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(54) **Titre : DERIVES SPIRO SUBSTITUES**
(54) **Title: SUBSTITUTED SPIRO DERIVATIVES**

(57) **Abrégé/Abstract:**
The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, pharmaceutical composition comprising such compounds, and their use as menin/MLL protein/protein interaction inhibitors, useful for treating diseases such as cancer, myelodysplastic syndrome (MDS) and diabetes.

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Abstract:

The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, pharmaceutical composition comprising such compounds, and their use as menin/MLL protein/protein interaction inhibitors, useful for treating diseases such as cancer, myelodysplastic syndrome (MDS) and diabetes.

SUBSTITUTED SPIRO DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical agents useful for therapy and/or prophylaxis in a mammal, pharmaceutical composition comprising such compounds, and their use as menin/MLL protein/protein interaction inhibitors, useful for treating diseases such as cancer, myelodysplastic syndrome (MDS) and diabetes.

BACKGROUND OF THE INVENTION

Chromosomal rearrangements affecting the mixed lineage leukemia gene (*MLL*; *MLL1*; *KMT2A*) result in aggressive acute leukemias across all age groups and still represent mostly incurable diseases emphasizing the urgent need for novel therapeutic approaches. Acute leukemias harboring these chromosomal translocations of *MLL* represent as lymphoid, myeloid or biphenotypic disease and constitute 5 to 10% of acute leukemias in adults and approximately 70% in infants (Marschalek, Br J Haematol 2011. 152(2), 141-54; Tomizawa et al., Pediatr Blood Cancer 2007. 49(2), 127-32).

MLL is a histone methyltransferase that methylates histone H3 on lysine 4 (H3K4) and functions in multiprotein complexes. Use of inducible loss-of-function alleles of *Mll1* demonstrated that Mll1 plays an essential role in sustaining hematopoietic stem cells (HSCs) and developing B cells although its histone methyltransferase activity is dispensable for hematopoiesis (Mishra et al., Cell Rep 2014. 7(4), 1239-47).

Fusion of MLL with more than 60 different partners has been reported to date and has been associated with leukemia formation/progression (Meyer et al., Leukemia 2013. 27, 2165–2176). Interestingly, the SET (Su(var)3–9, enhancer of zeste, and trithorax) domain of MLL is not retained in chimeric proteins but is replaced by the fusion partner (Thiel et al., Bioessays 2012. 34, 771-80). Recruitment of chromatin modifying enzymes like Dot1L and/or the pTEFb complex by the fusion partner leads to enhanced transcription and transcriptional elongation of MLL target genes including *HOXA* genes (e.g. *HOXA9*) and the *HOX* cofactor *MEIS1* as the most prominent ones. Aberrant expression of these genes in turn blocks hematopoietic differentiation and enhances proliferation.

Menin which is encoded by the Multiple Endocrine Neoplasia type 1 (*MEN1*) gene is expressed ubiquitously and is predominantly localized in the nucleus. It has been shown to interact with numerous proteins and is, therefore, involved in a variety of cellular processes. The best understood function of menin is its role as an oncogenic cofactor of MLL fusion proteins. Menin interacts with two motifs within the N-terminal fragment of MLL that is retained in all fusion proteins, MBM1 (menin-binding motif 1) and MBM2 (Thiel et al., Bioessays 2012. 34, 771-80). Menin/MLL interaction leads to the formation of a new interaction surface for lens

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epithelium-derived growth factor (LEDGF). Although MLL directly binds to LEDGF, menin is obligatory for the stable interaction between MLL and LEDGF and the gene specific chromatin recruitment of the MLL complex via the PWWP domain of LEDGF (Cermakova et al., Cancer Res 2014. 15, 5139-51; Yokoyama & Cleary, Cancer Cell 2008. 8, 36-46). Furthermore, numerous genetic studies have shown that menin is strictly required for oncogenic transformation by MLL fusion proteins suggesting the menin/MLL interaction as an attractive therapeutic target. For example, conditional deletion of *Men1* prevents leukomogenesis in bone marrow progenitor cells ectopically expressing MLL fusions (Chen et al., Proc Natl Acad Sci 2006. 103, 1018-23). Similarly, genetic disruption of menin/MLL fusion interaction by loss-of-function mutations abrogates the oncogenic properties of the MLL fusion proteins, blocks the development of leukemia *in vivo* and releases the differentiation block of MLL-transformed leukemic blasts. These studies also showed that menin is required for the maintenance of *HOX* gene expression by MLL fusion proteins (Yokoyama et al., Cell 2005. 123, 207-18). In addition, small molecule inhibitors of menin/MLL interaction have been developed suggesting druggability of this protein/protein interaction and have also demonstrated efficacy in preclinical models of AML (Borkin et al., Cancer Cell 2015. 27, 589-602; Cierpicki and Grembecka, Future Med Chem 2014. 6, 447-462). Together with the observation that menin is not a requisite cofactor of MLL1 during normal hematopoiesis (Li et al., Blood 2013. 122, 2039-2046), these data validate the disruption of menin/MLL interaction as a promising new therapeutic approach for the treatment of MLL rearranged leukemia and other cancers with an active *HOX/MEIS1* gene signature. For example, an internal partial tandem duplication (PTD) within the 5'region of the *MLL* gene represents another major aberration that is found predominantly in de novo and secondary AML as well as myeloid dysplasia syndromes. Although the molecular mechanism and the biological function of MLL-PTD is not well understood, new therapeutic targeting strategies affecting the menin/MLL interaction might also prove effective in the treatment of MLL-PTD-related leukemias. Furthermore, castration-resistant prostate cancer has been shown to be dependent on the menin/MLL interaction (Malik et al., Nat Med 2015. 21, 344-52).

MLL protein is also known as Histone-lysine N-methyltransferase 2A (KMT2A) protein in the scientific field (UniProt Accession # Q03164).

Several references describe inhibitors targeting the menin-MLL interaction: WO2011029054, J Med Chem 2016, 59, 892-913 describe the preparation of thienopyrimidine and benzodiazepine derivatives; WO2014164543 describes thienopyrimidine and thienopyridine derivatives; *Nature Chemical Biology* March 2012, *8*, 277-284 and Ren, J.; *et al. Bioorg Med Chem Lett* (2016), *26(18)*, 4472-4476 describe thienopyrimidine derivatives; *J Med Chem* 2014, *57*, 1543-1556 describes hydroxy- and aminomethylpiperidine derivatives; *Future Med Chem* 2014, *6*, 447-462 reviews small molecule and peptidomimetic compounds; WO2016195776

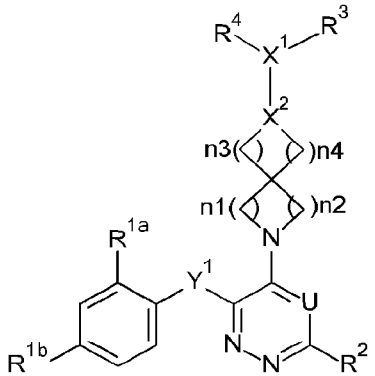
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describes furo[2,3-d]pyrimidine, 9H-purine, [1,3]oxazolo[5,4-d]pyrimidine, [1,3]oxazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-d]pyrimidine, thieno[2,3-b]pyridine and thieno[2,3-d]pyrimidine derivatives; WO2016197027 describes 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, 5,6,7,8-tetrahydropyrido]4,3-d]pyrimidine, pyrido[2,3-d]pyrimidine and quinoline derivatives; and WO2016040330 describes thienopyrimidine and thienopyridine compounds. WO2017192543 describes piperidines as Menin inhibitors. WO2017112768, WO2017207387, WO2017214367, WO2018053267 and WO2018024602 describe inhibitors of the menin-MLL interaction. WO2017161002 and WO2017161028 describe inhibitors of menin-MLL. WO2018050686, WO2018050684 and WO2018109088 describe inhibitors of the menin-MLL interaction. WO2018226976 describes methods and compositions for inhibiting the interaction of menin with MLL proteins. WO2019060365 describes substituted inhibitors of menin-MLL. Krivtsov et al., Cancer Cell 2019. No.6 Vol.36, 660-673 describes a menin-MLL inhibitor.

WO2020069027 discloses inhibitors of Menin. WO2018175746 discloses methods for treating hematological malignancies and ewing's sarcoma. WO2020045334 discloses azabicyclic derivative used in pharmaceutical compositions. WO2019120209 discloses substituted heterocyclic compounds as menin/MLL protein/protein interaction inhibitors. CN111297863 discloses use of menin-mixed lineage leukemia (MLL) inhibitors. WO2021121327 describes substituted straight chain spiro derivatives and their use as menin/MLL protein/protein interaction inhibitors.

DESCRIPTION OF THE INVENTION

The present invention concerns novel compounds of Formula (I),



(I)

,

and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered

aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O-, -S-, or $-NR^{5c}-$;

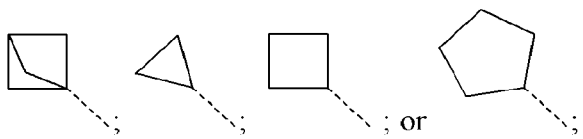
R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents C_{1-5}alkyl;



R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of Het^1, Het^2, Cy^2 and $-C_{1-6}$alkyl-$NR^{xc}R^{xd}$;

R^{xc} represents Cy^1; Het^5; $-C_{1-6}$alkyl-Cy^1; $-C_{1-6}$alkyl-Het^3; $-C_{1-6}$alkyl-Het^4; or $-C_{1-6}$alkyl-phenyl;

R^{xd} represents hydrogen; C_{1-4}alkyl; or C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;
or R^{xc} and R^{xd} are taken together to form together with the N-atom to which they are attached a 4- to 7-membered monocyclic fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;

wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, C_{1-4}alkyl, oxo, -$NR^{9a}R^{9b}$ and -OH;

Het^2 represents C-linked pyrazolyl or triazolyl; which may be optionally substituted on one nitrogen atom with R^{6a};

R^6 and R^{6a} are each independently selected from the group consisting of
Het^3; Het^4; -C(=O)-NH-Cy^1; -C(=O)-NH-R^8;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl-C_{3-6}cycloalkyl, -C(=O)-OH, -$NR^{11a}R^{11b}$, and -NH-S(=O)$_2$-C_{1-4}alkyl; and
C_{3-6}cycloalkyl optionally substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -NH-S(=O)$_2$-C_{1-4}alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl and -NH-S(=O)$_2$-C_{1-4}alkyl;

R^8 represents -O-C_{1-6}alkyl, C_{1-6}alkyl; or C_{1-6}alkyl substituted with one, two or three substituents each independently selected from -OH, halo, cyano, -$NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

Het^3, Het^{3a}, Het^5 and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or S(=O)$_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or S(=O)$_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -OH, -$NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two, three or four heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl or –(C=O)-O-C_{1-}

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$_{4}$alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, C_{1-4}alkyl-$NR^{11a}R^{11b}$, -NH-C(=O)-C_{1-4}alkyl, cyano, -COOH, -NH-C(=O)-O-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -NH-C(=O)-$NR^{10a}R^{10b}$, -(C=O)-O-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, Het^{8a}, -C_{1-4}alkyl- Het^{8a}, Het^{8b}, Het^9, and -C(=O)-$NR^{10a}R^{10b}$;

Het^{6a}, Het^8 and Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl, -$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl, -C_{1-4}alkyl-OH, -O-C_{1-4}alkyl, -O-(C=O)-$NR^{10a}R^{10b}$, and -O-(C=O)-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and -(C=O)-$NR^{10a}R^{10b}$;

Het^{6b} and Het^{8b} each independently represent a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl, -C(=O)-Cy^3, -(C=O)-C_{1-4}alkyl-OH, -C(=O)-C_{1-4}alkyl-O-C_{1-4}alkyl, -C(=O)-C_{1-4}alkyl-$NR^{11a}R^{11b}$, and C_{1-4}alkyl;

Het^9 represents a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, and C_{1-4}alkyl;

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Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH, -NH-C(=O)-C_{1-4}alkyl, C_{1-4}alkyl, -NH-S(=O)$_2$-C_{1-4}alkyl, -S(=O)$_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl;

Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, -$NR^{9a}R^{9b}$, -OH, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or two substituents each independently selected from the group consisting of Het^{3a}, Het^{6a}, Het^{6b}, and -$NR^{9a}R^{9b}$;

Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-C_{3-6}cycloalkyl; -S(=O)$_2$-C_{1-4}alkyl; Het^5; Het^7; -C_{1-4}alkyl-R^{16}; -C(=O)-C_{1-4}alkyl-Het^{3a}; -C(=O)-R^{14}; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano; and C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{15a}, R^{15b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents Het^{5a}; Het^7; Het^{8a}; -O-C_{1-4}alkyl; -C(=O)$NR^{15a}R^{15b}$; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl and halo; or C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl, -$NR^{13a}R^{13b}$, halo, cyano, -OH, Het^{8a}, and Cy^1;

R^{16} represents -C(=O)-$NR^{17a}R^{17b}$, -S(=O)$_2$-C_{1-4}alkyl, Het^5, Het^7, or Het^8;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and a pharmaceutically acceptable carrier or excipient.

Additionally, the invention relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use as a medicament, and to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the

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prevention of cancer, myelodysplastic syndrome (MDS) and diabetes.

In a particular embodiment, the invention relates to a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or in the prevention of cancer.

In a specific embodiment said cancer is selected from leukemias, myeloma or a solid tumor cancer (e.g. prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma, etc.). In some embodiments, the leukemias include acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, leukemias exhibiting *HOX/MEIS1* gene expression signatures etc.

The invention also relates to the use of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, in combination with an additional pharmaceutical agent for use in the treatment or prevention of cancer, myelodysplastic syndrome (MDS) and diabetes.

Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof.

The invention also relates to a product comprising a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of cancer, myelodysplastic syndrome (MDS) and diabetes.

Additionally, the invention relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, or a solvate thereof, as defined herein, or a pharmaceutical composition or combination as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The term 'halo' or 'halogen' as used herein represents fluoro, chloro, bromo and iodo.

The prefix 'C_{x-y}' (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon atoms, and so on.

The term 'C_{1-4}alkyl' as used herein as a group or part of a group represents a straight or

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branched chain saturated hydrocarbon radical having from 1 to 4 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl and the like.

The term 'C_{3-6}cycloalkyl' as used herein as a group or part of a group defines a saturated, cyclic hydrocarbon radical having from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term 'C_{3-7}cycloalkyl' as used herein as a group or part of a group defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

It will be clear for the skilled person that $S(=O)_2$ or SO_2 represents a sulfonyl moiety.

It will be clear for the skilled person that CO or C(=O) represents a carbonyl moiety.

It will be clear for the skilled person that a group such as -CRR- represents  . An example of such a group is $-CR^{5a}R^{5b}-$.

It will be clear for the skilled person that a group such as -NR- represents  . An example of such a group is $-NR^{5c}-$.

The term 'monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N', defines a fully saturated, cyclic hydrocarbon radical having from 4 to 7 ring members and containing at least 1 nitrogen atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, such as for example C-linked azetidinyl, C-linked pyrrolidinyl, C-linked morpholinyl and C-linked piperidinyl. The term 'monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N', is defined similar but is attached to the remainder of the molecule of formula (I) via a nitrogen atom. Examples are N-linked azetidinyl, N-linked pyrrolidinyl, N-linked morpholinyl, N-linked thiomorpholinyl, N-linked piperazinyl, N-linked 1,4-diazepanyl, and N-linked piperidinyl. Two R groups taken together to form together with the N-atom to which they are attached a 4- to 7-membered monocyclic fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O, S, and N, are defined similar.

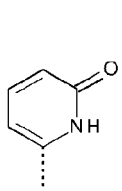
The term 'monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N', defines a fully saturated, cyclic hydrocarbon radical having from 4 to 7 ring members and containing one, two or three heteroatoms each independently selected from O, S, and N, such as for example C-

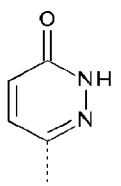
linked azetidinyl, C-linked pyrrolidinyl, C-linked morpholinyl, C-linked tetrahydrofuranyl, C-linked thiolanyl, C-linked oxetanyl, C-linked thietanyl, C-linked tetrahydropyranyl, C-linked tetrahydrothiopyranyl, and C-linked piperidinyl. The term 'monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing two N-atoms and optionally one additional heteroatom selected from O, S, and N', defines a fully saturated, cyclic hydrocarbon radical having from 4 to 7 ring members and containing 2 nitrogen atoms and optionally one additional heteroatom selected from O, S, and N, such as for example N-linked piperazinyl, and N-linked 1,4-diazepanyl.

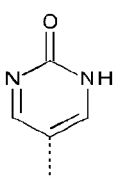
For clarity, the 4- to 7-membered fully or partially saturated heterocyclyls have from 4 to 7 ring members including the heteroatoms.

Non-limiting examples of 'monocyclic 5- or 6-membered aromatic rings containing one, two or three nitrogen atoms and optionally a carbonyl moiety', include, but are not limited to pyrazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1H-1,2,4-triazolyl, 4H-1,2,4-triazolyl, 1,2,4-triazinyl, 1,2-dihydro-2-oxo-5-pyrimidinyl, 1,2-dihydro-2-oxo-6-pyridinyl, 1,2-dihydro-2-oxo-4-pyridinyl, and 1,6-dihydro-6-oxo-3-pyridazinyl.

The skilled person will understand that a 5- or 6-membered monocyclic aromatic ring containing one two or three nitrogen atoms and a carbonyl moiety includes, but is not limited to



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, and


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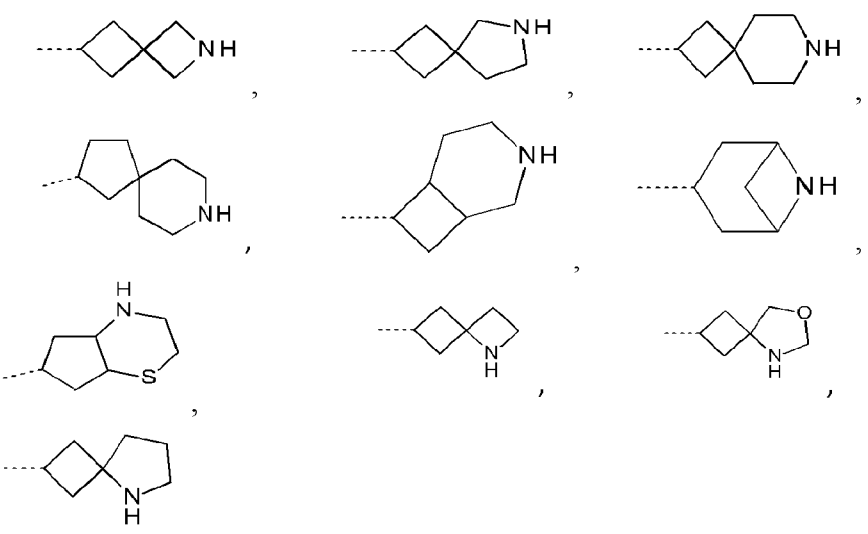
Non-limiting examples of 'monocyclic C-linked 5- or 6-membered aromatic rings containing one, two or three heteroatoms each independently selected from O, S, and N', include, but are not limited to C-linked pyrazolyl, C-linked imidazolyl, C-linked pyridinyl, C-linked triazolyl, C-linked pyridazinyl, C-linked pyrimidinyl, C-linked oxazolyl, C-linked furanyl, C-linked isothiazolyl, C-linked thiazolyl, C-linked thiadiazolyl, C-linked oxadiazolyl, or C-linked pyrazinyl.

Within the context of this invention, bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl groups, include fused, spiro and bridged bicycles.

Within the context of this invention, bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl groups, include fused, spiro and bridged bicycles.

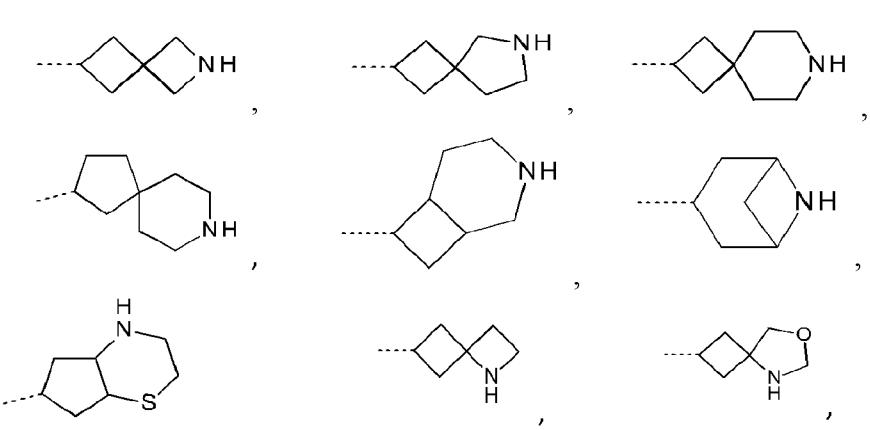
Fused bicyclic groups are two cycles that share two atoms and the bond between these atoms.
Spiro bicyclic groups are two cycles that are joined at a single atom.
Bridged bicyclic groups are two cycles that share more than two atoms.

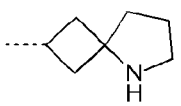
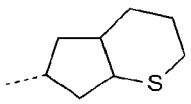
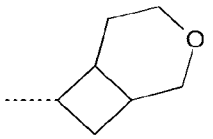
Examples of bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, include, but are not limited to



and the like.

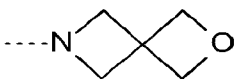
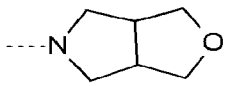
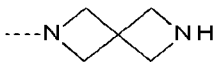
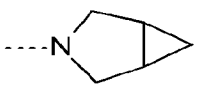
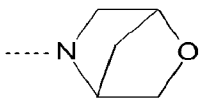
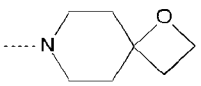
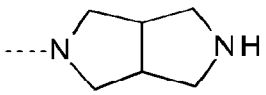
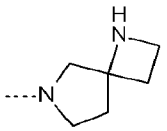
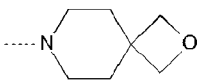
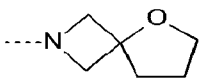
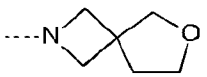
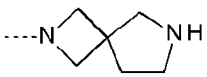
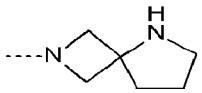
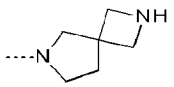
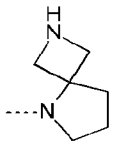
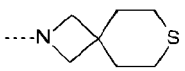
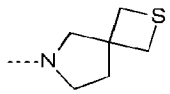
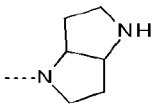
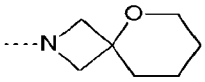
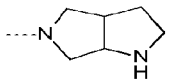
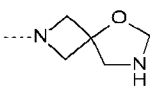
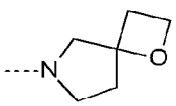
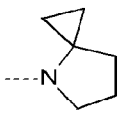
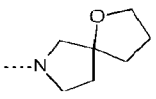
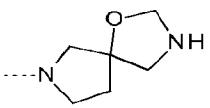
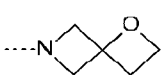
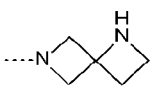
Examples of bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, include, but are not limited to

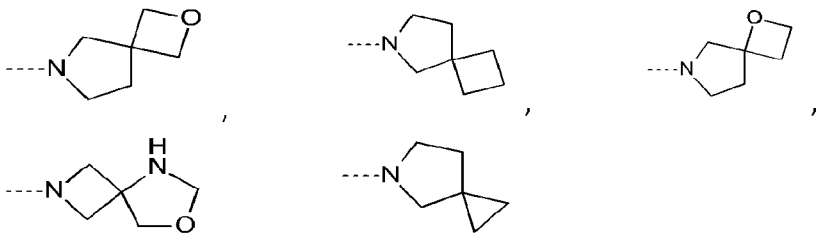


and the like.

