((4-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl *N*-[3-[[2-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]thiazol-4-yl]methoxy]propyl]carbamate (90.0 mg, 182 μmol) and di(1*H*-imidazol-1-yl)methanone (74.0 mg, 456 μmol) in DCM (5.0 mL) was added DIPEA (71.0 mg, 547 μmol). The mixture was stirred at 35 °C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((4-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (100 mg, crude). LC-MS: m/z 588.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(5-((4-((3-aminopropoxy)methyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A mixture of [(1*R*,3*S*)-3-[5-[[4-[3-(*tert*-butoxycarbonylamino)propoxymethyl]thiazol-2-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (100 mg, 170 μmol) in DCM : TFA = 2:1 (6.0 mL) was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((4-((3-aminopropoxy)methyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (80.0 mg, crude) LC-MS: m/z 488.1 $[M+H]^+$.

Step 5: (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

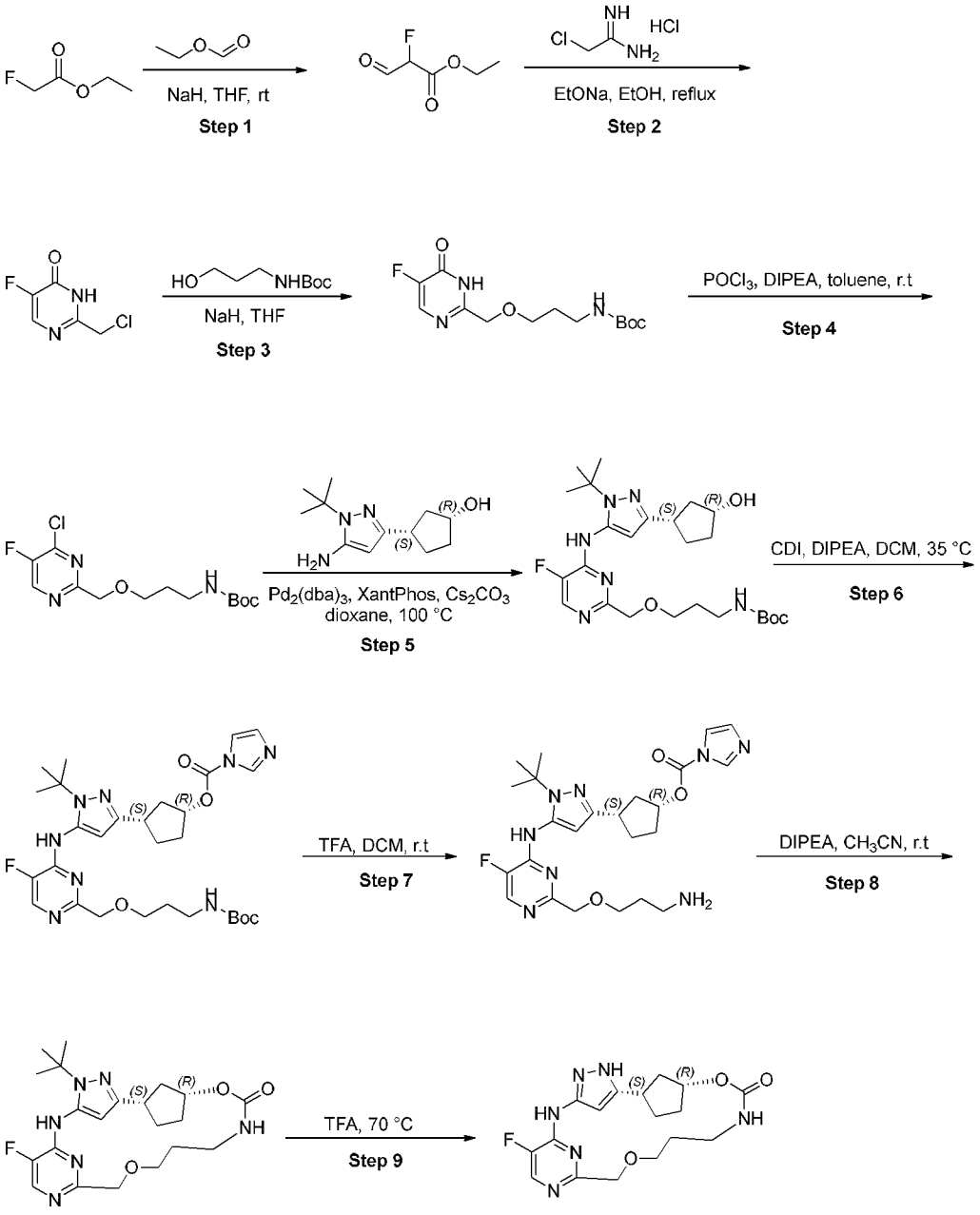
To a solution of [(1*R*,3*S*)-3-[5-[[4-(3-aminopropoxymethyl)thiazol-2-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (80.0 mg, 164 μmol) in CH_3CN (15 mL) was added Et_3N (332 mg, 3.28 mmol). The mixture was heated to 80 °C and stirred at 80 °C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure to give (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (15.0 mg, 20% yield). LC-MS: m/z 420.2 $[M+H]^+$.

Step 6: (1^1S,1^3R,2^4Z,4^2Z)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (15.0 mg, 35.8 μmol) in TFA (2.0 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by Pre-HPLC (with CH_3CN CH_3CN from 30% to 70% in 15 min) to give (1^1S,1^3R,2^4Z,4^2Z)-2^1H-6,12-dioxa-3,10-diaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (1.00 mg, 8% yield) as a white solid. LC-MS:(ESI) $[M+H]^+$364.1.

Example **32**

(1^{1}S,1^3*R*,*Z*)-4^5-fluoro-2^1*H*-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: ethyl 2-fluoro-3-oxopropanoate

To a suspension of NaH (5.65 g, 141 mmol, 60% purity) in THF (30 mL) was added dropwise of the mixture solution of ethyl 2-fluoroacetate (5.00 g, 47.1 mmol, 4.57 mL) and ethyl formate (5.24 g, 70.7 mmol, 5.69 mL) in THF (5.0 mL) at 0 °C. Then the reaction mixture was warmed to 25 °C and stirred at 25 °C for 13 h. The mixture was concentrated under reduced pressure to afford the crude product ethyl 2-fluoro-3-oxo-propanoate (6.30 g, crude) as a yellow solid, which was used for next step directly. LC-MS: (ESI) m/z No Ms.

Step 2: 2-(chloromethyl)-5-fluoropyrimidin-4(3*H*)-one

The mixture suspension of ethyl 2-fluoro-3-oxo-propanoate (6.30 g, crude), 2-chloroacetamidine (7.88 g, 61.1 mmol, HCl) and NaOEt (4.80 g, 70.5 mmol) in Ethanol (40 mL) was stirred at 85 °C for 3 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (100 mL), then the mixture was filtered, and the filter cake was washed with EtOAc (200 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/DCM with EtOAc from 0 to 100% in 20 min to afford the product 2-(chloromethyl)-5-fluoropyrimidin-4(3*H*)-one (700 mg, 9% yield) as a pale-yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 163.0.

Step 3: *tert*-butyl (3-((5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of 2-(chloromethyl)-5-fluoro-1*H*-pyrimidin-6-one (1.00 g, 6.15 mmol) and tert-butyl N-(3-hydroxypropyl)carbamate (1.13 g, 6.46 mmol) in THF (15 mL) was added NaH (984 mg, 24.6 mmol, 60% purity) at 0 °C. Then the reaction was allowed warmed to 20 °C and stirred at 20 °C for 3 h. The mixture was quenched with 5.0 mL water, adjusted the pH to 6 with 1 N HCl, then the mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 100% in 20 min to afford the product *tert*-butyl (3-((5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate (690 mg, 37% yield) as a pale yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 302.1.

Step 4: *tert*-butyl (3-((4-chloro-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of tert-butyl (3-((5-fluoro-6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate (470 mg, 1.56 mmol) in toluene (13 mL) was added DIPEA (1.74 g, 13.5 mmol, 2.35 mL), followed by $POCl_3$ (1.32 g, 8.58 mmol) at 25 °C. Then the reaction mixture was stirred at 25 °C for 6 h. The mixture was diluted with EtOAc (100 mL), then the mixture was washed with brine (80 mL), the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 50% in 15 min to afford the product *tert*-butyl (3-((4-chloro-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate (166 mg, 33% yield) as a pale yellow gum. LC-MS: (ESI) m/z $[M+Na]^+$ 342.1.

Step 5: *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl (3-((4-chloro-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate (160 mg, 500 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (111 mg, 500 μmol) in dioxane (5.0 mL) was added $Pd_2(dba)_3$ (68.7 mg, 75.1 μmol), XanPhos (86.9 mg, 150 μmol) and

K_2CO_3 (207 mg, 1.50 mmol) under the atmosphere of N_2. Then the reaction mixture was stirred at 100 °C under the atmosphere of N_2 for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 100% in 20 min to afford the product *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate (230 mg, 91% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 507.3.

Step 6: (1*R*,3*S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyrimidin-2-yl)methoxy)propyl)carbamate (200 mg, 395 μmol) in DCM (10 mL) was added DIPEA (371 mg, 2.87 mmol, 0.500 mL) at 20 °C, then di(imidazol-1-yl)methanone (192 mg, 1.18 mmol) was added to the reaction mixture, the mixture was heated to 60 °C and stirred at 60 °C for 5 h. The mixture was concentrated under reduced pressure to afford the product (1*R*,3*S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (250 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 601.3.

Step 7: (1*R*,3*S*)-3-(5-((2-((3-aminopropoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (250 mg, 416 μmol) in DCM (5.0 mL) was added TFA (4.44 g, 38.94 mmol, 3.00 mL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford the product (1*R*,3*S*)-3-(5-((2-((3-aminopropoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 501.2.

Step 8: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

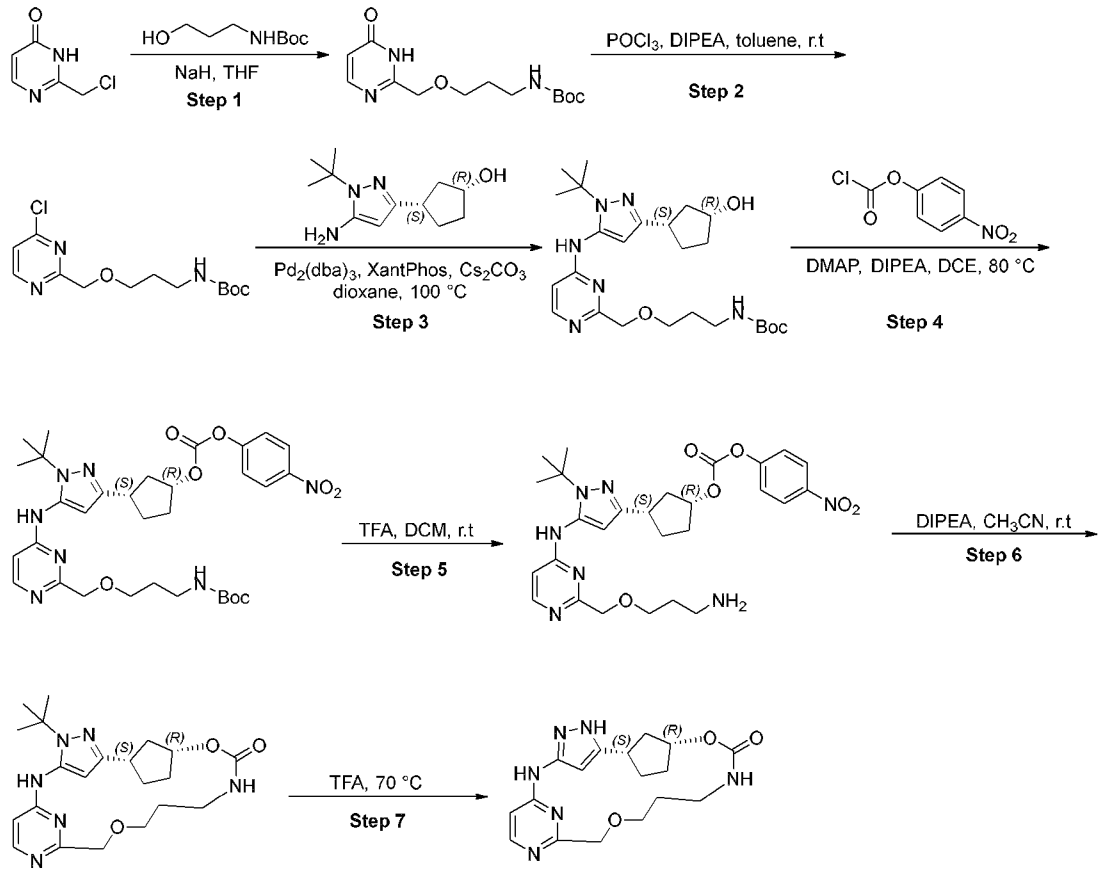
The solution of (1*R*,3*S*)-3-(5-((2-((3-aminopropoxy)methyl)-5-fluoropyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, 420 μmol) in CH_3CN (30 mL) was added DIPEA (3.71 g, 28.7 mmol, 5.00 mL) at 20 °C. Then the reaction mixture was heated to 80 °C and stirred at 80 °C for 15 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 100% in 20 min to afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (150 mg, 83% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 433.2.

Step 9: (1^1S,1^3R,*Z*)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (150 mg, 347 μmol) in TFA (5.0 mL) was stirred at 80 °C for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by Prep-HPLC (eluting with CH_3CN in water with CH_3CN from 20% to 50% in 9 min) to afford the product (1^1S,1^3R,*Z*)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (56.0 mg, 43% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 377.1.

Example **33**

(1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-((6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl *N*-(3-hydroxypropyl)carbamate (299 mg, 1.71 mmol) in THF (10 mL) was added NaH (263 mg, 6.57 mmol, 60% purity) at 0 °C. Then the reaction mixture was stirred at 0 °C

for 10 min. Then 2-(chloromethyl)-1*H*-pyrimidin-6-one (190 mg, 1.31 mmol) was added to the reaction mixture. The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was quenched with MeOH (5 mL), then the mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with PE/EtOAc (with EtOAc from 0~60% in 15 min) to afford *tert*-butyl (3-((6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate (295 mg, 79% yield) as a pale yellow oil. LC-MS: (ESI) m/z $[M+H]^+$ 284.2.

Step 2: *tert*-butyl (3-((4-chloropyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl (3-((6-oxo-1,6-dihydropyrimidin-2-yl)methoxy)propyl)carbamate (200 mg, 706 μmol) in toluene (8.0 mL) was added DIPEA (456 mg, 3.53 mmol, 614 μL) and $POCl_3$ (216 mg, 1.41 mmol) at 25 °C. Then the reaction mixture was stirred at 25 °C for 72 h. The mixture was diluted with EtOAc (100 mL), then the mixture was washed with brine (80 mL), the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, the residue was purified by flash column chromatography eluting with PE/EtOAc (with EtOAc from 0~50% in 15 min) to afford *tert*-butyl (3-((4-chloropyrimidin-2-yl)methoxy)propyl)carbamate (80.0 mg, 38% yield) as a pale yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 302.1.

Step 3: *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl (3-((4-chloropyrimidin-2-yl)methoxy)propyl)carbamate (80.0 mg, 265 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (59.2 mg, 265 μmol) in dioxane (8.0 mL) was added $Pd_2(dba)_3$ (24.3 mg, 26.5 μmol), XantPhos (30.7 mg, 53.0 μmol) and Cs_2CO_3 (216 mg, 663 μmol) under the atmosphere of N_2. Then the reaction mixture was heated to 100 °C and stirred at 100 °C under the atmosphere of N_2 for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with PE/EtAOc (with EtOAc from 0~60% in 15 min) to afford *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidin-2-yl)methoxy)propyl) carbamate (60.0 mg, 46% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 489.2.

Step 4: *tert*-butyl (3-((4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl *N*-[3-[[4-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]pyrimidin-2-yl]methoxy]propyl]carbamate (60.0 mg, 123 μmol) in DCE (37 mL) was added DMAP (3.00 mg, 24.56 μmol) and DIPEA (79.3 mg, 614 μmol, 107 μL), then (4-nitrophenyl) carbonochloridate (74.3 mg, 368 μmol) was added to the reaction mixture. The reaction mixture was heated to 80 °C and stirred at 80 °C for 15 h. The mixture was not disposed for the weekend. The mixture was diluted with DCM (100 mL), the mixture was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by

flash column chromatography eluting with PE /EtOAc (with EtOAc from 0~60% in 10 min) to afford [(1*R*,3*S*)-3-[5-[[2-[3-(*tert*-butoxycarbonylamino)propoxymethyl]pyrimidin-4-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (36.0 mg, 45% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 654.3.

Step 5: (1*R*,3*S*)-3-(5-((2-((3-aminopropoxy)methyl)pyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a solution of [(1*R*,3*S*)-3-[5-[[2-[3-(*tert*-butoxycarbonylamino)propoxymethyl]pyrimidin-4-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (36.0 mg, 55.1 μmol) in DCM (5.0 mL) was added TFA (37.6 mg, 330 μmol, 25.5 μL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[2-(3-aminopropoxymethyl)pyrimidin-4-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (40.0 mg, crude, TFA) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 554.2.

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of [(1*R*,3*S*)-3-[5-[[2-(3-aminopropoxymethyl)pyrimidin-4-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (40.0 mg, 59.9 μmol, TF) in CH_3CN (15 mL) was added dropwise the DIPEA (77.4 mg, 599 μmol, 104 μL) slowly. Then the reaction mixture was stirred at 20 °C for 15 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with PE/EtOAc (with EtOAc from 0~50% in 10 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (18.0 mg, 72% yield) as a yellow solid, LC-MS: (ESI) m/z $[M+H]^+$ 415.2.

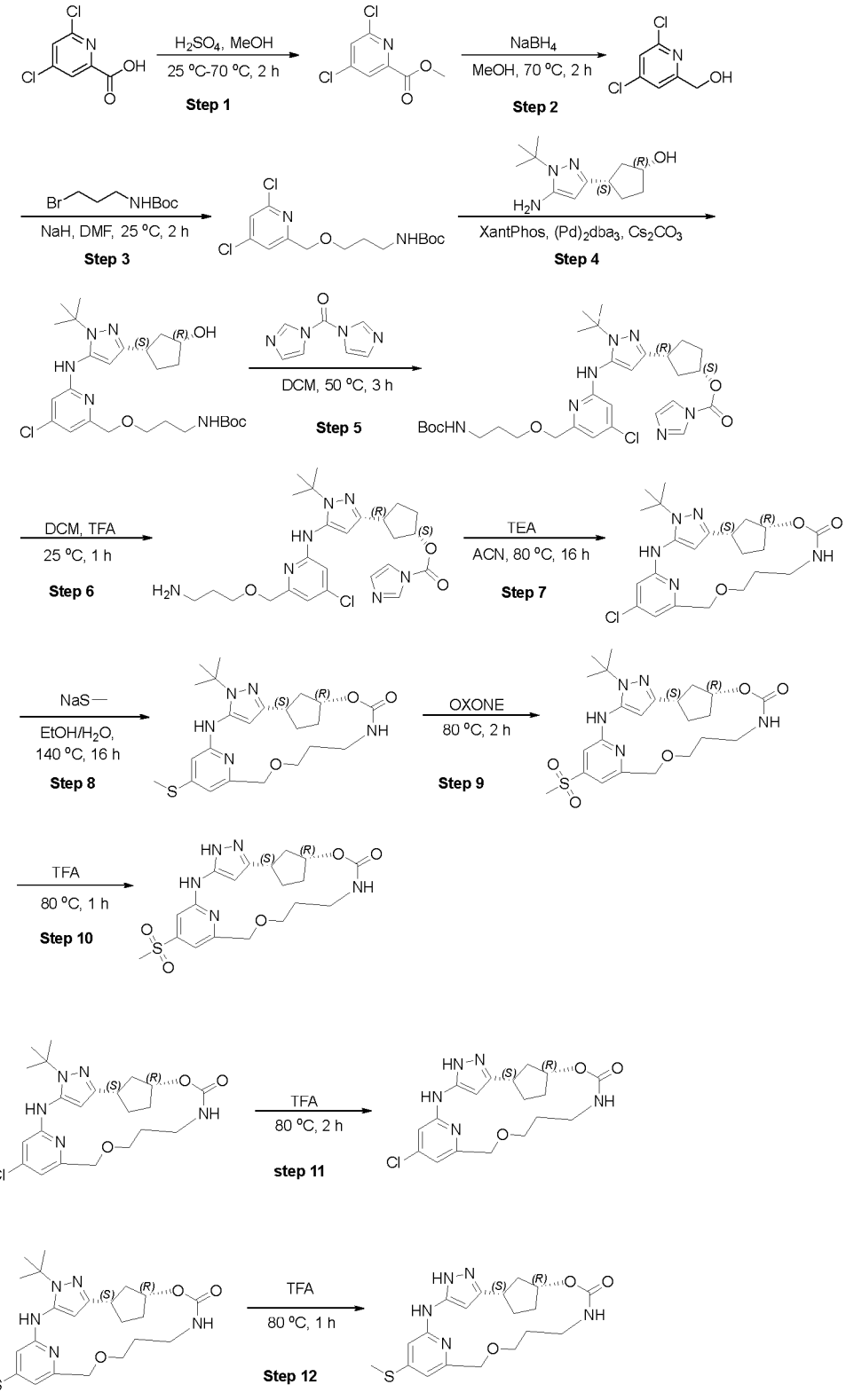
Step 7: (1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (18.0 mg, 43.43 μmol) in TFA (5.0 mL) was heated to 70 °C and stirred at 70 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC (with CH_3CN from 10% to 20% in 8 min) to afford (1^1S,1^3R,*Z*)-2^1H-6,12-dioxa-3,10-diaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (7.00 mg, 45% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 359.1.

Example **34**, **35** and **36**

(1^1S,1^3R,*Z*)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one, (1^1S,1^3R,*Z*)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1S,1^3R,*Z*)-4^4-

(methylthio)-2[1]*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: methyl 4,6-dichloropicolinate

To a stirring solution of 4,6-dichloropicolinic acid (3.00 g, 15.6 mmol) in Methanol (30 mL) was added conc. H_2SO_4 (1.80 g, 18.6 mmol) at 25 °C. The reaction mixture was heated to 70 °C and stirred at 70 °C for 2 h. The reaction mixture was concentrated under reduce pressure, diluted with EtOAc (100 mL) and poured into saturated $NaHCO_3$ solution (80 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with H_2O (100 mL) and brine (100 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford methyl 4,6-dichloropicolinate (2.80 g, 87% yield) as a yellow solid. LC-MS: m/z 206.7 $[M+H]^+$.

Step 2: (4,6-dichloropyridin-2-yl)methanol

To a solution of methyl 4,6-dichloropyridine-2-carboxylate (3.00 g, 14.6 mmol) in Methanol (12 mL) was added $NaBH_4$ (2.20 g, 58.2 mmol) at 0 °C. The mixture was heated to 70 °C and stirred at 70 °C for 16 h. The mixture was cooled to 25 °C, concentrated under reduce pressure, portioned into H_2O (50 mL) and extracted with DCM (50 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to afford (4,6-dichloropyridin-2-yl)methanol (2.40 g, 93% yield) as a white solid. LC-MS: m/z 178.7 $[M+H]^+$.

Step 3: *tert*-butyl (3-((4,6-dichloropyridin-2-yl)methoxy)propyl)carbamate

To a solution of NaH (202 mg, 8.4 mmol) in DMF (25 mL) was added (4,6-dichloropyridin-2-yl)methanol (1 g, 5.62 mmol) at 0 °C. The mixture was stirred at this temperature under N_2 for 0.5 hour. After adding *tert*-butyl (3-bromopropyl)carbamate (1.6 g, 6.74 mmol) at 0 °C, the mixture was stirred at 25 °C under N_2 for 2 h. The mixture was diluted with H_2O (20 ml) and extracted with EtOAc (20 mL × 2). Organic layer was washed with LiCl solution (20 mL), then concentrated to get a residue, which was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0~50% in 10 min) to afford *tert*-butyl (3-((4,6-dichloropyridin-2-yl)methoxy)propyl)carbamate (370 mg, 20% yield) as a yellow liquid. LC-MS: m/z 335.7 $[M+H]^+$.

Step 4: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-chloropyridin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl *N*-[3-[(4,6-dichloro-2-pyridyl)methoxy]propyl]carbamate (450 mg, 1.34 mmol) and (1*R*,3*S*)-3-(5-amino-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (250 mg, 1.12 mmol) in 1, 4-dioxane (20 mL) was added $Pd_2(dba)_3$ (205 mg, 223 μmol) , XantPhos (259 mg, 447 μmol) and Cs_2CO_3 (1.10 g, 3.36 mmol) . The mixture was heated to 100 °C and stirred at 100 °C under N_2 for 8 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatograthy eluting with EtOAc/PE (with EtOAc from 0~50% in 15 min) to get *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-chloropyridin-2-yl)methoxy)propyl)carbamate (420 mg, 72% yield) as a yellow liquid. LC-MS: m/z 522.7 $[M+H]^+$.

Step 5: (1*S*,3*R*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-4-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl *N*-[3-[[6-[[2-tert-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-chloro-2-pyridyl]methoxy]propyl]carbamate (100 mg, 191 μmol) in DCM (10 mL) was added Et_3N (58.0 mg, 574 μmol) . The mixture was stirred at 50 °C for 3 h. The mixture was diluted with NaCl solution (10 mL) and extracted with EtOAc (10 mL × 2). Organic layers were dried with Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0~70% in 15 min) to afford [(1*S*,3*R*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propoxymethyl]-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (110 mg, 93% yield) as a yellow liquid. LC-MS: m/z 616.7 $[M+H]^+$.

Step 6: (1*S*,3*R*)-3-(5-((6-((3-aminopropoxy)methyl)-4-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of [(1*S*,3*R*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propoxymethyl]-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (110 mg, 178 μmol) in DCM (4.0 mL) was added TFA (2.0 mL) . The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to get (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-4-chloropyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90.0 mg, 98% yield) as a yellow liquid. LC-MS: m/z $[M+H]^+$ 516.7.

Step 7: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of [(1*S*,3*R*)-3-[5-[[6-(3-aminopropoxymethyl)-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (80.0 mg, 155 μmol) in CH_3CN (615 μL) was added Et_3N (313 mg, 3.10 mmol) . The mixture was stirred at 80 °C under N_2 for 16 hours. The mixture was concentrated to get a residue. The residue was purified by flash chromatography column eluting with EtOAc/PE (with EtOAc from 0~70% in 15 min) to get (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (60.0 mg, 86% yield) as a yellow liquid. LC-MS: m/z $[M+H]^+$ 448.7.

Step 8: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3-cyclopentanacyclododecaphan-11-one (50.0 mg, 111 μmol) in Ethanol/H_2O = 1:1 (2.0 mL) was added sodium; methane thiolate (31.0 mg, 446 μmol). The mixture was heated to 140 °C and stirred at 140 °C for 16 h. The mixture was diluted with H_2O (5.0 mL) and extracted with EtOAc (5 mL × 2). Organic layers were combined and dried over Na_2SO_4, filtered and concentrated to get a residue, which was purified by flash chromatography column eluting with EtOAc/PE (with

EtOAc from 0~70% in 15 min) to get ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (29.0 mg, 56% yield) as a yellow solid. LC-MS: (ESI) $[M+H]^+$ = 460.2.

Step 9: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (20.0 mg, 43.5 μmol) in acetone (2.0 mL) was added Potassium Peroxomonosulfate 4.5% (actice oxygen) (80.0 mg, 130 μmol) at 0 °C. The mixture was stirred at 25 °C for 5 h. The mixture was filtered and concentrated under reduced pressure to afford ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (18.0 mg, 84% yield) as a yellow liquid. LC-MS: (ESI) $[M+H]^+$ = 492.1.

Step 10: ($1^1S,1^3R,Z$)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (15.0 mg, 30.5 μmol) in TFA (2.0 mL) was heated to 80 °C and stirred at 80 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 25% to 75% in 8 min) to give ($1^1S,1^3R,Z$)-4^4-(methylsulfonyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (8.00 mg, 60% yield) as a white solid. LC-MS: (ESI) $[M+H]^+$ = 436.1.

Step 11: ($1^1S,1^3R,Z$)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (59.0 mg, 131 μmol) in TFA (5.0 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 40% to 60% in 8 min) to give ($1^1S,1^3R,Z$)-4^4-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3) cyclopentanacyclododecaphan-11-one (15.0 mg, 29% yield) as a white solid. LC-MS:(ESI) $[M+H]^+$=392.1.

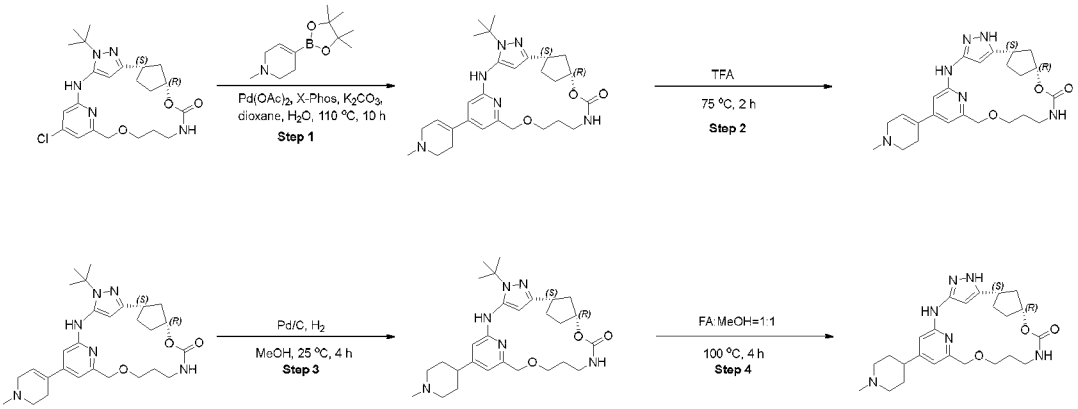
Step 12: ($1^1S,1^3R,Z$)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of ($1^1S,1^3R,Z$)-2^1-(*ter*t-butyl)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (10.0 mg, 21.7 μmol) in TFA (1.0 mL) was heated to 80 °C and stirred at 80 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 40% to 60% in 8 min) to give ($1^1S,1^3R,Z$)-4^4-(methylthio)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-

cyclopentanacyclododecaphan-11-one (6.00 mg, 68% yield) as a white solid. LC-MS: (ESI) $[M+H]^+$ = 404.1.

Example **37** and **38**

($1^1S,1^3R,Z$)-44-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and ($1^1S,1^3R,Z$)-4^4-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-44-chloro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 67.0 μmol) in dioxane (2.0 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (30.0 mg, 134 μmol), $Pd(OAc)_2$ (3.00 mg, 13.4 μmol), X-Phos (12.0 mg, 26.8 μmol), K_2CO_3 (27.0 mg, 200 μmol) and H_2O (0.10 mL). The suspension was degassed with N_2 for 5 times. The reaction mixture was heated to 110 °C and stirred at 110 °C for 10 h. The mixture was concentrated to dryness. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL × 3). The combined organic layer was washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography eluting with DCM/MeOH (with MeOH from 0~9% in 10 min) to afford ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (22.0 mg, 64% yield) as a light yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 509.3.

Step 2: ($1^1S,1^3R,Z$)-44-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (20.0 mg, 39.3 μmol) in TFA (1.5 mL) was heated to 75 °C and stirred at 75 °C for 2 h. The mixture was

concentrated to afford crude product, which was purified by prep-HPLC (with CH_3CN from 30% to 100% in 8 min) to afford the product ($1^1S,1^3R,Z$)-4^4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (5.80 mg, 32% yield) as a white solid. LC-MS:(ESI) m/z $[M+H]^+$ 453.2.

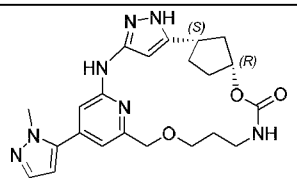
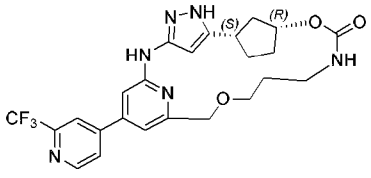
Step 3: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

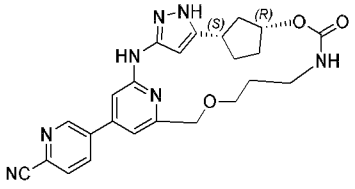
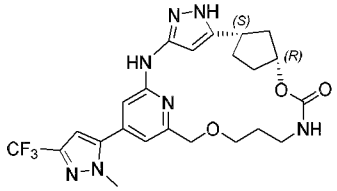
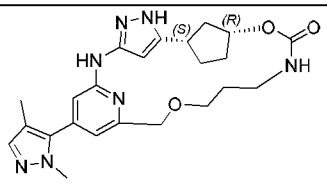
To a solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, 49.2 μmol) in Methanol (2.0 mL) was added Pd/C (3.00 mg, 19.7 μmol) . The mixture was stirred at 25 °C for 3 h. The mixture was filtered and concentrated under reduced pressure to give ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (20.0 mg, 80% yield) as a yellow gum. LC-MS: m/z 511.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(2-cyclohexyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)cyclopentyl isopropylcarbamate

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, 48.9 μmol) in TFA (2.0 mL) was heated to 80 °C and stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 40% to 60% in 12 min) to give ($1^1S,1^3R,Z$)-4^4-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (6.00 mg, 30% yield) as a white solid. LC-MS:(ESI) $[M+H]^+$=455.2.

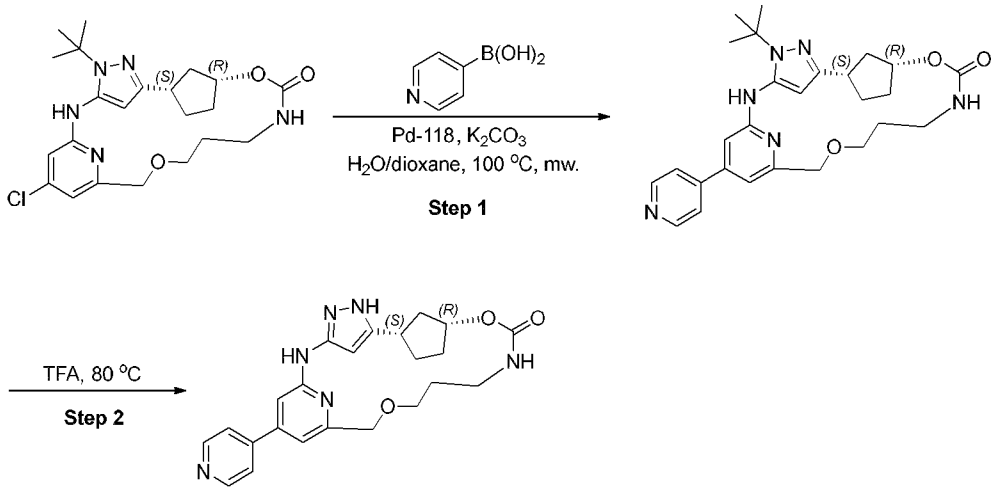
The following compounds were prepared using the similar procedure disclosed in synthetic example **38**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
39		438.2
40		503.2

41		460.1
42		506.2
43		452.2

Example **44**

(1^1*S*,1^3*R*,*Z*)-4^4-(pyridin-4-yl)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-(pyridin-4-yl)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

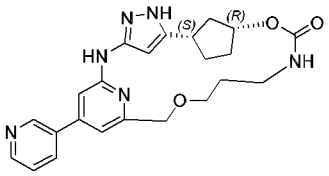
To a solution of (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (40.0 mg, 89.2 μmol) in dioxane (5.0 mL) and H_2O (1.0 mL) was added K_2CO_3 (37.0 mg, 267 μmol), Pd(dppf)Cl_2 (11.5 mg, 17.8 μmol) and 4-pyridylboronic acid (21.9 mg, 178 μmol). The reaction mixture was irradiated in a microwave reactor at 120 °C for 0.5 h. The residue was purified by flash column chromatography eluting with

EtOAc/PE (with EtOAc from 0 to 50% in 15 min) to give ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(pyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (40.0 mg, 91% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 491.2.

Step 2: ($1^1S,1^3R,Z$)-4^4-(pyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

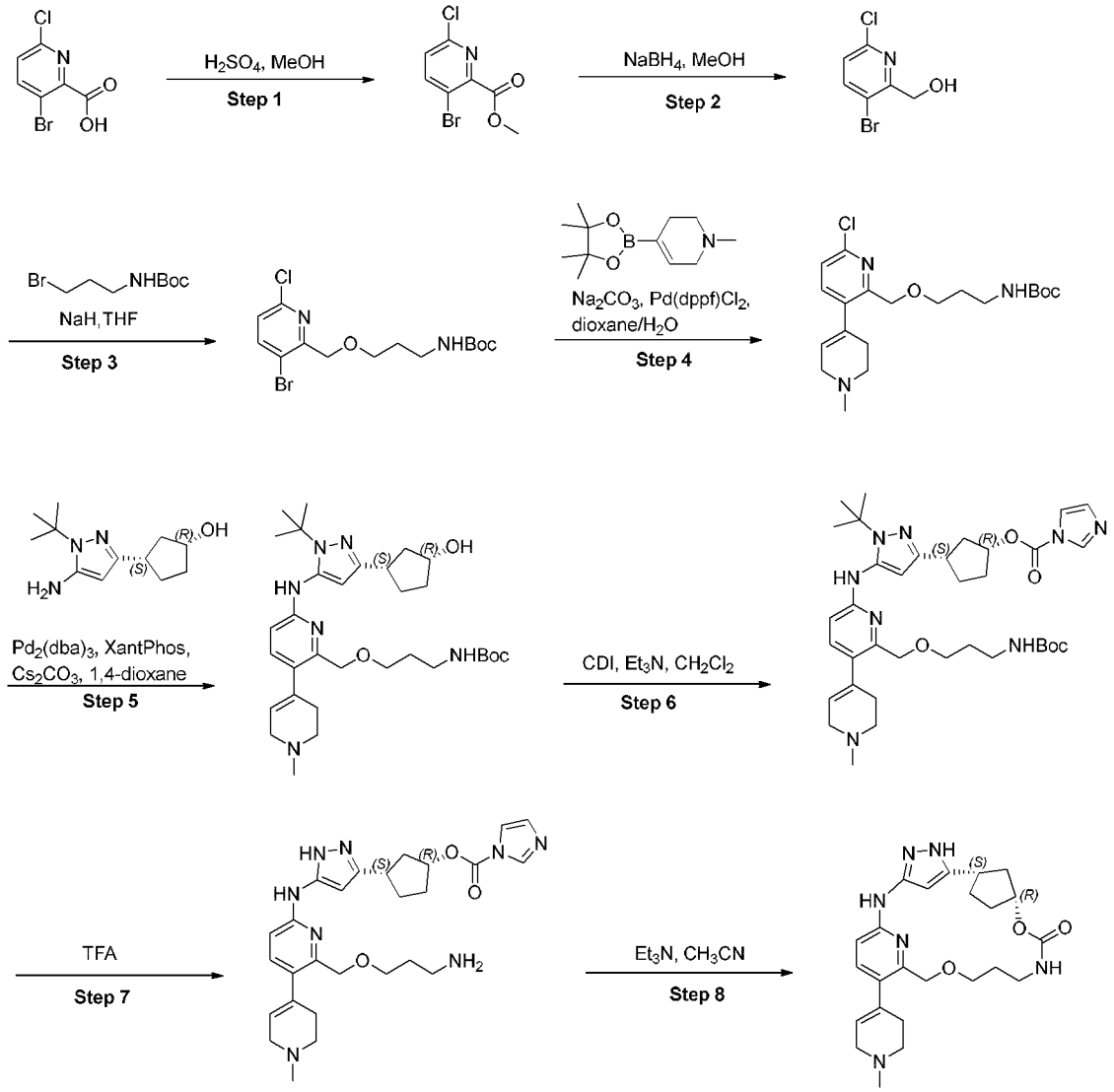
A suspension of ($1^1S,1^3R,Z$)-21-(*tert*-butyl)-4^4-(pyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 61.1 μmol) in TFA (5.0 mL) was heated to 80 °C and stirred at 80 °C for 1 h under N_2. LCMS showed the starting material was consumed and desired product was detected. The crude product was purified by prep-HPLC (with CH_3CN from 8% to 38% in 9 min) to give ($1^1S,1^3R,Z$)-4^4-(pyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (13.9 mg, 52% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 435.2.

The following compounds were prepared using the similar procedure disclosed in synthetic example **44**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
45		435.2

Example **46**

($1^1S,1^3R,Z$)-4^5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-21*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: methyl 3-bromo-6-chloropicolinate

To a stirred solution of 3-bromo-6-chloropicolinic acid (100 mg, 423 umol) in MeOH (2.0 mL) was added H_2SO_4 (0.1 mL, 42 mg, 423 umol) at 25 °C. The reaction mixture was warmed to 90 °C and stirred at that temperature for 16 h before it was treated with ice-cold water (20 mL) and extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with PE/EtOAc with EtOAc from 0 to 20% in 15 min to afford methyl 3-bromo-6-chloropicolinate (80.0 mg, 76% yield) as a white solid.LC-MS: m/z [M+H]$^+$ 249.9.

Step 2: (3-bromo-6-chloropyridin-2-yl)methanol

To a suspension of methyl 3-bromo-6-chloropicolinate (100 mg, 399 umol) in MeOH (2.0 mL) was slowly added $NaBH_4$ (75.9 mg, 2.00 mmol) at 0 °C. The mixture was warmed to 25 °C and stirred at that temperature for 16 h before it was treated with ice-cold water (20 mL) and extracted with EtOAc

(50 mL ×3). The organic phases was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with PE/EtOAc with EtOAc from 0 to 30% in 25 min to afford (3-bromo-6-chloropyridin-2-yl)methanol (70.0 mg, 79% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 222.0.

Step 3: *tert*-butyl (3-((3-bromo-6-chloropyridin-2-yl)methoxy)propyl)carbamate

To a stirred solution of NaH (2.59 g, 64.7 mmol, 60% purity) in THF (80.0 mL) was added (3-bromo-6-chloropyridin-2-yl)methanol (4.80 g, 21.6 mmol). The mixture was stirred at 0 °C for 20 min under N_2. Then *tert*-butyl (3-bromopropyl)carbamate (5.14 g, 21.6 mmol) in THF (80.0 mL) was added to the mixture. The resulting mixture was stirred at 25 °C for 20 h under N_2 before it was quenched with water (100 mL) and then extracted with EtOAc (150 mL × 2). The combined organic phases were dried over Na_2SO_4 and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 10% in 20 min to give *tert*-butyl (3-((3-bromo-6-chloropyridin-2-yl)methoxy)propyl)carbamate (3.00 g, 37% yield) as a yellow oil. LC-MS: m/z $[M+Na]^+$ 400.5.

Step 4: *tert*-butyl (3-((6-chloro-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate

To a stirred solution of *tert*-butyl (3-((3-bromo-6-chloropyridin-2-yl)methoxy)propyl)carbamate (1.00 g, 2.63 mmol) in 1,4-dioxane (10.0 mL) were sequentially added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (588 mg, 2.63 mmol), $Pd(dppf)Cl_2$ (193 mg, 263 μmol) and Na_2CO_3 (698 mg, 6.58 mmol) and H_2O (2.0 mL) at 25 °C. The mixture was warmed to 95 °C and stirred at that temperature for 3 h under N_2 before it was cooled to 25 °C, diluted with water (25 mL) and extracted with EtOAc (50 mL × 2). The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 65% in 25 min to give *tert*-butyl (3-((6-chloro-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate (500 mg, 48% yield) as a brown solid. LC-MS: m/z $[M+H]^+$ 396.1.

Step 5: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate

To a stirred solution of *tert*-butyl (3-((6-chloro-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate (355 mg, 896 μmol) in 1,4-dioxane (10.0 mL) were sequentially added (*1R,3S*)-3-(5-amino-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentan-1-ol (100 mg, 448 μmol) , $Pd_2(dba)_3$ (41.0 mg, 44.8 μmol), XantPhos (25.9 mg, 44.8 μmol) and Cs_2CO_3 (292 mg, 896 μmol) at 25 °C. The reaction mixture was warmed to 100°C and stirred at that temperature for 3 h under N_2 atomosphere before it was cooled and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether/EtOAc with EtOAc from 0 to 70% in 25 min to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-

pyrazol-5-yl)amino)-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate (60.0 mg, 22% yield) as a yellow solid. LC-MS: m/z $[1/2M+H]^+$ 292.0.

Step 6: (*1R,3S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a suspension *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-2-yl)methoxy)propyl)carbamate (60.0 mg, 103 μmol) in CH_2Cl_2 (2.0 mL) was added CDI (44.5 mg, 309 μmol) and Et_3N (72 μL, 52.1 mg, 515 μmol) at 25 °C and stirred for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue (*1R,3S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 677.6.

Step 7: (*1R,3S*)-3-(5-((2-((3-aminopropoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

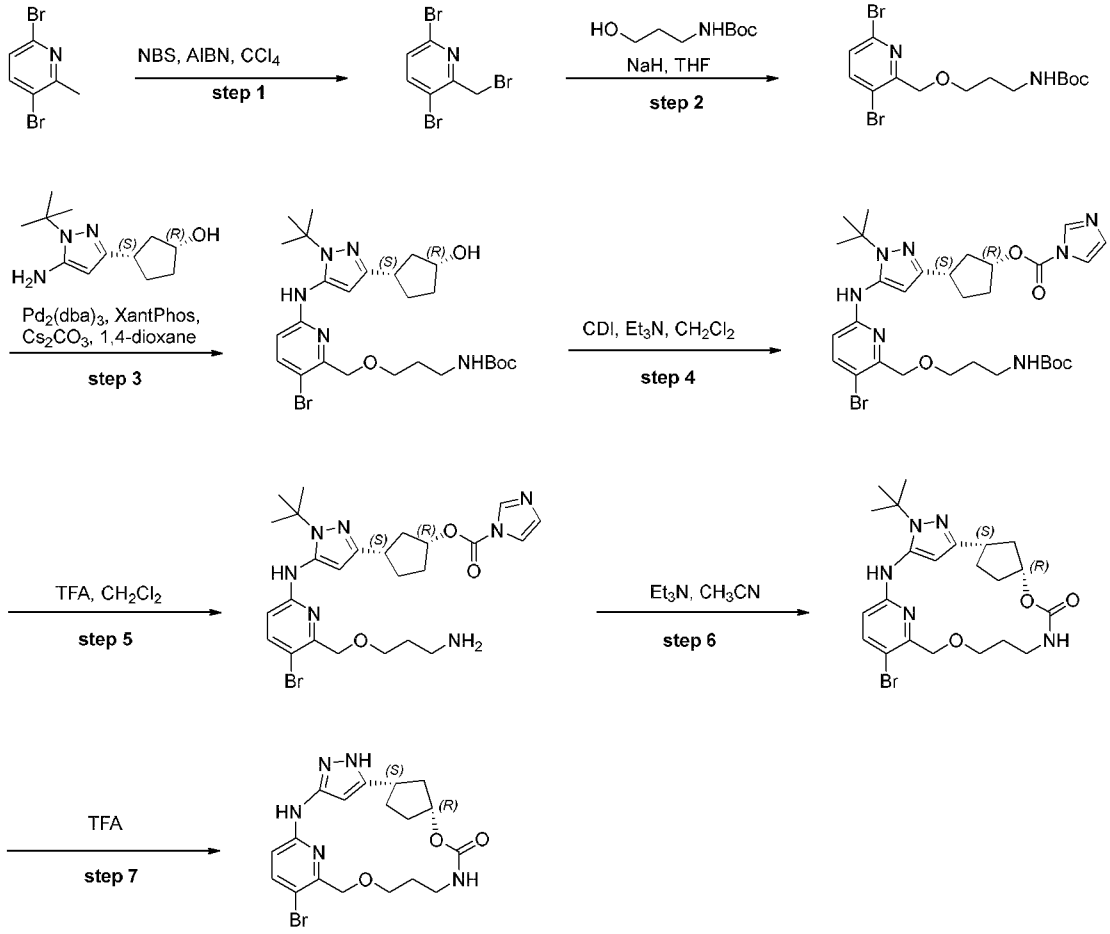
A mixture of (*1R,3S*)-3-(5-((2-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in TFA (4.0 mL) was stirred for 16 h at 70 °C. Then it was concentrated to give (*1R,3S*)-3-(5-((2-((3-aminopropoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate as a brown oil which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 520.7.

Step 8: ($1^1S,1^3R,Z$)-4^5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a suspension of (*1R,3S*)-3-(5-((2-((3-aminopropoxy)methyl)-1'-methyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in CH_3CN (5.0 mL) was added Et_3N (269 μL, 196 mg, 1.94 mmol) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 5 h. Then it was concentrated and purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 70% in 30 min) to afford ($1^1S,1^3R,Z$)-45-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (1.30 mg, 4% yield) as an light yellow solid. LC-MS: m/z $[M+H]^+$ 453.3.

Example 47

(1^1*S*,1^3*R*,*Z*)-4^5-bromo-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 3,6-dibromo-2-(bromomethyl)pyridine

A mixture of 3,6-dibromo-2-methylpyridine (10.0 g, 39.9 mmol), AIBN (6.54 g, 39.9 mmol) and NBS (14.2 g, 79.7 mmol) in CCl_4 (100.0 mL) was stirred at 90 °C for 16 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10% in 20 min) to give 3,6-dibromo-2-(bromomethyl)pyridine (9.00 g, 69% yield). LC-MS: m/z $[M+H]^+$ 329.4.

Step 2: *tert*-butyl (3-((3,6-dibromopyridin-2-yl)methoxy)propyl)carbamate

To a stirred solution of NaH (0.67 g, 16.7 mmol, 60% purity) in THF (30.0 mL) was added *tert*-butyl (3-hydroxypropyl)carbamate (2.93 g, 16.7 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min before a solution of 3,6-dibromo-2-(bromomethyl)pyridine (5.00 g, 15.2 mmol) in THF (50.0 mL) was added. The resulting mixture was stirred at 0 °C for 1 h before it was diluted with H_2O (50 mL) and warmed to 25 °C. The mixture was extracted with EtOAc (150 mL × 2). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel

chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 20 min) to afford *tert*-butyl (3-((3,6-dibromopyridin-2-yl)methoxy)propyl)carbamate (2.10 g, 33% yield) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 424.9.

Step 3: *tert*-butyl (3-((3-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)propyl)carbamate

To a mixture of *tert*-butyl (3-((3,6-dibromopyridin-2-yl)methoxy)propyl)carbamate (360 mg, 849 μmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (190 mg, 849 μmol) and Cs_2CO_3 (553 mg, 1.70 mmol) in 1,4-dioxane (8.0 mL) were sequentially added XantPhos (49.2 mg, 84.9 μmol) and $Pd_2(dba)_3$ (77.8 mg, 84.9 μmol) at 25 °C. The reaction mixture was stirred at 80 °C under N_2 atmosphere for 3 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 20 min) to afford *tert*-butyl (3-((3-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)propyl)carbamate (280 mg, 58% yield) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 565.6.

Step 4: (1*R*,3*S*)-3-(5-((5-bromo-6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (3-((3-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)propyl)carbamate (280 mg, 494 μmol) in CH_2Cl_2 (12.0 mL) were sequentially added Et_3N (207 μL, 150 mg, 1.48 mmol) and CDI (213 mg, 1.48 mmol) at 25 °C. The reaction mixture was warmed to 35 °C and stirred at that temperature for 2 h before it was cooled, diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 20 min) to afford (1*R*,3*S*)-3-(5-((5-bromo-6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (280 mg, 85% yield) as a light-yellow solid. LC-MS: m/z $[M+H]^+$ 659.6.

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((5-bromo-6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (280 mg, 424 μmol) in CH_2Cl_2 (20.0 mL) was added TFA (97.96 μL, 145 mg, 1.27 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (crude) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 559.5.

Step 6: ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

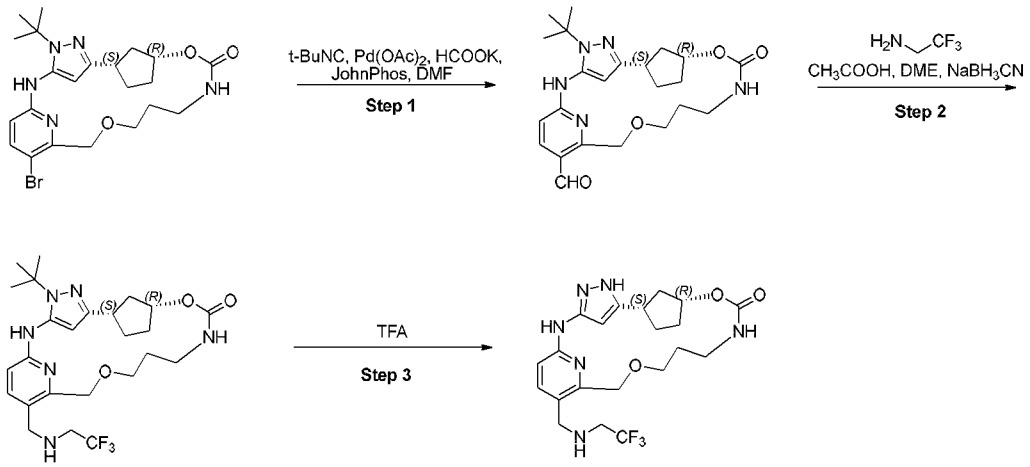
To a stirred solution (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (crude) in CH_3CN (10.0 mL) was added Et_3N (1 mL) at 25 °C . The reaction mixture was warmed to 70 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 20 min) to afford ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (150 mg, 62% yield for 2 steps) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 492.0.

Step 7: ($1^1S,1^3R,Z$)-4^5-bromo-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, 50.9 mmol) in TFA (2.0 mL) was stirred for 16 h at 70 °C. Then it was concentrated and purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 45% in 40 min) to give ($1^1S,1^3R,Z$)-4^5-bromo-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.6 mg, 21% yield). LC-MS: m/z $[M+H]^+$ 435.9.

Example 48

($1^1S,1^3R,Z$)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-11-oxo-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbaldehyde

To a stirred solution of ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (100.0 mg, 0.20 mmol) and

$Pd(OAc)_2$ (13.7 mg, 0.06 mmol), JohnPhos (18.2 mg, 0.06 mmol), HCOOK (199 mg, 2.03 mmol) and t-BuNC (2.81 mg, 0.41 mmol) were sequentially added DMF (5.0 mL) under N_2 atmosphere at 25 °C. The mixture was warmed to 60 °C and stirred at that temperature for 12 h before it was cooled to 25 °C. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The mixture was concentrated and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40 % in 30 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)- cyclopentanacyclododecaphane-4^5-carbaldehyde (50.0 mg, 56% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 442.24.

Step 2: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

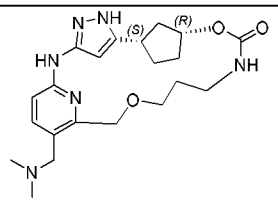
To a stirred solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-11-oxo-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbaldehyde (50.0 mg, 0.11 mmol), 2,2,2-trifluoroethanamine (56.1 mg, 56.6 mmol), Sodium cyanoborohydride(28.0 mg, 0.453 mmol) in DME (2.0 mL) was added acetic acid (2 drops) at 25 °C and the reaction mixture was stirred at that temperature for 12 h under N_2 atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 25 min) to give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one afford (30.0 mg, 51% yield) as a brown oil. LC-MS: m/z $[M+H]^+$ 525.3.

Step 3: (1^1S,1^3R,*Z*)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A stirred solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one in TFA (2.0 mL) was stirred at 70 °C for 12 h before it was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 40% in 40 min) to give (1^1S,1^3R,*Z*)-4^5-(((2,2,2-trifluoroethyl)amino)methyl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (2.60 mg, 9.7% yield) as an off-white solid.LC-MS: m/z $[M+H]^+$ 469.2.

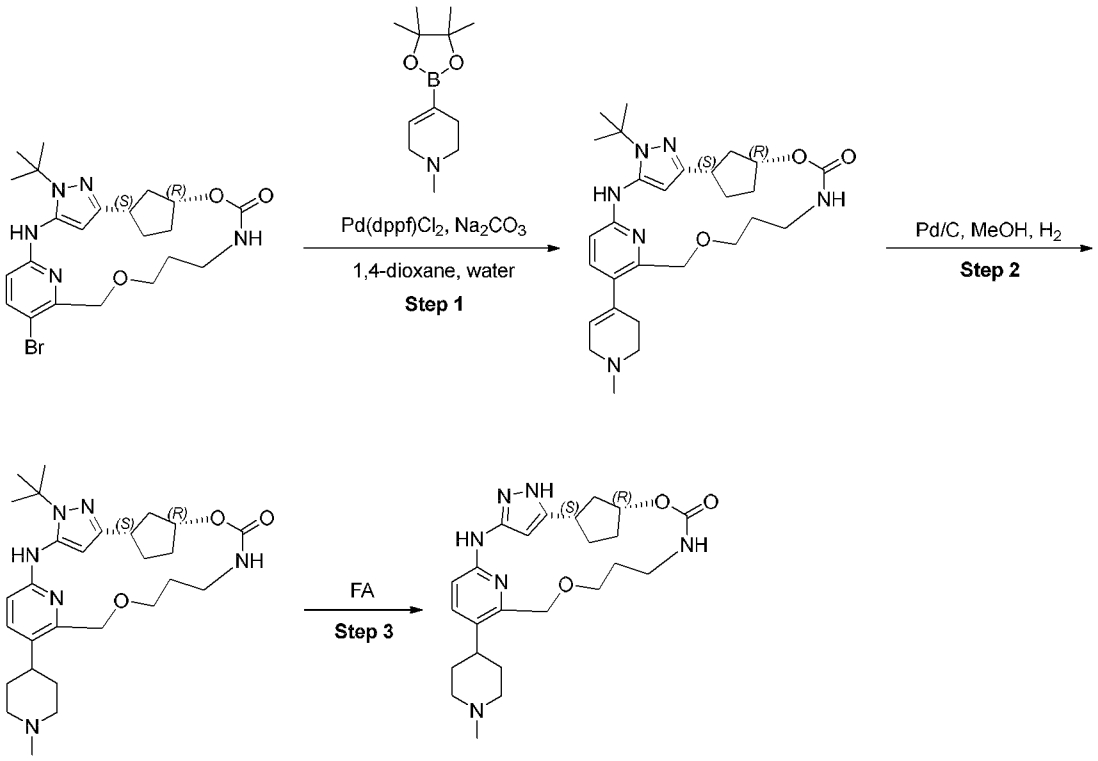
The following compounds were prepared using the similar procedure disclosed in synthetic example **48**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$

49		415.3

Example **50**

(1^1*S*,1^3*R*,*Z*)-4^5-(1-methylpiperidin-4-yl)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a suspension of (1^1*S*,1^3*R*,*Z*)-4^5-bromo-2^1-(*tert*-butyl)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (35.0 mg, 0.071 mmol) in 1,4-dioxane (2.0 mL) and water (0.2 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (31.7 mg, 0.142 mmol), Na_2CO_3 (22.6 mg, 0.213 mmol) and $Pd(dppf)Cl_2$ (10.4 mg, 0.014 mmol) at room temperature. The reaction was stirred at 80 °C for 2 h under N_2, before it was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10% in 30 min) to afford (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1*H*-6,12-dioxa-3,10-diaza-

4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, 70% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 509.3.

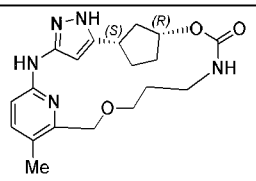
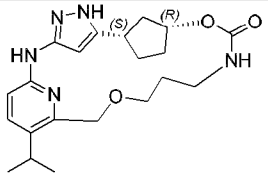
Step 2: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

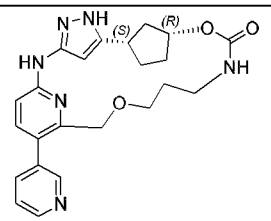
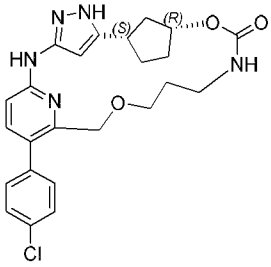
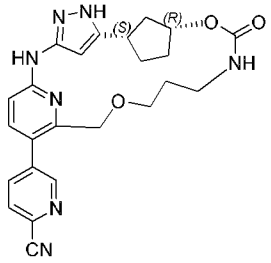
To a suspension of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, 0.049 mmol) in MeOH (2.0 mL) was added slowly Pd/C (11.0 mg, 0.098 mmol) at room temperature and stirred for 16 h under H_2. After completion of the reaction as judged by LCMS, reaction mixture was filtered and concentrated under reduced pressure. The crude product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, crude) was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 511.0.

Step 3: (1^1S,1^3R,*Z*)-4^5-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.0 mg, crude) in HCO_2H (2.0 mL) was stirred for 2 h at 80 °C, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated under reduced pressure, purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 2% to 15% in 30 min) to give (1^1S,1^3R,*Z*)-4^5-(1-methylpiperidin-4-yl)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (1.5 mg) as a white solid. LC-MS: m/z $[M+H]^+$ 455.3.

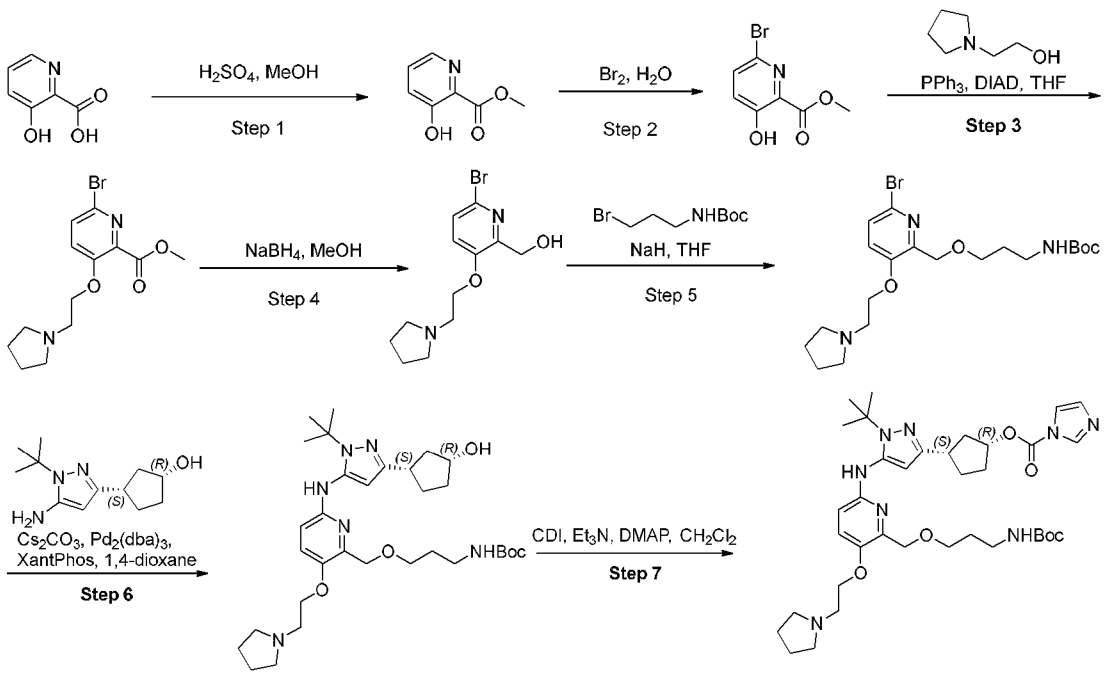
The following compounds were prepared using the similar procedure disclosed in synthetic example **50**.

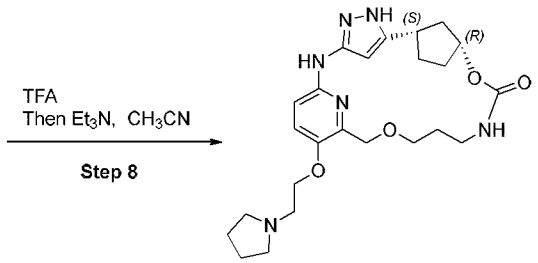
Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
51		372.1
52		400.2

53		435.2
183		468.0
184		460.2

Example **54**

(1^1*S*,1^3*R*,*Z*)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: methyl 3-hydroxypicolinate

To a stirred solution of 3-hydroxypyridine-2-carboxylic acid (7.0 g, 50.3 mmol) in MeOH (400 mL) was added H_2SO_4 (4.0 mL) at 25 °C. The mixture was warmed to 60 °C and stirred at that temperature for 16 h before it was cooled to 25 °C. The mixture was diluted with water (100 mL), neutralized with saturated aqueous of $NaHCO_3$, extracted with EtOAc (50 mL × 3). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give methyl 3-hydroxypyridine-2-carboxylate (5.6 g) as a yellow solid, which was directly used into the next step without any further purification. LC-MS: m/z $[M+H]^+$ 154.1.

Step 2: methyl 6-bromo-3-hydroxypicolinate

To a stirred solution of methyl 3-hydroxypyridine-2-carboxylate (5.60 g, 36.6 mmol) in H_2O (400 mL) was added bromine (8.20 g, 51.31 mmol) at 25 °C and the mixture was stirred at that temperature for 3 h. The mixture was extracted with CH_2Cl_2 (100 mL × 2). The combined organic phases were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give methyl 6-bromo-3-hydroxy-pyridine-2-carboxylate (6.50 g) as a yellow oil which was directly used into the next step without any further purification. LC-MS: m/z $[M+H]^+$ 231.8.

Step 3: methyl 6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)picolinate

To a stirred mixture of methyl 6-bromo-3-hydroxy-pyridine-2-carboxylate (500 mg, 2.15 mmol) in THF (10.0 mL) were sequentially added 2-pyrrolidin-1-ylethanol (377 μL, 372 mg, 3.23 mmol) and PPh_3 (848 mg, 3.23 mmol), DIAD (479 mg, 2.37 mmol) at 25 °C. The mixture was stirred at that temperature for 2 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with CH_2Cl_2/MeOH (with MeOH from 0 to 5% in 25 min) to give methyl 6-bromo-3-(2-pyrrolidin-1-ylethoxy)pyridine-2-carboxylate (500 mg, 70% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 328.7.

Step 4: (6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methanol

To a stirred solution of methyl 6-bromo-3-(2-pyrrolidin-1-ylethoxy)pyridine-2-carboxylate (500 mg, 152 μmol) in MeOH (10.0 mL) was added $NaBH_4$ (17.2 mg, 456 μmol) at 25 °C and the resulting mixture was stirred at that temperature for 12 h. The mixture was diluted with water (50 mL), extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine (50 mL),

dried over Na_2SO_4 filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with CH_2Cl_2/MeOH (with MeOH from 0 to 10% in 25 min) to give (6-bromo-3-(2-pyrrolidin-1-ylethoxy)-2-pyridyl]methanol (400 mg, 87% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 300.8.

Step 5:*tert*-butyl(3-((6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2- yl) methoxy)propyl) carbamate

To a stirred solution of (6-bromo-3-(2-pyrrolidin-1-ylethoxy)-2-pyridyl]methanol (400 mg, 1.33 mmol) in THF (10.0 mL) was added NaH (80.0 mg, 60 wt.% in mineral oil, 2.0 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 1 h at that temperature before *tert*-butyl N-(3-bromopropyl)carbamate (474 mg, 2.0 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h before it was quenched with H_2O (30 mL), extracted with EtOAc (30 mL × 3). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-((6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methoxy)propyl)carbamate (600 mg) as a yellow oil which was directly used into the next step without any further purification. LC-MS: m/z $[M+H]^+$ 457.9.

Step 6: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methoxy)propyl)carbamate

To a stirred solution of (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (100 mg, 447. μmol) in 1,4-dioxane (5.0 mL) were sequentially added *tert*-butyl(3-((6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methoxy)propyl) carbamate (307 mg, 672 μmol), $Pd_2(dba)_3$ (82.0 mg, 89.6 μmol), XantPhos (104 mg, 179 μmol) and Cs_2CO_3 (438 mg, 1.34 mmol) at 25 °C. The reaction mixture was warmed up to 80 °C and stirred at that temperature for 16 h under N_2 atmosphere before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 60% in 50 min) to give *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methoxy)propyl)carbamate (110 mg, 41% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 601.9.

Step 7: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)methoxy)propyl)carbamate (90.0 mg, 150 μmol) in CH_2Cl_2 (5.0 mL) were sequentially added CDI (72.9 mg, 449 μmol), Et_3N (62.3 μL, 45.5 mg, 449 μmol) and DMAP (18.3 mg, 150 μmol) at 25 °C and the mixture was stirred at that temperature for 1 h. The mixture was concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-

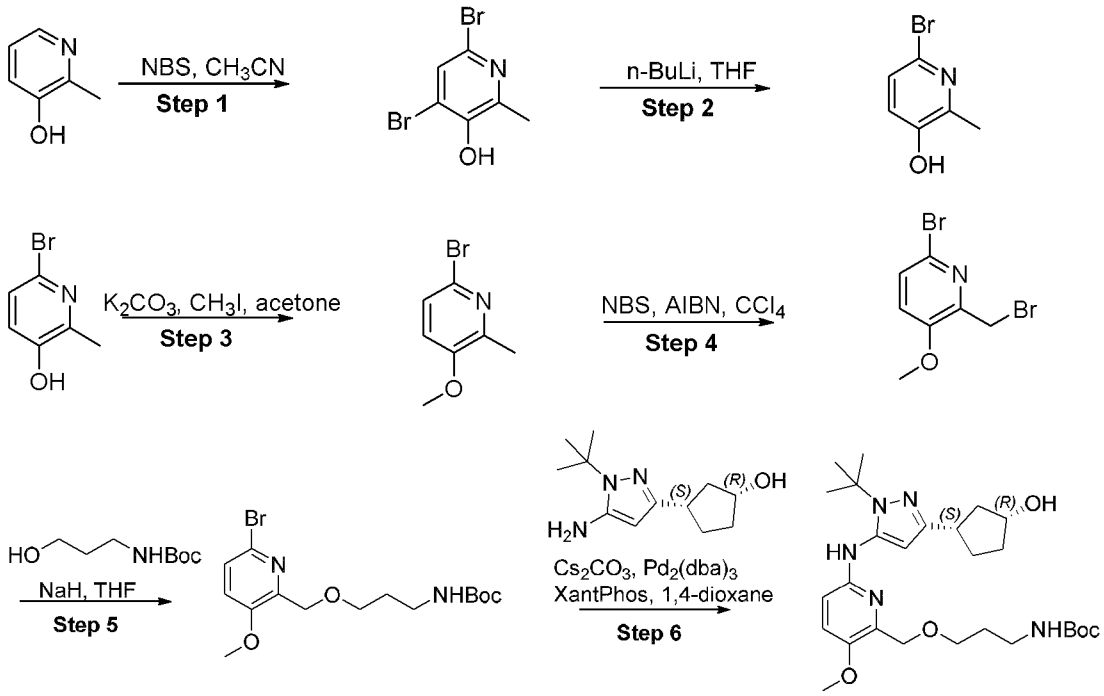
1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90 mg) as a yellow oil which was directly used into the next step without any further purification. LC-MS: m/z $[M+H]^+$ 694.9.