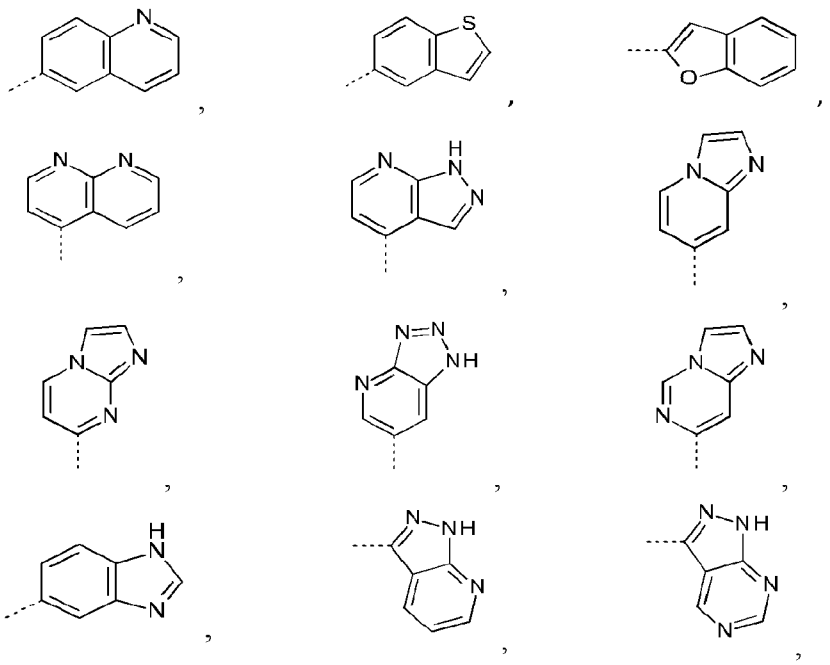
Examples of bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, include, but are not limited to



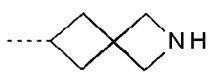
and the like.

Examples of fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two, three or four heteroatoms each independently selected from O, S, and N, include but are not limited to



and the like.

Whenever substituents are represented by chemical structure, such as for example



'----' represents the bond of attachment to the remainder of the molecule of Formula (I).

When any variable occurs more than one time in any constituent, each definition is independent.

When any variable occurs more than one time in any formula (e.g. Formula (I)), each definition is independent.

In this context, it will also be clear that a term like "optionally substituted with one, two or

three substituents selected from the group consisting of" is equivalent to "optionally substituted with one, two or three substituents each independently selected from the group consisting of".

In general, whenever the term 'substituted' is used in the present invention, it is meant, unless otherwise indicated or clear from the context, to indicate that one or more hydrogens, in particular from 1 to 4 hydrogens, more in particular from 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using 'substituted' are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture. In a particular embodiment, when the number of substituents is not explicitly specified, the number of substituents is one.

Combinations of substituents and/or variables are permissible only if such combinations result in chemically stable compounds. 'Stable compound' is meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture.

The skilled person will understand that the term 'optionally substituted' means that the atom or radical indicated in the expression using 'optionally substituted' may or may not be substituted (this means substituted or unsubstituted respectively).

When two or more substituents are present on a moiety they may, where possible and unless otherwise indicated or clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.

Within the context of this invention 'saturated' means 'fully saturated', if not otherwise specified.

Unless otherwise specified or clear from the context, aromatic rings and heterocyclyl goups, can be attached to the remainder of the molecule of Formula (I) through any available ring carbon atom (C-linked) or nitrogen atom (N-linked).

Unless otherwise specified or clear from the context, aromatic rings and heterocyclyl goups, may optionally be substituted, where possible, on carbon and/or nitrogen atoms according to the embodiments.

The term "subject" as used herein, refers to an animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medicinal doctor

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or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "treatment", as used herein, is intended to refer to all processes wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

The term "compound(s) of the (present) invention" or "compound(s) according to the (present) invention" as used herein, is meant to include the compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof.

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. *R*, *S*) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

Hereinbefore and hereinafter, the term "compound(s) of Formula (I)" is meant to include the tautomers thereof and the stereoisomeric forms thereof.

The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture.

Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present invention.

Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration.

Substituents on bivalent cyclic saturated or partially saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration.

Therefore, the invention includes enantiomers, atropisomers, diastereomers, racemates, *E*

isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

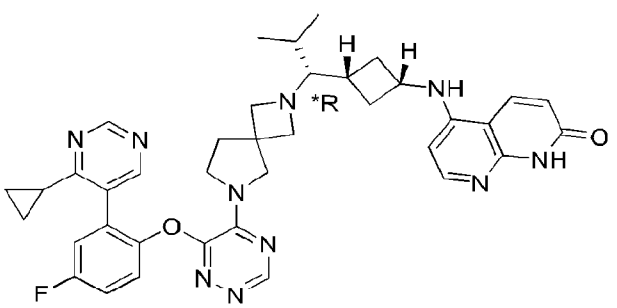
The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either *R* or *S*. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

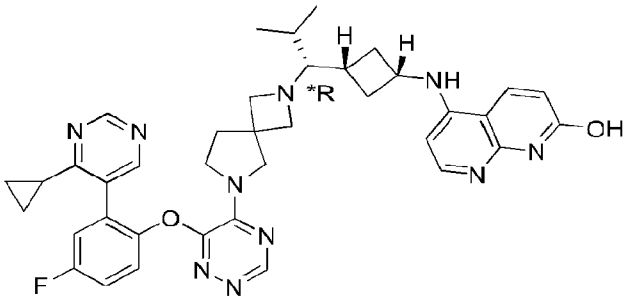
When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of Formula (I) is for instance specified as (*R*), this means that the compound is substantially free of the (*S*) isomer; when a compound of Formula (I) is for instance specified as *E*, this means that the compound is substantially free of the *Z* isomer; when a compound of Formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds according to Formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above Formula (I) are intended to be included within the scope of the present invention. It follows that a single compound may exist in both stereoisomeric and tautomeric form.

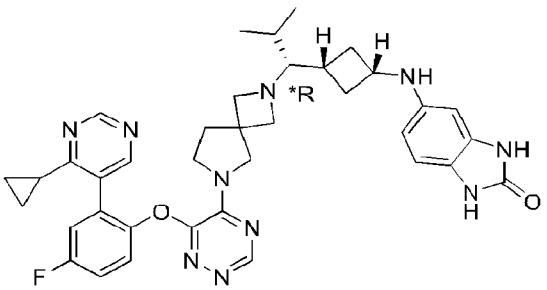
For example



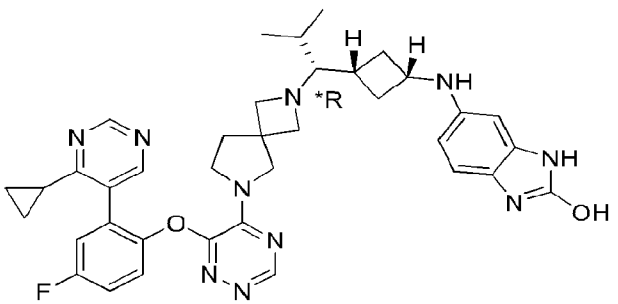
also covers the other tautomeric form



For example



also covers the other tautomeric form



Pharmaceutically acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form with one or more equivalents of an appropriate base or acid, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

The pharmaceutically acceptable salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base salt forms which the compounds of Formula (I) and solvates thereof, are able to form.

Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic

acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of Formula (I) and solvates thereof containing an acidic proton may also be converted into their non-toxic metal or amine salt forms by treatment with appropriate organic and inorganic bases.

Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, cesium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term solvate comprises the solvent addition forms as well as the salts thereof, which the compounds of Formula (I) are able to form. Examples of such solvent addition forms are e.g. hydrates, alcoholates and the like.

The compounds of the invention as prepared in the processes described below may be synthesized in the form of mixtures of enantiomers, in particular racemic mixtures of enantiomers, that can be separated from one another following art-known resolution procedures. A manner of separating the enantiomeric forms of the compounds of Formula (I), and pharmaceutically acceptable salts, and solvates thereof, involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The term "enantiomerically pure" as used herein means that the product contains at least 80% by weight of one enantiomer and 20% by weight or less of the other enantiomer. Preferably the product contains at least 90% by weight of one enantiomer and 10% by weight or less of the other enantiomer. In the most preferred embodiment the term "enantiomerically pure" means that the composition contains at least 99% by weight of one enantiomer and 1% or less of the

other enantiomer.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature).
All isotopes and isotopic mixtures of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C , ^{13}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the isotope is selected from the group of ^{2}H, ^{3}H, ^{11}C and ^{18}F. More preferably, the isotope is ^{2}H. In particular, deuterated compounds are intended to be included within the scope of the present invention.
Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) may be useful for example in substrate tissue distribution assays. Tritiated (^{3}H) and carbon-l4 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies. PET imaging in cancer finds utility in helping locate and identify tumours, stage the disease and determine suitable treatment. Human cancer cells overexpress many receptors or proteins that are potential disease-specific molecular targets. Radiolabelled tracers that bind with high affinity and specificity to such receptors or proteins on tumour cells have great potential for diagnostic imaging and targeted radionuclide therapy (Charron, Carlie L. et al. Tetrahedron Lett. 2016, 57(37), 4119-4127). Additionally, target-specific PET radiotracers may be used as biomarkers to examine and evaluate pathology, by for example, measuring target expression and treatment response (Austin R. et al. Cancer Letters (2016), doi: 10.1016/j.canlet.2016.05.008).

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-

membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O-, -S-, or $-NR^{5c}-$;

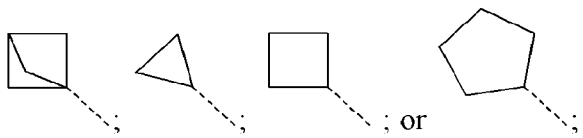
R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents C_{1-5}alkyl;



R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of Het^1, Het^2, Cy^2 and $-C_{1-6}$alkyl-$NR^{xc}R^{xd}$;

R^{xc} represents Cy^1; Het^5; $-C_{1-6}$alkyl-Cy^1; $-C_{1-6}$alkyl-Het^3; $-C_{1-6}$alkyl-Het^4; or $-C_{1-6}$alkyl-phenyl;

R^{xd} represents hydrogen; C_{1-4}alkyl; or C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

or R^{xc} and R^{xd} are taken together to form together with the N-atom to which they are attached a 4- to 7-membered monocyclic fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected

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from the group consisting of R^6 and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, C_{1-4}alkyl, oxo, -$NR^{9a}R^{9b}$ and -OH;

Het^2 represents C-linked pyrazolyl or triazolyl; which is substituted on one nitrogen atom with R^{6a};

R^6 is selected from the group consisting of
Hct^3; -C(=O)-NH-R^8;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl-C_{3-6}cycloalkyl,
-C(=O)-OH, -$NR^{11a}R^{11b}$, and -NH-S(=O)$_2$-C_{1-4}alkyl; and
C_{3-6}cycloalkyl optionally substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -NH-S(=O)$_2$-C_{1-4}alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl and -NH-S(=O)$_2$-C_{1-4}alkyl;

R^{6a} represents C_{1-6}alkyl substituted with one substituent selected from the group consisting of -$NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

R^8 represents C_{1-6}alkyl optionally substituted with one, two or three substituents each independently selected from -OH, halo, cyano, -$NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

Het^3 and Het^5 each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or S(=O)$_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or S(=O)$_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -OH, -$NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^{3a} and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom, and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be

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substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom, and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -OH, $-NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said 5-membered aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl; and wherein said 5- or 6-membered aromatic ring is optionally substituted on one carbon atom with -OH;

Het^{6a} and Het^8 each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, $-(C=O)-NR^{10a}R^{10b}$, $-O-C_{3-6}$cycloalkyl, $-S(=O)_2-C_{1-4}$alkyl, cyano, C_{1-4}alkyl, $-C_{1-4}$alkyl-OH, $-O-C_{1-4}$alkyl, $-O-(C=O)-NR^{10a}R^{10b}$, and $-O-(C=O)-C_{1-4}$alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl and $-(C=O)-NR^{10a}R^{10b}$;

Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing two N-atoms and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, $-(C=O)-NR^{10a}R^{10b}$, $-O-C_{3-6}$cycloalkyl, $-S(=O)_2-C_{1-4}$alkyl, cyano, C_{1-4}alkyl, C_{1-4}alkyl-OH, $-O-C_{1-4}$alkyl, $-O-(C=O)-NR^{10a}R^{10b}$, and $-O-(C=O)-C_{1-4}$alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl and $-(C=O)-NR^{10a}R^{10b}$;

Het^{6b} represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl

containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl, -C(=O)-Cy^3, -(C=O)-C_{1-4}alkyl-OH, -C(=O)-C_{1-4}alkyl-O-C_{1-4}alkyl, -C(=O)-C_{1-4}alkyl-$NR^{11a}R^{11b}$, and C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH, -NH-C(=O)-C_{1-4}alkyl, C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl;
Cy^2 represents C_{3-7}cycloalkyl substituted with one or two substituents each independently selected from the group consisting of -$NR^{9a}R^{9b}$; Het^{6a}; Het^{6b}; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of Het^{3a}, Het^{6a}, Het^{6b}, and -$NR^{9a}R^{9b}$; and said C_{3-7}cycloalkyl is optionally substituted with one or two additional substituents each independently selected from the group consisting of halo, R^6, C_{1-4}alkyl, and -OH;
Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; Het^5; -C_{1-4}alkyl-R^{16}; -C(=O)-C_{1-4}alkyl-Het^{3a}; -C(=O)-R^{14}; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano; and
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{15a}, R^{15b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents Het^{5a}; Het^{8a}; or
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -$NR^{13a}R^{13b}$ and Het^{8a};

R^{16} represents -C(=O)-$NR^{17a}R^{17b}$, -$S(=O)_2$-C_{1-4}alkyl, Het^5, Het^7, or Het^8;

and the pharmaceutically acceptable salts and the solvates thereof.

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The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of cyano, and C_{1-4}alkyl;

R^{1b} represents F;

Y^1 represents -O-;

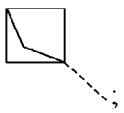
R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents C_{1-5}alkyl; or



R^3 is selected from the group consisting of Het^1 and Cy^2;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6 and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of oxo and -OH;

R^6 and R^{6a} are each independently selected from the group consisting of Het^4; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^{6a}, and Cy^1; and

C_{3-6}cycloalkyl;

R^8 represents -O-C_{1-6}alkyl;

Het^3, Het^{3a}, Het^5 and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two, three or four heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl or –(C=O)-O-C_{1-4}alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, C_{1-4}alkyl,
-O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, C_{1-4}alkyl-$NR^{11a}R^{11b}$, -NH-C(=O)-C_{1-4}alkyl, cyano, -COOH,
-NH-C(=O)-O-C_{1-4}alkyl, -NH-C(=O)-$NR^{10a}R^{10b}$, –(C=O)-O-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, Het^{8a}, -C_{1-4}alkyl- Het^{8a}, Het^{8b}, Het^9, and -C(=O)-$NR^{10a}R^{10b}$;

Het^{6a}, Het^8 and Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo,
-NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl,
-$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl, -C_{1-4}alkyl-OH, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and
-(C=O)-$NR^{10a}R^{10b}$;

Het^{6b} and Het^{8b} each independently represent a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be

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substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl, -C(=O)-Cy^3, and C_{1-4}alkyl;

Het^9 represents a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one or two carbon atoms with C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH and C_{1-4}alkyl;
Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of R^6, Het^{6a}, Het^{6b},
-$NR^{9a}R^{9b}$, -OH, and C_{1-4}alkyl;

Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-C_{3-6}cycloalkyl; Het^5; Het^7; -C_{1-4}alkyl-R^{16}; -C(=O)-C_{1-4}alkyl-Het^{3a}; -C(=O)-R^{14}; and
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, and -O-C_{1-4}alkyl;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents -O-C_{1-4}alkyl; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl and halo; or
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl, -$NR^{13a}R^{13b}$, and cyano;

R^{16} represents -C(=O)-$NR^{17a}R^{17b}$ or -$S(=O)_2$-C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and

the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

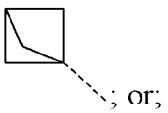
Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of cyano and C_{1-4}alkyl;

R^{1b} represents F; Y^1 represents -O-; R^2 represents hydrogen; U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents C_{1-5}alkyl or



; or;

R^3 is selected from the group consisting of Het^1 and Cy^2;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one nitrogen with R^6; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of oxo and -OH;

R^6 is selected from the group consisting of
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^{6a}, and Cy^1; and
C_{3-6}cycloalkyl;

R^{6a} represents C_{1-6}alkyl substituted with one substituent selected from the group consisting of Het^{3a} and Het^{6a};

Het^3 and Het^5 each independently represent a monocyclic C-linked 4- to 7-membered fully

saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl;

Het^{3a} represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom, and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said 5-membered aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl; and wherein said 5- or 6-membered aromatic ring is optionally substituted on one carbon atom with -OH;

Het^{6a} and Het^8 each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, $-(C=O)-NR^{10a}R^{10b}$, $-O-C_{3-6}$cycloalkyl, $-S(=O)_2-C_{1-4}$alkyl, cyano, C_{1-4}alkyl, $-C_{1-4}$alkyl-OH, and $-O-C_{1-4}$alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl and $-(C=O)-NR^{10a}R^{10b}$;

Het^{6b} represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, $-(C=O)-NR^{10a}R^{10b}$, $-NH-C(=O)-C_{1-4}$alkyl, $-NH-C(=O)-Cy^3$, and $-O-C_{1-4}$alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl, $-C(=O)-Cy^3$, and C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents

selected from the group consisting of -OH and C_{1-4}alkyl;
Cy^2 represents C_{3-7}cycloalkyl substituted with one or two substituents each independently selected from the group consisting of $-NR^{9a}R^{9b}$; Het^{6a}; and Het^{6b}; and said C_{3-7}cycloalkyl is optionally substituted with one or two additional substituents each independently selected from the group consisting of R^6, C_{1-4}alkyl, and -OH;
Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; Hct^5; $-C_{1-4}$alkyl-R^{16}; $-C(=O)-C_{1-4}$alkyl-Hct^{3a}; $-C(=O)-R^{14}$; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, $-O-C_{1-4}$alkyl, $-NR^{11a}R^{11b}$, and cyano; and
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -OH and $-O-C_{1-4}$alkyl;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents C_{1-4}alkyl substituted with one, two or three $-NR^{13a}R^{13b}$ substituents;

R^{16} represents $-C(=O)-NR^{17a}R^{17b}$ or $-S(=O)_2-C_{1-4}$alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one C_{1-4}alkyl;

R^{1b} represents F; Y^1 represents -O-; R^2 represents hydrogen; U represents N;

n1 is 1, n2 is 2, n3 is 1, and n4 is 1;
X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents Cy^2;

Het^{6a} represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom;

Het^{6b} represents a fused bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O and N; wherein said heterocyclyl is optionally substituted on one nitrogen with -C(=O)-C_{1-4}alkyl;

Cy^2 represents C_{3-7}cycloalkyl substituted with one substituent selected from the group consisting of Het^{6a}, Het^{6b}, and $-NR^{9a}R^{9b}$;

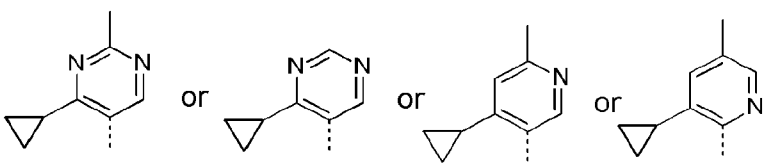
R^{9a} and R^{9b} are each independently selected from C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

The present invention relates in particular to compounds of Formula (I) as defined herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents Het;

Het represents



;

R^{1b} represents F; Y^1 represents -O-; R^2 represents hydrogen; U represents N;

n1 is 1, n2 is 2, n3 is 1, and n4 is 1;
X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^3 represents Cy^2;

Het^{6a} represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom;

Het^{6b} represents a fused bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O and N; wherein said heterocyclyl is optionally substituted on one nitrogen with -C(=O)-C_{1-4}alkyl;

Cy^2 represents cyclobutyl substituted with one substituent selected from the group consisting of Het^{6a}, Het^{6b}, and $-NR^{9a}R^{9b}$;

R^{9a} and R^{9b} are each independently selected from C_{1-4}alkyl;

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and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^2 represents hydrogen.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein n1 is 1, n2 is 2, n3 is 1, and n4 is 1.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Y^1 represents -O-.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-; and U represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein U represents N.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-; U represents N;
R^{1b} represents F; and R^2 represents hydrogen.

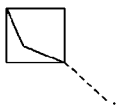
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
Y^1 represents -O-; U represents N;
R^{1b} represents F; R^2 represents hydrogen; and R^4 represents isopropyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as

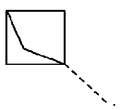
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mentioned in any of the other embodiments, wherein
R^4 represents isopropyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^4 represents

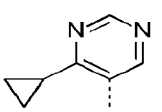


In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^4 represents isopropyl; or

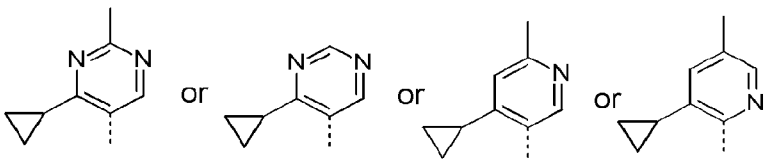


In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^6 and R^{6a} are each independently selected from the group consisting of
Het^4; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, and Cy^1; and C_{3-6}cycloalkyl;
Het^3, Het^{3a}, Het^5 and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents



In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents



In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b} C_{1-4}alkyl, oxo, -$NR^{9a}R^{9b}$ and -OH.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of oxo and -OH.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing at least 1 N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b} C_{1-4}alkyl, oxo, -$NR^{9a}R^{9b}$ and -OH.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing at least 1 N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of oxo and -OH.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^6 is selected from the group consisting of Het^4; C_{3-6}cycloalkyl; and C_{1-6}alkyl optionally further substituted with one or two substituents each independently selected from the group consisting of Het^3 and Cy^1.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^6 and R^{6a} are each independently selected from the group consisting of
Het^3; Het^4; -C(=O)-NH-Cy^1; -C(=O)-NH-R^8;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl-C_{3-6}cycloalkyl,
-C(=O)-OH, -$NR^{11a}R^{11b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl; and
C_{3-6}cycloalkyl substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl,
-NH-$S(=O)_2$-C_{1-4}alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl and
-NH-$S(=O)_2$-C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^6 is selected from the group consisting of
Het^3; -C(=O)-NH-R^8;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl-C_{3-6}cycloalkyl,

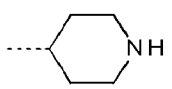
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-C(=O)-OH, -$NR^{11a}R^{11b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl; and
C_{3-6}cycloalkyl substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl and -NH-$S(=O)_2$-C_{1-4}alkyl;
R^{6a} represents C_{1-6}alkyl substituted with one substituent selected from the group consisting of -$NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^6 and R^{6a} are each independently selected from the group consisting of Het^4; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^{6a}, and Cy^1.
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^6 is selected from the group consisting of Het^4; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^{6a}, and Cy^1;
R^{6a} represents C_{1-6}alkyl substituted with one substituent selected from the group consisting of Het^{3a} and Het^{6a}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^6 is selected from the group consisting of Het^4; and C_{1-6}alkyl optionally further substituted with one or two substituents each independently selected from the group consisting of Het^3 and Cy^1.

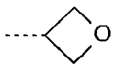
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 represents



optionally substituted on the nitrogen as defined in any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^3 represents

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In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl; and R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one cyano.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 5- or 6-membered aromatic ring containing one or two nitrogen atoms; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one cyano; and R^{1b} represents F.

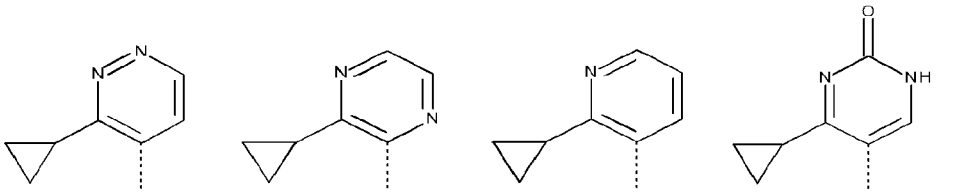
In an embodiment, the present invention relates to those compounds of Formula (I) and the

pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl; and
R^{1b} represents F.

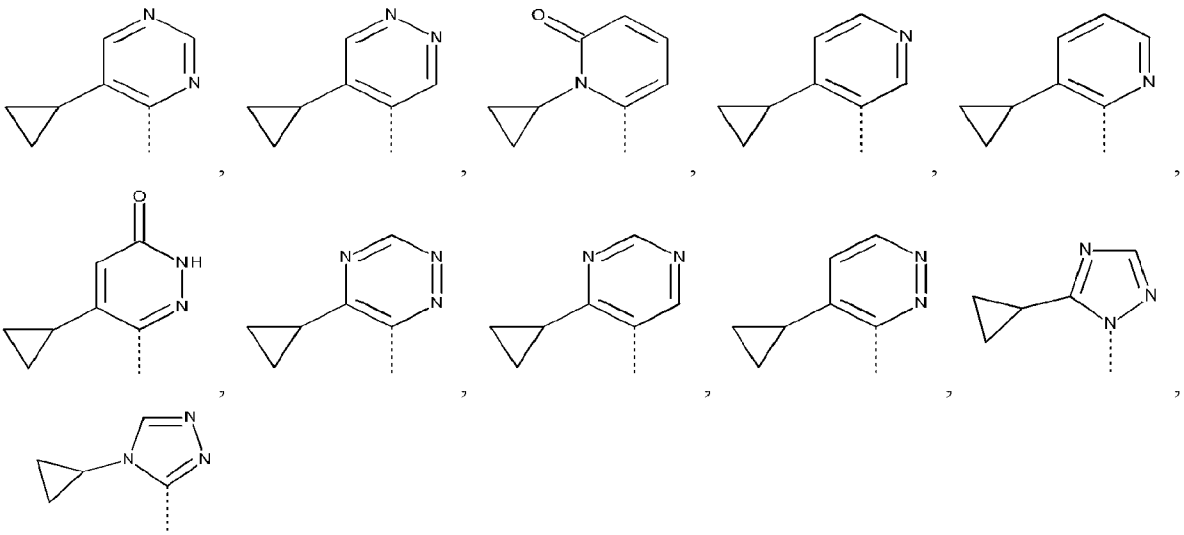
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl.
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents a monocyclic 6-membered aromatic ring containing one, two or three nitrogen atoms; wherein said monocyclic 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl; and
R^{1b} represents F.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het represents



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or ,

each optionally substituted with one cyano or C_{1-4}alkyl.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^3 represents Cy^2.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is substituted with one, two, three or four substituents each independently selected from the group consisting of Het^{6a}, Het^{6b}, and $-NR^{9a}R^{9b}$.

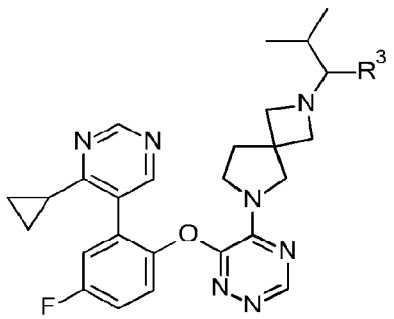
In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is substituted with one or two substituents each independently selected from the group consisting of Het^{6a} and Het^{6b}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^3 represents Cy^2; and Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is substituted with one or two substituents each independently selected from the group consisting of Het^{6a} and Het^{6b}.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^3 represents cyclobutyl substituted as defined in any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the

pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to compounds of Formula (I-y):

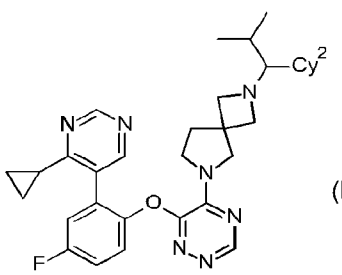


(I-y)

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wherein R^3 is as defined for the compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

In an embodiment, the present invention relates to those compounds of Formula (I) and the pharmaceutically acceptable salts, and the solvates thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein the compounds of Formula (I) are restricted to compounds of Formula (I-z):

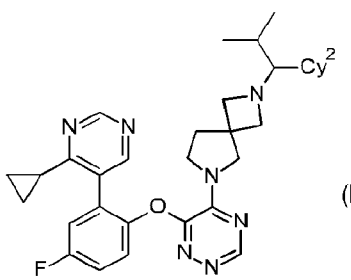


(I-z)

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wherein Cy^2 is as defined for the compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments.

In an embodiment, the present invention concerns novel compounds of Formula (I-z),



(I-z)

,

and the tautomers and the stereoisomeric forms thereof, wherein

Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is substituted on one or two carbon

atoms with one substituent selected from the group consisting of Het^{6a}, Het^{6b}, and $-NR^{9a}R^{9b}$;
R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen;
C_{1-4}alkyl; C_{3-6}cycloalkyl; $-C(=O)-C_{1-4}$alkyl; $-C(=O)-C_{3-6}$cycloalkyl; and
$-S(=O)_2-C_{1-4}$alkyl;

Het^{6a} represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of $-O-C_{1-4}$alkyl; $-O-C_{3-6}$cycloalkyl; $-S(=O)_2-C_{1-4}$alkyl; and C_{1-4}alkyl;

Het^{6b} represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O and N; wherein said heterocyclyl is optionally substituted on one carbon atom with one $-O-C_{1-4}$alkyl; and in case a second nitrogen atom is present in said heterocyclyl, said second nitrogen atom is substituted with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl and C_{1-4}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the present invention relates to a subgroup of Formula (I) as defined in the general reaction schemes.

In an embodiment the compound of Formula (I) is selected from the group consisting of any of the exemplified compounds,
tautomers and stereoisomeric forms thereof,
and the free bases, any pharmaceutically acceptable salts, and the solvates thereof.

All possible combinations of the above indicated embodiments are considered to be embraced within the scope of the invention.

METHODS FOR THE PREPARATION OF COMPOUNDS OF FORMULA (I)

In this section, as in all other sections unless the context indicates otherwise, references to Formula (I) also include all other sub-groups and examples thereof as defined herein.
The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art of organic chemistry. The following schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.
Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes commonly used by those skilled in the art.

The skilled person will realize that in the reactions described in the Schemes, although this is not always explicitly shown, it may be necessary to protect reactive functional groups (for example hydroxy, amino, or carboxy groups) where these are desired in the final product, to avoid their unwanted participation in the reactions. In general, conventional protecting groups can be used in accordance with standard practice. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The skilled person will realize that in the reactions described in the Schemes, it may be advisable or necessary to perform the reaction under an inert atmosphere, such as for example under N_2-gas atmosphere.

It will be apparent for the skilled person that it may be necessary to cool the reaction mixture before reaction work-up (refers to the series of manipulations required to isolate and purify the product(s) of a chemical reaction such as for example quenching, column chromatography, extraction).

The skilled person will realize that heating the reaction mixture under stirring may enhance the reaction outcome. In some reactions microwave heating may be used instead of conventional heating to shorten the overall reaction time.

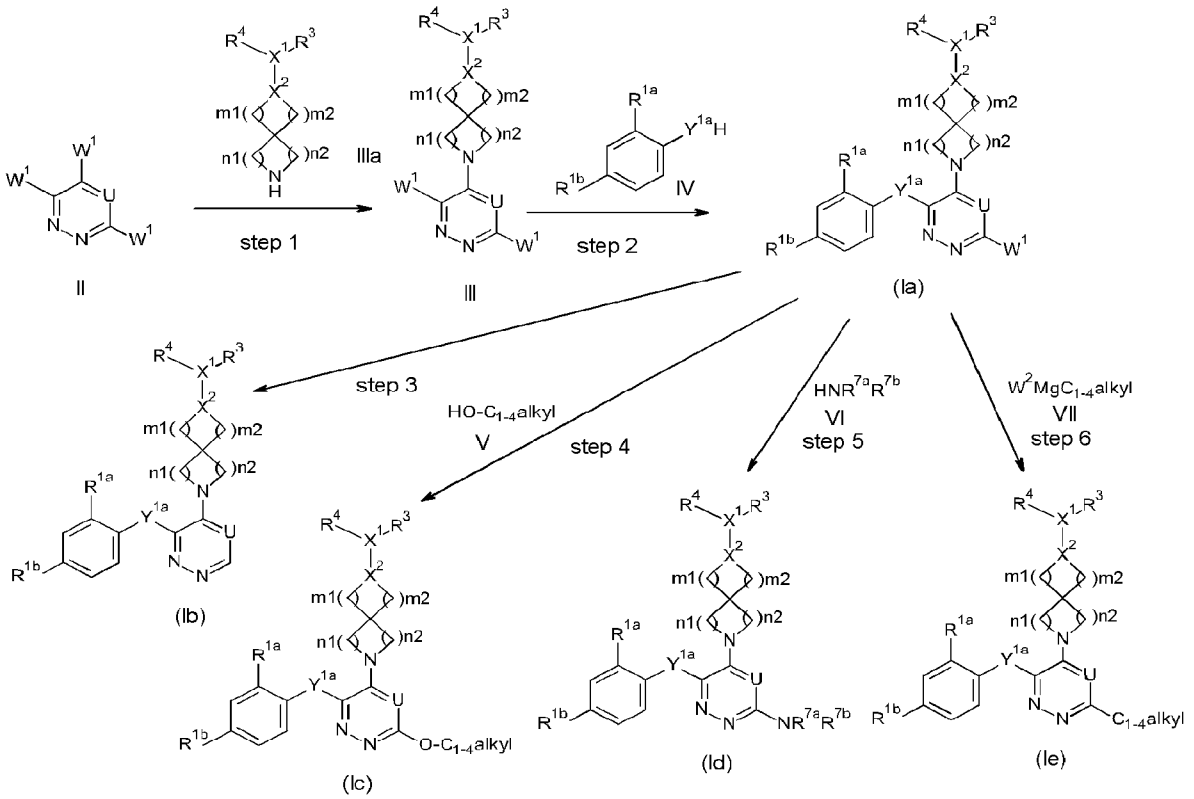
The skilled person will realize that another sequence of the chemical reactions shown in the Schemes below, may also result in the desired compound of Formula (I).

The skilled person will realize that intermediates and final compounds shown in the Schemes below may be further functionalized according to methods well-known by the person skilled in the art. The intermediates and compounds described herein can be isolated in free form or as a salt, or a solvate thereof. The intermediates and compounds described herein may be synthesized in the form of mixtures of tautomers and stereoisomeric forms that can be separated from one another following art-known resolution procedures.

SCHEME 1

In general, compounds of Formula (I) wherein Y^1 is limited to Y^{1a} being -O- or -NR^{5c}-, hereby named compounds of Formula (Ia), (Ib), (Ic), (Id), (Ie), can be prepared according to the following reaction Scheme 1. In Scheme 1, W^1 represents fluoro, chloro , bromo or iodo; all other variables are defined according to the scope of the present invention.

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In Scheme 1, the following reaction conditions apply:

Step 1: at a suitable temperature such as ranged from room temperature to 90 °C, in the presence of a suitable base such as for example diisopropylethylamine or triethylamine or sodium carbonate, in a suitable solvent such as for example acetonitrile or dimethylformamide or dichloromethane;

Step 2: at a suitable temperature range from room temperature to 130°C, in presence of a suitable base such as for example cesium carbonate, in a suitable solvent such as for example dimethylformamide or 1-methyl-2-pyrrolidinone;

Alternatively, at a suitable temperature such as for example room temperature, in the presence of a suitable deprotonating agent such as for example sodium hydride, in a suitable solvent such as for example dimethylsulfoxide;

Alternatively, at a suitable temperature such as room temperature, in the presence a suitable base such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), in a suitable solvent such as for example tetrahydrofuran;

Step 3: at a suitable temperature such as room temperature, in the presence of a suitable catalyst such as palladium on charcoal (Pd/C), in a suitable solvent such as methanol, under H_2 pressure such as for example from 1 to 3 bar, optionally in the presence of a base such as triethylamine;

Alternatively, at a suitable temperature such as room temperature, in the presence of a suitable

catalyst such as for example 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, a suitable reducing agent such sodium borohydride, a suitable base such as for example *N,N,N',N'*-tetramethylethylenediamine, in a suitable solvent such as for example tetrahydrofuran;

Step 4: at a suitable temperature range from 100 to 130°C, in presence of a suitable base such as for example cesium carbonate, in a suitable solvent such as for example dimethylformamide or 1-methyl-2-pyrrolidinone;

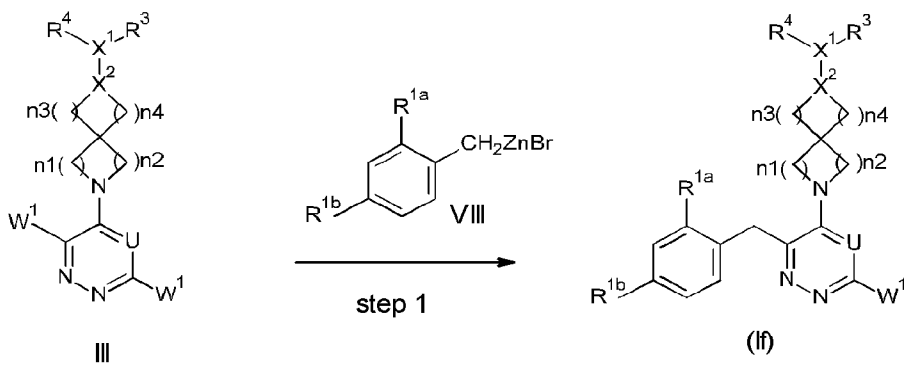
Step 5: at a suitable temperature range from 100 to 130°C, in presence of a suitable base such as for example cesium carbonate, in a suitable solvent such as for example dimethylformamide or 1-methyl-2-pyrrolidinone;

alternatively, at a suitable temperature ranged from 80 to 100°C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$), in presence of a suitable ligand such as for example 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, in presence of a suitable base such as cesium carbonate, in a suitable solvent such as for example dioxane;

Step 6: at a suitable temperature from room temperature to 60°C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$) or Tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3), in presence or not of a suitable ligand such as for example triphenylphosphine, in a suitable solvent such as for example dioxane;

SCHEME 2

In general, compounds of Formula (I) wherein Y^1 is limited to -CH_2-, and R^2 is limited to W^1, hereby named compounds of Formula (If), can be prepared according to the following reaction Scheme 2. In Scheme 2, all other variables are defined according to the scope of the present invention.



In Scheme 2, the following reaction conditions apply:

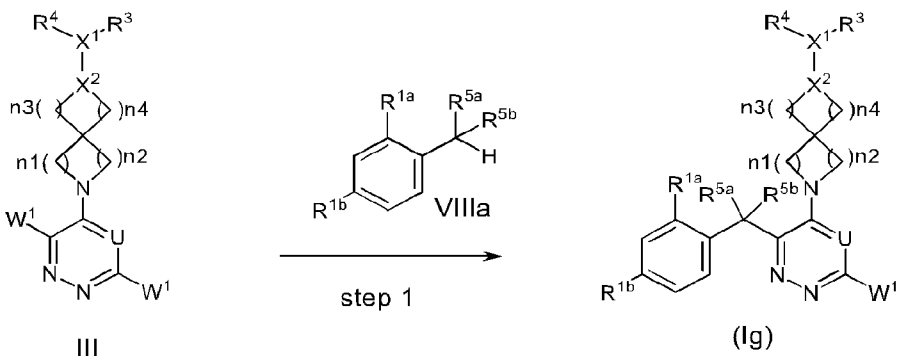
Step 1: at a suitable temperature ranged from 60°C to 100°C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$) or Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) or Tetrakis(triphenylphosphine)palladium(0), in a suitable solvent such as for

example tetrahydrofuran or dioxane.

The skilled person will realize that starting from compound (If), analogous chemistry as reported in steps 3, 4, 5 and 6 in scheme 1 could be performed.

SCHEME 3

In general, compounds of Formula (I) wherein Y^1 is limited to $-CR^{5a}R^{5b}-$ and R^2 is limited to W^1, hereby named compounds of Formula (Ig), can be prepared according to the following reaction Scheme 3. In Scheme 3 at least one of R^{5a} and R^{5b} is other than hydrogen. All other variables are defined according to the scope of the present invention.



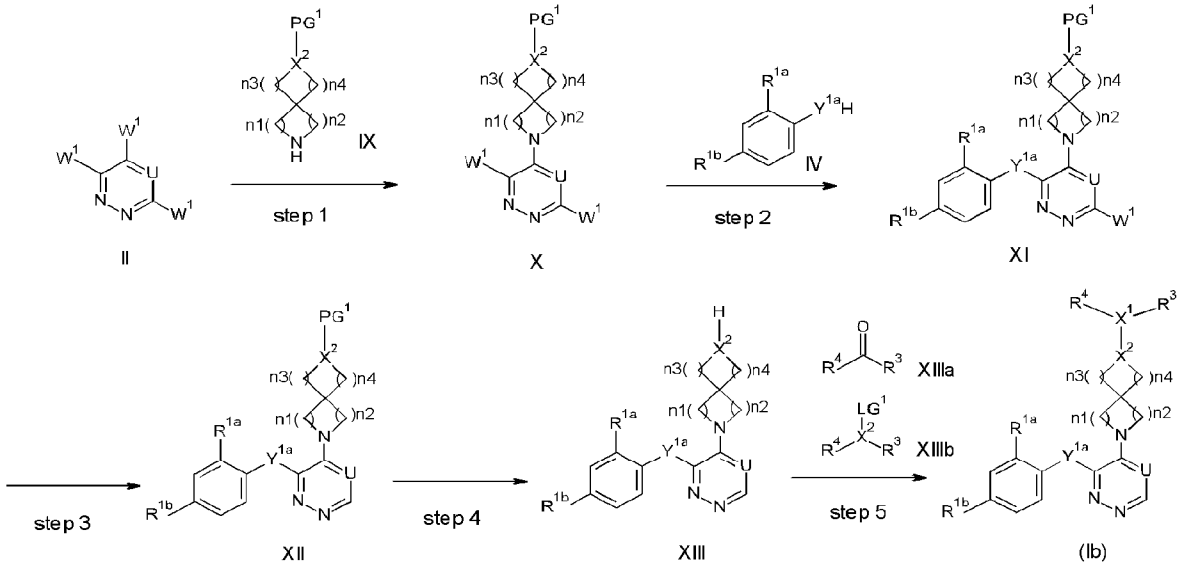
In Scheme 3, the following reaction condition apply:

Step 1: at a suitable temperature ranged from 80°C to 200°C, in presence of a suitable catalyst such as palladium acetate ($Pd(OAc)_2$), in the presence of a suitable ligand such as for example triphenylphosphine or tricyclohexylphosphine, in a suitable solvent such as for example dioxane, preferably in sealed conditions, optionally under microwave irradiation.

The skilled person will realize that starting from compound (Ig), analogous chemistry as reported in steps 3, 4, 5 and 6 in scheme 1 could be performed.

SCHEME 4

In general, compounds of Formula (I) hereby named compounds of Formula (Ib) can be alternatively prepared according to the following reaction Scheme 4. In Scheme 4, PG^1 represents a suitable protecting group, such as for example *tert*-butyloxycarbonyl and LG^1 is a leaving group such as for example chloro, bromo, iodo or tosylate or mesylate; all other variables are defined as listed before or according to the scope of the present invention.



In Scheme 4, the following reaction conditions apply:

Step 1: at a suitable temperature such as ranged from room temperature to 90 °C, in the presence of a suitable base such as for example diisopropylethylamine or triethylamine or sodium carbonate, in a suitable solvent such as for example acetonitrile or dimethylformamide or dichloromethane;

Step 2: at a suitable temperature range from room temperature to 130°C, in presence of a suitable base such as for example cesium carbonate, in a suitable solvent such as for example dimethylformamide or 1-methyl-2-pyrrolidinone;

Alternatively, at a suitable temperature such as for example room temperature, in the presence of a suitable deprotonating agent such as for example sodium hydride, in a suitable solvent such as for example dimethylsulfoxide;

Alternatively, at a suitable temperature such as room temperature, in the presence a suitable base such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), in a suitable solvent such as for example tetrahydrofuran;

Step 3: at a suitable temperature such as room temperature, in the presence of a suitable catalyst

such as palladium on charcoal (Pd/C), in a suitable solvent such as methanol, under H_2 pressure such as for example from 1 to 3 bar;

Alternatively, at a suitable temperature such as room temperature, in the presence of a suitable catalyst such as for example 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, a suitable reducing agent such sodium borohydride , a suitable base such as for example *N,N,N',N'*-tetramethylethylenediamine, in a suitable solvent such as for example tetrahydrofuran;

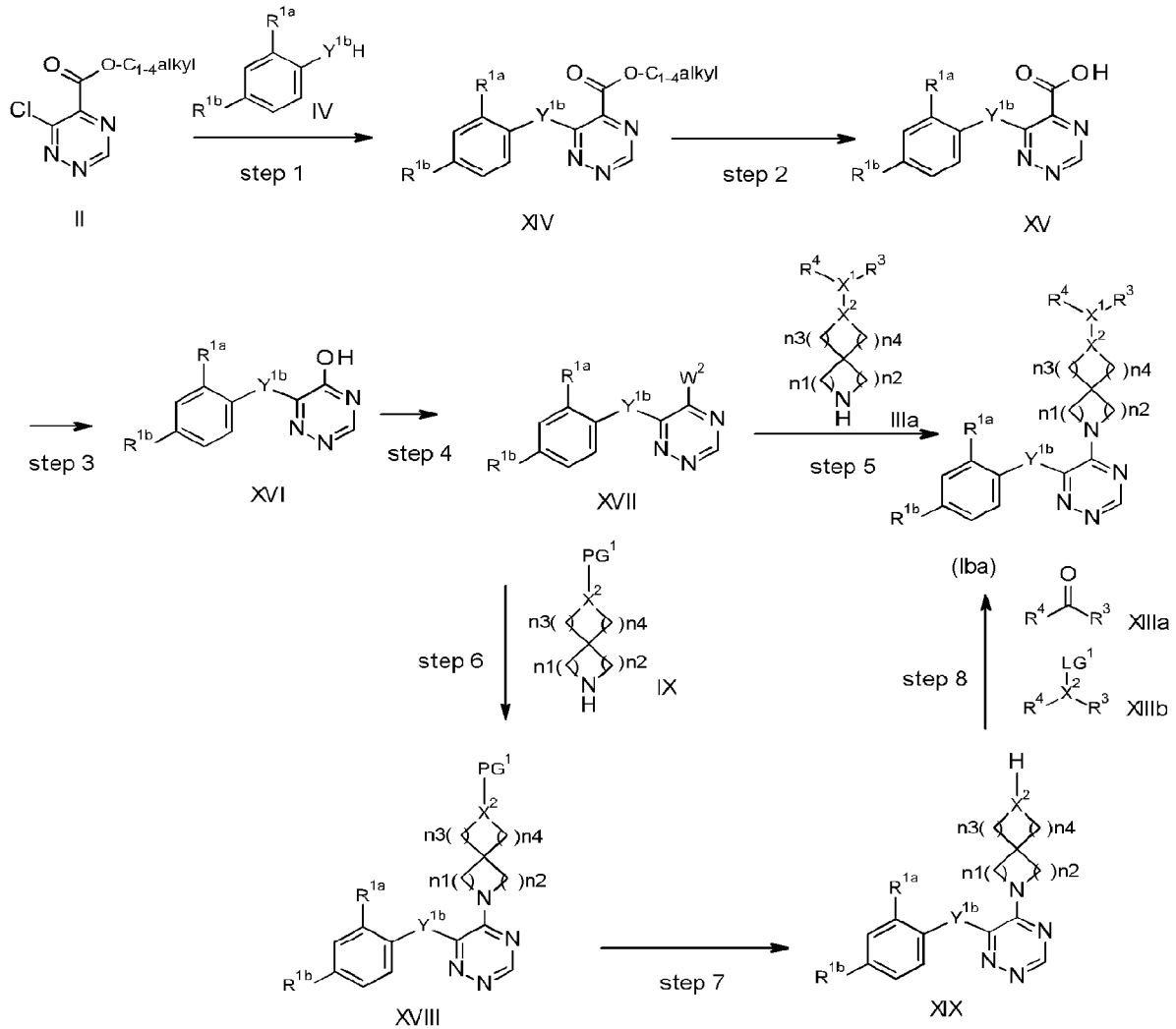
Step 4: when PG^1 is *tert*-butyloxycarbonyl, at a suitable temperature range such as for example from 0 °C to room temperature, in the presence of suitable cleavage conditions, such as for example an acid such as HCl or trifluoroacetic acid in a suitable solvent such as acetonitrile or DCM or methanol (MeOH);

Step 5: represents all type of reactions, such as for examples reductive amination, nucleophilic substitution, leading to final examples (Ib);

The skilled person will realize that starting from intermediate XI, analogous chemistry as reported in steps 3, 4, 5 and 6 in scheme 1 could be performed.

SCHEME 5

In general, compounds of Formula (I) wherein U is limited to N and Y^1 is limited to Y^{1b} being O, hereby named compounds of Formula (Iba) can be prepared according to the following reaction Scheme 5. In Scheme 5, PG^1 represents a suitable protecting group, such as for example *tert*-butyloxycarbonyl and W^2 a leaving group such as for example chloro, tosylate or mesylate; all other variables are defined according to the scope of the present invention.