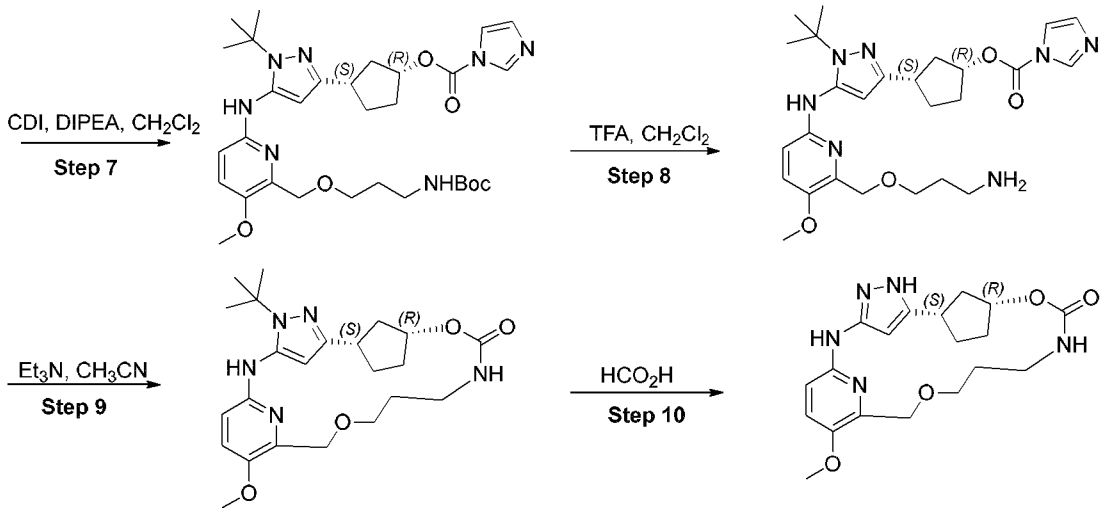
Step 8: (1^1*S*,1^3*R*,*Z*)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A stirred solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90.0 mg, 129 μmol) in TFA (3.0 mL) was warmed up to 80 °C and stirred at that temperature for 2 h before it was cooled to 25 °C. The mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL), and then Et_3N (89.7 μL, 65.5 mg, 648 μmol) was added into this mixture at 25 °C. The mixture was warmed up to 80 °C and stirred at that temperature for 4 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 45% in 45 min) to give (1^1*S*,1^3*R*,*Z*)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (5.0 mg, 8.0% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 470.9.

Example **55**

(1^1*S*,1^3*R*,*Z*)-4^5-methoxy-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: 4,6-dibromo-2-methylpyridin-3-ol

To a suspension of 2-methylpyridin-3-ol (3.0 g, 27.5 mmol) in CH_3CN (30.0 mL) was added NBS (9.79 g, 54.9 mmol) at 25 °C. The reaction mixture was warmed to 90 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15 % in 25 min) to afford 4,6-dibromo-2-methylpyridin-3-ol (5.0 g, 68% yield) as a yellow solid. C-MS: m/z [M+H]+ 265.8

Step 2: 6-bromo-2-methylpyridin-3-ol

To a stirred suspension of 4,6-dibromo-2-methylpyridin-3-ol (4.50 g, 16.9 mmol) in THF (30.0 mL) was stirred at -78 °C for 10 min under N_2. Then *n*-BuLi (13.5 mL, 2.5 M, 33.8 mmol) was added slowly to the solution and stirred another 2h at that temperature. The reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (20 mL× 3). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 12 % in 25 min) to afford 6-bromo-2-methylpyridin-3-ol (2.60 g, 83% yield) as a white solid. LC-MS: m/z [M+H]+ 188.0

Step 3: 6-bromo-3-methoxy-2-methylpyridine

To a suspension of 6-bromo-2-methylpyridin-3-ol (2.60 g, 13.9 mmol) in acetone (40.0 mL) was added CH_3I (1.29 mL, 2.94 g, 20.9 mmol) and K_2CO_3 (5.76 g, 41.7 mmol) at 25 °C. The reaction mixture was warmed to 50 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 8 % in 25 min) to afford 6-bromo-3-methoxy-2-methylpyridine (1.60 g, 57% yield) as a white solid. LC-MS: m/z [M+H]+ 202.0

Step 4: 6-bromo-2-(bromomethyl)-3-methoxypyridine

To a suspension of 6-bromo-3-methoxy-2-methylpyridine (1.60 g, 7.96 mmol) in CCl_4 (20.0 mL) was added NBS (2.12 g, 11.9 mmol) and AIBN (261 mg, 1.59 mmol) at 25 °C. The reaction mixture was warmed to 70 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10 % in 25 min) to afford 6-bromo-2-(bromomethyl)-3-methoxypyridine (2.0 g, 50% yield) as a white solid. LC-MS: m/z [M+H]+ 279.7

Step 5: *tert*-butyl (3-((6-bromo-3-methoxypyridin-2-yl)methoxy)propyl)carbamate

To a stirred suspension of *tert*-butyl (3-hydroxypropyl)carbamate (3.70 g, 21.4 mmol) in THF (20.0 mL) was added NaH (860 mg, 60 wt.% in mineral oil, 21.4 mmol) at 0 °C. The mixture was stirred for 30 min at that temperature before 6-bromo-2-(bromomethyl)-3-methoxypyridine (2.0 g, 7.14 mmol) was added. The mixture was stirred at 25 °C for 2 h. Then it was quenched with ice-water (20 mL) and extracted with EtOAc (20 mL × 3). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10 % in 25 min) to afford *tert*-butyl (3-((6-bromo-3-methoxypyridin-2-yl)methoxy)propyl)carbamate (1.90 g, 71% yield) as a white solid. LC-MS: m/z [M+H]+ 374.9

Step 6: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-methoxypyridin-2-yl)methoxy)propyl)carbamate

To a stirred suspension of *tert*-butyl (3-((6-bromo-3-methoxypyridin-2-yl)methoxy)propyl)carbamate (600 mg, 1.60 mmol) in 1,4-dioxane (10.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (358 mg, 1.60 mmol), Cs_2CO_3 (1.56 g, 4.80 mmol), XantPhos (185 mg, 320 μmol) and $Pd_2(dba)_3$ (146 mg, 160 μmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30 % in 25 min) to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-methoxypyridin-2-yl)methoxy)propyl)carbamate (400 mg, 48% yield) as a yellow oil. LC-MS: m/z [M+H]+ 518.0

Step 7: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred suspension of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-methoxypyridin-2-yl)methoxy)propyl)carbamate (400 mg, 770 μmol) in CH_2Cl_2 (10.0 mL) was added CDI (374 mg, 2.31 mmol) and DIPEA (663 μL, 500 mg, 3.85 mmol) at 25 °C. The reaction mixture was warmed to 35 °C and stirred at that temperature for 12 h. The reaction mixture was quenched with ice-cold water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (crude) as a yellow oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 612.0

Step 8: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred suspension of (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (10.0 mL) was added slowly TFA (396 μL, 586 mg, 5.14 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as a yellow oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 512.1

Step 9: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-methoxy-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

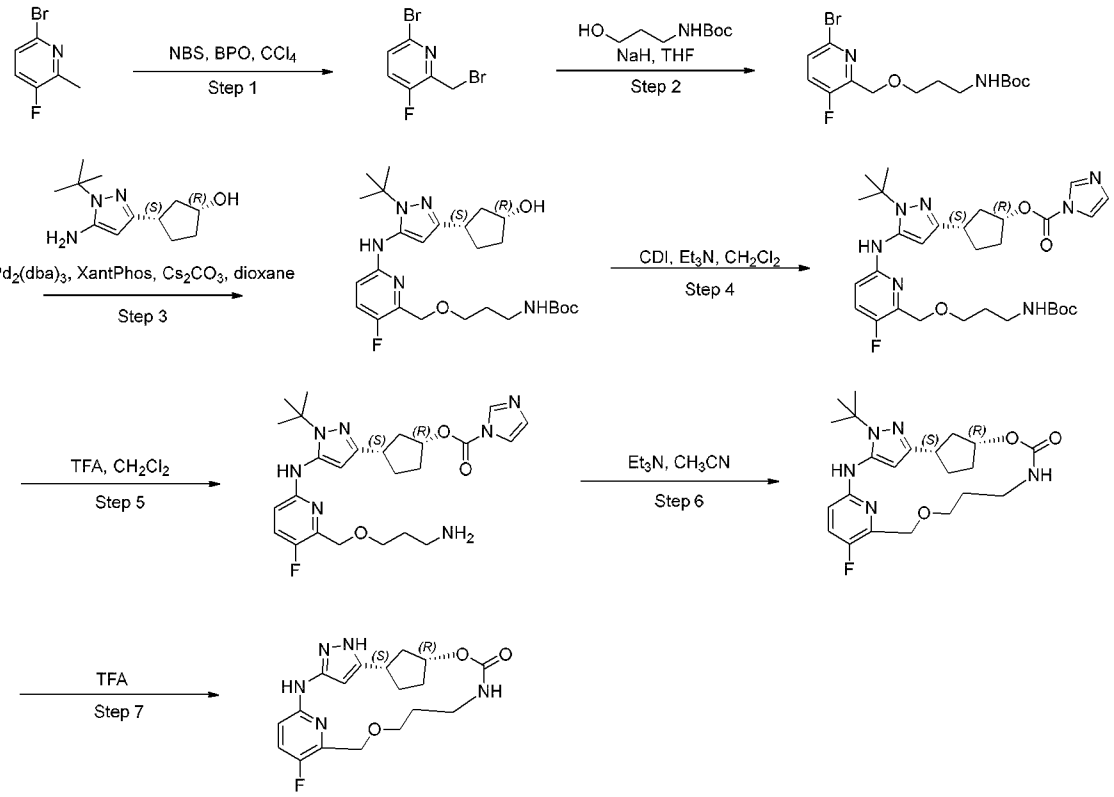
To a suspension of (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-methoxypyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (10.0 mL) was added Et_3N (1.23 mL, 902 mg, 8.91 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h. The reaction mixture was concentrated under reduced pressure to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-methoxy-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one as a yellow oil. LC-MS: m/z [M+H]+ 444.0

Step 10: (1^1S,1^3R,*Z*)-4^5-methoxy-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-methoxy-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one in HCO_2H (5.0 mL) was warmed to 100 °C and stirred at that temperature for 5 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 25% in 20 min) to afford (1^1S,1^3R,*Z*)-4^5-methoxy-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25.4 mg, 4.1% yield) as a white solid. LC-MS: m/z [M+H]+ 387.9.

Example 56

(1^1S,1^3R,*Z*)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 6-bromo-2-(bromomethyl)-3-fluoropyridine

A stirred solution of 6-bromo-3-fluoro-2-methylpyridine (1.0 g, 5.26 mmol), BPO (63.7 mg, 263 μmol) and NBS (1.03 g, 5.79 mmol) in CCl_4 (50.0 mL) was warmed to 90 °C and stirred for 4 h at that time before it was cooled to 25 °C. The mixture was concentrated to afford 6-bromo-2-(bromomethyl)-3-fluoropyridine as a yellow solid which was directly used into the next step without further purification. (1.40 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.4, 3.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 4.53 (s, 2H).

Step 2: *tert*-butyl (3-((6-bromo-3-fluoropyridin-2-yl)methoxy)propyl)carbamate

To a stirred solution of NaH (53.6 mg, 60 wt.% in mineral oil, 2.23 mmol) in THF (10.0 mL) solution was added *tert*-butyl (3-hydroxypropyl)carbamate (360 mg, 2.23 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min before a solution of 6-bromo-2-(bromomethyl)-3-fluoropyridine (500 mg, 1.86 mmol) in THF (10.0 mL) was added dropwise. The mixture was stirred at that temperature for 1 h before it was diluted with H_2O (50 mL) and warmed to 25 °C. The mixture was extracted with EtOAc (15 mL × 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30 % in 25 min) to afford *tert*-butyl (3-((6-bromo-3-fluoropyridin-2-yl)methoxy)propyl)carbamate (350 mg, 52 % yield) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 363.0.

Step 3: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-fluoropyridin-2-yl)methoxy)propyl)carbamate

To a stirred mixture of *tert*-butyl (3-((3,6-dibromopyridin-2-yl)methoxy)propyl)carbamate (350 mg, 849 μmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (189 mg, 849 μmol) and Cs_2CO_3 (553 mg, 1.70 mmol) in 1,4-dioxane (10.0 mL) were sequentially added XantPhos (49.2 mg, 84.9 μmol) and $Pd_2(dba)_3$ (77.8 mg, 84.9 μmol) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 3 h under N_2 atmosphere before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 30 min) to afford *tert*-butyl (3-((3-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2- yl)methoxy) propyl) carbamate(280 mg, 58% yield) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 506.3.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (3-((3-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)propyl)carbamate (260 mg, 395 μmol) in CH_2Cl_2 (12.0 mL) were sequentially added Et_3N (214 μL, 156 mg, 1.54 mmol) and CDI (167 mg, 1.03 mmol) at 25 °C . The mixture was warmed to 40 °C and stirred at that temperature for 2 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (350 mg) as a light-yellow solid which was used to the next step without further purification. LC-MS: m/z $[M+H]^+$ 600.3.

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (340 mg, 567 μmol) in CH_2Cl_2 (10.0 mL) was added TFA (2.0 mL) at 25 °C and the mixture was stirred at that temperature for 2 h. The mixture was concentrated to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg) as a light-yellow oil which was used to the next step without further purification. LC-MS: m/z $[M+H]^+$ 500.1.

Step 6: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^5-fluoro-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-5-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (290 mg, 580 μmol) in CH_3CN (10.0 mL) was added Et_3N (1.0 mL) at 25 °C . The mixture was warmed to 70 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc/PE (with EtOAc from

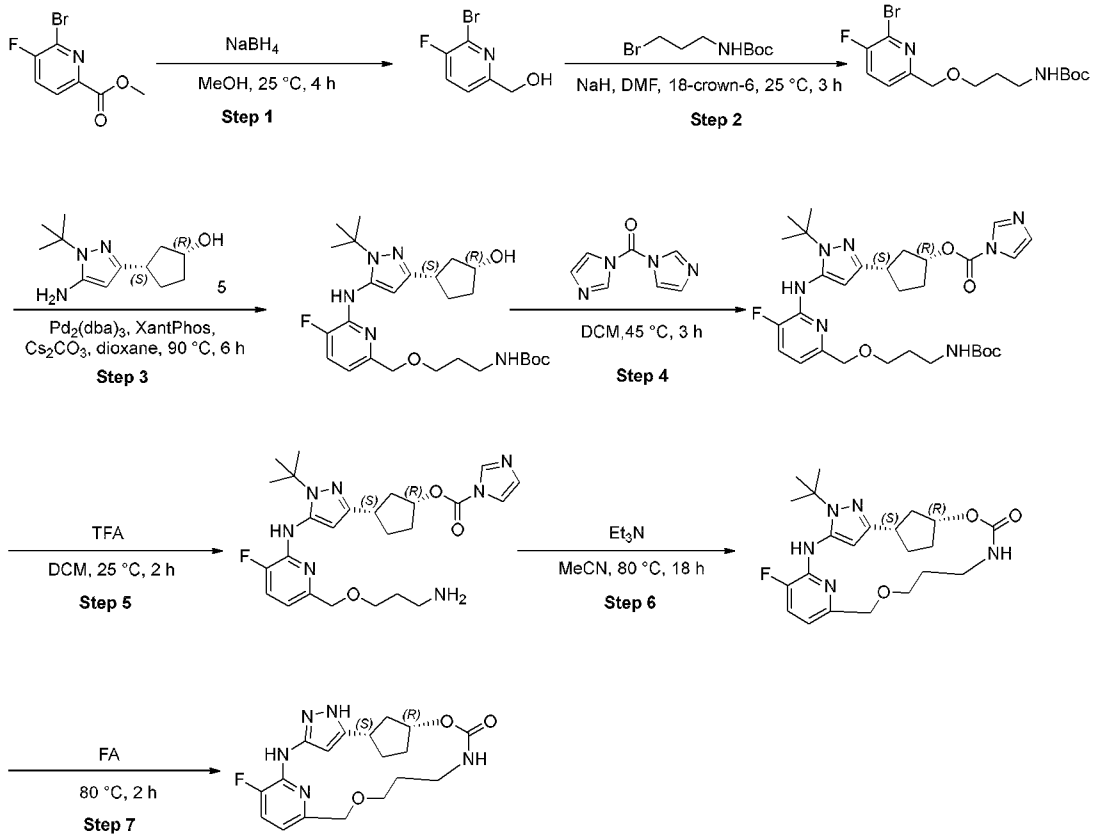
0 to 40 % in 30 min) to afford ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (150 mg, 60% yield) as a light-yellow oil. LC-MS: m/z $[M+H]^+$ 432.2.

Step 7: ($1^1S,1^3R,Z$)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (100 mg, 232 μmol) in TFA (2.0 mL) at 25 °C. The mixture was warmed to 70 °C and stirred at that temperature for 12 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 40% in 45 min) to give ($1^1S,1^3R,Z$)-4^5-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (7.40 mg, 8.5% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 376.0.

Example **57**

($1^1S,1^3R,Z$)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: (6-bromo-5-fluoropyridin-2-yl)methanol

To a solution of methyl 6-bromo-5-fluoropicolinate (1.00 g, 4.27 mmol) in Methanol (20 mL) was added Sodium borohydride (485 mg, 12.82 mmol) at 0 °C. The reaction was stirred at 25 °C for 4 h under nitrogen atmosphere. The mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 35% in 15 min) to afford (6-bromo-5-fluoropyridin-2-yl)methanol (795 mg, 90% yield) as a white solid. LC-MS: m/z 206.0 $[M+H]^+$

Step 2: *tert*-butyl (3-((6-bromo-5-fluoropyridin-2-yl)methoxy)propyl)carbamate

A solution of (6-bromo-5-fluoropyridin-2-yl)methanol (745 mg, 3.62 mmol) in DMF (2.0 mL) was added to a stirring suspension of NaH (289 mg, 7.23 mmol, 60% purity) and 18-Crown-6 (191mg, 723 μmol) in DMF (4.0 mL) at 0 °C. The mixture was stirred at 0 °C for 50 min. Then a solution of *tert*-butyl (3-bromopropyl)carbamate (1.29 g, 5.42 mmol) in DMF (4.0 mL) was added to the above reaction solution . The reaction mixtrue was stirred at 25°C for 3 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with saturated LiCl solution (50 mL × 2), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 20% in 20 min) to afford *tert*-butyl (3-((6-bromo-5-fluoropyridin-2-yl)methoxy)propyl)carbamate (300 mg, 23% yield) as a yellow solid. LC-MS: m/z 385.0 $[M+Na]^+$

Step 3: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)methoxy)propyl)carbamate

To a suspension of *tert*-butyl (3-((6-bromo-5-fluoropyridin-2-yl)methoxy)propyl)carbamate (200 mg, 551 μmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (135 mg, 606 μmol) in dioxane (6.0 mL) was added $Pd_2(dba)_3$ (100 mg, 110 μmol), Cs_2CO_3 (538 mg, 1.65 mmol) and XantPhos (127 mg, 220 μmol). The suspension was degassed with N_2 for 5 times. The mixture was heated to 90 °C and stirred at 90 °C for 6 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 72% in 15 min) to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)methoxy)propyl)carbamate (277 mg, 99% yield) as a yellow oil. LC-MS: m/z 506.2 $[M+H]^+$

Step 4: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)methoxy)propyl)carbamate (257 mg, 508 μmol) in DCM (8.0 mL) was added 1,1'-Carbonyldiimidazole (494 mg, 3.05 mmol) at 25 °C. The reaction was stirred at 45 °C for 3 h in a sealed tube. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 62% in 15 min) to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-

butoxycarbonyl)amino)propoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg, 98% yield) as a yellow oil. LC-MS: m/z 600.3 $[M+H]^+$

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (250 mg, 417 μmol) in DCM (4.0 mL) was added TFA (2.0 mL) at 0 °C. The reaction was stirred under nitrogen atmosphere at 25 °C for 2 h. The mixture was concentrated to provide (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (500 mg, crude) as a yellow oil. LC-MS: m/z 500.1 $[M+H]^+$

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

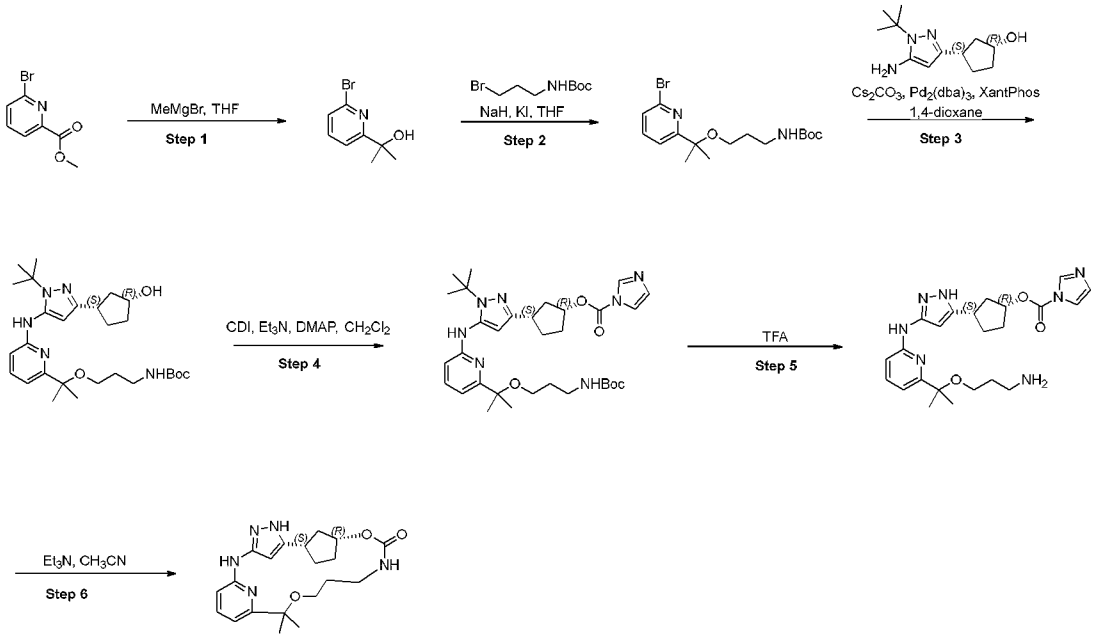
To a solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (500 mg, 1.00 mmol) in MeCN (20 mL) was added Et_3N (1.29 g, 10.0 mmol, 1.74 mL) at 0 °C. The reaction was heated to 80 °C and stirred at 80 °C for 18 h under nitrogen atmosphere. The mixture was concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 70% in 15 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (146 mg, 34% yield) as a yellow solid. LC-MS: m/z 432.1 $[M+H]^+$

Step 7: (1^1S,1^3R,*Z*)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (126 mg, 292 μmol) in FA (2.0 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was concentrated to dryness. The residue was purified by Prep-HPLC (with CH_3CN from 50% to 70% in 8 min) to afford (1^1S,1^3R,*Z*)-4^3-fluoro-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (2.30 mg, 3% yield) as a yellow solid. LC-MS: m/z 376.1[M+H] $^+$.

Example **58**

(*1^1S,1^3R,Z*)-5,5-dimethyl-2^1H-12-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 2-(6-bromopyridin-2-yl)propan-2-ol

To a stirred solution of methyl 6-bromopyridine-2-carboxylate (5.00 g, 23.1 mmol) in THF (80.0 mL) was added MeMgBr (30.9 mL, 92.6 mmol, 3 M in diethyl ether) at 0 °C. The reaction mixture was warmed to 25 °C and stirred at that temperature for 16 h. The reaction mixture was cooled to 0 °C and quenched with aqueous 10% HCl (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 20% in 25 min) to afford 2-(6-bromo-2-pyridyl)propan-2-ol (3.30 g, 66% yield). LC-MS: m/z $[M+H]^+$ 216.0.

Step 2: *tert*-butyl (3-((2-(6-bromopyridin-2-yl)propan-2-yl)oxy)propyl)carbamate

To a stirred solution of 2-(6-bromo-2-pyridyl)propan-2-ol (2.70 g, 12.5 mmol) in THF (50.0 mL) was added NaH (1.00 g, 60 wt.% in mineral oil, 25.0 mmol) at 0 °C. The reaction mixture was stirred for 30 min before *tert*-butyl *N*-(3-bromopropyl)carbamate (8.93 g, 37.5 mmol) and KI (6.22 g, 37.5 mmol) were added at that temperature. The reaction mixture was warmed to 25 °C and stirred at that temperature for 12 h. The reaction mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30 % in 20 min) to afford *tert*-butyl *N*-[3-[1-(6-bromo-2-pyridyl)-1-methyl-ethoxy]propyl]carbamate (2.00 g, 43% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 372.9.

Step 3: *tert*-butyl (3-((2-(6-((1-(tert-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)propan-2-yl)oxy)propyl)carbamate

To a stirred solution of tert-butyl*N*-[4-[[6-bromo-3-(1-methylpyrazol-4-yl)-2-pyridyl]oxy]butyl]carbamate (351 mg, 940 μmol) in 1,4-dioxane (20.0 mL) were sequentially added (*1R,3S*)-3-(5-amino-2-*tert*-butyl-pyrazol-3-yl)cyclopentanol (140 mg, 627 μmol), $Pd_2(dba)_3$ (57.4 mg, 62.7 μmol), XantPhos (36.3 mg, 62.7 μmol) and Cs_2CO_3 (409 mg, 1.25 mmol) at 25 °C. The reaction was warmed to 100 °C and stirred at that temperature for 16 h under N_2 atmosphere before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 25 min) to afford *tert*-butyl(3-((2-(6-((1-(tert-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)propan-2-yl)oxy)propyl)carbamate (230 mg, 57% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 516.4.

Step 4: (*1R,3S*)-3-(5-((6-(2-(3-((*tert*-butoxycarbonyl)amino)propoxy)propan-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (3-((2-(6-((1-(tert-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)propan-2-yl)oxy)propyl)carbamate (230 mg, 446 μmol) in CH_2Cl_2 (5.0 mL) were sequentially added CDI (217 mg, 1.34 mmol), DMAP (16.4 mg, 134 μmol) and Et_3N (311 μL, 226 mg, 2.23 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated under reduced pressure to give product (*1R,3S*)-3-(5-((6-(2-(3-((*tert*-butoxycarbonyl)amino)propoxy)propan-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate which was directly used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 610.4.

Step 5: (*1R,3S*)-3-(3-((6-(2-(3-aminopropoxy)propan-2-yl)pyridin-2-yl)amino)-*1H*-pyrazol-5-yl)cyclopentyl *1H*-imidazole-1-carboxylate

A solution of (*1R,3S*)-3-(5-((6-(2-(3-((*tert*-butoxycarbonyl)amino)propoxy)propan-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in TFA (4.0 mL) was warmed to 70 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated to give (*1R,3S*)-3-(3-((6-(2-(3-aminopropoxy)propan-2-yl)pyridin-2-yl)amino)-*1H*-pyrazol-5-yl)cyclopentyl *1H*-imidazole-1-carboxylate as a brown oil, which was directly used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 453.7.

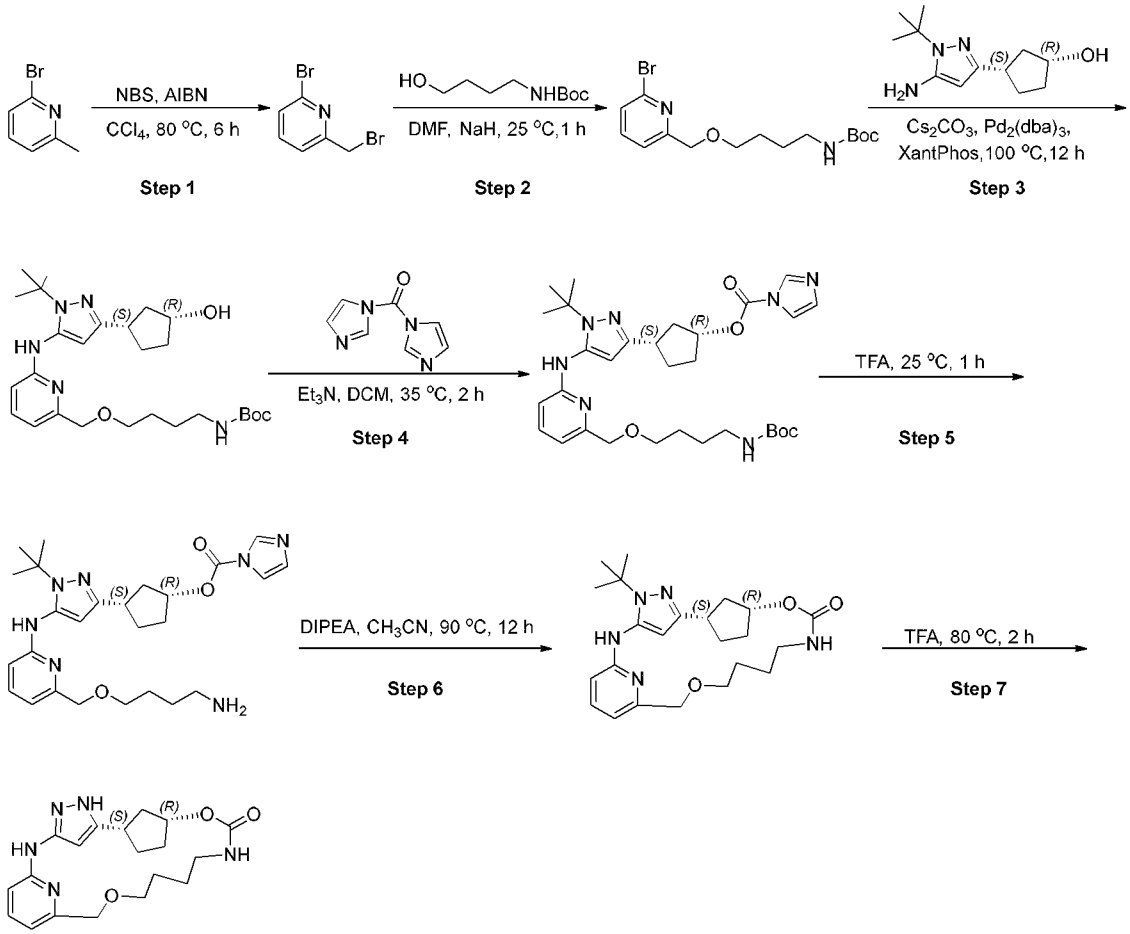
Step 6: (*1^{1}S,1^{3}R,Z*)-5,5-dimethyl-*2^{1}H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution of (*1R,3S*)-3-(3-((6-(2-(3-aminopropoxy)propan-2-yl)pyridin-2-yl)amino)-*1H*-pyrazol-5-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in CH_3CN (5.0 mL) was added Et_3N (271 μL, 196 mg, 1.94 mmol) at 25 °C. The mixture was warmed to 80 °C and stirred at that

temperature for 5 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 50% in 40 min) to afford (*1'S,1³R,Z*)-5,5-dimethyl-*2'H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (9.60 mg, 8.1% yield) as an off-white solid. LC-MS: m/z $[M+H]^+$ 385.8.

Example **59**

(1¹*S*,1³*R*,*Z*)-2¹*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one



Step 1: 2-bromo-6-(bromomethyl)pyridine

To a solution of 2-bromo-6-methyl-pyridine (5.00 g, 29.1 mmol) in CCl_4 (50 mL) was added NBS (5.43 g, 30.5 mmol) and 2-[(*E*)-(1-cyano-1-methyl-ethyl)azo]-2-methyl-propanenitrile (238 mg, 1.45 mmol) .The mixture was heated to 80 °C and stirred at 80 °C for 16 h. The mixture was concentrated under reduce pressure. The reisdue was purified with flash column chromatography eluting with DCM/PE (with DCM from 0 to 20% in 25 min) to give 2-bromo-6-(bromomethyl)pyridine (4.10 g, 56% yield) as a white solid. LC-MS: m/z 251.1 $[M+H]^+$

Step 2: *tert*-butyl (4-((6-bromopyridin-2-yl)methoxy)butyl)carbamate

To a solution of *tert*-butyl N-(4-hydroxybutyl)carbamate (226 mg, 1.20 mmol) in DMF (5.0 mL) was added NaH (37.3 mg, 1.55 mmol). The mixture was stirred at 0 °C for 1 h under N_2. Then 2-bromo-6-(bromomethyl)pyridine (300 mg, 1.20 mmol) was added. The mixture was warmed to 25 °C for 1 h. The mixture was quenched by NH_4Cl (2 mol/L in water, 3.0 mL), extracted with ethyl acetate (5.0 mL × 2). The combined organic layer was concentrated under reduced pressure, the residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 20 min) to give *tert*-butyl *N*-[4-[(6-bromo-2-pyridyl)methoxy]butyl]carbamate (278 mg, 64% yield) as an off-white solid. LC-MS: m/z 361.1 $[M+H]^+$.

Step 3: *tert*-butyl (4-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)butyl)carbamate

The solution of *tert*-butyl N-[4-[(6-bromo-2-pyridyl)methoxy]butyl]carbamate (50.0 mg, 139 μmol), (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (31.0 mg, 139 μmol), (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one;palladium (12.7 mg, 13.9 μmol), Cs_2CO_3 (136 mg, 417 μmol) and XantPhos (16.1 mg, 27.8 μmol) in 1,4-Dioxane (1.5 mL) was heated to 120 °C and stirred at 120 °C for 18 h under N_2. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 20 min) to give *tert*-butyl *N*-[4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]butyl]carbamate (31.0 mg, 44% yield) as a yellow oil. LC-MS: m/z 502.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(5-((6-((4-((*tert*-butoxycarbonyl)amino)butoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

The stirring solution of *tert*-butyl *N*-[4-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]butyl]carbamate (234 mg, 466 μmol) and di(imidazol-1-yl)methanone (227 mg, 1.40 mmol) in DCM (645 μL) was added DIPEA (301 mg, 2.33 mmol) at 25 °C for 2 h under N_2. The mixture was concentrated under reduced pressure to give [(1*R*,3*S*)-3-[5-[[6-[4-(*tert*-butoxycarbonylamino)butoxymethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (270 mg, 82% yield) as a yellow oil. LC-MS: m/z 596.3 $[M+H]^+$.

Step 5: (1*R*,3*S*)-3-(5-((6-((4-aminobutoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

The solution of [(1*R*,3*S*)-3-[5-[[6-[4-(tert-butoxycarbonylamino)butoxymethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (230 mg, 386 μmol) in 2,2,2-trifluoroacetic acid (440 mg, 3.86 mmol) was stirred at 25 °C for 5 min. The mixture was concentrated under reduced pressure to give [(1*R*,3*S*)-3-[5-[[6-(4-aminobutoxymethyl)-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (190 mg, 99% yield) as a yellow oil. LC-MS: m/z 496.3 $[M+H]^+$.

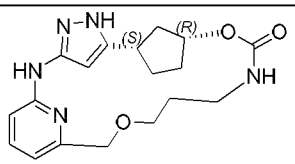
Step 6: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one

The solution [(1*R*,3*S*)-3-[5-[[6-(4-aminobutoxymethyl)-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (190 mg, 319 μmol) in CH_3CN (3.0 mL) was added DIPEA (206 mg, 1.59 mmol) The mixture was heated to °C and stirred at 80 °C for 18 h. The mixture was concentrated under reduced pressure, the residue was purified by prep-TLC (petroleum ether/EtOAc = 2:1) to give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (48.0 mg, 35% yield) as a yellow solid. LC-MS: m/z 428.2 $[M+H]^+$.

Step 7: (1^1S,1^3R,*Z*)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one

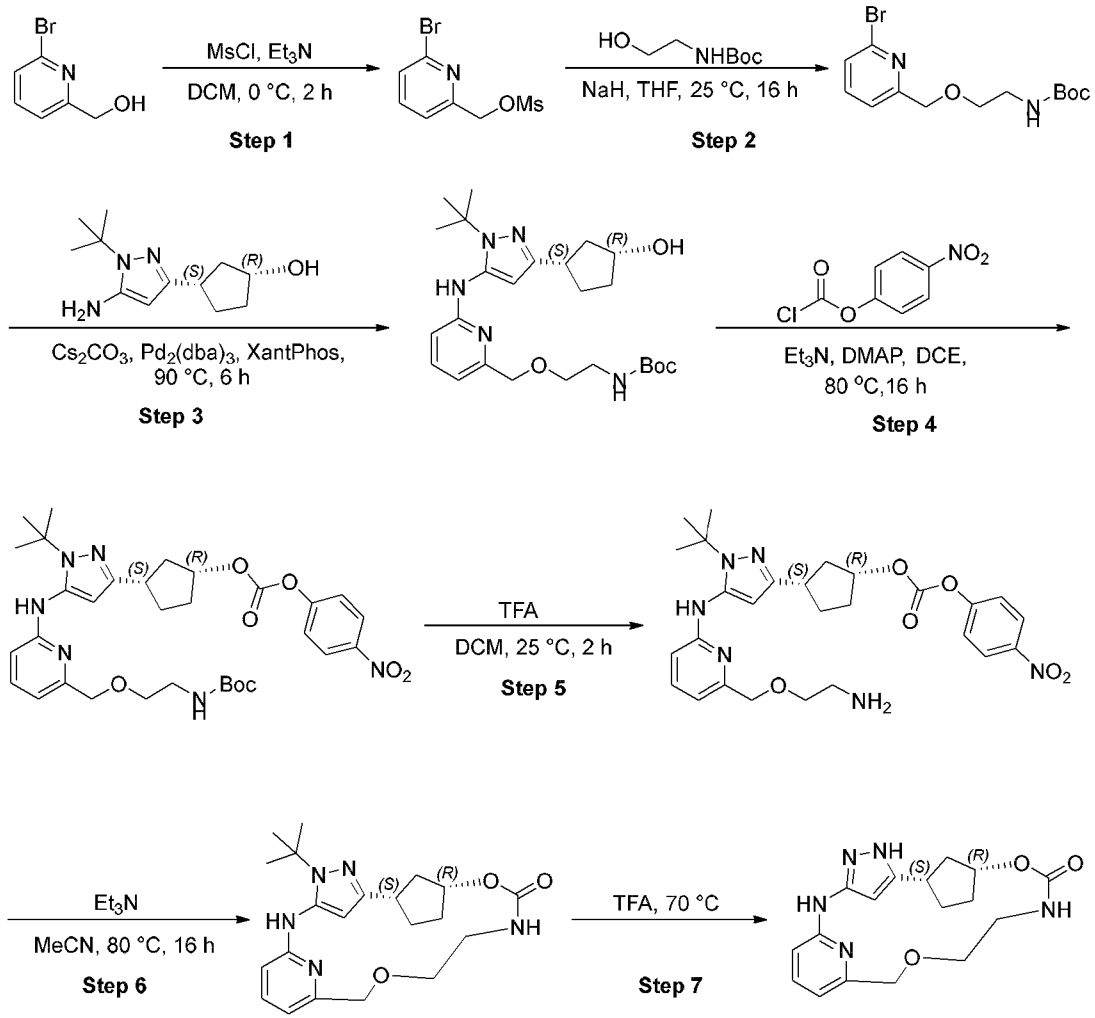
The solution (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (45.0 mg, 105 μmol) in trifluoroacetic acid (120 mg, 1.05 mmol) was heated to 80 °C and stirred at 80 °C for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (with CH_3CN from 20% to 30% in 8 min) to afford (1^1S,1^3R,*Z*)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (6.60 mg, 16% yield) as a white solid. LC-MS: m/z 372.2 $[M+H]^+$.

The following compounds were prepared using the similar procedure disclosed in synthetic example **59**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
178		358.1

Example **60**

(1^1S,1^3R,*Z*)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one



Step 1: (6-bromopyridin-2-yl)methyl methane sulfonate

To a solution of (6-bromopyridin-2-yl)methanol (1.00 g, 5.32 mmol) and Et_3N (700 mg, 6.91 mmol, 963 μL) in DCM (20 mL) was drop-wised added methane sulfonyl chloride (640 mg, 5.58 mmol, 433 μL) at 0 °C. The reaction was stirred at 0 °C for 2 h. The mixture was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with DCM (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to afford (6-bromopyridin-2-yl) methyl methane sulfonate (1.60 g, crude) as a yellow oil. LC-MS: m/z 267.1 $[M+H]^+$

Step 2: *tert*-butyl (2-((6-bromopyridin-2-yl) methoxy) ethyl) carbamate

A solution of *tert*-butyl(2-hydroxyethyl)carbamate (200 mg, 1.24 mmol) in THF (1.0 mL) was added to a stirring suspension of NaH (99.2 mg, 2.48 mmol, 60% purity) in THF (5.0 mL) at 0°C. The mixture was stirred at 0 °C for 30 mi. After that, a solution of (6-bromopyridin-2-yl) methyl methane sulfonate (660 mg, 2.48 mmol) in THF (2 mL) was added to the above reaction solution. The mixture was stirred at 25 °C for 16 h. The mixture was quenched with saturated NH_4Cl solution (50 mL)

and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 18% in 15 min) to afford *tert*-butyl (2-((6-bromopyridin-2-yl) methoxy) ethyl) carbamate (345 mg, 64% yield) as a yellow oil. LC-MS: m/z 331.0 $[M+H]^+$

Step 3: *tert*-butyl (2-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino) pyridin-2-yl) methoxy)ethyl)carbamate

To a suspension of *tert*-butyl(2-((6-bromopyridin-2-yl)methoxy)ethyl) carbamate (240 mg, 725 μmol) and (1*R*,3*S*)-3-(5-amino-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (178 mg, 797 μmol) in dioxane (8.0 mL) was added $Pd_2(dba)_3$ (133 mg, 290 μmol), Cesium carbonate (708 mg, 2.17 mmol) and XantPhos (168 mg, 290 μmol). The suspension was degassed with N_2 for 5 times. The mixture was heated to 90 °C and stirred at 90 °C for 6 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography eluting with MeOH/DCM (with MeOH from 0 to 5% in 15 min) to afford *tert*-butyl (2-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyridin-2-yl) methoxy) ethyl) carbamate (300 mg, 87% yield) as a yellow solid. LC-MS: m/z 474.2 $[M+H]^+$.

Step 4: *tert*-butyl (2-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy) carbonyl)oxy)cyclopentyl) -1*H*-pyrazol-5-yl) amino) pyridin-2-yl)methoxy)ethyl)carbamate

To a solution of *tert*-butyl (2-((6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)ethyl)carbamate (210 mg, 443 μmol) and 4-nitrophenyl carbonochloridate (358 mg, 1.77 mmol) in DCE (8.0 mL) was added DMAP (10.8 mg, 88.7 μmol) and Et_3N (224 mg, 2.22 mmol, 309 μL) at 25 °C. The reaction was stirred under nitrogen atmosphere at 80 °C for 20 hours. The mixture was washed by brine (50 mL) and extracted with DCM (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (with EtOAc from 0 to 50% in 15 min) to afford *tert*-butyl (2-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl) amino)pyridin-2-yl)methoxy) ethyl)carbamate (114 mg, 41% yield) as a yellow oil. LC-MS: m/z 639.3 $[M+H]^+$

Step 5: (1*R*,3*S*)-3-(5-((6-((2-aminoethoxy) methyl) pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl(4-nitrophenyl)carbonate

To a solution of *tert*-butyl (2-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy) carbonyl) oxy) cyclopentyl)-1*H*-pyrazol-5-yl) amino) pyridin-2-yl)methoxy)ethyl)carbamate (114 mg, 178 μmol) in DCM (1.0 mL) was added TFA (0.50 mL) at 0 °C. The reaction was stirred at 25 °C for 2 h. The mixture was concentrated to afford (1*R*,3*S*)-3-(5-((6-((2-aminoethoxy) methyl)pyridin-2-yl) amino)-1-

(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl(4-nitrophenyl)carbonate (140 mg, crude) as a yellow oil. LC-MS: m/z 539.2 $[M+H]^+$

Step 6: (1^1S,1^3R, *Z*)-2^1-(*tert*-butyl)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one

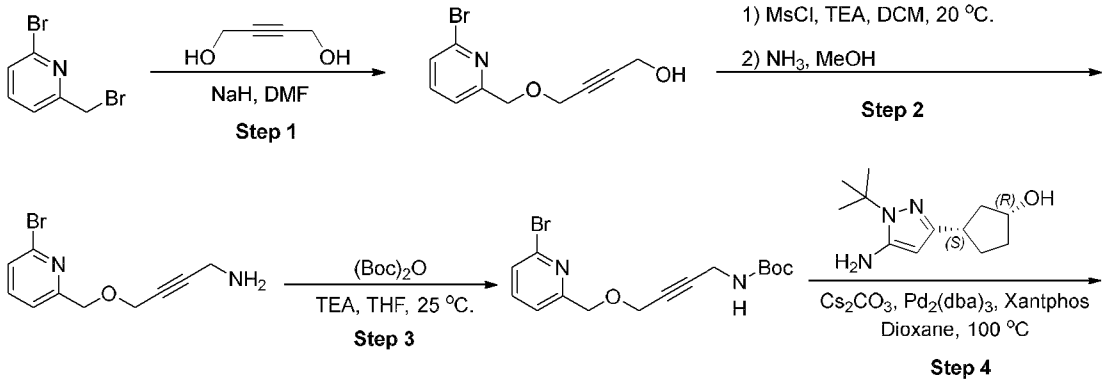
To a solution of (1*R*,3*S*)-3-(5-((6-((2-aminoethoxy) methyl) pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl(4-nitrophenyl)carbonate (140 mg, 260 μmol) in MeCN (11 mL) was added Et_3N (526 mg, 5.20 mmol, 724 μL) at 0 °C. The reaction was stirred under nitrogen atmosphere at 25 °C for 16 h. The mixture was concentrated to dryness. The residue was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 10 min) to afford (1^1S,1^3R, *Z*)-2^1-(*tert*-butyl)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one (46.0 mg, 44% yield) as a yellow oil. LC-MS: m/z 400.2 $[M+H]^+$

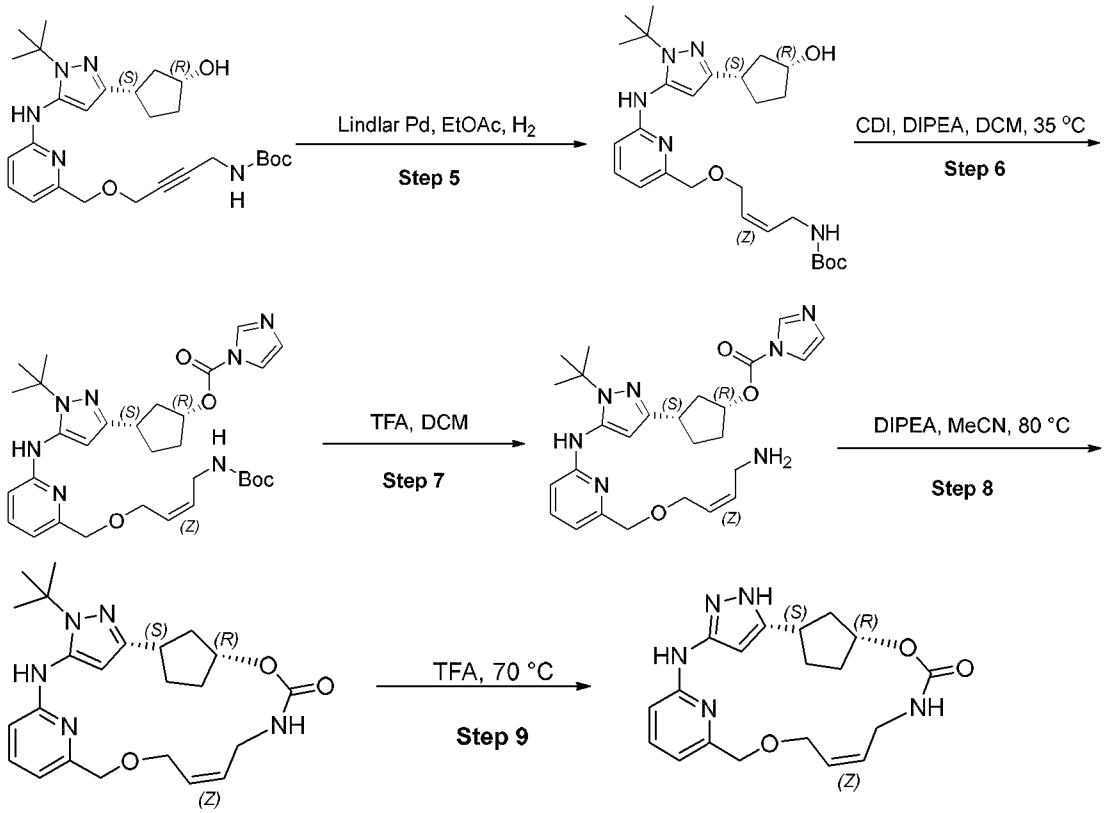
Step 7: (1^1S,1^3R, *Z*)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one

A solution of (1^1S,1^3R, *Z*)-21-(*t*ert-butyl)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one (46.0 mg, 115 μmol) in TFA (2.0 mL) was heated to 80 °C and stirred at 80 °C for 18 h. The mixture was concentrated to afford the crude solid, which was purified by prep-HPLC (with CH_3CN from 22% to 32% in 8 min) to afford (11*S*,13*R*, *Z*)-2^1H-6,11-dioxa-3,9-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphan-10-one (15.6 mg, 39% yield) as a white solid. LC-MS: m/z 344.2 $[M+H]^+$.

Example **61**

(1^1S,1^3R,2^4Z,8*Z*)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one





Step 1: 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-ol

To a solution of but-2-yne-1,4-diol (1.37 g, 15.9 mmol) in DMF (10 mL) was added NaH (1.59 g, 39.9 mmol, 60% purity) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Then the solution of 2-bromo-6-(bromomethyl)pyridine (2.00 g, 7.97 mmol) in DMF (5.0 mL) was added dropwise to the reaction mixture. Then the reaction mixture was warmed to 20 °C and stirred at 20 °C for 2 h. The mixture was quenched with ice water (80 mL), the mixture was extracted with EtOAc (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 20 min) to afford 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-ol (1.50 g, 73% yield) as a pale yellow oil. LC-MS: (ESI) m/z $[M+H]^+$ 256.0.

Step 2: 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-amine

To a solution of 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-ol (500 mg, 1.95 mmol) in DCM (10 mL) was added DIPEA (757 mg, 5.86 mmol, 1.02 mL), then methanesulfonyl chloride (447 mg, 3.90 mmol, 303 µL) was added to the reaction mixture at 15 °C. The reaction mixture was stirred at 15 °C for 2 h. Then the reaction was diluted with DCM (50 mL), washed with brine (50 mL), the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude intermediate. The intermediate was dissolved in NH_3 (7 M in MeOH, 10 mL), then reaction mixture was stirred at 15 °C for 12 h. The mixture was concentrated under reduced pressure and the

residue was redissolved in DCM (100 mL), washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-amine (500 mg, crude) as a yellow oil. LC-MS: (ESI) m/z $[M+H]^+$ 255.0.

Step 3: *tert*-butyl (4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate

To a solution of 4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-amine (500 mg, 1.96 mmol) in THF (10 mL) was added TEA (992 mg, 9.80 mmol, 1.37 mL) and tert-butoxycarbonyl tert-butyl carbonate (1.28 g, 5.88 mmol, 1.35 mL). Then the reaction mixture was stirred at 25 °C for 5 h. The mixture was concentrated under reduced pressure, the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 30% in 15 min to afford the product *tert*-butyl (4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate (320 mg, 46% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 355.1.

Step 4: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate

To a solution of *tert*-butyl (4-((6-bromopyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate (320 mg, 901 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (201 mg, 901 μmol) in dioxane (8.0 mL) was added $Pd_2(dba)_3$ (123 mg, 135 μmol), XantPhos (156 mg, 270 μmol) and Cs_2CO_3 (881 mg, 2.70 mmol) under the atmosphere of N_2. Then the reaction mixture was stirred at 100 °C under the atmosphere of N_2 for 3 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 60% in 15 min to afford the product *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate (320 mg, 71% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 498.3.

Step 5: *tert*-butyl ((*Z*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate

To a solution of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-yn-1-yl)carbamate (380 mg, 763.62 μmol) in EtOAc (10 mL) was added $Pd/CaCO_3$ (100 mg, 46.9 μmol, 5% purity), then the reaction mixture was degassed with H_2 (ballon) for 3 times. Then the reaction mixture was stirred at 20 °C under the atmosphere of H_2 for 5 h. The mixture was filtered and concentrated under reduced pressure, the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 50% in 15 min to afford the product *tert*-butyl ((*Z*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (380 mg, 70% yield) as a yellow solid. LC-MS: (ESI) m/z [M+H]+ 500.3.

Step 6: (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl ((*Z*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (200 mg, 400 μmol) in dioxane (10 mL) was added DIPEA (742 mg, 5.74 mmol, 1.00 mL) at 20 °C, then di(imidazol-1-yl)methanone (195 mg, 1.20 mmol) was added to the reaction mixture, the mixture was stirred at 35 °C for 5 h. The mixture was concentrated under reduced pressure to afford the product (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (230 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 594.3.

Step 7: (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-((tert-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (230 mg, 387 μmol) in DCM (5.0 mL) was added TFA (2.96 g, 25.96 mmol, 2.00 mL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 13 h. The mixture was concentrated under reduced pressure to afford the mixture of product (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (190 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 494.3.

Step 8: (1^1*S*,1^3*R*,2^4*Z*,8*Z*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one

The solution of (1*R*,3*S*)-3-(5-((6-((((*Z*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (190 mg, 192 μmol) in CH_3CN (30 mL) was added DIPEA (1.86 g, 14.4 mmol, 2.50 mL) at 20 °C. Then the reaction mixture was heated to 80 °C and stirred at 80 °C for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 70% in 20 min to afford the product (1^1*S*,1^3*R*,2^4*Z*,8*Z*)-2^1-(*tert*-butyl)-2^1H-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (25.0 mg, 31% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 426.2.

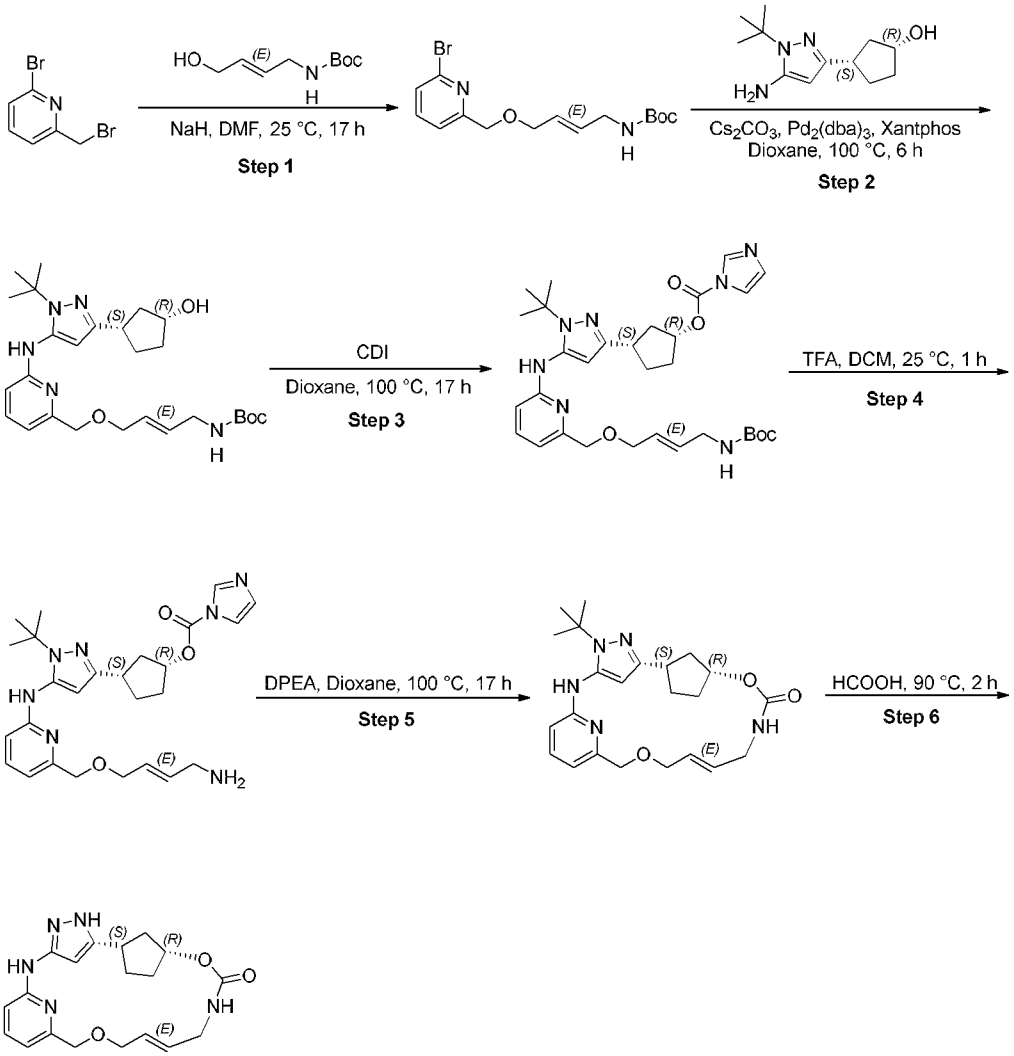
Step 9: (1^1*S*,1^3*R*,2^4*Z*,8*Z*)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one

The solution of (1^1*S*,1^3*R*,2^4*Z*,8*Z*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (25.0 mg, 58.8 μmol) in TFA (5.0 mL) was stirred at 80 °C for 5 h. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC eluting with CH_3CN in water with CH_3CN from 17% to 27% in 9 min to afford the product 1 (1^1*S*,1^3*R*,2^4*Z*,8*Z*)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-

pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (2.50 mg, 12% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 370.1.

Example **62**

(1^1*S*,1^3*R*,2^4*Z*,8*E*)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one



Step 1: *tert*-butyl (*E*)-(4-((6-bromopyridin-2-yl)methoxy)but-2-en-1-yl)carbamate

To a solution of *tert*-butyl (*E*)-(4-hydroxybut-2-en-1-yl)carbamate (507 mg, 2.71 mmol) in DMF (10 mL) was added NaH (141 mg, 3.52 mmol) at 0 °C, after addition, the mixture was stirred at 0 °C for 1 h. To the mixture was added 2-bromo-6-(bromomethyl)pyridine (680 mg, 2.71 mmol), the mixture was warmed to 25 °C and stirred at this temperature for 17 h. The mixture was quenched with aqueous NH_4Cl (50 mL), and the aqueous layer was extracted with EtOAc (35 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure. the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 10 to 30% in 20 min) to give

tert-butyl (*E*)-(4-((6-bromopyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (380 mg, 39% yield) as a colorless oil. LC-MS: m/z 357.1 $[M+H^{++}$.

Step 2: *tert*-butyl ((*E*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate

The mixture of *tert*-butyl (*E*)-(4-((6-bromopyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (150 mg, 0.42 mmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (93.8 mg, 0.42 mmol), XantPhos (48.6 mg, 84.0 μmol), $Pd_2(dba)_3$ (38.5 mg, 42.0 μmol) and Cs_2CO_3 (274 mg, 0.84 mmol) in 1,4-dioxane (10 mL) was heated to and stirred at 100 °C for 6 h under N_2. The mixture was cooled to 25 °C and was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/DCM (with MeOH from 0 to 7% in 20 min) to give *tert*-butyl ((*E*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (180 mg, 86% yield) as a brown oil. LC-MS: m/z 500.4 $[M+H]^+$.

Step 3: (1*R*,3*S*)-3-(5-((6-((((*E*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl ((*E*)-4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)but-2-en-1-yl)carbamate (140 mg, 0.28 mmol) and DIEA (2.0 mL, 11.5 mmol) in 1,4-dioxane (5 mL) was added CDI (136 mg, 0.84 mmol) at 25 °C. After addition, the mixture was stirred at 100 °C for 17 h. The mixture was cooled to 25 °C and was concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((6-((((*E*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (160 mg, 96% yield) as a brown oil, which was used directly into the next step without further purification. LC-MS: m/z $[M+H]^+$ 594.3

Step 4: (1*R*,3*S*)-3-(5-((6-((((*E*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-((((*E*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (160 mg, 0.27 mmol) in DCM (4 mL) at 0 °C was added TFA (2.0 mL, 26.0 mmol). After addtion, the mixture was warmed to 25 °C and stirred at this temperature for 1 h. The mixture was concentrated to give (1*R*,3*S*)-3-(5-((6-((((*E*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (150 mg, 85% yield) as a brown oil, which was used directly into the next step without further purification. LC-MS: m/z $[M+H]^+$ 494.2.

Step 5: (1^1S,1^3R,2^4*Z*,8*E*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one

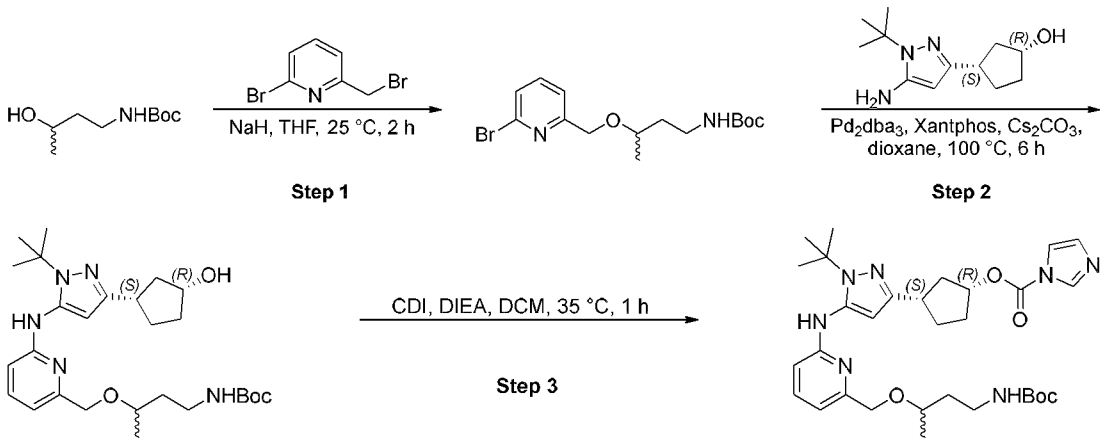
The mixture of (1*R*,3*S*)-3-(5-(((6-((((*E*)-4-aminobut-2-en-1-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (150 mg, 0.30 mmol) and DIEA (393 mg, 3.03 mmol) in 1,4-dioxane (5 mL) was heated 100 °C for 17 h. The mixture was cooled to 25 °C and was concentrated under reduced pressure. The residue was purified by prep-TLC (EtOAc/PE = 1:1) to give (1^1S,1^3R,2^4*Z*,8*E*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (25.0 mg, 19% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 426.1

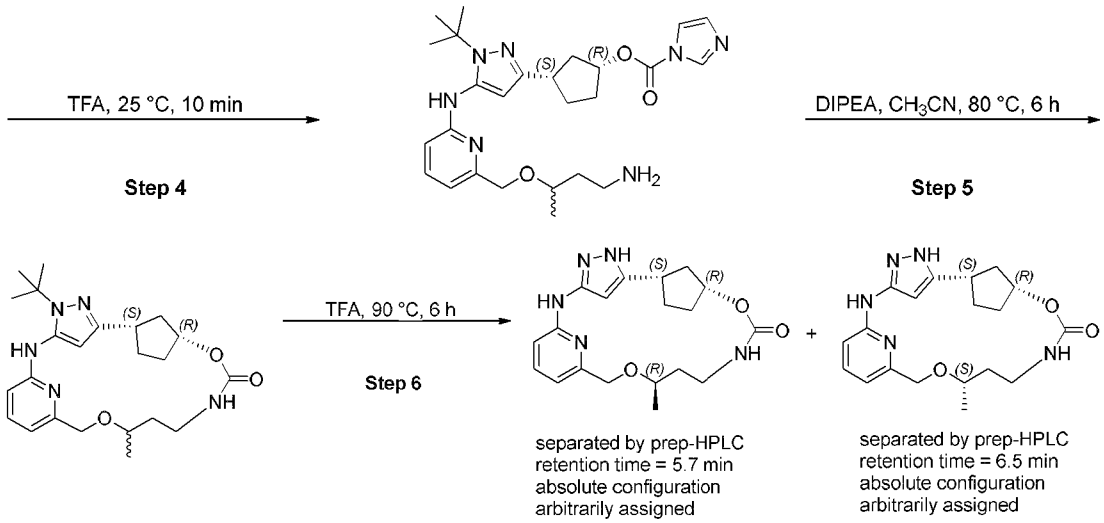
Step 6: (1^1*S*,1^3*R*,2^4*Z*,8*E*)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one

The mixture of (1^1S,1^3R,2^4*Z*,8*E*)-2^1-(*tert*-butyl)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (25 mg, 58.8 μmol) and HCOOH (5.0 mL, 132 mmol) was heated to 90 °C and stirred at 90 °C for 2 h. The mixture was cooled to 25 °C and was concentrated under reduced pressure, the residue was purified by Pre-HPLC eluting with CH_3CN in water with CH_3CN from 5% to 35% in 8 min to give (1^1*S*,1^3*R*,2^4*Z*,8*E*)-2^1*H*-6,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-8-en-12-one (2.40 mg, 11% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 370.2.

Example **63** and **64**

(1^1*S*,1^3*R*,7*R*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1*S*,1^3*R*,7*S*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)butyl)carbamate

To a solution of *tert*-butyl *N*-(3-hydroxybutyl)carbamate (317 mg, 1.67 mmol) in THF (30 mL) was added NaH (167 mg, 4.18 mmol, 60% purity) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 min and then 2-bromo-6-(bromomethyl)pyridine (350 mg, 1.39 mmol) was added. The reaction was warmed to 25 °C and stirred at 25 °C for 17 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (25 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15% in 25 min) to afford *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)butyl)carbamate (305 mg, 61% yield) as a colorless oil. LC-MS: m/z 359.1 $[M+H]^+$.

Step 2: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)butyl)carbamate

To a mixture of *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)butyl)carbamate (386 mg, 1.07 mmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (200 mg, 896 μmol) and Cs_2CO_3 (584 mg, 1.79 mmol) in 1,4-dioxane (10 mL) was added $Pd_2(dba)_3$ (82.0 mg, 89.6 μmol) and Xantphos (104 mg, 179 μmol) under nitrogen. The reaction was heated to 100 °C and stirred at 100 °C under nitrogen for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80%) in 25 min to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)butyl)carbamate (306 mg, 68% yield) as a brown oil. LC-MS: m/z $[M+H]^+$ 502.3.

Step 3: (1*R*,3*S*)-3-(5-((6-(((4-((*tert*-butoxycarbonyl)amino)butan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)butyl)carbamate (270 mg, 538 μmol) in DCM (15 mL) was added CDI (262 mg, 1.61 mmol) and DIPEA (2.69 mmol, 469 μL) at 25 °C. Then the reaction mixture was heated

to 35 °C and stirred at 35 °C for 1 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-(((4-((*tert*-butoxycarbonyl)amino)butan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (310 mg, crude) as a brown oil, which was used directly in the next step without further purification. LC-MS: m/z $[M+H]^+$ 596.3.

Step 4: (1*R*,3*S*)-3-(5-((6-(((4-aminobutan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirring solution of (1*R*,3*S*)-3-(5-((6-(((4-((*tert*-butoxycarbonyl)amino)butan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg, 504 μmol) in DCM (10 mL) at 25 °C was added TFA (10 mL). After addition, the mixture was stirred at this temperature for 10 min. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-(((4-aminobutan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (240 mg, crude) as a brown oil, which was used directly in the next step without further purification. LC-MS: m/z $[M+H]^+$ 496.3.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

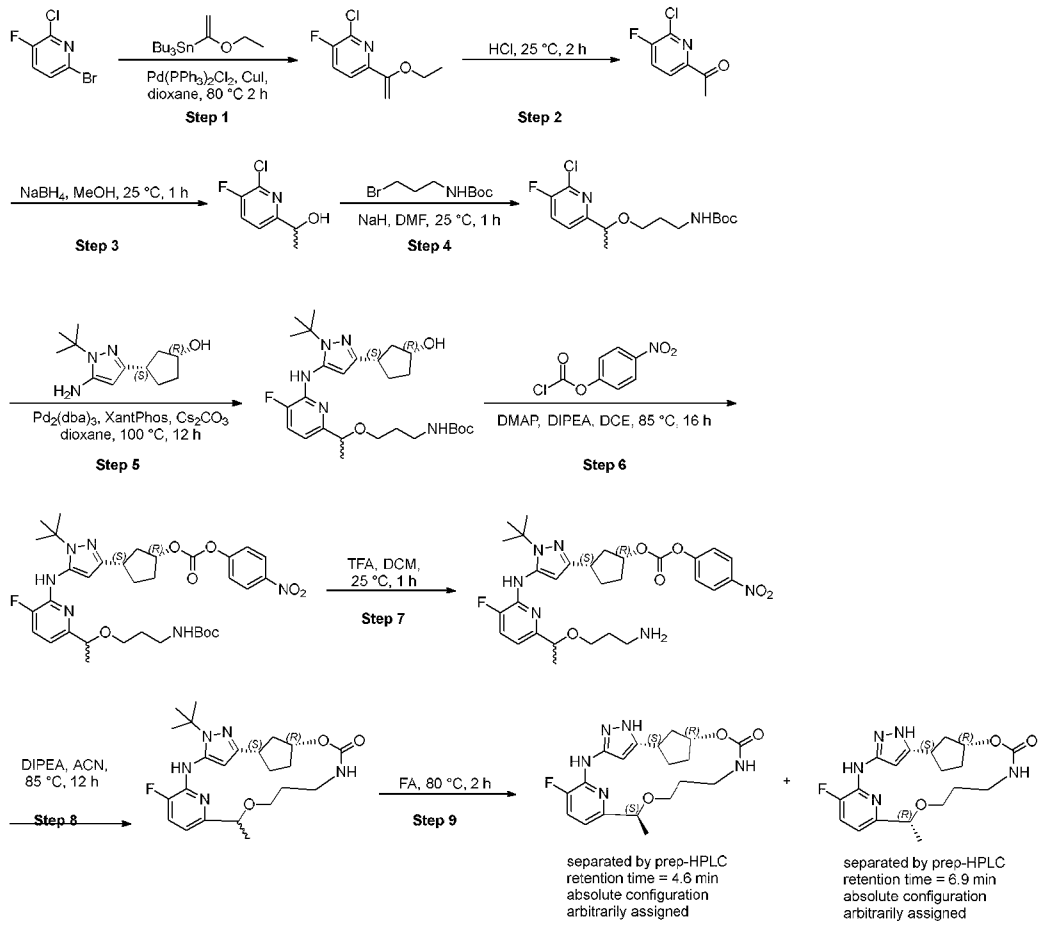
To a solution of (1*R*,3*S*)-3-(5-((6-(((4-aminobutan-2-yl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (240 mg, 484 μmol) in CH_3CN (10 mL) was added DIPEA (2.97 g, 22.97 mmol). The mixture was warmed to 80 °C and stirred at this temperature for 6 h. The mixture was cooled down to 25 °C and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (with EtOAc from 0 to 80%) in 25 min to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (90.0 mg, 43% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 428.3.