In Scheme 5, the following reaction conditions apply:

Step 1: at a suitable temperature such as room temperature, in the presence of a suitable base such as for example potassium carbonate, in a suitable solvent such as for example dimethylformamide;

Step 2: at a suitable temperature such as room temperature, in presence of a suitable base such as lithium hydroxyde, in a suitable solvent such as for example a mixture of tetrahydrofurane, ethanol and water;

Step 3: at a suitable temperature such as room temperature, in the presence of a dibromoisocyanurate, in a suitable solvent such as dichloroethane;

Step 4: when W^2 is chloro, at a suitable temperature range such as room temperature, in the presence of a chlorinating reagent such as oxalyl chlorine, in the presence of a catalytic amount of dimethylformamide, in the presence of a suitable base such as triethylamine, in a suitable

solvent such as dichloromethane;

When W^2 is a trifluoroethoxy, at a suitable temperature such as 65°C, in the presence of 2,2,2-trifluoroethanol as solvent or not, suitable activating agents such as 1,3-dibromo-1,3,5-triazinane-2,4,6-trione, in the presence of molecular sieve;

Step 5: At a suitable temperature such as room temperature, in the presence of a suitable base such as for example triethylamine or 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), in a suitable solvent such as for example dichloromethane or acetonitrile;

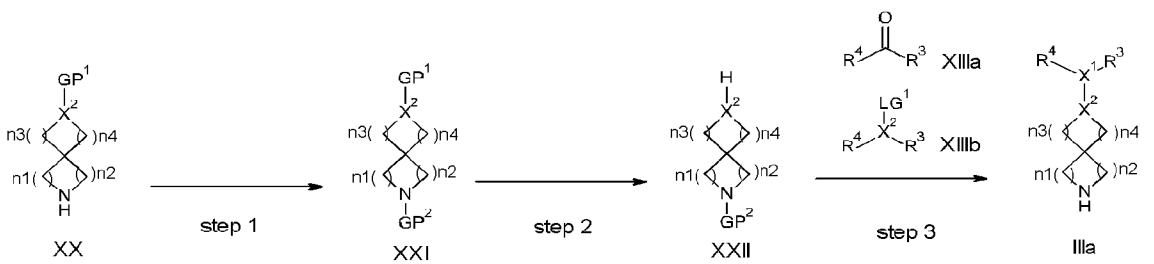
Step 6: At a suitable temperature such as room temperature, in the presence of a suitable base such as for example triethylamine or 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), in a suitable solvent such as for example dichloromethane or acetonitrile;

Step 7: when PG^1 is *tert*-butyloxycarbonyl, at a suitable temperature range such as for example from 0 °C to room temperature, in the presence of suitable cleavage conditions, such as for example an acid such as HCl or trifluoroacetic acid in a suitable solvent such as acetonitrile or DCM or methanol (MeOH);

Step 8: represents all type of reactions, such as for examples reductive amination, nucleophilic substitution leading to final examples (Iba).

SCHEME 6

In general, intermediates of formula IIIa can be prepared according to the following reaction Scheme 5. In Scheme 5, PG^2 represents a suitable protecting group, such as for example benzyloxycarbonyl; all other variables are defined according to the scope of the present invention or as defined in the previous schemes.



Step 1: at a suitable temperature such as room temperature, in the presence of benzyl chloroformate, in the presence of a suitable base such as for example triethymaine, in a suitable solvent such as for example dichloromethane;

Step 2: when PG^1 is *tert*-butyloxycarbonyl, at a suitable temperature range such as for example from 0 °C to room temperature, in the presence of suitable cleavage conditions, such as for example an acid such as HCl or trifluoroacetic acid in a suitable solvent such as acetonitrile or DCM or methanol (MeOH);

Step 3: represents all type of reactions, such as for examples reductive amination, nucleophilic substitution leading to intermediate IIIa.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) containing a basic nitrogen atom may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 4th ed., Wiley, Hoboken, New Jersey, 2007.

PHARMACOLOGY

It has been found that the compounds of the present invention block the interaction of menin with MLL proteins and oncogenic MLL fusion proteins. Therefore the compounds according to the present invention and the pharmaceutical compositions comprising such compounds may be useful for the treatment or prevention, in particular treatment, of diseases such as cancer, myelodysplastic syndrome (MDS) and diabetes.

In particular, the compounds according to the present invention and the pharmaceutical compositions thereof may be useful in the treatment or prevention of cancer. According to

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one embodiment, cancers that may benefit from a treatment with menin/MLL inhibitors of the invention comprise leukemias, myeloma or a solid tumor cancer (e.g. prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma, etc.). In some embodiments, the leukemias include acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, leukemias exphibiting *HOX/MEIS1* gene expression signatures etc.

Hence, the invention relates to compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable salts, and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament.

The present invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for use in the treatment, prevention, amelioration, control or reduction of the risk of disorders associated with the interaction of menin with MLL proteins and oncogenic MLL fusion proteins in a mammal, including a human, the treatment or prevention of which is affected or facilitated by blocking the interaction of menin with MLL proteins and oncogenic MLL fusion proteins.

Also, the present invention relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of disorders associated with the interaction of menin with MLL proteins and oncogenic MLL fusion proteins in a mammal, including a human, the treatment or prevention of which is affected or facilitated by blocking the interaction of menin with MLL proteins and oncogenic MLL fusion proteins.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for use in the treatment or prevention of any one of the diseases mentioned hereinbefore.

The invention also relates to a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for use in treating or

preventing any one of the diseases mentioned hereinbefore.

The invention also relates to the use of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds of Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable salts, and the solvates thereof, there is provided a method of treating warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore.

Said method comprises the administration, i.e. the systemic or topical administration, of a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, to warm-blooded animals, including humans.

Therefore, the invention also relates to a method for the treatment or prevention of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof.

One skilled in the art will recognize that a therapeutically effective amount of the compounds of the present invention is the amount sufficient to have therapeutic activity and that this amount varies *inter alias*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. An effective therapeutic daily amount would be from about 0.005 mg/kg to 100 mg/kg. The amount of a compound according to the present invention, also referred to herein as the active ingredient, which is required to achieve a therapeutically effect may vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to administration.

The present invention also provides compositions for preventing or treating the disorders referred to herein. Said compositions comprising a therapeutically effective amount of a compound of Formula (I), a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt, or a solvate thereof, and a pharmaceutically acceptable carrier or diluent.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further

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provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture).

The compounds of the present invention may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound according to the present invention and one or more additional therapeutic agents, as well as administration of the compound according to the present invention and each additional therapeutic agent in its own separate pharmaceutical dosage formulation.

Therefore, an embodiment of the present invention relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular condition, in particular tumour, being treated and the particular host being treated.

The following examples further illustrate the present invention.

EXAMPLES

Several methods for preparing the compounds of this invention are illustrated in the following examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification, or alternatively can be synthesized by a skilled person by using well-known methods.

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Abbreviation	Meaning
ACN	acetonitrile
AcOH	acetic acid
aq.	aqueous
Ar	argon
Boc	*tert*-butyloxycarbonyl
DCE	dichloroethane
DCM	dichloromethane
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIEA or DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
ee	enantiomeric excess
ESI	electrospray ionization
EtOAc or EA	ethyl acetate
EDCI	*N*'-(ethylcarbonimidoyl)-*N*,*N*-dimethyl-1,3-propanediamine monohydrochloride
EtOH	ethanol
h	hour(s)
min	minute(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HPLC	high performance liquid chromatography
Prep-HPLC	Preparative HPLC
Prep CC	Preparative column chromatography
MeOH	methanol
MeTHF	2-methyltetrahydrofuran
$NaBH(OAc)_3$	sodium triacetoxyborohydride
$NaBH_3CN$	sodium cyanoborohydride
$Pd(dppf)Cl_2$	[1,1′-bis(diphenyl-phosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2$·DCM	[1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane
PE	petroleum ether
RT or r.t.	room temperature
SFC	super critical fluid chromatography

Abbreviation	Meaning
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Celite®	diatomaceous earth
PyBroP	bromotripyrrolidinophosphonium hexafluorophosphate
Cbz	benzyloxycarbonyl
FCC	flash column chromatography
HOBt	1-hydroxy-1H-benzotriazole
Rf	retention factor
FA	formic acid
T_3P	propylphosphonic anhydride
i-PrMgCl	isopropylmagnesium chloride
i-PrOH or IPA	2-propanol
$iPrNH_2$	isopropylamine
'sat.' or 'Sat.'	saturated
Psi	pounds per square inch
THP	tetrahydropyran
Dess-Martin periodinane	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
Et_2O	diethylether
Na_2SO_4	sodium sulfate
$MgSO_4$	magnesium sulfate
N_2	nitrogen
NH_4Cl	ammonium chloride
$NaHCO_3$	sodium hydrogenocarbonate
Na_2CO_3	sodium carbonate
K_2CO_3	potassium carbonate
NaOH	sodium hydroxide
$LiOH.H_2O$	lithium hydroxide monohydrate
EtOH	ethanol
$LiAlH_4$	lithium aluminium hydride
HCl	hydrochloric acid
$ZnCl_2$	zinc chloride
Na_2SO_3	sodium sulfite
$NH_3.H_2O$	ammonium hydroxide

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Abbreviation	Meaning
v/v	volume to volume
Pd(amphos)Cl_2	Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)
SPhos Pd G2	Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TBAF	Tetra-n-butylammonium fluoride
TBACN	Tetrabutylammonium cyanide
TsCl	p-Toluenesulfonyl chloride
TsOH	p-Toluenesulfonic acid
DABCO	1,4-diazabicyclo[2,2,2]octane
KF	potassium fluoride
$(NH_4)_2S_2O_8$	Ammonium peroxydisulfate
$AgNO_3$	Silver nitrate
$NaBH_4$	Sodium borohydride
TMEDA	N,N,N',N'-tetramethylethylenediamine
EA	Ethyl acetate
Catacxium A-Pd-G3	Mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II), [(Di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
PPh_3	triphenylphosphine
Pd(PPh_3)$_4$	Tetrakis(triphenylphosphine)palladium(0)
Cs_2CO_3	Cesium Carbonate
$POCl_3$	phosphorus trichloride
LCMS	Liquid Chromatography Mass Spectometry
TMSI	Iodotrimethylsilane
Brettphos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Brettphos-Pd-G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate methanesulfonate
MTBE	ethyl tert-butyl ether
TBDPS	tert-Butyldiphenylsilyl
MeMgBr	Methyl magnesium bromide

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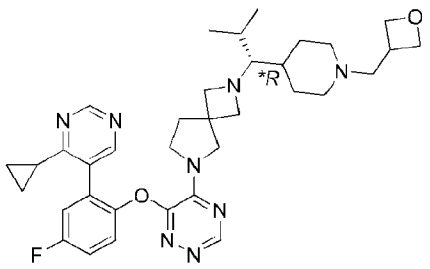
Abbreviation	Meaning
MS	Mass Spectometry
hex	n-hexane
Josiphos SL-J009-1 Pd G3	{(R)-1-[(Sp)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine}[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
DMA	dimethylacetamide
tBu XPhos or t-Bu XPhos	2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl
tBu XPhos-Pd-G3, t-BuXPhos-Pd-G3, t-BuXPhos Pd G3 or tBuXPhos Pd G3	[(2-Di-tert-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate
NMP	N-Methyl-2-pyrrolidone
t-BuONa	Sodium tert-butoxide
n-BuLi	n-butyllithium
[Ph_3P]Pd	Tetrakis(triphenylphosphine)palladium(0)

As understood by a person skilled in the art, compounds synthesized using the protocols as indicated may exist as a solvate e.g. hydrate, and/or contain residual solvent or minor impurities. Compounds isolated as a salt form, may be integer stoichiometric i.e. mono- or di-salts, or of intermediate stoichiometry. When an intermediate or compound in the experimental part below is indicated as 'HCl salt' without indication of the number of equivalents of HCl, this means that the number of equivalents of HCl was not determined.

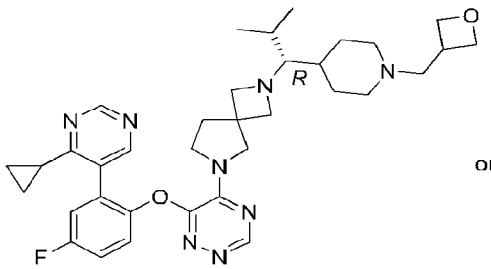
The stereochemical configuration for centers in some compounds may be designated "*R*" or "*S*" when the mixture(s) was separated; for some compounds, the stereochemical configuration at indicated centers has been designated as "**R*" or "**S*" when the absolute stereochemistry is undetermined (even if the bonds are drawn stereo specifically) although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure.

For example, it will be clear that Compound 5

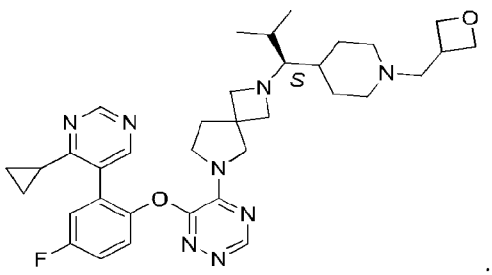
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is

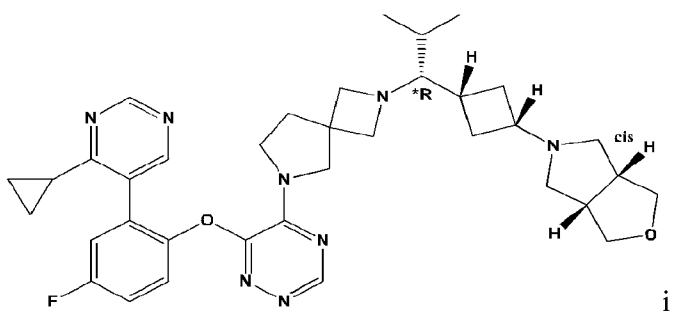


or

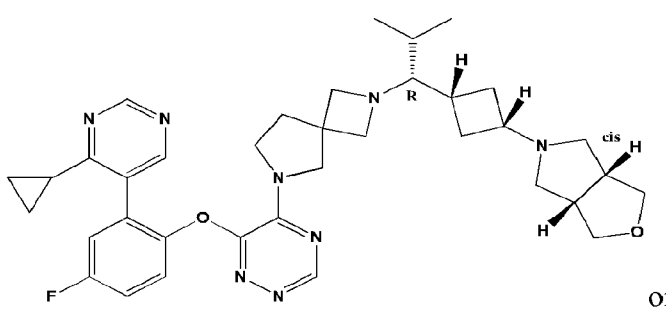


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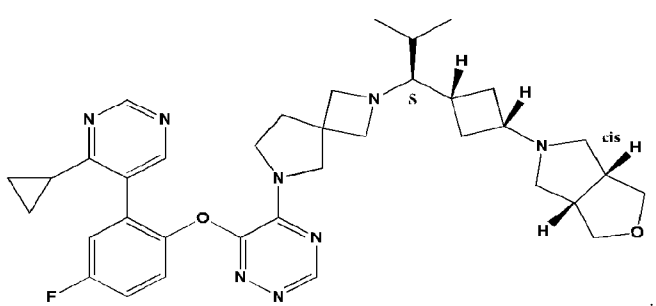
For example, it will be clear that Compound 14



is



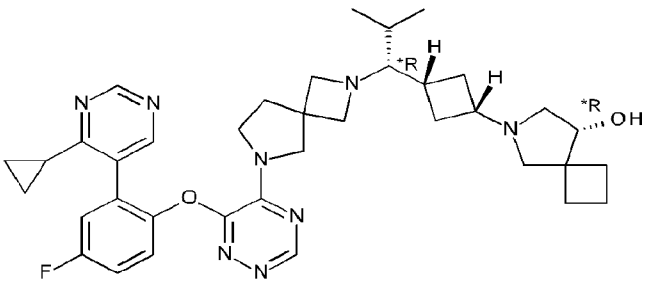
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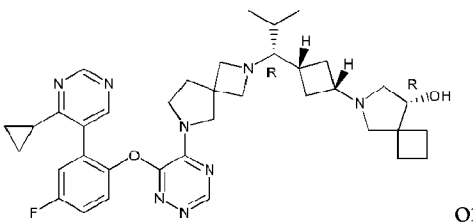
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For compounds such as for example 214 and 215, wherein the stereochemical configuration of two stereocenters is indicated by * (e.g. *R or *S), the absolute stereochemistry of the stereocenters is undetermined (even if the bonds are drawn stereospecifically), although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure. In this case, the configuration of the first stereocenter is independent of the configuration of the second stereocentre in the same compound.

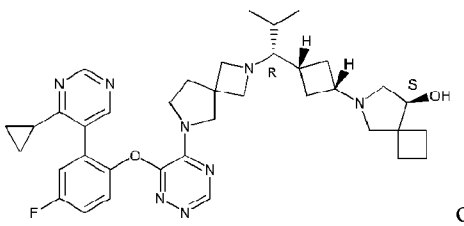
For example, for Compound 214:



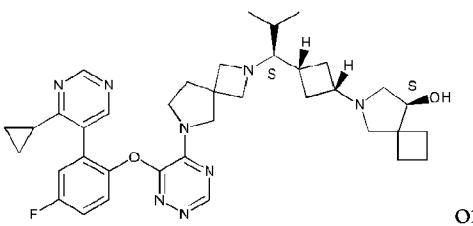
this means that the compound is



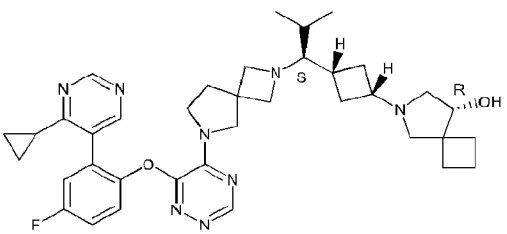
or



or



or



.

The paragraphs above about stereochemical configurations, also apply to intermediates.

The term "enantiomerically pure" as used herein means that the product contains at least 80% by weight of one enantiomer and 20% by weight or less of the other enantiomer. Preferably the product contains at least 90% by weight of one enantiomer and 10% by weight or less of the other enantiomer. In the most preferred embodiment the term "enantiomerically pure" means that the composition contains at least 99% by weight of one enantiomer and 1% or less of the other enantiomer.

A skilled person will realize that, even where not mentioned explicitly in the experimental protocols below, typically after a column chromatography purification, the desired fractions were collected and the solvent was evaporated.

In case no stereochemistry is indicated, this means it is a mixture of stereoisomers, unless

otherwise is indicated or is clear from the context.

When a stereocenter is indicated with 'RS' this means that a racemic mixture was obtained at the indicated centre, unless otherwise indicated.

A skilled person will understand that when Intermediates or Compounds are reported in Tables, the synthetic methodology from the indicated starting material to desired Intermediate/Compound might go over one or more reaction steps.

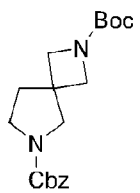
When two enantiomers, diastereomers or isomers are present in the same cell of one of the tables below (e.g. Compound 1a and Compound 1b), a skilled person will understand that these Intermediates or Compounds were separated from each other by using a suitable chromatographic method e.g. SFC or reversed phase separation.

Preparation of intermediates

For intermediates that were used in a next reaction step as a crude or as a partially purified intermediate, in some cases no mol amounts are mentioned for such intermediate in the next reaction step or alternatively estimated mol amounts or theoretical mol amounts for such intermediate in the next reaction step are indicated in the reaction protocols described below.

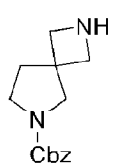
Example A1

Preparation of intermediate 2:



Benzyl chloroformate (6.03 g, 35.3 mmol) was added to a 0 °C (ice/water) mixture of *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (5.00 g, 23.6 mmol), TEA (16.5 mL, 117 mmol) and CH_2Cl_2 (50 mL). Then, DMAP (57.5 mg, 0.471 mmol) was added into the above mixture. The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated to dryness under reduced pressure to give the crude product, which was purified by FCC (eluent: petroleum ether: ethyl acetate = 100:1 to 2:1) to yield intermediate 2 (7.00 g, 83.7% yield) as a yellow oil.

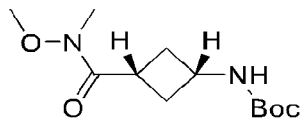
Preparation of intermediate 3:



To a solution of intermediate 2 (25.0 g, 72.2 mmol) in dry dichloromethane (15 mL) was added trifluoroacetic acid (30 mL). The reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was suspended into aqueous NaOH (4 g in H_2O (40 mL)) and extracted with dichloromethane (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield intermediate 3 (16.0 g) as a yellow oil.

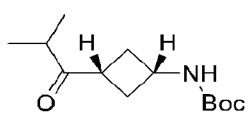
Example A2

Preparation of intermediate 5:



To a solution of *cis*-3-[[(1, 1-dimethylethoxy) carbonyl]amino] -cyclobutanecarboxylic acid (10.0 g, 46.5 mmol) in DMF (100 mL) was added HOBt (8.15 g, 60.3 mmol), EDCI (11.6 g, 60.5 mmol) and DIEA (30.0 mL, 182 mmol, 0.782 g/mL) at 0 °C. Then *N,O*-dimethylhydroxylamine hydrochloride (5.90 g, 60.5 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate (500 mL). The mixture was washed with 1 M HCl (150 mL), saturated $NaHCO_3$ (100 mL x 2) and brine (300 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate 5 (11.0 g, crude) as a white solid, which was used in the next step without further purification.

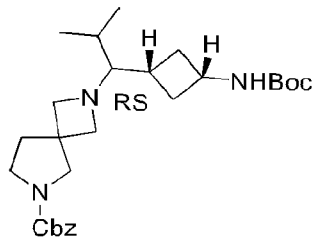
Preparation of intermediate 6:



To a solution of intermediate 5 (11.0 g, 6.97 mmol) in THF (100 mL) was added isopropylmagnesium chloride (64.0 mL, 128 mmol, 2M in THF) dropwise at 0 °C under N_2 atmosphere. The mixture was stirred at room temperature for 12 hours under N_2 atmosphere. The mixture was quenched with saturated NH_4Cl (100 mL). The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The mixture was extracted with ethyl acetate (200 mL x 2). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (eluent: petroleum ether: ethyl acetate from 1:0 to 5:1, TLC: petroleum ether: ethyl acetate = 5:1, Rf = 0.4) to yield intermediate 6 (6.30 g) as a white solid.

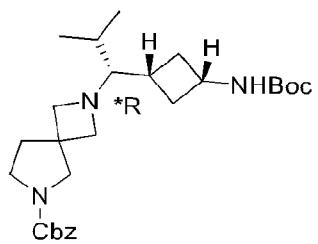
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Preparation of intermediate 7:



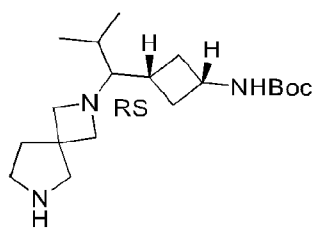
To a solution of intermediate 3 (2.80 g, 11.4 mmol) and intermediate 6 (3.00 g, 12.4 mmol) in MeOH (50 mL) was added acetic acid (1.50 g, 24.6 mmol). The mixture was stirred at 45 °C for 0.5 hrs. Then sodium cyanotrihydroborate (1.54 g, 24.5 mmol) was added. The mixture was stirred at 45 °C for 12 hrs. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with DCM (100 mL). The mixture was washed with saturated $NaHCO_3$ (50 mL x 2) and brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (eluent: dichloromethane: Methanol from 1:0 to 10:1, TLC: dichloromethane: Methanol = 10:1, Rf = 0.5) to yield intermediate 7 (3.40 g, 53.6 % purity as measured by LCMS) as a colorless oil.

Preparation of intermediate 293:



Intermediate 7 (10.0 g, 21.2 mmol) was separated by SFC (column: DAICEL CHIRALCEL OD (250mm*50mm, 10um), eluent: 25% (v/v) super critical CO_2 in 0.1% NH_3H_2O EtOH, flow rate: 200 mL/min) to yield intermediate 293 (3.80 g, 38% yield) as a yellow oil.

Preparation of intermediate 8:

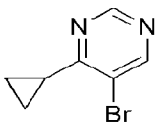


To a solution of intermediate 7 (1.00 g, 2.12 mmol, 53.6 % purity) in MeOH (50 mL) was added

1,1,2-trichloroethane (424 mg, 3.18 mmol) and Pd/C (500 mg, w/w % = 10 % Pd loading). The mixture was stirred under H_2 atmosphere (50 psi) at 40 °C for 4 hrs. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (eluent: dichlormathane: methanol (0.5 % $NH_3.H_2O$) from 1:0 to 3:1, TLC: dichloromethane: methanol (0.5 % $NH_3.H_2O$) = 3:1, Rf = 0.4) to yield intermediate 8 (380 mg, 99.1 % yield) as a white solid.

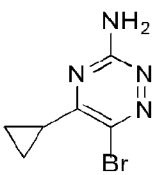
Example A3

Preparation of intermediate 10:

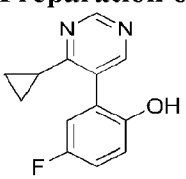


To a solution of 5-bromopyrimidine (30 g, 189 mmol) in 1000 mL of THF was added cyclopropylmagnesium bromide (396 mL, 198 mmol, 0.5 M) at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at room temperature for 4 hours, 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (42.8 g, 189 mmol) in 500 mL of THF was added drop wise into the reaction mixture at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated in vacuum and the residue was diluted with 200 mL of EtOAc and 200 mL of water, then separated and the aqueous layer was extracted with EtOAc (200 mL x 3), the combined extracts were washed with 1N NaOH (200 mL x 2), brine (200 mL), dried over Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by column chromatography (PE/EtOAc from 100/0 to 85/15) to yield intermediate 10 (21.4 g, 55% yield) as a white solid.

The intermediate reported below was prepared following an analogous methodology as described for intermediate 10 starting from the corresponding starting material:

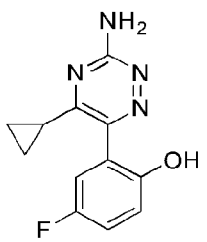
Intermediate 277	

Preparation of intermediate 11:

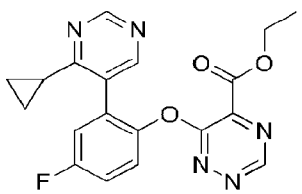


A mixture of intermediate 10 (16.4 g, 82.4 mmol), (5-fluoro-2-hydroxyphenyl)boronic acid (16.1 g, 103 mmol), $Pd(dppf)Cl_2$ (3.56 g, 4.86 mmol) and Na_2CO_3 (2M in water, 82.6 mL, 165 mmol) in dioxane (600 mL) was heated at 90 °C for 3 hours. The above reaction mixture was combined with another batch (prepared starting from 15 g of intermediate 10) for workup and purification. The combined solution was filtered through a pad of Celite® and the filtrate was concentrated in vacuum. The residue was diluted with 200 mL of EtOAc and 200 mL of water, then separated and the aqueous layer was extracted with EtOAc (200 mL x 3). The combined extracts were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated in vacuum until 100 mL left and filtered to yield intermediate 11 (20.0 g) as brown solid. The filtrate was concentrated and the residue was purified by column chromatography (PE/EtOAc from 100/0 to 50/50) to yield intermediate 11 (10 g) as a brown solid. In total: 30.0 g of intermediate 11 (84% yield).

The intermediate reported below was prepared following an analogous methodology as described for intermediate 11 starting from the corresponding intermediate:

Intermediate 278	 from intermediate 277

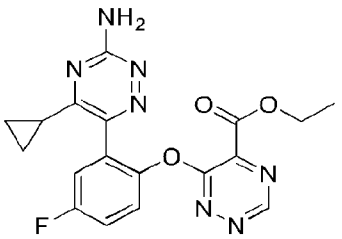
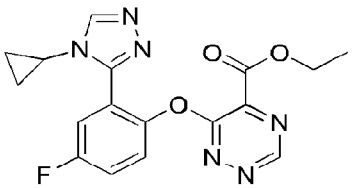
Preparation of intermediate 12:



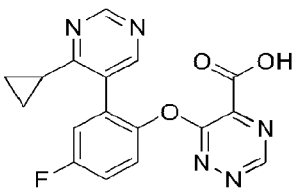
K_2CO_3 (9.27 g, 67.1 mmol) was added to a solution of intermediate 11 (5.15 g, 22.4 mmol), ethyl 6-chloro-1,2,4-triazine-5-carboxylate (5.60 g, 29.9 mmol) in DMF (50 mL). The reaction mixture was stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate (80 mL) and washed with H_2O (40 mL x 2) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by FCC (eluting with petroleum ether: ethyl acetate = 100:0 to 1:1) to yield

intermediate 12 (7.00 g, yield 59.1 %) as a white solid.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 12 starting from the corresponding intermediates:

Intermediate 279	 from intermediate 278
Intermediate 289	 from intermediate 288

Preparation of intermediate 13:



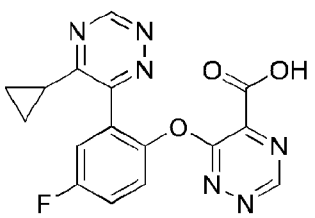
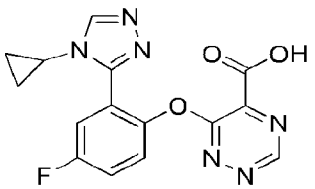
$LiOH.H_2O$ (3.85 g, 91.7 mmol) was added to a solution of intermediate 12 (7.00 g, 18.3 mmol) in THF (50 mL), H_2O (10 mL) and EtOH (5 mL). The mixture was stirred at 25 °C for 2 h. The resultant solution was acidified with 0.5M HCl to pH = 5-6, and extracted with ethyl acetate (10 mL). The aqueous phase was purified by preparative high performance liquid chromatography over Phenomenex Gemini-NX 150*30mm*5μm (eluent: (water (0.225%FA):ACN) from 95:5 to 65:35 v/v). The pure fractions were collected and the volatiles were removed under vacuum. The residue was lyophilized to remove the solvent residue completely yielding intermediate 13 (3.85 g, yield 59.4 %) as a white solid.

Alternative preparation of intermediate 13:

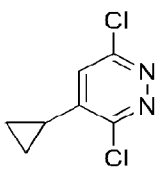
A solution of intermediate 12 (1.80 g, crude) in THF (30 mL) was added to a solution of

$LiOH{\cdot}H_2O$ (300 mg, 7.15 mmol) in H_2O (10 mL). The mixture was stirred at r.t. for 2 hours. The reaction mixture was adjusted with 1 N HCl to pH = 3~4 and then concentrated under reduced pressure to give a residue which was purified by inverse chromatography on fast silica column (Column: 80 g Agela C18, Mobile Phase A: water, Mobile Phase B: acetonitrile, Flow rate: 80 mL/min, gradient condition: from 5% B to 40% B) to yield intermediate 13 (1.40 g) as a white solid.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 13 starting from the corresponding intermediates:

intermediate 281	 from intermediate 280
intermediate 290	 from intermediate 289

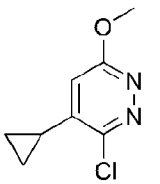
Preparation of intermediate 298:

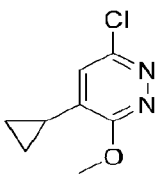


To the mixture of 3,6-dichloropyridazine (20.0 g, 134 mmol) in DCM (660 mL) and H_2O (600 mL) were added cyclopropanecarboxylic acid (23.0 g, 267 mmol), 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diiumtetrafluoroborate (95.0 g, 268 mmol) and TFA (10.0 mL, 135 mmol) at 25 °C under N_2 atmosphere. The resulting mixture was stirred at 25 °C for 5 min, then $AgNO_3$ (68.0 mL, 27.2 mmol, 0.4 M in H_2O) was added, the resulting mixture was stirred at 55 °C for 10 h under N_2 atmosphere. After cooling to RT, the reaction mixture was quenched with 2 N NaOH (90 mL) and extraction with EtOAc (500 mL x 3), the combined

organic layers were dried over Na_2SO_4. After filtration and concentration, the crude residue was purified by preparative HPLC (YMC-Triart Prep C18 250*50mm*10um, mobile phase A: water (0.225% formic acid), mobile phase B: ACN, flow rate: 100 mL/min, gradient condition from 15% B to 55% B). The desired fractions were collected and lyophilized to afford intermediate 298 (6.00 g, 24% yield) as a colorless oil.

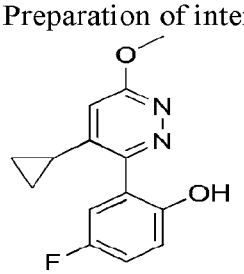
Preparation of intermediate 299 and intermediate 300:

intermediate 299: 

intermediate 300: 

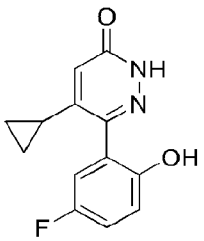
To a solution of intermediate 298 (6.00 g, 28.6 mmol) in MeOH (50 mL) was added sodium methanolate (7.72 g, 143 mmol) at 25 °C under N_2 atmosphere in portions and the reaction was stirred at this temperature for 0.5 h. The resulting mixture was quenched with 1N HCl (100 mL) to adjust the pH value to 7 and extracted with EtOAc (135 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to afford a mixture consisting of intermediate 299 and intermediate 300 (5.6 g, crude) as a colorless oil which was used directly in next step without further purification.

Preparation of intermediate 301:



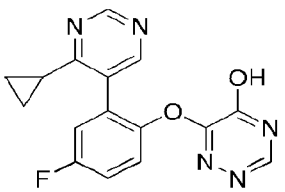
To the solution of a mixture consisting of intermediate 299 and intermediate 300 (5.60 g, crude) in dioxane (120 mL) and H_2O (24 mL) was added (5-fluoro-2-hydroxyphenyl)boronic acid (9.63 g, 61.7 mmol), Na_2CO_3 (9.82 g, 92.6 mmol) and $Pd(PPh_3)_4$ (1.78 g, 1.54 mmol). The resulting mixture reaction was stirred at 90 °C for 8 h under N_2 atmosphere. After cooling to RT, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by FCC (from PE to PE/EtOAc = 3/1) to afford intermediate 301 (1.20 g) as a white solid.

Preparation of intermediate 302:



To a solution of intermediate 301 (1.80 g, 6.92 mmol) in ACN (40 mL) were added cerium(III) chloride (2.56 g, 10.4 mmol) and NaI (1.56 g, 10.4 mmol). The resulting mixture was stirred at 70 °C for 8 h. After cooling to RT, the mixture was filtered and the filter cake was washed with EtOAc (30 mL x 2). The filtrate was concentrated under reduced pressure and the crude residue was purified by FCC (from PE to pure EtOAc) to afford intermediate 302 (1.4 g, 74% yield) as a white solid.

Preparation of intermediate 14:

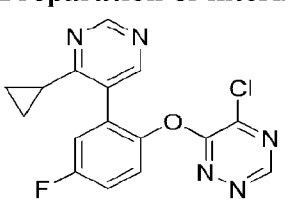


1,3-dibromo-1,3,5-triazinane-2,4,6-trione (1.22 g, 4.25 mmol) was added to a solution of intermediate 13 (1.00 g, 2.83 mmol) in DCE (20 mL). The resultant mixture was stirred at room temperature for 0.5 hours. The mixture was quenched with H_2O (1 mL), filtered, the filter cake was washed with CH_2Cl_2 (10 mL x 2), the filtrate was concentrated under reduced pressure to give the crude product, which was purified by FCC (eluting with ethyl acetate: methanol = 100:0 to 10:1) to yield intermediate 14 (600 mg, yield 60.8 %) as a yellow solid.

Alternative preparation of intermediate 14:

To a solution of intermediate 13 (700 mg, 1.98 mmol) in DCE (30 mL) was added 1,3-dibromo-1,3,5-triazinane-2,4,6-trione (900 mg, 3.14 mmol). The resultant mixture was stirred at room temperature for 0.5 hours. The suspension was isolated via filtration. The filter cake was purified by FCC (EtOAc:MeOH = 10:1) to yield intermediate 14 (500 mg, 73% yield) as a light brown solid.

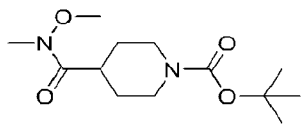
Preparation of intermediate 15:



To a solution of intermediate 14 (200 mg, 0.615 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (134 μL, 1.23 mmol) followed by 2 drops of DMF at room temperature. The mixture was stirred at this temperature for 1.5 h. The mixture was concentrated under reduced pressure to yield intermediate 15 (200 mg, crude) as a brown solid, which was used as such directly for the next reaction step.

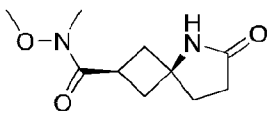
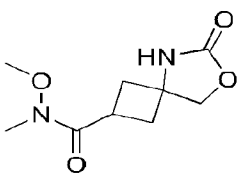
Example A4

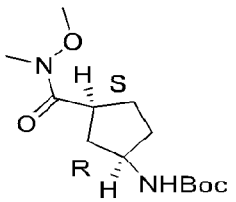
Preparation of intermediate 17:



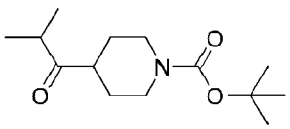
HATU (99.5 g, 262 mmol) was added in portions to a 0 °C (ice/water) mixture of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (50.0 g, 218 mmol), *N,O*-dimethylhydroxylamine hydrochloride (23.4 g, 240 mmol), and Et_3N (90.9 mL, 654 mmol) in dichloromethane (500 mL). The reaction mixture was stirred at room-temperature for 12 hours and then concentrated to dryness under reduced pressure. The residue was diluted with water (1500 mL) and extracted with dichloromethane (500 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (eluent: petroleum ether: ethyl acetate = 1: 0 to 1: 1) to yield intermediate 17 (54 g) as a yellow oil.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 17 starting from the corresponding intermediates or starting materials:

intermediate 235	 from intermediate 234
intermediate 244	 from 6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (synthesis refer to US20170283406A1)

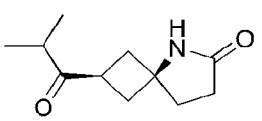
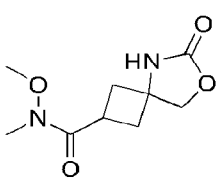
intermediate 256	 from (1*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)cyclopentane-1-carboxylic acid

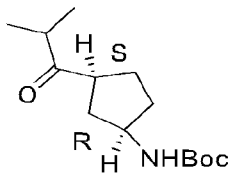
Preparation of intermediate 18:



Intermediate 17 (54.0 g, 198 mmol) and THF (500 mL) were added into a 1 L three-necked round-bottomed flask. Then, *i*-PrMgCl (198 mL, 397 mmol, 2 M in THF) was added dropwise into the mixture at 0 °C (ice/water) under N_2. The mixture was stirred with warming to room temperature for 10 hours before pouring into water (2000 mL), and extracted with EtOAc (1000 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude which was purified by FCC on silica gel (eluent: petroleum ether: ethyl acetate from 1: 0 to 2: 1, TLC: petroleum ether: ethyl acetate = 2: 1, R_f = 0.6) to yield intermediate 18 (19.2 g) as a yellow oil.

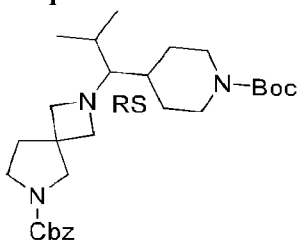
The intermediates reported below were prepared following an analogous methodology as described for intermediate 18 starting from the corresponding intermediates:

intermediate 236	 from intermediate 235
intermediate 245	 from intermediate 244

intermediate 266	 from intermediate 256

Example A5

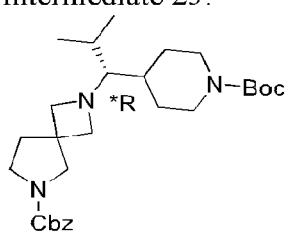
Preparation of intermediate 22:



To a solution of intermediate 3 (6.00 g, 24.4 mmol), intermediate 18 (6.22 g, 24.4 mmol) in dry methanol (180 mL) was added $ZnCl_2$ (6.64 g, 48.7 mmol). The reaction mixture was heated and stirred at 65 °C for 3 h and then, $NaBH_3CN$ (4.59 g, 73.1 mmol) was added. The reaction mixture was stirred at 65 °C for 12 hours. Then an additional amount of intermediate 18 was added (6.22 g, 24.4 mmol) and the reaction mixture was stirred at 65 °C for another 20 hours. The reaction mixture was cooled to room temperature, suspended into sat. $NaHCO_3$ (180 mL) and stirred for 30 min. The mixture was filtered and the filter cake was washed with EtOAc (50 mL). The filtrate was extracted with EtOAc (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by FCC on silica gel (eluent: petroleum ether: ethyl acetate from 1: 0 to 0: 1, TLC: petroleum ether: ethyl acetate = 0: 1, R_f = 0.3) to yield intermediate 22 (9.80 g) as a colorless oil.

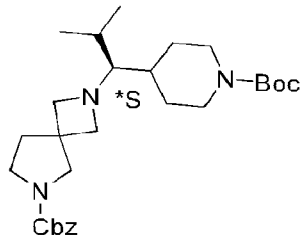
Preparation of intermediates 23 and 24:

intermediate 23:



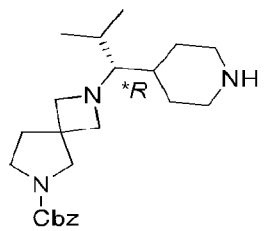
CA 03214746 2023-10-5

intermediate 24:



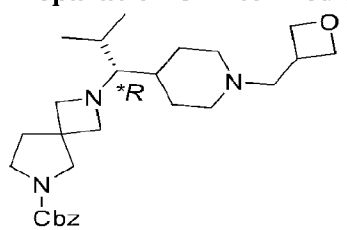
Intermediate 22 (50.0 g, 103 mmol) was further purified by SFC over DAICEL CHIRALPAK AD (isocratic elution: *i*-PrOH (containing 0.1% of 25% aq. NH_3): supercritical CO_2, 25%: 75% to 25%: 75% (v/v)). The pure fractions were collected and the volatiles were removed under reduced pressure to yield intermediate 23 (22 g, 44% yield) as a yellow oil and intermediate 24 (23 g, 46% yield) as a yellow oil.

Preparation of intermediate 26:



HCl/1,4-dioxane (10 mL, 40 mmol) was added to a solution of intermediate 23 (1.0 g, 2.1 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred at room-temperature for 3 hours. The reaction mixture was concentrated to dryness under reduced pressure, then NH_3H_2O (5 mL; concentrated, typically 25-28%)) was added into the mixture. The residue was suspended in water (10 mL) and the mixture was frozen using dry ice/acetone and then lyophilized to dryness to yield intermediate 26 (900 mg, crude), as a yellow solid, which was used in the next step without further purification.

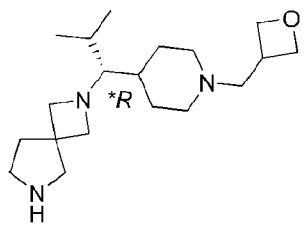
Preparation of intermediate 27:



TEA (1.3 mL, 9.3 mmol) was added to a solution of intermediate 26 (900 mg, crude) in dichloromethane (10 mL). Oxetane-3-carbaldehyde (310 mg, 14 mmol) was added to the above solution, and the resultant mixture was stirred at room-temperature of 0.5 hours. Then $NaBH(OAc)_3$ (1.5 g, 7.1 mmol) was added to the above solution, and the resultant mixture was stirred at room-temperature of 1.5 hours. The reaction mixture was diluted with

dichloromethane (30 mL) and washed with sat. $NaHCO_3$ (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC using a Waters Xbridge Prep OBD C18 150*40mm*10um with water (0.05% ammonia hydroxide v/v)/ACN from 100/0 to 20/80 (v/v) to afford pure product. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to yield intermediate 27 (500 mg), as a colorless oil.

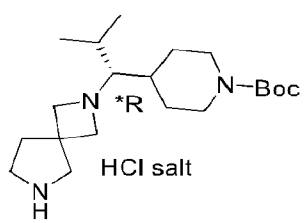
Preparation of intermediate 28:



Intermediate 27 (500 mg, 1.10 mmol), and dry Pd/C (150 mg, w/w % = 10 % Pd loading) were suspended in THF (30 mL). The reaction mixture was stirred at 45 °C for 4 hours under H_2 (50 Psi). The suspension was filtered through a pad of Celite® which was washed with THF (50 mL). The filtrate was concentrated to dryness under reduced pressure to yield intermediate 28 (350 mg) as a colorless oil which was used in the next step without further purification.

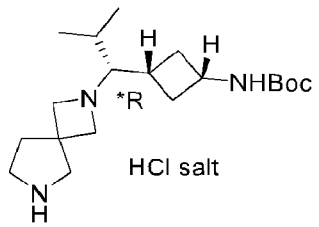
Example A6

Preparation of intermediate 25:



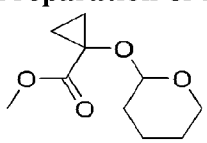
Dry Pd/C (1 g) was added to a mixture of intermediate 23 (7.5 g, 15 mmol), 1,1,2-trichloroethane (2.3 mL, 25 mmol) and MeOH (200 mL) under Ar. The mixture was stirred under H_2 (50 psi) at 40 °C for 4 hours. The mixture was filtered and the filtrate was concentrated to dryness to yield intermediate 25 as a white solid (5.8 g, HCl salt, 97% yield).

The intermediate reported below was prepared following an analogous methodology as described for intermediate 25 starting from the corresponding intermediate:

intermediate 283	 from intermediate 293

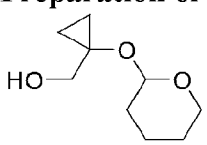
Example A7

Preparation of intermediate 1:



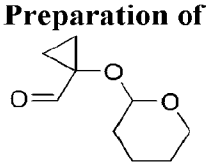
Pyridinium-*p*-toluene-sulfonic acid (2.16 g, 8.61 mmol) was added to a solution of methyl 1-hydroxycyclopropanecarboxylate (10.0 g, 86.1 mmol) and 3-4-dihydropyran (7.68 g, 91.3 mmol) in DCM (100 mL). After addition, the reaction mixture was stirred at 20 °C overnight. The reaction was washed with H_2O (70 mL), saturated aqueous brine solution (50 mL), dried over sodium sulfate and concentrated in vacuum to afford an oil. The oil was purified by FCC (PE:EA = 10:1) to yield intermediate 1 (13.5 g, 78 % yield) as a colorless oil.

Preparation of intermediate 4:



To a solution of $LiAlH_4$ (2.00 g, 52.7 mmol) in 80 mL of THF was added intermediate 1 (8.00 g, 40.0 mmol) in 20 mL of THF at 0 °C under N_2 atmosphere. After addition, the reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was cooled to 0 °C, and then water (2 mL), 10% NaOH aq. (2ml), water (6 mL) and 20 g Na_2SO_4 were added sequentially to the reaction mixture. The resulting mixture was filtered. The filter cake was washed with THF (80 mL), and the combined filtrate was concentrated under reduced pressure, to obtain the title Intermediate 3A (6.23 g, 81% yield) as a colorless oil.

Preparation of intermediate 9:

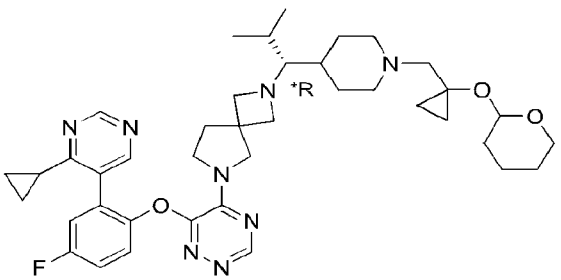


To a solution of intermediate 4 (4.00 g, 23.2 mmol) in 100 mL of DCM was added Dess-Martin periodinane (16.0 g, 37.7 mmol). After addition, the reaction mixture was stirred at 15 °C for 1.5 hours. The reaction mixture was diluted with 50 mL of DCM and stirred with 60 mL of sat.

$NaHCO_3$ and 60 mL of sat. $Na_2S_2O_3$ for 10 minutes. The mixture was then extracted with DCM (50 mL) three times. Then brine (100 mL) was added, the organic and brine layers were separated, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to yield intermediate 9 (2.98 g, 70% yield) as a light yellow oil.

Example A8

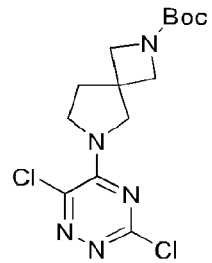
Preparation of intermediate 29:



To a solution of compound 3 (240 mg, crude) and intermediate 9 (500 mg, 2.94 mmol) in DCM (20 mL) was added TEA (363 mg, 3.59 mmol). The mixture was stirred at room temperature for 10 minutes, then $NaBH_3CN$ (300 mg, 4.77 mmol) was added in portions. The reaction mixture was stirred at rt overnight. The mixture was diluted with DCM (50 mL), washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield intermediate 29 (250 mg, crude) as a light brown oil (used as such for the next reaction step without further purification).