Step 6: (1^1S,1^3R,7*R*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1S,1^3R,7*S*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (80.0 mg, 187 μmol) in TFA (3.0 mL) was heated to 90 °C and stirred at 90 °C for 6 h. The mixture was cooled to 25 °C and was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 13% to 23% in 8 min) to afford (1^1S,1^3R,7*R*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (retention time = 5.7 min, 7.5 mg, absolute configuration arbitrarily assigned, 11% yield) as a white solid. LC-MS: m/z 372.2 $[M+H]^+$. And (1^1S,1^3R,7*S*,*Z*)-7-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (retention time = 6.5 min, 11.1 mg, absolute configuration arbitrarily assigned, 16% yield) as a white solid. LC-MS: m/z 372.2 $[M+H]^+$.

Example **65** and **66**

(11S,13R,5S,Z)-43-fluoro-5-methyl-21H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (11S,13R,5R,Z)-43-fluoro-5-methyl-21H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 2-chloro-6-(1-ethoxyvinyl)-3-fluoropyridine

To a solution of 6-bromo-2-chloro-3-fluoropyridine (800 mg, 3.80 mmol) in dioxane (50 mL) was added $PdCl_2(Ph_3P)_2$ (534 mg, 760 μmol), CuI (145 mg, 761 μmol, 25.8 μL) tributyl(1-ethoxyvinyl)stannane (2.06 g, 5.70 mmol, 1.93 mL) at 25 °C under N_2. The mixture was heated to 80°C and stirred at 80 °C under N_2 for 2 h. The reaction was cooled to room temperature and filtered. The filter cake was washed with acetonitrile and the organic layers were combined. The resulting solution was concentrated under reduced pressure to purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10% in 15 min) to afford 2-chloro-6-(1-ethoxyvinyl)-3-fluoropyridine (740 mg, 96% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 202.1.

Step 2: 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-one

To a solution of 2-chloro-6-(1-ethoxyvinyl)-3-fluoropyridine (730 mg, 3.62 mmol) in dioxane (20 mL) was added HCl (2.5 M, 10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The

mixture was diluted with water (20 mL) and extracted with EtOAc (5.0 mL × 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10% in 15 min) to afford 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-one (477 mg, 76% yield) as a yellow oil. LC-MS: m/z 174.0 $[M+H]^+$.

Step 3: 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-ol

To a solution of 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-one (477 mg, 2.75 mmol) in MeOH (50 mL) was added sodium borohydride (197 mg, 5.50 mmol) under N_2 at 0 °C. The mixture was warmed to 25°C and stirred at 25 °C under N_2 for 1 h. The mixture was quenched with saturated NaCl solution (100 mL) and then extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 20 min) to afford 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-ol (380 mg, 79% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 176.1.

Step 4: *tert*-butyl (3-(1-(6-chloro-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate

To a solution of 1-(6-chloro-5-fluoropyridin-2-yl)ethan-1-ol (380 mg, 2.16 mmol) in DMF (4.0 mL) was added NaH (173 mg, 4.33 mmol) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 min and then *tert*-butyl (3-bromopropyl)carbamate (1.03 g, 4.33 mmol) was added. The reaction was stirred at 25 °C for 1 h. The mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 15 min) to afford *tert*-butyl (3-(1-(6-chloro-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (450 mg, 62 % yield) as a colorless oil. LC-MS: m/z 355.1 $[M+Na]^+$.

Step 5: *tert*-butyl (3-(1-(6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate

To a solution of (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (130 mg, 582 μmol) in dioxane (10 mL) was added *tert*-butyl (3-(1-(6-chloro-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (232 mg, 699 μmol), Cs_2CO_3 (379 mg, 1.16 mmol) $Pd_2(dba)_3$ (107 mg, 116 μmol) and XantPhos (67.4 mg, 116 μmol) under N_2 at 25 °C. The reaction was heated to 100 °C and stirred at 100 °C under N_2 for 12 h. The mixture was cooled to room temperature. The mixture was diluted with water (20 mL) and extracted with EtOAc (5.0 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with MeOH/DCM (with MeOH from 0 to 7% in 15 min) to afford *tert*-butyl (3-(1-(6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (253 mg, 84% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 520.3.

Step 6: *tert*-butyl (3-(1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate

To a solution of *tert*-butyl (3-(1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (230 mg, 443 μmol) in DCE (20 mL) was added 4-nitrophenyl carbonochloridate (268 mg, 1.33 mmol), DMAP (54.1 mg, 443 μmol) and DIPEA (172 mg, 1.33 mmol, 232 μL) at 25 °C. The reaction was heated to 85 °C and stirred at 85 °C under N_2 for 16 h. The mixture was cooled to room temperature.The mixture was diluted with water (50 mL) and extracted with DCM (30 mL × 3). The combined organic layer dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 20 min) to afford *tert*-butyl (3-(1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (170 mg, 56% yield) as a brown oil. LC-MS: m/z 685.3 $[M+H]^+$.

Step 7: (1*R*,3*S*)-3-(5-((6-(1-(3-aminopropoxy)ethyl)-3-fluoropyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a solution of *tert*-butyl (3-(1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)ethoxy)propyl)carbamate (170 mg, 248μmol) in DCM/TFA=1:1 (10 mL) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-(1-(3-aminopropoxy)ethyl)-3-fluoropyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (200 mg, crude) as a yellow oil, which was used directly in the next step. LC-MS: m/z $[M+H]^+$ 585.2.

Step 8: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-5-methyl-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

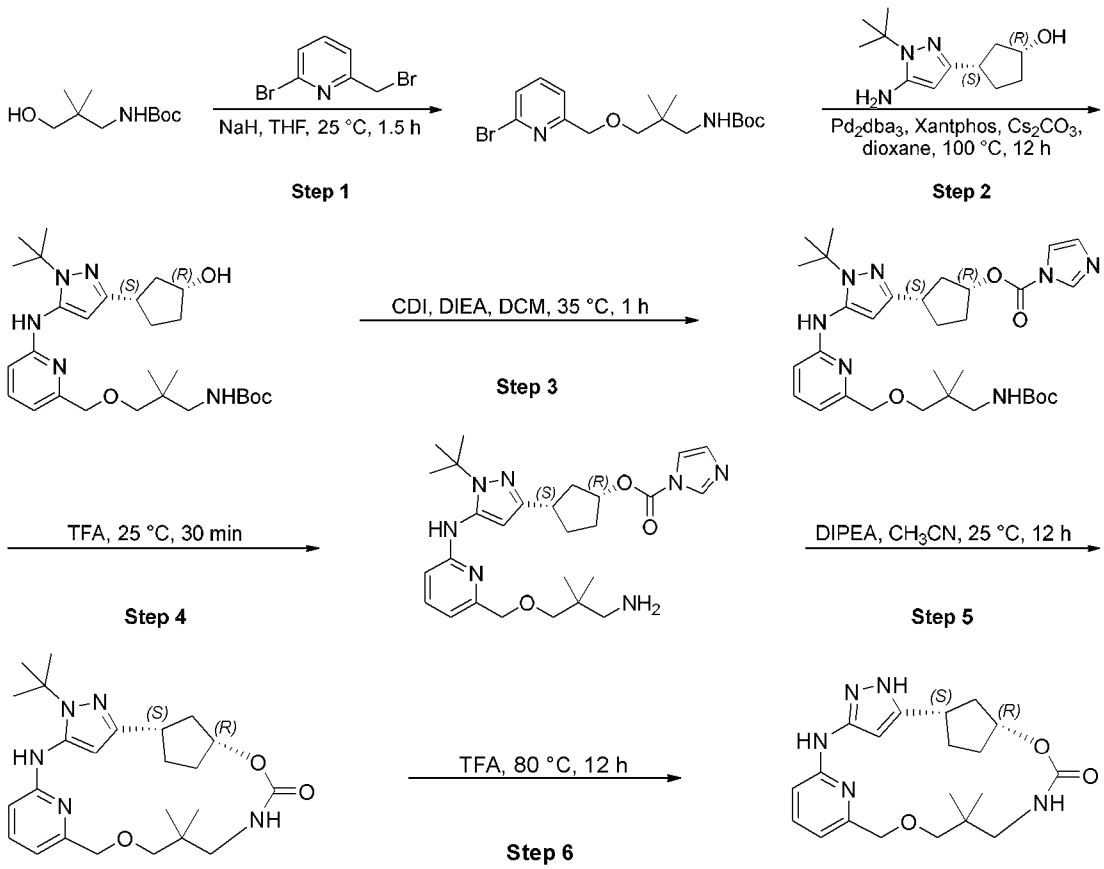
To a solution of (1*R*,3*S*)-3-(5-((6-(1-(3-aminopropoxy)ethyl)-3-fluoropyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (200 mg, 205 μmol) in CH_3CN (100 mL) was added DIPEA (2.23 g, 17.2 mmol, 3.00 mL) at 25 °C. The reaction was heated to 85 °C and stirred at 85 °C for 12 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 15 min) to afford (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-5-methyl-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (80.0 mg, 87% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 446.2.

Step 9: (1^1*S*,1^3*R*,5*S*,*Z*)-4^3-fluoro-5-methyl-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one & (1^1*S*,1^3*R*,5*R*,*Z*)-4^3-fluoro-5-methyl-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The solution of (1^1S,1^3R,Z)-2^1-(*tert*-butyl)-4^3-fluoro-5-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (80.0 mg, 180 μmol) in FA (5.0 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 25% to 55% in 8 min) to afford the product (1^1S,1^3R,5S,Z)-4^3-fluoro-5-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (retention time = 4.6 min, 10.6 mg, absolute configuration arbitrarily assigned, 15% yield) as white solid. LC-MS: m/z [M+H]+ 390.1. And (1^1S,1^3R,5R,Z)-4^3-fluoro-5-methyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (retention time = 6.9 min, 9.40 mg, absolute configuration arbitrarily assigned, 13% yield) as white solid. LC-MS: m/z $[M+H]^+$ 390.1.

Example **67**

(1^1S,1^3R,Z)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate

To a solution of *tert*-butyl (3-hydroxy-2,2-dimethylpropyl)carbamate (200 mg, 984 μmol) in THF (10 mL) was added NaH (157 mg, 3.94 mmol, 60% purity) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 min and then 2-bromo-6-(bromomethyl)pyridine (296 mg, 1.18 mmol) was added. The reaction was warmed to 25 °C stirred at 25 °C for 1 h. The mixture was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 20% in 15 min) to afford *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate (182 mg, 49% yield) as a brown oil. LC-MS: m/z 374.1 $[M+H]^+$.

Step 2: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate

To a mixture of *tert*-butyl (3-((6-bromopyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate (167 mg, 448 μmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (100 mg, 448 μmol) and Cs_2CO_3 (292 mg, 896 μmol) in 1,4-dioxane (10 mL) was added $Pd_2(dba)_3$ (82.0 mg, 90.0 μmol) and Xantphos (51.8 mg, 89.6 μmol) under nitrogen. The reaction was heated to 100 °C stirred at 100 °C under nitrogen for 12 h. The mixture was diluted with ice water (30 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 70%) in 15 min to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate (190 mg, 82% yield) as a brown oil. LC-MS: m/z $[M+H]^+$ 516.4.

Step 3: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)-2,2-dimethylpropyl)carbamate (190 mg, 368 μmol) in DCM (10 mL) was added CDI (179 mg, 1.11 mmol) and DIPEA (1.84 mmol, 321 μL) at 25 °C. Then the reaction mixture was heated to 35 °C and stirred at 35 °C for 1 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (198 mg, crude) as a yellow solid, which was used directly in the next step. LC-MS: m/z $[M+H]^+$ 610.3.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (198 mg, crude)

in TFA (5.0 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (170 mg, crude) as a brown oil, which was used directly in the next step. LC-MS: m/z $[M+H]^+$ 510.3.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

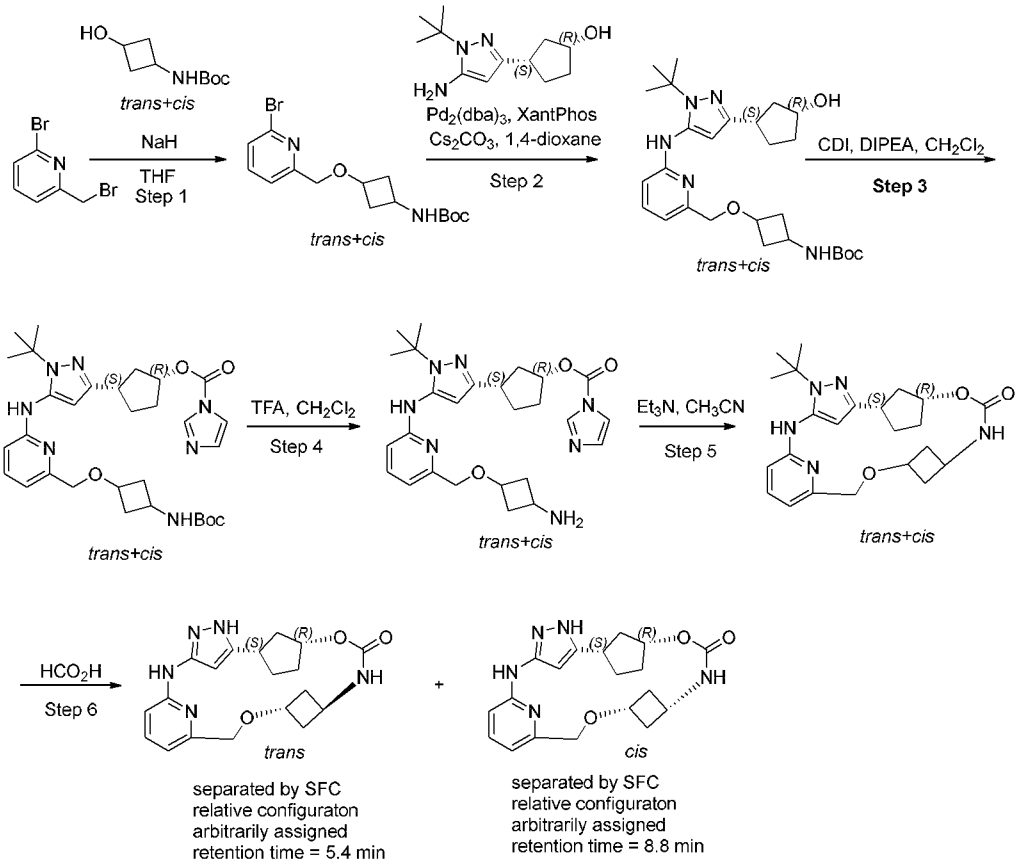
To a solution of (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-dimethylpropoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (170 mg, 267 μmol) in CH_3CN (30 mL) was added DIPEA (103 mg, 801 μmol). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (with EtOAc from 0 to 40%) in 15 min to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (60.0 mg, 51% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 442.2.

Step 6: (1^1S,1^3R,*Z*)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (50.0 mg, 113 μmol) in TFA (6.0 mL) was heated to 80 °C and stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (with CH_3CN from 10% to 40% in 8 min) to afford (1^1S,1^3R,*Z*)-8,8-dimethyl-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (4.00 mg, 9% yield) as a white solid. LC-MS: m/z 386.2 $[M+H]^+$.

Example **68** and **69**

(1^1S,1^3R,7^1R,7^3S,*Z*)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one and **(1^1S,1^3R,7^1S,7^3R,*Z*)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one**



Step 1: *tert*-butyl *N*-[3-[(6-bromo-2-pyridyl)methoxy]cyclobutyl]carbamate

To a suspension of *tert*-butyl *N*-(3-hydroxycyclobutyl)carbamate (400 mg, 2.14 mmol) in THF (10.0 mL) was added slowly NaH (76.0 mg, 60 wt.% in mineral oil, 3.20 mmol) at 0 °C. The suspension was stirred at that temperature for 15 min under N_2 before 2-bromo-6-(bromomethyl)pyridine (562 mg, 2.24 mmol)was added and the reaction was stirred at 20 °C for 16 h. The reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25% in 25 min) to afford *tert*-butyl *N*-[3-[(6-bromo-2-pyridyl)methoxy]cyclobutyl]carbamate (600 mg, 78% yield) as a yellow solid. LC-MS: m/z 356.8 $[M+H]^+$.

Step 2: *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]cyclobutyl]carbamate

To a suspension of *tert*-butyl *N*-[3-[(6-bromo-2-pyridyl)methoxy]cyclobutyl]carbamate (600 mg, 1.68 mmol) in 1,4-dioxane (10.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (375 mg, 1.68 mmol), Cs_2CO_3 (1.64 g, 5.04 mmol), XantPhos (194 mg, 0.335 mmol) and $Pd_2(dba)_3$ (153 mg, 0.167 mmol) at room temperature and the reaction was stirred at 100 °C for 16 h under N_2. After completion of the reaction as judged by LCMS, the reaction mixture was filtered

and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40% in 30 min) to afford *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]cyclobutyl]carbamate (450 mg, 53% yield) as a yellow solid. LC-MS: m/z 500.0 $[M+H]^+$.

Step 3: [(1*R*,3*S*)-3-[5-[[6-[[3-(*tert*-butoxycarbonylamino)cyclobutoxy]methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]cyclobutyl]carbamate (450 mg, 0.90 mmol) in CH_2Cl_2 (5.0 mL) was added CDI (388 mg, 2.70 mmol) and DIPEA (781 µL, 580 mg, 4.50 mmol) at 35 °Cand the reaction was stirred for 5 h. After completion of the reaction as judged by LCMS, the reaction mixture was quenched with ice-cold water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-[[3-(*tert*-butoxycarbonylamino)cyclobutoxy]methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z 594.1 $[M+H]^+$.

Step 4: [(1*R*,3*S*)-3-[5-[[6-[(3-aminocyclobutoxy)methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of [(1*R*,3*S*)-3-[5-[[6-[[3-(*tert*-butoxycarbonylamino)cyclobutoxy]methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) in CH_2Cl_2 (3.0 mL) was added slowly TFA (1.0 mL) at 25 °C and the reaction was stirred for 1 h. After completion of the reaction as judged by LCMS, the reaction mixture was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-[(3-aminocyclobutoxy)methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z 494.1 $[M+H]^+$.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

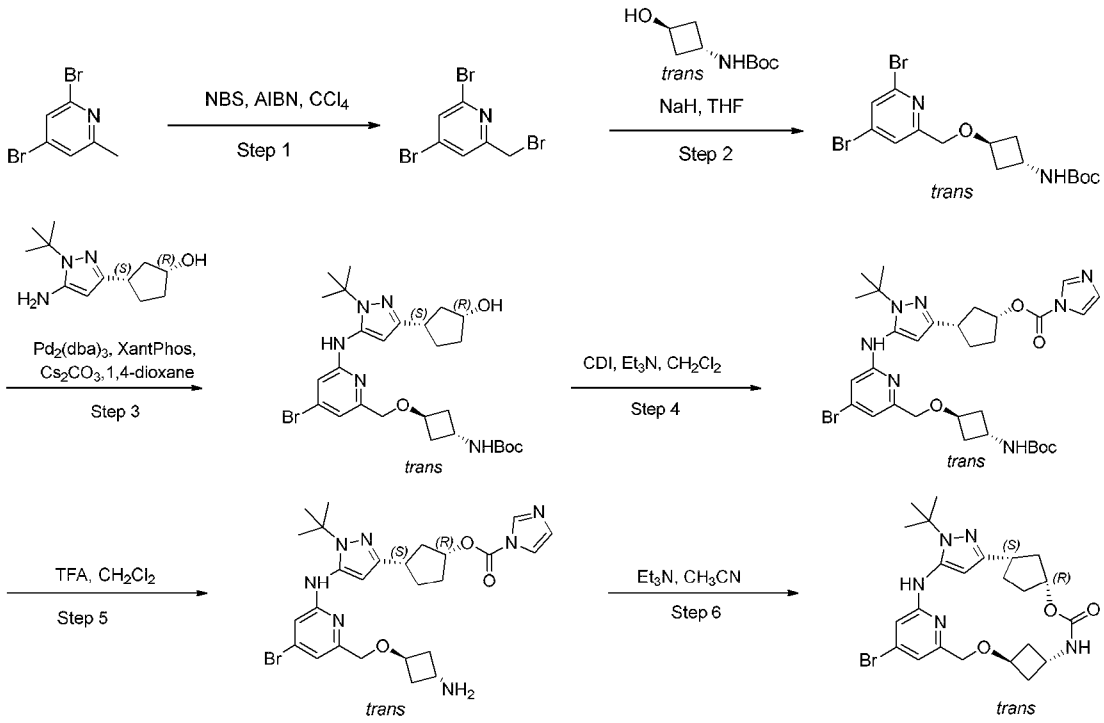
To a suspension of [(1*R*,3*S*)-3-[5-[[6-[(3-aminocyclobutoxy)methyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) in CH_3CN (5.0 mL) was added Et_3N (1.24 mL, 902 mg, 8.91 mmol) and the reaction was stirred at 80 °C for 16 h. After completion of the reaction as judged by LCMS, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 30 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (100 mg) as a yellow solid. m/z 426.1 $[M+H]^+$.

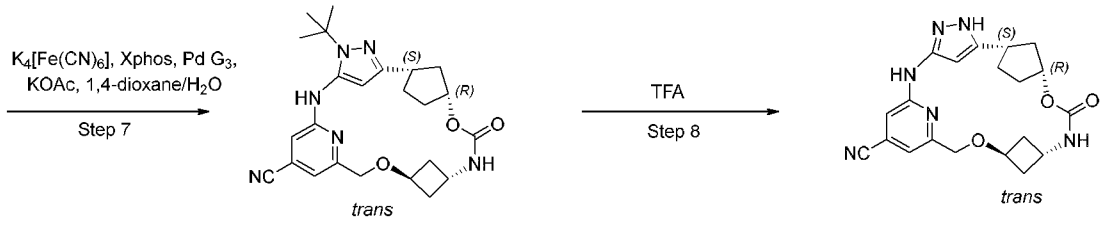
Step 6: ($1^1S,1^3R,7^1R,7^3S,Z$)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one and ($1^1S,1^3R,7^1S,7^3R,Z$)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (90.0 mg, 211 μmol) in HCO_2H (3.0 mL) was stirred for 5 h at 100 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 2% to 15% in 10 min (0.1% HCO_2H) and further purified by SFC eluting with CO_2 in EtOH (AD-H column, CO_2/EtOH = 60/40, EtOH with 0.2% NH_4OH, 40 g/min, 40 °C) to afford the desired product ($1^1S,1^3R,7^1R,7^3S,Z$)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (relative configuraton arbitrarily assigned, retention time = 5.4 min, 8.4 mg, 10% yield), LC-MS: m/z 370.0 $[M+H]^+$, and ($1^1S,1^3R,7^1S,7^3R,Z$)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (relative configuraton arbitrarily assigned, retention time = 8.8 min, 2.0 mg, 3% yield) as a white solid. LC-MS: m/z 370.0 $[M+H]^+$.

Example **70**

($1^1S,1^3R,7^1R,7^3S,Z$)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile





Step 1: 2,4-dibromo-6-(bromomethyl)pyridine

To a stirred solution of 2-bromoisonicotinonitrile (5.00 g, 19.9 mmol) in CCl_4 (50.0 mL) were sequentially added AIBN (654 mg, 3.99 mmol) and NBS (4.26 g, 23.9 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 16 h under N_2 atmosphere. The mixture was cooled and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 30 min) to afford 2,4-dibromo-6-(bromomethyl) pyridine (5.00 g, crude) as a yellow solid. LC-MS: m/z $[M+H]^+$ 327.7.

Step 2: *tert*-butyl ((1r,3r)-3-((4,6-dibromopyridin-2-yl)methoxy)cyclobutyl)carbamate

To a stirred solution of 2,4-dibromo-6-(bromomethyl)pyridine (5.00 g, 15.2 mmol) in THF (100 mL) was added NaH (1.21 g, 60%wt. in mineral oil, 30.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before *tert*-butyl ((1r,3r)-3-hydroxycyclobutyl)carbamate (2.84 g, 15.2 mmol) was added at that temperature. The reaction mixture was warmed to 25 °C and stirred at that temperature for 16 h before it was quenched with water (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 25 min) to afford *tert*-butyl ((1r,3r)-3-((4,6-dibromopyridin-2-yl)methoxy)cyclobutyl)carbamate (2.50 g, 36% yield) as a yellow oil. LC-MS: m/z $[M+Na]^+$ 458.8.

Step 3: *tert*-butyl ((1*S*,3r)-3-((4-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)cyclobutyl)carbamate

To a stirred solution of *tert*-butyl *N*-[3-[(4,6-dibromo-2-pyridyl)methoxy]cyclobutyl]carbamate (2.50 g, 5.73 mmol) in 1,4-Dioxane (60.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (1.28 g, 5.73 mmol), $Pd_2(dba)_3$ (525 mg, 0.573 mmol), XantPhos (663 mg, 1.15 mmol) and Cs_2CO_3 (3.74 g, 11.5 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 3 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/DCM (with MeOH from 0 to 10% in 25 min) and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 60 min) to give *tert*-butyl ((1*S*,3r)-3-((4-bromo-6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)cyclobutyl)carbamate(1.80 g, 52% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 578.1.

Step 4: (1*R*,3*S*)-3-(5-((4-bromo-6-(((1r,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutoxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred suspension of *tert*-butyl *N*-[3-[[4-bromo-6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]methoxy]cyclobutyl]carbamate (1.71 g, 2.96 mmol) in CH_2Cl_2 (50.0 mL) were sequentially added CDI (1.28 g, 8.87 mmol), Et_3N (822 μL, 599 mg, 5.91 mmol) and DMAP (289 mg, 2.36 mmol) at 25 °C. The reaction mixture was warmed to 40 °C and stirred at that temperature for 16 h before it was cooled to 25 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80 % in 30 min) to afford (1*R*,3*S*)-3-(5-((4-bromo-6-(((1r,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutoxy)methyl)pyridin-2-yl)amino)-1-(*ter*t-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (1.40 g, 66% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 672.2.

Step 5: (1*R*,3*S*)-3-(5-((6-(((1r,3*S*)-3-aminocyclobutoxy)methyl)-4-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((4-bromo-6-(((1r,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutoxy)methyl)pyridin-2-yl)amino)-1-(*ter*t-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (1.50 g, 2.23 mmol) in CH_2Cl_2 (20.0 mL) were added TFA (20.0 mL) at 25 °C. The resulting mixture was stirred at that temperature for 2 h. The mixture was concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((6-(((1r,3*S*)-3-aminocyclobutoxy)methyl)-4-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (1.50 g, crude) as a colorless oil. LC-MS: m/z $[M+H]^+$ 572.0.

Step 6: (1^1S,1^3R,7^1R,7^3S,*Z*)-4^4-bromo-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

To a stirred solution of (1*R*,3*S*)-3-(5-((6-(((1r,3*S*)-3-aminocyclobutoxy)methyl)-4-bromopyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (1.50 g, 2.62 mmol) in CH_3CN (20.0 mL) was added Et_3N (1.09 mL, 795 mg, 7.86 mmol) at 25 °C. The resulting mixture was stirred at that temperature for 16 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0% to 80% in 30 min) to give (1^1S,1^3R,7^1R,7^3S,*Z*)-4^4-bromo-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (450 mg, 31% yield) as a brown solid. LC-MS: m/z $[M+H]^+$ 504.0.

Step 7: (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile

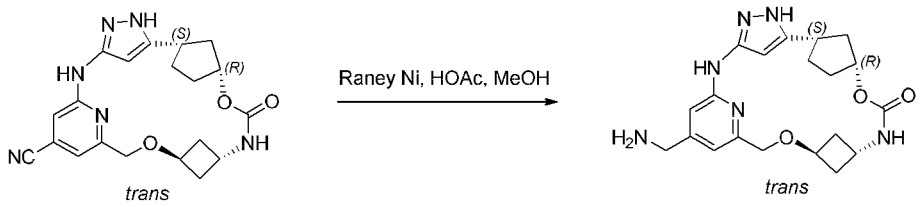
To a stirred solution of (1^1S,1^3R,7^1R,7^3S,Z)-4^4-bromo-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (180 mg, 357 μmol) in 1,4-Dioxane (10.0 mL) were sequentially added Potassium hexacyanoferrate(II) trihydrate (226 mg, 535 μmol), Xphos Pd G3 (18.1 mg, 21.4 μmol), KOAc (75.5 mg, 785 μmol) and H_2O (2.0 mL) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 16 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 30 min) to afford (1^1S,1^3R,71^R,7^3S,Z)-2^1-(*tert*-butyl)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile (120 mg, 63% yield) as a brown solid. LC-MS: m/z $[M+H]^+$ 451.1.

Step 8: (1^1S,1^3R,7^1R,7^3S,Z)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile

A solution of (1^1S,1^3R,71^R,7^3S,Z)-2^1-(*tert*-butyl)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile (120 mg, 266 μmol) in TFA (10.0 mL) was warmed to 50 °C and stirred at that temperature for 3 h before it was cooled to 25 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 40 min) to give (1^1S,1^3R,7^1R,7^3S,Z)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile (50.0 mg, 47% yield) as a yellow solid.LC-MS: m/z $[M+H]^+$ 395.1.

Example **182**

(1^1S,1^3R,7^1R,7^3S,Z)-4^4-(aminomethyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

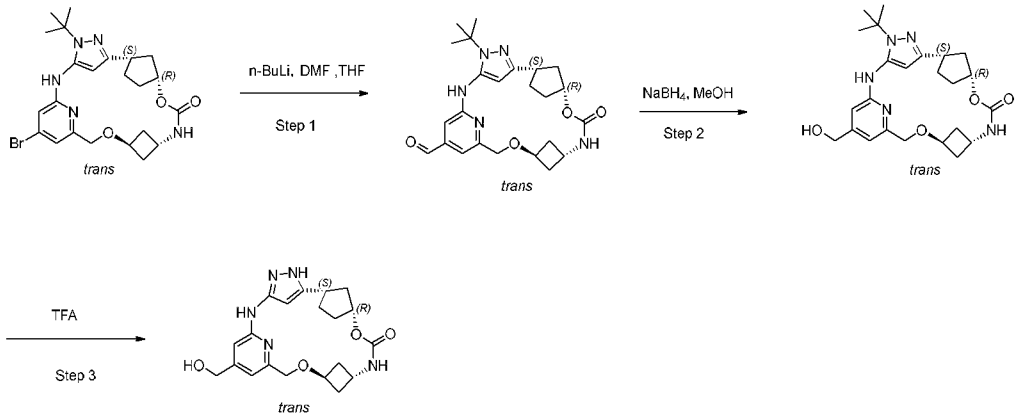


To a stirred solution of (1^1S,1^3R,7^1R,7^3S,Z)-9-oxo-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbonitrile (30.0 mg, 76.1 μmol) and HOAc (21.8 μL , 22.8 mg, 380 μmol,) in MeOH (20.0 mL) was added Raney Ni (22.3 mg, 380 μmol) at 25°C. The reaction mixture was warmed to 50 °C and stirred at that temperature for 16 h before it was cooled to 25 °C. The reaction mixture was filtered through a pad of Celite before the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 40 min) to give (1^1S,1^3R,7^1R,7^3S,Z)-4^4-

(aminomethyl)-2^{1}H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (7.90 mg, 26% yield) as a white solid.LC-MS: m/z [M+H]+ 399.0.

Example **71**

(1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-4^4-(hydroxymethyl)-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one



Step 1: (1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-2^1-(*tert*-butyl)-9-oxo-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbaldehyde

To a stirred solution of (1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-4^4-bromo-2^1-(*tert*-butyl)-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (180 mg, 357 μmol) in THF (20.0 mL) was added n-BuLi (1.78 mL, 356 μmol, 2M in THF) at -78°C. The reaction mixture was stirred at that temperature for 0.5 h under N_2 atmosphere before DMF (27.6 μL, 26.1 mg, 357 μmol) was added at that temperature. The reaction mixture was stirred at -78°C for 0.5 h under N_2 atmosphere before it was warmed to 25 °C. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (100 mL × 3). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 100 % in 40 min) to give (1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-2^1-(*tert*-butyl)-9-oxo-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbaldehyde (110 mg, 68% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 454.1.

Step 2: (1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-2^1-(*tert*-butyl)-4^4-(hydroxymethyl)-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

To a stirred solution of (1^1*S*,1^3*R*,7^1*R*,7^3*S*,*Z*)-2^1-(*tert*-butyl)-9-oxo-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphane-4^4-carbaldehyde (60.0 mg, 132 μmol) in MeOH (15.0 mL) was added $NaBH_4$ (15.0 mg, 397 μmol) at 0 °C. The reaction mixture was warmed to 25 °C and stirred at that temperature for 1 h. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic

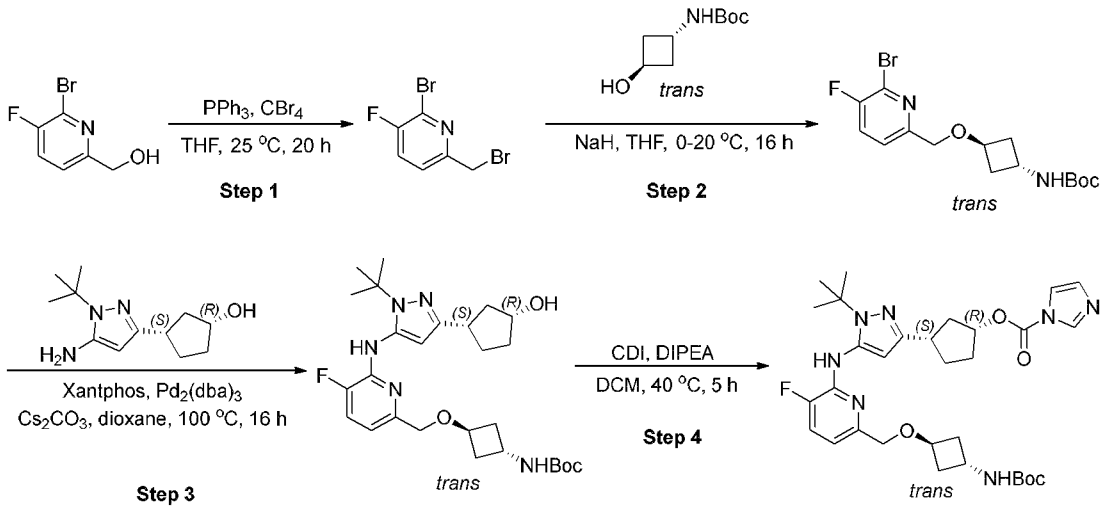
phases were washed with brine (15 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10 % in 20 min) to give (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-4^4-(hydroxymethyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (36.0 mg, 51% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 456.2.

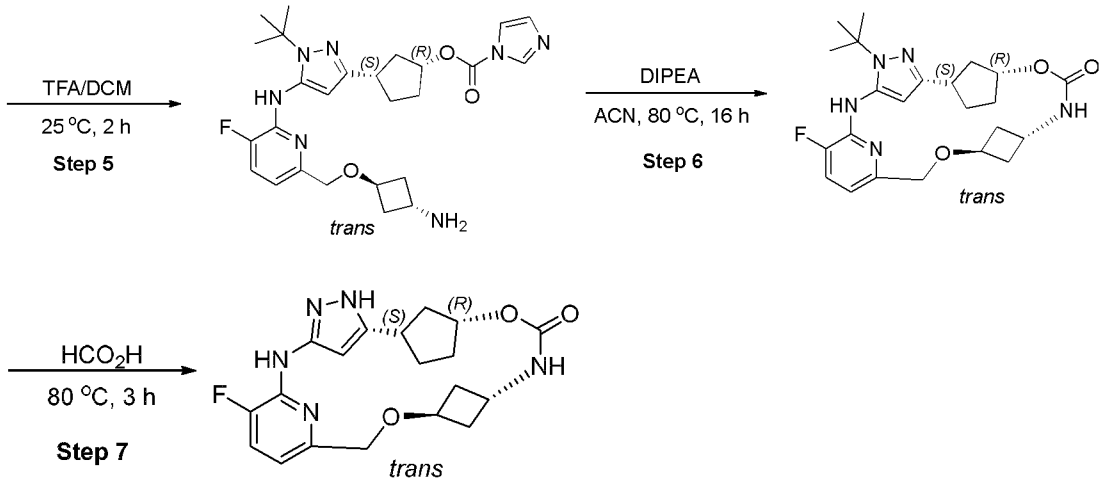
Step 3: (1^1S,1^3R,7^1R,7^3S,*Z*)-4^4-(hydroxymethyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

A stirred solution of (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-4^4-(hydroxymethyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (28.0 mg, 61.5 μmol) in TFA (5.0 mL) at 25 °C. The resulting mixture was warmed to 80 °C and stirred at that temperature for 3 h. The mixture was cooled to 25 °C. The residue was concentrated under reduced pressure and purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 40 min) to give (1^1S,1^3R,7^1R,7^3S,*Z*)-4^4-(hydroxymethyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (5.4 mg, 22% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 400.1.

Example **72**

(1^1S,1^3R,7^1R,7^3S,*Z*)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one





Step 1: 2-bromo-6-(bromomethyl)-3-fluoropyridine

To a solution of (6-bromo-5-fluoropyridin-2-yl)methanol (600 mg, 2.91 mmol) in THF (20 mL) was added carbon tetrabromide (1.93 g, 5.82 mmol) and triphenylphosphane (1.53 g, 5.82 mmol) . The mixture was stirred at 25 °C for 20 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 30%) in 20 min to give 2-bromo-6-(bromomethyl)-3-fluoropyridine (700 mg, 89% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 269.9.

Step 2: *tert*-butyl (3-((6-bromo-5-fluoropyridin-2-yl)methoxy)cyclobutyl)carbamate

To a solution of *tert*-butyl (3-hydroxycyclobutyl)carbamate (406 mg, 2.17 mmol) and NaH (260 mg, 10.8 mmol) in THF (5.0 mL) was added 2-bromo-6-(bromomethyl)-3-fluoro-pyridine (700 mg, 2.60 mmol) . The mixture was stirred at 25 °C for 16 h. The mixture was dulited with H_2O (10 mL) and extracted with EtOAc (10 ml × 2). The combined organic layer was dried over N_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 50%) in 15 min to give *tert*-butyl (3-((6-bromo-5-fluoropyridin-2-yl)methoxy)cyclobutyl)carbamate (700 mg, 86% yield) as a yellow liquid. LC-MS: m/z $[M+Na]^+$ 397.0.

Step 3: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropyridin-2-yl)methoxy)cyclobutyl)carbamate

To a solution of *tert*-butyl *N*-[3-[(6-bromo-5-fluoro-2-pyridyl)methoxy]cyclobutyl]carbamate (200 mg, 533 μmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (108 mg, 484 μmol) in 1,4-dioxane (2.0 mL) was added Cs_2CO_3 (474 mg, 1.45 mmol) , $Pd_2(dba)_3$ (88.7 mg, 96.9 μmol) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (112 mg, 194 μmol) . The mixture was heated to 100 °C and stirred at 100 °C under N_2 for 5 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by

silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 70%) in 15 min to give *tert*-butyl *N*-[3-[[6-[[2-tert-butyl-5-[(1*R*,3*S*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-5-fluoro-2-pyridyl]methoxy]cyclobutyl]carbamate (180 mg, 72% yield) as a yellow liquid. LC-MS: m/z $[M+H]^+$ 518.3.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)cyclobutoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*R*,3*S*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-5-fluoro-2-pyridyl]methoxy]cyclobutyl]carbamate (180 mg, 348 μmol) and di(1*H*-imidazol-1-yl)methanone (169 mg, 1.04 mmol) in DCM (10 mL) was added DIPEA (225 mg, 1.74 mmol) . The mixture was warmed to 40 °C and stirred at 40 °C for 5 h. The mixture was cooled to room temperature and concentrated under reduced pressure to get (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)cyclobutoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, 94% yield) as a yellow gum. LC-MS: m/z $[M+H]^+$ 612.3.

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminocyclobutoxy)methyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A mixture of [(1*R*,3*S*)-3-[5-[[6-[[3-(*tert*-butoxycarbonylamino)cyclobutoxy]methyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, 327 μmol) in DCM:TFA = 2:1 (15 mL) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to get [(1*R*,3*S*)-3-[5-[[6-[(3-aminocyclobutoxy)methyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (150 mg, 90% yield) as a yellow gum. LC-MS: m/z $[M+H]^+$ 512.3.

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

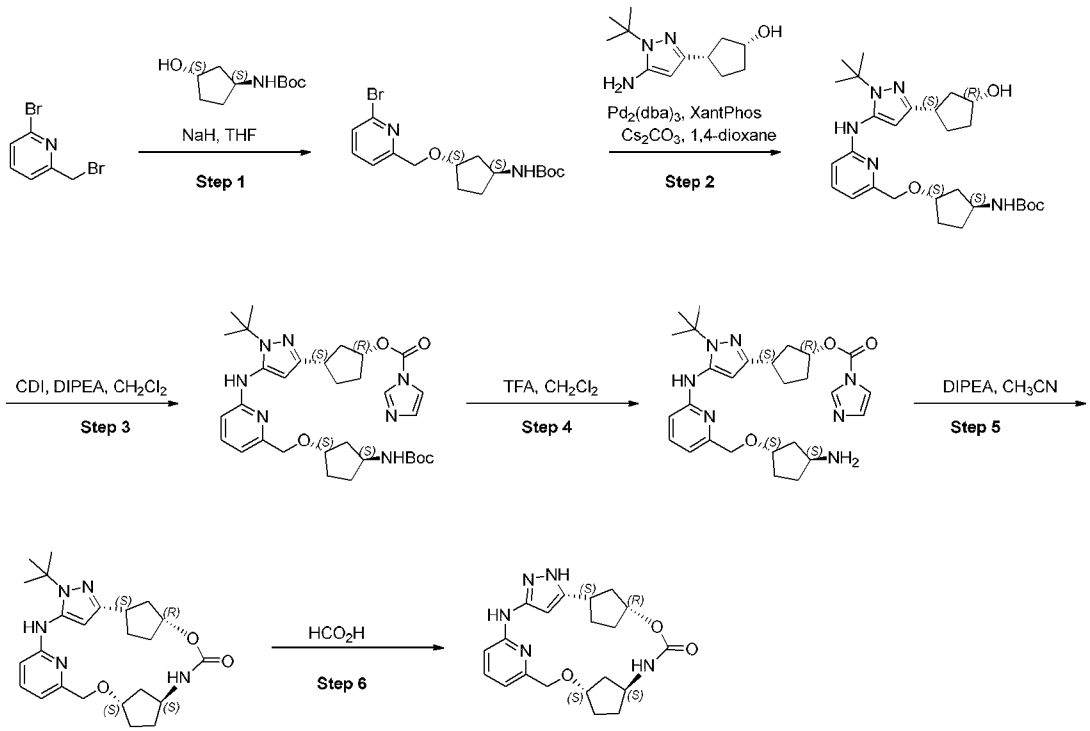
To a solution of [(1*R*,3*S*)-3-[5-[[6-[(3-aminocyclobutoxy)methyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (150 mg, 293 μmol) in CH_3CN (20 mL) was added DIPEA (148 mg, 1.15 mmol) . The mixture was heated to 80 °C and stirred at 80 °C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether (with EtOAc from 0 to 50%) in 15 min to give (1^1S,1^3R,7^1R,7^3S,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (90.0 mg, 69% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 444.2.

Step 7: (1^1S,1^3R,7^1R,7^3S,*Z*)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (150 mg, 338 μmol) in FA (8.0 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was washed with CH_3CN (3.0 mL) and filtered to get (1^1S,1^3R,7^1R,7^3S,*Z*)-4^3-fluoro-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-7(1,3)-cyclobutanacyclodecaphan-9-one (68.0 mg, 52% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 388.1.

Example **73**

(1^1*S*,1^3*R*,7^1*S*,7^3*S*,*Z*)-2^1*H*-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one



Step 1: *tert*-butyl ((1*S*,3*S*)-3-((6-bromopyridin-2-yl)methoxy)cyclopentyl)carbamate

To a stirred suspension of *tert*-butyl ((1*S*,3*S*)-3-hydroxycyclopentyl)carbamate (401 mg, 1.99 mmol) in THF (5.0 mL) was added slowly NaH (159 mg, 60 wt.% in mineral oil, 3.99 mmol) at 0 °C under N_2. The mixture was stirred at 25 °C for 30 min before 2-bromo-6-(bromomethyl)pyridine (500 mg, 1.99 mmol) in THF (5.0 mL) was added to it. The reaction mixture was stirred at 25 °C under N_2 for 16 h. The mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography

eluting with EtOAc/PE (with EtOAc from 0 to 30% in 15 min) to afford *tert*-butyl ((1*S*,3*S*)-3-((6-bromopyridin-2-yl)methoxy)cyclopentyl)carbamate (700 mg, 94% yield) as a yellow solid. LC-MS: m/z $[M-55]^+$ 314.8.

Step 2: *tert*-butyl ((1*S*,3*S*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)cyclopentyl)carbamate

To a stirred solution of *tert*-butyl ((1*S*,3*S*)-3-((6-bromopyridin-2-yl)methoxy)cyclopentyl)carbamate (400 mg, 1.08 mmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (241 mg, 1.08 mmol) in dioxane (8.0 mL) were sequentially added $Pd_2(dba)_3$ (98.7 mg, 108 μmol), XantPhos (125 mg, 215 μmol) and Cs_2CO_3 (1.05 g, 3.23 mmol). The reaction mixture was warmed to 100 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to 25 °C and filtered under reduced pressure. The filtrated was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 30 to 80 % in 20 min) to give *tert*-butyl ((1*S*,3*S*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)cyclopentyl)carbamate (350 mg, 63% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 514.3

Step 3: (1*R*,3*S*)-3-(5-((6-((((1*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl ((1*S*,3*S*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methoxy)cyclopentyl)carbamate (350 mg, 681 μmol) and DIPEA (475 μL, 352 mg, 2.73 mmol) in CH_2Cl_2 (10.0 mL) was added CDI (442 mg, 2.73 mmol) at 25 °C. The mixture was heated to 40 °C and stirred at that temperature for 6 h. The reaction mixture was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was used next step without further purification. LC-MS: m/z $[M+H]^+$ 608.4.

Step 4: (1*R*,3*S*)-3-(5-((6-((((1*S*,3*S*)-3-aminocyclopentyl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of crude (1*R*,3*S*)-3-(5-((6-((((1*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (3.0 mL) was added TFA (1 mL, 1.48 g, 12.98 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h. The mixture was concentrated under reduced pressure. The crude product was used next step without further purification. LC-MS: m/z $[M+H]^+$ 508.3.

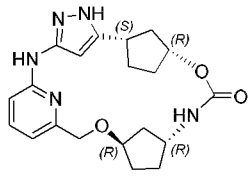
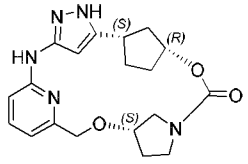
Step 5: (1^1S,1^3R,7^1S,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one

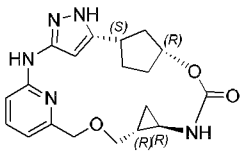
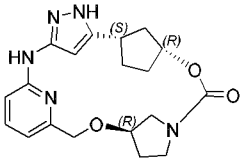
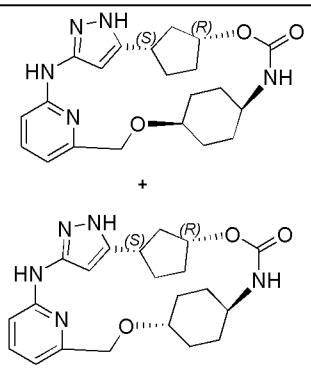
To a stirred solution of crude (1*R*,3*S*)-3-(5-((6-((((1*S*,3*S*)-3-aminocyclopentyl)oxy)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (40.0 mL) was added DIPEA (1.17 mL, 865 mg, 6.70 mmol) at 25 °C. The mixture was heated to 80 °C and stirred at that temperature for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 25 to 80 % in 20 min) to afford (1^1S,1^3R,7^1S,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one (100 mg, 33% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 440.3.

Step 6: (1^1S,1^3R,7^1S,7^3S,*Z*)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one

A solution of (1^1S,1^3R,7^1S,7^3S,*Z*)-2^1-(*tert*-butyl)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one (100 mg, 227 μmol) in HCO_2H (2.0 mL, 2.44 g, 53.01 mmol) was heated to 90 °C and stirred at that temperature for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 10% to 30% in 30 min) to afford (1^1S,1^3R,7^1S,7^3S,*Z*)-2^1H-6,10-dioxa-3,8-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1,7(1,3)-dicyclopentanacyclodecaphan-9-one (60.7 mg, 69% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 383.9.

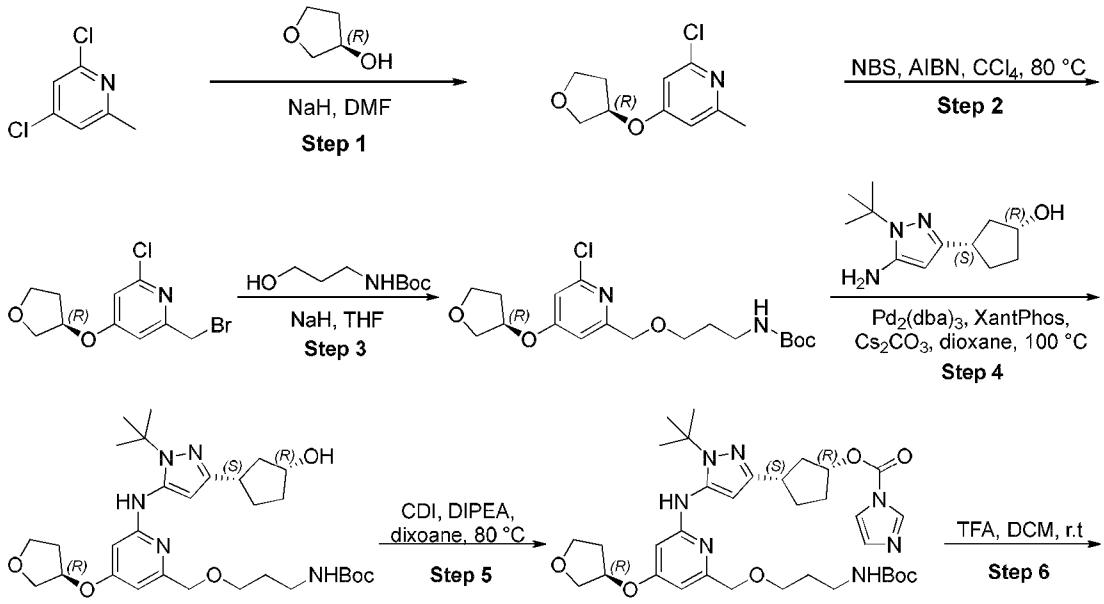
The following compounds were prepared using the similar procedure disclosed in synthetic example **73**.

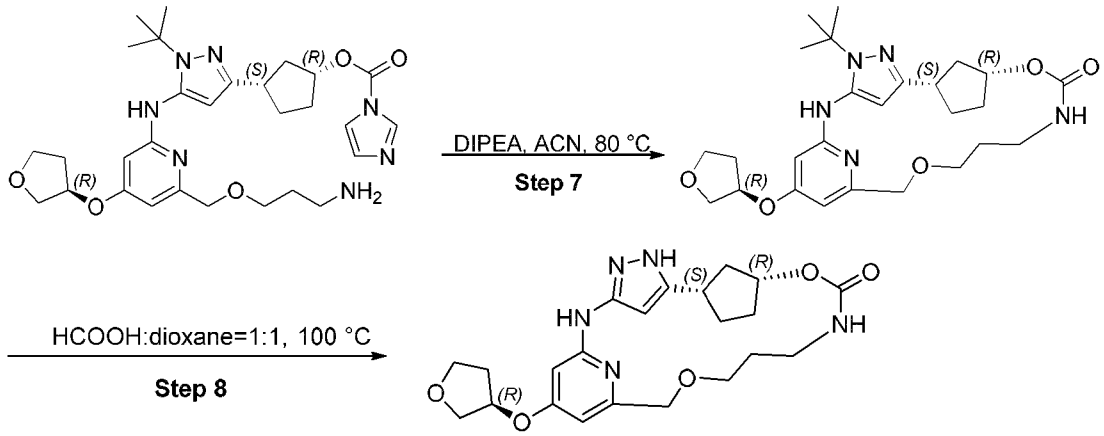
Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
74		384.2
75		370.2

76		370.2
179		370.1
180+181	 unseparated mixture	398.2

Example 77

(1^1*S*,1^3*R*,*Z*)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1*H*-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: (*R*)-2-chloro-6-methyl-4-((tetrahydrofuran-3-yl)oxy)pyridine

To a solution of (3*R*)-tetrahydrofuran-3-ol (2.00 g, 22.7 mmol) in DMF (15 mL) was added NaH (2.47 g, 61.7 mmol) at 0 °C. Then the reaction mixture was stirred at 0 °C for 10 min. Then the solution of 2,4-dichloro-6-methyl-pyridine (2.00 g, 12.3 mmol) in DMF (1.0 mL) was added dropwise to the reaction mixture. Then the reaction mixture was allowed warmed to 20 °C and stirred at 20 °C for 2 h. The mixture was quenched with ice water (80 mL). The mixture was extracted with EtOAc (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50%) in 15 min to afford 2-chloro-6-methyl-4-[(3R)-tetrahydrofuran-3-yl]oxy-pyridine (1.80 g, 68% yield) as a pale yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 214.1.

Step 2: (*R*)-2-(bromomethyl)-6-chloro-4-((tetrahydrofuran-3-yl)oxy)pyridine

To a solution of 2-chloro-6-methyl-4-[(3R)-tetrahydrofuran-3-yl]oxy-pyridine (500 mg, 2.34 mmol) in CCl_4 (15 mL) was added NBS (625 mg, 3.51 mmol, 298 μL) and AIBN (76.9 mg, 468 μmol) at 20 °C. Then the reaction mixture was heated to 80 °C and stirred at 80 °C under the atmosphere of N_2 for 3 h. The mixture was used for next step without further purification. LC-MS: (ESI) m/z $[M+H]^+$ 292.0. 244.1.

Step 3: *tert*-butyl (*R*)-(3-((6-chloro-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate

To the solution of *tert*-butyl *N*-(3-hydroxypropyl)carbamate (620 mg, 3.54 mmol) in THF (8.0 mL) was added NaH (236 mg, 5.90 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then the mixture was added to the suspension of 2-(bromomethyl)-6-chloro-4-[(3*R*)-tetrahydrofuran-3-yl]oxy-pyridine (690 mg, 2.36 mmol) in CCl_4 (13 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The mixture was diluted with DCM (150 mL). The mixture was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to

50%) in 15 min to afford *tert*-butyl (*R*)-(3-((6-chloro-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate (210 mg, 23% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 387.1.

Step 4: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate

To a solution of *tert*-butyl (*R*)-(3-((6-chloro-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate (200 mg, 517 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (121 mg, 543 μmol) in dioxane (5.0 mL) was added $Pd_2(dba)_3$ (71.0 mg, 77.6 μmol), XantPhos (89.7 mg, 155 μmol) and Cs_2CO_3 (505 mg, 1.55 mmol) under the atmosphere of N_2. Then the reaction mixture was heated to 100 °C and stirred at 100 °C under the atmosphere of N_2 for 5 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80%) in 15 min to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate (240 mg, 81% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 574.3.

Step 5: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)methoxy)propyl)carbamate (180 mg, 313 μmol) in dioxane (8.0 mL) was added DIPEA (324 mg, 437 μL) at 20 °C, then di(imidazol-1-yl)methanone (153 mg, 941 μmol) was added to the reaction mixture. The mixture was heated to 80 °C and stirred at 80 °C for 8 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 668.3.

Step 6: (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, 314 μmol) in DCM (3.0 mL) was added TFA (2.22 g, 19.5 mmol, 1.50 mL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-

imidazole-1-carboxylate (220 mg, crude, TF) as a yellow gum, which was used in next step without further purification. LC-MS: (ESI) m/z $[M+H]^+$ 568.3.

Step 7: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

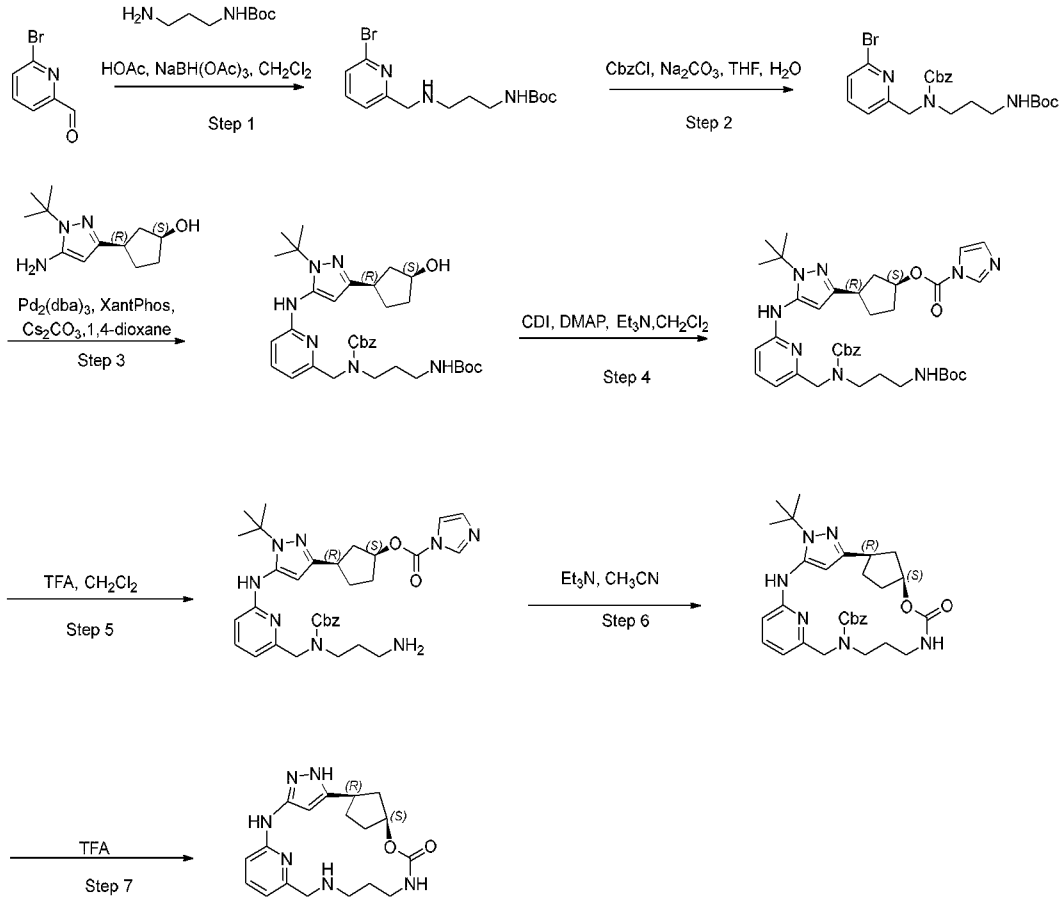
The solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropoxy)methyl)-4-(((*R*)-tetrahydrofuran-3-yl)oxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (220 mg, 387 μmol) in CH_3CN (20 mL) was added DIPEA (2.23 g, 17.2 mmol, 3.00 mL). Then the reaction mixture was heated to 80 °C and stirred at 80 °C for 13 h. The mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc (100 mL), the mixture was washed brine (80 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, the residue was purified silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 100%) in 20 min to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (50.0 mg, 26% yield) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 500.2.

Step 8: (1^1S,1^3R,*Z*)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

The solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (35.0 mg, 70.1 μmol) in FA (1.0 mL) and dioxane (1.0 mL) was stirred at 90 °C for 5 h. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC (with CH_3CN from 30% to 60% in 9 min) to afford the product (1^1S,1^3R,*Z*)-4^4-(((*R*)-tetrahydrofuran-3-yl)oxy)-2^1H-6,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (6.00 mg, 19% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 444.3.

Example **78**

(1^1R,1^3S,*Z*)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)propyl)carbamate

To a stirred solution of *tert*-butyl (3-aminopropyl)carbamate (2.00 g, 2.00 mL , 11.5 mmol) in CH_2Cl_2 (20.0 mL) were sequentially added 6-bromopyridine-2-carbaldehyde (2.14 g, 11.5 mmol) and HOAc (0.5 mL) at 25 °C. The resulting mixture was stirred at that temperature for 2 h before $NaBH(OAc)_3$ (2.92 g, 13.8 mmol) was added at 25 °C. The reaction mixture was stirred at 25 °C for 16 h before it was quenched with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 25 min) to afford *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)propyl)carbamate (2.00 g, 54% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 344.0.

Step 2: benzyl ((6-bromopyridin-2-yl)methyl)(3-((tert-butoxycarbonyl)amino)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)propyl)carbamate (1.00 g, 2.90 mmol) in THF (10.0 mL) and H_2O (2.0 mL) were sequentially added Na_2CO_3 (308 mg, 2.90 mmol) and CbzCl (496 mg, 2.90 mmol) at 25°C. The resulting mixture was stirred at that temperature for 16 h before it was quenched with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to

30% in 25 min) to afford benzyl ((6-bromopyridin-2-yl)methyl)(3-((*tert*-butoxycarbonyl)amino)propyl)carbamate (0.65 g, 47% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 477.6.

Step 3: benzyl (3-((*tert*-butoxycarbonyl)amino)propyl)((6-((1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)carbamate

To a stirred solution of benzyl ((6-bromopyridin-2-yl)methyl)(3-((*tert*-butoxycarbonyl)amino)propyl)carbamate (600 mg, 1.25 mmol) in 1,4-Dioxane (10.0 mL) were sequentially added XantPhos (72.3 mg, 0.125 mmol), $Pd_2(dba)_3$ (115 mg, 0.125 mmol), Cs_2CO_3 (815 mg, 2.50 mmol) and (1*S*,3*R*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (279 mg, 1.25 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/DCM (with MeOH from 0 to 10% in 25 min) to give benzyl (3-((*tert*-butoxycarbonyl)amino)propyl)((6-((1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)carbamate(550 mg, 71% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 620.7

Step 4: (1*S*,3*R*)-3-(5-((6-((((benzyloxy)carbonyl)(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred suspension of benzyl (3-((*tert*-butoxycarbonyl)amino)propyl)((6-((1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)carbamate (500 mg, 0.805 mmol) in CH_2Cl_2 (10.0 mL) were sequentially added CDI (580 mg, 4.03 mmol) and Et_3N (560 μL, 408 mg, 4.03 mmol) at 25 °C. The reaction mixture was warmed to 40 °C and stirred at that temperature for 16 h before it was cooled to 25 °C. The reaction mixture was concentrated under reduced pressure to afford (1*S*,3*R*)-3-(5-((6-((((benzyloxy)carbonyl)(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (550 mg, 96% yield) as a yellow oil which was directly used for the next step without further purification. LC-MS: m/z $[M+H]^+$ 715.3.

Step 5: (1*S*,3*R*)-3-(5-((6-(((3-aminopropyl)((benzyloxy)carbonyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*S*,3*R*)-3-(5-((6-((((benzyloxy)carbonyl)(3-((*tert*-butoxycarbonyl)amino)propyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (550 mg, 0.770 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at 25 °C. The resulting mixture was stirred at that temperature for 12 h. The mixture was concentrated under reduced pressure to give (1*S*,3*R*)-3-(5-((6-(((3-aminopropyl)((benzyloxy)carbonyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (450 mg, crude) as a colorless oil. LC-MS: m/z $[M+H]^+$ 615.3.

Step 6: ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-11-oxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6-carboxylate

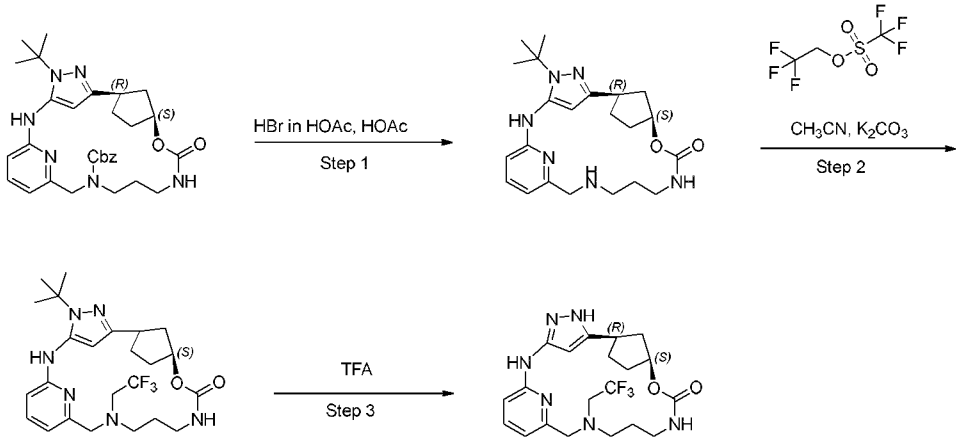
To a stirred solution of (1*S*,3*R*)-3-(5-(((6-(((3-aminopropyl)((benzyloxy)carbonyl)amino)methyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (400 mg, 0.651 mmol) in CH_3CN (5.0 mL) was added Et_3N (0.45 mL, 330 mg, 3.25 mmol) at 25 °C. The reaction mixture was warmed to 70 °C and stirred at that temperature for 2 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0% to 80% in 30 min) to give ($1^1R,1^3S,Z$)-21-(*tert*-butyl)-11-oxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6-carboxylate (200 mg, 59% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 546.7.

Step 7: ($1^1R,1^3S,Z$)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A stirred solution of ($1^1R,1^3S,Z$)-21-(*tert*-butyl)-11-oxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6-carboxylate (50.0 mg, 91.0 μmol) in TFA (5.0 mL) at 25 °C was warmed to 70 °C and stirred at that temperature for 2 h before it was cooled to 25 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 40 min) to give ($1^1R,1^3S,Z$)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (2.0 mg, 6% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 357.2.

Example **79**

($1^1R,1^3S,Z$)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a stirred solution of benzyl (1^1R,1^3S,Z)-2^1-(tert-butyl)-11-oxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6-carboxylate (200 mg, 265 μmol) in HOAc (3.0 mL) was added HBr (gas) in AcOH (5.0 mL) at 25 °C. The resulting mixture was stirred at that temperature for 4 h before it was quenched with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 25 min) to afford (1^1R,1^3S,Z)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (100 mg, 63% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 413.2.

Step 2: (1^1R,1^3S,Z)-2^1-(*tert*-butyl)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

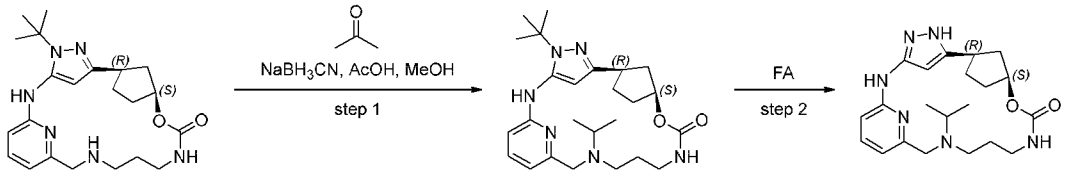
To a stirred solution of (1^1R,1^3S,Z)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (100 mg, 242 μmol) in CH_3CN (5.0 mL) were sequentially added 2,2,2-trifluoroethyl trifluoromethanesulfonate (84.0 mg, 363 μmol) and K_2CO_3 (100 mg, 727 μmol) at 25°C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 25 min) to afford (1^1R,1^3S,Z)-2^1-(*tert*-butyl)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 23% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$ 495.3.

Step 3: (1^1R,1^3S,Z)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A stirred solution of (1^1R,1^3S,Z)-21-(*tert*-butyl)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (30.0 mg, 60.0 μmol) in TFA (8.0 mL) was warmed to 50 °C and stirred at that temperature for 16 h. The mixture was cooled to 25 °C before it was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 30% to 70% in 40 min) to give (1^1R,1^3S,Z)-6-(2,2,2-trifluoroethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (7.2 mg, 27% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 439.2.

Example **80**

(1^1R,1^3S,Z)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



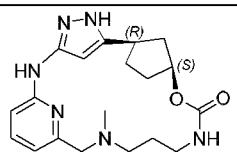
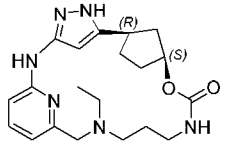
Step 1: ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of ($1^1R,1^3S,Z$)-21-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (60 mg, 0.145 mmol) in acetone (0.2 mL) and MeOH (8 mL) was added AcOH (3 drops). The reaction solution was stirred at 25 °C for 2 hours and $NaBH_3CN$ (27 mg, 0.435 mmol) was added. The resulting solution was stirred at 25 °C for 16 hours. Then it was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with $MeOH/CH_2Cl_2$ from 0 to 12% in 15 min to afford ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (45 mg, 68% yield) as a white solid. LC-MS: m/z 455.3 $[M+H]^+$.

Step 2: ($1^1R,1^3S,Z$)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

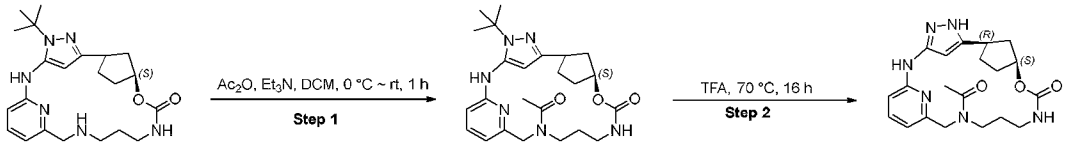
A solution of ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (45 mg, 0.099 mmol) in FA (6 mL) was stirred at 80°C for 12 hours. The reaction solution was concentrated *in vacuo* and the residue was purified by prep-HPLC (C18, 10-30% MeCN in 0.1% FA/water) to afford ($1^1R,1^3S,Z$)-6-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (16.3 mg, 41% yield) as a white solid. LC-MS: m/z 399.2 $[M+H]^+$.