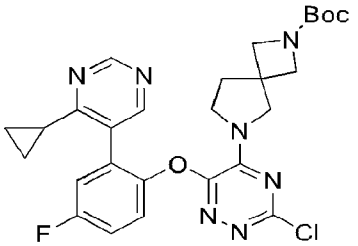
Example A9

Preparation of intermediate 30:



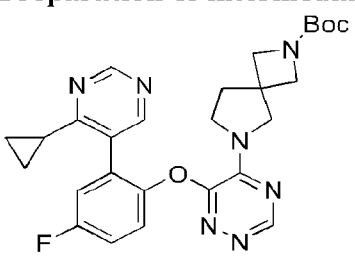
At room temperature, *tert*-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (1.27 g; 5.96 mmol) and triethylamine (1.7 mL; 11.93 mmol) were added to a stirred solution of trichlorotriazine (1.1 g; 5.96 mmol) in DCM (40 mL). The reaction mixture was stirred overnight at room temperature and, then, diluted with water and extracted with DCM. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was taken with Et_2O. The precipitate was filtered and dried to give 1.76 g of intermediate 30 (81%).

Preparation of intermediate 31:



A mixture of intermediate 30 (3.25 g; 9.017 mmol), intermediate 11 (2.18 g; 9.468 mmol) and cesium carbonate (3.23 g; 9.919 mmol) in DMF (100 mL) was stirred at r.t. overnight. The solution was cooled to r.t., poured into cold water and extracted with EtOAc. The organic layer was decanted, washed with water, then brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (5.8g) was purified by chromatography over silica gel (irregular SiOH, 40g+80g; mobile phase: gradient from 40% EtOAc, 60% heptane to 100% EtOAc, 0% heptane). The pure fractions were collected and evaporated to dryness yielding 3.41 g of (68%) intermediate 31 and 600 mg of an impure fraction which was gathered with another impure fraction (700 mg) coming from a reaction performed on 1g of intermediate 30. The resulting residue was purified by chromatography over silica gel (irregular SiOH, 24g+24g; mobile phase: gradient from 40% EtOAc, 60% heptane to 100% EtOAc, 0% heptane). The pure fractions were collected and evaporated to dryness yielding additional 1.04 g of intermediate 31.

Preparation of intermediate 32:



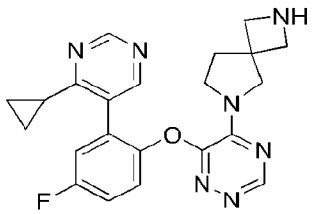
A mixture of intermediate 31 (500 mg; 0.902 mmol), Pd/C (144 mg; 0.135 mmol) in MeOH (25 mL) and triethylamine (125 µL; 0.902 mmol) was hydrogenated under a pressure of H_2 (1bar) for 40min. The catalyst was removed by filtration through a pad of Celite® and washed with DCM. The filtrate was washed with water, decanted, filtered through Chromabond® and evaporated to dryness. The residue (520mg) was purified by chromatography over silica gel (irregular SiOH, 24g; mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.5% NH_4OH, 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness yielding 300 mg (64%) of intermediate 32.

Alternative preparation :

A mixture of intermediate 31 (13.60 g, 24.58 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.00 g, 1.23 mmol), sodium borohydride

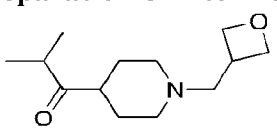
(1.58 g, 41.73 mmol) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (6.3 mL, 41.73 mmol) in THF (280 mL) was stirred overnight at room temperature under an atmosphere of nitrogen. The reaction mixture was quenched with water (250 mL) and extracted with EtOAc (4 x 250 mL). The combined organic layers were washed with water (600 mL), brine (600 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (mobile phase: EtOAc/petroleum ether 10:1). The pure fractions were collected and evaporated to dryness yielding 10.4 g (79%) of intermediate 32 as light a yellow oil.

Preparation of intermediate 33:



TFA (1 mL; 13.067 mmol) was added to a solution of intermediate 32 (300 mg; 0.577 mmol) in DCM (10 mL) and the reaction mixture was stirred for 4 hours at room temperature. The reaction was diluted with ACN and evaporated to dryness several times. The residue was then dissolved in DCM and basified with diluted 15% aqueous NH_4OH. The organic layer was decanted, washed again with water, filtered through Chromabond® and evaporated to dryness yielding 245 mg of intermediate 33.

Preparation of intermediate 34:

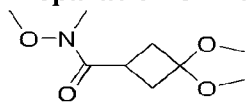


Under N_2, to a solution of 2-methyl-1-(4-piperidinyl)-1-propanone (450 mg; 0.23 mmol), oxetane-3-carbaldehyde (1g; 5.22mmol) in DCM (50mL) was added triethylamine (4.65mL; 26.13mmol). The reaction mixture was stirred at rt for 15min, then $NaBH(OAc)_3$ (3.32g; 15.7mmol) was added by portion and the reaction was stirred at r.t. overnight. The reaction mixture was diluted with water, extracted with DCM (x 2) and washed with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue (1.4 g) was purified by silica gel chromatography (Stationary phase: irregular SiOH 15-40µm 40g , Mobile phase: Gradient from 100% HEPTANE, 0% EtOAc to 80% HEPTANE, 20% EtOAc) yielding 0.88g of (75%) of intermediate 34.

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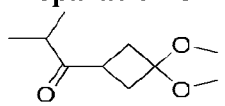
Example A10

Preparation of intermediate 35:



To a solution of 3,3-dimethoxycyclobutanecarboxylic acid (12.0 g, 75 mmol) in DCM (145 mL) was added T_3P (100 mL, 168 mmol. 50% in EtOAc) and DIEA (64 mL, 372 mmol) at 0 °C. Then *N,O*-dimethylhydroxylamine hydrochloride (8.8 g, 89.5 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 hours. The mixture was poured onto a saturated solution $NaHCO_3$ and EtOAc was added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give intermediate 35 (16.0 g, crude) which was used in the next step without further purification.

Preparation of intermediate 36:

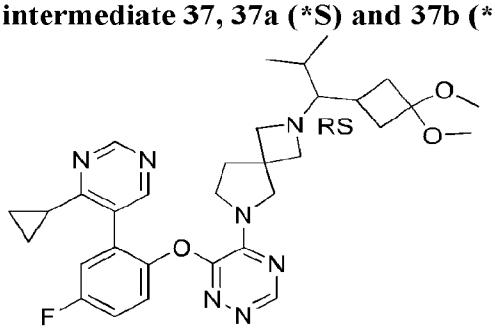


The reaction was performed twice on 15.7 g of intermediate 35 and respective reaction media were mixed for the work-up and purification.

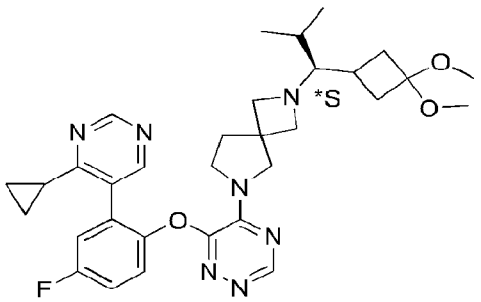
To a solution of intermediate 35 (15.7 g, 77.7 mmol) in THF (420 mL) was added isopropylmagnesium chloride (178.5 mL, 232 mmol, 2M in THF) dropwise at 0 °C under N_2 atmosphere. The reaction mixtures were stirred at room temperature for 12 hours under N_2 atmosphere and then, poured onto ice-water and a 10% aqueous solution of NH_4Cl. The mixture obtained was combined with the mixture obtained from the 2nd reaction, and the combined mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (mobile phase: Heptane: EtOAc 9:1). The pure fractions were collected and evaporated to dryness yielding 22 g (76%) of intermediate **36** as a colourless oil.

Example A11

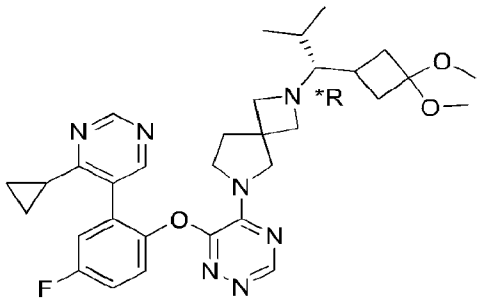
Preparation of intermediate 37, 37a (*S) and 37b (*R):

intermediate 37: 

intermediate 37a (*S):



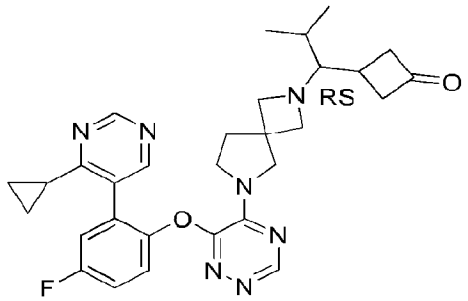
intermediate 37b (*R):



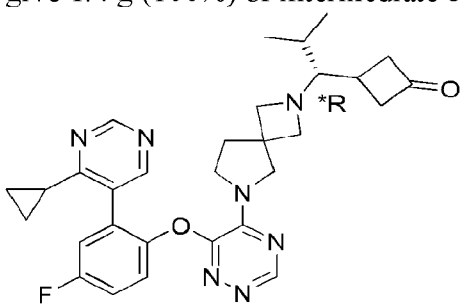
The reaction was performed twice: once on 5.09 g of intermediate 33, and once on 10.9 g of intermediate 33. The resulting crude mixtures were combined for the work up and purification.

A mixture of intermediate 33 (5.09 g; 12.14 mmol), intermediate 36 (2.26 g; 12.14 mmol), AcOH (764 µL; 13.35 mmol) and $NaBH_3CN$ (763 mg; 12.14 mmol) in MeOH (50 mL) was stirred at 50°C overnight. The two reaction mixtures were combined and poured onto a 10% aqueous solution of K_2CO_3. DCM was added. The layers were separated and then, the aqueous layer was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (mobile phase: from 100% DCM to 95% DCM, 5% MeOH, 0.5% NH_4OH). The pure fractions were collected and the solvent was evaporated to afford 7.84 g of intermediate 37. This residue was combined with other batches coming from the same reaction performed on 10.9 g of intermediate 33. Then, resulting intermediate 37 (18g) was purified by chiral SFC (CHIRALPAK AD-H 5µm 250*30 mm, mobile phase: 78% CO_2, 22% EtOH (0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated to give 9.04 g of intermediate 37a (*S) (ee100%) and 8.88 g of intermediate 37b (*R) as an off-white foam (ee 98.9%).

Preparation of intermediate 38, 38a and 38b :

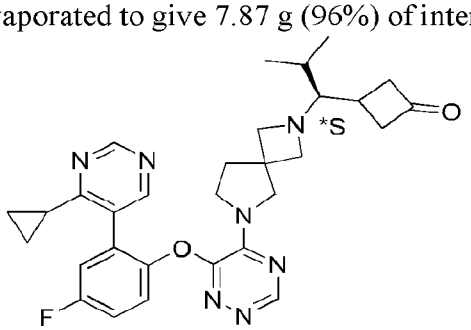
intermediate 38: 

At 5°C, TFA (4 mL; 52.7 mmol) was added dropwise to a solution of intermediate 37 (1.55 g; 2.63 mmol) in DCM (40 mL) and the reaction mixture was stirred overnight at rt. The mixture was diluted with ACN and evaporated to dryness. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1 h. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 1.4 g (100%) of intermediate 38 as an off-white foam.

intermediate 38b: 

The reaction was performed twice on 4.44 g of intermediate 37b (*R) and the obtained mixtures were combined for the work up.

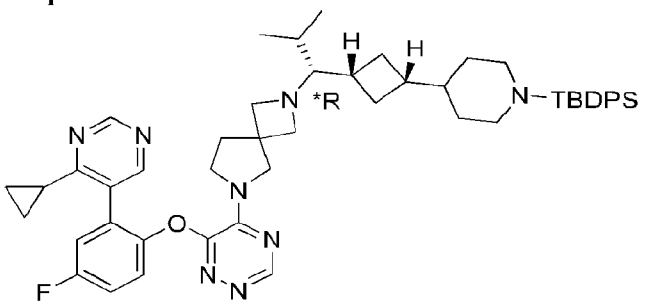
At 5°C, TFA (11.5 mL; 150.6 mmol) was added dropwise to a solution of intermediate 37b (*R) (4.44 g; 7.53 mmol) in DCM (110 mL) and the reaction mixture was stirred for 18h at rt. The mixture obtained was combined with the mixture obtained from the 2nd reaction, and the combined mixture was diluted with ACN and evaporated to dryness. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1h. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 7.87 g (96%) of intermediate 38b (*R) as an off-white foam.

intermediate 38a: 

At 5°C, TFA (13 mL; 170 mmol) was added dropwise to a solution of intermediate 37a (*S) (5 g; 8;48 mmol) in DCM (130 mL) and the reaction mixture was stirred for 4 h at rt. The mixture was diluted with ACN and evaporated to dryness. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1 h. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 4.6 g (100%) of intermediate 38a (*S) as an off-white foam.

Example A12

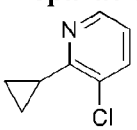
Preparation of intermediate 39:



$NaBH_3CN$ (278 mg; 4.42 mmol) was added to a mixture of intermediate 38b (1.2g; 2.21 mmol), *tert*-butyl-diphenyl-(4-piperidyloxy)silane (2.4 g; 7.1 mmol), AcOH (126 µL; 2.21 mmol) in MeOH (65 mL). Then, the reaction mixture was heated at 60°C for 48 h. The reaction mixture was cooled to r.t, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 7% MeOH, 93% DCM). The pure fractions were collected and evaporated to dryness to give 1.09 g (57%) of intermediate 39 (*R).

Example A13

Preparation of intermediate 40 :

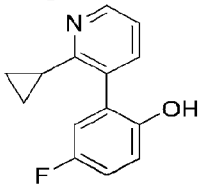


To a solution of 2,3-dichloropyridine (6.0 g, 40.54 mmol) in THF (210 mL) in *N*-Methyl-2-pyrrolidinone (54 mL) was added ferric acetylacetonate (530 mg, 1.50 mmol). Then, cyclopropylmagnesium bromide (47 mL, 46.63 mmol) was added at 0 °C. After stirring for 1 h at room temperature, additional cyclopropylmagnesium bromide (23 mL, 23.313 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The solid was filtered out and the filtrate was extracted with EtOAc. The organic layers were combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase: ethyl acetate/hexane, 1:20) to give 3.0 g (48% yield) of the intermediate 40 as a light

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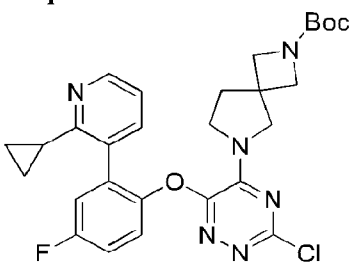
yellow oil.

Preparation of intermediate 41 :



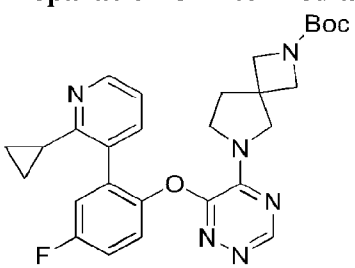
To a solution of intermediate 40 (4.5 g, 29.30 mmol) in 1,4-dioxane (90 mL) were added 4-fluoro-2-hydroxyphenylboronic acid (4.6 g, 29.30 mmol), Pd(amphos)Cl_2 (1.0 g, 1.46 mmol) and Na_2CO_3 (30 mL, 2 M in water). After stirring for 2 h at 90 °C, the reaction mixture was cooled to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase : ethyl acetate/hexane, 1:2) to give 5.5 g (81.1% yield) of the intermediate 41 as a yellow solid.

Preparation of intermediate 42 :



To a solution of intermediate 41 (5.5 g, 24.0 mmol) in THF (137 mL) were added intermediate 30 (8.6 g, 24.0 mmol) and DBU (3.6 g, 24.0 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase: ethyl acetate/hexane, 1:1) to give 8.8 g (63.5% yield) of the intermediate 42 as a yellow solid.

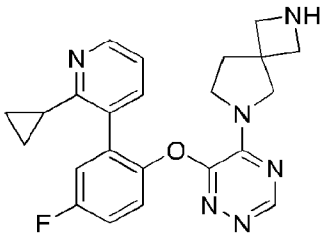
Preparation of intermediate 43 :



Intermediate 42 (6.7 g, 12.12 mmol) in THF (167 mL) were added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (989 mg,

1.21 mmol), sodium borohydride (779 mg, 20.60 mmol) and *N,N,N',N'*-tetramethylethylenediamine (2.4 g, 20.60 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase : ethyl acetate/hexane, 2:3) to give 6.1 g (95.5% yield) of the intermediate 43 as a yellow brown solid.

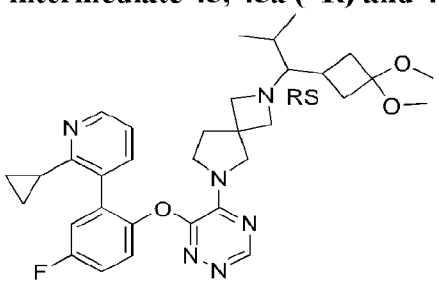
Preparation of intermediate 44 :



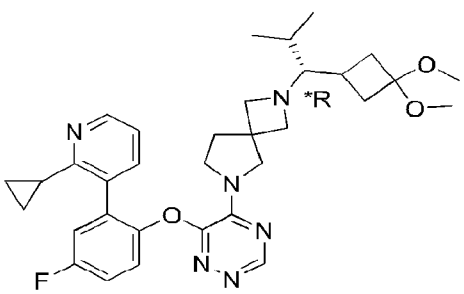
At 0°C, TFA (16 mL; 212 mmol) was added to a solution of intermediate 43 (7.33g; 14.1 mmol) in DCM (150 mL) and the reaction mixture was stirred for 5 hours at room temperature. The reaction was concentrated under vaccum. The residue was dissolved in 40 mL of water andthe solution was basified with 15% aqueous solution of NH_4OH. The aqueous layer was extracted with DCM (*3). The organic layer was decanted, washed again with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 6.3 g of intermediate 44 which was used in the next step without further purification.

Preparation of intermediate 45, 45a (*R) and 45b (*S):

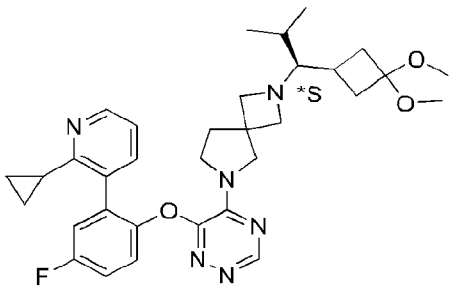
intermediate 45:



intermediate 45a (*R):

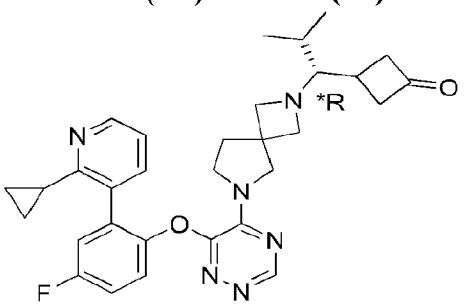


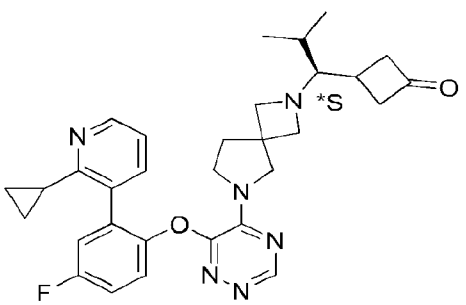
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intermediate 45b (*S): 

A mixture of intermediate 44 (5 g; 11.2 mmol), intermediate 36 (2.51 g; 13.5 mmol), AcOH (707 µL; 12.4 mmol) and $NaBH_3CN$ (2.1 g; 34 mmol) in MeOH (47 mL) was stirred at 50°C overnight. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and DCM was added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (mobile phase: from 99% DCM, 1% *i*-PrOH to 88% DCM, 12% *i*-PrOH). The pure fractions were collected and the solvent was evaporated. This residue (4.6 g) was purified by chiral SFC (CHIRALPAK AD-H 5µm 250*30 mm, mobile phase: 85% CO_2, 15% EtOH (0.3% *i*$PrNH_2$)). The pure fractions were collected and the solvent was evaporated to give 1.98 g (30%) of intermediate 45a (*R) (ee 100%) and 2.09 g (31%) of intermediate 45b (*S) as an off-white foam (ee 99.4%).

Preparation of intermediate 46a (*R) and 46b (*S):

Intermediate 46a (*R): 

Intermediate 46b (*S): 

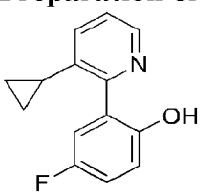
At 5°C, TFA (5.1 mL; 67 mmol) was added dropwise to a solution of intermediate 45a (*R) (1.98 g; 3.36 mmol) in DCM (76 mL) and the reaction mixture was stirred for 2h at rt. The reaction was evaporated to dryness. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1h. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated

to give 1.90 g (100%) of intermediate 46a (*R).

At 5°C, TFA (5.4 mL; 71 mmol) was added dropwise to a solution of intermediate 45b (*S) (2.09 g; 3.55 mmol) in DCM (81 mL) and the reaction mixture was stirred for 2h at rt. The reaction was evaporated to dryness. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1h. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 1.95 g (97%) of intermediate 46b (*S).

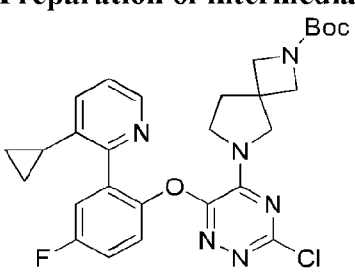
Example A14

Preparation of intermediate 47:



A mixture of 2-chloro-3-cyclopropylpyridine (5 g; 32.55 mmol) , 5-fluoro-2-hydroxyphenylboronic pinacol ester (10.1 mL; 48.82 mmol) and potassium fluoride (9.46 g; 162.75 mmol) in dioxane (125 mL) and water (30 mL). The reaction mixture was degassed and Sphos Pd G2 (469 mg; 0.65 mmol) was added. Then, the reaction was heated at 100°C for 2h. The mixture was cooled to RT, then poured into water. EtOAc was added and the reaction mixture was filtered through of pad of celite ®. The organic layer was decanted, washed with brine then water, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was crystallized from Et_2O. The precipitate was filtered and dried to give 6.8 g (91%) of intermediate 47.

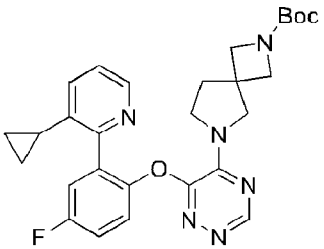
Preparation of intermediate 48:



To a solution of intermediate 47 (5.6 g, 15.7 mmol) in THF (180 mL) were added intermediate 30 (3.6 g, 15.7 mmol) and DBU (4.9 mL, 33 mmol). After stirring for 72h at room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase: gradient from 0.1% NH_4OH, 1% MeOH, 99% DCM to 0.3% NH_4OH, 3% MeOH, 97% DCM) to give 6.4g (74%) of the intermediate 48.

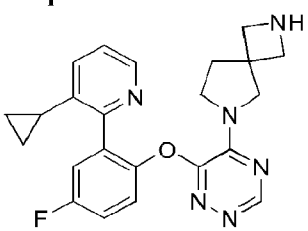
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Preparation of intermediate 49:



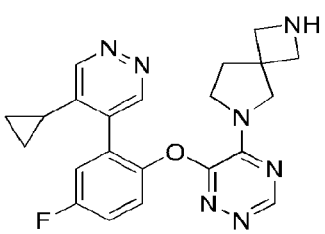
Intermediate 48 (6.4 g, 11.58 mmol) in THF (300 mL) were added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (956 mg, 1.16 mmol), sodium borohydride (875 mg, 24 mmol) and *N,N,N',N'*-tetramethylethylenediamine (3.5 mL, 23.14 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column (mobile phase from 0.1% NH_4OH, 1% MeOH, 99% DCM) to give 3 g (50% yield) of the intermediate 49.