The following compounds were prepared using the similar procedure disclosed in synthetic example **80**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
81		371.1
82		385.3

Example **83**

($1^1R,1^3S,Z$)-6-acetyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: ($1^1R,1^3S,Z$)-6-acetyl-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

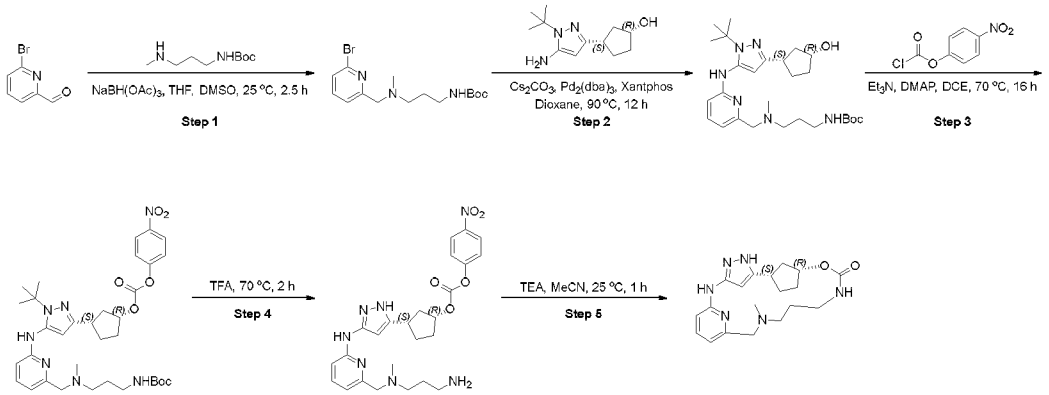
To a suspension of ($1^1R,1^3S,Z$)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (60 mg, 145 μmol) and Ac_2O (22 mg, 218 μmol, 20 μL) in DCM (1 mL) was added slowly TEA (74 mg, 727 μmol, 101 μL) at 0 °C and then it was warmed up to room temperature and stirred for 1 hour under N_2. After completion of the reaction as judged by LCMS, reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, DCM/ MeOH:12:1) to afford ($1^1R,1^3S,Z$)-6-acetyl-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (35 mg, 77 μmol, 53% yield) as a colorless liquid. LC-MS: m/z 455.2 $[M+H]^+$.

Step 2: ($1^1R,1^3S,Z$)-6-acetyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of ($1^1R,1^3S,Z$)-6-acetyl-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (35 mg, 80 μmol) in TFA (3 mL) was stirred for 16 hours at 70 °C under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*, purified by column chromatography followed by Prep-HPLC purification 2-35% MeCN in H_2O (0.1% FA) to give the desired product ($1^1R,1^3S,Z$)-6-acetyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (5.5 mg, 14 μmol, 17% yield) as a white solid. LC-MS: m/z 399.2 $[M+H]^+$.

Example **84**

($1^1S,1^3R,Z$)-6-methyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)(methyl)amino)propyl)carbamate

To a solution of 6-bromopicolinaldehyde (1.0 g, 5.38 mmol) in THF (10 mL) was added tert-butyl (3-(methylamino)propyl)carbamate (1.1 g, 5.64 mmol) at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 1 h and then a solution of $NaBH(OAc)_3$ (1.2 g, 5.64 mmol) in DMSO (10 mL) was added. The reaction mixture was stirred at 25 °C for 2.5 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-30% EtOAc in PE to afford *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (1.7 g, 88% yield) as colorless oil. LC-MS: m/z 358.1 $[M+H]^+$.

Step 2: *tert*-butyl (3-(((6-((1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate

To a mixture of *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (300 mg, 837 μmol), (1R,3S)-3-(5-amino-1-(tert-butyl)-1H-pyrazol-3-yl)cyclopentan-1-ol (187 mg, 837 μmol) and Cs_2CO_3 (818 mg, 2.5 mmol) in dioxane (5 mL) was added XantPhos (97 mg, 167 μmol) and $Pd_2(dba)_3$ (153 mg, 167 μmol) under nitrogen. The reaction was stirred at 90 °C under nitrogen for 16 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-9% MeOH in DCM to afford *tert*-butyl (3-(((6-((1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (370 mg, 88% yield) as yellow oil. LC-MS: m/z 501.3 $[M+H]^+$.

Step 3: *tert*-butyl (3-(((6-((1-(tert-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate

A mixture of *tert*-butyl (3-(((6-((1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (100 mg, 200 μmol), 4-nitrophenyl

carbonochloridate (121 mg, 600 μmol), Et_3N (101 mg, 1.0 mmol) and DMAP (5 mg, 40 μmol) in DCE (5 mL) was stirred at 70 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-90% EtOAc in PE to afford *tert*-butyl (3-((((6-((1-(tert-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (106 mg, 80% yield) as yellow oil. LC-MS: m/z 666.2 $[M+H]^+$.

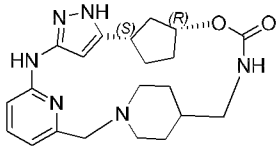
Step 4: (1R,3S)-3-(3-((6-(((3-aminopropyl)(methyl)amino)methyl)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate

A solution of *tert*-butyl (3-((((6-((1-(tert-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (106 mg, 159 μmol) in TFA (5 mL) was stirred at 70 °C for 2 h. The solvent was removed under reduced pressure to afford (1R,3S)-3-(3-((6-(((3-aminopropyl)(methyl)amino)methyl)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate (Crude 80 mg) as yellow oil, which was used in the next step directly. LC-MS: m/z 510.2 $[M+H]^+$.

Step 5: (1^1S,1^3R,Z)-6-methyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

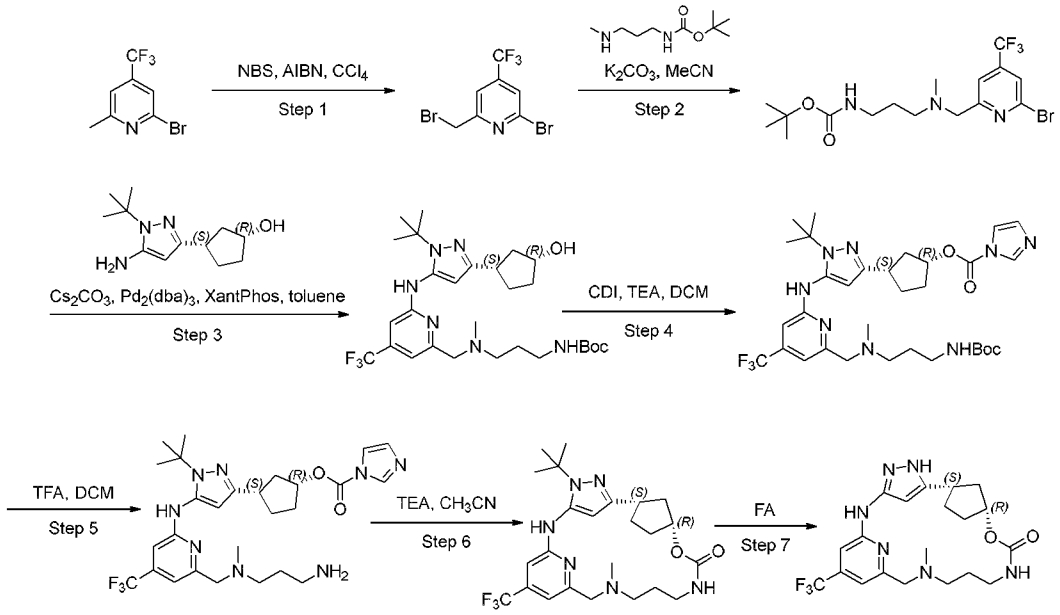
To a mixture of (1R,3S)-3-(3-((6-(((3-aminopropyl)(methyl)amino)methyl)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate (80 mg, 157 μmol) in CH_3CN (10 mL) was added Et_3N (364 mg, 3.60 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The solvent was evaporated and the residue was purified by prep-HPLC (C18, 13% to 23% CH_3CN in 0.1% TFA/water, 20 mL/min) to afford (1^1S,1^3R,Z)-6-methyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (3.0 mg, 5% yield) as colorless gum. LC-MS: m/z 371.1 $[M+H]^+$.

The following compounds were prepared using the similar procedure disclosed in synthetic example **84**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
185		397.5

Example **85**

(*1¹S,1³R,Z*)-6-methyl-44-(trifluoromethyl)-*2¹H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 2-bromo-6-(bromomethyl)-4-(trifluoromethyl)pyridine

To a suspension of 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (1 g, 4.2 mmol) and NBS (822 mg, 4.62 mmol) in CCl_4 (30 mL) was added AIBN (689 mg, 4.2 mmol). The reaction mixture was stirred at 80 °C for 4 hours. After completion of the reaction as judged by LCMS. The reaction solution was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 10% in 15 min to afford 2-bromo-6-(bromomethyl)-4-(trifluoromethyl)pyridine (360 mg, 42% yield) as a light red oil.

Step 2: *tert*-butyl (3-(((6-bromo-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate

To a suspension of 2-bromo-6-(bromomethyl)-4-(trifluoromethyl)pyridine (360 mg, 1.13 mmol) and *tert*-butyl (3-(methylamino)propyl)carbamate (212 mg, 1.13 mmol) in CH_3CN (20 mL) was added K_2CO_3 (312 mg, 2.26 mmol). The reaction mixture was stirred at 80 °C for 1 hour. After completion of the reaction as judged by LCMS. The reaction solution was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 10% in 15 min to afford *tert*-butyl (3-(((6-bromo-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (350 mg, 73% yield) as a light yellow solid. LC-MS: m/z 425.7 $[M+H]^+$.

Step 3: *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate

To a suspension of *tert*-butyl (3-(((6-bromo-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (350 mg, 0.82 mmol), (*1R,3S*)-3-(3-amino-1-(*tert*-butyl)-*1H*-pyrazol-5-yl)cyclopentan-1-ol (183 mg, 0.82 mmol) in toluene (20 mL) was added $Pd_2(dba)_3$ (75 mg, 0.082 mmol), XantPhos (95 mg, 0.164 mmol) and Cs_2CO_3 (535 mg, 1.64 mmol). The reaction mixture was stirred at 80 °C for 16 hours under N_2. Then it was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 80% in 25 min to afford *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (200 mg, 43% yield) as a red oil. LC-MS: m/z 568.9 $[M+H]^+$.

Step 4: (*1R,3S*)-3-(5-((6-(((3-((*tert*-butoxycarbonyl)amino)propyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)-4-(trifluoromethyl)pyridin-2-yl)methyl)(methyl)amino)propyl)carbamate (200 mg, 0.35 mmol) and CDI (57 mg, 0.35 mmol) in DCM (15 mL) was added TEA (139 mg, 1.38 mmol) and the reaction mixture was stirred at 35 °C for 2 hours. The reaction solution was concentrated *in vacuo* to afford (*1R,3S*)-3-(5-((6-(((3-((*tert*-butoxycarbonyl)amino)propyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (400 mg, crude) as a light red solid. LC-MS: m/z 662.8 $[M+H]^+$.

Step 5: (*1R,3S*)-3-(5-((6-(((3-aminopropyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

A mixture of (*1R,3S*)-3-(5-((6-(((3-((*tert*-butoxycarbonyl)amino)propyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (400 mg, crude) in TFA/DCM (3 mL/9 mL) was stirred at 25°C for 1 hour. The reaction solution was concentrated *in vacuo* to give (*1R,3S*)-3-(5-((6-(((3-aminopropyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (500 mg, crude) as a red oil, which was used in the next step without further purification. LC-MS: m/z 562.9 $[M+H]^+$.

Step 6: (*1^{1}S,1^{3}R,Z*)-2^1-(*tert*-butyl)-6-methyl-4^4-(trifluoromethyl)-*2^{1}H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a solution of (*1R,3S*)-3-(5-((6-(((3-aminopropyl)(methyl)amino)methyl)-4-(trifluoromethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (500 mg, crude) in CH_3CN (30 mL) was added TEA (270 mg, 2.67 mmol). The reaction

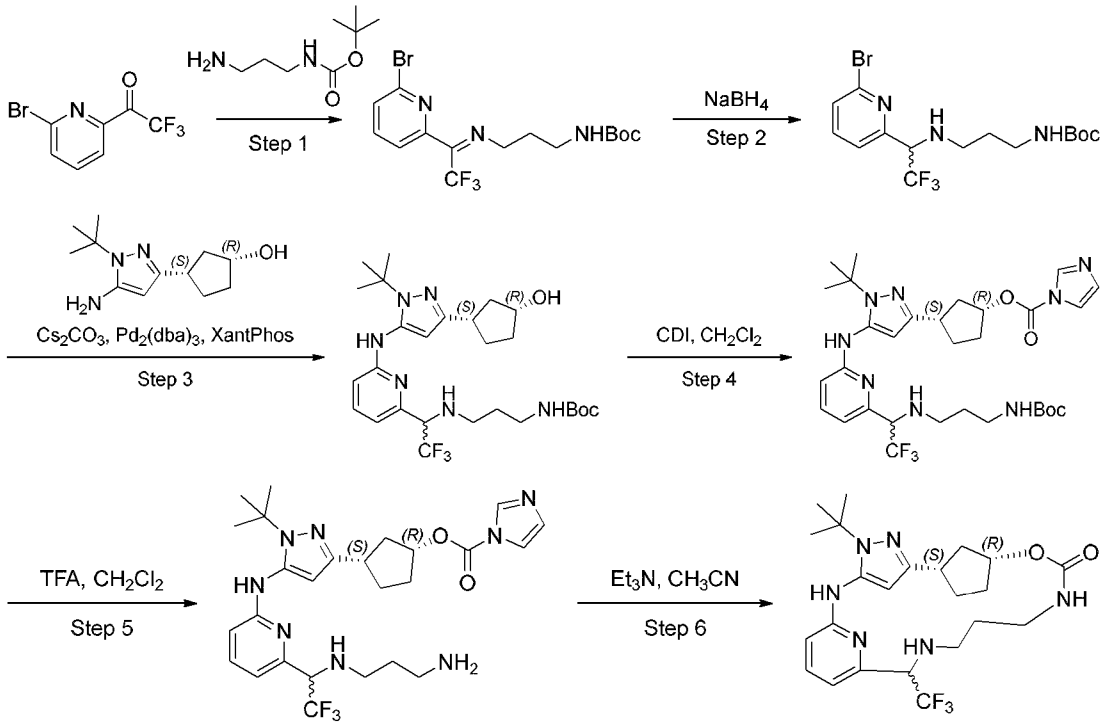
mixture was stirred at 50 °C for 20 hours. Then it was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 from 0 to 5% in 10 min to afford (*1*^{1}*S*,*1*^{3}*R*,*Z*)-2^1-(*tert*-butyl)-6-methyl-4^4-(trifluoromethyl)-*2*^{1}*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (250 mg, purity: 70%) as a white solid. LC-MS: m/z 494.8 $[M+H]^+$.

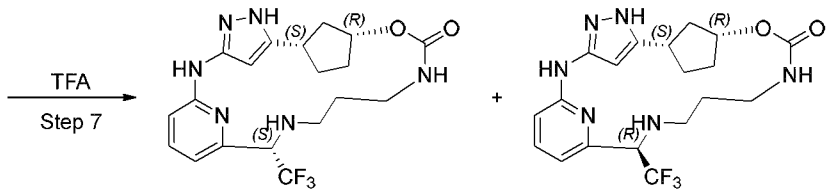
Step 7: (*1*^{1}*S*,*1*^{3}*R*,*Z*)-6-methyl-44-(trifluoromethyl)-*2*^{1}*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of (*1*^{1}*S*,*1*^{3}*R*,*Z*)-2^1-(*tert*-butyl)-6-methyl-4^4-(trifluoromethyl)-*2*^{1}*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (250 mg, purity: 70%) in FA (10 mL) was stirred at 80°C for 6 hours. The reaction solution was concentrated *in vacuo* to give the residue, which was purified by prep-HPLC (10-40% MeCN in 0.1% FA/water) to afford (*1*^{1}*S*,*1*^{3}*R*,*Z*)-6-methyl-4^4-(trifluoromethyl)-*2*^{1}*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (13 mg, 8% yield) as a white solid. LC-MS: m/z 438.8 $[M+H]^+$.

Example **86** and **87**

(1^1*S*,1^3*R*,5*S*,*Z*)-5-(trifluoromethyl)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1*S*,1^3*R*,5*R*,*Z*)-5-(trifluoromethyl)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: *tert*-butyl *N*-[3-[(*Z*)-[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethylidene]amino]propyl]carbamate

To a suspension of 1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethanone (500 mg, 1.97 mmol) in toluene (10.0 mL) was slowly added *tert*-butyl *N*-(3-aminopropyl)carbamate (342 mg, 1.97 mmol) and Ti(O-*i*-Pr)$_4$ (615 mg, 2.17 mmol) at room temperature. The reaction was stirred for 3 h at 80 °C, before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was concentrated under reduced pressure to give the crude product *tert*-butyl *N*-[3-[(*Z*)-[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethylidene]amino]propyl]carbamate, which was used in the next step without further purification. LC-MS: m/z $[M-100]^+$ 309.8.

Step 2: *tert*-butyl *N*-[3-[[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethyl]amino]propyl]carbamate

To a suspension of *tert*-butyl *N*-[3-[(*Z*)-[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethylidene]amino]propyl]carbamate in MeOH (15.0 mL) was added slowly $NaBH_4$ (148 mg, 3.90 mmol) and $NiCl_2{\cdot}6H_2O$ (695 mg, 2.93 mmol) at 0 °C and stirred for 2 h at 25 °C. After completion of the reaction as judged by LCMS, reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 30 min) to afford *tert*-butyl *N*-[3-[[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethyl]amino]propyl]carbamate (400 mg) as a yellow oil. LC-MS: m/z $[M+H]^+$ 411.9.

Step 3: *tert*-butyl *N*-[3-[[1-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]-2,2,2-trifluoro-ethyl]amino]propyl]carbamate

To a suspension of *tert*-butyl *N*-[3-[[1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethyl]amino]propyl]carbamate (200 mg, 0.485 mmol) in 1,4-dioxane (10.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (108 mg, 0.485 mmol), Cs_2CO_3 (474 mg, 1.46 mmol), XantPhos (56.0 mg, 0.097 mmol) and $Pd_2(dba)_3$ (44.4 mg, 0.048 mmol) at room temperature. The reaction was stirred at 100 °C for 16 h under N_2, before it was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60% in 30 min) to afford *tert*-butyl *N*-[3-[[1-[6-[[2-*tert*-butyl-

5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]-2,2,2-trifluoro-ethyl]amino]propyl]carbamate (200 mg, 74% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 555.0.

Step 4: [(1*R*,3*S*)-3-[5-[[6-[1-[3-(*tert*-butoxycarbonylamino)propylamino]-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[3-[[1-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]-2,2,2-trifluoro-ethyl]amino]propyl]carbamate (200 mg, 0.360 mmol) in CH_2Cl_2 (15.0 mL) was added CDI (175 mg, 1.08 mmol) and DIPEA (313 μL, 232 mg, 1.80 mmol) at 35 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-[1-[3-(*tert*-butoxycarbonylamino)propylamino]-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 648.9.

Step 5: [(1*R*,3*S*)-3-[5-[[6-[1-(3-aminopropylamino)-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of [(1*R*,3*S*)-3-[5-[[6-[1-[3-(*tert*-butoxycarbonylamino)propylamino]-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) in CH_2Cl_2 (3.0 mL) was added slowly TFA (1.0 mL) at 25 °C. The reaction was stirred for 1 h, before it was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-[1-(3-aminopropylamino)-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 548.9.

Step 6: (1^1S,1^3R,5*S*,*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1S,1^3R,5*R*,*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

To a suspension of [(1*R*,3*S*)-3-[5-[[6-[1-(3-aminopropylamino)-2,2,2-trifluoro-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) in CH_3CN (3.0 mL) was added Et_3N (379 μL, 276 mg, 2.73 mmol) and the reaction was stirred at 80 °C for 16 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10% in 20 min) to afford the mixture of (1^1S,1^3R,5*S*,*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and (1^1S,1^3R,5*R*,*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-

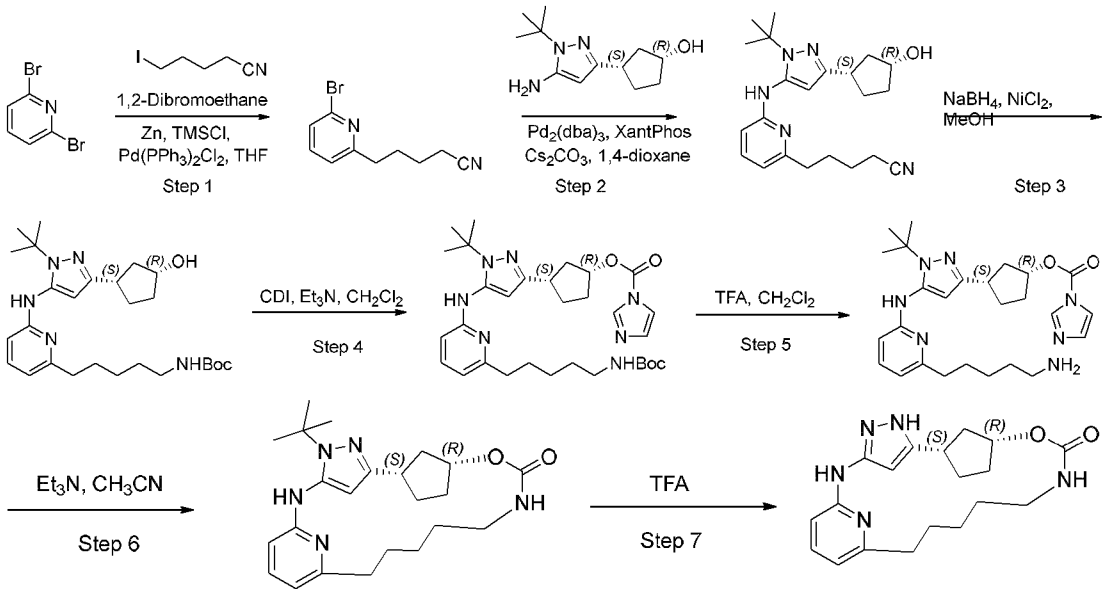
oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (130 mg) as a yellow solid. LC-MS: m/z $[M+H]^+$ 480.9.

Step 7: ($1^1S,1^3R,5S,Z$)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and **($1^1S,1^3R,5R,Z$)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one**

A mixture of ($1^1S,1^3R,5S,Z$)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one and ($1^1S,1^3R,5R,Z$)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (130 mg) in TFA (3.0 mL) was stirred for 24 h at 100 °C, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated under reduced pressure, purified by prep-HPLC eluting with CH_3CN in water (with CH_3CN from 15% to 40% in 30 min) to give ($1^1S,1^3R,5S,Z$)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (24.6 mg, retention time = 8.5 min, absolute configuration arbitrarily assigned), LC-MS: m/z $[M+H]^+$ 424.9, and ($1^1S,1^3R,5R,Z$)-5-(trifluoromethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (22.6 mg, retention time = 10.9 min, absolute configuration arbitrarily assigned) as a white solid. LC-MS: m/z $[M+H]^+$ 424.9.

Example **88**

($1^1S,1^3R,Z$)-2^1H-12-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 5-(6-bromopyridin-2-yl)pentanenitrile

To a round-bottom flask containing zinc (2.98 g, 45.6 mmol), 1,2-dibromoethane (327 μL, 714 mg, 3.80 mmol) was added, and the resulting mixture was warmed to 60 °C and then allowed to cool for 1 min. This heating/cooling process was repeated three more times, and then the flask was allowed to cool for an additional 3 min. TMSCl (119 μL, 102 mg, 937 μmol) in THF (20.0 mL) was added. The resulting mixture was warmed to 60 °C, and a solution of 5-iodopentanenitrile (3.18 g, 15.2 mmol) in THF (2.5 mL) was added. The mixture was stirred at 60 °C for 1 h. The resulting solution of alkylzinc iodide was transferred to a second flask charged with 2,6-dibromopyridine (1.20 g, 5.07 mmol) and $Pd(PPh_3)_2Cl_2$ (178 mg, 253 μmol). The resulting mixture was stirred at 60 °C under N_2 for 18 h, cooled to 25 °C, and the reaction quenched with saturated aqueous NH_4Cl solution (5 mL). The resulting mixture was stirred at 25 °C for 20 min and diluted with EtOAc (100 mL). The organic phase was washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 40 % in 20 min) to afford 5-(6-bromopyridin-2-yl)pentanenitrile (390 mg, 32% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 239.1.

Step 2: 5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentanenitrile

To a mixture of 5-(6-bromopyridin-2-yl)pentanenitrile (390 mg, 1.63 mmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (219 mg, 978 μmol) in 1,4-dioxane (5.0 mL) were sequentially added $Pd_2(dba)_3$ (149 mg, 160 μmol), XantPhos (189 mg, 326 μmol) and Cs_2CO_3 (1.06 g, 3.26 mmol). The mixture was heated to 100 °C and stirred at that temperature for 3 h. The reaction mixture was filtered and the combined organics were concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 15 to 70 % in 15 min) to afford 5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentanenitrile (290 mg, 46% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 382.3.

Step 3: *tert*-butyl (5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentyl)carbamate

A mixture of 5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentanenitrile (290 mg, 760 μmol) and NiCl (9.85 mg, 76.0 μmol) in MeOH (5.0 mL) was cooled down to 0 °C. To the stirring solution were sequentially added $NaBH_4$ (173 mg, 4.56 mmol) and Boc_2O (349 μL, 332 mg, 1.52 mmol). The mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with cold water (20 mL) and extracted with EA (30 mL × 3). The combined organics

were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25 % in 15 min) to afford *tert*-butyl (5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentyl)carbamate (150 mg, 40% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 486.4.

Step 4: (1*R*,3*S*)-3-(5-((6-(5-((*tert*-butoxycarbonyl)amino)pentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a mixture of *tert*-butyl (5-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)pentyl)carbamate (160 mg, 329 μmol) in CH_2Cl_2 (5.0 mL) were sequentially added CDI (107 mg, 659 μmol) and Et_3N (459 μL, 333 mg, 3.29 mmol). The mixture was heated to 40 °C and stirred at that temperature for 5 h. The mixture was washed with H_2O (10 mL × 2) and dried over Na_2SO_4, the combined organics were concentrated under reduced pressure to give crude (1*R*,3*S*)-3-(5-((6-(5-((*tert*-butoxycarbonyl)amino)pentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as yellow oil. LC-MS: m/z $[M+H]^+$ 580.4.

Step 5: (1*R*,3*S*)-3-(5-((6-(5-aminopentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of (1*R*,3*S*)-3-(5-((6-(5-((*tert*-butoxycarbonyl)amino)pentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (3.0 mL) was added slowly TFA (1.0 mL, 1.49 g, 13.1 mmol). The mixture was stirred for 30 min at 25 °C. The reaction mixture was concentrated under reduced pressure to afford crude (1*R*,3*S*)-3-(5-((6-(5-aminopentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as a yellow oil. LC-MS: m/z $[M+H]^+$.

Step 6: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-12-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

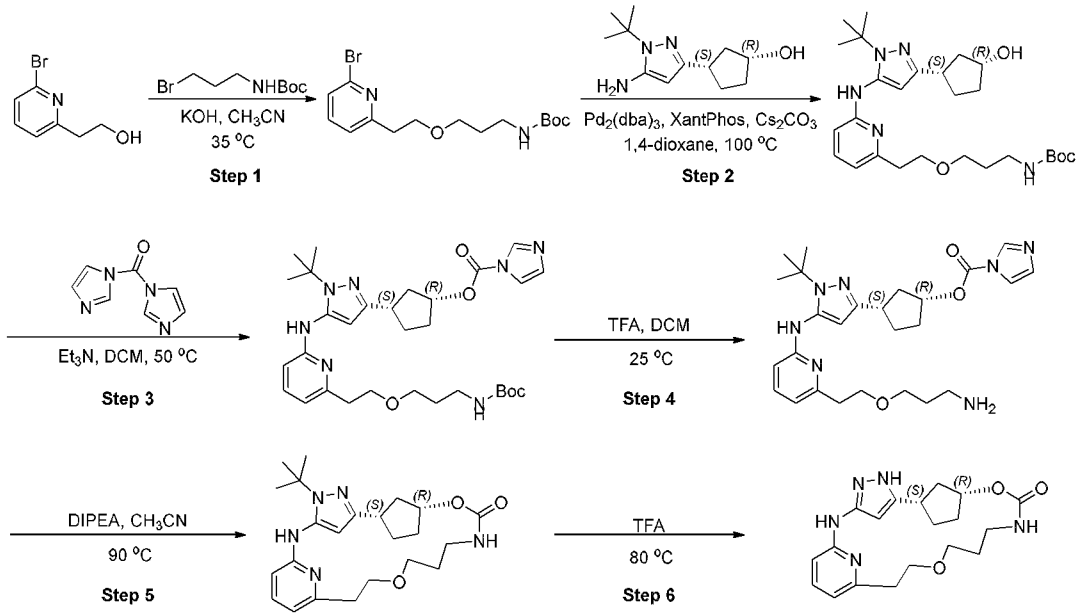
To a solution of (1*R*,3*S*)-3-(5-((6-(5-aminopentyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (10.0 mL) was added Et_3N (872 μL, 633 mg, 6.26 mmol). The mixture was heated to 80 °C and stirred at that temperature for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 15 to 75 % in 20 min) to afford (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-12-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (90.0 mg, 69% yield) as pale yellow solid. LC-MS: m/z $[M+H]^+$ 412.3.

Step 7: (1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (90.0 mg, 219 μmol) in TFA (2.0 mL) was heated to 100 °C and stirred at that temperature for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 10% to 30% in 30 min) to afford (1^1S,1^3R,*Z*)-2^1H-12-oxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (31.0 mg, 39% yield) as white solid. LC-MS: m/z $[M+H]^+$ 356.2.

Example **89**

(11S,13R,Z)-21H-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one



Step 1: *tert*-butyl (3-(2-(6-bromopyridin-2-yl)ethoxy)propyl)carbamate

To a solution of 2-(6-bromopyridin-2-yl)ethan-1-ol (350 mg, 1.73 mmol) in MeOH (18 mL) was sequentially added KOH (485 mg, 8.66 mmol) and *tert*-butyl (3-bromopropyl)carbamate (1.24 g, 5.20 mmol) at 25 °C. The reaction mixture was heated to 35 °C and stirred at 35 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25% in 20 min) to afford the product *tert*-butyl (3-(2-(6-bromopyridin-2-yl)ethoxy)propyl)carbamate (500 mg, 80% yield) as a colorless oil. LC-MS: (ESI) m/z $[M+H]^+$ 359.0.

Step 2: *tert*-butyl (3-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)propyl)carbamate

To a solution of *tert*-butyl (3-(2-(6-bromopyridin-2-yl)ethoxy)propyl)carbamate (300 mg, 835 μmol) in 1,4-dioxane (8.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-

3-yl)cyclopentan-1-ol (242 mg, 1.09 mmol), $Pd_2(dba)_3$ (153 mg, 167 μmol), XantPhos (193 mg, 334 μmol) and Cs_2CO_3 (816 mg, 2.51 mmol) at 25 °C. The suspension was degassed with N_2 for 5 times. The reaction mixture was heated to 80 °C and stirred at 80 °C under the atmosphere of N_2 for 16 h. The mixture was cooled to room temperature, concentrated under reduced pressure, diluted with water (30 mL) and extracted with DCM (30 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 67% in 20 min) to afford the product *tert*-butyl (3-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)propyl)carbamate (400 mg, 95% yield) as a light yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 502.0.

Step 3: (1*R*,3*S*)-3-(5-((6-(2-(3-((*tert*-butoxycarbonyl)amino)propoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)propyl)carbamate (350 mg, 697 μmol) in DCM (6.0 mL) was sequentially added Et_3N (353 mg, 3.49 mmol) and di(1*H*-imidazol-1-yl)methanone (452 mg, 2.79 mmol) at 25 °C. The reaction mixture was heated to 50 °C and stirred at 50 °C for 3 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 76% in 20 min) to afford the product (1*R*,3*S*)-3-(5-((6-(2-(3-((*tert*-butoxycarbonyl)amino)propoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (100 mg, 24% yield) as a yellow oil. LC-MS: (ESI) m/z $[M+H]^+$ 596.3.

Step 4: (1*R*,3*S*)-3-(5-((6-(2-(3-aminopropoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1H-imidazole-1-carboxylate

A solution of [(1*R*,3*S*)-3-[5-[[6-[2-[3-(*tert*-butoxycarbonylamino)propoxy]ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (100 mg, 167 μmol) and TFA (95.0 mg, 839 μmol) in DCM (2.0 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure to afford the product (1*R*,3*S*)-3-(5-((6-(2-(3-aminopropoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1i-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (60.0 mg, 73% yield) as a yellow oil, which was used in the next step without further purification. LC-MS: (ESI) m/z $[M+H]^+$ 496.3.

Step 5: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one

The solution of [(1*R*,3*S*)-3-[5-[[6-[2-(3-aminopropoxy)ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (300 mg, 605 μmol) and DIPEA (782 mg, 6.05 mmol) in CH_3CN (40 mL) was heated to 90 °C and stirred at 90 °C for 16 h. The mixture was concentrated under reduced pressure, diluted with water (30 mL) and extracted with DCM (30 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over anhydrous Na_2SO_4 and

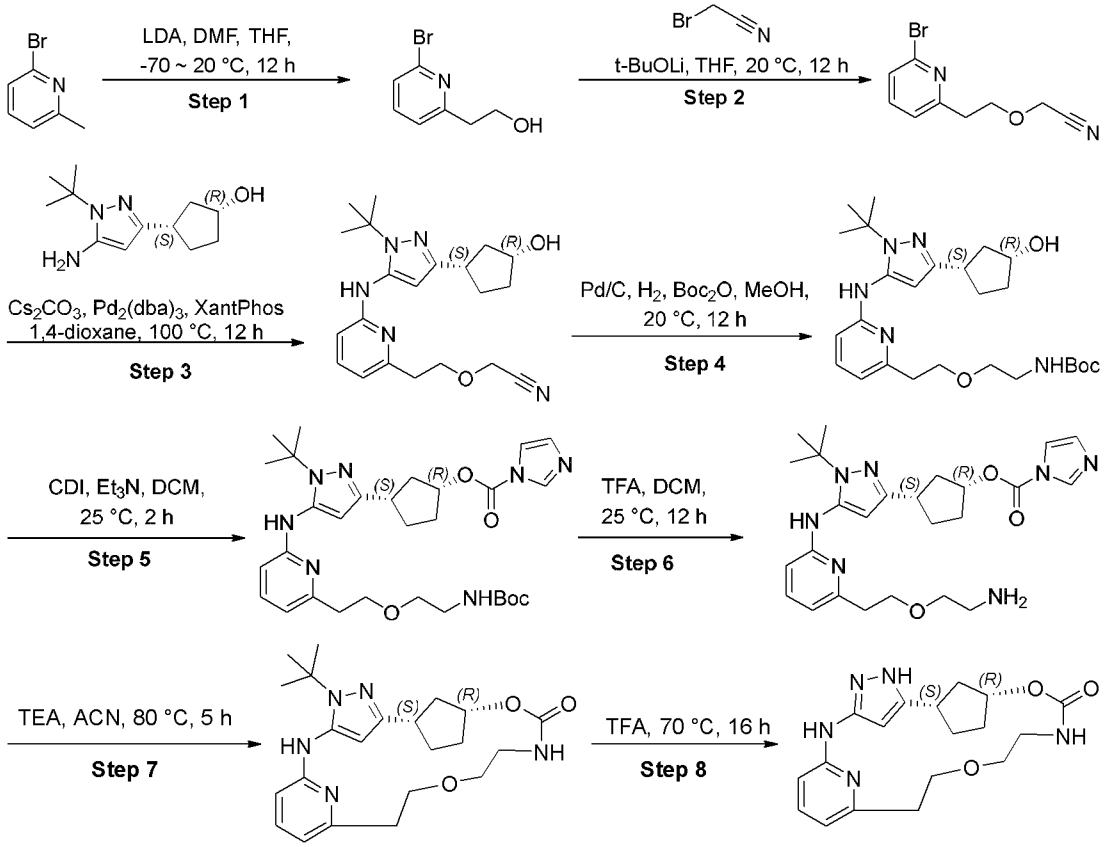
filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 75% in 20 min) to give the product ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (130 mg, 50% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 428.2.

Step 6: ($1^1S,1^3R,Z$)-2^1H-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one

The solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (130 mg, 304 μmol) in TFA (10 mL) was heated to 80 °C and stirred at 80 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (with CH_3CN from 30% to 100% in 8 min) to give the product ($1^1S,1^3R,Z$)-2^1H-7,13-dioxa-3,11-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphan-12-one (34.0 mg, 30% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 372.2.

Example **90**

($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one



Step 1: 2-(6-bromopyridin-2-yl)ethan-1-ol

To a solution of (diisopropylamino)lithium (14.24 mL, 28.48 mmol, 2M in THF) in THF (15 mL) was added dropwise a solution of 2-bromo-6-methyl-pyridine (3.5 g, 20.35 mmol) in THF (15 mL) and the resulting mixture was stirred at -70 °C for 0.5 hour. Then a solution of N,N-dimethylformamide (1.49 g, 20.35 mmol, 1.58 mL) in THF (5 mL) was added dropwise. After a stirring at -70 °C for 0.5 hour, MeOH (30 mL), AcOH (1.22 g, 20.35 mmol) and $NaBH_4$ (769.75 mg, 20.35 mmol) were added sequentially at -70 °C and the resulting mixture was stirred at 20 °C for 11 hours. Then it was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to give 2-(6-bromopyridin-2-yl)ethan-1-ol (3.2 g, 15.84 mmol, 77.84% yield) as a yellow oil. LC-MS: m/z 202.0 $[M+H]^+$.

Step 2: 2-(2-(6-bromopyridin-2-yl)ethoxy)acetonitrile

To a solution of 2-(6-bromopyridin-2-yl)ethan-1-ol (2 g, 9.90 mmol) in THF was added dropwise lithium *tert*-butoxide, 99.9% (metals basis) (9.00 mL, 18 mmol, 2.2 M in THF) and 2-bromoacetonitrile (2.37 g, 19.80 mmol, 1.38 mL) at 20 °C simultaneously and the resulting mixture was stirred at 20 °C for 12 hours. The mixture was poured into H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to give 2-(2-(6-bromo-2-pyridyl)ethoxy)acetonitrile (1 g, 4.15 mmol, 41.90% yield) as a yellow oil. LC-MS: m/z 241.0 $[M+H]^+$.

Step 3: 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)acetonitrile

To a stirred solution of 2-(2-(6-bromo-2-pyridyl)ethoxy)acetonitrile (500 mg, 2.07 mmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (250 mg, 1.12 mmol) in dioxane (2 mL) was added Cs_2CO_3 (729.51 mg, 2.24 mmol), $Pd_2(dba)_3$ (205.03 mg, 223.90 μmol) and XantPhos (194.33 mg, 335.85 μmol) at 25 °C. The mixture was stirred at 100 °C for 12 hours under N_2. The reaction mixture was concentrated under reduced pressure to give the residue. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 60% in 20 min to give 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)acetonitrile (220 mg, 573.68 μmol, 51.24% yield) as a yellow oil. LC-MS: m/z 384.2 $[M+H]^+$.

Step 4: *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)ethyl)carbamate

To a stirred solution of 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)acetonitrile (200 mg, 521.53 μmol) in methanol (5 mL) was added Boc_2O (341.47 mg, 1.56 mmol) and Pd/C (100 mg, 82.34 μmol, 10% purity) at 20 °C. The mixture was stirred at 20 °C for 12 hours under H_2. The reaction solution was filtered, concentrated under reduced pressure to give the residue. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 50% in 20 min to give *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)ethyl) carbamate (60 mg, 123.04 μmol, 23.59% yield) as a yellow oil. LC-MS: m/z 488.0 $[M+H]^+$.

Step 5: (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethoxy)ethyl) carbamate (55 mg, 112.79 μmol) in DCM (1.96 mL) was added Et_3N (34.24 mg, 338.37 μmol, 47.16 μL), CDI (54.87 mg, 338.37 μmol) and DMAP (6.89 mg, 56.39 μmol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The reaction solution was concentrated under reduced pressure to give the crude product (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentyl 1*H*-imidazole-1-carboxylate (65 mg, 111.74 μmol, 99.07% yield) as a yellow oil, which was used into next step without further purification. LC-MS: m/z 582.3 $[M+H]^+$.

Step 6: (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentyl 1*H*-imidazole-1-carboxylate (65 mg, 111.74 μmol) in DCM (3 mL) was added TFA (1.48 g, 12.98 mmol, 1 mL) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The reaction solution was concentrated under reduced pressure to give the crude product (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (50 mg, 103.82 μmol, 92.91% yield) as a yellow oil, which was used into next step without further purification. LC-MS: m/z 482.3 $[M+H]^+$.

Step 7: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

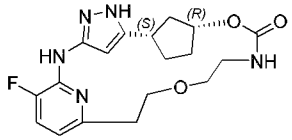
To a stirred solution of (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)ethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (50 mg, 103.82 μmol) in MeCN (2 mL) was added TEA (363.00 mg, 3.59 mmol, 0.5 mL) at 25 °C. The mixture was stirred at 80 °C for 5 hours. The reaction solution was cooled, concentrated under reduced pressure to give the residue. The residue was purified by prep-TLC to afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-

3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (15 mg, 36.27 μmol, 34.94% yield) as a yellow oil. LC-MS: m/z 562.2 $[M+H]^+$.

Step 8: ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

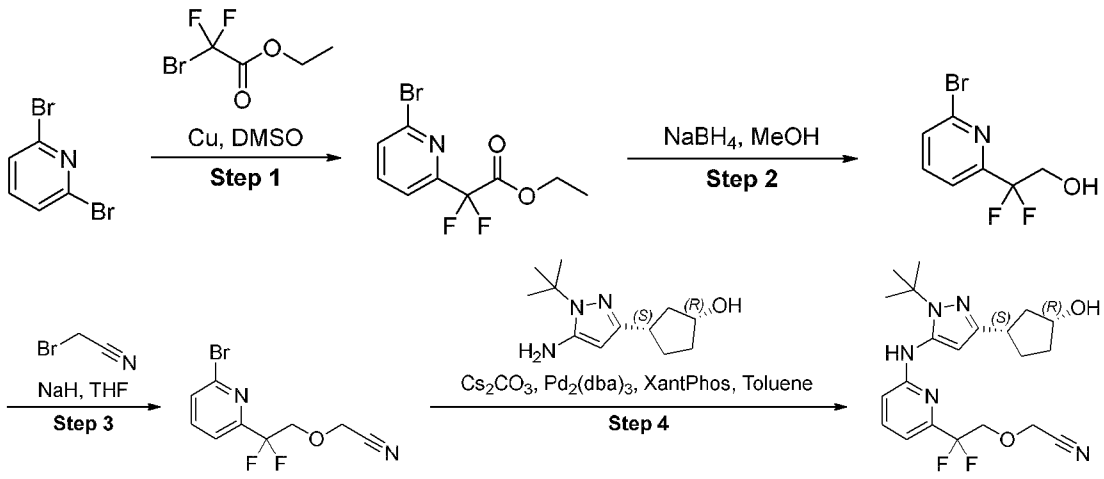
A solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (15 mg, 36.27 μmol) in TFA (1 mL) was stirred at 70 °C for 16 hours. The reaction solution was concentrated under reduced pressure to give the residue. The residue was purified by prep-HPLC (FA condition) to afford the product ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana cyclododecaphan-11-one (0.9 mg, 2.52 μmol, 6.94% yield) as a yellow oil. LC-MS: m/z 358.1 $[M+H]^+$.

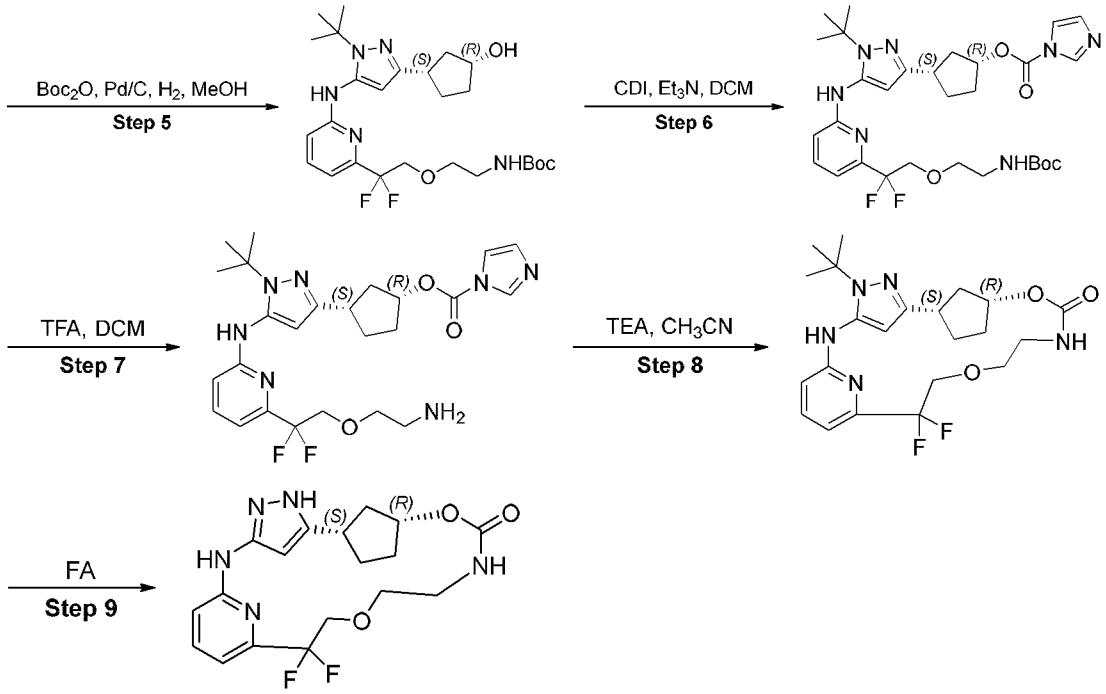
The following compounds were prepared using the similar procedure disclosed in synthetic example **90**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
186		376.2

Example **91**

($1^1S,1^3R,Z$)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one





Step 1: ethyl 2-(6-bromopyridin-2-yl)-2,2-difluoroacetate

To a suspension of 2,6-dibromopyridine (1 g, 4.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (1 g, 5 mmol) in DMSO (10 mL) was added Cu (538 mg, 8.4 mmol). The reaction mixture was stirred at 100 °C for 4 h in a sealed tube. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 8% in 10 min) to afford ethyl 2-(6-bromopyridin-2-yl)-2,2-difluoroacetate (520 mg, 44% yield) as a colorless liquid. LC-MS: m/z 280.0 $[M+H]^+$.

Step 2: 2-(6-bromopyridin-2-yl)-2,2-difluoroethan-1-ol

To a suspension of ethyl 2-(6-bromopyridin-2-yl)-2,2-difluoroacetate (480 mg, 1.71 mmol) in MeOH (10.0 mL) was added $NaBH_4$ (130 mg, 3.42 mmol). The reaction mixture was stirred at 25 °C for 1 h. The reaction solution was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 20% in 15 min) to afford 2-(6-bromopyridin-2-yl)-2,2-difluoroethan-1-ol (310 mg, 76% yield) as a colorless liquid. LC-MS: m/z 238.0 $[M+H]^+$.

Step 3: 2-(2-(6-bromopyridin-2-yl)-2,2-difluoroethoxy)acetonitrile

To a suspension of 2-(6-bromopyridin-2-yl)-2,2-difluoroethan-1-ol (250 mg, 1.05 mmol) in THF (10.0 mL) was added NaH (84 mg, 60 wt.% in mineral oil, 2.1 mmol). The reaction mixture was stirred at 25 °C for 0.5 h before 2-bromoacetonitrile (150 mg, 1.26 mmol) was added to the reaction mixture. The solution was stirred at 25 °C for another 2 h before it was poured into ice water (50 mL) and extracted with CH_2Cl_2 (20 mL*3). The organic layer was collected and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from

0 to 20% in 15 min) to afford 2-(2-(6-bromopyridin-2-yl)-2,2-difluoroethoxy)acetonitrile (160 mg, 55% yield) as a light yellow liquid. LC-MS: m/z 277.0 $[M+H]^+$.

Step 4: 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2-difluoroethoxy)acetonitrile

To a suspension of 2-(2-(6-bromopyridin-2-yl)-2,2-difluoroethoxy)acetonitrile (110 mg, 0.4 mmol) and (1*R*,3*S*)-3-(3-amino-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)cyclopentan-1-ol (89 mg, 0.4 mmol) in toluene (8.0 mL) was added $Pd_2(dba)_3$ (37 mg, 0.04 mmol), XantPhos (46 mg, 0.08 mmol) and Cs_2CO_3 (261 mg, 0.8 mmol). The reaction mixture was stirred at 80 °C for 16 h under N_2 atmosphere. Then it was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 25 min) to afford 2-(2-(6-((1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2-difluoroethoxy)acetonitrile (140 mg, 84% yield) as a light yellow solid. LC-MS: m/z 420.2 $[M+H]^+$.

Step 5: *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2-difluoroethoxy)ethyl)carbamate

To a suspension of 2-(2-(6-((1-(*tert*-butyl)-3-((1*R*,3*S*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2-difluoroethoxy)acetonitrile (140 mg, 0.33 mmol) and Boc_2O (144 mg, 0.66 mmol) in MeOH (10 mL) was added Pd/C (70 mg, 10%wt). The reaction mixture was stirred at 20 °C for 1 h under H_2 atmosphere, before it was filtrated and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 70% in 25 min) to afford *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2-difluoroethoxy)ethyl)carbamate (70 mg, 40% yield) as a yellow solid. LC-MS: m/z 524.3 $[M+H]^+$.

Step 6: (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl (6-(2-((1-(*tert*-butyl)-3-((*1R,3S*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)carbamoyl)pyrrolidin-1-yl)hexyl)carbamate (70 mg, 0.13 mmol) and CDI (105 mg, 0.65 mmol) in DCM (15 mL) was added DIEA (84 mg, 0.65 mmol). The reaction mixture was stirred at 35 °C for 3 h. The reaction solution was concentrated *in vacuo* to afford (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (110 mg, crude) as a light red oil. LC-MS: m/z 618.3 $[M+H]^+$.

Step 7: (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

A mixture of (1*R*,3*S*)-3-(5-((6-(2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in TFA/DCM (3

mL/9 mL) was stirred at 20 °C for 1 h. The reaction solution was concentrated *in vacuo* to afford (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90 mg, crude) as a red oil, which was used in the next step without further purification. LC-MS: m/z 518.2 $[M+H]^+$.

Step 8: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

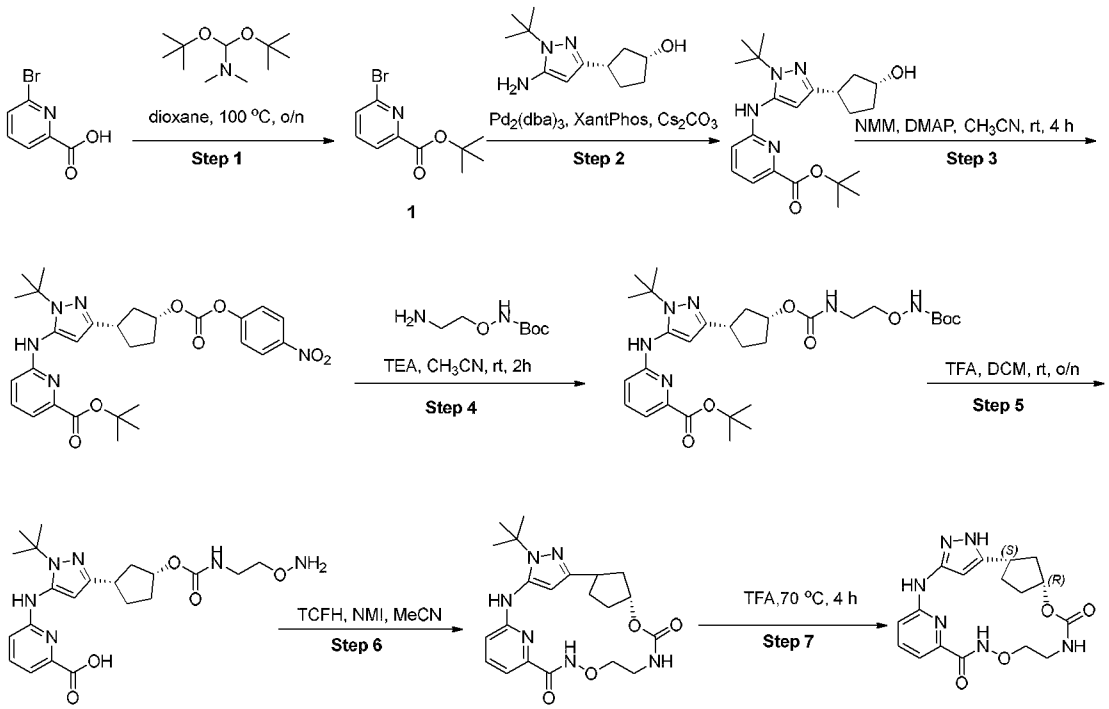
To a suspension of (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethoxy)-1,1-difluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (20.0 mL) was added TEA (0.12 mL, 86 mg, 0.85 mmol). The reaction mixture was stirred at 60 °C for 24 h. Then it was concentrated *in vacuo* and the residue was purified by flash column chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 25 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25 mg) as a light yellow solid. LC-MS: m/z 450.2 $[M+H]^+$.

Step 9: (1^1S,1^3R,*Z*)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (25 mg, 0.056 mmol) in HCO_2H (5.0 mL) was stirred at 80 °C for 1 h. The reaction solution was concentrated *in vacuo*, the residue was purified by prep-HPLC eluting with CH_3CN in water (with CH_3CN from 15% to 50% in 10 min (0.1% FA condition)) to afford (1^1S,1^3R,*Z*)-5,5-difluoro-2^1H-7,12-dioxa-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one (2.3 mg, 10% yield) as a white solid. LC-MS: m/z 394.1$[M+H]^+$.

Example **187**

(1^1S,1^3R,*Z*)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl 6-bromopicolinate

A mixture of 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), 1,1-ditert-butoxy-*N*,*N*-dimethyl-methanamine (2.01 g, 9.90 mmol) in dioxane (20 mL) was stirred for 12 hours at 100 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*.The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with EtOAc from 0 to 10% in 15 min to give the desired product *tert*-butyl 6-bromopyridine-2-carboxylate (350 mg, 1.36 mmol, 54.78% yield) as a white solid. LC-MS: m/z 280.0 $[M+Na]^+$.

Step 2: *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate

A mixture of *tert*-butyl 6-bromopyridine-2-carboxylate (350 mg, 1.36 mmol), (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (302.81 mg, 1.36 mmol), $Pd_2(dba)_3$ (124.07 mg, 135.60 μmol), XantPhos (157.03 mg, 271.20 μmol), Cs_2CO_3 (881.40 mg, 2.71 mmol) in dioxane (30 mL) was stirred for 2 hours at 80 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was filtered through a pad of Celite with EtOAc, and the combined organics were concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with EtOAc from 0 to 30% in 25 min to give the desired product *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate (500 mg, 1.25 mmol, 92.06% yield) as a pale yellow oil. LC-MS: m/z 400.8 $[M+H]^+$.

Step 3: *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate

A mixture of *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate (200 mg, 499.36 μmol), 4-nitrophenyl carbonochloridate (301.96 mg, 1.50 mmol), DMAP (122.01 mg, 998.72 μmol) and NMM (252.55 mg, 2.50 mmol, 274.51 μL) in MeCN (10 mL) was stirred for 1 hour at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with EtOAc from 0 to 30% in 25 min to give the desired product *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate (220 mg, 388.96 μmol, 77.89% yield) as a pale yellow solid. LC-MS: m/z 566.2 $[M+H]^+$.

Step 4: *tert*-butyl 6-((3-((1*S*,3*R*)-3-(((2-(((*tert*-butoxycarbonyl)amino)oxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinate

A mixture of *tert*-butyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinate (220 mg, 388.96 μmol), *tert*-butyl *N*-(2-aminoethoxy)carbamate (137.08 mg, 0.78mmol), TEA (118.08 mg, 1.17 mmol, 162.64 μL) in MeCN (10 mL) was stirred for 1 hour at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with EtOAc from 0 to 50% in 25 min to give the desired product *tert*-butyl 6-((3-((1*S*,3*R*)-3-(((2-(((*tert*-butoxycarbonyl)amino)oxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinate (140 mg, 232.28 μmol, 59.72% yield) as a pale yellow oil. LC-MS: m/z 603.4 $[M+H]^+$.

Step 5: 6-((3-((1*S*,3*R*)-3-(((2-(aminooxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinic acid

A mixture of *tert*-butyl 6-((3-((1*S*,3*R*)-3-(((2-(((*tert*-butoxycarbonyl)amino)oxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinate (140 mg, 232.28 μmol), TFA (1.32 g, 11.61 mmol, 894.75 μL) in DCM (10 mL) was stirred for 12 hours at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo* to give the desired crude product 6-((3-((1*S*,3*R*)-3-(((2-(aminooxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinic acid (120 mg, 161.25 μmol, 69.42% yield, 60% purity) as a pale yellow oil as TFA salt. LC-MS: m/z 447.3 $[M+H]^+$.

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of 6-((3-((1*S*,3*R*)-3-(((2-(aminooxy)ethyl)carbamoyl)oxy)cyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinic acid (140 mg, 313.55 μmol), TCFH (175.59 mg, 627.10 μmol), NMI (128.56 mg, 1.57 mmol) in MeCN (50 mL) was stirred for 2 hours at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*.

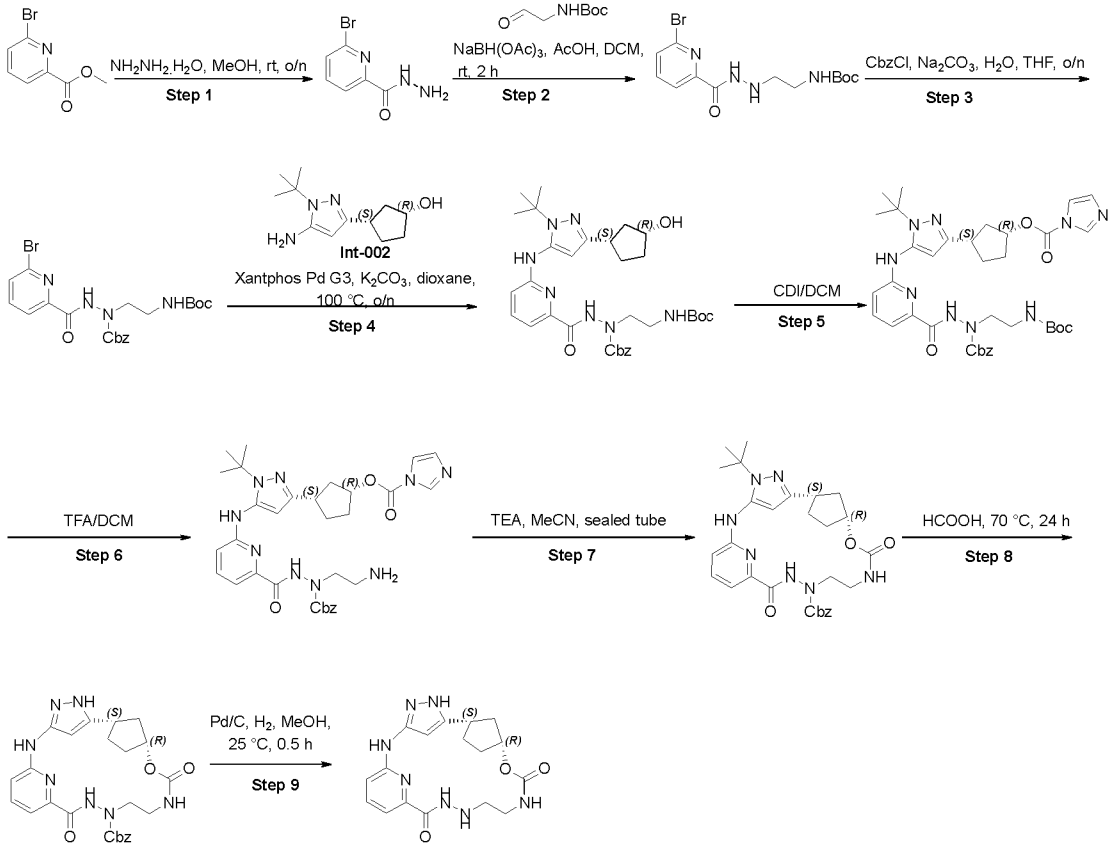
The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with EtOAc from 0 to 100% in 25 min to give the desired product ($1^1S,1^3R,Z$)-2^1-(tert-butyl)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (40 mg, 93.35 μmol, 29.77% yield) as a pale yellow solid. LC-MS: m/z 429.2 $[M+H]^+$.

Step 7: ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (40 mg, 93.35 μmol) in TFA (10 mL) was stirred for 4 hours at 70 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated in *vacuo*. The residue was purified by prep-HPLC to give the desired product ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (11.7 mg, 31.42 μmol, 33.66% yield) as a white solid. LC-MS: m/z 373.0 $[M+H]^+$.

Example **188**

($1^1S,1^3R,Z$)-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: 6-bromopicolinohydrazide

To a stirred suspension of methyl 6-bromopyridine-2-carboxylate (5.0 g, 23.14 mmol) in MeOH (50 mL) was sequentially added hydrazine hydrate (1.16 g, 23.14 mmol) at 25 °C. The resulting mixture was stirred at that temperature overnight. The reaction mixture was quenched with water (30 mL) and then extracted with EA (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel chromatography eluting with EtOAc/PE with MeOH from 0 to 60 % in 20 min to give 6-bromopicolinohydrazide (2.0 g, 9.26 mmol, 66.67% yield) as a colorless oil. LC-MS: m/z 215.9 $[M+H]^+$.

Step 2: *tert*-butyl (2-(2-(6-bromopicolinoyl)hydrazineyl)ethyl)carbamate

To a stirred suspension of *tert*-butyl (2-oxoethyl) carbamate (957.89 mg, 6.02 mmol) in DCM (20 mL) was added 6-bromopicolinohydrazide (1.3 g, 6.02 mmol) and AcOH (0.5 mL) at 0 °C. The resulting mixture was warmed to 25°C and stirred at that temperature for 2 h. Then $NaBH(OAc)_3$ (1.53 g, 7.22 mmol) was added. The reaction mixture was kept at room temperature overnight. it was quenched with water (30 mL) and then extracted with EA (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 50 % in 40 min to give (2-(2-(6-bromopicolinoyl)hydrazineyl)ethyl)carbamate (2 g, 5.57 mmol, 92.52% yield) as a colorless oil. LC-MS: m/z 258.9 $[M+H]^+$

Step 3: benzyl 2-(6-bromopicolinoyl)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)hydrazine-1-carboxylate

To a stirred solution of *tert*-butyl (2-(2-(6-bromopicolinoyl)hydrazineyl)ethyl)carbamate (2 g, 5.57 mmol) in THF (10 mL) and H_2O (2 mL) were sequentially added Na_2CO_3 (1.18 g, 11.14 mmol) and CbzCl (949.80 mg, 5.57 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred at that temperature overnight. The mixture was cooled and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 50 % in 30 min to give benzyl 2-(6-bromopicolinoyl)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)hydrazine-1-carboxylate (1.2 g, 2.43 mmol, 43.69% yield) as a colorless oil. LC-MS: m/z 515.0 $[M+Na]^+$

Step 4: benzyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2-(6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)picolinoyl)hydrazine-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (100 mg, 447.80 μmol) and benzyl 2-(6-bromopicolinoyl)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl) hydrazine-1-carboxylate (397.66 mg, 806.04 μmol) in 1,4-dioxane (10 mL) was added XantPhos Pd G3 (127.49 mg, 134.34 μmol) and K_2CO_3 (124.49 mg, 895.60 μmol) at 25 °C. The mixture was stirred at 100 °C for 12 hours under N_2. The reaction solution was concentrated under reduced pressure to give the residue. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 60% in 20 min to give benzyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2-(6-

((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinoyl)hydrazine-1-carboxylate (100 mg, 157.29 μmol, 35.13% yield) as a yellow oil. LC-MS: m/z 636.3 $[M+H]^+$.

Step 5: (1*R*,3*S*)-3-(5-((6-(2-((benzyloxy)carbonyl)-2-(2-((*tert*-butoxycarbonyl)amino)ethyl)hydrazine -1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of benzyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinoyl)hydrazine-1-carboxylate (100 mg, 157.29 μmol) in DCM (3.0 mL) was added DIEA (31.83 mg, 314.59 μmol,), CDI (51.01 mg, 314.59 μmol) and DMAP (3.84 mg, 31.46 μmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. The mixture was poured into H_2O (5 mL) and extracted with DCM (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated to give (1*R*,3*S*)-3-(5-((6-(2-((benzyloxy)carbonyl)-2-(2-((*tert*-butoxycarbonyl)amino)ethyl) hydrazine-1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (110 mg, 150.72 μmol, 95.82% yield) as a yellow oil which was used directly for the next step without further purification. LC-MS: m/z 729.8 $[M+H]^+$.

Step 6: (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethyl)-2-((benzyloxy)carbonyl)hydrazine-1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-(2-((benzyloxy)carbonyl)-2-(2-((*tert*-butoxycarbonyl)amino)ethyl)hydrazine-1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (110 mg, 150.72 μmol) in DCM (2.0 mL) was added TFA (407.00 mg, 3.57 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated to give (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethyl)-2-((benzyloxy)carbonyl) hydrazine-1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90 mg, 142.92 μmol, 94.83% yield) as a yellow oil which was used directly for the next step without further purification. LC-MS: m/z $[M+H]^+$ 631.3.

Step 7: benzyl (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-(2-(2-aminoethyl)-2-((benzyloxy)carbonyl) hydrazine-1-carbonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (90 mg, 142.92 μmol) in ACN (2 mL) was added TEA (145.20 mg, 1.43 mmol, 0.2 mL) at 25 °C. The mixture was stirred at 80 °C for 3 hours. The mixture was concentrated and purified by prep-TLC to give benzyl (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate (30 mg, 53.42 μmol, 37.37% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 562.2.

Step 8: benzyl (1^1S,1^3R,*Z*)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate

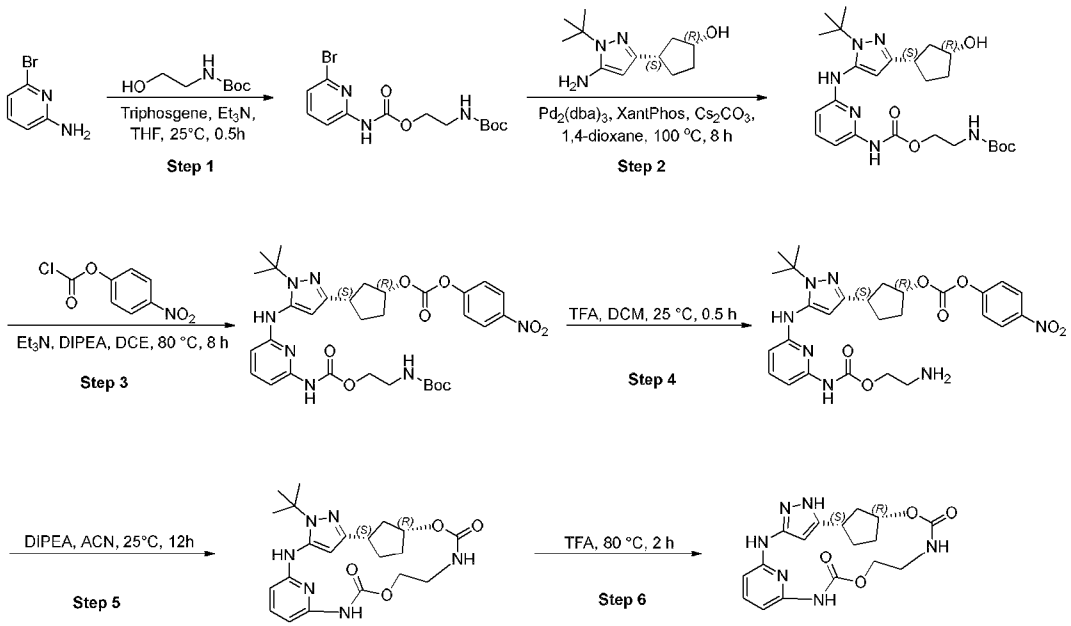
A solution of benzyl ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate (30 mg, 53.42 μmol) in HCOOH (1 mL) was stirred at 70 °C for 24 hours. The mixture was concentrated and purified by prep-HPLC to give benzyl ($1^1S,1^3R,Z$)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate (10 mg, 19.78 μmol, 37.03% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 506.2.

Step 9: ($1^1S,1^3R,Z$)-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a solution of benzyl ($1^1S,1^3R,Z$)-5,11-dioxo-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7-carboxylate (10 mg, 19.78 μmol) in MeOH (2 mL) was added Pd/C (10 mg, 8.23 μmol, 10% purity) and the resulting mixture was stirred at 25 °C for 0.5 hour under H_2 (15 psi). The reaction mixture was filtered and concentrated to give the residue. The residue was purified by prep-HPLC (FA condition) to afford the product ($1^1S,1^3R,Z$)-2^1H-12-oxa-3,6,7,10-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.4 mg, 3.70 μmol, 18.69% yield, 98.06% purity) as a white solid. LC-MS: m/z $[M+H]^+$ 372.2.

Example **189**

($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione



Step 1: 2-((*tert*-butoxycarbonyl)amino)ethyl (6-bromopyridin-2-yl)carbamate

To a solution of 6-bromopyridin-2-amine (600 mg, 3.47 mmol) in THF (20 mL) was added Triphosgene (514 mg, 1.73 mmol) and Et_3N (1.05 g, 10.4 mmol, 1.45 mL) at 0 °C under nitrogen. The

reaction was stirred at 0 °C for 5 minutes and then *tert*-butyl (2-hydroxyethyl)carbamate (559 mg, 3.47 mmol, 536 μL) was added. The reaction was stirred at 25 °C for 20 minutes. The reaction was diluted with water (40 mL) and then extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/petroleum ether with EtOAc from 0 to 20% in 10 minutes to afford 2-((*tert*-butoxycarbonyl)amino)ethyl (6-bromopyridin-2-yl)carbamate (820 mg, 65% yield) as a white solid.LC-MS: m/z 361.0 $[M+H]^+$

Step 2: 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate

To a mixture of 2-((*tert*-butoxycarbonyl)amino)ethyl (6-bromopyridin-2-yl)carbamate (242 mg, 671 μmol), (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (150 mg, 671 μmol) and Cs_2CO_3 (656 mg, 2.02 mmol) in 1,4-dioxane (2 mL) was added $Pd_2(dba)_3$ (123 mg, 134 μmol) and XantPhos (38.8 mg, 67.2 μmol) under nitrogen. The reaction was stirred at 100 °C under nitrogen for 8 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with MeOH/DCM with MeOH from 0 to 8% in 10 minutes to afford 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (263 mg, 77% yield) as a yellow solid. LC-MS: m/z 503.2 $[M+H]^+$.

Step 3: 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate

A mixture of 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (263 mg, 523 μmol), 4-nitrophenyl carbonochloridate (316 mg, 1.57 mmol), DIPEA (202 mg, 1.57 mmol, 273 μL) and DMAP (63.9 mg, 523 μmol) in DCE (10 mL) was stirred at 85 °C for 8 hours. The mixture was quenched with water (10 mL) and then extracted with DCM (5 mL × 3). The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with MeOH/DCM with MeOH from 0 to 6% in 15 minutes to afford 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (280 mg, 80% yield) as a yellow solid.LC-MS: m/z 668.2 $[M+H]^+$.

Step 4: 2-aminoethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate

A mixture of 2-((*tert*-butoxycarbonyl)amino)ethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (280 mg, 419 μmol) in TFA/DCM=1/1 (6 mL) was stirred at 25 °C for 30 minutes. The mixture was concentrated under reduced pressure to afford 2-aminoethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-

nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (360 mg, crude) as a yellow oil, which was used directly in the next step. LC-MS: m/z 568.3 $[M+H]^+$.

Step 5: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione

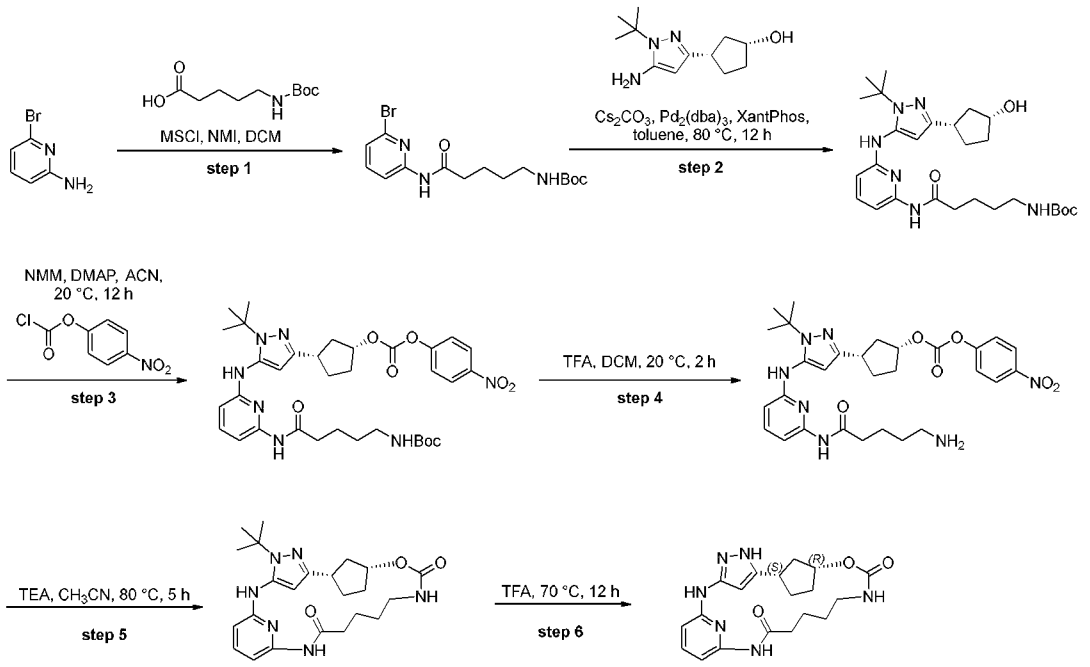
To a solution of 2-aminoethyl (6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)carbamate (360 mg, 634 μmol) in ACN (50 mL) was added DIPEA (320 mg, 2.48 mmol, 432 μL). Then the reaction mixture was stirred at 25 °C for 12 hours. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether with MeOH/DCM with MeOH from 0 to 10% in 20 minutes to afford ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (80 mg, 29% yield) as a yellow solid. LC-MS: m/z 429.2 $[M+H]^+$.

Step 6: ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione

The solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (80 mg, 187 μmol) in TFA (6 mL) was stirred at 80 °C for 2 hours. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC (Chromatographic columns: Xbridge-C18 150 × 19 mm,5 μm; Mobile Phase: ACN/H_2O (0.1%FA); Gradient: 10%-20%) to afford ($1^1S,1^3R,Z$)-2^1H-7,12-dioxa-3,5,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (13.2 mg, 19% yield) as a white solid. LC-MS: m/z 373.1 $[M+H]^+$.

Example **190**

($1^1S,1^3R,Z$)-2^1H-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione



Step 1: *tert*-butyl (5-((6-bromopyridin-2-yl)amino)-5-oxopentyl)carbamate

A solution of 5-(*tert*-butoxycarbonylamino)pentanoic acid (753 mg, 3.47 mmol) and 1-methylimidazole (1.66 g, 20.23 mmol, 1.61 mL) in DCM (10 mL) was stirred at 0 °C. Then MsCl (370 mg, 3.23 mmol, 250.51 μL) was added and the resulting mixture was stirred at 0 °C for 30 min. Then 6-bromopyridin-2-amine (500 mg, 2.89 mmol) was added and the mixture was stirred at room temperature overnight. The resulting solution was diluted with water (20 mL), then extracted with DCM (3 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried and concentrated *in vacuo*. The residue was applied on a silica gel column and eluted with PE/EA (4/1) to give *tert*-butyl (5-((6-bromopyridin-2-yl)amino)-5-oxopentyl)carbamate (1.0 g, 2.69 mmol, 92.95% yield) as a colorless oil. LC-MS: m/z 371.8. $[M+H]^+$.

Step 2: *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)amino)-5-oxopentyl)carbamate

To a solution of (*1R,3S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (130 mg, 582.14 μmol) and *tert*-butyl (5-((6-bromopyridin-2-yl)amino)-5-oxopentyl)carbamate (325.06 mg, 873.21 μmol) in toluene (10 mL) was added Cs_2CO_3 (378.39 mg, 1.16 mmol), $Pd_2(dba)_3$ (106.62 mg, 116.43 μmol) and XantPhos (101.05 mg, 174.64 μmol) at 20 °C and stirred at 80 °C for 12 hours under N_2. The reaction solution was concentrated under reduced pressure to get the residue. The residue was purified by prep-HPLC (FA condition) to afford *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)amino)-5-oxopentyl)carbamate (100 mg, 194.30 μmol, 33.38% yield) as a white solid. LC-MS: m/z 515.3. $[M+H]^+$.

Step 3: *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)amino)-5-oxopentyl)carbamate

To a solution of *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridin-2-yl)amino)-5-oxopentyl)carbamate (70 mg, 136.01 μmol) in MeCN (2 mL) was added 4-methylmorpholine (68.79 mg, 680.06 μmol, 74.77 μL), DMAP (33.23 mg, 272.03 μmol) and (4-nitrophenyl) carbonochloridate (54.83 mg, 272.03 μmol) at 20 °C and the reaction mixture was stirred at 20 °C for 12 hours. The reaction solution was concentrated under reduced pressure to give *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-*1H*-pyrazol-5-yl)amino) pyridine -2-yl)amino)-5-oxopentyl)carbamate (85 mg, 125.04 μmol, 91.94% yield) as a yellow oil, which was used in the next step without further purification. LC-MS: m/z 680.3[M+H]$^+$.

Step 4: (*1R,3S*)-3-(5-((6-(5-aminopentanamido)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a solution of *tert*-butyl (5-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-(((4-nitrophenoxy)carbonyl)oxy) cyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridine-2-yl)amino)-5-oxopentyl) carbamate (85 mg, 125.04 μmol) in DCM (3 mL) was added TFA (722.56 mg, 6.34 mmol, 488.22 μL) and the reaction mixture was stirred at 20 °C for 2 hours. The reaction solution was concentrated under reduced pressure to give (*1R,3S*)-3-(5-((6-(5-aminopentanamido)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (70 mg, 120.76 μmol, 96.58% yield) as a yellow oil, which was used in the next step without further purification. LC-MS: m/z 680.3[M+H]$^+$.

Step 5: (*1^{1}S,1^{3}R,Z*)-21-(*tert*-butyl)-*2^{1}H*-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione

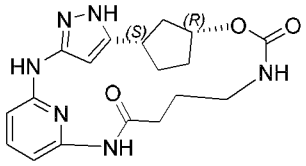
To a solution of (*1R,3S*)-3-(5-((6-(5-aminopentanamido)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (70 mg, 120.76 μmol) in MeCN (2 mL) was added TEA (217.80 mg, 2.15 mmol, 0.3 mL) and the reaction solution was stirred at 80 °C for 5 hours. The reaction solution was concentrated under reduced pressure and purified by prep-TLC to afford the product (*11S,13R,Z*)-21-(*tert*-butyl)-*21H*-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione (30 mg, 68.10 μmol, 56.39% yield) as a yellow oil. LC-MS: m/z [M+H]$^+$ 441.2.

Step 6: (*1^{1}S,1^{3}R,Z*)-*2^{1}H*-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione

A solution of (*1^{1}S,1^{3}R,Z*)-21-(*tert*-butyl)-*2^{1}H*-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione (30 mg, 68.10 μmol) in TFA (1 mL) was stirred at 70 °C for 12 hours. The reaction solution was cooled, concentrated under reduced pressure and the residue was diluted with DCM (5 mL), washed with saturated aqueous solution of $NaHCO_3$ (5 mL). The precipitate was collected by filtration and the filter cake was washed with MeCN (2 mL) and

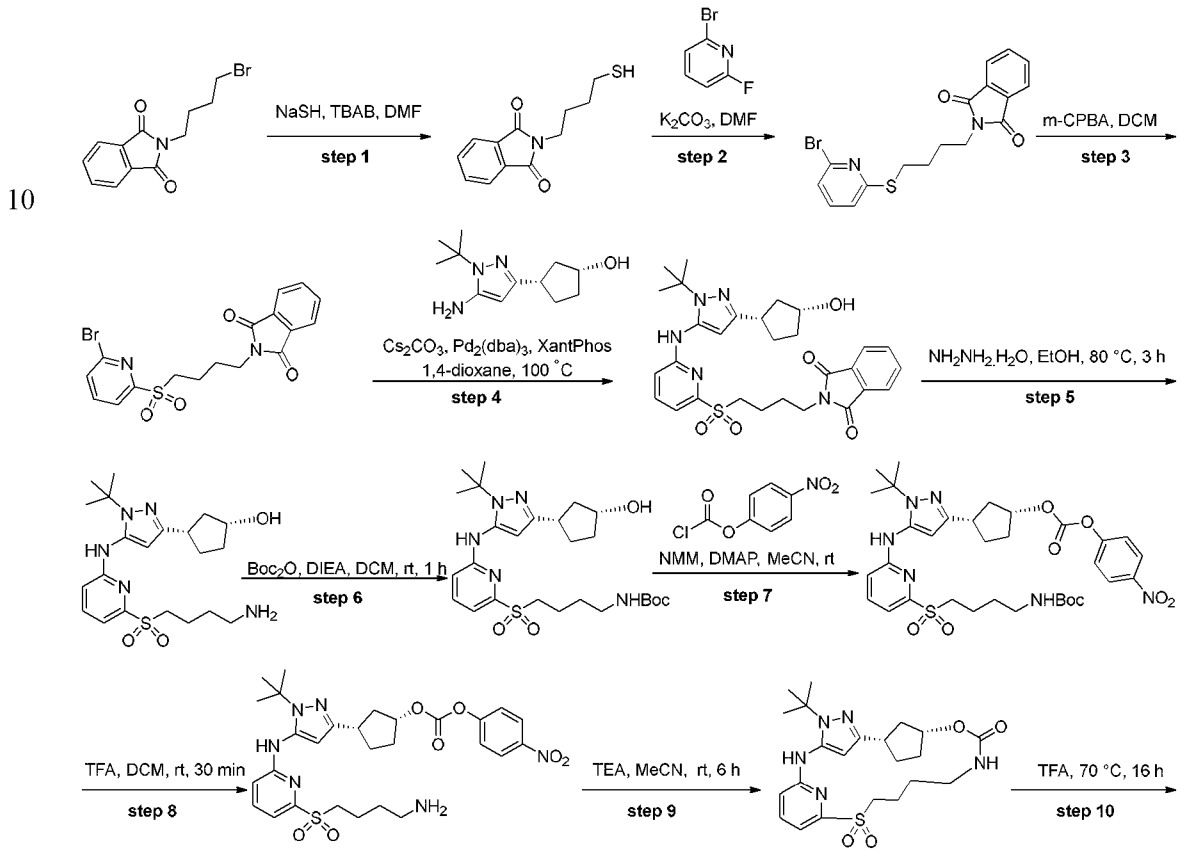
dried *in vacuo* to afford (*11S,13R,Z*)-*21H*-13-oxa-3,5,11-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclotridecaphane-6,12-dione (8 mg, 30.6% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 385.2.

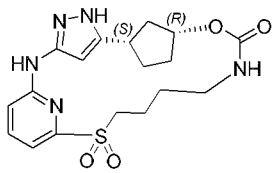
The following compounds were prepared using the similar procedure disclosed in synthetic example **190**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
191		370.9

Example **192**

(1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide





Step 1: 2-(4-sulfanylbutyl)isoindoline-1,3-dione

A mixture of 2-(4-bromobutyl)isoindoline-1,3-dione (1.8 g, 6.38 mmol), TBAB (617 mg, 1.91 mmol) and NaSH (562 mg, 7.02 mmol, 70% purity) in DMF (20 mL) was stirred for 16 hours at 20 °C under N_2, until the reaction was complete as indicated by LCMS. The reaction mixture was quenched with ice-cold water (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phase was washed with brine (500 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 10:1) to afford 2-(4-sulfanylbutyl)isoindoline-1,3-dione (0.95 g, 4.04 mmol, 63% yield) as a colorless liquid. LC-MS: m/z 236.1 $[M+H]^+$.

Step 2: 2-(4-((6-bromopyridin-2-yl)thio)butyl)isoindoline-1,3-dione

A mixture of 2-bromo-6-fluoro-pyridine (647 mg, 3.68 mmol, 379 µL), 2-(4-sulfanylbutyl)isoindoline-1,3-dione (865 mg, 3.68 mmol), K_2CO_3 (1.01 g, 7.35 mmol) in DMF (30 mL) was stirred for 12 hours at 25 °C. After completion of the reaction as judged by LCMS, reaction mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 3:1) to afford 2-[4-[(6-bromo-2-pyridyl)sulfanyl]butyl]isoindoline-1,3-dione (300 mg, 767 µmol, 21% yield) as a white solid. LC-MS: m/z 391.0 $[M+H]^+$.

Step 3: 2-(4-((6-bromopyridin-2-yl)sulfonyl)butyl)isoindoline-1,3-dione

A mixture of 2-[4-[(6-bromo-2-pyridyl)sulfanyl]butyl]isoindoline-1,3-dione (270 mg, 690 µmol), m-CPBA (475 mg, 2.76 mmol) in DCM (20 mL) was stirred for 12 hours at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was diluted with EtOAc (60 mL) and washed with brine (20 mL). The organic phase was concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to afford 2-(4-((6-bromopyridin-2-yl)sulfonyl)butyl)isoindoline-1,3-dione (250 mg, 0.59 mmol, 85% yield) as a white solid. LC-MS: m/z 423.0$[M+H]^+$.

Step 4: 2-(4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)isoindoline-1,3-dione

A mixture of 2-[4-[(6-bromo-2-pyridyl)sulfonyl]butyl]isoindoline-1,3-dione (210 mg, 496 µmol), (1*R*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (111 mg, 496 µmol), $Pd_2(dba)_3$ (45 mg, 50 µmol) and XantPhos (57 mg, 99 µmol), Cs_2CO_3 (322 mg, 992 µmol) in dioxane (20 mL) was stirred for 4 hours at 100 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was filtered through a pad of Celite with EtOAc (50 mL), and the combined organics

were concentrated *in vacuo*, purified by silica gel chromatography (SiO_2, hexane/ethyl acetate 1:1) to give the desired product 2-(4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)isoindoline-1,3-dione (150 mg, 265 μmol, 53% yield) as a pale yellow solid. LC-MS: m/z 566.2 $[M+H]^+$.

Step 5: (*1R,3S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol

To a suspension of 2-(4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)isoindoline-1,3-dione (150 mg, 264 μmol) in EtOH (100 mL) was added $NH_2NH_2.H_2O$ (330 mg, 5.28 mmol, 320 μL, 80% purity) at room temperature and the resulting mixture was stirred for 3 hours at 80 °C under N_2. After completion of the reaction as judged by LCMS, reaction mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, DCM/MeOH:10:1) to afford (1*R*,3*S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (100 mg, 230 μmol, 87% yield) as a colorless oil. LC-MS: m/z 436.2 $[M+H]^+$.

Step 6: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate

A mixture of (1*R*,3*S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (100 mg, 230 μmol), Boc_2O (100 mg, 460 μmol, 105 μL) and DIEA (148 mg, 1.15 mmol, 190 μL) in DCM (2 mL) was stirred for 1 hour at room temperature under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*, purified by silica gel chromatography (DCM/ MeOH= 20:1) to give the desired product *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate (110 mg, 205 μmol, 89% yield) as a colorless oil. LC-MS: m/z 536.3 $[M+H]^+$.

Step 7: *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate

To a suspension of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate (100 mg, 186 μmol), (4-nitrophenyl) carbonochloridate (113 mg, 560 μmol) and 4-methylmorpholine (189 mg, 1.87 mmol, 205 μL) in MeCN (5 mL) was added DMAP (46 mg, 373 μmol) at room temperature and the resulting mixture was stirred for 2 hours under N_2. After completion of the reaction as judged by LCMS, reaction mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to afford *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate (60 mg, 86 μmol, 46% yield) as a colorless oil. LC-MS: m/z 701.2 $[M+H]^+$.

Step 8: (1*R*,3*S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

A mixture of *tert*-butyl (4-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)sulfonyl)butyl)carbamate (60 mg, 86 μmol) in DCM (4.7 mL) and TFA (488 mg, 4.28 mmol, 330 μL) was stirred for 20 minutes at room temperature under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo* to give the desired product (1*R*,3*S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (50 mg, 83 μmol, 97% yield) as a colorless oil which was used to the next step without further purification. LC-MS: m/z 601.2 $[M+H]^+$.

Step 9: (1^1S,1^3R,*Z*)-2^1-(tert-butyl)-2^1H-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide

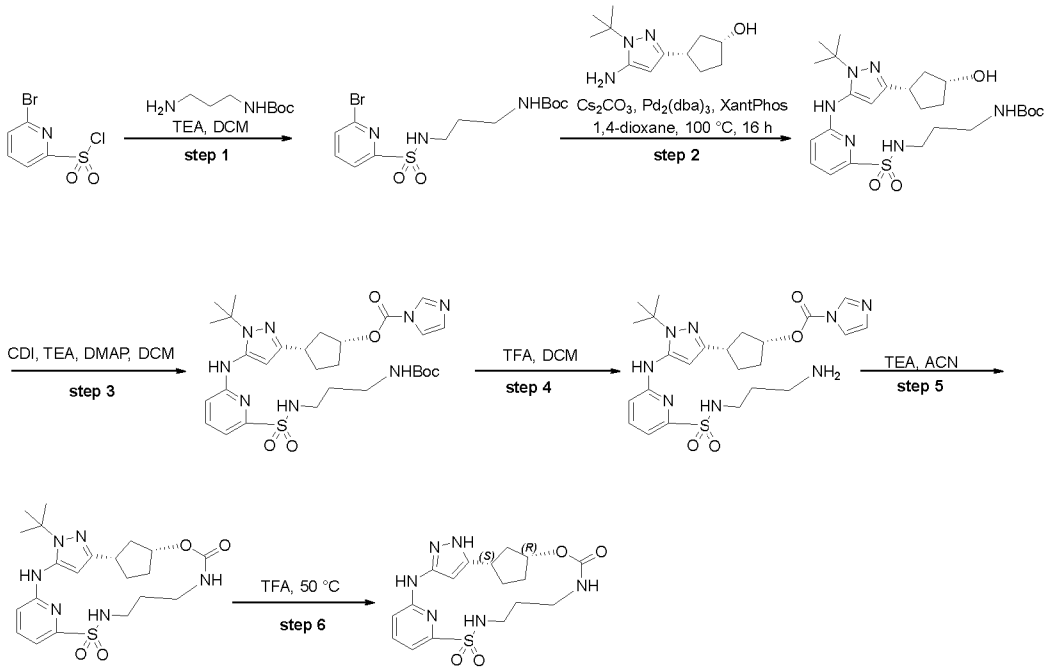
A mixture of (1*R*,3*S*)-3-(5-((6-((4-aminobutyl)sulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (50 mg, 83.24 μmol) and TEA (336.92 mg, 3.33 mmol, 464.07 μL) in MeCN (4.6 mL) was stirred for 6 hours at room temperature under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*, purified by silica gel chromatography (DCM/MeOH = 10:1) to give the desired product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (25 mg, 54 μmol, 65% yield) as a white solid. LC-MS: m/z 462.2 $[M+H]^+$.

Step 10: (1^1S,1^3R,*Z*)-2^1H-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide

A mixture of (1^1S,1^3R,*Z*)-2^1-(tert-butyl)-2^1H-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (25 mg, 54.16 μmol) in TFA (4 mL) was stirred for 16 hours at 70 °C under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*, purified by column chromatography followed by prep. HPLC purification 2 - 40% MeCN in H_2O (0.1% FA) to give the desired product (1^1S,1^3R,*Z*)-2^1H-12-oxa-5-thia-3,10-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (10.2 mg, 25 μmol, 46% yield) as an off-white solid. LC-MS: m/z 406.1 $[M+H]^+$.

Example **193**

(1^1S,1^3R,*Z*)-2^1H-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide



Step 1: *tert*-butyl (3-((6-bromopyridine)-2-sulfonamido)propyl)carbamate

To a suspension of 6-bromopyridine-2-sulfonyl chloride (500 mg, 1.95 mmol) in DCM (15 mL) was added *tert*-butyl N-(3-aminopropyl)carbamate (339.64 mg, 1.95 mmol) and TEA (394.50 mg, 3.90 mmol). The reaction mixture was stirred at 25 °C for 16 hours. Then it was concentrated *in vacuo* and purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 30% in 25 min to afford *tert*-butyl N-[3-[(6-bromo-2-pyridyl)sulfonylamino]propyl]carbamate (690 mg, 1.75 mmol, 89.78% yield). LC-MS: m/z 294.0 $[M+H]^+$.

Step 2: *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridine)-2-sulfonamido)propyl)carbamate

To a suspension of *tert*-butyl N-[3-[(6-bromo-2-pyridyl)sulfonylamino]propyl]carbamate (330 mg, 836.96 μmol) in toluene (10 mL) was added (*1R,3S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (150 mg, 671.70 μmol), XantPhos Pd G3 (150 mg, 430.43 μmol) and K_2CO_3 (210 mg, 1.52 mmol). The reaction was stirred at 80 °C for 16 hours under nitrogen. Then it was concentrated *in vacuo* and purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 60% in 25 min to afford *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridine)-2-sulfonamido)propyl)carbamate (300 mg, 558.99 μmol, 83.22% yield) as a brown oil.

LC-MS: m/z 536.7 $[M+H]^+$.

Step 3: (*1R,3S*)-3-(5-((6-(N-(3-((*tert*-butoxycarbonyl)amino)propyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl (3-((6-((1-(*tert*-butyl)-3-((*1S,3R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-5-yl)amino)pyridine)-2-sulfonamido)propyl)carbamate (137 mg, 255.27 μmol) in DCM (4 mL) was

added CDI (82.78 mg, 510.54 μmol), DMAP (31.19 mg, 255.27 μmol) and TEA (129.15 mg, 1.28 mmol, 177.90 μL) and it was stirred for 16 hours at 35 °C. Then the reaction mixture was quenched with ice-cold water (10 mL) and extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (*1R,3S*)-3-(5-((6-(N-(3-((*tert*-butoxycarbonyl)amino)propyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate was used in the next step without further purification. LC-MS: m/z 630.6 $[M+H]^+$.

Step 4: (*1R,3S*)-3-(5-((6-(N-(3-aminopropyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate

A mixture of (*1R,3S*)-3-(5-((6-(N-(3-((*tert*-butoxycarbonyl)amino)propyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in DCM (2 ml) and TFA (2 mL) was stirred at 25 °C for 1 hour. Then it was concentrated to afford crude (*1R,3S*)-3-(5-((6-(N-(3-aminopropyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate as a brown oil, which was used in the next step without further purification. LC-MS: m/z 530.6 $[M+H]^+$.

Step 5: (*1^{1}S,1^{3}R,Z*)-2^1-(*tert*-butyl)-*2^{1}H*-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide

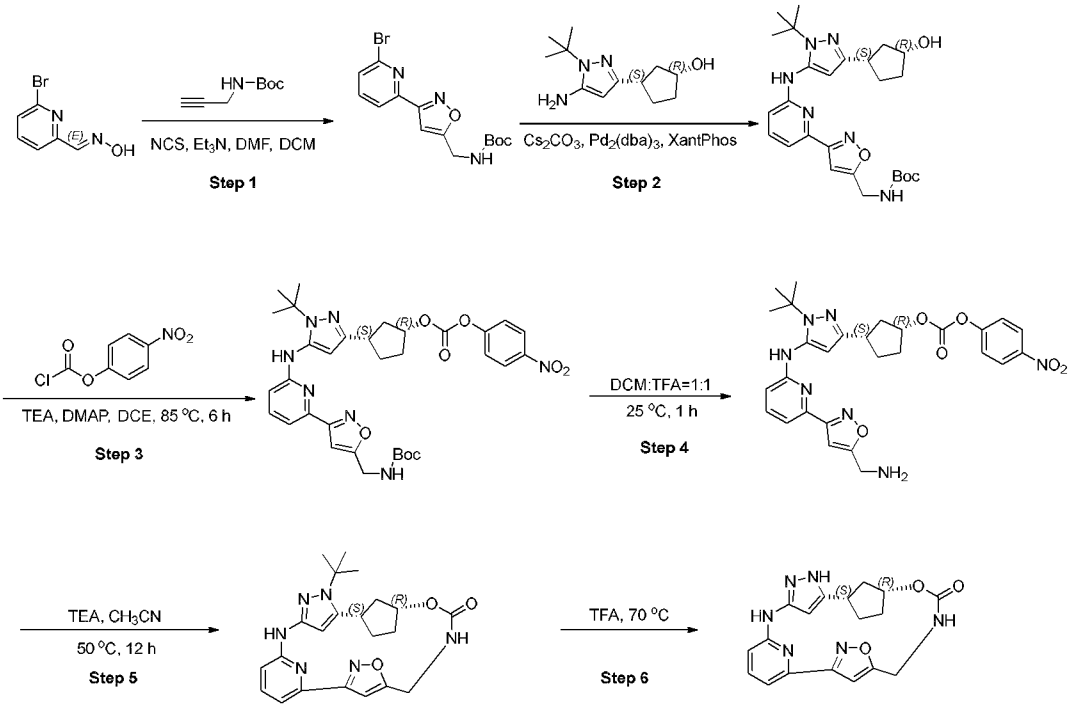
To a suspension of (*1R,3S*)-3-(5-((6-(N-(3-aminopropyl)sulfamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-*1H*-pyrazol-3-yl)cyclopentyl *1H*-imidazole-1-carboxylate (crude) in CH_3CN (5 mL) was added TEA (196 mg, 1.94 mmol) at room temperature. The reaction was stirred at 80 °C for 16 hours. Then it was cooled, concentrated *in vacuo* and purified by flash column chromatography eluting with methyl alcohol/dichloromethane ether from 0 to 4.6% in 25 min to afford (*1^{1}S,1^{3}R,Z*)-2^1-(*tert*-butyl)-*2^{1}H*-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (13 mg, 28.10 μmol, 14.91% yield) as a colorless oil.. LC-MS: m/z 462.7 $[M+H]^+$.

Step 6: (*1^{1}S,1^{3}R,Z*)-*2^{1}H*-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide

A solution of (*1^{1}S,1^{3}R,Z*)-2^1-(*tert*-butyl)-*2^{1}H*-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (13 mg, 28.10 μmol) in FA (2 mL) was stirred at 80 °C for 5 hours. Then it was concentrated and purified by Prep-HPLC (FA; CH_3CN: water: 30%~55%) to afford (*1^{1}S,1^{3}R,Z*)-*2^{1}H*-12-oxa-5-thia-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-11-one 5,5-dioxide (5 mg, 12.30 μmol, 43.77% yield) as an off-white solid. LC-MS: m/z 406.7 $[M+H]^+$.

Example 194

(1^{4}Z,4^{4}Z,5^{1}S,5^{3}R)-4^{1}H-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one



Step 1: *tert*-butyl ((3-(6-bromopyridin-2-yl)isoxazol-5-yl)methyl)carbamate

To a suspension of (2E)-6-bromopyridine-2-carbaldehyde oxime (400 mg, 2.0 mmol) in DMF (10 mL) was added slowly three portions 1-chloropyrrolidine-2,5-dione (266 mg, 2.0 mmol, 161 µL) at 0 °C and stirred for 1 h at 50 °C under N_2. The reaction was cooled to 0 °C and a solution of tert-butyl N-prop-2-ynylcarbamate (309 mg, 2.0 mmol) in DCM (10 mL) and N,N-diethylethanamine (201 mg, 2.0 mmol, 277 µL) was added dropwise. The reaction mixture was stirred at ambient temperature for 3 h, quenched with saturated sodium bicarbonate (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (50 mL X 3), dried over anhydrous sodiusulfate and evaporated under reduced pressure. LCMS showed the starting material was consumed and desired product was detected. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 10% to give *tert*-butyl ((3-(6-bromopyridin-2-yl)isoxazol-5-yl)methyl)carbamate (323 mg, 0.9 mmol, 46% yield) as white solid. LC-MS: m/z $[M+H]^+$ 354.0.

Step 2: *tert*-butyl ((3-(6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)isoxazol-5-yl)methyl)carbamate

A mixture of *tert*-butyl N-[[3-(6-bromo-2-pyridyl)isoxazol-5-yl]methyl]carbamate (262 mg, 738 µmol) , (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (150 mg, 671 µmol), Tris(Dibenzylideneacetone)Dipalladium(O) (123 mg, 134 µmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (155 mg, 268 µmol) and Cesium carbonate (657 mg, 2.02 mmol) in dioxane (15 mL) was stirred for 3 h at 100 °C in under N_2 until the reaction was complete as indicated by LCMS. The resulting mixture was concentrated under reduced pressure. The

residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50% to give *tert*-butyl ((3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)isoxazol-5-yl)methyl)carbamate (320 mg, 644 μmol, 96% yield) as yellow oil. LC-MS: m/z $[M+H]^+$ 497.2.

Step 3: *tert*-butyl ((3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)isoxazol-5-yl)methyl)carbamate

To a suspension of *tert*-butyl N-[[3-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]isoxazol-5-yl]methyl]carbamate (300 mg, 604 μmol) in DCE (10 mL) was added slowly (4-nitrophenyl) carbonochloridate (365 mg, 1.81 mmol)and DMAP (15 mg, 120 μmol) at 25 °C and stirred for 6 hours at 85 °C under N_2. LCMS showed the starting material was consumed and the desired product was detetced. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50%, then it was purified by flash column chromatography eluting with MeOH in DCM from 0 to 1% to give *tert*-butyl ((3-(6-((1-(tert-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)isoxazol-5-yl)methyl)carbamate (250 mg, 377 μmol, 62% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 662.2.

Step 4: (1*R*,3*S*)-3-(5-((6-(5-(aminomethyl)isoxazol-3-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a stirred solution of *tert*-butyl ((3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)isoxazol-5-yl)methyl)carbamate (240 mg, 362 μmol) in DCM (5 mL) solution at 25 °C was added TFA (5 mL). The reaction mixture was stirred at 25 °C for 1 hour. LCMS showed the desired product was detected. The resulting mixture was concentrated under reduced pressure. The crude product was used immediately in the next step without further purification. LC-MS: m/z $[M+H]^+$ 562.2.

Step 5: (1^4Z,4^4Z,5^1S,5^3R)-4^1-(*tert*-butyl)-4^1*H*-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one

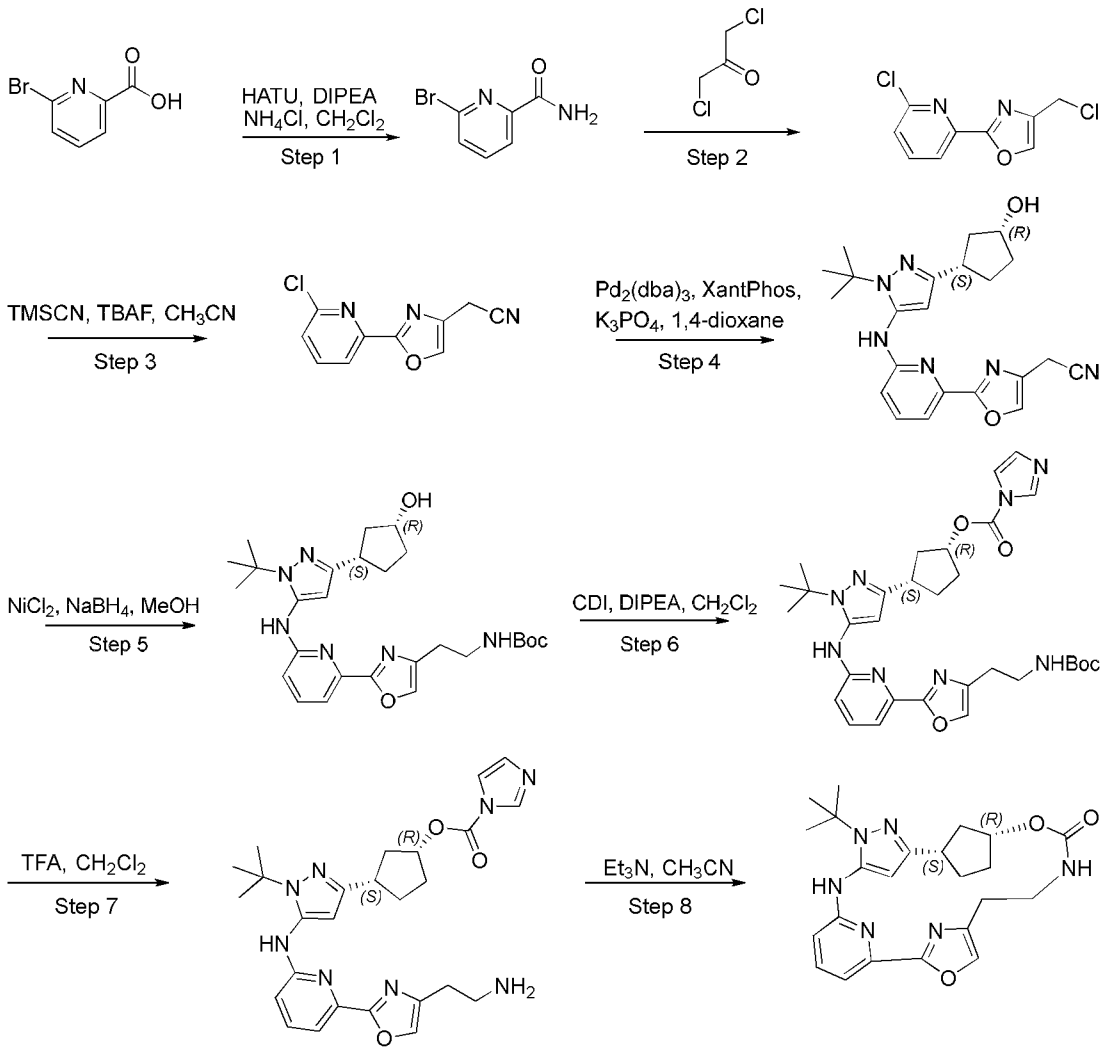
To a stirred solution of (1*R*,3*S*)-3-(5-((6-(5-(aminomethyl)isoxazol-3-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (200 mg, 356 μmol) in CH_3CN (30 mL) solution at 25 °C was added TEA (5 mL) The reaction mixture was stirred at 50 °C for 12 h under N_2. LCMS showed the starting material was consumed and desired product was detected. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50% to give (1^4Z,4^4Z,5^1S,5^3R)-41-(*tert*-butyl)-4^1*H*-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one (60 mg, 142 μmol, 40% yield) as yellow solid and crude pruduct (150 mg crude). LC-MS: m/z $[M+H]^+$ 423.2.

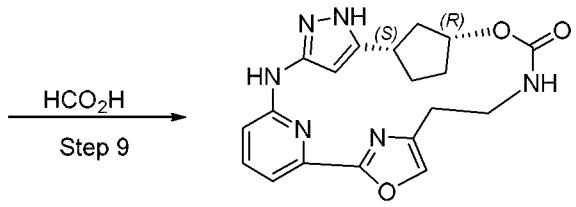
Step 6: (1^4Z,4^4Z,5^1S,5^3R)-4^1H-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one

A suspension of (1^4Z,4^4Z,5^1S,5^3R)-4^1-(*tert*-butyl)-4^1H-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one (60 mg, 142 μmol) in TFA (4 mL) at 0 °C and stirred for 3 hours at 70 °C under N_2. LCMS showed the desired product was detected. The product was further purified by prep-HPLC (C18, 20-50% MeCN in 0.1% FA/water, 20 mL/min) to give (1^4Z,4^4Z,5^1S,5^3R)-4^1H-6-oxa-3,8-diaza-1(3,5)-isoxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclononaphan-7-one (20 mg, 54.8 μmol, 39 % yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 367.1.

Example **92**

(1^2Z,4^4Z,5^1S,5^3R)-4^1H-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one





Step 1: 6-bromopicolinamide

To a suspension of 6-bromopicolinic acid (5.0 g, 24.8 mmol) in CH_2Cl_2 (25.0 mL) was added NH_4Cl (1.97 g, 37.2 mmol), HATU (9.40 g, 24.8 mmol) and DIPEA (12.7 mL, 9.59 g, 74.4 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 42 % in 20 min) to afford 6-bromopicolinamide (4.0 g, 80% yield) as a white solid. LC-MS: m/z [M+H]+ 201.0

Step 2: 4-(chloromethyl)-2-(6-chloropyridin-2-yl)oxazole

To a suspension of 6-bromopicolinamide (300 mg, 1.50 mmol) in 1,3-dichloropropan-2-one (950 mg, 7.50 mmol) at 25 °C. The reaction mixture was warmed to 130 °C and stirred at that temperature for 12 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 12 % in 20 min) to afford 4-(chloromethyl)-2-(6-chloropyridin-2-yl)oxazole (40.0 mg, 12% yield) as a white solid. LC-MS: m/z [M+H]+ 229.0

Step 3: 2-(2-(6-chloropyridin-2-yl)oxazol-4-yl)acetonitrile

To a suspension of 4-(chloromethyl)-2-(6-chloropyridin-2-yl)oxazole (40.0 mg, 180 μmol) in CH_3CN (10.0 ml) was added TBAF (270 μL, 1 M in THF, 270 μmol) and TMSCN (27.0 mg, 270 μmol) at 25 °C. The reaction mixture was warmed to 90 °C and stirred at that temperature for 30 min. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10 % in 20 min) to afford 2-(2-(6-chloropyridin-2-yl)oxazol-4-yl)acetonitrile (38.0 mg, 97% yield) as a white solid. LC-MS: m/z [M+Na]+ 242.2.

Step 4: 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)acetonitrile

To a stirred suspension of 2-(2-(6-chloropyridin-2-yl)oxazol-4-yl)acetonitrile (38.0 mg, 170 μmol) in 1,4-dioxane (10.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (38.0 mg, 170 μmol), Cs_2CO_3 (166 mg, 510 μmol), XantPhos (20.0 mg, 34.0 μmol) and $Pd_2(dba)_3$ (16.0 mg, 17.0 μmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred

at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 25 % in 20 min) to afford 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)acetonitrile (50.0 mg, 72% yield) as a yellow oil. LC-MS: m/z [M+H]+ 407.2

Step 5: *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)ethyl)carbamate

To a suspension of 2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)acetonitrile (50.0 mg, 120 μmol) in MeOH (10.0 mL) was added $NiCl_2$ (1.60 mg, 12.0 μmol), $NaBH_4$ (28.0 mg, 720 μmol), $(Boc)_2O$ (0.42 mL, 40.0 mg, 180 μmol) at 0 °C. The reaction mixture was stirred at that temperature for 2 h before it was filtered and concentrated *in vacuo* to afford *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)ethyl)carbamate (40.0 mg, 65% yield) as a yellow oil. LC-MS: m/z [M+H]+ 511.2

Step 6: (1*R*,3*S*)-3-(5-((6-(4-(2-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)oxazol-4-yl)ethyl)carbamate (40.0 mg, 78.0 μmol) in CH_2Cl_2 (10.0 mL) were sequentially added CDI (38.0 mg, 240 μmol) and DIPEA (66.0 μL, 50.0 mg, 390 μmol) at 25 °C. The reaction mixture was warmed to 35 °C and stirred at that temperature for 12 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-(4-(2-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as a yellow oil. . LC-MS: m/z [M+H]+ 605.2

Step 7: (1*R*,3*S*)-3-(5-((6-(4-(2-aminoethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-(4-(2-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (10.0 ml) was added TFA (396 μL, 586 mg, 5.14 mmol) at 25 °C. The mixture was stirred at that temperature for 3 h before it was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-(4-(2-aminoethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as a yellow oil, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 505.2

Step 8: (1^2*Z*,4^4*Z*,5^1*S*,5^3*R*)-4^1-(*tert*-butyl)-4^1*H*-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(5,3)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one

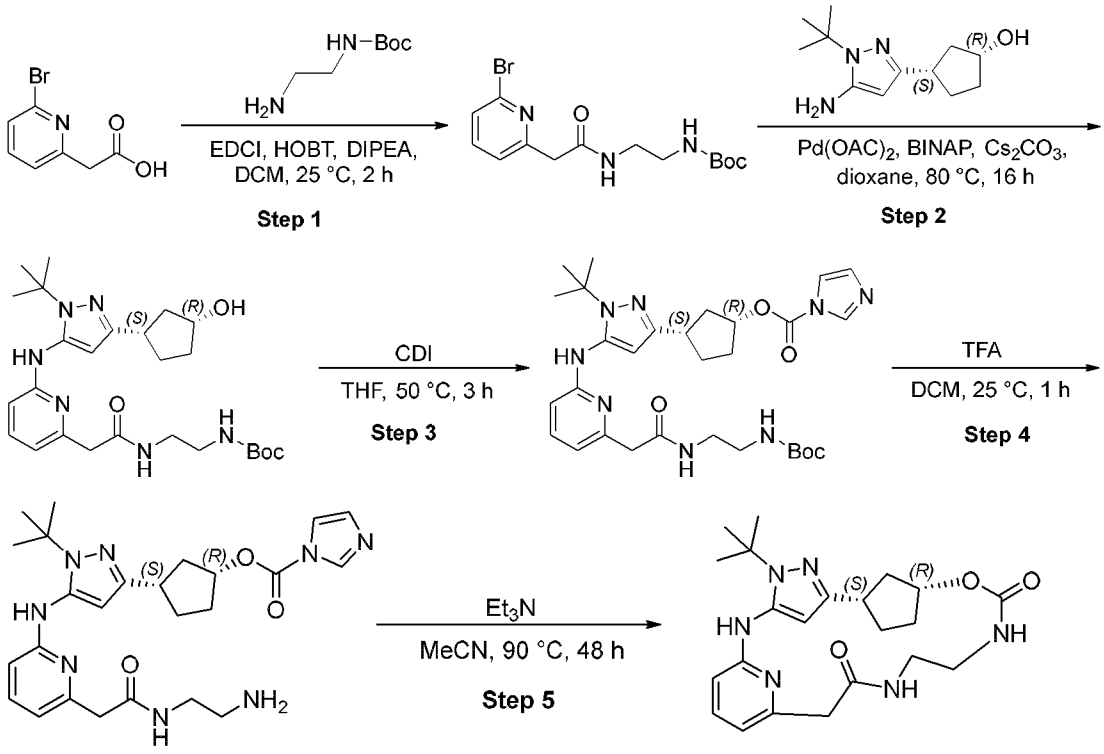
To a stirred suspension of (1*R*,3*S*)-3-(5-((6-(4-(2-aminoethyl)oxazol-2-yl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (10.0 mL) was added Et_3N (269 μL, 196 mg, 1.94 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to 25 °C, filtered and concentrated under reduced pressure. Then it was concentrated to afford (1^2Z,4^4Z,5^1S,5^3R)-4^1-(*tert*-butyl)-4^1H-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(5,3)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one as a yellow oil, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 437.3

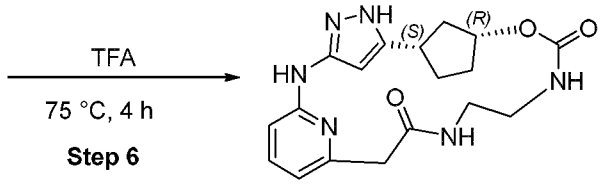
Step 9: (1^2Z,4^4Z,5^1S,5^3R)-4^1H-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one

A solution of (1^2Z,4^4Z,5^1S,5^3R)-4^1-(*tert*-butyl)-4^1H-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(5,3)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one in HCO_2H (5.0 mL) was warmed to 100 °C and stirred at that temperature for 5 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 65% in 20 min) to afford (1^2Z,4^4Z,5^1S,5^3R)-4^1H-6-oxa-3,8-diaza-1(2,4)-oxazola-2(2,6)-pyridina-4(3,5)-pyrazola-5(1,3)-cyclopentanacyclodecaphan-7-one (0.5 mg, 1.7% yield) as a white solid. LC-MS: m/z [M+H]+ 380.9.

Example **195**

(1^1S,1^3R,*Z*)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione





Step 1: *tert*-butyl (2-(2-(6-bromopyridin-2-yl)acetamido)ethyl)carbamate

To a solution of 2-(6-bromopyridin-2-yl)acetic acid (250 mg, 1.16 mmol) in DCM (7 mL) was added *tert*-butyl (2-aminoethyl)carbamate (241 mg, 1.50 mmol) , EDCI (443 mg, 2.31 mmol) , HOBT (312 mg, 2.31 mmol) and DIPEA (448 mg, 3.47 mmol) in DCM (1 mL). The reaction mixture was stirred at 25 °C for 3 hours. The mixture was diluted with water (50 ml) and extracted with DCM (2 x 50 ml). The combined organic layers were washed by brine (50 ml) and dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, Petrol ether/EtOAc with EtOAc from 0~74%) to afford the product *tert*-butyl (2-(2-(6-bromopyridin-2-yl)acetamido)ethyl)carbamate (400 mg, 1.12 mmol, 96% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 358.0.

Step 2: *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)acetamido)ethyl)carbamate

To a suspension of *tert*-butyl (2-(2-(6-bromopyridin-2-yl)acetamido)ethyl)carbamate (210 mg, 586 μmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (157 mg, 703 μmol) in dioxane (8 mL) was added diacetoxypalladium (26 mg, 117 μmol), Cesium carbonate (573 mg, 1.76 mmol) and [1-[(1*R*)-2-diphenylphosphanyl-1-naphthyl]-2-naphthyl]-diphenyl-phosphane (146 mg, 234 μmol). The suspension was degassed with N_2 for 5 times. The mixture was stirred at 80 °C for 16 hour. The mixture was dilutied with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, DCM/MeOH with MeOH from 0~10%) to afford *tert*-butyl (2-(2-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)acetamido)ethyl)carbamate (285 mg, 569 μmol, 97% yield) as a black oil. LC-MS: (ESI) m/z $[M+H]^+$ 501.3.

Step 3: (1*R*,3*S*)-3-(5-((6-(2-((2-((*tert*-butoxycarbonyl)amino)ethyl)amino)-2-oxoethyl)pyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl *N*-[2-[[2-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]acetyl]amino]ethyl]carbamate (200 mg, 399 μmol) in DCM (4 mL) was added 1,1'-Carbonyldiimidazole (324 mg, 2.00 mmol) . The reaction mixture was degassed with N_2 for 5 times. The mixture was stirred at 50 °C for 6 hours. The mixture was diluted with water (30 mL) and extracted with DCM (30mL × 3). The combined organic layer was washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, Petrol ether/EtOAc with EtOAc from 0~95%) to afford the

product (1*R*,3*S*)-3-(5-((6-(2-((2-((*tert*-butoxycarbonyl)amino)ethyl)amino)-2-oxoethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (110 mg, 185 μmol, 46% yield). LC-MS: (ESI) m/z $[M+H]^+$ 595.2.

Step 4: (1*R*,3*S*)-3-(5-((6-(2-((2-aminoethyl)amino)-2-oxoethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-(2-((2-((*tert*-butoxycarbonyl)amino)ethyl)amino)-2-oxoethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (110 mg, 185 μmol) in DCM (2 mL) was added TFA (740 mg, 6.49 mmol) .The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated to afford the crude product (1*R*,3*S*)-3-(5-((6-(2-((2-aminoethyl)amino)-2-oxoethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (365 mg) as a yellow oil which was used in the next step without purification. LC-MS: (ESI) m/z $[M+H]^+$ 495.3.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione

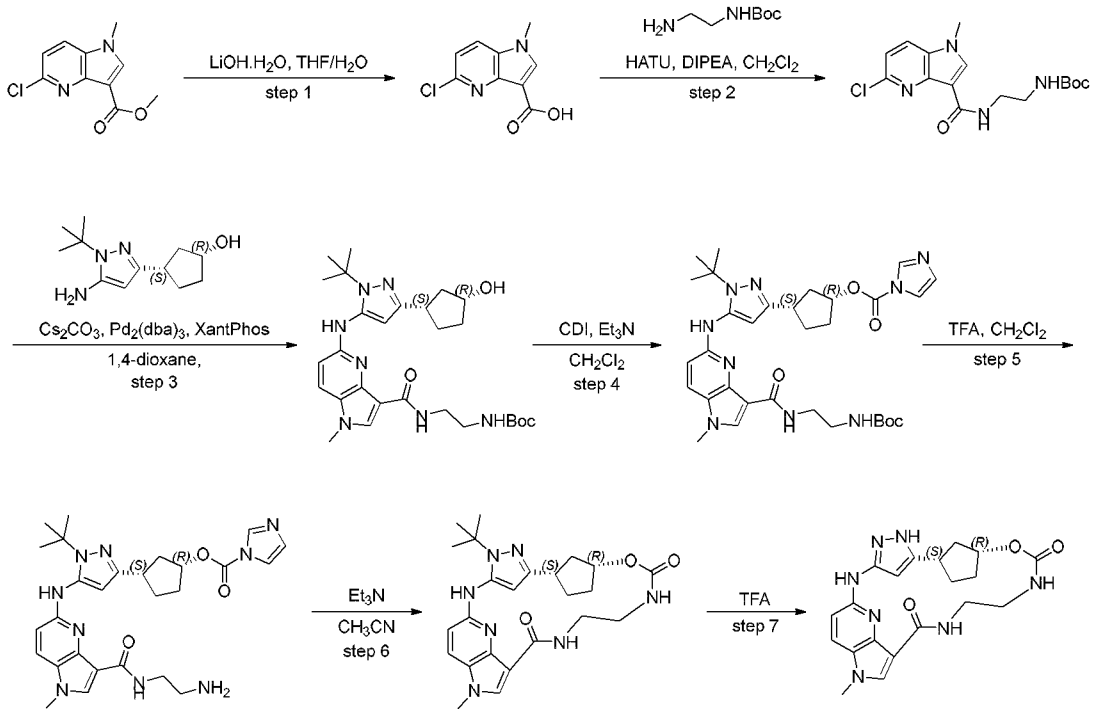
To a solution of [(1*R*,3*S*)-3-[5-[[6-[2-(2-aminoethylamino)-2-oxo-ethyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (90 mg, 182 μmol) in MeCN (40 mL) was added Et_3N (368 mg, 3.64 mmol). The reaction mixture was degassed with N_2 for 5 times. The reaction was stirred at 90 °C for 48 hours. The mixture was concentrated to dryness. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (4 g silica gel column, DCM/MeOH with MeOH from 0~6%) to afford the product afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (75 mg, 175 μmol, 96% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 427.2.

Step 6: (1^1S,1^3R,*Z*)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione

The solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (70 mg, 164 μmol) in TFA (5 mL) was stirred at 75 °C for 5 hours. The mixture was concentrated to afford crude solid which was purified by prep-HPLC (Chromatographic columns: C18 50 x 2.1 mm, Mobile Phase: ACN-H_2O(0.05%TFA)Gradient:5%-95%) to afford the product (1^1S,1^3R,*Z*)-2^1H-12-oxa-3,7,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-6,11-dione (10.2 mg, 27.0 μmol, 16% yield, 98% purity) as a white solid. LC-MS:(ESI) m/z $[M+H]^+$ 371.2.

Example **93**

(1^1S,1^3R,*Z*)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione



Step 1: 5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid

To a suspension of methyl 5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carboxylate (200 mg, 0.89 mmol) in THF (5.0 mL) and H_2O (5.0 mL) was added $LiOH{\cdot}H_2O$ (74.7 mg, 1.78 mmol) at 25 °C and stirred for 16 h. The reaction mixture was concentrated and adjusted to pH = 2~3 with 2 M HCl and extracted with EtOAc (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford 5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (200 mg, crude) as a yellow solid. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 210.9.

Step 2: *tert*-butyl *N*-[2-[(5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl)amino]ethyl] carbamate

To a suspension of 5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (200 mg, crude) in CH_2Cl_2 (20.0 mL) was sequentially added *tert*-butyl *N*-(2-aminoethyl)carbamate (152 mg, 0.949 mmol), HATU (722 mg, 1.9 mmol) and DIPEA (330 μL, 245 mg, 1.90 mmol) at 25 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with MeOH / CH_2Cl_2 (with MeOH from 0 to 5% in 25 min) to afford *tert*-butyl *N*-[2-[(5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl)amino]ethyl]carbamate (280 mg, 83% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 352.9.

Step 3: *tert*-butyl *N*-[2-[[5-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl]amino]ethyl]carbamate

To a suspension of *tert*-butyl *N*-[2-[(5-chloro-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl)amino]ethyl]carbamate (240 mg, 0.680 mmol) in 1, 4-dioxane (20.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (151 mg, 0.680 mmol), Cs_2CO_3 (665 mg, 2.04 mmol), XantPhos (78 mg, 0.136 mmol) and $Pd_2(dba)_3$ (62 mg, 0.068 mmol). The reaction was warmed to 100 °C stirred at that temperature for 16 h under N_2. After completion of the reaction as judged by LCMS. The reaction was filtered and concentrated under reduced pressure, the crude product was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 5% in 20 min) to afford *tert*-butyl *N*-[2-[[5-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl]amino]ethyl]carbamate (200 mg, 54% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 539.9.

Step 4: [(1*R*,3*S*)-3-[5-[[3-[2-(*tert*-butoxycarbonylamino)ethylcarbamoyl]-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[2-[[5-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-1-methyl-pyrrolo[3,2-*b*]pyridine-3-carbonyl]amino]ethyl]carbamate (180 mg, 0.333 mmol) in CH_2Cl_2 (10.0 mL) was added Et_3N (231 μL, 168 mg, 1.67 mmol) and CDI (128 mg, 0.888 mmol) at 35 °C and stirred for 16 h. After completion of the reaction as judged by LCMS, reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product [(1*R*,3*S*)-3-[5-[[3-[2-(*tert*-butoxycarbonylamino)ethylcarbamoyl]-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 633.9.

Step 5: [(1*R*,3*S*)-3-[5-[[3-(2-aminoethylcarbamoyl)-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of [(1*R*,3*S*)-3-[5-[[3-[2-(*tert*-butoxycarbonylamino)ethylcarbamoyl]-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in CH_2Cl_2 (3.0 mL) was added slowly TFA (1.0 mL) at 25 °C and stirred for 1 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[3-(2-aminoethylcarbamoyl)-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 534.0.

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione

To a suspension of [(1*R*,3*S*)-3-[5-[[3-(2-aminoethylcarbamoyl)-1-methyl-pyrrolo[3,2-*b*]pyridin-5-yl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in CH_3CN (5.0 mL) was added Et_3N (312 μL, 227 mg, 2.25 mmol) at room temperature and the reaction was stirred at 80 °C for 16 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated

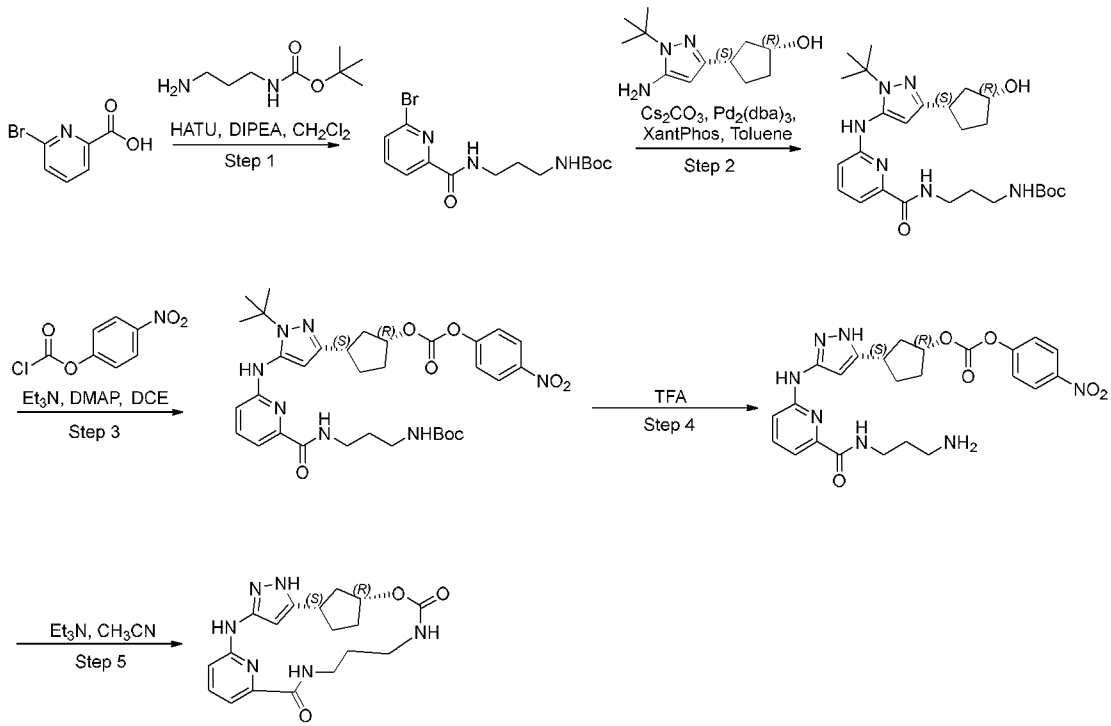
under reduced pressure. The crude product was purified by prep-TLC (CH_2Cl_2/MeOH = 15/1) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (60 mg) as a yellow solid. LC-MS: m/z $[M+H]^+$ 466.0.

Step 7: (1^1S,1^3R,*Z*)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (50.0 mg, 0.107 mmol) in TFA (3.0 mL) was stirred at 70 °C for 6 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 15% in 25 min) to give (1^1S,1^3R,*Z*)-4^1-methyl-2^1H,4^1H-11-oxa-3,6,9-triaza-4(5,3)-pyrrolo[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (37.6 mg, 85% yield) as an off-white solid. LC-MS: m/z $[M+H]^+$ 409.8.

Example **94**

(1^1S,1^3R,*Z*)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate

To a stirred solution of 6-bromopicolinic acid (2.0 g, 9.90 mmol) and *tert*-butyl (3-aminopropyl)carbamate (1.72 g, 9.90 mmol) in CH_2Cl_2 (30.0 mL) were sequentially added HATU

(7.52 g, 19.8 mmol) and DIPEA (3.44 mL, 2.55 g, 19.8 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 15 min) to give *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate (3.1 g, 88% yield) as a yellow oil. LC-MS: m/z $[M+Na]^+$ 379.7.

Step 2: *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate (500 mg, 1.40 mmol) and (1*R*,3*S*)-3-(3-amino-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)cyclopentan-1-ol (312 mg, 1.40 mmol) in toluene (20.0 mL) were sequentially added $Pd_2(dba)_3$ (128 mg, 140 μmol), XantPhos (162 mg, 280 μmol) and Cs_2CO_3 (913 mg, 2.80 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 16 h under N_2 before it was cooled to 25 °C, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80 % in 25 min) to give *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (500 mg, 71% yield) as a red solid. LC-MS: m/z $[M+H]^+$ 500.9.

Step 3: *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-(((4nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (300 mg, 599 μmol) and 4-nitrophenyl carbonochloridate (133 mg, 659 μmol) in DCE (10.0 mL) were sequentially added DMAP (15.0 mg, 120 μmol) and Et_3N (166 μL, 121 mg, 1.20 mmol) at 25 °C. The reaction mixture was warmed to 70 °C and stirred at that temperature for 16 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 65 % in 20 min) to give *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (140 mg, 35% yield) as a light red solid. LC-MS: m/z $[M+H]^+$ 666.2.

Step 4: (1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate

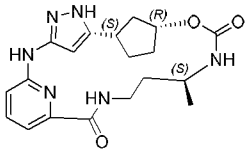
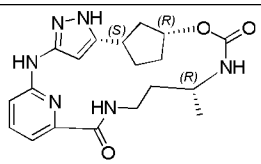
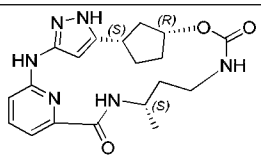
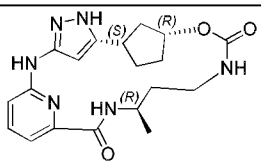
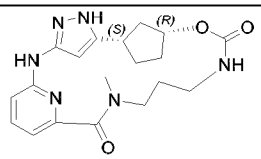
A solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (120 mg, 180 μmol) in TFA (10.0 mL) was warmed to 100 °C and stirred at that temperature for 3 h before it was cooled to 25 °C and concentrated under reduced pressure. The crude (1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl)

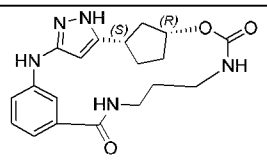
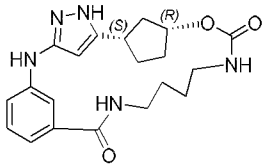
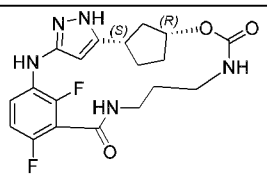
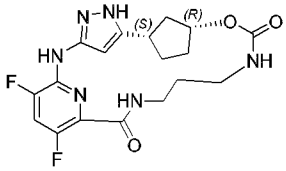
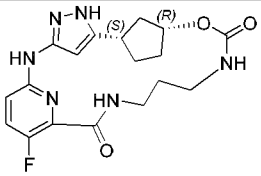
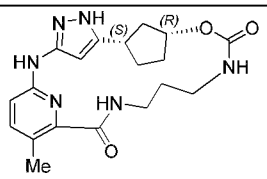
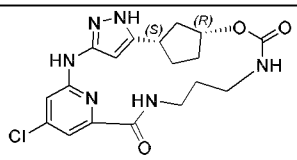
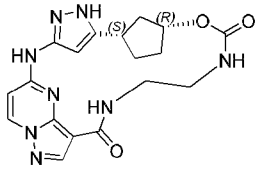
carbonate (220 mg) was directly used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 509.8.

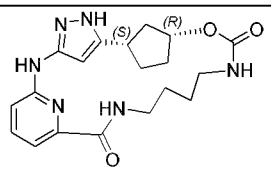
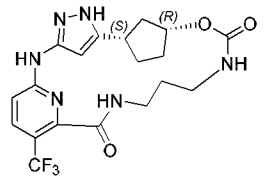
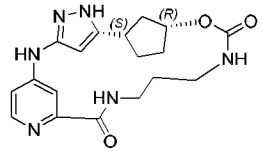
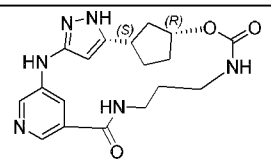
Step 5: (1^1S,1^3R,Z)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a stirred solution of (1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate (220 mg, crude) in CH_3CN (10.0 mL) was added Et_3N (298 μL, 217 mg, 2.15 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 3 h before it was filtrated and the filter cake was washed with MeOH to give (1^1S,1^3R,Z)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (27 mg) as an off-white solid. LC-MS: m/z $[M+H]^+$ 370.8.

The following compounds were prepared using the similar procedure disclosed in synthetic example **94**.

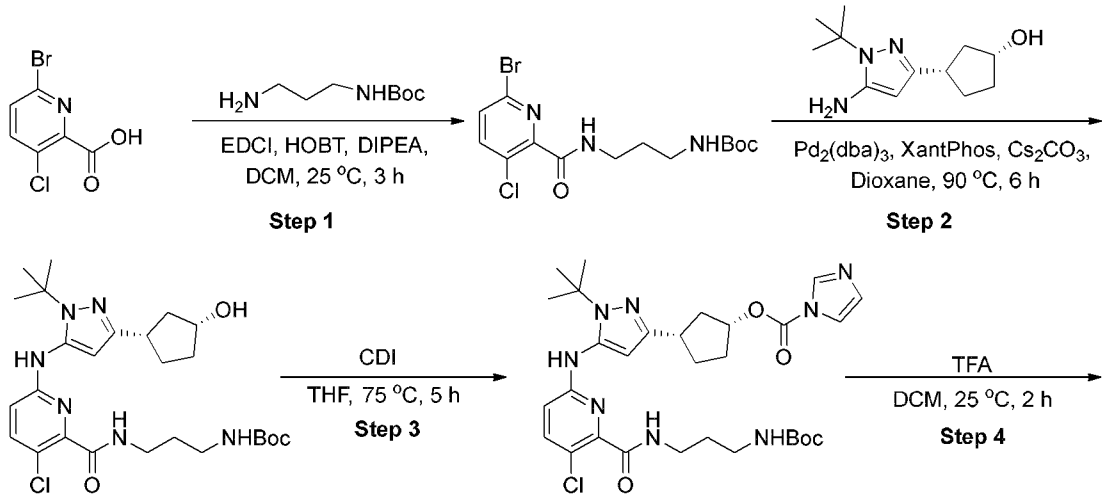
Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
95		385.2
96		384.8
97		384.8
98		385.1
99		384.8

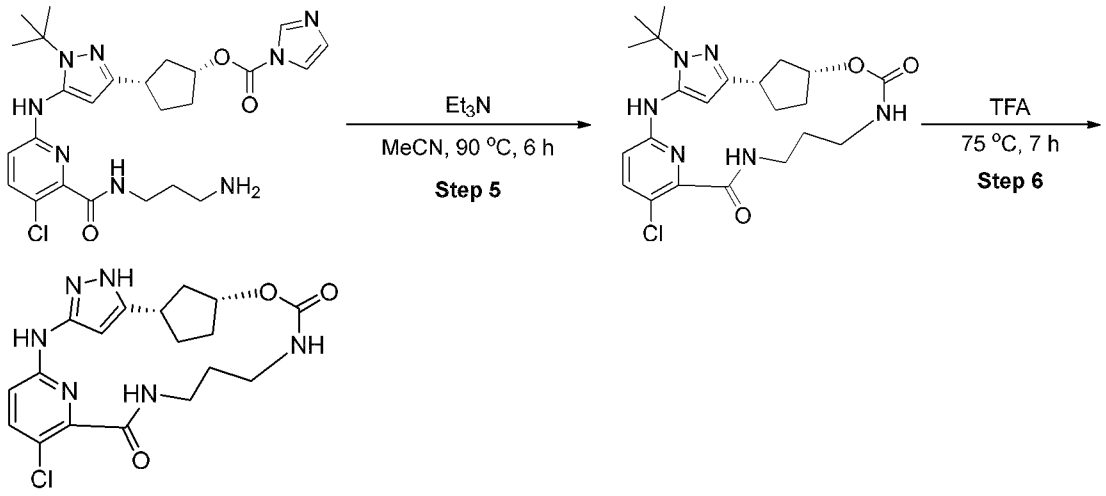
100		370.1
101		384.2
102		406.2
103		407.2
104		389.2
105		385.1
106		405.2
107		385.1

108		385.1
109		439.1
110		371.2
111		371.1

Example **112**

(1^1*S*,1^3*R*,*Z*)-4^5-chloro-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione





Step 1: *tert*-butyl (3-(6-bromo-3-chloropicolinamido)propyl)carbamate

A solution of *tert*-butyl (3-aminopropyl)carbamate (200 mg, 1.15 mmol) in DCM (1 mL) was added to a solution of 6-bromo-3-chloropicolinic acid (407 mg, 1.72 mmol) in DCM (7 mL). The reaction mixtrue was stirred at 25 °C for 3 hours. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic layer was washed by brine (50 mL) and dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, Petrol ether/EtOAc from 0~45%) to afford the product *tert*-butyl (3-(6-bromo-3-chloropicolinamido)propyl)carbamate (420 mg, 1.07 mmol, 93% yield) as a white solid. LC-MS: (ESI) m/z $[M+Na]^+$ 416.0.

Step 2: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-chloropicolinamido)propyl)carbamate

To a suspension of *tert*-butyl (3-(6-bromo-3-chloropicolinamido)propyl)carbamate (220 mg, 560 μmol) and (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (150 mg, 672 μmol) in dioxane (6 mL) was added $Pd_2(dba)_3$ (102 mg, 112 μmol), Cs_2CO_3 (548 mg, 1.68 mmol) and XantPhos (129 mg, 224 μmol). The suspension was degassed with N_2 for 5 times and stirred at 90°C for 6 hours. The mixture was dilutied with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, Petrol ether/EtOAc from 0~61%) to afford the product *tert*-butyl (3-(6-((1-(tert-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-chloropicolinamido)propyl)carbamate (270 mg, 504 μmol, 90% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 535.2.

Step 3: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-chloropicolinamido)propyl)carbamate (180 mg, 336 μmol) in THF (6 mL) was added di(1*H*-imidazol-1-yl)methanone (436 mg, 2.69 mmol). The reaction mixture was degassed with N_2 for 5 times. The mixture was stirred at 75 °C for 5 hours. The mixture was concentrated to dryness. The residue was purified by flash column chromatography (12 g silica gel column, Petrol ether/EtOAc from 0~81%) to afford the product (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl) carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, 296 μmol, 88% yield, 89% purity) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 629.2.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, 334 μmol) in DCM (6.0 mL) was added TFA (2.2 g, 19.4 mmol, 1.49 mL). The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated to afford the product (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (454 mg, crude) as a yellow gum. LC-MS: (ESI) m/z $[M+H]^+$ 529.1.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

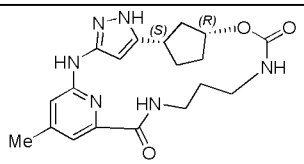
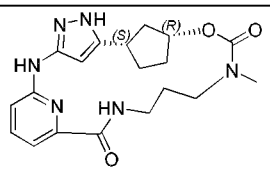
To a solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (454 mg, 858 μmol) in MeCN (90.0 mL) was added Et_3N (1.20 mL) at 25 °C. The reaction mixture was degassed with N_2 for 5 times. The mixture was stirred at 90 °C for 6 hours and then concentrated to dryness. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography (4 g silica gel column, DCM/MeOH from 0~5%) to afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (100 mg, 154 μmol, 18% yield, 71% purity) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 461.2.