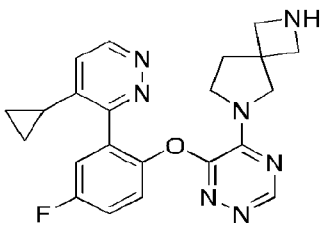
Preparation of intermediate 50:



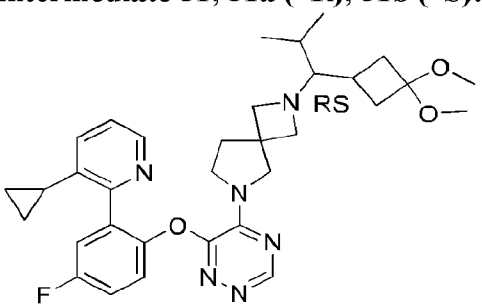
At 0°C, TFA (8.9 mL; 73.28 mmol) was added to a solution of intermediate 49 (3 g; 5.78 mmol) in DCM (90 mL) and the reaction mixture was stirred for 18 hours at room temperature. The reaction was concentrated under vaccum. The residue was dissolved in 40 mL of water, the solution was basified with 15% aqueous solution of NH_4OH. The aqueous layer was extracted with DCM (*3). The organic layer was decanted, washed again with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 2.4 g of intermediate 50 which was used in the next step without further purification.

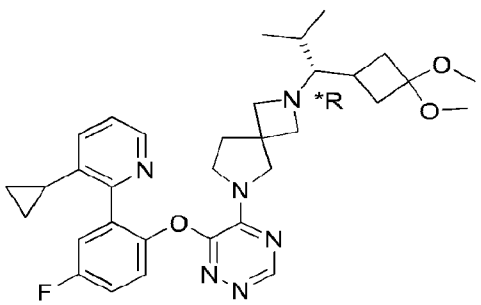
The intermediates reported below were prepared following an analogous methodology as described for intermediate 50 starting from the corresponding intermediates:

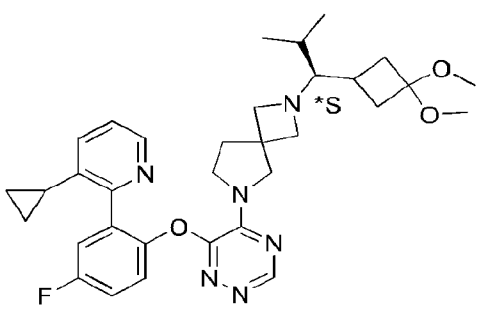
Intermediate 296	 from intermediate 109

Intermediate 297	 from intermediate 106

Preparation of intermediate 51, 51a (*R), 51b (*S):

intermediate 51: 

intermediate 51a (*R): 

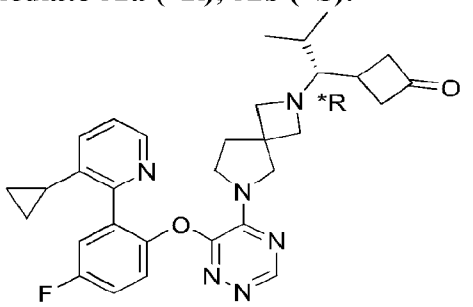
intermediate 51b (*S): 

A mixture of intermediate 50 (1.3 g; 3.1 mmol), intermediate 36 (0.752 g; 4.08 mmol), AcOH (178 µL; 3.11 mmol) and $NaBH_3CN$ (0.29 g; 4.66 mmol) in MeOH (50 mL) was stirred at 50°C overnight. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and DCM was added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, % MeOH, 99% DCM to 0.1% NH_4OH, 5% MeOH, 95% DCM). The pure fractions were collected and the solvent was evaporated. This residue (1.2 g) was purified by chiral SFC (CHIRALPAK AD-H 5µm

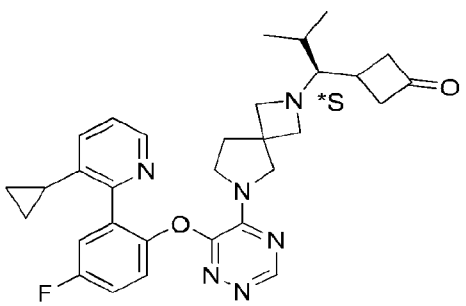
250*30 mm, mobile phase: 70% CO_2, 30% *i*-PrOH (0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated to give 464 mg (25%) of intermediate 51a (*R) (ee100%) and 476 mg (26%) of intermediate 51b (*S) as an off-white (ee 100%) solid.

Preparation of intermediate 52a (*R), 52b (*S):

Intermediate 52a (*R):



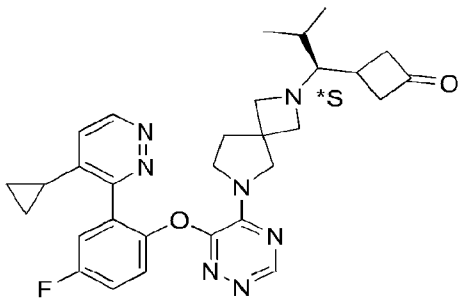
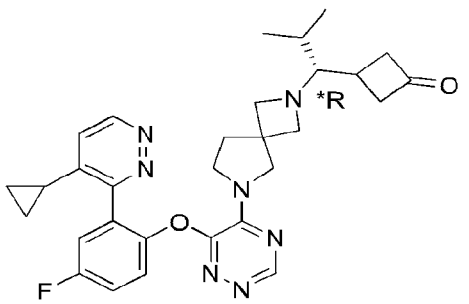
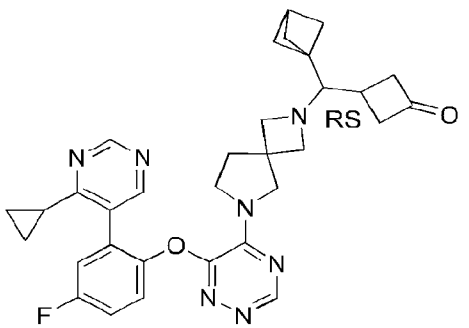
Intermediate 52b (*S):



At 5°C, TFA (1.2 mL; 15.76 mmol) was added dropwise to a solution of intermediate 51a (*R) (464 mg; 0.79 mmol) in DCM (16 mL) and the reaction mixture was stirred for 15 h at rt. The reaction was evaporated to dryness. The residue was dissolved in DCM and basified with a 10% aqueous solution of K_2CO_3. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 400 mg (94%) of intermediate 52a (*R).

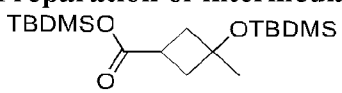
At 5°C, TFA (1.2 mL; 15.76 mmol) was added dropwise to a solution of intermediate 51b (*S) (476 mg; 0.81 mmol) in DCM (15 mL) and the reaction mixture was stirred for 15 h at rt. The reaction was evaporated to dryness. The residue was dissolved in DCM and basified with a 10% aqueous solution of K_2CO_3. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 430 mg (98%) of intermediate 52b (*S).

The intermediates reported below were prepared following an analogous methodology as described for intermediate 52a and intermediate 52b starting from the corresponding intermediates:

Intermediate 249a Intermediate 249b	  from intermediate 297
Intermediate 295	 from intermediate 33

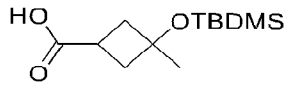
Example A15

Preparation of intermediate 53:



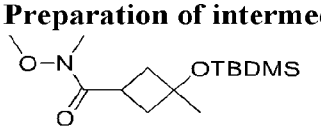
Under nitrogen atmosphere, *tert*-butylchlorodimethylsilane (2.9 g, 19.3 mmol) and 1H-imidazole (1.66 g, 24.3 mmol) were added to a solution of 3-hydroxycyclobutane-1-carboxylic acid (1.13 g, 9.7 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature overnight. The reaction was filtered to remove insoluble, washing with DCM and, then concentrated in vacuo to give 2.9 g of the intermediate 53 The intermediate was used without any further purification in the next step.

Preparation of intermediate 54:



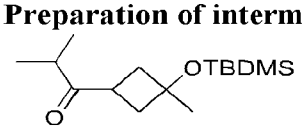
A solution of K_2CO_3 (141 mg; 1 mmol) in water (2.2 mL) was added to a solution of intermediate 53 (913 mg; 2.54 mmol) in MeOH (6.5 mL) and THF (2.2 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvents were evaporated. The reaction was cooled to 0 °C with an ice bath. Then, an aqueous solution of HCl (1.5 N) was added dropwise until pH <2. The mixture was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to obtain 493 mg (79%) of intermediate 54 which was directly used in the next step without any further purification

Preparation of intermediate 55:



A mixture of intermediate 54 (261 mg; 1 mmol), EDCI (307 mg; 1.6 mmol), *N,O*-dimethylhydroxylamine hydrochloride (156 mg; 1.6 mmol) then, DMAP (6.5 mg; 0.054 mmol) and DIPEA (0.75 mL; 4.3 mmol) in DCM (6 mL) was stirred at rt overnight. The reaction mixture was diluted with DCM (10 mL) and washed with an aqueous solution of HCl (1 N) (2 x 5 mL), water (10 mL) then with a saturated solution of $NaHCO_3$ (2 x 10 mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to dryness to give 144 mg (45%) of intermediate 55 which was directly used in the next step without any further purification

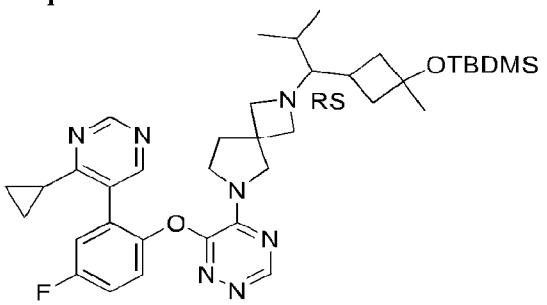
Preparation of intermediate 56:



Under nitrogen atmosphere and at 0°C, isopropylmagnesium chloride (2.3 mL; 3 mmol, 1.3 M in THF) was added to a solution of intermediate 55 (144 mg; 0.5 mmol) in THF dry (5 mL). The reaction mixture was stirred at 0°C for 1 hour. Then, the solution was allowed to slowly warm to room temperature and stirred for 2 hours. The reaction mixture was poured into iced water and EtOAc was added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give 117 mg (86%) of intermediate 56.

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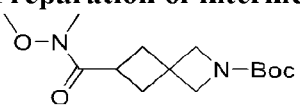
Preparation of intermediate 57:



A mixture of intermediate 33 (140 mg; 0.33 mmol), intermediate 56 (117 mg; 0.43 mmol), AcOH (19 µL; 0.33 mmol) and $NaBH_3CN$ (47 mg; 0.75 mmol) in MeOH (5 mL) was stirred at 50°C overnight. The reaction mixture was poured onto a saturated solution of $NaHCO_3$ and DCM was added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product (258 mg) was purified by chromatography over silica gel (Mobile phase: Gradient from 99% DCM, 1% MeOH (+10% NH_4OH) to 95% DCM, 5% MeOH (+10% NH_4OH)). The pure fractions were collected and the solvent was evaporated to give 104 mg (46%) of intermediate 57.

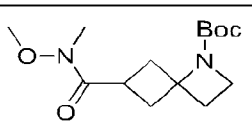
Example A16

Preparation of intermediate 59:

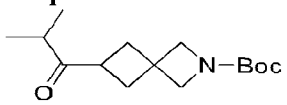


To a mixture of 2-(*tert*-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (900 mg; 3.7 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (400 mg; 4.1 mmol) in DCM (15 mL) was added HATU (2.1 g; 5.6 mmol) and DIPEA (0.96 mL; 5.6 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was poured into water. A saturated aqueous solution of $NaHCO_3$ and DCM were added. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The residue (2.26 g) was purified by chromatography over silica gel (Mobile phase: Gradient from 80% heptane, 20% EtOAc to 40% heptane, 60% EtOAc). The pure fractions were collected, and the solvent was evaporated to give 1 g (100%) of the intermediate 59.

The intermediate 60 reported below was prepared following an analogous methodology starting from 1-boc-1-azaspiro[3.3]heptane-6-carboxylic acid

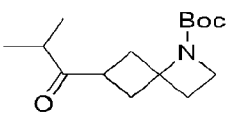
intermediate 60	

Preparation of intermediate 61:



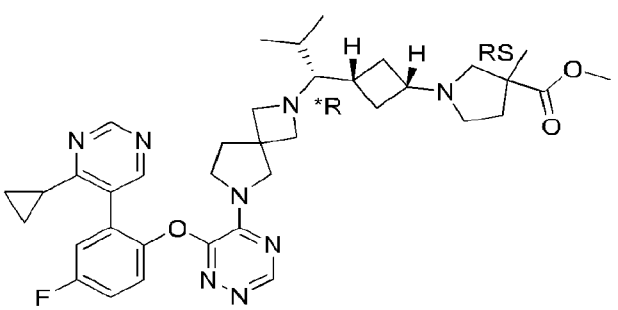
Under nitrogen atmosphere and at 0°C, isopropylmagnesium chloride (29 mL; 37.3 mmol, 1.3 M in THF) was added to a solution of intermediate 59 (2.12 g; 7.46 mmol) in THF dry (36 mL). The reaction mixture was stirred at 0°C for 1 hour. Then, the solution was allowed to slowly warm to room temperature and stirred for 2 hours. The reaction mixture was quenched by 10% aqueous solution of NH_4Cl and EtOAc was added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (1.9 g) was purified with chromatography over silica gel (Mobile phase: Gradient from 80% heptane, 20% EtOAc to 40% heptane, 60% EtOAc). The pure fractions were collected, and the solvent was evaporated to give 1.47 g (74%) of the intermediate 61.

The intermediate 62 reported below was prepared following an analogous methodology starting from intermediate 60

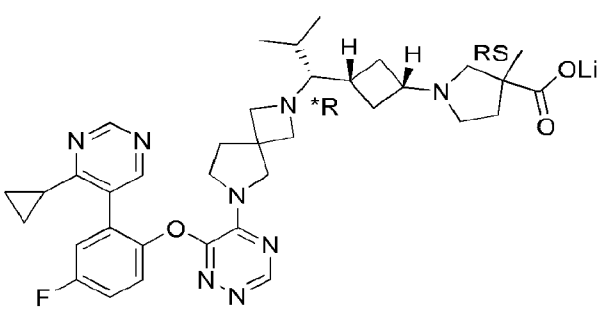
intermediate 62	

Example A17

The intermediate 58 reported below was prepared following an analogous methodology as for the preparation of compound 7, starting from intermediate 38b and methyl-3-methylpyrrolidine-3-carboxylate

intermediate 58	

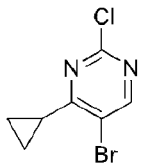
Preparation of intermediate 67:



Lithium hydroxyde (101 mg; 2.41 mmol) was added to a solution of intermediate 58 (270 mg; 0.4 mmol) in THF (25 mL) and water (3 mL) . The mixture was stirred at rt overnight and evaporated to dryness. The crude was then taken-up with Et_2O and filtered to give, 280 mg of intermediate 67 which was directly used in the next step without any further purification.

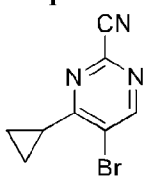
Example A18

Preparation of intermediate 68:



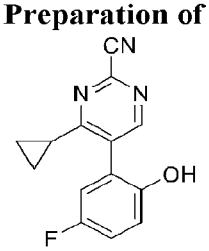
$(NH_4)_2S_2O_8$ (15 g; 65.73 mmol) and $AgNO_3$ (8.5 g; 50 mmol) were added to water (150 mL), cyclopropanecarboxylic acid (2.1 mL; 26.47 mmol) was added followed by 5-bromo-2-chloropyrimidine (5 g; 25.85 mmol) and CH_3CN (150 mL). The reaction mixture was stirred at room temperture for 72 hours, quenched by slow addition of iced water. EtOAc was added followed by a saturated NaCl solution. The solution was filtered through a celite® layer and then, extracted with EtOAc (2 x 500 mL), dried over $MgSO_4$, filtered and concentrated. The residue (5.83 g) was purified by chromatography over silica gel (Mobile phase: 40% DCM, 60% heptane). The pure fractions were collected, and the solvent was evaporated till dryness to give 3.05g (51%) of intermediate 68

Preparation of intermediate 69:



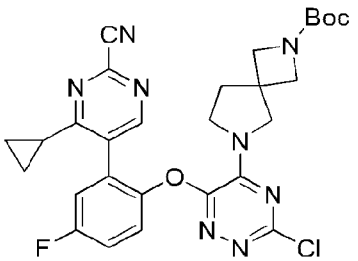
At rt, TBACN (1.75 g; 6.52 mmol) and DABCO (0.72 g; 6.42 mmol) were added to a solution of intermediate 68 (1 g; 4.28 mmol) in MeCN (20 mL) and the solution was stirred at rt for 2 hours. The solution was poured into cooled water and the product was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (1.6 g) was purified by chromatography over silica gel (Mobile phase Gradient from 0% DCM, 100% heptane to 30% DCM, 70% heptane). The pure fractions were collected, and the solvent was evaporated till dryness to give 860 mg (90%) of intermediate 69.

Preparation of intermediate 70:



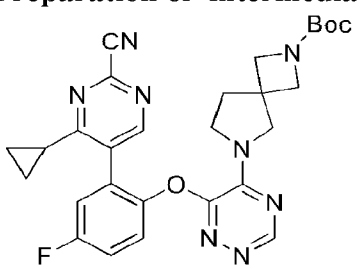
To a previously degassed mixture of intermediate 69 (860 mg; 3.84 mmol), 5-fluoro-2-hydroxyphenylboronic pinacol ester (1.3 g; 5.46 mmol) and potassium fluoride (1.1 g; 18.93 mmol) in 1,4-dioxane (20 mL) were added water (3.9 mL) and SPhos Pd G2 (56 mg; 0.08 mmol). The mixture was heated at 100°C for 2.30 h in a Schlenk apparatus. The mixture was cooled at room temperature, poured into water. EtOAc was added and the mixture was filtered through of pad of celite ®. The organic layer was decanted, washed with brine then water, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (2.12 g) was purified by chromatography over silica gel (mobile phase: gradient from 100% DCM, 0% MeOH to 98% DCM, 2% MeOH). The pure fractions were collected, and the solvent was evaporated till dryness to give 630 mg (64%) of intermediate 70.

Preparation of intermediate 71:



A solution of intermediate 70 (2 g; 7.835 mmol), intermediate 30 (2.8 g; 7.77 mmol) and DBU (5.7 mL; 38.94 mmol) in THF (100 mL) was stirred at rt for 24 hours. The solution was poured into cooled water and the product was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (5 g) was purified by chromatography over silica gel (Mobile phase: 0.1% NH_4OH, 99% DCM, 1% MeOH). The pure fractions were collected and the solvent was evaporated till dryness. A second purification (3.5 g) was performed via chiral SFC (Stationary phase: CHIRALPAK IC 5µm 250*30mm, Mobile phase: 50% CO_2, 50% MeOH). The pure fractions were collected and the solvent was evaporated till dryness yielding 2.6g (57%) of intermediate 71.

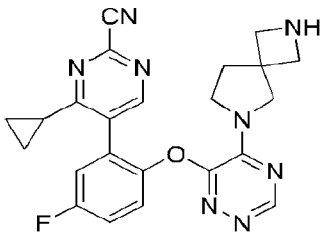
Preparation of intermediate 72:



A mixture of intermediate 71 (2.6 g; 4.49 mmol) and TMEDA (1 mL; 6.71 mmol) in dry THF (100 mL) was degassed by N_2 bubbling. Then, $Pd(dppf)Cl_2.DCM$ (415 mg; 0.50 mmol) and $NaBH_4$ (260 mg; 6.87 mmol) were added. The reaction mixture was stirred at 50°C overnight

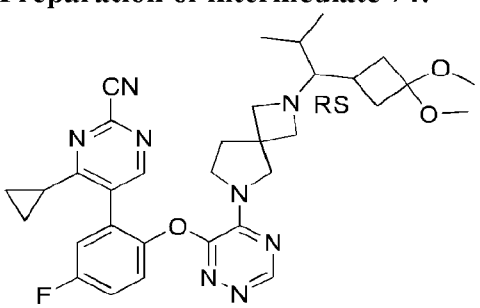
in a sealed glassware. The solution was cooled, poured into cooled water and EtOAc was added. The reaction mixture was filtered through a pad of Celite®. The product was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (Mobile phase: Gradient from 100% DCM, 0% MeOH (+10% NH_4OH) to 95% DCM, 5% MeOH (+10% NH_4OH)). The pure fractions were collected, and the solvent was evaporated till dryness yielding 1.84 g (75%) of intermediate 72.

Preparation of intermediate 73:



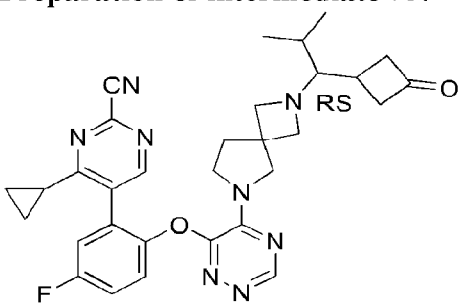
The solution of intermediate 72 (3 g; 5.51 mmol) and TFA (9 mL; 117.5 mmol) in DCM (90 mL) was stirred at rt overnight. The solution was evaporated to dryness and the mixture was poured into cooled water, basified with NH_4OH and the product was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to afford 2.49g of intermediate 73 which was used directly for the next step.

Preparation of intermediate 74:



Under N_2, at rt, to a mixture of intermediate 73 (2 g; 4.5 mmol), intermediate 36 (1.1 g; 5.91 mmol) and AcOH (260 µL; 4.55 mmol) in MeOH (60 mL) was added $NaBH_3CN$ (424 mg; 6.75 mmol) and the reaction was heated at 60°C overnight. The reaction mixture was cooled, poured onto a mixture of 10% aqueous solution of K_2CO_3 and EtOAc. The mixture was extracted with EtOAc (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (2.6 g) (Mobile phase: Gradient from 100% DCM, 0% MeOH (+10% NH_4OH) to 95% DCM, 5% MeOH (+10% NH_4OH)). The pure fractions were collected and the solvent was evaporated till dryness yielding 450 mg (16% on two steps) of intermediate 74.

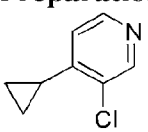
Preparation of intermediate 75:



At 5°C, TFA (1.2 mL; 15.7 mmol) was added dropwise to a solution of intermediate 74 (450 mg; 0.73 mmol) in DCM (12 mL) and the reaction mixture was stirred for 3 h at rt. MeCN was added and the solution was evaporated to dryness. The residue was dissolved in EtOAc and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The organic layer was decanted, washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated to give 414 mg (99 %) of intermediate 75 which was used directly for the next step.

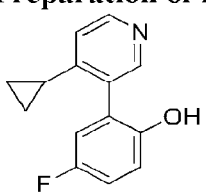
Example A19

Preparation of intermediate 76:



In a 1L schlenk round bottom flask, cyclopropylzinc bromide 0.5M in THF (100 mL; 50 mmol) was added dropwise to a previously degassed solution of 4-bromo-3-chloropyridine (6.41 g; 33.33 mmol) and $Pd(PPh_3)_4$ (1.93 g; 1.67 mmol) in THF (200 mL). The reaction was heated at 65°C for 18 hours. The reaction mixture was cooled to rt, neutralized with 10% aqueous solution of K_2CO_3 and extracted with Et_2O (twice). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 80g; mobile phase: gradient from 10% EtOAc, 90% heptane to 20% EtOAc, 80% heptane). The pure fractions were collected and evaporated to dryness yielding 3.93 g (77%) of intermediate 76.

Preparation of intermediate 77:

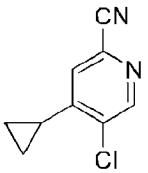


In a Schlenk round bottom flask, a previously degassed mixture of intermediate 76 (3.91 g; 25.4 mmol), 5-fluoro-2-hydroxyphenylboronic pinacol ester (7.88 g; 33.09 mmol), potassium fluoride (7.39 g; 127 mmol) and SPhos Pd G2 (366 mg; 0.509 mmol) in dioxane (80 mL) and

water (27 mL) was refluxed for 3 hours. The reaction mixture was cooled to rt, diluted with EtOAc and poured onto water. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was allowed to stand all over the week end. The residue was taken up with DCM and, then, the precipitate was filtered, washed with Et_2O and dried yielding 4.86g (83%) of intermediate 77.