Step 6: (1^1S,1^3R,*Z*)-4^5-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (90.0 mg, 195 μmol) in TFA (5 mL) was

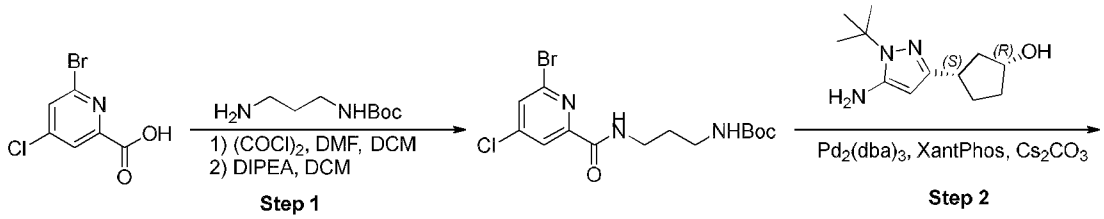
stirred at 75 °C for 7 hours. The mixture was concentrated to afford crude solid, which was purified by prep-HPLC (Chromatographic columns: C18 50 x 2.1 mm, Mobile Phase: ACN-H_2O (0.05% TFA) Gradient:5%-95%) to afford the product ($1^1S,1^3R,Z$)-4^5-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (15.1 mg, 19% yield) as a white solid. LC-MS:(ESI) m/z $[M+H]^+$ 405.1.

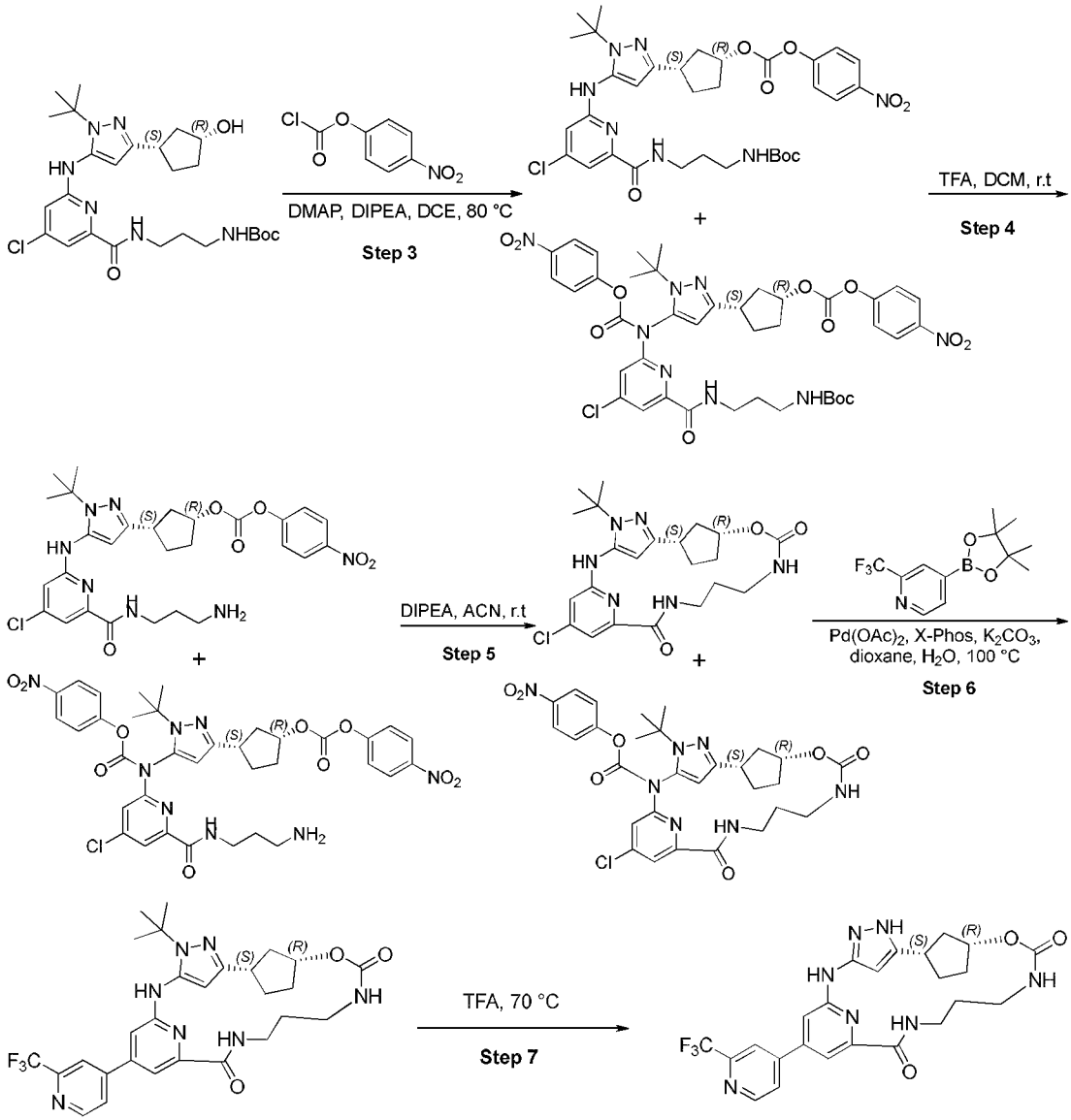
The following compounds were prepared using the similar procedure disclosed in synthetic example **112**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
113		385.2
201		385.2

Example **114**

(1^1*S*,1^3*R*,*Z*)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione





Step 1: *tert*-butyl (3-(6-bromo-4-chloropicolinamido)propyl)carbamate

To a solution of 6-bromo-4-chloro-pyridine-2-carboxylic acid (2.80 g, 11.8 mmol) in DCM (20 mL) was added oxalyl dichloride (2.25 g, 17.8 mmol, 1.59 mL) and one drop of DMF at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL). The solution of the intermediate was added dropwise to the solution of *tert*-butyl *N*-(3-aminopropyl)carbamate (3.09 g, 17.8 mmol, 3.11 mL) and DIPEA (7.65 g, 59.2 mmol, 10.3 mL) in DCM (20 mL). Then the reaction mixture was stirred at 25 °C for 2 h. The mixture was quenched with MeOH (10 mL), then the mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 40% in 15 min to afford the product *tert*-butyl *N*-[3-[(6-bromo-4-chloro-pyridine-2-

carbonyl)amino]propyl]carbamate (3.80 g, 82% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+Na]^+$ 413.9.

Step 2: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-chloropicolinamido)propyl)carbamate

To a solution of *tert*-butyl *N*-[3-[(6-bromo-4-chloro-pyridine-2-carbonyl)amino]propyl]carbamate (3.80 g, 9.68 mmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (2.16 g, 9.68 mmol) in dioxane (25 mL) was added $Pd_2(dba)_3$ (532 mg, 581 μmol), XantPhos (672 mg, 1.16 mmol) and Cs_2CO_3 (7.88 g, 24.2 mmol) under the atmosphere of N_2 at 20 °C. Then the reaction mixture was heated to 100 °C and stirred at 100 °C under the atmosphere of N_2 for 5 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 60% in 20 min to afford the product *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-chloro-pyridine-2-carbonyl]amino]propyl]carbamate (4.80 g, 93% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 535.3.

Step 3: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)-4-chloropicolinamido)propyl)carbamate & 4-nitrophenyl (6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-4-chloropyridin-2-yl)(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)carbamate

To a solution of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-chloro-pyridine-2-carbonyl]amino]propyl]carbamate (4.80 g, 8.97 mmol) in DCE (30 mL) was added DMAP (219 mg, 1.79 mmol) and DIPEA (5.80 g, 44.9 mmol, 7.80 mL), then (4-nitrophenyl) carbonochloridate (5.42 g, 26.9 mmol) was added to the reaction mixture. The reaction mixture was heated to 80 °C and stirred at 80 °C for 15 h. The mixture was cooled to room temperature and diluted with DCM (150 mL), then the mixture was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE with EtOAc from 0 to 60% in 15 min to afford the mixture of product [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate and 4-nitrophenyl (6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-4-chloropyridin-2-yl)(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)carbamate (5.60 g, 89% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 700.3. 865.1

Step 4: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-4-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate & 4-nitrophenyl (6-((3-

aminopropyl)carbamoyl)-4-chloropyridin-2-yl)(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)carbamate

To a solution of [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (5.60 g, 8.00 mmol) in DCM (10 mL) was added TFA (5.47 g, 48.0 mmol, 3.71 mL) at 20 °C. Then the reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to afford the mixture of product [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-4-chloro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate and 4-nitrophenyl (6-((3-aminopropyl)carbamoyl)-4-chloropyridin-2-yl)(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)carbamate (6.00 g, crude, TFA) as a yellow gum which was used for next step without further purification. LC-MS: (ESI) m/z $[M+H]^+$ 600.3, 765.1.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione & 4-nitrophenyl (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-5,11-dioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-3-carboxylate

To a solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-4-chloropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (6.00 g, 8.40 mmol, TFA) and 4-nitrophenyl (6-((3-aminopropyl)carbamoyl)-4-chloropyridin-2-yl)(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)carbamate in CH_3CN (80 mL) was added dropwise the DIPEA (10.9 g, 84.0 mmol, 15.0 mL) slowly at 20 °C. Then the reaction mixture was stirred at 20 °C for 72 h. The mixture was concentrated under reduced pressure, and the residue was redissolved in CH_3CN (15 mL). Then DIPEA (50.0 mL) was added to the reaction mixture. The reaction mixture was stirred at 85 °C for 3 d. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting with EtOAc/DCM with EtOAc from 0 to 50% in 20 min to afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (2.00 g, 52% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 461.3. And the by-product 4-nitrophenyl (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-5,11-dioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-3-carboxylate (0.500 g, 10% yield) as a yellow solid, LC-MS: (ESI) m/z [M+H]+ 626.1.

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

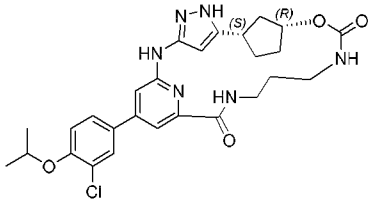
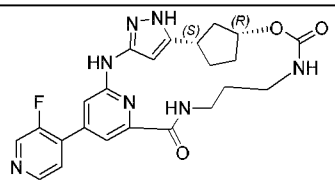
To a solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (30.0 mg, 65.1 μmol) and 4-(4,4,5,5-

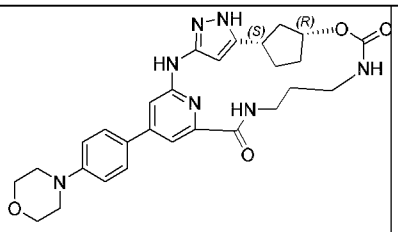
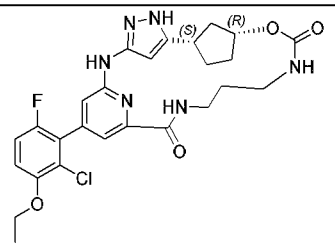
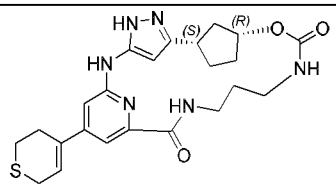
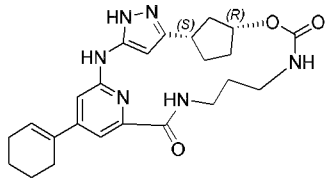
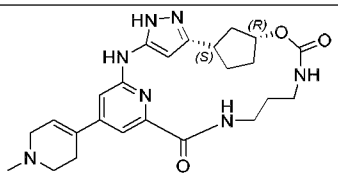
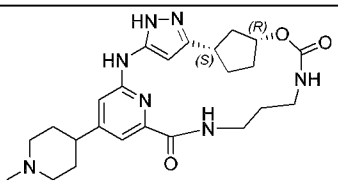
tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (35.5 mg, 130 μmol) in dioxane (8.0 mL) was added $Pd(OAc)_2$ (2.92 mg, 13.0 μmol), X-Phos (12.4 mg, 26.0 μmol) and Water (0.10 mL) under the atmosphere of N_2. Then the reaction mixture was heated to 100 °C and stirred at 100 °C for 5 h. The mixture was cooled to room temperature and diluted with DCM (20 mL), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc=4:5) to afford the product (1^1S,1^3R,Z)-2^1-(*tert*-butyl)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (36.0 mg, 97% yield) as a yellow solid. LCMS:(ESI) m/z $[M+H]^+$ 572.2.

Step 7: (1^1S,1^3R,Z)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The solution of (1^1S,1^3R,Z)-2^1-(*tert*-butyl)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (36.0 mg, 63.0 μmol) in TFA (8.0 mL) was stirred at 70 °C for 4 d. The mixture was concentrated under reduced pressure, and the residue was purified by Prep-HPLC eluting with CH_3CN in water with CH_3CN from 30% to 40% in 8 min to afford the product (1^1S,1^3R,Z)-4^4-(2-(trifluoromethyl)pyridin-4-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (21.0 mg, 65% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 516.2.

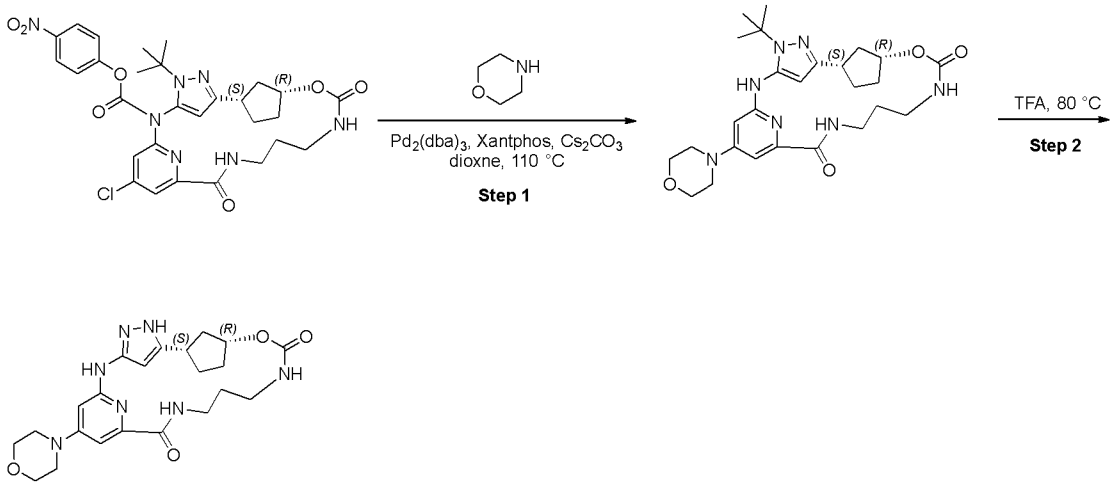
The following compounds were prepared using the similar procedure disclosed in synthetic example **114**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
115		539.2
116		466.1

117		532.7
118		543.2
119		469.1
120		451.2
121		466.2
122		468.2

Example **123**

(1^{1}*S*,1^{3}*R*,*Z*)-4^{4}-morpholino-2^{1}*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-morpholino-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

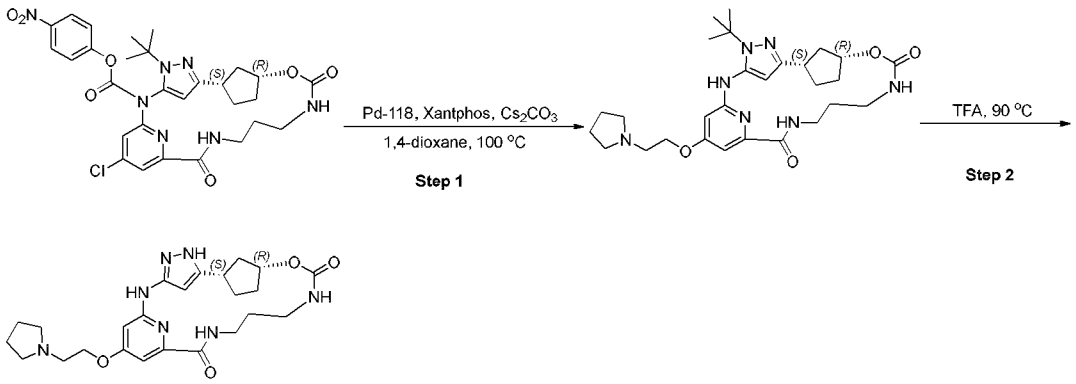
To a solution of 4-nitrophenyl (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-5,11-dioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-3-carboxylate (150 mg, 239 μmol) and morpholine (41.8 mg, 480 μmol) in dioxane (8 mL) was added Pd2(dba)3 (21.9 mg, 23.9 μmol), XantPhos (27.7 mg, 47.9 μmol) and Cs_2CO_3 (234 mg, 718 μmol) under the atmosphere of N_2. Then the reaction mixture was stirred at 100 °C under the atmosphere of N_2 for 5 hours. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (25 g silica gel column, PE/EtAOc with EtOAc from 0~80%) to afford the product (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-44-morpholino-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (27 mg, 22% yield) as a yellow solid. LC-MS: (ESI) m/z $[M+H]^+$ 512.2.

Step 2: (1^1S,1^3R,*Z*)-4^4-morpholino-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^4-morpholino-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (27 mg, 52.77 μmol) in TFA (5 mL) was stirred at 80 °C for 6 hours. The mixture was concentrated under reduced pressure, and the residue was sent to purified by Prep-HPLC (Chromatographic columns: -Xbridge-C18 150 × 19 mm,5 μm; Mobile Phase: ACN/H_2O (0.1% FA); Gradient: 20%-50%) to afford the product (1^1S,1^3R,*Z*)-4^4-morpholino-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (5 mg, 21% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 456.2.

Example **124**

($1^1S,1^3R,Z$)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

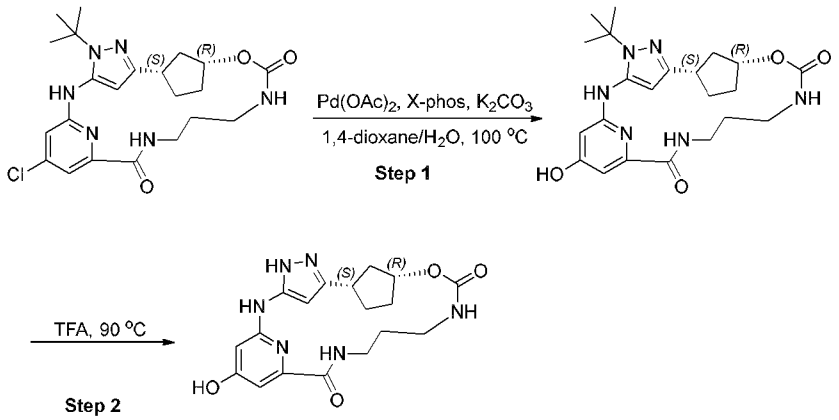
To a solution of 4-nitrophenyl ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-chloro-5,11-dioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-3-carboxylate (100 mg, 159 μmol) in 1-4,dioxane (5 mL) was added 2-pyrrolidin-1-ylethanol (55 mg, 479 μmol), Pd-118 (10 mg, 15.9 μmol) and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (9 mg, 15.9 μmol). The mixture was stirred at 100 °C under N_2 atmosphere for 12 hours. LCMS showed the starting material was consumed and desired product was formed. The mixture was concentrated. The residue was diluted with H_2O (30 mL) and extracted with DCM (30 mL x2). The combined organic layers were washed by brine (50 mL) and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (5% MeOH in DCM) to provide the ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (30 mg, 55.5 μmol, 34% yield) as a white solid. LC-MS: m/z 540.3 $[M+H]^+$.

Step 2: ($1^1S,1^3R,Z$)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (25 mg, 46.3 μmol) in TFA (5 mL) was stirred at 90 °C for 12 hours. LCMS showed the starting material was consumed and desired product was formed. The mixture was concentrated. The residue was purified by prep-HPLC (Chromatographic columns: -Xbridge-C18 250 x 10 mm, Mobile Phase: ACN--H_2O (0.1% FA)) to provide ($1^1S,1^3R,Z$)-4^4-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1 mg, 2.07 μmol, 4% yield) as a colorless solid. LC-MS: m/z 484.3 $[M+H]^+$.

Example **196**

(1^1*S*,1^3*R*,*Z*)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

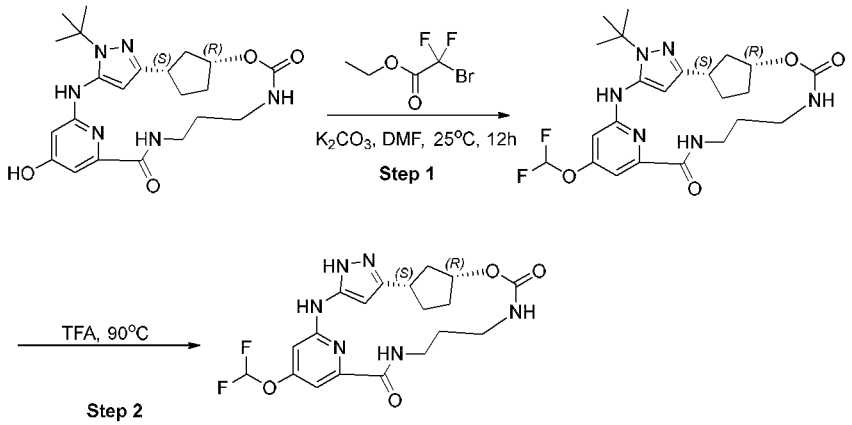
To a solution of (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-chloro-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (100 mg, 216 μmol) in 1,4-dioxane (5.0 mL) and H_2O (0.50 mL) was added X-Phos (10.0 mg, 20.0 μmol), $Pd(OAc)_2$ (10.0 mg, 44.0 μmol) and Potassium carbonate (60.0 mg, 434 μmol). The mixture was heated to 100 °C and stirred at 100 °C under N_2 atmosphere for 10 h. The mixture was concentrated. The residue was diluted with H_2O (30 mL) and extracted with DCM (30 mL × 2). The combined organic layers were washed by brine (50 mL) and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with MeOH /DCM (with MeOH from 0 to 5% in 10 min) to provide the (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80.0 mg, 83% yield) as a white solid. LC-MS: m/z 443.3 $[M+H]^+$.

Step 2: (1^1*S*,1^3*R*,*Z*)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The mixture of (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 45.2 μmol) in TFA (5.0 mL) was heated to 90 °C and stirred at 90 °C for 12 h. The mixture was concentrated. The residue was purified by prep-HPLC (with CH_3CN from 25% to 55% in 10 min) to provide (1^1*S*,1^3*R*,*Z*)-4^4-hydroxy-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (6.00 mg, 34% yield) as a white solid. LC-MS: m/z 387.2 $[M+H]^+$.

Example **197**

($1^1S,1^3R,Z$)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

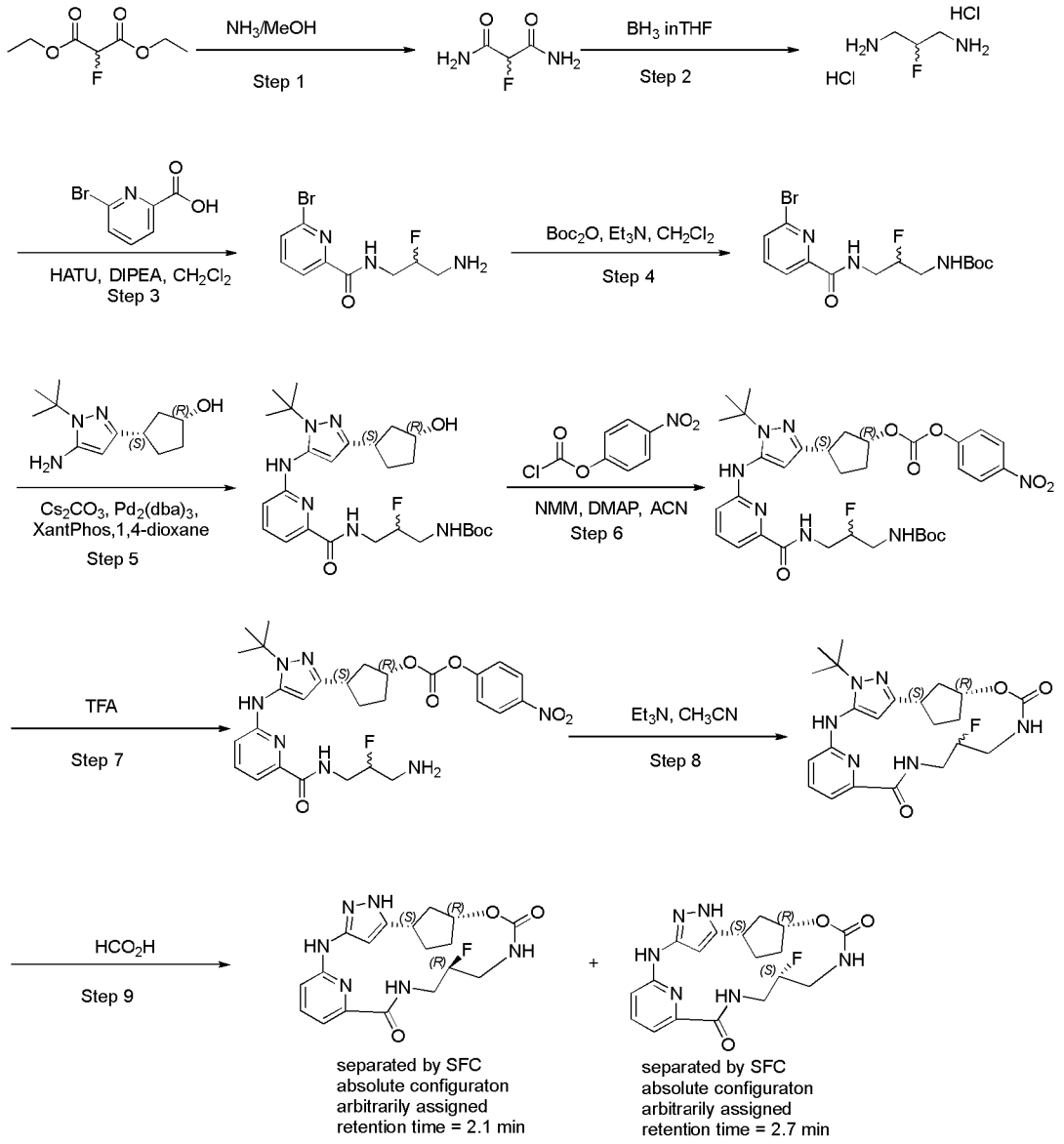
To a mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-hydroxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (25.0 mg, 56.5 μmol) in DMF (5.0 mL) was added ethyl 2-bromo-2,2-difluoro-acetate (34.4 mg, 169 μmol, 21.7 μL) and Potassium carbonate (23.4 mg, 169 μmol). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed by brine (50 mL) and dried over Na_2SO_4, filtered and concentrated to provide the ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 72% yield) as a white solid. LC-MS: m/z 493.1 $[M+H]^+$.

Step 2: ($1^1S,1^3R,Z$)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

The mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 40.6 μmol) in TFA (5.0 mL) was heated to 90 °C and stirred at 90 °C for 12 h. The mixture was concentrated. The residue was purified by prep-HPLC (with CH_3CN from 25% to 55% in 10 min) to provide ($1^1S,1^3R,Z$)-4^4-(difluoromethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (8.00 mg, 45% yield) as a white solid. LC-MS: m/z 437.2 $[M+H]^+$.

Example **125** and **126**

(*1¹S,1³R,8R,Z*)-8-fluoro-*2¹H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione and (*1¹S,1³R,8S,Z*)-8-fluoro-*2¹H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: 2-fluoromalonamide

A mixture of dimethyl 2-fluoropropanedioate (5.0 g, 33.3 mmol) in NH_3/ MeOH (5 mL,7 mol/L, 35mmol) was stirred for 4 h at 25 °C, before it was concentrated to give crude 2-fluoropropanediamide as a white solid, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 121.1.

Step 2: 2-fluoropropane-1,3-diamine

To a suspension of 2-fluoropropanediamide (3.3 g, 27.5 mmol) in THF (40.0 mL) was added BH_3 in THF (137.5 mL, 1 moL/L, 137mmol). The reaction was stirred at 70 °C for 4h, before it was concentrated *in vacuo*. The mixture was quenched with KOH aq. (40 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford 2-fluoropropane-1,3-diamine (500 mg, crude) as a colorless oil. LC-MS: m/z $[M+H]^+$ 93.1.

Step 3: *N*-(3-amino-2-fluoropropyl)-6-bromopicolinamide

To a suspension of 6-bromopyridine-2-carboxylic acid (320 mg, 1.6 mmol) and 2-fluoropropane-1,3-diamine (434 mg, 4.8 mmol) in DMF (10.0 mL) was added DIPEA (0.83 mL, 613 mg, 4.8 mmol) and HATU (602 mg, 1.6 mmol) at 25 °C and stirred for 2 h, before the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with CH_2Cl_2/MeOH (with MeOH from 0 to 20 % in 25 min) to afford *N*-(3-amino-2-fluoro-propyl)-6-bromo-pyridine-2-carboxamide (320 mg, 73% yield) as a brown oil. LC-MS: m/z $[M+H]^+$ 275.8.

Step 4: *tert*-butyl *N*-[3-[(6-bromopyridine-2-carbonyl)amino]-2-fluoro-propyl]carbamate

To a suspension of *N*-(3-amino-2-fluoro-propyl)-6-bromo-pyridine-2-carboxamide (270 mg, 1.0 mmol) and Boc_2O (213 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (272 μL, 198 mg, 1.96 mmol) at 25 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 35 % in 20 min) to afford *tert*-butyl *N*-[3-[(6-bromopyridine-2-carbonyl)amino]-2-fluoro-propyl]carbamate (220 mg, 59% yield) as a yellow solid. LC-MS: m/z $[M-55]^+$ 319.9.

Step 5: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2-fluoropropyl)carbamate

To a suspension of *tert*-butyl *N*-[3-[(6-bromopyridine-2-carbonyl)amino]-2-fluoro-propyl]carbamate (220 mg, 0.585 mmol) in 1,4-dioxane (10.0 mL) was added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (131 mg, 0.585 mmol), $Pd_2(dba)_3$ (54 mg, 0.058 mmol), XantPhos (68 mg, 0.117 mmol) and Cs_2CO_3 (381 mg, 1.17 mmol). The reaction was stirred at 90 °C for 2 h under N_2, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with CH_2Cl_2/MeOH (with MeOH from 0 to 10 % in 20 min) to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2-fluoropropyl)carbamate (230 mg, 75% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 519.2.

Step 6: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2-fluoropropyl)carbamate

To a suspension of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2-fluoropropyl)carbamate (230 mg, 0.443 mmol) in THF (5.0 mL) was added 4-nitrophenyl carbonochloridate (268 mg, 1.33 mmol), DMAP (108 mg, 0.887 mmol) and NMM (243 μL, 224 mg, 2.21 mmol) at rt. The reaction was stirred for 16 h, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 20 min) to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2-fluoropropyl)carbamate (200 mg, 65% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 684.3.

Step 7: (1*R*,3*S*)-3-(5-((6-((3-amino-2-fluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

A mixture of [(1*R*,3*S*)-3-[5-[[6-[[3-(*tert*-butoxycarbonylamino)-2-fluoro-propyl]carbamoyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (200 mg, 0.29 mmol) in TFA (5.0 mL) was stirred for 2 h at 25 °C, before it was concentrated *in vacuo* to give crude (1*R*,3*S*)-3-(5-((6-((3-amino-2-fluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 584.3.

Step 8: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a suspension of (1*R*,3*S*)-3-(5-((6-((3-amino-2-fluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) in CH_3CN (3 mL) was added Et_3N (239 μL, 174 mg, 1.72 mmol) at room temperature. The mixture was stirred at room temperature for 2 h, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 65 % in 25 min) to afford (1^1S,1^3R, *Z*)-2^1-(*tert*-butyl)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80 mg) as a yellow solid. LC-MS: m/z $[M+H]^+$ 445.2.

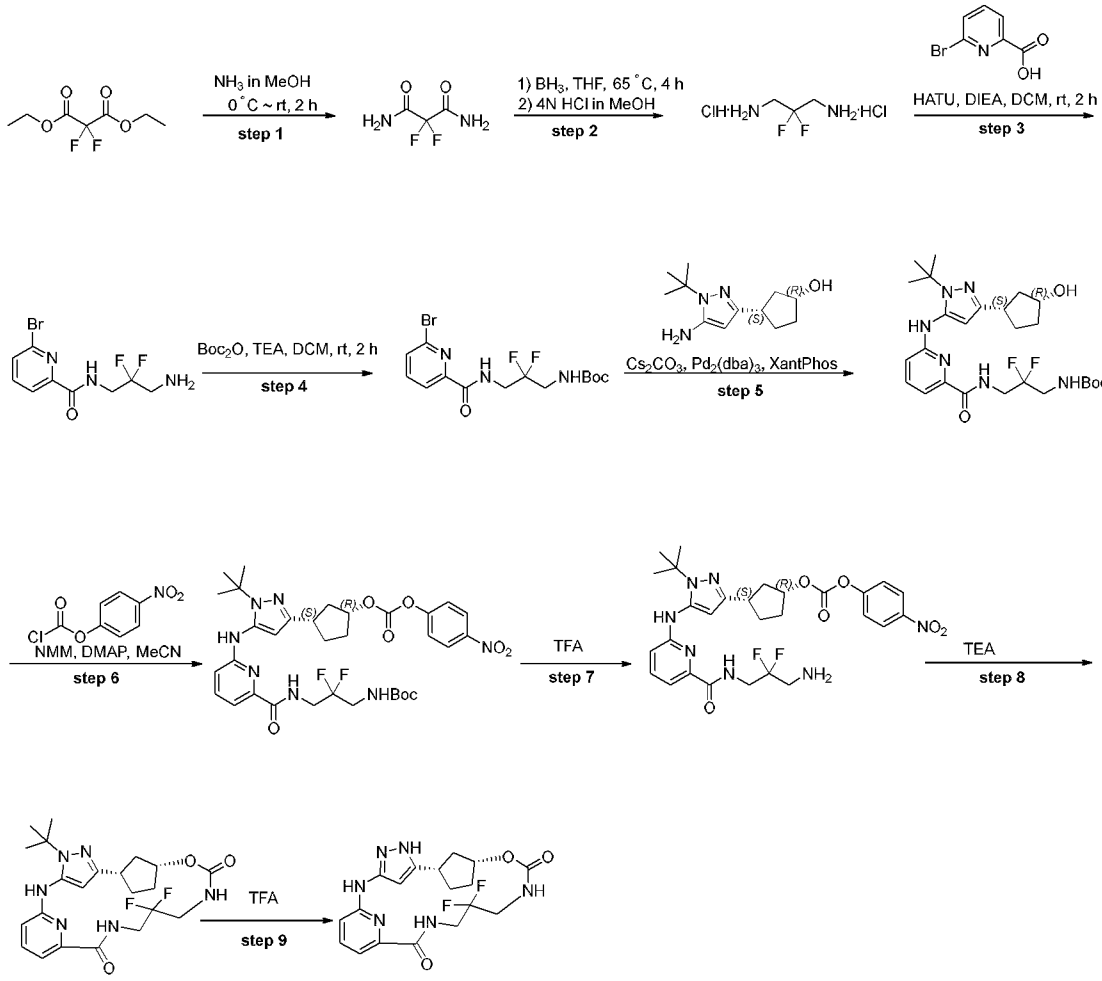
Step 9: (1^1S,1^3R,8*R*,*Z*)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione and (1^1S,1^3R,8*S*,*Z*)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80 mg) in HCO_2H (2.0 mL) was stirred at 100 °C for 16 h, before it was concentrated and purified by SFC eluting with CO2 in EtOH (CHIRALPAK OJ-H 250 mm × 20 mm, 5 μm column, CO_2/EtOH = 60/40, EtOH with 0.2% NH_4OH,

40 g/min, 40 °C) to afford ($1^1S,1^3R,8R,Z$)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (7.8 mg, retention time = 2.1 min, absolute configuration arbitrarily assigned) as a white solid, LC-MS: m/z $[M+H]^+$ 389.2, and ($1^1S,1^3R,8S,Z$)-8-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (9.3 mg, retention time = 2.7 min, absolute configuration arbitrarily assigned) as a white solid. LC-MS: m/z $[M+H]^+$ 389.2.

Example **127**

(11*S*,13*R*,*Z*)-8,8-difluoro-21H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: 2,2-difluoromalonamide

Diethyl 2,2-difluoropropanedioate (1 g, 5.10 mmol),NH_3 in MeOH (4 M, 38.17 mL) in THF (30 mL) was stirred for 2 hours at 0 °C in a RBF under N_2, until the reaction was complete as indicated by

LCMS, the reaction mixture was concentrated to give the desired product 2,2-difluoropropanediamide (600 mg, 4.35 mmol, 85.24% yield) as a white solid. LC-MS: m/z 139.1 $[M+H]^+$.

Step 2: 2,2-difluoropropane-1,3-diamine dihydrochloride

To a suspension of 2,2-difluoropropanediamide (1 g, 7.24 mmol) in THF (30 mL) was added slowly BH_3 in THF (1 M, 36.21 mL) at 65 °C and the resulting mixture was stirred for 30 minutes under N_2.Then the mixture was stirred at 65 °C for 4 hours. After completion of the reaction as judged by LCMS, reaction mixture was quenched with MeOH (20 mL) and concentrated *in vacuo*. The procedure was repeated for 3 times. The crude product was treated with 20 mL HCl (gas, 4N in MeOH), a white solid appeared. The mixture was filtered to give 2,2-difluoropropane-1,3-diamine;dihydrochloride (600 mg, 3.28 mmol, 45.26% yield) as a white solid. LC-MS: m/z 111.1 $[M+H]^+$.

Step 3: *N*-(3-amino-2,2-difluoropropyl)-6-bromopicolinamide

A mixture of 6-bromopyridine-2-carboxylic acid (223 mg, 1.10 mmol), 2,2-difluoropropane-1,3-diamine (364.65 mg, 3.31 mmol), HATU (629.62 mg, 1.66 mmol) and DIEA (712.04 mg, 5.52 mmol) in DCM (10 mL) was stirred for 1 hour at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 100% in 25 min to afford N-(3-amino-2,2-difluoropropyl)-6-bromopicolinamide (300 mg, 0.91mmol, 83.16% yield, 90% purity). LC-MS: m/z 294.1 $[M+H]^+$.

Step 4: *tert*-butyl (3-(6-bromopicolinamido)-2,2-difluoropropyl)carbamate

A mixture of *N*-(3-amino-2,2-difluoro-propyl)-6-bromo-pyridine-2-carboxamide (300 mg, 1.02 mmol), Boc_2O (444.75 mg, 2.04 mmol), TEA (516.11 mg, 5.10 mmol, 710.89 µL) in DCM (10 mL) and MeCN (3 mL) was stirred for 2 hours at 25 °C in a RBF under N_2, until the reaction wascomplete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 100% in 25 min to afford *tert*-butyl (3-(6-bromopicolinamido)-2,2-difluoropropyl)carbamate (260 mg, 659.55 µmol, 64.66% yield) as a light-yellow liquid. LC-MS: m/z 416.0 $[M+H]^+$.

Step 5: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2,2-difluoropropyl)carbamate

A mixture of *tert*-butyl *N*-[3-[(6-bromopyridine-2-carbonyl)amino]-2,2-difluoro-propyl]carbamate (240 mg, 608.81 µmol), (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (135.96 mg, 608.81 µmol), $Pd_2(dba)_3$ (55.71 mg, 60.88 µmol) and XantPhos (70.50 mg, 121.76 µmol), Cs_2CO_3 (395.73 mg, 1.22 mmol) in dioxane (20 mL) was stirred for 6 hours at 100 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in*

vacuo. The crude product was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 50% in 25 min to afford to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)picolinamido)-2,2-difluoropropyl)carbamate (280 mg, 521.79 μmol, 85.71% yield) as a light-yellow oil. LC-MS: m/z 537.3 $[M+H]^+$.

Step 6: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)picolinamido)-2,2-difluoropropyl)carbamate

A mixture of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]pyridine-2-carbonyl]amino]-2,2-difluoro-propyl]carbamate (280 mg, 521.79 μmol), (4-nitrophenyl) carbonochloridate (315.52 mg, 1.57 mmol), DMAP (127.49 mg, 1.04 mmol) and NMM (263.90 mg, 2.61 mmol, 286.84 μL) in MeCN (10 mL) was stirred for 2 hours at 25°C in a RBF under N2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 50% in 25 min to afford to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2,2-difluoropropyl)carbamate (240 mg, 342.02 μmol, 65.55% yield) as a colorless oil. LC-MS: m/z 702.2 $[M+H]^+$.

Step 7: (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-difluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

A mixture of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)-2,2-difluoropropyl)carbamate (220 mg, 313.52 μmol), TFA (1.79 g, 15.68 mmol, 1.21 mL) in DCM (8.82 mL) was stirred for 2 hours at 25°C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated in *vacuo* to give the desired product (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-difluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (220 mg, crude) as pale yellow oil. LC-MS: m/z 602.3 $[M+H]^+$.

Step 8: (11*S*,13*R*,*Z*)-21-(*tert*-butyl)-8,8-difluoro-21*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

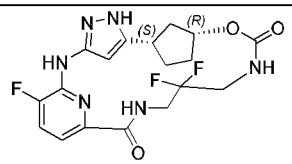
A mixture of (1*R*,3*S*)-3-(5-((6-((3-amino-2,2-difluoropropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (180 mg, 299.20 μmol), NMM (151.32 mg, 1.50 mmol, 164.48 μL), DMAP (73.11 mg, 598.40 μmol) in MeCN (20 mL) was stirred for 1 hour at 25 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate/petroleum ether from 0 to 100% in 25 min to afford (11*S*,13*R*,*Z*)-21-(*tert*-butyl)-

8,8-difluoro-21*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (74 mg, 160.0 μmol, 53.48% yield) as colorless oil. LC-MS: m/z 462.7 $[M+H]^+$.

Step 9: (11*S*,13*R*,*Z*)-8,8-difluoro-21*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

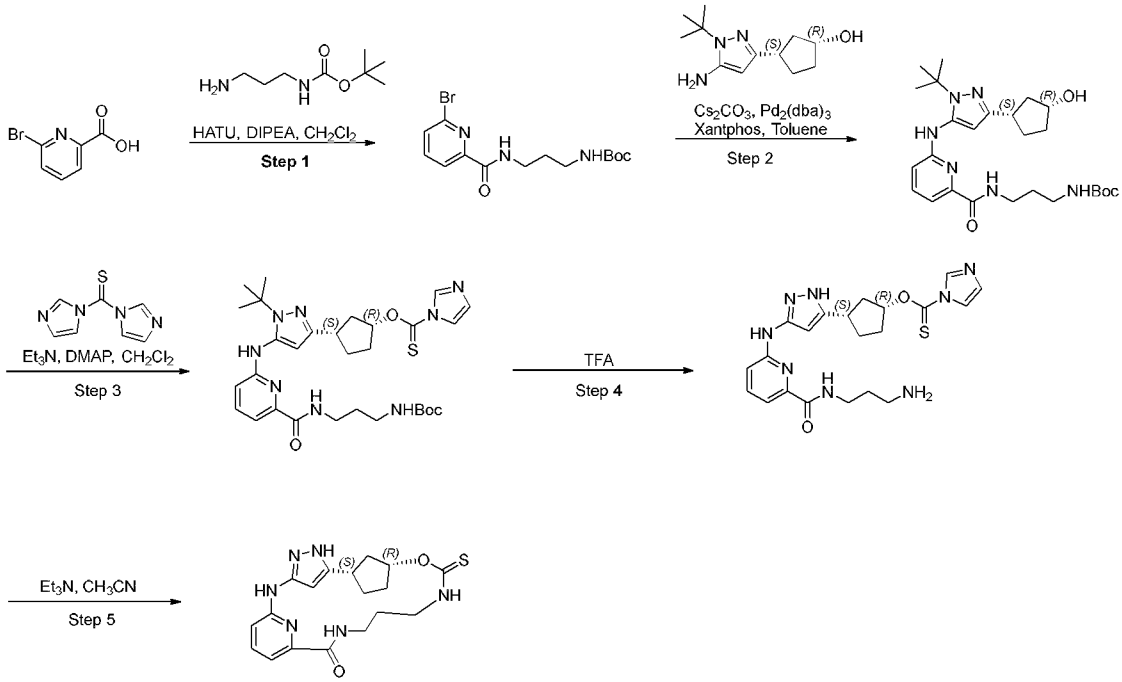
(11*S*,13*R*,*Z*)-21-(*tert*-butyl)-8,8-difluoro-21*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (74 mg, 160.00 μmol) in TFA (5 mL) was stirred for 12 hours at 70 °C in a RBF under N_2, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (5 ml) and was added to H_2O (20 mL). Then the solid was collected by filtraation to give the desired product (11*S*,13*R*,*Z*)-8,8-difluoro-21H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (26 mg, 63.98 μmol, 39.99% yield) as a pale yellow solid. LC-MS: m/z 407.1 $[M+H]^+$.

The following compounds were prepared using the similar procedure disclosed in synthetic example **127**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
128		425.0

Example 129

(1*S*,1*R*,*Z*)-11-thioxo-2*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-one



Step 1: *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate

To a stirred solution of 6-bromopicolinic acid (2.00 g, 9.90 mmol) and *tert*-butyl (3-aminopropyl)carbamate (1.72 g, 9.90 mmol) in CH_2Cl_2 (30.0 mL) were added HATU (7.52 g, 19.8 mmol) and DIPEA (2.55 g, 19.8 mmol). The reaction mixture was stirred at 20 °C for 1 h before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 15 min) to afford *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate (3.10 g, 88% yield) as a yellow oil. LC-MS: m/z $[M+Na]^+$ 379.7.

Step 2: *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate (500 mg, 1.40 mmol) in toluene (20.0 mL) were sequentially added (1*R*,3*S*)-3-(3-amino-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)cyclopentan-1-ol (312 mg, 1.40 mmol), $Pd_2(dba)_3$ (128 mg, 0.140 mmol), XantPhos (162 mg, 0.280 mmol) and Cs_2CO_3 (913 mg, 2.80 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 16 h before it was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 70% in 30 min) to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-*1H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (500 mg, 71% yield) as a red solid. LC-MS: m/z $[M+H]^+$ 500.9.

Step 3: O-((1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate

To a stirred solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-3-yl)amino)picolinamido)propyl)carbamate (300 mg, 0.600 mmol) in CH_2Cl_2 (5.0 mL) were sequentially added di(imidazol-1-yl)methanethione (214 mg, 1.20 mmol), DMAP (73.2 mg, 0.600 mmol) and Et_3N (251 μL 182 mg, 1.80 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give O-((1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 610.6.

Step 4: O-((1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate

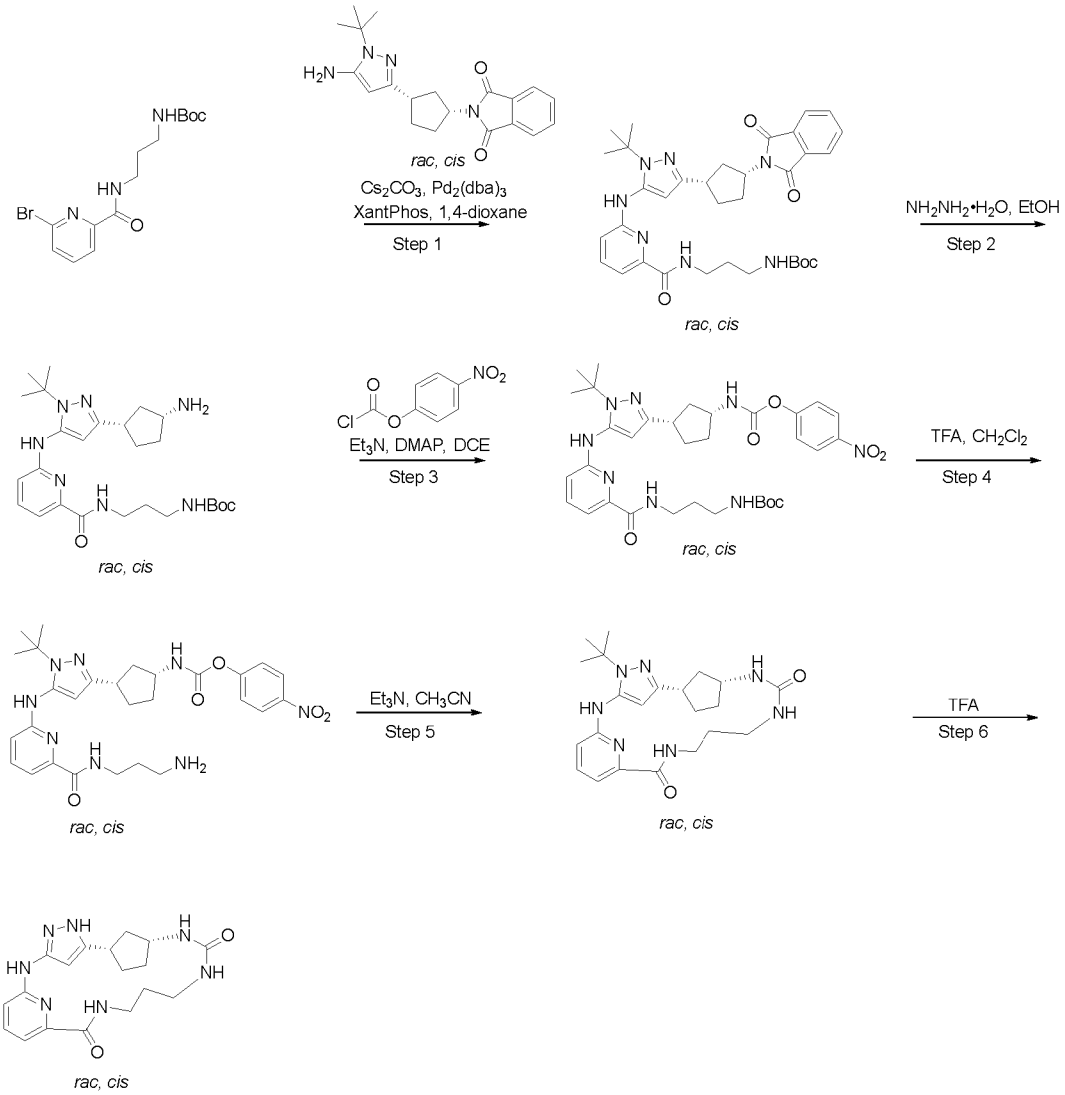
A solution of O-((1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate (crude) in TFA (2.0 mL) was warmed to 70 °C and stirred at that temperature for 16 h. The mixture was concentrated under reduced pressure to give O-((1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 454.6.

Step 5: (1^1S,1^3R,*Z*)-11-thioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-one

To a stirred solution of O-((1*R*,3*S*)-3-(3-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl) 1*H*-imidazole-1-carbothioate (crude) in CH_3CN (5.0 mL) was added Et_3N (270 μL, 196 mg, 1.94 mmol) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 5 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 50% in 40 min) to afford (1^1S,1^3R,*Z*)-11-thioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-one (2.00 mg, 4.7% yield) as light yellow solid. LC-MS: m/z $[M+H]^+$ 387.

Example **130**

(*rac, cis*)-2^1H-3,6,10,12-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate

To a stirred suspension of *tert*-butyl (3-(6-bromopicolinamido)propyl)carbamate (200 mg, 560 μmol) in 1,4-dioxane (15.0 mL) were sequentially added 2-((1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl)isoindoline-1,3-dione (197 mg, 560 μmol), $Pd_2(dba)_3$ (51.0 mg, 56.0 μmol), XantPhos (65.0 mg, 112 μmol) and Cs_2CO_3 (547 mg, 1.68 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 25 min) to afford (*rac, cis*)-*tert*-butyl (3-(6-((1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (300 mg, 85% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 629.8.

Step 2: (*rac, cis*)-*tert*-butyl (3-(6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate

To a stirred solution of (*rac, cis*)-*tert*-butyl (3-(6-((1-(*tert*-butyl)-3-(3-(1,3-dioxoisoindolin-2-yl)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (300 mg, 480 μmol) in ethanol (15.0 mL) was added $NH_2NH_2 \cdot H_2O$ (248 μL, 255 mg, 5.10 mmol, 80% wt) at 25 °C. The mixture was warmed to 80 °C and stirred at that temperature for 3 h before it was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 90 % in 25 min) to afford (*rac, cis*)-*tert*-butyl (3-(6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (150 mg, 63% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 500.0

Step 3: (*rac, cis*)-*tert*-butyl (3-(6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate

To a suspension of (*rac, cis*)-*tert*-butyl (3-(6-((3-(3-aminocyclopentyl)-1-(*tert*-butyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (150 mg, 300 μmol) in DCE (10.0 mL) were sequentially added 4-nitrophenyl carbonochloridate (203 mg, 1.01 mmol), DMAP (21.0 mg, 170 μmol) and Et_3N (125 μL, 91.0 mg, 900 μmol) at 25 °C. The reaction mixture was warmed to 70 °C and stirred at that temperature for 12 h. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 25 min) to afford (*rac, cis*)-*tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (150 mg, 75% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 664.7

Step 4: (*rac, cis*)-4-nitrophenyl (3-(5-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl)carbamate

To a stirred solution of (*rac, cis*)-*tert*-butyl (3-(6-((1-(*tert*-butyl)-3-(3-(((4-nitrophenoxy)carbonyl)amino)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (150 mg, 230 μmol) in CH_2Cl_2 (10.0 ml) was added TFA (90.0 μL, 131 mg, 1.15 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to afford (*rac, cis*)-4-nitrophenyl (3-(5-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl)carbamate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 564.8

Step 5: (*rac, cis*)-2^1-(*tert*-butyl)-2^1*H*-3,6,10,12-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

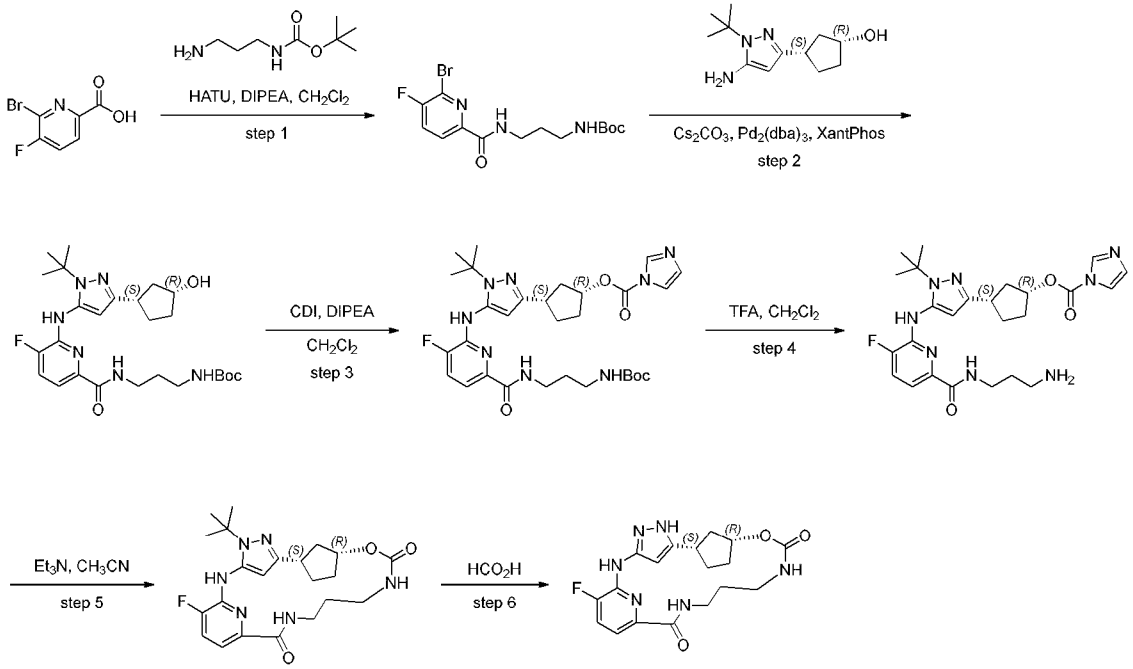
To a suspension of (*rac, cis*)-4-nitrophenyl (3-(5-((6-((3-aminopropyl)carbamoyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl)carbamate in CH_3CN (10.0 mL) was added Et_3N (268 µL, 196 mg, 1.94 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h. Then it was concentrated *in vacuo* and the residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 2.5 % in 25 min) to afford (*rac, cis*)-2^1-(*tert*-butyl)-2^1*H*-3,6,10,12-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80.0 mg, 83% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 425.9

Step 6: (*rac, cis*)-2^1*H*-3,6,10,12-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A solution of (*rac, cis*)-2^1-(*tert*-butyl)-2^1*H*-3,6,10,12-tetraaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (70.0 mg, 160 µmol) in TFA (5.0 mL) was warmed to 80 °C and stirred at that temperature for 2 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 60% in 20 min) to afford (*rac, cis*)-2^1*H*-3,6,10,12-tetraaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (5.60 mg, 16% yield) as an off-white solid. LC-MS: m/z $[M+H]^+$ 370.1.

Example **131**

(1^1*S*,1^3*R*,*Z*)-4^3-fluoro-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl *N*-[3-[(6-bromo-5-fluoro-pyridine-2-carbonyl)amino]propyl]carbamate

To a suspension of 6-bromo-5-fluoro-pyridine-2-carboxylic acid (500 mg, 2.27 mmol) in CH_2Cl_2 (20.0 mL) was sequentially added *tert*-butyl *N*-(3-aminopropyl)carbamate (396 mg, 2.27 mmol), HATU (1.73 g, 4.55 mmol) and DIPEA (790 μL, 586 mg, 4.55 mmol) at 25 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 25 min) to afford *tert*-butyl *N*-[3-[(6-bromo-5-fluoro-pyridine-2-carbonyl)amino]propyl]carbamate (850 mg, 99% yield) as a yellow oil. LC-MS: m/z $[M\text{-Boc}]^+$ 275.9.

Step 2: *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-5-fluoro-pyridine-2-carbonyl]amino]propyl]carbamate

To a suspension of *tert*-butyl *N*-[3-[(6-bromo-5-fluoro-pyridine-2-carbonyl)amino]propyl]carbamate (730 mg, 1.94 mmol) in 1,4-dioxane (20.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (216 mg, 0.97 mmol), Cs_2CO_3 (1.90 g, 5.82 mmol), XantPhos (224 mg, 0.388 mmol) and $Pd_2(dba)_3$ (177 mg, 0.194 mmol) at room temperature and the reaction was stirred at 100 °C for 16 h under N_2. After completion of the reaction as judged by LCMS, reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 30 min) to afford *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-5-fluoro-pyridine-2-carbonyl]amino]propyl]carbamate (410 mg, 40% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 519.0.

Step 3: [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-5-fluoro-pyridine-2-carbonyl]amino]propyl]carbamate (380 mg, 0.73 mmol) in CH_2Cl_2 (20.0 mL) was added CDI (356 mg, 2.20 mmol) and DIPEA (636 μL, 472 mg, 3.66 mmol) at 35 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, the reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 612.8.

Step 4: [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in CH_2Cl_2 (6.0 mL) was added slowly TFA (2.0 mL) at 25 °C and stirred for 1 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 512.9.

Step 5: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

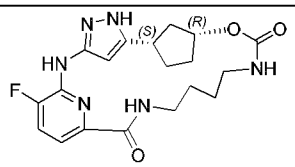
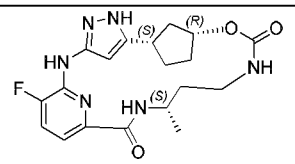
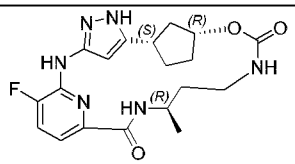
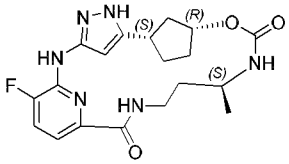
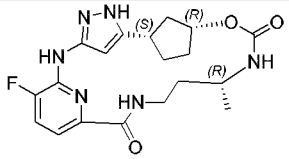
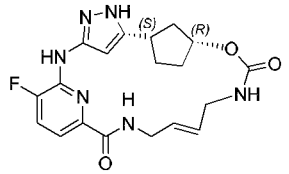
To a suspension of [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-3-fluoro-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in CH_3CN (10.0 mL) was added Et_3N (894 µL, 651 mg, 6.44 mmol) and the reaction was stirred at 80 °C for 16 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10% in 20 min) to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (240 mg) as a yellow solid. LC-MS: m/z $[M+H]^+$ 444.9.

Step 6: (1^1S,1^3R,*Z*)-4^3-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^3-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (240 mg, 0.54 mmol) in HCO_2H (4.0 mL) was stirred for 5 h at 100 °C, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated under reduced pressure, purified by prep-HPLC eluting with CH_3CN in water (with CH_3CN from 40% to 95% in 10 min (0.1% HCO_2H condition)) to give (1^1S,1^3R,*Z*)-4^3-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (126.9 mg, 60% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 389.1.

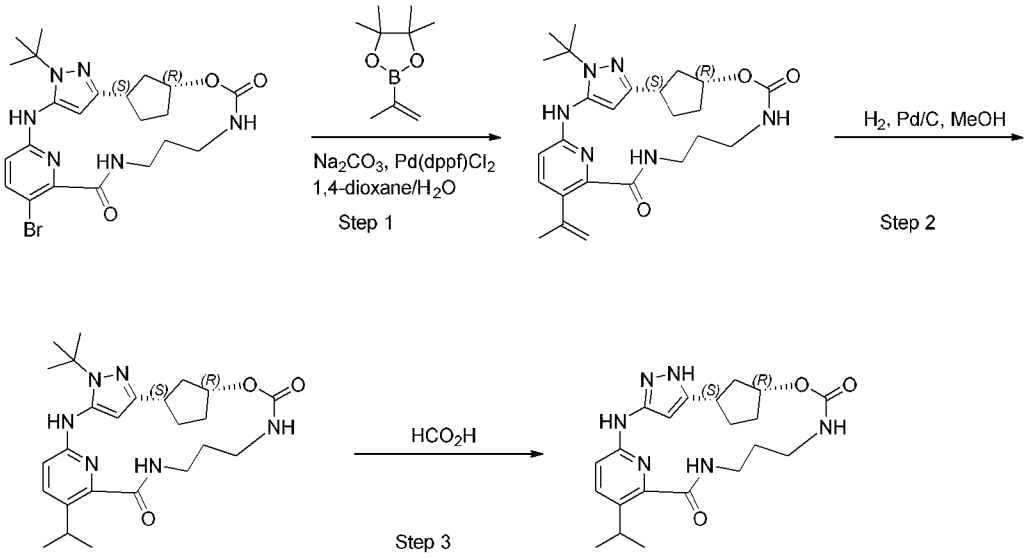
The following compounds were prepared using the similar procedure disclosed in synthetic example **131**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$

132		403.2
133		403.0
134		403.2
135		403.2
136		403.2
137		401.2

Example **138**

(1^1*S*,1^3*R*,*Z*)-4^5-isopropyl-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(prop-1-en-2-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a mixture of ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (100 mg, 198 μmol) in H_2O (0.15 mL) and 1,4-dioxane (1.5 mL) were sequentially added 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (133 mg, 791 μmol), Na_2CO_3 (52.4 mg, 495 μmol) and $Pd(dppf)Cl_2$ (28.9 mg, 39.6 μmol). The mixture was heated to 80 °C and stirred at that temperature under N_2 for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 15 to 70% in 15 min) to afford ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(prop-1-en-2-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80.0 mg, 86% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$ 467.3.

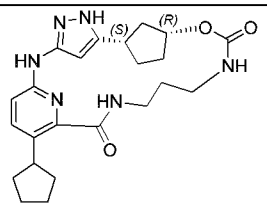
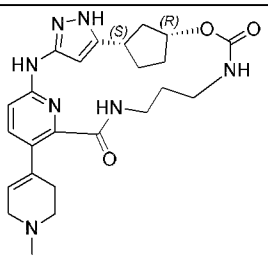
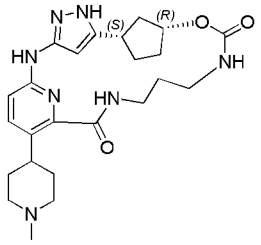
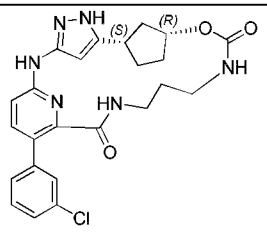
Step 2: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

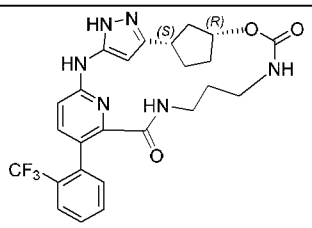
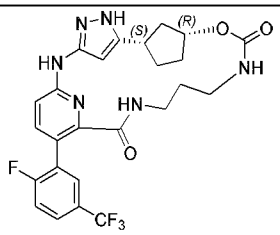
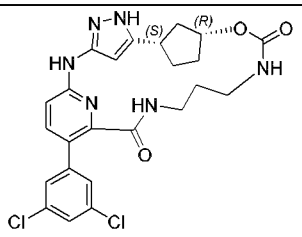
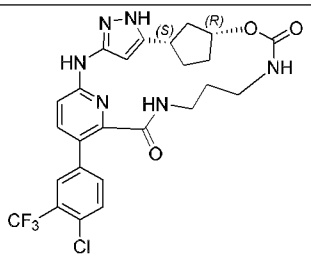
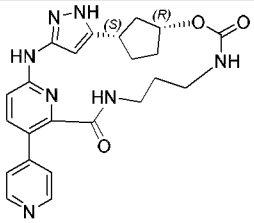
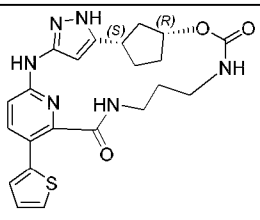
To a solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(prop-1-en-2-yl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (80.0 mg, 171 μmol) in MeOH (10.0 mL) was added Pd/C (40.0 mg, 50 wt.% in H_2O). The mixture was stirred for 2.5 h at 25 °C under H_2 atmosphere. The mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure to give the crude product as a yellow solid. LC-MS: m/z $[M+H]^+$ 469.3.

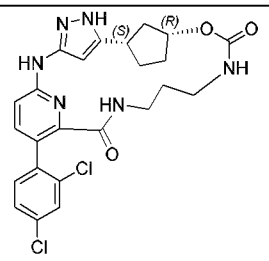
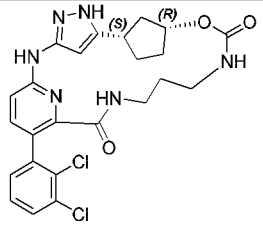
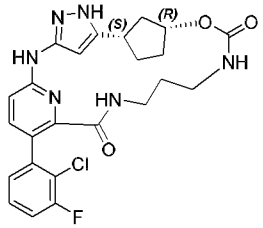
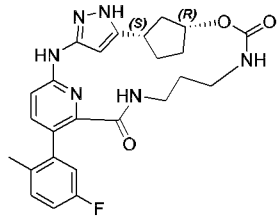
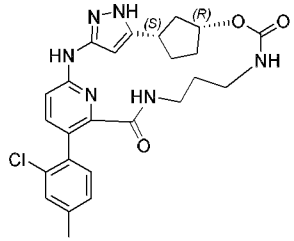
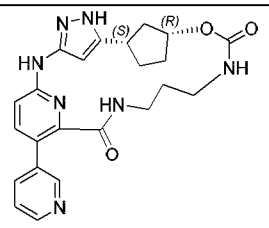
Step 3: ($1^1S,1^3R,Z$)-4^5-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

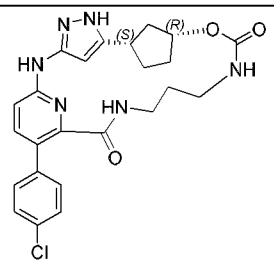
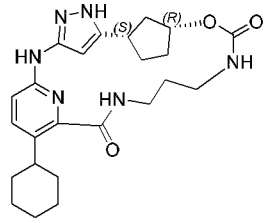
A mixture of crude ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione in HCO_2H (1.5 mL) was heated to 100 °C and stirred at that temperature for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was purified prep-HPLC eluting with CH_3CN in water (with CH_3CN from 20% to 40% in 30 min) to afford ($1^1S,1^3R,Z$)-4^5-isopropyl-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (34.0 mg, 47% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 413.2.

The following compounds were prepared using the similar procedure disclosed in synthetic example **138**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
139		439.1
140		466.3
141		468.1
142		481.1

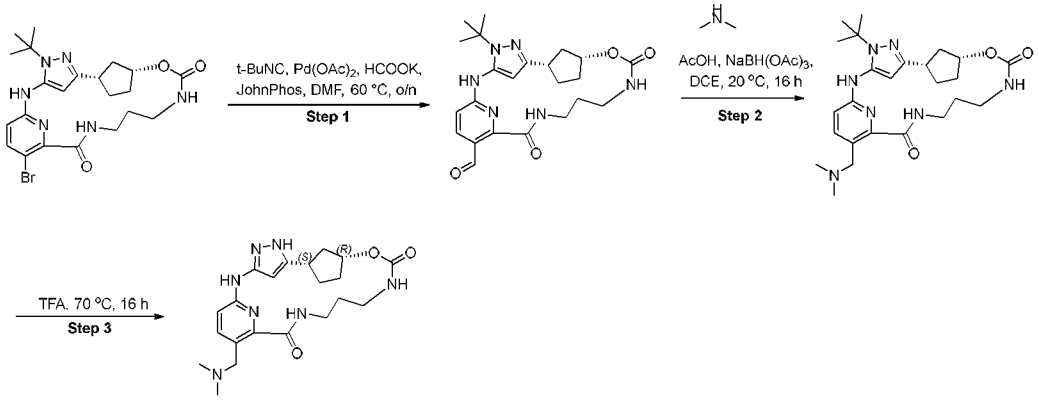
143		515.2
144		533.2
145		515.1
146		549.0
147		448.2
148		453.2

149		515.1
150		515.0
151		499.1
152		479.0
153		495.1
154		448.2

199		481.2
200		453.1

Example **198**

(1^1*S*,1^3*R*,*Z*)-4^5-((dimethylamino)methyl)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-5,11-dioxo-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbaldehyde

To a solution of (1^1*S*,1^3*R*,*Z*)-4^5-bromo-2^1-(*tert*-butyl)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (100 mg, 197.48 μmol) and t-BuNC (82.02 mg, 987.38 μmol) in DMF (4 mL) was added HCOOK (51.03 mg, 592.43 μmol), JohnPhos (5.89 mg, 19.75 μmol) and $Pd(OAc)_2$ (4.42 mg, 19.75 μmol) at 20 °C, and the mixture was stirred at 60 °C for 16 hours. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC to give (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-5,11-dioxo-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana cyclododecaphane-4^5-carbaldehyde (60 mg, 131.72 μmol, 66.70% yield) as a yellow oil. LC-MS: m/z 455.3 $[M+H]^+$.

Step 2: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-((dimethylamino)methyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

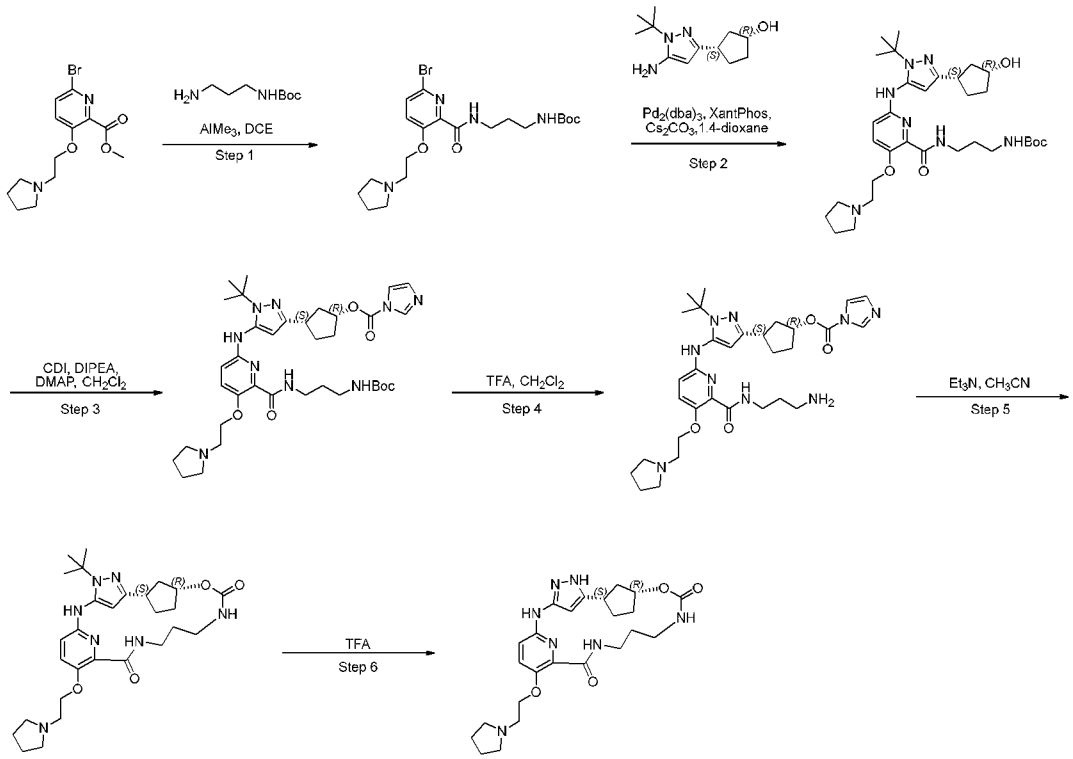
To a solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-5,11-dioxo-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-4^5-carbaldehyde (60 mg, 0.13 mmol) and N-methylmethanamine (660.04 μL, 1.32 mmol, 2 M in THF) in DCE (3 mL) was added AcOH (15.85 mg, 264.01 μmol) at 20 °C and stirred at 20 °C for 1 hour. Then $NaBH(OAc)_3$ (55.98 mg, 264.01 μmol) was added at 20 °C and stirred at 20 °C for 15 hours. The mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with DCM (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated to afford (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-((dimethylamino)methyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (15 mg, 31.02 μmol, 23.50% yield) as a yellow oil. LC-MS: m/z 484.3 $[M+H]^+$.

Step 3: (1^1S,1^3R,*Z*)-4^5-((dimethylamino)methyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-((dimethylamino)methyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (15 mg, 31.02 μmol) in TFA (1 mL) was stirred at 85 °C for 16 hours. The reaction solution was concentrated, the residue was diluted with DCM (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), dried over and concentrated under reduced pressure to give the residue. The residue was purified by Prep-HPLC (FA condition) to afford the product (1^1S,1^3R,*Z*)-4^5-((dimethylamino)methyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (5.9 mg, 13.56 μmol, 43.71% yield, 98.23% purity) as a pale yellow solid. LC-MS: m/z 428.2 $[M+H]^+$.

Example **155**

(1^1S,1^3R,*Z*)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl (3-(6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)picolinamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-aminopropyl)carbamate (1.43 g, 8.20 mmol) in DCE (10.0 mL) was added $AlMe_3$ (8.2 mL, 8.20 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was stirred at that temperature for 30 min before a solution of methyl 6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)picolinate (900 mg, 2.73 mmol) in DCE (5.0 mL) was added. The resulting mixture was warmed up to 20 °C and stirred at that temperature for 12 h before it was quenched with MeOH (3 mL). The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50% in 30 min) to give *tert*-butyl (3-(6-bromo-3-(2-(pyrrolidin-1-yl)ethoxy)picolinamido)propyl)carbamate as a pale yellow oil (0.95 g, 63% yield). LC-MS: m/z $[M+H]^+$ 471.1.

Step 2: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)picolinamido)propyl)carbamate

To a solution of (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (250 mg, 1.12 mmol) and *tert*-butyl *N*-[4-[[6-bromo-3-(2-pyrrolidin-1-ylethoxy)-2-pyridyl]amino]-4-oxo-butyl]carbamate (792 mg, 1.68 mmol) in 1,4-dioxane (2.0 mL) were sequentially added Cs_2CO_3 (730 mg, 2.24 mmol), $Pd_2(dba)_3$ (205 mg, 224 μmol) and XantPhos (194 mg, 336 μmol) at 20 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h under N_2 atmosphere. The reaction mixture was cooled to 20 °C, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 50% in 50 min) to

afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)picolinamido)propyl)carbamate (500 mg, 814.61 μmol, 72.77% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 614.4.

Step 3: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(2-(pyrrolidin-1-yl)ethoxy)picolinamido)propyl)carbamate (300 mg, 488.77 μmol) in CH_2Cl_2 (10.0 mL) were sequentially added CDI (238 mg, 1.47 mmol), DMAP (59.7 mg, 489 μmol) and DIEA (0.2 mL, 1.47 mmol, 148 mg) at 25 °C and the resulting mixture was stirred at that temperature for 12 h. The reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg) as a yellow oil which was directly used into the next step without further purification. LC-MS: m/z $[M+H]^+$ 708.3.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg, 0.42 mmol) in CH_2Cl_2 (5.0 mL) was added slowly TFA (2.0 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h before it was concentrated to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg) as a yellow oil which was directly used into the next step without further purification. LC-MS: m/z $[M+H]^+$ 608.3.

Step 5: (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

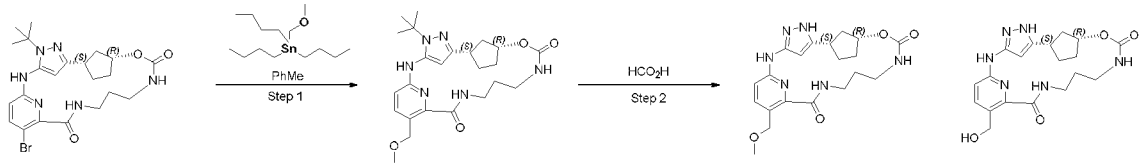
To a suspension of (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (300 mg, crude) in CH_3CN (5.0 mL) was added Et_3N (1.45 g, 14.4 mmol) at 20 °C. The reaction was warmed to 80 °C and stirred at that temperature for 3 h before it was cooled to 20 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 50% in 50 min) to afford (1^1*S*,1^3*R*,*Z*)-2^1-(*tert*-butyl)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (60.0 mg, 23% yield for 3 steps) as a pale yellow solid. LC-MS: m/z $[M+H]^+$ 540.3.

Step 6: ($1^1S,1^3R,Z$)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(2-(pyrrolidin-1-yl)ethoxy)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (60.0 mg, 0.11 mmol) in FA (4.0 mL) was stirred at 70 °C for 4 h before it was cooled to 20 °C and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 50% in 50 min) to afford (*rac,cis*)-($1^1S,1^3R,Z$)-2^1H-13-oxa-3,6,11-triaza-2(5,3)-triazola-4(1,3)-benzena-1(1,3)-cyclopentanacyclotridecaphane-5,12-dione (34.7 mg, 65% yield) as a pale yellow solid. LC-MS: m/z $[M+H]^+$ 484.0.

Example **156** and **157**

($1^1S,1^3R,Z$)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione and ($1^1S,1^3R,Z$)-4^5-(hydroxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a stirred solution of ($1^1S,1^3R,Z$)-4^5-bromo-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (100 mg, 198 μmol) and tributyl(methoxymethyl)stannane (133 mg, 396 μmol) in toluene (1.5 mL) was added $Pd(PPh_3)_4$ (22.9 mg, 19.8 μmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 16 h before it was cooled to 25 °C. The mixture was poured into H_2O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (EtOAc/PE = 2: 1) to give ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (40.0 mg, 43% yield) as a yellow oil. LC-MS: m/z $[M+H]^+$.471.3.

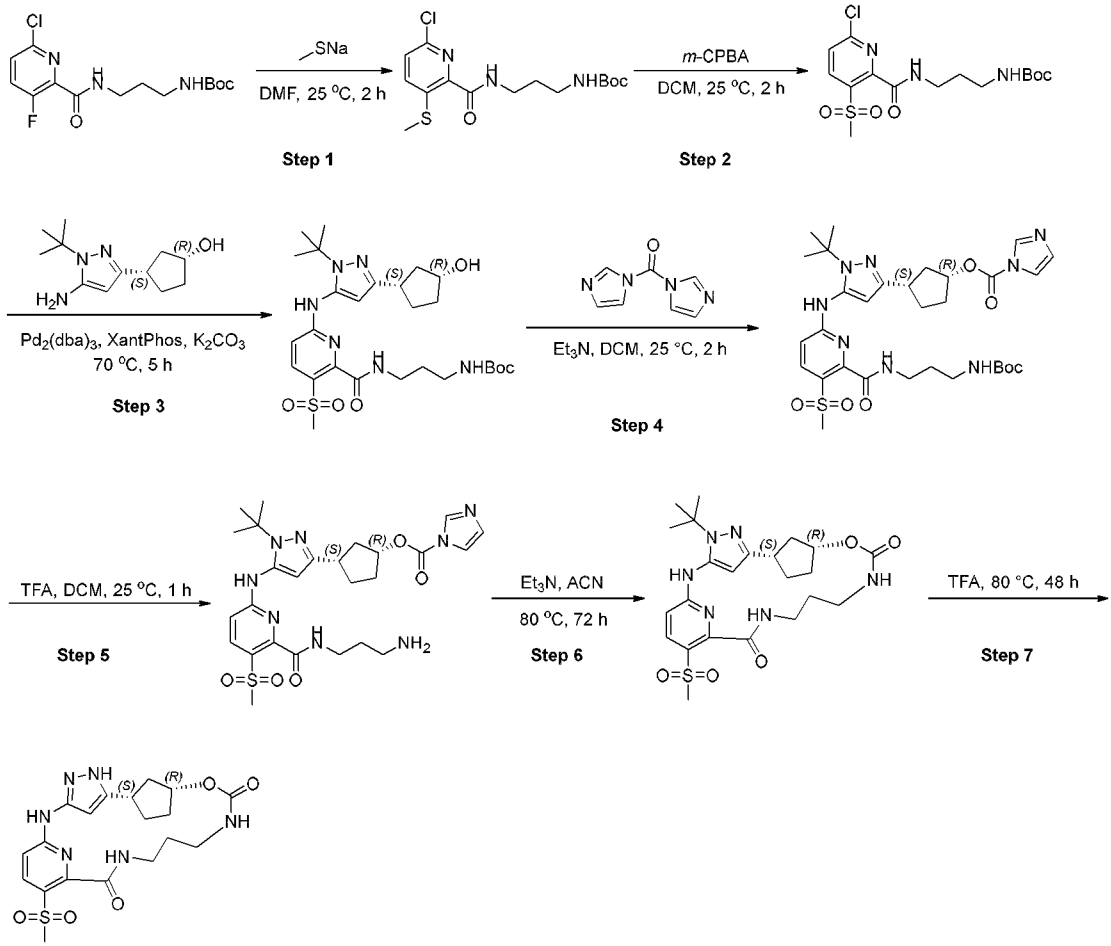
Step 2: ($1^1S,1^3R,Z$)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione and ($1^1S,1^3R,Z$)-4^5-(hydroxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A stirred solution of ($1^1S,1^3R,Z$)-2^1-(*tert*-butyl)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (40 mg, 85.00 μmol) in HCO_2H (1.0 mL) was warmed to 70 °C and stirred at that temperature for 16 h before it was cooled to

25 °C. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC HPLC eluting with CH_3CN in water (with CH_3CN from 0% to 45% in 40 min)to afford (1^1S,1^3R,Z)-4^5-(methoxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.9 mg, 5.3% yield) as a white solid LC-MS: m/z $[M+H]^+$ 415.2. And (1^1S,1^3R,Z)-4^5-(hydroxymethyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (2.4 mg, 6.4% yield) as a white solid. LC-MS: m/z 401.2 $[M+H]^+$.

Example **158**

(1^1S,1^3R,Z)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl (3-(6-chloro-3-(methylthio)picolinamido)propyl)carbamate

To a solution of *tert*-butyl (3-(6-chloro-3-fluoropicolinamido)propyl)carbamate (500 mg, 1.51 mmol) in DMF (5 mL) was added sodium;methanethiolate (105 mg, 1.51 mmol) at 25 °C. The reaction mixture was stirred at 20 °C for 1.5 hours. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum from 0% to 50%

to give *tert*-butyl (3-(6-chloro-3-(methylthio)picolinamido)propyl)carbamate (527 mg, 1.32 mmol, 87% yield, 90% purity) as a white solid. LC-MS: m/z 382.0 $[M+Na]^+$.

Step 2: *tert*-butyl (3-(6-chloro-3-(methylsulfonyl)picolinamido)propyl)carbamate

To a solution of *tert*-butyl (3-(6-chloro-3-(methylthio)picolinamido)propyl)carbamate (527 mg, 1.5 mmol) in DCM (8 mL) was added *m*-CPBA (758 mg, 4.3 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 3 hours. The reaction mixture was poured into saturated $NaHSO_3$ (50 mL). The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 x 50 mL). The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum from 0% to 50% to give tert-butyl (3-(6-chloro-3-(methylsulfonyl)picolinamido)propyl)carbamate (490 mg, 1.2 mmol, 81% yield, 95% purity) as a white solid. LC-MS: m/z 414.0 $[M+Na]^+$.

Step 3: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(methylsulfonyl)picolinamido)propyl)carbamate

To a solution of *tert*-butyl (3-(6-chloro-3-(methylsulfonyl)picolinamido)propyl)carbamate (263 mg, 671 μmol) in dioxane (40 mL) was added (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (150 mg, 671 μmol), K_2CO_3 (278 mg, 2.02 mmol), $Pd_2(dba)_3$ (61.5 mg, 67.2 μmol) and XantPhos (77.7 mg, 134 μmol) at 25 °C. The reaction mixture was stirred at 70 °C under N_2 for 5 hours. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH in DCM from 0% to 4% to give *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(methylsulfonyl)picolinamido)propyl)carbamate (237 mg, 368 μmol, 54% yield, 90% purity) as a yellow solid. LC-MS: m/z 579.2 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-(methylsulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-3-(methylsulfonyl)picolinamido)propyl)carbamate (144 mg, 248 μmol) in DCM (5 mL) was added di(imidazol-1-yl)methanone (121 mg, 746 μmol) and Et_3N (126 mg, 1.24 mmol, 173 μL) at 25 °C. The reaction mixture was stirred at 25 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum from 0% to 100% to give (1*R*,3*S*)-3-(5-((6-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)-5-(methylsulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-

pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, 237 μmol, 95% yield, 80% purity) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 673.3.

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)-5-(methylsulfonyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

[(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-5-methylsulfonyl-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, 297 μmol) was dissolved in TFA/DCM=1/1 (8 mL) then stirred at 25 °C under N_2 for 1 hours. The mixture was concentrated under reduced pressure to give [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-5-methylsulfonyl-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, 279 μmol, 93% yield, 80% purity) as a yellow oil, which was used directly in the next step without further purification. LC-MS: (ESI) m/z $[M+H]^+$:573.2.

Step 6: (1^1S,1^3R,*Z*)-21-(*tert*-butyl)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

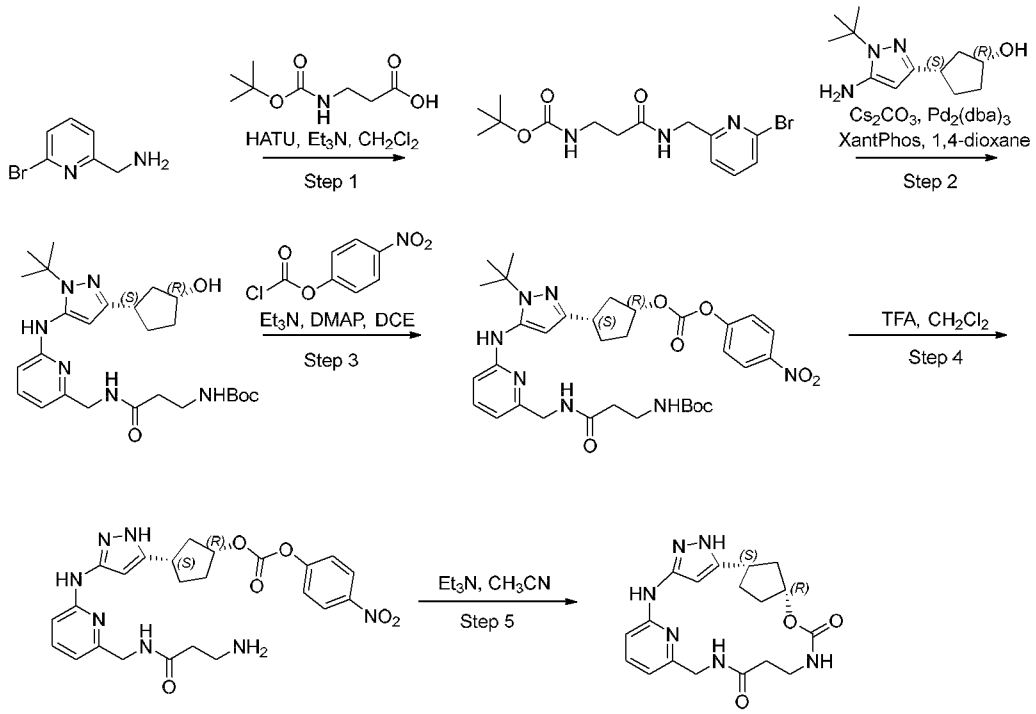
To a solution of [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-5-methylsulfonyl-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, 349 μmol) in ACN (80 mL) was added Et_3N (14 mL) at 25 °C. The reaction mixture was stirred at 80 °C for 72 hours. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc in petroleum from 0% to 100% to give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (150 mg, 297.26 μmol) as a yellow oil. LC-MS: (ESI) m/z $[M+H]^+$505.2.

Step 7: (1^1S,1^3R,*Z*)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

(1^1S,1^3R,*Z*)-21-(*tert*-butyl)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (180 mg, 356 μmol) was dissolved in TFA (8 mL) then stirred at 80 °C for 48 hours. The mixture was concentrated under reduced pressure. The residue was purified preparative reverse-phase HPLC (Column: Xbridge-C18, 250*21.2 mm 10 um; Mobile phase: MeCN-H_2O (0.1% FA); Gradient: 14% to 100%; Flow rate: 25 ml/min) to give (1^1S,1^3R,*Z*)-4^5-(methylsulfonyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (36.5 mg, 81.4 μmol, 23% yield) as a white solid. LC-MS: (ESI) m/z $[M+H]^+$ 449.0.

Example **159**

($1^1S,1^3R,Z$)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7,11-dione



Step 1: *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate

To a stirred solution of (6-bromopyridin-2-yl)methanamine (500 mg, 2.69 mmol) in CH_2Cl_2 (15.0 mL) were sequentially added 3-((*tert*-butoxycarbonyl)amino)propanoic acid (510 mg, 2.69 mmol), HATU (1.50 g, 4.04 mmol) and DIPEA (1.38 mL, 1.04 g, 8.07 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with water (30 mL). The organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 25 min) to afford *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate (800 mg, 83% yield) as a white solid. LC-MS: m/z [M+H]+ 357.9

Step 2: *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate

To a stirred suspension of *tert*-butyl (3-(((6-bromopyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate (200 mg, 560 μmol) in 1,4-dioxane (15.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-2-*tert*-butyl-pyrazol-3-yl)cyclopentanol (125 mg, 560 μmol), $Pd_2(dba)_3$ (51.0 mg, 56.0 μmol), XantPhos (65.0 mg, 112 μmol) and Cs_2CO_3 (550 mg, 1.68 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 85 % in 25 min) to afford

tert-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate (240 mg, 85% yield) as a yellow oil. LC-MS: m/z [M+H]+ 500.9

Step 3: *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate

To a stirred suspension of *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate (90.0 mg, 180 μmol) in DCE (15.0 ml) were added 4-nitrophenyl carbonochloridate (110 mg, 540 μmol), DMAP (13.0 mg, 110 μmol) and Et_3N (74 μL, 55 mg, 540 μmol). The reaction was warmed to 70 °C and stirred for 12 hours. Then the reaction mixture was quenched with ice-cold water (10 mL) and extracted with DCM (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate was used in the next step without further purification LC-MS: m/z [M+H]+ 665.7.

Step 4: (1*R*,3*S*)-3-(3-((6-((3-aminopropanamido)methyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate

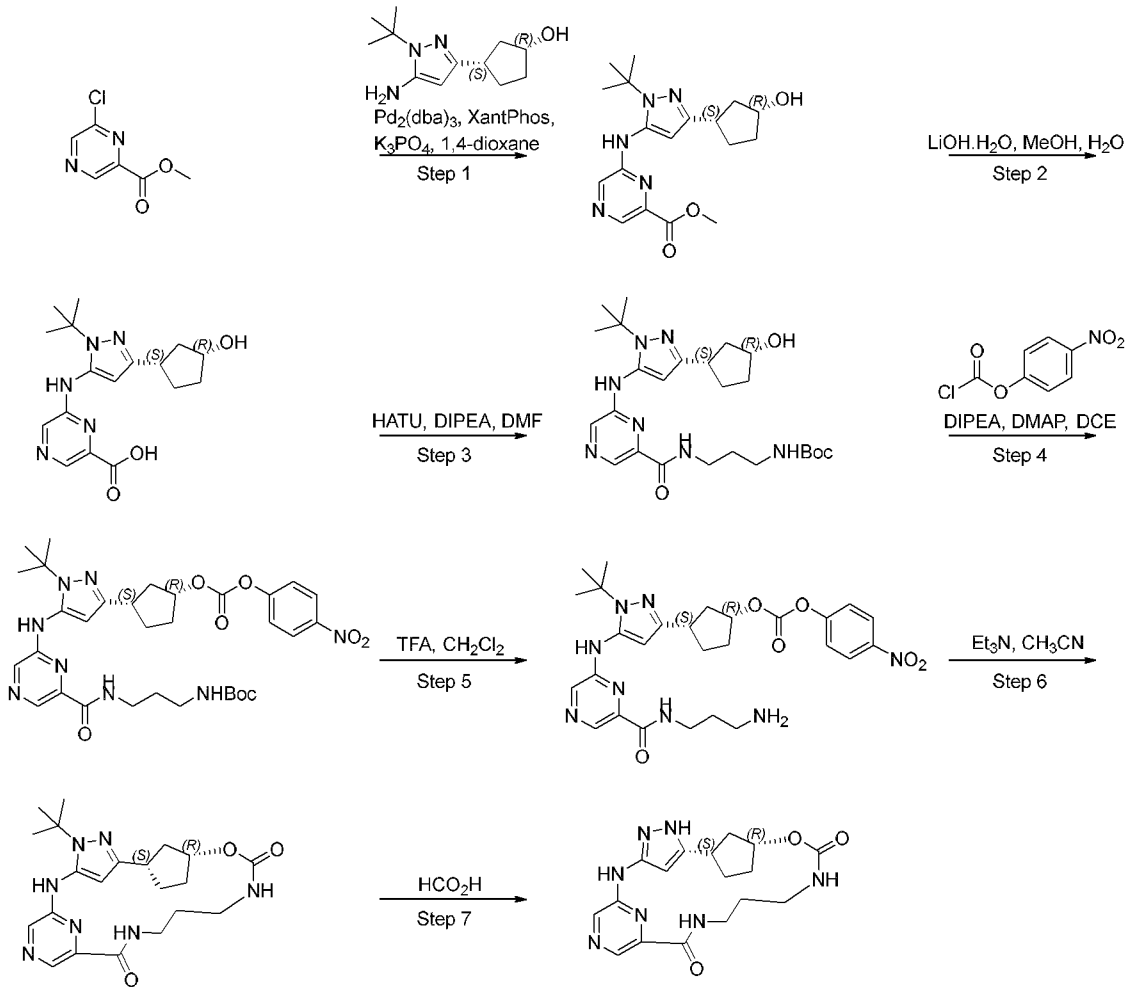
A solution of *tert*-butyl (3-(((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methyl)amino)-3-oxopropyl)carbamate in TFA (5.0 mL) was warmed to 100 °C and stirred at that temperature for 2 h. The mixture was concentrated under reduced pressure to give (1*R*,3*S*)-3-(3-((6-((3-aminopropanamido)methyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 509.8

Step 5: (1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7,11-dione

To a stirred solution of (1*R*,3*S*)-3-(3-((6-((3-aminopropanamido)methyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate in CH_3CN (5.0 mL) was added Et_3N (2.65 mL, 196 mg, 1.94 mmol). The reaction mixture was stirred at 25 °C for 2 h. Then it was concentrated and the residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 3% to 50% in 30 min) to afford (1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-7,11-dione (14.2 mg, 22% yield) as an off-white solid. LC-MS: m/z [M+H]+ 371.0.

Example **160**

($1^1S,1^3R,Z$)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: methyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazine-2-carboxylate

To a stirred suspension of methyl 6-chloropyrazine-2-carboxylate (500 mg, 2.91 mmol) in 1,4-dioxane (10.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentan-1-ol (648 mg, 2.91 mmol), $Pd_2(dba)_3$ (133 mg, 145 μmol), XantPhos (168 mg, 290 μmol) and K_3PO_4 (1.85 g, 8.73 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80 % in 25 min) to afford methyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxylate (300 mg, 29% yield) as a yellow solid. LC-MS: m/z [M+H]+ 360.2

Step 2: 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazine-2-carboxylic acid

To a suspension of methyl 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxylate (300 mg, 0.84 mmol) in MeOH/H_2O (5:1, 12.0 mL) was added $LiOH·H_2O$ (106 mg, 2.52 mmol) at 25 °C. The reaction mixture was warmed to 60 °C and stirred at that temperature for 12 h. The reaction mixture was concentrated and adjusted to pH = 2~3 with 2 M HCl and extracted with EtOAc (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxylic acid (240 mg, 82% yield) as a colorless oil. was used directly in the next step without further purification. LC-MS: m/z [M+H]+ 346.1

Step 3: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazine-2-carboxamido)propyl)carbamate

To a suspension of 6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxylic acid (240 mg, 0.69 mmol) in DMF (10.0 mL) was added *tert*-butyl (3-aminopropyl)carbamate (180 mg, 1.04 mmol), HATU (393 mg, 1.03 mmol) and DIPEA (356 μL, 269 mg, 2.07 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 20 min) to afford *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxamido) propyl) carbamate (200 mg, 58% yield) as a yellow oil LC-MS: m/z [M+H]+ 502.2

Step 4: *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazine-2-carboxamido)propyl)carbamate

To a stirred suspension of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxamido) propyl) carbamate (200 mg, 0.40 mmol) in DCE (10.0 mL) was added 4-nitrophenyl carbonochloridate (241 mg, 1.20 mmol), DMAP (24.0 mg, 200 μmol) and DIPEA (205 μL, 155 mg, 1.20 mmol) at 25 °C. The mixture was heated to 70 °C and stirred at that temperature for 12 h. The reaction mixture was quenched with water (30 mL). The organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30 % in 25 min) to give *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy) carbonyl) oxy) cyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxamido) propyl) carbamate (60.0 mg, 23% yield) as a yellow oil. LC-MS: m/z [M+H]+ 667.2

Step 5: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)pyrazin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

A solution of *tert*-butyl (3-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy) carbonyl) oxy) cyclopentyl)-1*H*-pyrazol-5-yl) amino) pyrazine-2-carboxamido) propyl) carbamate (60.0 mg, 0.90 mmol) in CH_2Cl_2 (10.0 mL) was added slowly TFA (2.0 mL) at 25 °C. The mixture was stirred at that temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)pyrazin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z [M+H]+ 567.2

Step 6: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

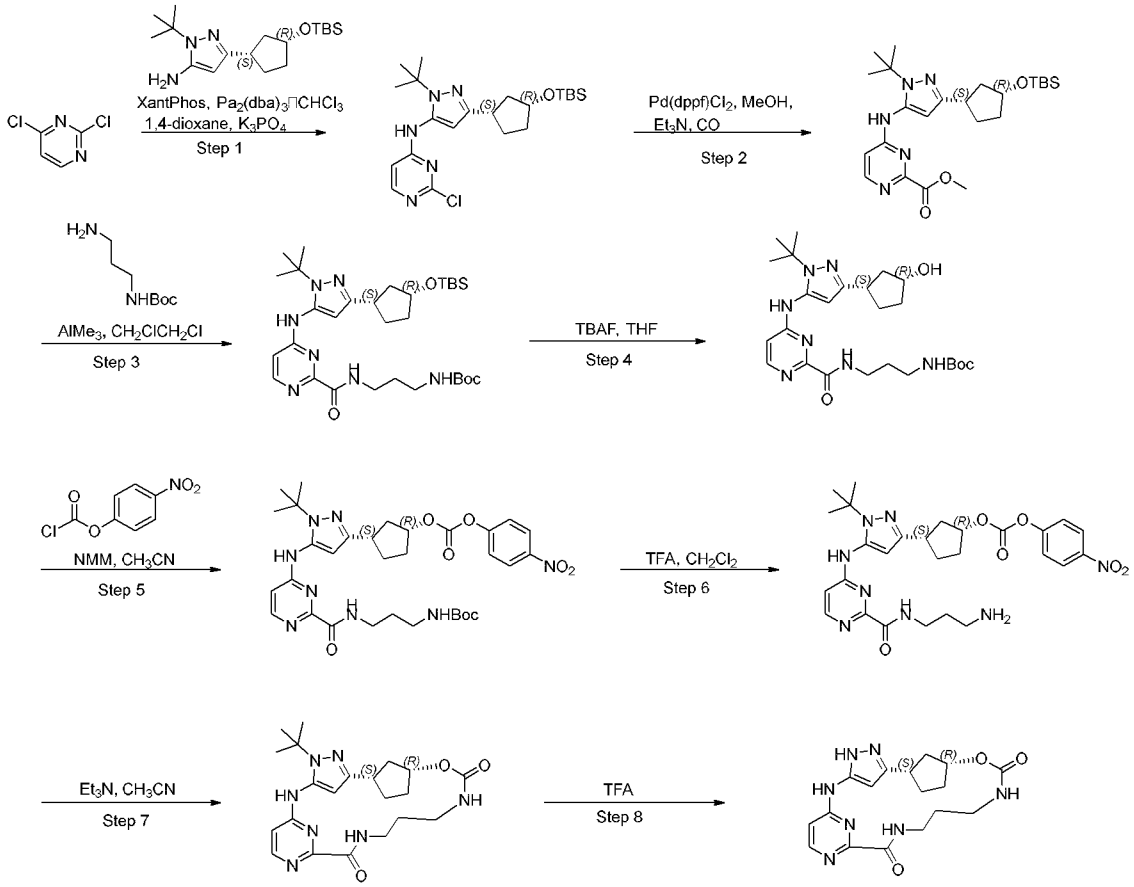
To a suspension of (1*R*,3*S*)-3-(5-((6-((3-aminopropyl) carbamoyl) pyrazin-2-yl) amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl) cyclopentyl (4-nitrophenyl) carbonate in CH_3CN (10.0 mL) was added Et_3N (170 μL, 122 mg, 1.21 mmol) at 25 °C. The reaction was stirred at that temperature for 2 h. The mixture was concentrated *in vacuo* to afford (1^1S,1^3R,*Z*)-21-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z [M+H]+ 428.2

Step 7: (1^1S,1^3R,*Z*)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A solution of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione in HCO_2H (5.0 mL) was warmed to 100 °C and stirred at that temperature for 5 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 65% in 20 min) to afford (1^1S,1^3R,*Z*)-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (6.2 mg, 18% yield) as a yellow solid. LC-MS: m/z [M+H]+ 372.1,

Example **161**

(1^1S,1^3R,*Z*)-2^1H-12-oxa-3,6,10-triaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *N*-(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)-2-chloropyrimidin-4-amine

To a stirred solution of 2,4-dichloropyrimidine (700 mg, 4.70 mmol) in 1,4-dioxane (50.0 mL) were sequentially added 1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-amine (1.10 g, 3.26 mmol), $Pa_2(dba)_3 \cdot CHCl_3$ (973 mg, 0.940 mmol), XantPhos (816 mg, 1.41 mmol) and K_3PO_4 (2.00 g, 9.40 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 16 h under N_2 atmosphere before it was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 20 min) to afford *N*-(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)-2-chloropyrimidin-4-amine (350 mg, impure) as a brown oil. LC-MS: m/z $[M+H]^+$ 450.2.

Step 2: methyl 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxylate

To a stirred solution of *N*-(1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)-2-chloropyrimidin-4-amine (250 mg, 555 μmol) in MeOH (15.0 mL) were sequentially added $Pd(dppf)Cl_2$ (81.3 mg, 111 μmol) and Et_3N (169 mg, 1.67 mmol) at 25 °C. The reaction

mixture was warmed to 100 °C and stirred at that temperature for 16 h under CO atmosphere. The reaction mixture was cooled to 25 °C, concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 20 min) to afford methyl 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxylate (80.0 mg, 30% yield) as a pale yellow oil. LC-MS: m/z $[M+H]^+$ 474.3.

Step 3: *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate

To a stirred solution of methyl 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxylate (95.0 mg, 201 μmol) in CH_2ClCH_2Cl (20.0 mL) were sequentially added *tert*-butyl (3-aminopropyl)carbamate (35.0 μL, 34.9 mg, 201 μmol) and TMA (28.9 mg, 401 μmol) at 20 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30 % in 25 min) to afford *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (70.0 mg, 57% yield) as a yellow oil. LC-MS: m/z $[M+1]^+$ 616.4.

Step 4: *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (70.0 mg, 114 μmol) in THF (5.0 mL) was added TBAF (44.6 mg, 170 μmol) at 25 °C. The reaction mixture was warmed to 40 °C and stirred at that temperature for 2 h. The reaction mixture was diluted with water (30 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 concentrate under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 20 min) to afford *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (45.0 mg, 78% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 502.1.

Step 5: *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (40.0 mg, 79.7 μmol) in CH_3CN (4.0 mL) were sequentially added NMM (17.5 μL, 16.1 mg, 159 μmol), 4-nitrophenyl carbonochloridate (48.2

mg, 239 μmol) and DMAP (9.74 mg, 79.7 μmol) 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was diluted with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrate under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 20 min) to afford *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (20.0 mg, 38% yield) as a pale light yellow solid. LC-MS: m/z $[M+H]^+$ 667.1.

Step 6: (1*R*,3*S*)-3-(5-((2-((3-aminopropyl)carbamoyl)pyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a solution of *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrimidine-2-carboxamido)propyl)carbamate (20.0 mg, 30.0 μmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at 20 °C. And the reaction mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to give (1*R*,3*S*)-3-(5-((2-((3-aminopropyl)carbamoyl)pyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate which was directly used for the next step without further purification. LC-MS: m/z $[M+H]^+$ 567.3.

Step 7: (1^1S,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-12-oxa-3,6,10-triaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

To a stirred solution of (1*R*,3*S*)-3-(5-((2-((3-aminopropyl)carbamoyl)pyrimidin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (crude) in CH_3CN (2.0 mL) was added TEA (499 μL, 363 mg, 3.59 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure. The ressidue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10% in 25 min) to afford (1^1S,1^3*R*,*Z*)-21-(*tert*-butyl)-2^1*H*-12-oxa-3,6,10-triaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.50 mg, 10% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 428.

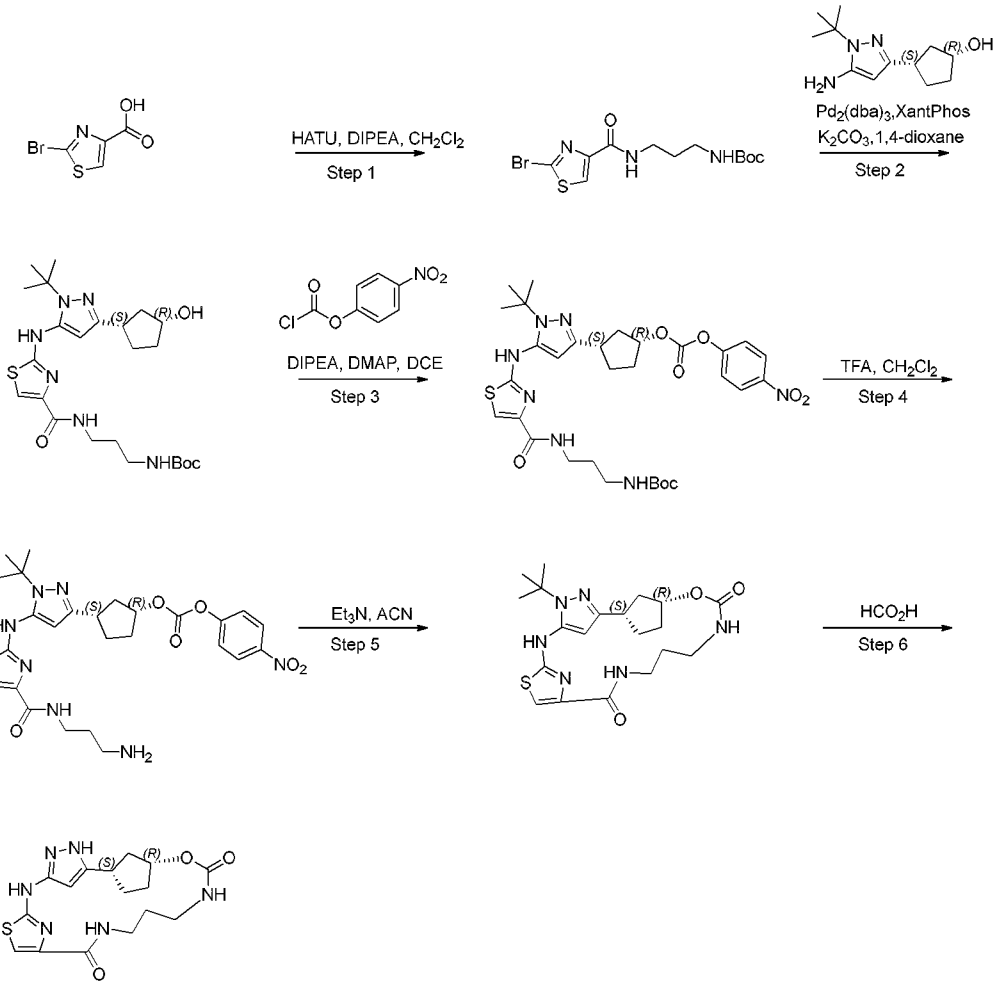
Step 8: (1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-3,6,10-triaza-4(4,2)-pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A solution of (1^1S,1^3*R*,*Z*)-2^1-(*tert*-butyl)-2^1*H*-12-oxa-3,6,10-triaza-4(4,2)-pyrimidina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.50 mg, 3.51 μmol) in TFA (3.0 mL) was warmed to 70 °C and stirred at that temperature for 16 h. The reaction mixture was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 50% in 40 min) to give (1^1*S*,1^3*R*,*Z*)-2^1*H*-12-oxa-3,6,10-triaza-4(4,2)-

pyrimidina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (0.900 mg, 69% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 372.2.

Example **162**

(1¹*S*,1³*R*,2⁴*Z*,4²*Z*)-2¹*H*-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: *tert*-butyl (3-(2-bromothiazole-4-carboxamido)propyl)carbamate

To a suspension of 2-bromothiazole-4-carboxylic acid (500 mg, 2.42 mmol) in CH_2Cl_2 (15.0 mL) was added tert-butyl (3-aminopropyl)carbamate (630 mg, 3.63 mmol), HATU (1.38 g, 3.63 mmol) and DIPEA (1.24 mL, 936 mg, 7.26 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 22 % in 20 min) to *tert*-butyl (3-(2-bromothiazole-4-carboxamido)propyl)carbamate (700 mg, 80% yield) as a white solid. LC-MS: m/z [M-55]+ 308.0.

Step 2: *tert*-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate

To a stirred solution of *tert*-butyl (3-(2-bromothiazole-4-carboxamido)propyl)carbamate (300 mg, 830 μmol) in 1,4-dioxane (10.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-2-*tert*-butyl-pyrazol-3-yl)cyclopentanol (185 mg, 830 μmol), $Pd_2(dba)_3$ (75.9 mg, 83.0 μmol), XantPhos (96.1 mg, 166 μmol) and K_2CO_3 (344 mg, 2.49 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 4 % in 25 min) to give *tert*-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate (150 mg, 36% yield) as a yellow oil. LC-MS: m/z [M+H]+ 507.3

Step 3: *tert*-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate

To a stirred suspension of *tert*-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate (150 mg, 290 μmol) in DCE (15.0 ml) was added 4-nitrophenyl carbonochloridate (175 mg, 870 μmol), DMAP (35.0 mg, 290 μmol) and DIPEA (149 μL, 112 mg, 870 μmol) at 25 °C. The mixture was heated to 70 °C and stirred at that temperature for 12 h. The reaction mixture was quenched with water (30 mL). The organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15 % in 25 min) to afford *tert*-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate (100 mg, 30% yield) as a yellow oil. LC-MS: m/z [M+H]+ 672.2

Step 4: (1*R*,3*S*)-3-(5-((4-((3-aminopropyl)carbamoyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a stirred solution of tert-butyl (3-(2-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)thiazole-4-carboxamido)propyl)carbamate (100 mg, 175 μmol) in CH_2Cl_2 (10.0 ml) was added TFA (396 μL, 586 mg, 5.14 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((4-((3-aminopropyl)carbamoyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate as a yellow oil, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 572.2

Step 5: (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

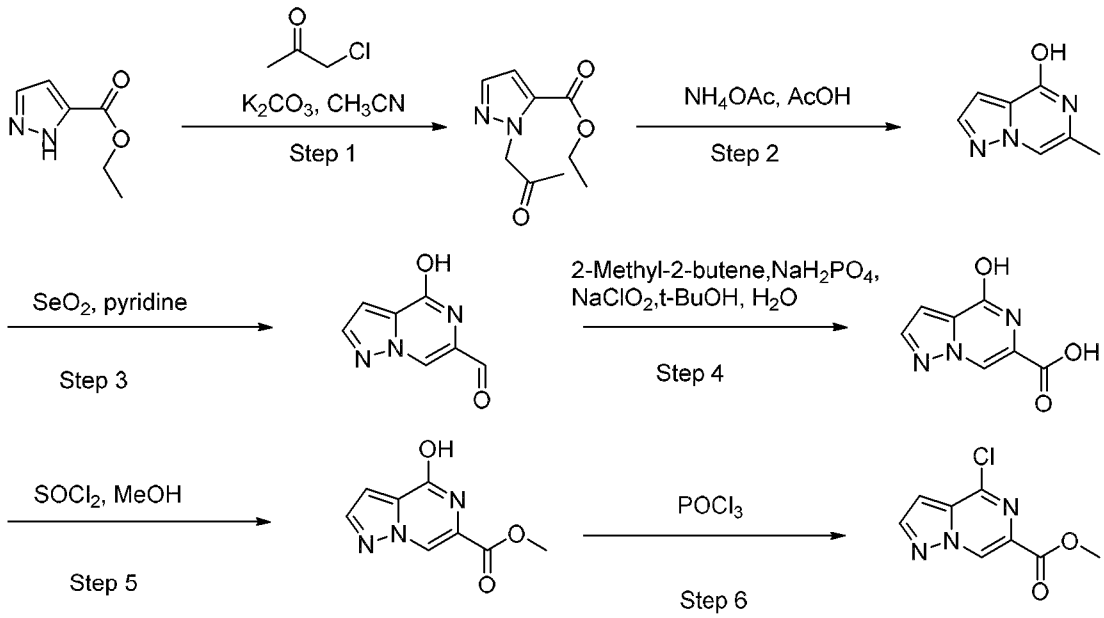
To a stirred suspension of (1*R*,3*S*)-3-(5-((4-((3-aminopropyl)carbamoyl)thiazol-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate in CH_3CN (10.0 mL) was added Et_3N (0.27 mL, 196 mg, 1.94 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated *in vacuo* to afford (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 433.1

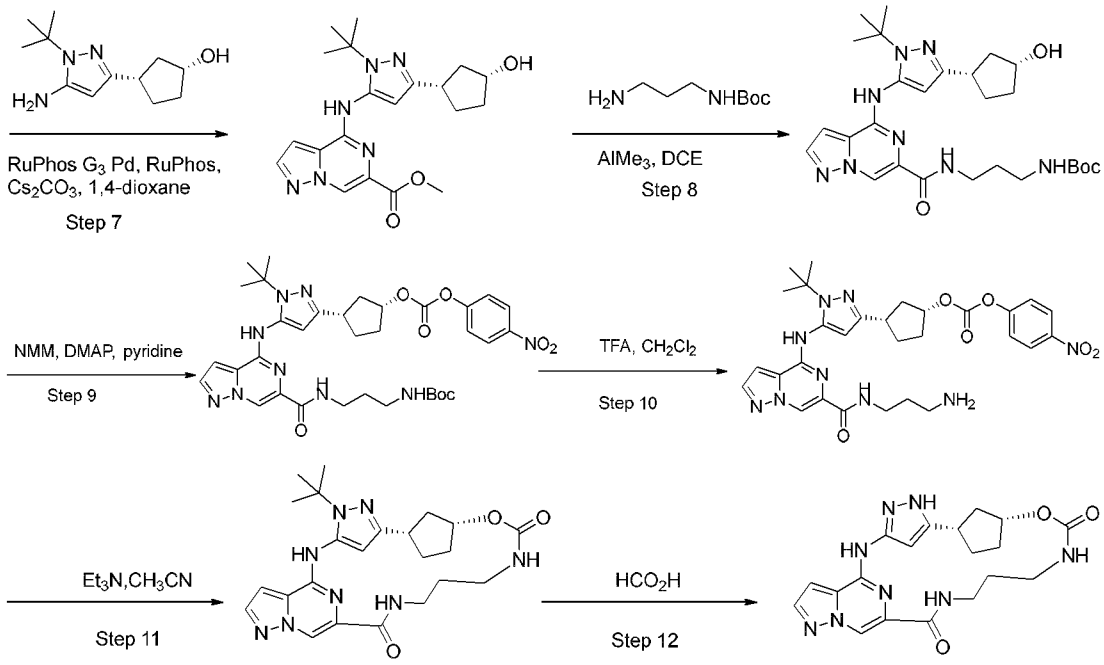
Step 6: (1^1S,1^3R,2^4Z,4^2Z)-2^1H-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A solution of (1^1S,1^3R,2^4Z,4^2Z)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione in HCO_2H (5.0 mL) was warmed to 100 °C and stirred at that temperature for 5 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 75% in 20 min) to afford (1^1S,1^3R,2^4Z,4^2Z)-2^1H-12-oxa-3,6,10-triaza-4(2,4)-thiazola-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.20 mg, 2% yield) as a white solid. LC-MS: m/z [M+H]+ 377.1.

Example **163**

(1^1S,1^3R,*E*)-2^4-fluoro-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione





Step 1: ethyl 1-(2-oxopropyl)-1H-pyrazole-5-carboxylate

To a suspension of ethyl 1*H*-pyrazole-5-carboxylate (5.5 g, 39.2 mmol) in CH_3CN (100 mL) was added K_2CO_3 (10.9 g, 78.5 mmol). The reaction was stirred at 25 °C for 16 h, before it was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10 % in 15 min) to afford ethyl 1-(2-oxopropyl)-1*H*-pyrazole-5-carboxylate (1.3 g, 18% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 197.2.

Step 2: 6-methylpyrazolo[1,5-a]pyrazin-4-ol

To a suspension of ethyl 1-(2-oxopropyl)-1*H*-pyrazole-5-carboxylate (1.0 g, 5.1 mmol) in AcOH (10.0 mL) was added NH_4OAc (3.93 g, 51.0 mmol). The reaction was stirred at 60 °C for 5 h, before it was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 10 % in 15 min) to afford 6-methylpyrazolo[1,5-a]pyrazin-4-ol (450 mg, 59% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 150.1.

Step 3: 4-hydroxypyrazolo[1,5-a]pyrazine-6-carbaldehyde

To a suspension of 6-methylpyrazolo[1,5-a]pyrazin-4-ol (450 mg, 3.02 mmol) in pyridine (5.0 mL) was added SeO_2 (669 mg, 6.03 mmol) . The reaction was stirred at 100 °C for 2 h, before it was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 5 % in 15 min) to afford 4-hydroxypyrazolo[1,5-a]pyrazine-6-carbaldehyde (220 mg, 44% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 164.0.

Step 4: 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylic acid

To a suspension of 4-hydroxypyrazolo[1,5-a]pyrazine-6-carbaldehyde (220 mg, 1.35 mmol) in t-BuOH (3.0 ml)/H_2O (1.0 mL) was added 2-methylbut-2-ene (284 mg, 4.05 mmol), NaH_2PO_4 (210 mg, 1.35 mmol) and $NaClO_2$ (366 mg, 4.05 mmol) . The reaction was stirred at 25 °C for 2 h, before it was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with $MeOH/CH_2Cl_2$ (with MeOH from 0 to 10 % in 10 min) to afford 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylic acid (200 mg, 82% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 180.1.

Step 5: methyl 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylate

A mixture of 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylic acid (100 mg, 0.558 mmol) in $SOCl_2$ (2.0 mL) was stirred for 2 h at 60 °C, before MeOH (2.0 mL) was added. The mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 5 % in 15 min) to afford methyl 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylate (100 mg, 92% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 194.2.

Step 6: methyl 4-chloropyrazolo[1,5-a]pyrazine-6-carboxylate

A mixture of *tert*-butyl (3-(6-((1-(*tert*-butyl)-4-fluoro-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)picolinamido)propyl)carbamate (70 mg, 0.102 mmol) in $POCl_3$ (2.0 mL) was stirred for 2 hours at 80 °C. The mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 5 % in 15 min) to afford methyl 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylate (100 mg, 92% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 212.1.

Step 7: methyl 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxylate

To a suspension of methyl 4-hydroxypyrazolo[1,5-a]pyrazine-6-carboxylate (70 mg, 310 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (69.28 mg, 310 μmol) in 1,4-dioxane (3.0 mL) was added RuPhos Pd G3 (25.9 mg, 31.0 μmol), RuPhos (28.9 mg, 62.1 μmol) and Cs_2CO_3 (202 mg, 620 μmol). The reaction was stirred at 100 °C for 16 h under N_2, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 35 % in 20 min) to give methyl 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxylate (50 mg, 40% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 399.2.

Step 8: *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate

To a suspension of 4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxylate (45 mg, 112 μmol) in DCE (2.0 mL) was added dropwise $AlMe_3$ in THF (0.16 mL, 2.0 M, 0.32 mmol). The reaction was stirred at 25 °C for 5 h under N_2, before it was filtered and concentrated *in vacuo*. The residue was purified by silica gel

chromatography eluting with EtOAc/PE (with EtOAc from 0 to 45 % in 20 min) to afford *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate (35 mg, 57% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 541.1.

Step 9: *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate

To a suspension of *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate (30 mg, 55.4 μmol) in CH_3CN (5.0 mL) was added 4-nitrophenyl carbonochloridate (33.5 mg, 166 μmol), DMAP (13.5 mg, 111 μmol) and NMM (30.5 μL, 28.1 mg, 277 μmol). The reaction was stirred at 25 °C for 16 h under N_2, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 50 % in 20 min) to give *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate (20 mg, 51% yield) as a yellow solid. LC-MS: m/z 705.9 $[M+H]^+$.

Step 10: (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)pyrazolo[1,5-a]pyrazin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

A mixture of *tert*-butyl (3-(4-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)pyrazolo[1,5-a]pyrazine-6-carboxamido)propyl)carbamate (20 mg, 28.3 μmol) in TFA (1.0 mL) was stirred for 1 h at 25 °C, before it was concentrated *in vacuo* to give crude (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)pyrazolo[1,5-a]pyrazin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 605.8.

Step 11: (1^1S,1^3R,2^4Z,4^4E)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(4,6)-pyrazolo[1,5-a]pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

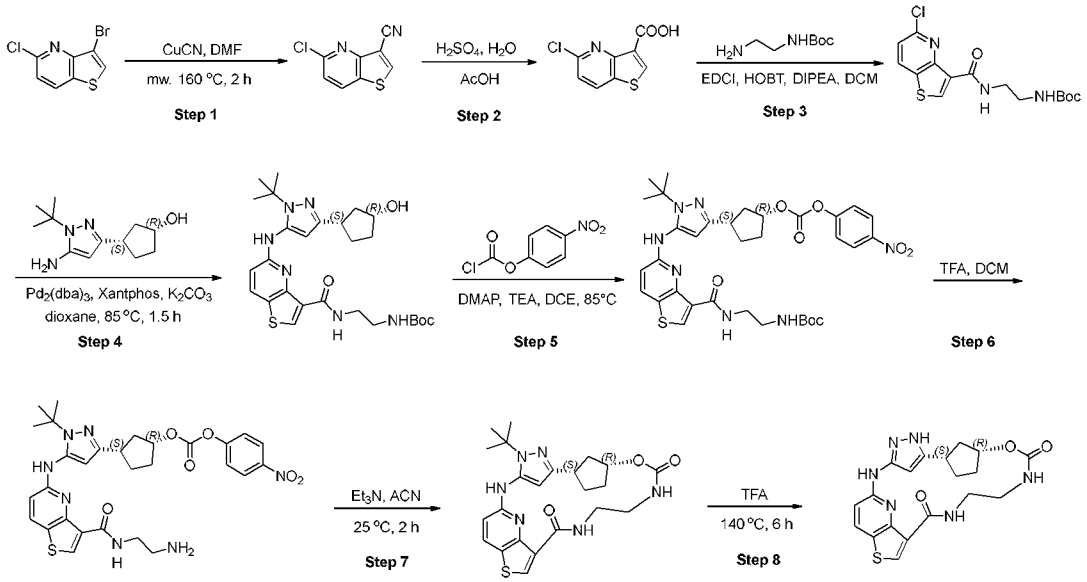
To a solution of (1*R*,3*S*)-3-(5-((6-((3-aminopropyl)carbamoyl)pyrazolo[1,5-a]pyrazin-4-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate in CH_3CN (1.0 mL) was added Et_3N (23μL, 16.7 mg, 165 μmol) at room temperature. The mixture was stirred at room temperature for 2 h, before it was concentrated *in vacuo* and purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 60 % in 20 min) to afford (1^1S,1^3R,2^4Z,4^4E)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(4,6)-pyrazolo[1,5-a]pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 26% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 466.9.

Step 12: (1^1S,1^3R,2^4Z,4^4E)-2^1H-12-oxa-3,6,10-triaza-4(4,6)-pyrazolo[1,5-a]pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of (1^1S,1^3R,2^4Z,4^4E)-2^1-(*tert*-butyl)-2^1H-12-oxa-3,6,10-triaza-4(4,6)-pyrazolo[1,5-a]pyrazina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 21.4 μmol) in HCO_2H (2.0 mL) was stirred at 80 °C for 2 h, before it was concentrated and purified by prep-HPLC eluting with CH_3CN in water (with CH_3CN from 15% to 40% in 10 min (0.1% FA condition)) to afford (1^1S,1^3R,2^4Z,4^4E)-2^1H-12-oxa-3,6,10-triaza-4(4,6)-pyrazolo[1,5-a]pyrazina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (1.3 mg, 14%) as a white solid. LC-MS: m/z $[M+H]^+$ 410.9.

Example **164**

(1^1S,1^3R,*Z*)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione



Step 1: 5-chlorothieno[3,2-*b*]pyridine-3-carbonitrile

To a suspension of 3-bromo-5-chloro-thieno[3,2-*b*]pyridine (100 mg, 402 μmol) in DMF (15 mL) at 25 °C was added CuCN (113 mg, 1.21 mmol). Then the reaction mixture was irradiated in a microwave reactor at 160 °C for 2 hours. The mixture was quenched with MeOH (5 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE form 0 to 50%, then it was purified by flash column chromatography eluting with methanol in dichloromethane from 0 to 5% to give 5-chlorothieno[3,2-*b*]pyridine-3-carbonitrile (78 mg, 401 μmol, 99% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 194.9.

Step 2: 5-chlorothieno[3,2-*b*]pyridine-3-carboxylic acid

To a suspension of 5-chlorothieno[3,2-*b*]pyridine-3-carbonitrile (100 mg, 514 μmol) in AcOH (2 mL) was added H_2O (2 mL) and H_2SO_4 (2 mL) at 25 °C. Then the reaction mixture was stirred at 110 °C for 12 hours in sealed tube. The reaction was quenched with water (30 mL), extracted with EtOAc

(3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 5-chlorothieno[3,2-*b*]pyridine-3-carboxylic acid (90 mg, 421μmol, 82% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 213.9.

Step 3: *tert*-butyl (2-(5-chlorothieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate

To a stirred solution of 5-chlorothieno[3,2-*b*]pyridine-3-carboxylic acid (90 mg, 421 μmol) in DCM (4 mL) was added tert-butyl *N*-(2-aminoethyl)carbamate (67.4 mg, 421 μmol), EDCI (162 mg, 843 μmol), HOBT (114 mg, 843 μmol) and DIPEA (163 mg, 1.26 mmol, 220 μL). The reaction mixture was stirred at 25°C for 12 hours. The reaction was quenched with addition of saturation water (20 mL), extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50%, tnen it was purified by flash column chromatography eluting with methanol in dichloromethane from 0 to 5% to give *tert*-butyl (2-(5-chlorothieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (130 mg, 365 μmol, 87% yield) as white solid. LC-MS: m/z $[M+H]^+$ 356.0.

Step 4: *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate

To a solution of *tert*-butyl (2-(5-chlorothieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (110 mg, 309 μmol) in dioxane (20 mL) was added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (69.0 mg, 309 μmol), Tris(Dibenzylideneacetone)Dipalladium(O) (56.6 mg, 61.8 μmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (71.5 mg, 123 μmol) and tripotassium;carbonate (128 mg, 927 μmol, 55.9 μL). The mixture was stirred for 12 hours at 100 °C in under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE formed 0 to 50%, then it was purified by flash column chromatography eluting with MeOH in DCM from 0 to 10% to give *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (152 mg, 280 μmol, 91% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 543.2.

Step 5: *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate

To a suspension of *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (130 mg, 239 μmol) in DCE (15 mL) was added slowly (4-nitrophenyl) carbonochloridate (145 mg, 718 μmol), DMAP (11.7 mg, 95.8 μmol) and DIPEA (309 mg, 2.40 mmol, 417 μL) at 25 °C and stirred for 24 h at 85 °C under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE form 0 to 50%, then it was purified by flash column chromatography eluting with methanol in dichloromethane from 0 to 5% to give *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-

yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (125 mg, 176 μmol, 74% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 708.2.

Step 6: (1*R*,3*S*)-3-(5-((3-((2-aminoethyl)carbamoyl)thieno[3,2-*b*]pyridin-5-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate

To a stirred solution of *tert*-butyl (2-(5-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1*H*-pyrazol-5-yl)amino)thieno[3,2-*b*]pyridine-3-carboxamido)ethyl)carbamate (100 mg, 141 μmol) in DCM (4 mL) at 25 °C was added Et_3N (4 mL). The reaction mixture was stirred at 25 °C for 0.5 hours. The resulting mixture was concentrated under reduced pressure. The crude product was used immediately in the next step without purification. LC-MS: m/z $[M+H]^+$ 608.1.

Step 7: (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione

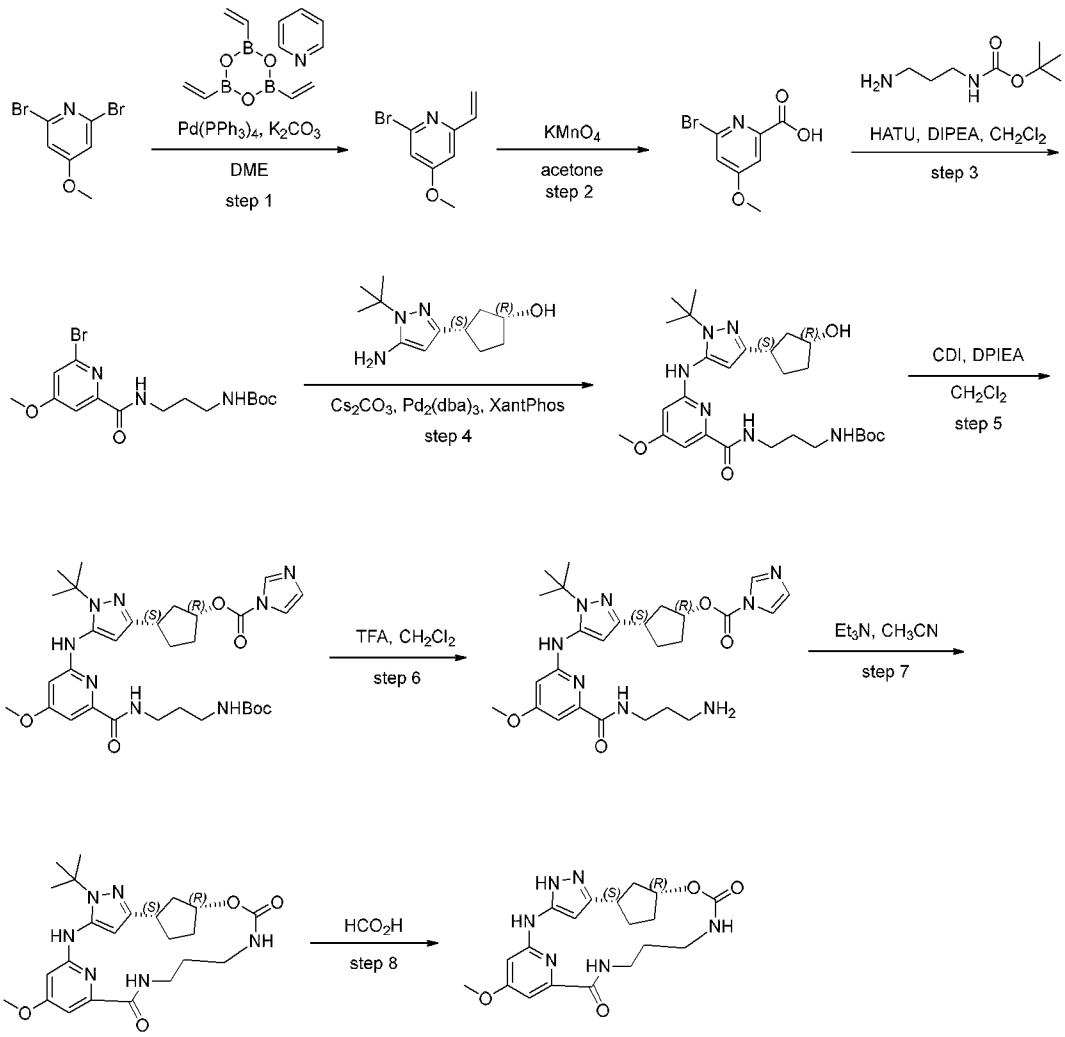
To a stirred solution of (1*R*,3*S*)-3-(5-((3-((2-aminoethyl)carbamoyl)thieno[3,2-*b*]pyridin-5-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl (4-nitrophenyl) carbonate (85 mg, 139 μmol) in CH_3CN (30 mL) at 25 °C was added Et_3N (5 mL). The reaction mixture was stirred at 25 °C for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc in PE from 0 to 50%, then it was purified by flash column chromatography eluting with MeOH in DCM from 0 to 5% to give (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (65 mg, 139 μmol, 99% yield). LC-MS: m/z $[M+H]^+$ 469.1.

Step 7: (1^1S,1^3R,*Z*)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione

A suspension of (1^1S,1^3R,*Z*)-2^1-(*tert*-butyl)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (65 mg, 138 μmol) at 25 °C and stirred for 6 h at 140 °C under N_2. The resulting mixture was concentrated under reduced pressure. The product was further purified by prep-HPLC (C18, 30-40% MeCN in 0.1% FA/water, 25 mL/min) to give (1^1S,1^3R,*Z*)-2^1H-11-oxa-3,6,9-triaza-4(5,3)-thieno[3,2-*b*]pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacycloundecaphane-5,10-dione (21 mg, 50.91 μmol, 36.70% yield). LC-MS: m/z $[M+H]^+$ 413.0.

Example **165**

(1^1S,1^3R,*Z*)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione



Step 1: 2-bromo-4-methoxy-6-vinylpyridine

To a suspension of 2,6-dibromo-4-methoxy-pyridine (500 mg, 1.87 mmol) in DME (15.0 mL) was added aq. K_2CO_3 (1.72 mL, 2 M, 3.37 mmol), 1-(2,4,6-trivinyl-1,3,5-trioxa-4,6-dibora-2-boranuidacyclohex-2-yl)pyridin-1-ium (270 mg, 1.12 mmol) and $Pd(PPh_3)_4$ (43.3 mg, 0.037 mmol) at room temperature. The mixture was warmed to 85 °C and stirred at that temperature for 2 hours under N_2, before it was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15% in 20 min) to afford 2-bromo-4-methoxy-6-vinyl-pyridine (320 mg, 79% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 213.9.

Step 2: 6-bromo-4-methoxypicolinic acid

To a suspension of 2-bromo-4-methoxy-6-vinyl-pyridine (320 mg, 1.49 mmol) in acetone (15.0 mL) was added $KMnO_4$ (472 mg, 2.99 mmol) at 0 °C and stirred for 10 min before it was warmed to 25

°C. The mixture was stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was filtered, the solid was washed with water and acetone and the filtrate was concentrated. The residue was dissolved in 10% aq. citric acid solution and extracted with EtOAc (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 6-bromo-4-methoxy-pyridine-2-carboxylic acid (300 mg, 86% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 231.8.

Step 3: *tert*-butyl *N*-[3-[(6-bromo-4-methoxy-pyridine-2-carbonyl)amino]propyl]carbamate

To a suspension of 6-bromo-4-methoxy-pyridine-2-carboxylic acid (280 mg, 1.21 mmol) in CH_2Cl_2 (10.0 mL) was sequentially added *tert*-butyl *N*-(3-aminopropyl)carbamate (210 mg, 1.21 mmol), HATU (917mg, 2.41 mmol) and DIPEA (419 µL, 311 mg, 2.41 mmol) at 25 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 30% in 25 min) to afford *tert*-butyl *N*-[3-[(6-bromo-4-methoxy-pyridine-2-carbonyl)amino]propyl]carbamate (300 mg, 64% yield) as a yellow solid. LC-MS: m/z $[M-55]^+$ 331.8.

Step 4: *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-methoxy-pyridine-2-carbonyl]amino]propyl]carbamate

To a suspension of *tert*-butyl *N*-[3-[(6-bromo-4-methoxy-pyridine-2-carbonyl)amino]propyl]carbamate (280 mg, 0.721 mmol) in 1,4-dioxane (15.0 mL) was sequentially added (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (161 mg, 0.721 mmol), Cs_2CO_3 (705 mg, 2.16 mmol), XantPhos (83.5 mg, 0.144 mmol) and $Pd_2(dba)_3$ (66.0 mg, 0.072 mmol) at room temperature. The reaction was warmed to 100 °C and stirred at that temperature for 16 h under N_2, before it was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/PE (with EtOAc from 0 to 80% in 30 min) to afford *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-methoxy-pyridine-2-carbonyl]amino]propyl]carbamate (200 mg, 52% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 530.9.

Step 5: [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of *tert*-butyl *N*-[3-[[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-4-methoxy-pyridine-2-carbonyl]amino]propyl]carbamate (200 mg, 0.376 mmol) in CH_2Cl_2 (10.0 mL) was added CDI (162 mg, 1.13 mmol) and DIPEA (327 µL, 243 mg, 1.88 mmol) at 35 °C and stirred for 2 h. After completion of the reaction as judged by LCMS, reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

pressure to afford [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 624.9.

Step 6: [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate

To a suspension of [(1*R*,3*S*)-3-[5-[[6-[3-(*tert*-butoxycarbonylamino)propylcarbamoyl]-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate in CH_2Cl_2 (3.0 mL) was added slowly TFA (1.0 mL, 12.9 mmol) at 25 °C and stirred for 1 h. After completion of the reaction as judged by LCMS, reaction mixture was concentrated under reduced pressure to afford [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) as a yellow oil. The crude product was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 525.0.

Step 7: (1^1S,1^3R,*Z*)-21-(*tert*-butyl)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

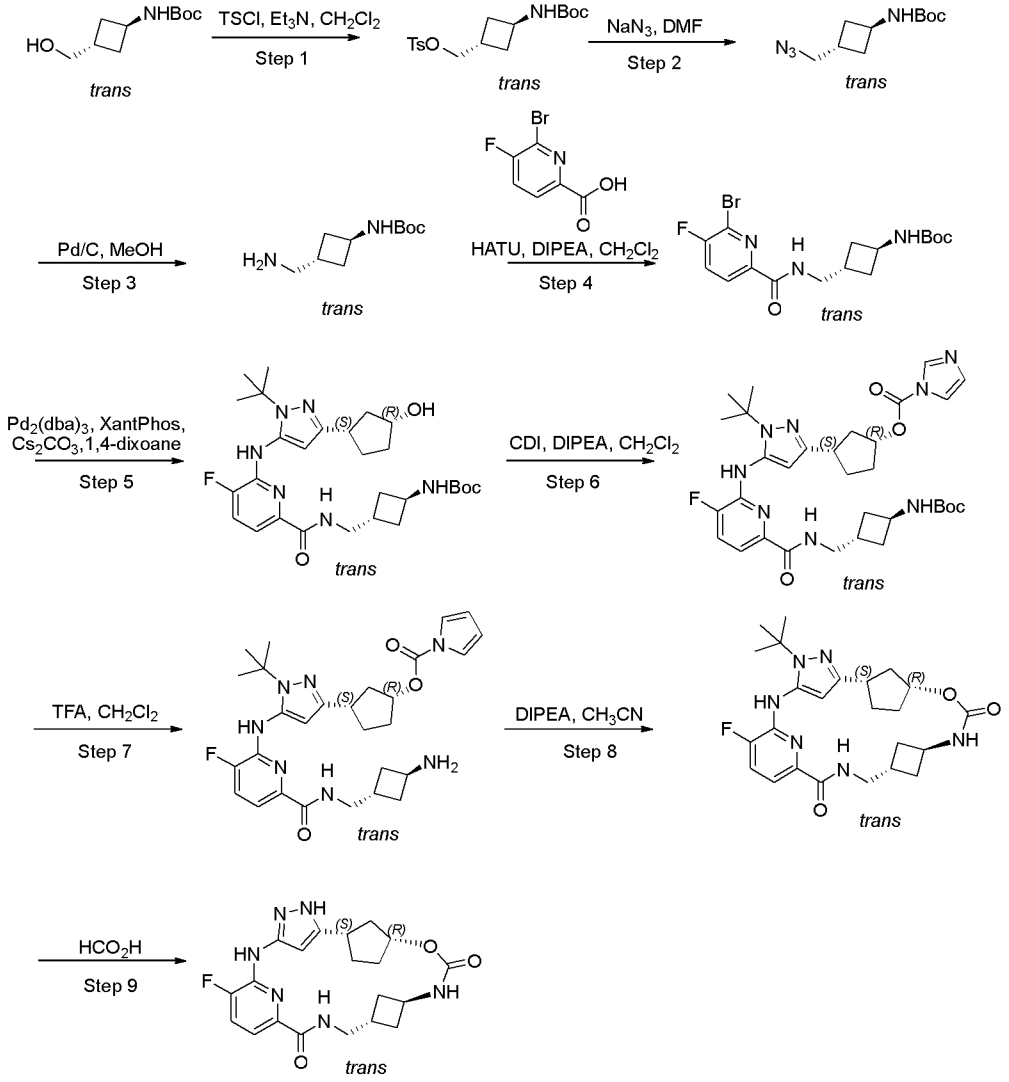
To a suspension of [(1*R*,3*S*)-3-[5-[[6-(3-aminopropylcarbamoyl)-4-methoxy-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (crude) in CH_3CN (3.0 mL) was added Et_3N (397 µL, 289 mg, 2.86 mmol). The reaction was warmed to 80 °C and stirred at that temperature for 16 h, before it was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10% in 20 min) to afford (1^1S,1^3R,*Z*)-21-(*tert*-butyl)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (85 mg) as a yellow solid. LC-MS: m/z $[M+H]^+$ 457.0.

Step 8: (1^1S,1^3R,*Z*)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione

A mixture of (1^1S,1^3R,*Z*)-21-(*tert*-butyl)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (20.0 mg, 0.043 mmol) in HCO_2H (2.0 mL) was stirred for 5 h at 100 °C, until the reaction was complete as indicated by LCMS, the reaction mixture was concentrated under reduced pressure, purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 15% to 50% in 10 min (0.1% HCO_2H condition)) to give the desired product (1^1S,1^3R,*Z*)-4^4-methoxy-2^1H-12-oxa-3,6,10-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentanacyclododecaphane-5,11-dione (6.6 mg, 37% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 401.2.

Example **166**

($1^1S,1^3R,8^1R,8^3S,Z$)-4^3-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione



Step 1: ((1*r*,3*r*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl 4-methylbenzenesulfonate

To a suspension of *tert*-butyl ((1*r*,3*r*)-3-(hydroxymethyl)cyclobutyl)carbamate (1.0 g, 4.97 mmol) in CH_2Cl_2 (15.0 mL) was added TsCl (1.89 g, 9.95 mmol), Et_3N (1.98 mL, 1.50 g, 14.9 mmol) at 0 °C. The reaction mixture was warmed to 25 °C and stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 12 % in 20 min) to afford ((1*r*,3*r*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl 4-methylbenzenesulfonate (1.50 g, impure) as a yellow solid. LC-MS: m/z $[M+Na]^+$ 378.0

Step 2: *tert*-butyl ((1*r*,3*r*)-3-(azidomethyl)cyclobutyl)carbamate

To a stirred solution of ((1*r*,3*r*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl 4-methylbenzenesulfonate (1.50 g, impure) in DMF (20.0 mL) was added NaN_3 (1.65 g, 25.3 mmol) at 25 °C. The reaction mixture was warmed to 120 °C and stirred at that temperature for 1 h. The solution was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford *tert*-butyl ((1*r*,3*r*)-3-(azidomethyl)cyclobutyl)carbamate (900 mg, crude) as a yellow oil. LC-MS: m/z [M - 55] 171.0

Step 3: *tert*-butyl ((1*r*,3*r*)-3-(aminomethyl)cyclobutyl)carbamate

To a stirred suspension of *tert*-butyl ((1*r*,3*r*)-3-(azidomethyl)cyclobutyl)carbamate in MeOH (15.0 mL) was added Pd/C (900 mg, 10 wt.% in H_2O) at 25 °C. The reaction mixture was stirred at that temperature for 2 h under hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to give *tert*-butyl ((1*r*,3*r*)-3-(aminomethyl)cyclobutyl)carbamate, which was used directly in the next step without further purification.

Step 4: *tert*-butyl ((1*r*,3*r*)-3-((6-bromo-5-fluoropicolinamido)methyl)cyclobutyl)carbamate

To a stirred solution of 6-bromo-5-fluoropicolinic acid (400 mg, 1.83 mmol) in CH_2Cl_2 (10.0 ml) was added *tert*-butyl ((1*r*,3*r*)-3-(aminomethyl)cyclobutyl)carbamate (400 mg, crude), HATU (1.04 g, 2.75 mmol) and DIPEA (940 µL, 708 mg, 5.49 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 15 % in 20 min) to afford *tert*-butyl ((1*r*,3*r*)-3-((6-bromo-5-fluoropicolinamido)methyl)cyclobutyl)carbamate (600 mg, 82% yield) as a yellow solid LC-MS: m/z $[M + Na]^+$ 424.0.

Step 5: *tert*-butyl ((1*S*,3*r*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropicolinamido)methyl)cyclobutyl)carbamate

To a stirred solution of *tert*-butyl ((1*r*,3*r*)-3-((6-bromo-5-fluoropicolinamido)methyl)cyclobutyl)carbamate (400 mg, 1.00 mmol) in 1,4-dioxane (10.0 mL) were sequentially added (1*R*,3*S*)-3-(5-amino-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (224 mg, 1.00 mmol), $Pd_2(dba)_3$ (100 mg, 100 µmol), XantPhos (116 mg, 200 µmol) and Cs_2CO_3 (978 mg, 3.00 mmol) at 25 °C. The reaction mixture was warmed to 100 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 82 % in 25 min) to afford *tert*-butyl ((1*S*,3*r*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropicolinamido)methyl)cyclobutyl)carbamate (430 mg, 79% yield) as a yellow solid. LC-MS: m/z [M+H]+ 544.9

Step 6: (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred suspension of *tert*-butyl ((1*S*,3*r*)-3-((6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)-5-fluoropicolinamido)methyl)cyclobutyl)carbamate (430 mg, 790 μmol) in CH_2Cl_2 (10.0 mL) were sequentially added CDI (384 mg, 2.37 mmol) and DIPEA (675 μL, 509 mg, 3.95 mmol) at 25 °C. The reaction mixture was stirred at that temperature for 2 h before it was quenched with ice-cold water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate was used directly in the next step without further purification. LC-MS: m/z $[M+H]^+$ 639.3

Step 7: (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-aminocyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a stirred solution of (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (10.0 ml) was added TFA (396 μL, 586 mg, 5.14 mmol) at 25 °C. The mixture was stirred at that temperature for 1 h before it was concentrated under reduced pressure to afford (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-aminocyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate as a brown oil, which was used in the next step without further purification. LC-MS: m/z $[M+H]^+$ 539.3

Step 8: (1^1S,1^3R,8^1R,8^3S,*Z*)-2^1-(*tert*-butyl)-43-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione

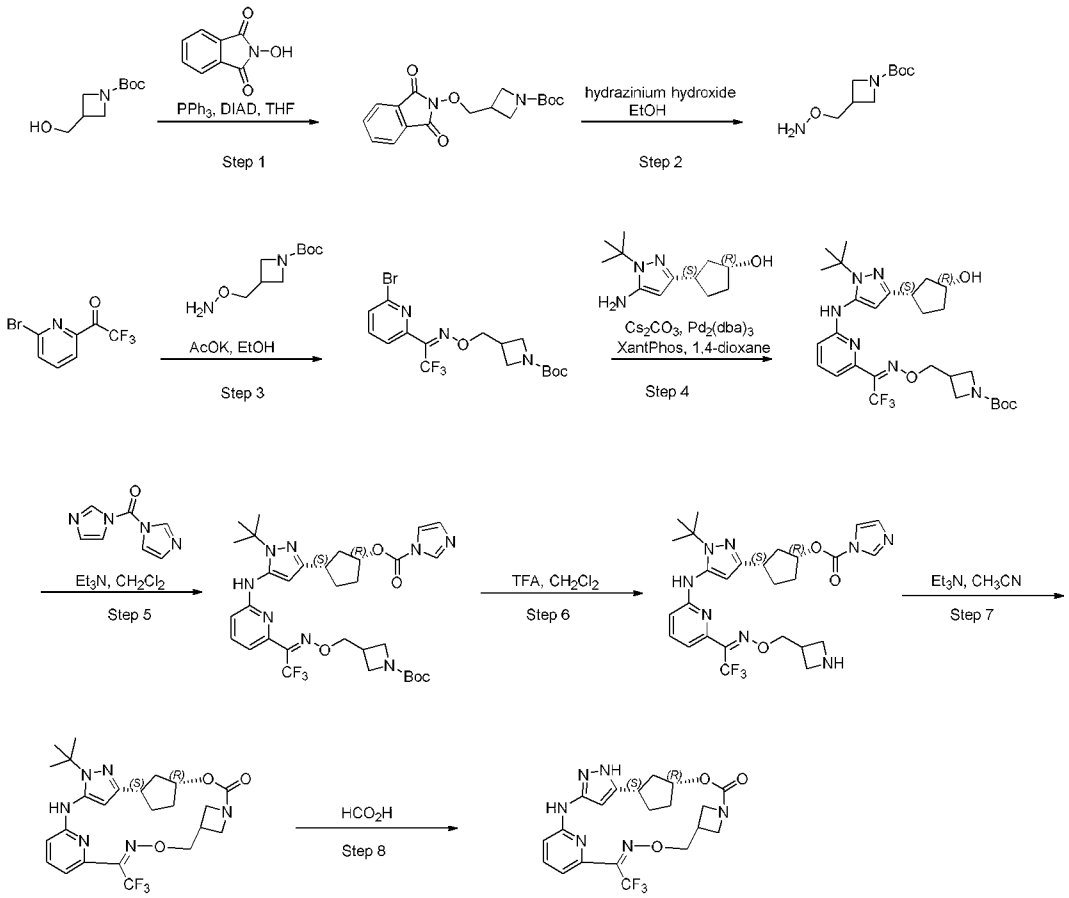
To a stirred solution of (1*R*,3*S*)-3-(5-((6-((((1*r*,3*S*)-3-aminocyclobutyl)methyl)carbamoyl)-3-fluoropyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (5.0 mL) was added Et_3N (269 μL, 196 mg, 1.94 mmol) at 25 °C. The reaction mixture was warmed to 80 °C and stirred at that temperature for 12 h. The reaction mixture was cooled to 25 °C, filtered and concentrated under reduced pressure. Then it was concentrated to afford (1^1S,1^3R,8^1R,8^3S,*Z*)-2^1-(*tert*-butyl)-43-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione, which was used in the next step without further purification. LC-MS: m/z [M+H]+ 471.3

Step 9: (1^1S,1^3R,8^1R,8^3S,*Z*)-43-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione

A solution of (1^1S,1^3R,8^1R,8^3S,*Z*)-2^1-(*tert*-butyl)-43-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(3,5)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione in HCO_2H (5.0 mL) was warmed to 50 °C and stirred at that temperature for 12 h before it was cooled, concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 5% to 65% in 20 min) to afford (1^1S,1^3R,8^1R,8^3S,*Z*)-43-fluoro-2^1H-11-oxa-3,6,9-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentana-8(1,3)-cyclobutanacycloundecaphane-5,10-dione (36.5 mg, 9% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 415.2.

Example **167**

(1^1S,1^3R,2^4Z,5*Z*)-5-(trifluoromethyl)-2^1H-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one



Step 1: *tert*-butyl 3-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)azetidine-1-carboxylate

A solution of 2-hydroxyisoindoline-1,3-dione (1.60 g, 9.81 mmol), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (1.84 g, 9.81 mmol) and PPh_3 (3.09 g, 11.8 mmol) in THF (20.0 mL) was cooled down to 0 °C under N_2 before DIAD (2.3 mL, 2.38 g, 11.7 mmol) was added to the mixture dropwise. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with EA (50 mL) and washed with water (20 mL × 3). The organic layers were dried over Na_2SO_4 and

concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 10 to 50 % in 15 min) to afford *tert*-butyl 3-[(1,3-dioxoisoindolin-2-yl)oxymethyl]azetidine-1-carboxylate (3.00 g, 92% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 277.0.

Step 2: *tert*-butyl 3-((aminooxy)methyl)azetidine-1-carboxylate

To a suspension of *tert*-butyl 3-[(1,3-dioxoisoindolin-2-yl)oxymethyl]azetidine-1-carboxylate (3.00 g, 9.18 mmol) in EtOH (50.0 mL) was added slowly hydrazinium hydroxide (2.2 mL, 2.30 g, 45.9 mmol). The mixture was heated to 80 °C and stirred at that temperature for 3 h. The reaction mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH/CH_2Cl_2 (with MeOH from 0 to 10 % in 15 min) to afford *tert*-butyl 3-(aminooxymethyl)azetidine-1-carboxylate (1.50 g, 70% yield) as a colorless oil. LC-MS: m/z $[M+H]^+$147.1.

Step 3: *tert*-butyl (*Z*)-3-((((1-(6-bromopyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate

A suspension of 1-(6-bromo-2-pyridyl)-2,2,2-trifluoro-ethanone (350 mg, 1.38 mmol), *tert*-butyl 3-(aminooxymethyl)azetidine-1-carboxylate (507 mg, 1.38 mmol) and CH_3COOK (406 mg, 4.13 mmol) in EtOH (10.0 mL) was heated to 80 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 0 to 20 % in 15 min) to afford *tert*-butyl (*Z*)-3-((((1-(6-bromopyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate (520 mg, 86% yield) as a colorless oil. LC-MS: m/z $[M+Na]^+$ 460.

Step 4: *tert*-butyl 3-(((((*Z*)-1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate

To a mixture of *tert*-butyl (*Z*)-3-((((1-(6-bromopyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate (520 mg, 1.19 mmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl)cyclopentanol (159 mg, 710 μmol) in 1,4-dioxane (5.0 mL) were sequentially added $Pd_2(dba)_3$ (109 mg, 120 μmol), XantPhos (137 mg, 240 μmol) and Cs_2CO_3 (1.16 g, 3.56 mmol). The mixture was heated to 100 °C and stirred at that temperature under N_2 for 6 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 30 to 60 % in 15 min) to afford *tert*-butyl 3-(((((*Z*)-1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate (650 mg, 94% yield) as yellow solid. LC-MS: m/z $[M+H]^+$ 581.3.

Step 5: (1*R*,3*S*)-3-(5-((6-((*Z*)-1-(((1-(*tert*-butoxycarbonyl)azetidin-3-yl)methoxy)imino)-2,2,2-trifluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a mixture of *tert*-butyl 3-(((((*Z*)-1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)-2,2,2-trifluoroethylidene)amino)oxy)methyl)azetidine-1-carboxylate (650 mg, 1.12 mmol) in CH_2Cl_2 (10.0 mL) were sequentially added CDI (363 mg, 2.24 mmol) and Et_3N (780 μL, 566 mg, 5.60 mmol). The mixture was heated to 40 °C and stirred at that temperature for 16 h. The reaction mixture was washed with water (10 mL × 2) and dried over Na_2SO_4, concentrated under reduced pressure to give the crude product as pale yellow oil. LC-MS: m/z $[M+H]^+$ 675.3.

Step 6: (1*R*,3*S*)-3-(5-((6-((*Z*)-1-((azetidin-3-ylmethoxy)imino)-2,2,2-trifluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a suspension of crude (1*R*,3*S*)-3-(5-((6-((*Z*)-1-(((1-(*tert*-butoxycarbonyl)azetidin-3-yl)methoxy)imino)-2,2,2-trifluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_2Cl_2 (6.0 mL) was added slowly TFA (2.0 mL, 2.96 g, 25.9 mmol) at 25 °C and stirred for 30 min. The reaction mixture was concentrated under reduced pressure. The crude product was used for next step without further purification. LC-MS: m/z $[M+H]^+$ 575.3.

Step 7: (1^1S,1^3R,2^4Z,5*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one

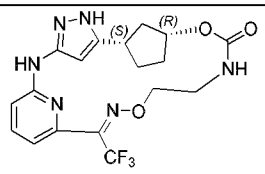
To a mixture of (1*R*,3*S*)-3-(5-((6-((*Z*)-1-((azetidin-3-ylmethoxy)imino)-2,2,2-trifluoroethyl)pyridin-2-yl)amino)-1-(*tert*-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate in CH_3CN (100 mL) was added Et_3N (1.46 mL, 1.06 g, 10.4 mmol) at 25 °C. The mixture was heated to 80 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc/PE (with EtOAc from 40 to 90 % in 15 min) to afford (1^1S,1^3R,2^4Z,5*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one (365 mg, 69% yield) as a yellow solid. LC-MS: m/z $[M+H]^+$ 507.2.

Step 8: (1^1S,1^3R,2^4Z,5*Z*)-5-(trifluoromethyl)-2^1H-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one

A mixture of (1^1S,1^3R,2^4Z,5*Z*)-2^1-(*tert*-butyl)-5-(trifluoromethyl)-2^1H-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(3,5)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one (365 mg, 721 μmol) in HCO_2H (2.0 mL) was heated to 100 °C and stirred at that temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with CH_3CN in water (with CH_3CN from 20% to 50% in 30 min) to afford (1^1S,1^3R,2^4Z,5*Z*)-5-

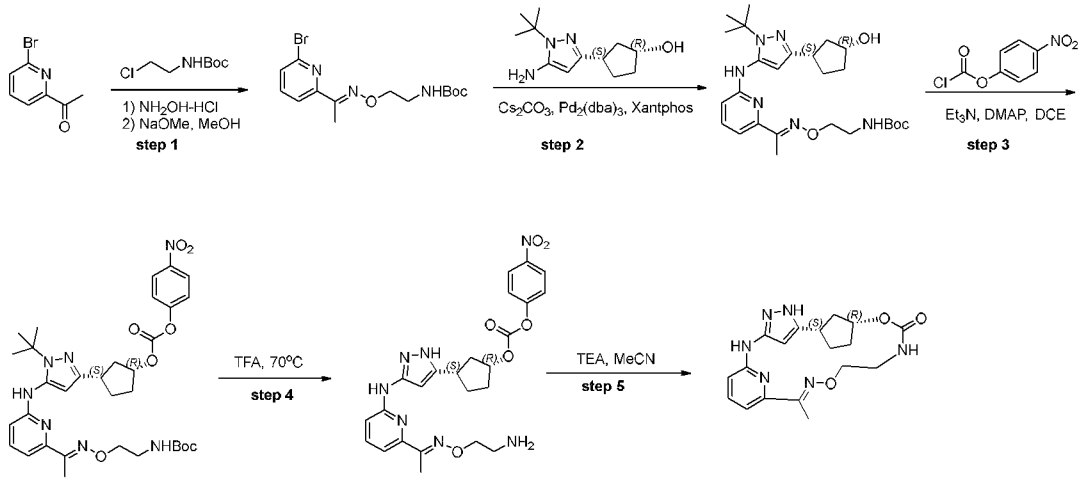
(trifluoromethyl)-2[1]*H*-7,11-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-9(3,1)-azetidina-1(1,3)-cyclopentanacycloundecaphan-5-en-10-one (132 mg, 40% yield) as a white solid. LC-MS: m/z $[M+H]^+$ 451.2.

The following compounds were prepared using the similar procedure disclosed in synthetic example **167**.

Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
168		424.8

Example **169**

(11S,13R,24Z,5E)-5-methyl-21H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one



Step 1: tert-butyl (E)-(2-(((1-(6-bromopyridin-2-yl)ethylidene)amino)oxy)ethyl)carbamate

To a solution of 1-(6-bromo-2-pyridyl) ethanone (1.0 g, 5.0 mmol) and tert-butyl N-(2-chloroethyl)carbamate (1.0 g, 6.0 mmol) in DMSO (25 mL) and H_2O (10 mL) was added hydroxylamine hydrochloride (416 mg, 6.0 mmol) and KOH (2.4 g, 43.0 mmol) at 25°C, The reaction was stirred under nitrogen atmosphere at 80 °C for 6 h. The mixture was quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0 to 40% EtOAc in PE to afford tert-butyl N-[2-[(E)-1-(6-bromo-2-pyridyl)ethylideneamino]oxyethyl]carbamate (1.3 g, 72% yield) as yellow oil. LC-MS: m/z 358.0 $[M+H]^+$.

Step 2: tert-butyl (2-((((E)-1-(6-((1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)ethylidene)amino)oxy)ethyl)carbamate

To a mixture of tert-butyl N-[2-[(E)-1-(6-bromo-2-pyridyl) ethylideneamino] oxyethyl] carbamate (600 mg, 1.6 mmol) and (1R,3S)-3-(5-amino-1-tert-butyl-pyrazol-3-yl) cyclopentanol (486 mg, 2.1 mmol) in 1,4-dioxane (30 mL) was added $Pd_2(dba)_3$ (306 mg, 335 umol), XantPhos (387 mg, 670 μmol) and Cs_2CO_3 (1.36 g, 4.19 mmol) at 25 °C under nitrogen, The reaction was stirred at 90 °C for 6 h.The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0 to 40% EtOAc in PE to afford tert-butyl (2-((((E)-1-(6-((1-(tert-butyl)-3-((1S,3R)-3-hydroxycyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)ethylidene)amino)oxy)ethyl)carbamate (790 mg, 94% yield) as yellow oil. LC-MS: m/z 501.3 $[M+H]^+$.

Step 3: tert-butyl (2-((((E)-1-(6-((1-(tert-butyl)-3-((1S,3R)-3-(((4-nitrophenoxy)carbonyl)oxy)cyclopentyl)-1H-pyrazol-5-yl)amino)pyridin-2-yl)ethylidene)amino)oxy)ethyl)carbamate

A mixture of tert-butyl N-[2-[(E)-1-[6-[[2-tert-butyl-5-[(1S,3R)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]ethylideneamino]oxyethyl]carbamate (100 mg, 200 μmol), 4-Nitrophenyl chloroformate (121 mg, 599 μmol), Et_3N (101 mg, 999 μmol) and DMAP (12 mg, 100 μmol) in DCE (5 mL) was stirred at 70 °C for 12 h. The mixture was diluted with water (50 mL) and extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0 to 30% EtOAc in PE to afford [(1R,3S)-3-[5-[[6-[(E)-N-[2-(tert-butoxycarbonylamino)ethoxy]-C-methyl- carbonimidoyl]-2-pyridyl]amino]-1-tert-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (60 mg, 45% yield) as yellow oil. LC-MS: m/z 666.3 $[M+H]^+$.

Step 4: (1R,3S)-3-(3-((6-((E)-1-((2-aminoethoxy)imino)ethyl)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate

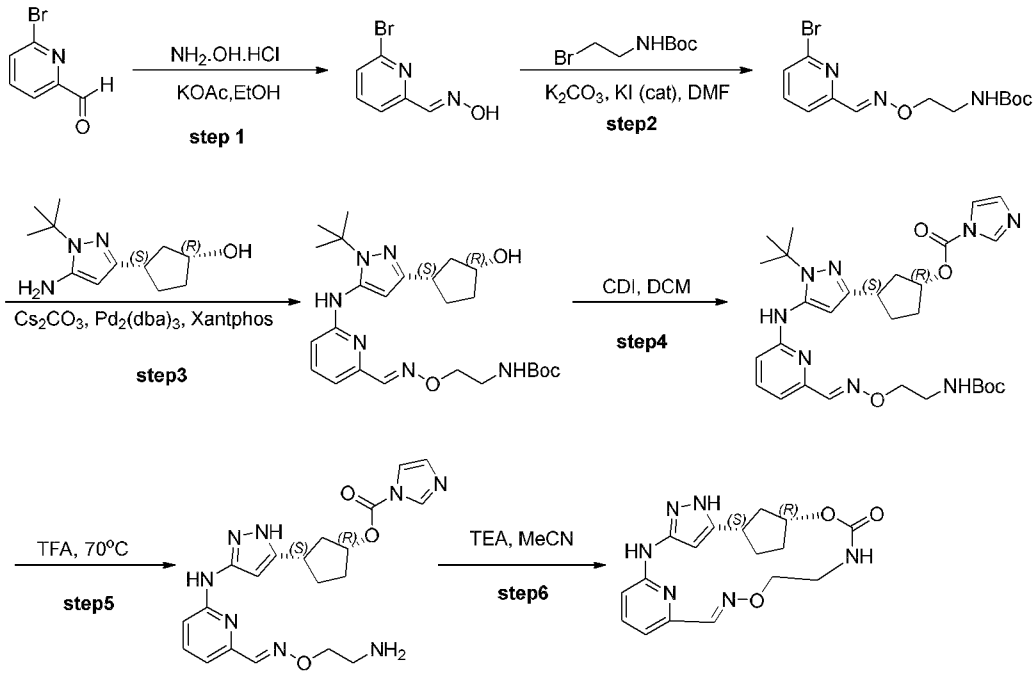
A mixture of [(1R,3S)-3-[5-[[6-[(E)-N-[2-(tert-butoxycarbonylamino)ethoxy]-C-methyl-carbonimidoyl]-2-pyridyl]amino]-1-tert-butyl-pyrazol-3-yl]cyclopentyl] (4-nitrophenyl) carbonate (60 mg, 90 μmol) in TFA (1 mL) was stirred at 70 °C for 4 h. The solvent was removed under reduced pressure to afford (1R,3S)-3-(3-((6-((E)-1-((2- aminoethoxy)imino)ethyl)pyridin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl (4-nitrophenyl) carbonate 2,2,2-trifluoroacetic acid (45 mg, 100% yield) as yellow oil, which was used in the next step directly. LC-MS: m/z 510.1 $[M+H]^+$.

Step 5: (11S,13R,24Z,5E)-5-methyl-21H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one

To a mixture of [(1R,3S)-3-[3-[[6-[(E)-N-(2-aminoethoxy)-C-methyl-carbonimidoyl]-2-pyridyl]amino]-1H-pyrazol-5-yl]cyclopentyl] (4-nitrophenyl) carbonate 2,2,2-trifluoroacetic acid (45 mg, 90 μmol) in CH_3CN (10 mL) was added Et_3N (91 mg, 900 μmol) at 25 °C. The reaction was stirred at 25 °C for 1 h. The solvent was removed under reduced pressure. The residue was purified by prep-HPLC (C18, 22% to 32% CH_3CN in 0.1% FA/water, 20 mL/min) to afford (11S,13R,24Z,5E)-5-methyl-21H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one (4.7 mg, 14% yield) as a white solid. LC-MS: m/z 371.1 $[M+H]^+$.

Example **170**

(1¹*S*,1³*R*,2⁴*Z*,5*E*)-2¹*H*-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one



Step 1: (*E*)-6-bromopicolinaldehyde oxime

To a solution of 6-bromopicolinaldehyde (1.0 g, 5.4 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (747 mg, 10.8 mmol) and Potassium Acetate (1.1 g, 10.8 mmol) at 25°C. The reaction was stirred under nitrogen atmosphere at 90 °C for 3 hours. The mixture was washed with water (50 mL) and extracted with EtOAc (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford (*E*)-6-bromopicolinaldehyde oxime (1.0 g, 93% yield) as white solid. LC-MS: m/z 201.0 $[M+H]^+$

Step 2: *tert*-butyl (*E*)-(2-((((6-bromopyridin-2-yl)methylene)amino)oxy)ethyl)carbamate

To a solution of (*E*)-6-bromopicolinaldehyde oxime (500 mg, 2.5 mmol) and *tert*-butyl (2-bromoethyl)carbamate (669 mg, 3.0 mmol) in DMF (10 mL) was added Potassium carbonate (1.0 g, 7.5 mmol) and Sodium iodide (41 mg, 249 μmol) at 25°C. The reaction was stirred under nitrogen atmosphere at 60 °C for 3.5 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with 0 to 45% EtOAc in PE to afford *tert*-butyl (*E*)-(2-((((6-bromopyridin-2-yl)methylene)amino)oxy)ethyl)carbamate (794 mg, 93%yield) as yellow oil. LC-MS: m/z 288.1 [M-56+H] $^+$

Step 3: *tert*-butyl (2-((((*E*)-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methylene)amino)oxy)ethyl)carbamate

To a solution of *tert*-butyl (*E*)-(2-((((6-bromopyridin-2-yl)methylene)amino)oxy)ethyl)carbamate (224 mg, 651 μmol) and (1*R*,3*S*)-3-(5-amino-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentan-1-ol (160 mg, 716 μmol) in dioxane (8 mL) was added Tris(dibenzylideneacetone)dipalladium (119 mg, 130 μmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (151 mg, 260 μmol) and Cesium carbonate (636 mg, 1.9 mmol). The suspension was degassed with N2 for 5 times. The mixture was stirred at 90 °C for 6 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with EtOAc in PE from 0 to 80% to afford *tert*-butyl (2-((((*E*)-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methylene)amino)oxy)ethyl)carbamate (242 mg, 71% yield) as a yellow solid. LC-MS: m/z 487.1 [M+H] $^+$

Step 4: (1*R*,3*S*)-3-(1-(*tert*-butyl)-5-((6-((*E*)-9,9-dimethyl-7-oxo-3,8-dioxa-2,6-diazadec-1-en-1-yl)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of *tert*-butyl (2-((((*E*)-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)methylene)amino)oxy)ethyl)carbamate (210 mg, 432 μmol) in DCM (8 mL) was added carbonyl diimidazole (210 mg, 1.3 mmol) at 25 °C. The reaction was stirred under nitrogen atmosphere at 40 °C for 2 hours. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with EA in PE from 0 to 60% to afford (1*R*,3*S*)-3-(1-(*tert*-butyl)-5-((6-((*E*)-9,9-dimethyl-7-oxo-3,8-dioxa-2,6-diazadec-1-en-1-yl)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (231 mg, 80% yield) as a yellow solid. LC-MS: m/z 581.3 [M+H] $^+$

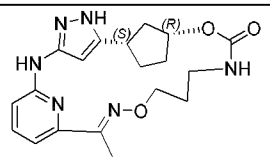
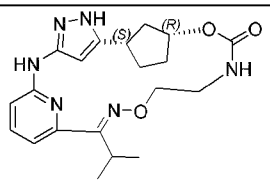
Step 5: (1*R*,3*S*)-3-(1-(*tert*-butyl)-5-((6-((*E*)-9,9-dimethyl-7-oxo-3,8-dioxa-2,6-diazadec-1-en-1-yl)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

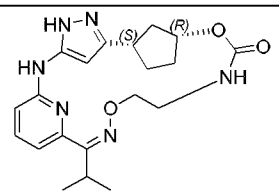
A solution of (1*R*,3*S*)-3-(1-(*tert*-butyl)-5-((6-((*E*)-9,9-dimethyl-7-oxo-3,8-dioxa-2,6-diazadec-1-en-1-yl)pyridin-2-yl)amino)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (231 mg, 398 μmol) in TFA (10 mL) was stirred under nitrogen atmosphere at 75 °C for 3 hours. The mixture was concentrated to afford (1*R*,3*S*)-3-(3-((6-((*E*)-((2-((2,2,2-trifluoroacetyl)-l4-azaneyl)ethoxy)imino)methyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, crude) as a yellow oil, which was used in the next step without purification. LC-MS: m/z 425.1[M+H] $^+$

Step 6: (1^1S,1^3R,2^4Z,5*E*)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one

To a solution of (1*R*,3*S*)-3-(3-((6-((*E*)-((2-((2,2,2-trifluoroacetyl)-l4-azaneyl)ethoxy)imino)methyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (210 mg, 495 μmol) in ACN (10 mL) was added Triethylamine (501 mg, 5.0 mmol) at 25°C. The reaction was stirred under nitrogen atmosphere at 90 °C for 6 hours. The mixture was concentrated to dryness. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL ×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with MeOH in DCM from 0 to 7% to afford the crude solid which was purified by Prep-TLC (6%MeOH in DCM) to give as a yellow solid. The residue was purified by prep-HPLC (C18, 30% to 40% CH_3CN in 0.05% NH_3/water, 20 mL/min) to afford (1^1S,1^3R,2^4Z,5*E*)-2^1H-7,12-dioxa-3,6,10-triaza-4(2,6)-pyridina-2(5,3)-pyrazola-1(1,3)-cyclopentanacyclododecaphan-5-en-11-one (9.5 mg, 5% yield) as a white solid. LC-MS: m/z 357.1 $[M+H]^+$.

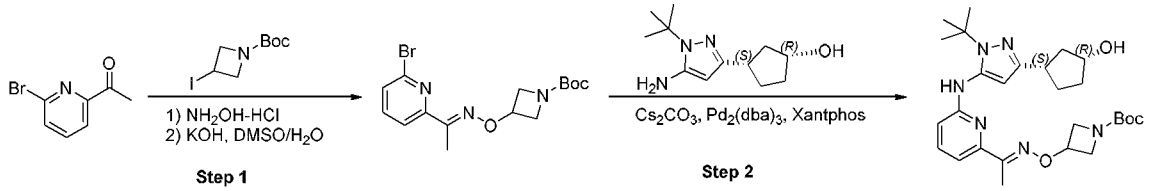
The following compounds were prepared using the similar procedure disclosed in synthetic example **170**.

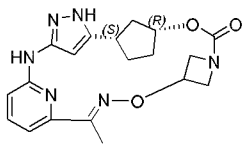
Synthetic Example	Structure	LC-MS: m/z $[M+H]^+$
171		385.1
172		399.1

173		399.2

Example **174**

(1^1*S*,1^3*R*,2^4*Z*,5*E*)-5-methyl-2^1*H*-7,10-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-8(3,1)-azetidina-1(1,3)-cyclopentanacyclodecaphan-5-en-9-one





Step 1: *tert*-butyl (*E*)-3-(((1-(6-bromopyridin-2-yl) ethylidene) amino) oxy) azetidine-1-carboxylate

To a solution of 1-(6-bromo-2-pyridyl)ethanone (1 g, 5.0 mmol) and *tert*-butyl 3-iodoazetidine-1-carboxylate (1.4 g, 5.0 mmol) in DMSO (14 mL) and Water (4 mL) were added potassium; hydroxide (2.4 g, 43.0 mmol, 1.2 mL) and hydroxylamine hydrochloride (521 mg, 7.5 mmol, 312 µL). The mixture was stirred at 90 °C for 16 hours. LCMS showed the starting material was consumed and the desired product was detected. The mixture was quenched with water (50 ml). The mixture was extracted with EtOAc (200 ml *2). The organic layer was washed with brine (50 ml*2), dried over Na_2SO_4. The combined organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate in petroleum ether from 0 to 10% in 25 minutes to give *tert*-butyl 3-[(*E*)-1-(6-bromo-2-pyridyl)ethylideneamino]oxyazetidine-1-carboxylate (420 mg, 1.2 mmol, 23% yield, as white solid). LC-MS: m/z 392.0, 394.0 [M+ Na] $^+$.

Step 2: *tert*-butyl 3-((((*E*)-1-(6-((1-(*tert*-butyl)-3-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-5-yl)amino)pyridin-2-yl)ethylidene)amino)oxy)azetidine-1-carboxylate

To a solution of tert-butyl 3-[(*E*)-1-(6-bromo-2-pyridyl)ethylideneamino]oxyazetidine-1-carboxylate (258 mg, 698 μmol) and (1*R*,3*S*)-3-(5-amino-1-*tert*-butyl-pyrazol-3-yl) cyclopentanol (130 mg, 582 μmol) in Dioxane (3 mL) were added dicesium; carbonate (569 mg, 1.70 mmol), (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one;palladium (53.3 mg, 58.2 μmol) and XantPhos (67.3 mg, 116 μmol). The mixture was degassed with N_2 and stirred at 110 °C for 6 hours. LCMS showed the starting material was consumed and the desired product was detected. The mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate in petroleum ether from 0 to 50% in 25 minutes to give tert-butyl N-[2-[(*E*)-1-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]ethylideneamino]oxyethyl]carbamate (248 mg, 495 μmol, 86% yield) as yellow solid. LC-MS: m/z 513.3 $[M+H]^+$.

Step 3: (1*R*,3*S*)-3-(5-((6-((*E*)-1-(((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)imino)ethyl)pyridin-2-yl)amino)-1-(tert-butyl)-1*H*-pyrazol-3-yl)cyclopentyl 1*H*-imidazole-1-carboxylate

To a solution of tert-butyl 3-[(*E*)-1-[6-[[2-*tert*-butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]pyrazol-3-yl]amino]-2-pyridyl]ethylideneamino]oxyazetidine-1-carboxylate (50.1 mg, 97.5 μmol) and N,N-diethylethanamine (49.3 mg, 487 μmol, 67.9 μL) in DCM (4 mL) was added di(imidazol-1-yl)methanone (47.4 mg, 292 μmol). The resulting mixture was stirred at 35 °C for 1 hour. LCMS showed the starting material was consumed and the desired product was detected. The mixture was concentrated under reduced pressure. The mixture was quenched with water (20 mL). The mixture was extracted with DCM (20 ml *2). The organic layer was washed with brine (10 mL), dried over Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give [(1*R*,3*S*)-3-[5-[[6-[(*E*)-N-(1-*tert*-butoxycarbonylazetidin-3-yl)oxy-C-methyl-carbonimidoyl]-2-pyridyl]amino]-1-*tert*-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (240 mg, crude) as yellow oil. LC-MS: m/z 607.3 $[M+H]^+$.

Step 4: (1*R*,3*S*)-3-(3-((6-((*E*)-1-((azetidin-3-yloxy) imino) ethyl) pyridin-2-yl) amino)-1*H*-pyrazol-5-yl) cyclopentyl 1*H*-imidazole-1-carboxylate

A solution of [(1*R*,3*S*)-3-[5-[[6-[(*E*)-N-(1-*tert*-butoxycarbonylazetidin-3-yl)oxy-C-methyl-carbonimidoyl]-2-pyridyl]amino]-1-tert-butyl-pyrazol-3-yl]cyclopentyl] imidazole-1-carboxylate (240 mg, 95.6 μmol) in TFA (2 mL) was stirred at 70 °C for 1 h. LCMS showed the starting material was consumed and the desired product was detected. The mixture was concentrated under reduced pressure to give [(1*R*,3*S*)-3-[3-[[6-[(*E*)-N-(azetidin-3-yloxy)-C-methyl-carbonimidoyl]-2-pyridyl]amino]-1*H*-pyrazol-5-yl]cyclopentyl] imidazole-1-carboxylate (200 mg, crude) as yellow oil. LC-MS: m/z 451.2 $[M+H]^+$.

Step 5: (1^1S,1^3R,2^4Z,5*E*)-5-methyl-2^1H-7,10-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-8(3,1)-azetidina-1(1,3)-cyclopentanacyclodecaphan-5-en-9-one

To a solution of (1*R*,3*S*)-3-(3-((6-((*E*)-1-((azetidin-3-yloxy)imino)ethyl)pyridin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentyl 1*H*-imidazole-1-carboxylate (200 mg, 443 μmol) in ACN (20 mL) was added Et_3N (134 mg, 1.3 mmol, 185 μL). The mixture was stirred at 80 °C for 16 hours. LCMS showed the starting material was consumed and the desired product was detected. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with MeOH in DCM from 0 to 6% in 25 minutes to give crude product (20 mg, as yellow oil), which was further purified by Prep-HPLC eluting with acetonitrile in water (35~45%) containing 0.1% NH_3 to give (1^1S,1^3R,2^4Z,5*E*)-5-methyl-2^1H-7,10-dioxa-3,6-diaza-4(2,6)-pyridina-2(5,3)-pyrazola-8(3,1)-azetidina-1(1,3)-cyclopentanacyclodecaphan-5-en-9-one (6.8 mg, 5% yield) as white solid. LC-MS: m/z 383.1 $[M+H]^+$.

Biological Example 1. Assay for Inhibition of CDK2/Cyclin E1

The homogeneous time-resolved fluorescence (HTRF) assay was performed to detect CDK2/Cyclin E1 catalyzed phosphorylation of peptide substrate in assay buffer containing 50 mM HEPES, PH=7.5, 10 mM MgCl2, 1mM EGTA, 2 mM DTT, 0.01% Tween, 0.1% BSA. The enzymatic reaction was carried out in a 10 μL volume containing 2 nM CDK2/Cyclin E1 enzyme (Merk, 14-475), 80 μM ATP, 20 nM LANCE Ultra ULight™-eIF4E-binding protein 1 (Thr37/46) Peptide (PerkinElmer, TRF0128-M) and 1 % DMSO (or the test compound at appropriate dilutions in DMSO) in the assay buffer. All the components were added to the 384-well plate (PerkinElmer, 6008280), and incubated at Room Temperature for 4 hours. The reaction was terminated by addition of 10 μL detection buffer (PerkinElmer, CR97-100) containing 20 mM EDTA and 4 nM LANCE® Ultra Europium-anti-phospho-eIF4E-bindingprotein 1 (Thr37/46) (PerkinElmer, TRF0216-M) antibody. Then incubate the plate at Room Temperature for 1 hour. Plate was read using Envision Reader (PerkinElmer, EnVision Multilabel Reader). The IC_{50} values of the test compound were determined by fitting the inhibition curves by 4 parameter sigmoidal dose-response model using the GraphPad Prism 8 software.

Biological Example 2. Assay for Inhibition of CDK1/Cyclin A2

The homogeneous time-resolved fluorescence (HTRF) assay was performed to detect CDK1/Cyclin A2 catalyzed phosphorylation of peptide substrate in assay buffer containing 50 mM HEPES, PH=7.5, 10 mM MgCl2, 1mM EGTA, 2 mM DTT, 0.01% Tween, 0.1% BSA. The enzymatic reaction was carried out in a 10 μL volume containing 0.4 nM CDK1/Cyclin A2 enzyme (SignalChem, C22-18G), 10 μM ATP, 20 nM LANCE Ultra ULight™-eIF4E-binding protein 1 (Thr37/46) Peptide (PerkinElmer, TRF0128-M)) and 1 % DMSO (or the test compound at appropriate

dilutions in DMSO) in the assay buffer. All the components were added to the 384-well plate (PerkinElmer, 6008280), and incubated at Room Temperature for 2 hours. The reaction was terminated by addition of 10 μL detection buffer (PerkinElmer, CR97-100) containing 20 mM EDTA and 4 nM LANCE® Ultra Europium-anti-phospho-eIF4E-bindingprotein 1 (Thr37/46) (PerkinElmer, TRF0216-M) antibody. Then incubate the plate at Room Temperature for 1 hour. Plate was read using Envision Reader (PerkinElmer, EnVision Multilabel Reader). The IC_{50} values of the test compound were determined by fitting the inhibition curves by 4 parameter sigmoidal dose-response model using the GraphPad Prism 8 software.

The IC_{50} values of each exemplified compound against CDK2 and the ratio of CDK1/CDK2 are provided in the the Table 2. The IC_{50} values are indicated as "+", for values less than or equal to 10 nM; "++", for values less than or equal to 100 nM; "+++", for values less than or equal to 1 μM; and "++++", for values greater than 1 μM, respectively.the ratio of CDK1/CDK2 are indicated as "+", for values less than or equal to 5 folds; "++", for values less than or equal to 10 folds; "+++", for values less than or equal to 20 folds; "++++", for values greater than 20 folds.

Biological Example 3. Anti-proliferation Assay in OVCAR3 Cell

OVCAR3 cells (ATCC, HTB-161) were plated at 5000 cells/well in 96-well plates respectively, and were incubated in RPMI 1640 medium (Gibco, 31800105) with 10% FBS at 37°C, 5% CO_2. After overnight incubation, baseline values were measured of the samples from one plate using CyQUANT reagent (Invitrogen, C35011) following manufacturer's recommendations. Cells were incubated with the detection reagent for 1 hour at 37°C, and then the fluorescence was measured with excitation at 485 nm and emission at 535 nm using Envision Multilabel Plate Reader (PerkinElmer). Other plates were dosed with tested compounds in a 3-fold dilution scheme. On day 6 after compound addition, CyQUANT reagent was added and the fluorescence was measured using Envision. The IC_{50} values of the test compound's anti-proliferation activity was determined from the baseline subtracted viability readout curve using GraphPad Prism 5 software.

The cellular data obtained from biological examples 3 are listed in the Table A below. The IC_{50} values are indicated as "+", for values less than or equal to 100 nM; "++", for values less than or equal to 500 nM; "+++", for values less than or equal to 1 μM; and "++++", for values greater than 1 μM, respectively.

Table 2

Synthetic Example	CDK2 (IC_{50})	CDK1/CDK2 (folds)	OVCAR3 (IC_{50})
1	+	+++	+
2	+	++	+
3	+	+	++
4	+	++++	++
5	+	++	+
6	++	+	++++

7	+	+++	++
8	+	++	+
9	+	+++	+
10	+	+++	+
11	+	++	N/A
12	++	++	++++
13	+	++++	++++
14	+	+	+
15	+	+++	+
16	+	+++	+
17	+	++	+
18	+++	++	++++
19	+	++	+
20	+	+++	+
21	++	++	++
22	+	+	+
23	+	+	+
24	+	++++	++
25	+	+	+
26	+	+	+
27	+	+	+
28	+	++	+
29	+	+	+
30	+	+++	+
31	+	++++	++
32	+	++++	+
33	+	++++	+
34	+	++++	++
35	+	+++	+
36	+	+++	++
37	+	++	+
38	+	+++	++
39	+	++	+
40	+	++	++
41	+	++	+
42	+	++	+
43	+	++	+
44	+	++	+
45	+	++	+
46	+	++++	+
47	+	++++	+
48	+	++++	+
49	+	++++	+
50	+	++++	+
51	+	++++	+
52	+	++++	++
53	+	++++	++
54	+	++++	++
55	+	++++	++
56	+	++++	+
57	+	++++	++
58	+	++++	+
59	+	+++	+

60	+	++++	++
61	+	+++	++
62	+	++	++
63	+	++++	+
64	+	++++	+
65	+	++++	+
66	+	++++	++
67	+	++++	+
68	+	++++	+
69	+	++++	+
70	+	++	+
71	+	++++	+
72	+	++++	++
73	+	++++	+
74	+	++++	+
75	++	++++	++++
76	+	++++	+
77	++	+++	++++
78	+	+++	+
79	+	+++	+
80	+	+++	+
81	+	+++	+
82	+	+++	+
83	+	++	+
84	+	++	+
85	+	++	+
86	+	++	+
87	+	++	+
88	+	+++	+
89	+	+++	+
90	+	++++	+
91	+	++	+
92	++	++++	++++
93	+	++++	++
94	+	++++	+
95	+	+++	+
96	+	++++	+
97	+	++++	+
98	+	++++	+
99	+	++++	+
100	++	+++	++++
101	++	++++	++++
102	++	+++	++++
103	+	++++	++
104	+	++++	+
105	+	++++	+
106	+	+++	+
107	+	++++	+++
108	+	++++	+
109	+	++++	+
110	++	++++	++++
111	+	++++	++++
112	+	++++	++

113	+	++++	+
114	+	+++	+
115	+	++	++
116	+	++	+
117	+	++	+
118	+	+	+
119	+	++	+
120	+	+	+
121	+	+++	+
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161	+	++++	++++
162	+	++++	+
163	+	++++	+
164	+	++++	+
165	+	++++	+

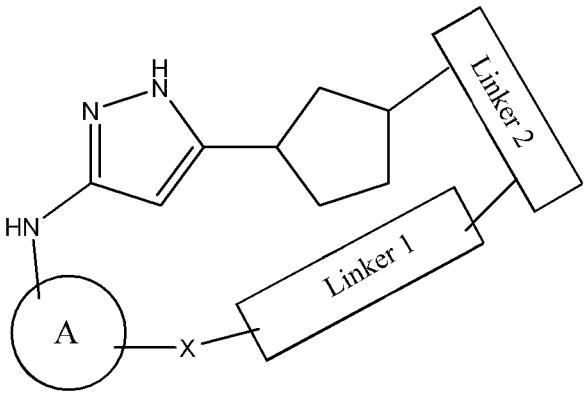
166	+	++++	++
167	+	+	+
168	+	++++	++
169	+	++++	+
170	+	++++	+
171	+	+++	++
172	+	++++	++
173	+	++++	++
174	+	++++	++
175	++++	N/A	N/A
176	++	++	++++
177	+	+	+
178	+	++++	+
179	+	++++	+
180+181	+	++	+
182	+	++++	+
183	+	++++	++
184	+	++++	+
185	++++	N/A	N/A
186	++++	N/A	N/A
187	+	++++	+
188	+	++++	+
189	+	++++	++
190	+	++++	++
191	+	+++	+
192	+	++	+
193	+	++	+
194	++	+++	N/A
195	+	+++	+++
196	+	+++	+
197	+	++++	+++
198	+	++++	++
199	+	++++	+++
200	+	++++	+++
201	+	++++	+
202	+	+	+
203	++	++	++

N/A: not available.

CLAIMS

What is claimed is:

1. A compound of Formula (I'):



(I'),

a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein:

ring A is 6-10 membered aryl or 5-10 memberaed heteroaryl; wherein said 6-10 membered aryl or 5-10 membered heteroaryl represented by ring A is optionally substituted by one or more R^1; wherein

R^1 is halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alknyl, C_{1-6}alkyleneamine, C_{1-6}alkylenehydroxyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-SR^{1a}$, $-NR^{1a}R^{1b}$, $-NR^{1a}C(O)R^{1b}$, $-NR^{1a}C(O)OR^{1b}$, $-NR^{1a}SO_2R^{1b}$, $-NR^{1a}SO_2NR^{1b}R^{1c}$, $-SO_2R^{1a}$, $-SO_2NR^{1a}R^{1b}$, or $-P(O)R^{1a}R^{1b}$, 3-6 membered carbocyclyl, 4-8 membered heterocyclyl, 6-10 membered aryl, 5-10 membered heteroaryl; wherein said C_{1-6}alkyleneamine, C_{1-6}alkylenehydroxyl, 3-6 membered carbocyclyl, 4-8 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl represented by R^1 is optionally substituted by one or more R^{10}, wherein

R^{10}, in each occurrence, is independently selected from the group consisting of halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxyl, and 4-6 membered heterocyclyl;

R^{1a}, R^{1b}, and R^{1c} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and $-C_{0-6}$alkyl-4-6 membered heterocyclyl;

X is absent, $\text{^-(CH}_2)_{0-1}\text{-O-^^}$, $-NR^2-$, $\text{^-(CH}_2)_{0-1}\text{-C(O)-^^}$, $\text{^-(CH}_2)_{0-1}\text{-NR}^2\text{C(O)-^^}$, $\text{^-(CH}_2)_{0-1}\text{-C(O)NR}^2\text{-^^}$, $\text{^-SO}_2\text{-^^}$, or $\text{^-C(R}^2\text{)=N-O-^^}$; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1; and

R^2, in each occurrence, is independently hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl;

Linker 1 is represented by formula

*-W-L-Z-**;

wherein *- represents the point which attaches to X; -** represents the point which attaches to Linker 2;

W is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by W is optionally substituted by one or more R^3;

L is absent, -O-, -NH-, 3-12 membered carbocyclyl, 3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-12 membered carbocyclyl,
3-12 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl represented by L is optionally substituted by one or more R^3; and

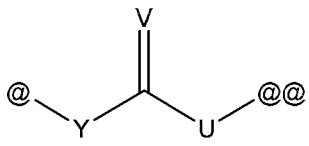
Z is absent, C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene; wherein said C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene represented by Z is optionally substituted by one or more R^3; wherein

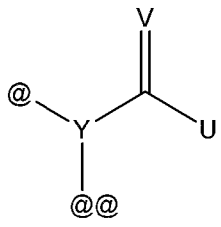
R^3, in each occurrence, is independently halogen, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{3a}$, $-C(=O)R^{3a}$, or $-NR^{3a}R^{3b}$; wherein

R^{3a} and R^{3b} are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, and 4-6 membered heterocyclyl;

wherein W, L, and Z are not absent simultaneously;

Linker 2 is represented by



or


,

wherein @- represents the point which attaches to the cyclopentyl shown in Formula (I'); -@@ represents the point which attaches to Linker1;

when U is connected with Linker1, Y is –O- or $-NR^{22}$-; and U is –O- or $-NR^4$-; wherein

R^{22} is hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl; and

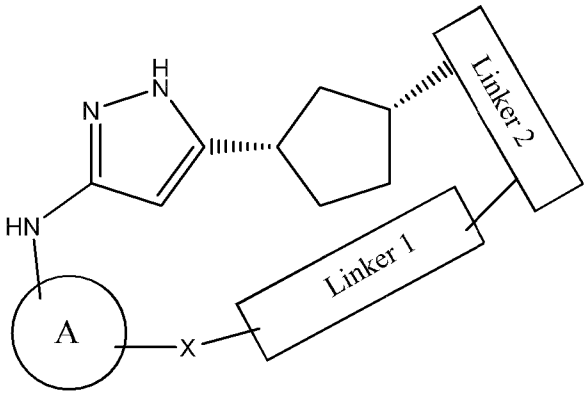
R^4 is hydrogen or C_{1-6}alkyl; or

R^4 and one R^3 attached to Z together with the atoms to which they are attached form 4-8 membered heterocyclyl;

when Y is connected with Linker1, Y is N; and U is $–N(R^5)_2$-; each R^5 is independently hydrogen or C_{1-6}alkyl; and

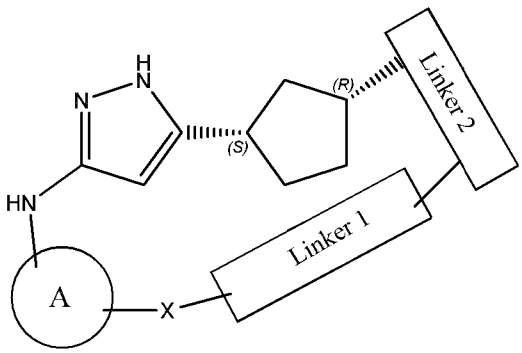
V is O or S.

2. The compound of claim 1, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is represented by Formula II':

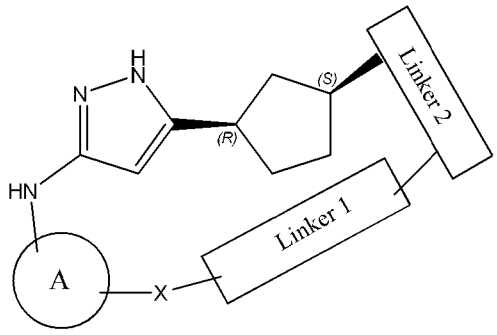


(II').

3. The compound of claim 1 or 2, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein the compound is represented by Formula (II'A) or (II'B):



(II'A); or



(II'B).

4. The compound of any one of claims 1-3, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is phenyl or nitrogen containing 5-10 membered heteroaryl; wherein said phenyl or nitrogen containing 5-10 membered heteroaryl represented by ring A is optionally substituted by one to three R^1; wherein

R^1 is halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkyleneamine, C_{1-4}alkylenehydroxyl, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-SR^{1a}$, $-SO_2R^{1a}$, 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein said C_{1-4}alkyleneamine, C_{1-4}alkylenehydroxyl, 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl represented by R^1 is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of halogen, -CN, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxyl, and 5-6 membered heterocyclyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and $-C_{0-3}$alkyl-4-6 membered heterocyclyl.

5. The compound of any one of claims 1-4, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

ring A is phenyl, nitrogen containing 5-6 membered heteroaryl, or nitrogen containing 9 membered bicyclic heteroaryl; wherein said phenyl, nitrogen containing 5-6 membered heteroaryl, or nitrogen containing 9 membered bicyclic heteroaryl represented by ring A is optionally substituted by one to two R^1; wherein

R^1 is halogen, -CN, C_{1-3}alkyl, C_{1-2}haloalkyl, C_{1-2}alkyleneamine, C_{1-2}alkylenehydroxyl, $-C(O)NR^{1a}R^{1b}$, $-OR^{1a}$, $-SR^{1a}$, $-SO_2R^{1a}$, 5-6 membered carbocyclyl, 5-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein said C_{1-2}alkyleneamine, C_{1-2}alkylenehydroxyl, 5-6 membered carbocyclyl, 5-6 membered

heterocyclyl, phenyl, or 5-6 membered heteroaryl represented by R^1 is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of F, Cl, -CN, C_{1-2}alkyl, C_{1-2}haloalkyl, C_{1-3}alkoxyl, and 5-6 membered heterocyclyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C_{1-2}alkyl, C_{1-2}haloalkyl, and -C_{0-2}alkyl-5 membered heterocyclyl.

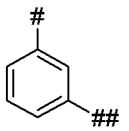
6. The compound of any one of claims 1-5, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from a group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, pyrrolopyridinyl, pyrazolopyrimidinyl, pyrazolopyrazinyl, thienopyridinyl, and imidazo[4,5-c]pyridinyl; wherein said phenyl, pyridyl, pyrimidinyl, pyrazinyl, thiophenyl, thiazolyl, pyrrolopyridinyl, pyrazolopyrimidinyl, pyrazolopyrazinyl, thienopyridinyl, and imidazo[4,5-c]pyridinyl is optionally substituted by one to two R^1; wherein

R^1 is F, Cl, Br, -CN, -CH_3, -$CH(CH_3)_2$, -CF_3, -OR^{1a}, -SR^{1a}, -SO_2R^{1a}, -$C(O)NR^{1a}R^{1b}$, -CH_2NH_2, -CH_2OH, cyclopentanyl, cyclohexanyl, cyclohexenyl, piperidinyl, tetrahydropyridinyl, 3,6-dihydro-2H-thiopyranyl, thiophenyl, pyrazolyl, phenyl, or pyridyl; wherein said -CH_2NH_2, -CH_2OH, cyclopentanyl, cyclohexanyl, cyclohexenyl, piperidinyl, tetrahydropyridinyl, 3,6-dihydro-2H-thiopyranyl, thiophenyl, pyrazolyl, phenyl, or pyridyl is optionally substituted by one to three R^{10}; wherein

R^{10}, in each occurrence, is independently selected from the group consisting of F, Cl, -CN, -CH_3, -CF_3, -CH_2CF_3, -OCH_2CH_3, -$OCH(CH_3)_2$, and morpholinyl; and

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, -CH_3, -$OCHF_2$, tetrahydrofuranyl, and -$(CH_2)_2$-pyrrolidinyl.

7. The compound of any one of claims 1-6, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein ring A is selected from the group consisting of



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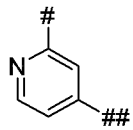

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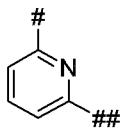

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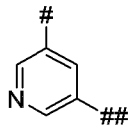

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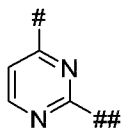

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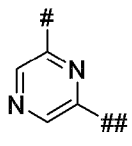

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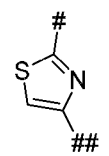

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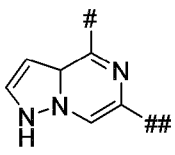

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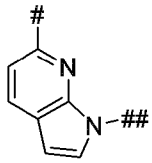

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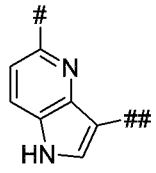

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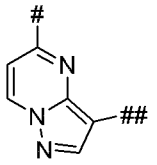

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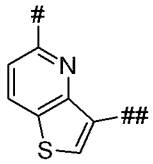


;

wherein

each of them is optionally substituted by one to two R^1; and

represents the point which attaches to the moiety –NH-; ## represents the point which attaches to X.

8. The compound of any one of claims 1-6, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, wherein ring A is pyridyl; wherein said pyridyl is optionally substituted by one R^1.

9. The compound of any one of claims 1-8, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

X is absent, -O-, ^-CH_2-O-^^, ^-CH_2-C(O)-^^, ^-NR^2C(O)-^^, ^-CH_2-NR^2C(O)-^^, ^-C(O)NR^2-^^, ^-CH_2-C(O)NR^2-^^, ^-SO_2-^^, or ^-C(R^2)=N-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1;

R^2, in each occurrence, is independently hydrogen, C_{1-3}alkyl, or C_{1-3}haloalkyl.

10. The compound of any one of claims 1-9, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

X is absent, -O-, ^-CH_2-O-^^, ^-CH_2-C(O)-^^, ^-NHC(O)-^^, ^-CH_2-NHC(O)-^^, ^-C(O)NH-^^, ^-CH_2-C(O)NH-^^, ^-SO_2-^^, or ^-C(R^2)=N-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1; and

R^2, in each occurrence, is independently hydrogen, -CH_3, -CF_3, or isopropyl.

11. The compound of any one of claims 1-10, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein X is absent or ^-CH_2-O-^^; wherein

^- represents the point which attaches to ring A; -^^ represents the point which attaches to Linker 1.

12. The compound of any one of claims 1-11 or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein

W is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by W is optionally substituted by one to three R^3;

L is absent, -O-, -NH-, 3-8 membered carbocyclyl, 3-8 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein said -NH-, 3-8 membered carbocyclyl, 3-6 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl represented by L is optionally substituted by one to three R^3; and

Z is absent, C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene; wherein said C_{1-4}alkylene, C_{2-4}alkenylene, or C_{2-4}alkynylene represented by Z is optionally substituted by one to three R^3; wherein

R^3, in each occurrence, is independently halogen, C_{1-4}alkyl, C_{1-4}haloalkyl, or -C(=O)R^{3a}; wherein

R^{3a} is hydrogen or C_{1-4}alkyl.

13. The compound of any one of claims 1-12, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by W is optionally substituted by one to two R^3;

L is absent, -O-, -NH-, 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic heteroaryl; wherein said 3-6 membered monocyclic carbocyclyl, 6-8 membered bicyclic carbocyclyl; 4-6 membered monocyclic heterocyclyl, phenyl, and 5-6 membered monocyclic heteroaryl represented by L is optionally substituted by one R^3; and

Z is absent, C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene; wherein said C_{1-3}alkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene represented by Z is optionally substituted by one to two R^3; wherein

R^3, in each occurrence, is independently halogen, C_{1-3}alkyl, C_{1-2}haloalkyl, or - C(=O)CH_3.

14. The compound of any one of claims 1-13, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene;

L is absent, -NH- or -O-; and

Z is C_{1-3}alkylene, C_{1-3}haloalkylene, C_{2-3}alkenylene, or C_{2-3}alkynylene.

15. The compound of any one of claims 1-14, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is C_{3-4}alkylene, C_{3-4}haloalkylene, C_{3-4}alkenylene, or C_{3-4}alkynylene;

L is absent; and

Z is absent.

16. The compound of any one of claims 1-15, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, C_{1-2}alkylene, or C_{1-2}haloalkylene;

L is 4-6 membered carbocyclyl, 4-6 membered heterocyclyl, or 5-6 membered heteroaryl; and

Z is absent or methylene.

17. The compound of any one of claims 1-16, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein

W is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH_2CH=CH-$, or $-CH_2C\equiv C-$; wherein said $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH_2CH=CH-$, or $-CH_2C\equiv C-$ represented by W is optionally substituted by one to two R^3

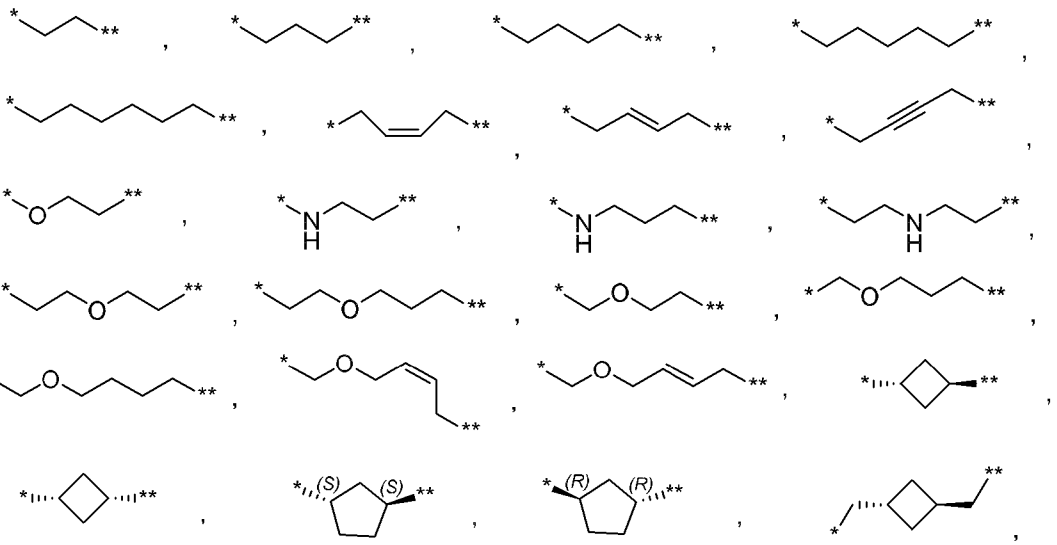
L is absent, -O-, -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, or thiozolyl; wherein said -NH-, cyclobutyl, cyclohexyl, spiro[3.3]heptanyl, azetidinyl, piperazinyl, piperidinyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, or thiozolyl is optionally substituted by one R^3;

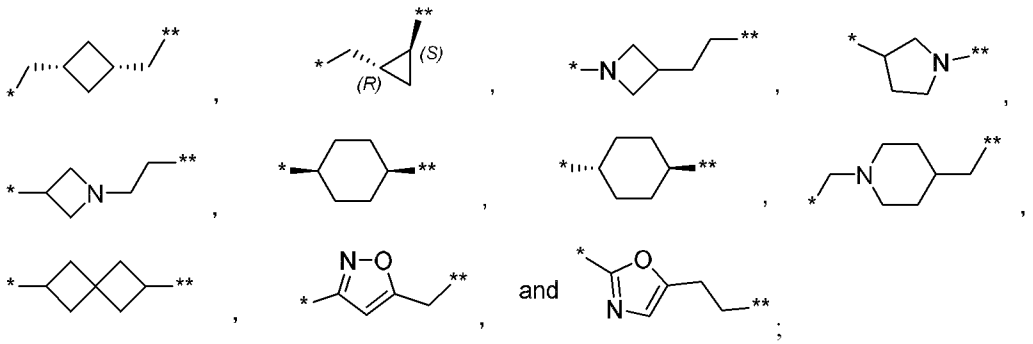
Z is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH=CHCH_2-$, or $-C\equiv CCH-$;

wherein

R^3 is F, $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, or $-C(=O)CH_3$.

18. The compound of any one of claims 1-13 and 17, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein *-W-L-Z-** is selected from the group consisting of





wherein each of them is optionally substituted by one to two R^3; wherein

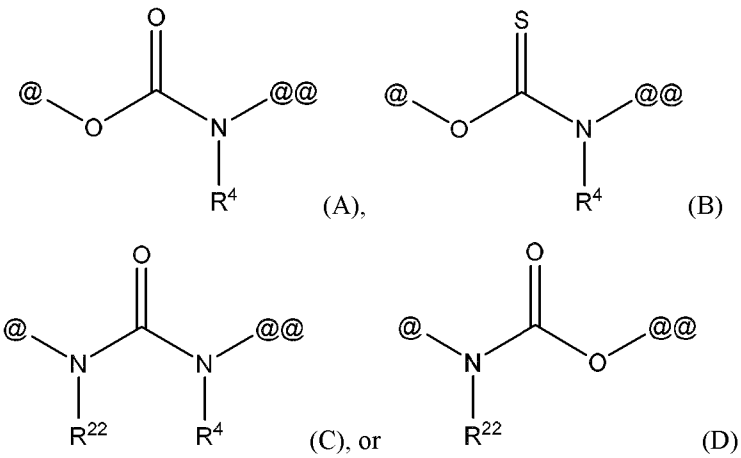
*- represents the point which attaches to X; -** represents the point which attaches to Linker 2.

19. The compound of any one of claims 1-13, 17 and 18, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein *-W-L-Z-** is selected from the group consisting of

; wherein

*- represents the point which attaches to X; -** represents the point which attaches to Linker 2.

20. The compound of any one of claims 1-19, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is represented by Formula A, B, C, or D,



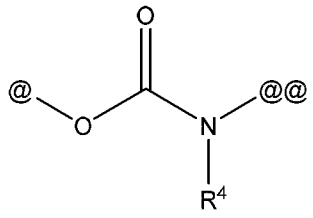
wherein

@- represents the point which attaches to the cyclopentyl shown in Formula (I'); -@@ represents the point which attaches to Linker1;

R^{22} is hydrogen, C_{1-4}alkyl, or C_{1-4}haloalkyl; and

R^4 is hydrogen or C_{1-4}alkyl; or R^4 and one R^3 attached to Z, together with the atoms to which they are attached, form 4-6 membered heterocyclyl.

21. The compound of claim 20, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is



(A);

wherein

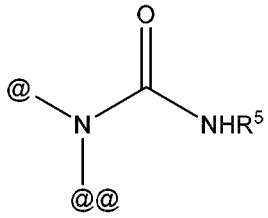
@- represents the point which attaches to the cyclopentyl shown in Formula (I');

-@@ represents the point which attaches to Linker1; and

R^4 is hydrogen or $-CH_3$; or R^4 and one R^3 attached to Z together with the atoms to which they are attached, form azetidinyl or pyrrolidinyl.

22. The compound of claim 21, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein R^4 is hydrogen.

23. The compound of any one of claims 1-19, a pharmaceutically acceptable salt, or a stereoisomer thereof, wherein Linker 2 is represented by Formula (E):



(E);

wherein

@- represents the point which attaches to the cyclopentyl shown in Formula (I');

-@@ represents the point which attaches to Linker1; and

R^5 is hydrogen or isopropyl.

24. A compound of Table 1 or a pharmaceutically acceptable salt or a stereoisomer thereof.

25. A pharmaceutical composition comprising the compound of any one of claims 1-24, a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

26. A method of treating a disease or condition modulated at least in part by CDK2 in a subject, comprising administering to the subject in need thereof, the compound of any one of claims 1-24, a pharmaceutically acceptable salt, or a stereoisomer thereof, or the pharmaceutical composition of claim 25.

27. A method of inhibiting CDK2 in a patient, comprising administering to the patient the compound of any one of claims 1-24, a pharmaceutically acceptable salt, or a stereoisomer thereof, or the pharmaceutical composition of claim 25.

28. A method of treating a disease or disorder associated with CDK2 in a patient, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-24, a pharmaceutically acceptable salt, or a stereoisomer thereof, or the pharmaceutical composition of claim 25; wherein the disease or disorder is associated with an amplification of the cyclin E1 (CCNE1) gene and/or overexpression of CCNE1.

29. The method of any one of claims 26-28, wherein the disease or disorder is cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CN2022/084355

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D491/18 A61K31/439
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/157652 A2 (PFIZER [US]) 6 August 2020 (2020-08-06)	1-14,17, 20-23, 25-29
A	claims 1, 18-20 table 4 -----	15,16, 18,19,24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2022	16/05/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brandstetter, T

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CN2022/084355

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