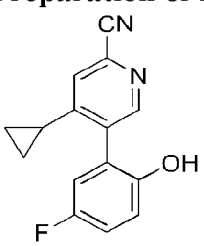
Example A21

Preparation of intermediate 81:



In a sealed tube, di-μ-iodobis(tri-t-butylphosphino)dipalladium(I) (180 mg; 207 μmol) was added to a mixture of 5-bromo-6-chloro-nicotinonitrile (1.8 g; 8.3 mmol) and a solution of cyclopropylzincbromide 0.5 M in THF (17 mL; 8.7 mmol) in dry THF (34 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and quenched with few drops of water. $MgSO_4$ and celite were added and the solvent were removed under vacuum to give a dry load which was purified by chromatography over silica gel (irregular SiOH, 80 g; mobile phase : gradient from heptane / EtOAc 95:5 to 80:20). The fractions containing product were combined and evaporated in vacuo to give 1.06 g of intermediate 81 (72%)as a brown oil which crystallized upon storage at rt.

Preparation of intermediate 82:

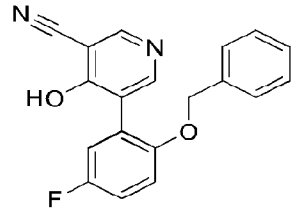


Under N_2 flow, Cs_2CO_3 (7.92 g; 24.3 mmol) followed by $Pd(PPh_3)_4$ (1.40 g; 1.22 mmol) were added to a stirred solution of intermediate 81 (2.17 g; 12.1 mmol) and 5-fluoro-2-hydroxyphenyl)boronic acid (4.17 g; 26.7 mmol) in a mixture ofwater (9.5 mL) and dioxane (28.6 mL). The reaction was degassed with N_2 and was then stirred at 90 °C for 18 h. The reaction mixture was cooled to rt, diluted with EtOAc and water was added. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 80 g, dry load; mobile phase : gradient from Heptane/EtOAc 95/5 to 70/30). The fractions containing product were combined and evaporated to give 2.41g (78%) of intermediate 82 as a yellow solid.

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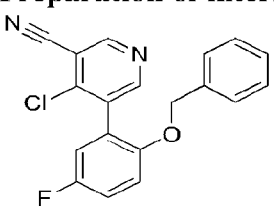
Example A22

Preparation of intermediate 83:



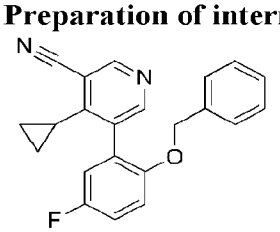
In a schlenk, a solution of 5-bromo-4-hydroxy-nicotinonitrile (2.00 g; 10.1 mmol), 2-benzyloxy-5-fluorophenylboronic acid (3.09 g; 12.6 mmol) and K_3PO_4 (3.20 g; 15.1 mmol) in a mixture of dioxane (40 mL) and H_2O (13.3 mL) was purged with nitrogen. CatacXium A Pd G3 (439 mg; 603 µmol) was added. The reaction mixture was purged again with nitrogen and stirred at 80 °C for 17 hours. The reaction mixture was poured in water and extracted twice with a mixture DCM / MeOH (98:2). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was warmed in *i*-PrOH (8 mL) and cooled down to room temperature. The precipitate was filtered, washed with diethyl ether and dried in vacuo to give 854 mg of intermediate 83 (27%) as a yellow solid.

Preparation of intermediate 84:



A mixture of intermediate 83 (854 mg; 2.67 mmol) in MeCN (10 mL) was treated with $POCl_3$ (2.03 mL; 21.9 mmol). The reaction mixture was stirred at 50 °C for 2 hours. The reaction mixture was then cooled down to room temperature, quenched with a 10% aqueous solution of K_2CO_3 and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo to give 914 mg (quantitative) of intermediate 84 as a yellow solid.

Preparation of intermediate 85:



A solution of intermediate 84 (914 mg; 2.70 mmol), cyclopropylboronic acid (464 mg; 5.40 mmol) and K_3PO_4 (859 mg; 4.05 mmol) in a mixture of dioxane (11 mL) and H_2O (3.6 mL) was purged with nitrogen. CatacXium A Pd G3 (117 mg; 0.162 mmol) was added. The reaction mixture was purged again with nitrogen and stirred at 80 °C for 4 hours. The reaction mixture

was cooled to room temperature and diluted with EtOAc. The organic mixture was washed with water, then with brine, dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The residue was purified by chromatography over silica gel (irregular SiOH, 40 g, dry load; mobile phase : gradient Heptane / EtOAc from 85/15 to 70/30). The fractions containing product were combined and evaporated to give 471 mg (51%) of intermediate 85 as a yellow gummy solid.

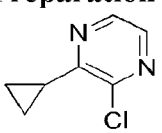
Preparation of intermediate 86:



A solution of intermediate 85 (450 mg; 1.31 mmol) and ammonium formate (412 mg; 6.53 mmol) in EtOH (7.6 mL) was treated with Palladium on charcoal (278 mg; 0.131 mmol) and stirred at 75 °C for 45 minutes. The reaction mixture was cooled down to rt, diluted with DCM and filtered through a pad of Celite®. The filtrate was evaporated in vacuo to give a residue which was purified by silica gel chromatography (irregular SiOH, 12 g; mobile phase : gradient DCM / MeOH from 100/0 to 98/2). The fractions containing product were combined and evaporated to give 190 mg of intermediate 86 (57%) as a yellow foam.

Example A23

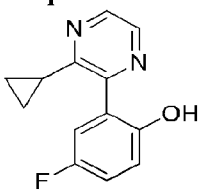
Preparation of intermediate 87:



To a mixture of 2,3-dichloropyrazine (5.0 g; 33.562 mmol), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.64 g; 33.562 mmol) and Pd(amphos)Cl_2 (2.38 g; 3.356 mmol) in 1,4-dioxane (100 mL) was added a solution of sodium carbonate (2M in water; 50.3 mL). The resulting mixture was stirred for 5 h at 80°C under an atmosphere of nitrogen. After cooling to room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (PE/EA from 100/0 to 80/20). The fractions containing product were combined and evaporated to give 3.0 g of intermediate 87 (57%) as a colorless oil.

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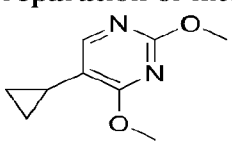
Preparation of intermediate 88:



To a mixture of intermediate 87 (1.21 g; 7.762 mmol) and tetrakis(triphenylphosphine)palladium (370 mg; 0.323 mmol) in 1,4-dioxane (50 mL) was added a solution of sodium carbonate (10 mL; 1M in water) and the reaction was stirred 3.5 hours at 90 °C under an atmosphere of nitrogen. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water then brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (mobile phase: ethyl acetate/petroleum ether 2:1). The fractions containing product were combined and evaporated to give 1.25 g of intermediate 88 (84%) as a light yellow solid.

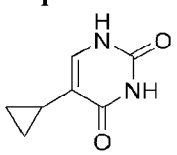
Example A24

Preparation of intermediate 89:



To a stirring solution of 5-bromo-2,4-dimethoxypyrimidine (10.0 g; 45.66 mmol) in 1,4-dioxane were added cyclopropylboronic acid (4.71 g; 65.74 mmol), sodium carbonate (2 M in water, 50 mL) and dichlorobis [di-*tert*-butyl (4-dimethylaminophenyl)phosphino]palladium(II) (3.23 g; 219.04 mmol). The reaction mixture stirred overnight at room temperature, quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase: PE:EtOAc: 93:7). The fractions containing product were combined and evaporated to give 4.3 g of intermediate 89 (50%) as a colorless oil.

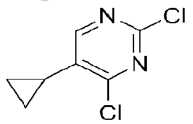
Preparation of intermediate 90:



To a stirring solution of intermediate 89 (4.8 g; 26.64 mmol) in MeCN (96 mL) was added sodium iodide (12.0 g; 79.91 mmol). The reaction mixture was cooled to 0°C and chlorotrimethylsilane (8.7 g; 79.91 mmol) was added. After stirring overnight at room temperature, the reaction mixture were quenched with water and stirred for 15 min. The solid

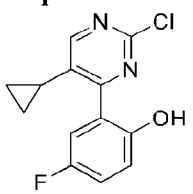
was filtered and dried under vacuum to give 3.0 g of intermediate 90 (73% yield) as a yellow solid.

Preparation of intermediate 91:



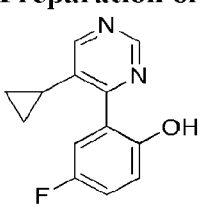
To a stirring solution of intermediate 90 (3.5 g; 23.00 mmol) in phosphorus oxychloride (300 mL) was added *N,N*-dimethylformamide (0.70 mL). After stirring 2 h at 100 °C, the reaction solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in a small amount of DMF and poured into ice water followed by extracting with EtOAc. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtred and concentrated under reduced pressure to give 4.2 g of intermediate 91 (96%) as a yellow oil.

Preparation of intermediate 92:



To a stirring solution of intermediate 91 (5.4 g; 28.56 mmol) in 1,4-dioxane (162 mL) were added (5-fluoro-2-hydroxyphenyl)boronic acid (4.45 g; 28.56 mmol) and tetrakis(triphenylphosphine)palladium (1.65 g; 1.43 mmol) and sodium bicarbonate (2 M in water, 54 mL). After stirring for 2 h at 80 °C under an atmosphere nitrogen, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase PE:EtOAc 3:1). The fractions containing product were combined and evaporated to give 2.7 g of intermediate 92 (29%, 81% purity evaluated by LCMS) as a light yellow solid.

Preparation of intermediate 93:

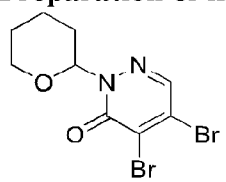


To a stirring solution of intermediate 92 (1.0 g; 2.08 mmol) in MeOH (55 mL) was added Et_3N (382 mg; 3.78 mmol) and 10% Pd/C (683 mg). After stirring for 30 min under a hydrogen stream (1 atm) at room temperature, the catalyst was filtered off. The filtrate cake was washed

with methanol. The collected filtrate was concentrated under reduced pressure to give 550 mg of intermediate 93 (62%).

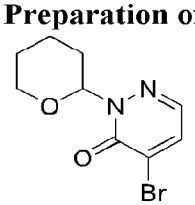
Example A25

Preparation of intermediate 94:



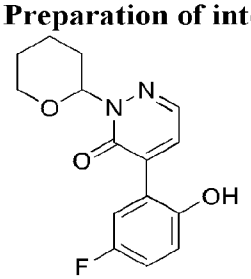
To a stirring solution of 4,5-dibromopyridazin-3(2*H*)-one (50 g; 196.95 mmol) in THF (300 mL) was added *p*-toluenesulfonic acid (3.4 g; 19.694 mmol) and 3,4-dihydro-2*H*-pyran (82.8 g; 988.72 mmol). After stirring overnight at 60°C, the reaction mixture was quenched with water and extracted EtOAc. The combined organic layer was washed with water then brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase: PE/EtOAc 81/19). The fractions containing product were combined and evaporated to give 65 g of intermediate 94 (83%) as a light yellow solid.

Preparation of intermediate 95 :



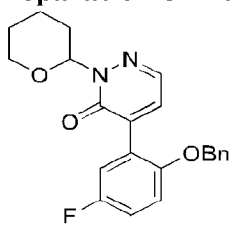
To a stirring solution of intermediate 94 (25g; 73.97 mmol) in 1,2-dimethoxyethane (200 mL) was added sodium borohydride (5.6 g; 147.93 mmol) at 0°C. After stirring for 18 h at room temperature, the reaction mixture was cooled to 0°C, quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water then brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase : PE/EA 70/30). The fractions containing product were combined and evaporated to give 2.3 g of intermediate 95 (12%) of as a white solid.

Preparation of intermediate 96 :



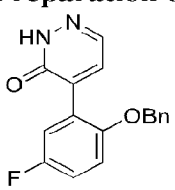
To a mixture of intermediate 95 (2.7 g; 10.42 mmol), (5-fluoro-2-hydroxyphenyl)boronic acid (1.6 g; 10.42 mmol) and $Pd(PPh_3)_4$ (1.2 g; 1.042 mmol) in dioxane (50 mL) was added sodium carbonate solution (20 mL; 2 M in water). After stirring at 90°C for 5 h, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase : PE/EA: from 100/0 to 80/20). The fractions containing product were combined and evaporated to give 2.46 g of intermediate 96 (78%) as a yellow solid.

Preparation of intermediate 97:



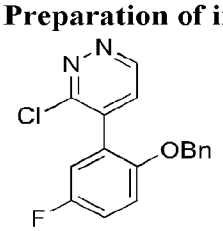
A mixture of intermediate 96 (2.46 g; 8.47 mmol), benzyl chloride (2 mL; 16.95 mmol) and K_2CO_3 (5.9 g; 42.37 mmol) in acetone (50 mL) was stirred at 60°C overnight. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The filtrate was purified by chromatography over silca gel (mobile phase : PE/EA: from 100/0 to 80/20). The fractions containing product were combined and evaporated to give 2.0 g of intermediate 97 (60%) as a yellow oil.

Preparation of intermediate 98:



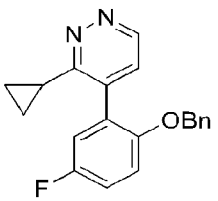
A solution of intermediate 97 (2.0 g; 5.26 mmol) in hydrochloric acid (37% in water, 5 mL) and methanol (15 mL) was stirred at 50°C for 1 h. The solution was concentrated under reduced pressure. The residue was taken up with Et_2O. The precipitate was filtered and dried under vacumm to give 1.0 g of intermediate 98 (64%) as a yellow solid.

Preparation of intermediate 99:



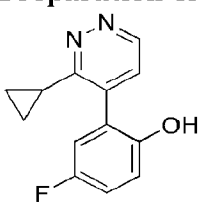
A solution of intermediate 98 (1 g; 3.38 mmol) in phosphorus oxychloride (15 mL) was stirred at 100 °C for 2 hours. The solution was concentrated under reduced pressure. The residue was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase : PE/EA from 100/0 to 30/70). The fractions containing product were combined and evaporated to give 600 mg of intermediate 99 (52%) as a yellow oil.

Preparation of intermediate 100:



To a solution of intermediate 99 (200 mg; 0.64 mmol) in THF (7.0 mL) were added palladium (II) acetate (14 mg; 0.06 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (52 mg; 0.13 mmol). The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled to 0°C and cyclopropylzinc bromide (0.5 M in THF; 1.9 mL; 0.95 mmol) was added dropwise. After stirring overnight at room temperature, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (irregular SiOH, 40 g; mobile phase : Petroleum ether:ethyl acetate 70%:30%). The fractions containing product were combined and evaporated to give 150 mg of intermediate 100 (67%) as a light brown oil.

Preparation of intermediate 101:

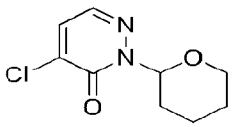


To a solution of intermediate 100 (150 mg; 0.47 mmol) in MeOH (10 mL) was added 10% Pd/C (150 mg; 0.14 mmol). After stirring at room temperature under hydrogen atmosphere (2-3 atm.) for 1h, the reaction mixture was filtered through a diatomite pad. The filtrate was concentrated under reduced pressure to give 100 mg of intermediate 101 (88%) as a light brown solid.

Example A26

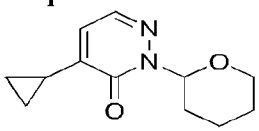
Preparation of intermediate 102:

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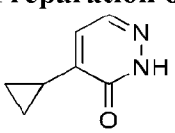
3,4-dihydro-2*H*-pyran (28 mL; 306.5 mmol) was added at room temperature to a mixture of 4-chloropyridazin-3(2*H*)-one (10 g; 76.61 mmol) and *p*-toluenesulfonic acid (1.4 g; 7.67 mmol) in THF (200 mL). The mixture was stirred at 70°C overnight. After cooling to room temperature, the reaction solution was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (mobile phase : PE/EA : from 100/0 to 30/70). The fractions containing product were combined and evaporated to give 16 g of intermediate 102 (84%) as a yellow solid.

Preparation of intermediate 103:



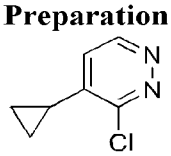
A mixture of intermediate 102 (5 g; 23.29 mmol), cyclopropylboronic acid (2.1 g; 24.46 mmol) and Pd(amphos)Cl_2 (1.65 g; 2.33 mmol) in 1,4-dioxane (75 mL) and 2M sodium carbonate aqueous solution (25 mL) was stirred at 90°C for 5h. After cooling to room temperature, the reaction solution was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase : PE/EA : from 100/0 to 30/70). The fractions containing product were combined and evaporated to give 3.5 g of intermediate 103 (67%) as a yellow solid.

Preparation of intermediate 104:



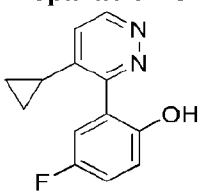
A solution of intermediate 103 (10.0 g; 45.40 mmol) in hydrochloric acid (37% in water, 50 mL) and methanol (150 mL) was stirred at 50°C for 1 h. The solution was evaporated under reduced pressure. The residue was dissloved in water. The resulting solution was adjusted to pH=7 with NaOH (2M in water) and extracted with (MeOH/DCM=1/10). The combined organic layers were dried over Na_2SO_4. The solid was filtered off. The filtrate was concentrated under reduced pressure to give 5.2 g of intermediate 104 (76%) as a yellow solid.

Preparation of intermediate 105:



To a solution of intermediate 104 (12.1 g; 88.14 mmol) in acetonitrile (200 mL) was added $POCl_3$ (41.1 mL; 440.69 mmol). After stirring at 50°C for 1.5 h, the solution was poured slowly into ice water (200 mL). The resulting solution was adjusted to pH=7 using a saturated aqueous solution of Na_2CO_3 and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (PE/EA : from 100/0 to 30/70). The fractions containing product were combined and evaporated to give 9.0 g of intermediate 105 (61%) as a yellow oil.

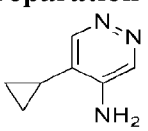
Preparation of intermediate 106:



A mixture of intermediate 105 (9 g; 58.22 mmol), 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (13.86 g; 58.22 mmol), $Pd(PPh_3)_4$ (3.36 g; 2.91 mmol) and sodium carbonate solution (43.9 mL; 2M) in 1,4-dioxane (130 mL) was stirried 90°C for 3 h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase : PE/EA : from 100/0 to 30/70). The fractions containing product were combined and evaporated to give 13 g of intermediate 106 (86%) as a light yellow solid.

Example A27

Preparation of intermediate 107:

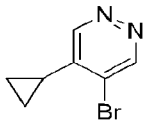


To a solution of 5-bromopyridazin-4-amine (7.7 g; 44.25 mmol) in 1,4-dioxane (130 mL) were added cyclopropylboronic acid (5.7 g; 66.38 mmol), bis-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (4.7 g; 6.64 mmol) and sodium carbonate solution (2 M in water; 66.4 mL; 132.8 mmol). The resulting mixture was stirred at 90°C for 36 hours under nitrogen atmosphere. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (120 g; mobile phase : dichloromethane/methanol 95%/5%). The fractions containing product were combined and

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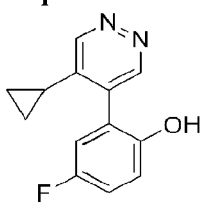
evaporated to give 2.5 g of intermediate 107 (39%) as a red oil.

Preparation of intermediate 108:



To a solution of intermediate 107 (2.5 g; 18.50 mmol) in acetonitrile (50 mL) were added cupric bromide (3.31 g; 14.80 mmol) and isoamyl nitrite (2.73 mL; 20.35 mmol). The resulting mixture was stirred at 70°C for 2.5 hours under nitrogen atmosphere. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (60 g; mobile phase : Petroleum ether/ethyl acetate 50/50). The fractions containing the product were combined and evaporated to give 1.6 g of intermediate 108 (42%) as a yellow oil.

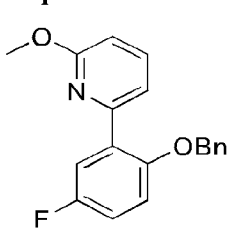
Preparation of intermediate 109:



To a solution of intermediate 108 (1.6 g; 8.04 mmol) in 1,4-dioxane (24 mL) were added (5-fluoro-2-hydroxyphenyl)-boronic acid (1.38 g; 8.84 mmol), bis-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (570 mg; 0.80 mmol) and sodium carbonate solution (2 M in water; 12.1 mL; 24.11 mmol). The resulting mixture was stirred at 90°C for 16 hours. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (irregular SiOH, 60 g; mobile phase : PE/EA: 100/0 to 0/100). The fractions containing product were combined and evaporated to give 1.3 g of intermediate 109 (62%) as a red solid.

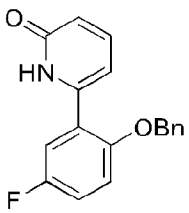
Example A28

Preparation of intermediate 110:



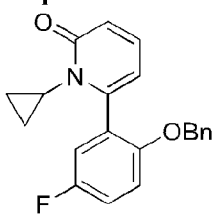
To a stirred solution of 2-bromo-6-methoxypyridine (16.8 g; 89.35 mmol) in 1,4-dioxane (450 mL) were added (2-(benzyloxy)-5-fluorophenyl)boronic acid (22 g; 89.35 mmol), $Pd(PPh_3)_4$ (5.1 g; 34.69 mmol) and sodium carbonate (168 mL; 2 M). The reaction mixture was stirred for 2 h at 90°C under an atmosphere of nitrogen, quenched with water and extracted with ethyl acetate. The combined organic layers were washed water, then brine, dried over anhydrous sodium sulfate, filtered and evaportaed under reduced pressure. The residue was purified by chromatography over silica gel (eluting system: PE:EA 98:2). The fractions containing product were combined and evaporated to give 26 g of intermediate 110 (94%) as a colorless oil.

Preparation of intermediate 111:



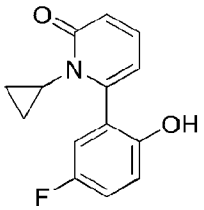
To a stirring solution of intermediate 110 (23.0 g; 74.353mmol) in acetonitrile (400 mL) was added *p*-toluenesulfonic acid monohydrate (17.0 g; 89.24 mmol) and lithium iodide (20.0 g; 148.71 mmol). After stirring 1 h at 80°C, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by chromatography over silica gel (eluting system: PE:EA 50:50). The fractions containing product were combined and evaporated to give 23.0 g.(90%) of intermediate 111 as a grey solid.

Preparation of intermediate 112:



To a stirred solution of intermediate 111 (6.0 g; 20.32 mmol) in acetonitrile (60 mL) were added potassium cyclopropyltrifluoroborate (9,0g; 60.9mmol), cupric acetate (923 mg; 5.08 mmol) and and *o*-phenanthroline (458 mg; 2.540 mmol) and potassium carbonate (5.6 g; 40.64 mmol) and water (18 mL). After stirring overnight at 70°C under an atmosphere of oxygen, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers was dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE:EA:35:65). The fractions containing product were combined and evaporated to give 2.9 g (39%) of intermediate 112 as a off-white solid.

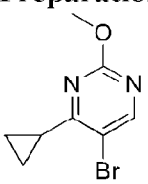
Preparation of intermediate 113:



To a stirred solution of intermediate 112 (1.0 g, 2.98 mmol) in acetonitrile (15 mL) was added iodotrimethylsilane (17.9 g, 89.45 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed water, then brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was purified by chromatography over silica gel (DCM:MeOH 96:4). The fractions containing product were combined and evaporated to give 630 mg (83%) of intermediate 113 as a dark brown solid.

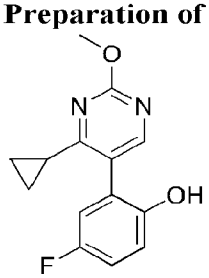
Example A29 (all remaining intermediates)

Preparation of the intermediate 114:



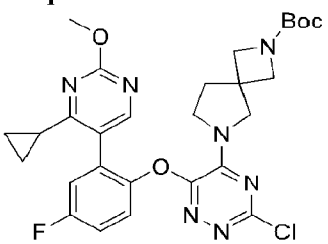
To a solution of 5-bromo-2-methoxypyrimidine (23.8 g, 0.13 mol) in diethyl ether (950 mL) and THF (170 mL) was added cyclopropylmagnesium bromide (133 mL, 0.13 mol, 1M in THF) at 0 °C. After stirring at room temperature for 1 h, the resulting mixture was quenched with water (2.3 mL, 0.13 mol) and followed by the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (28.6 g, 0.13 mol, dissolved in 70 mL of tetrahydrofuran). The resulting mixture was stirred at room temperature overnight, quenched with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase: EtOAc/hexanes (1/10)). The pure fractions were collected and evaporated to dryness to give 12.0 g (40%,) of desired intermediate 114 as a yellow solid.

Preparation of intermediate 115 :



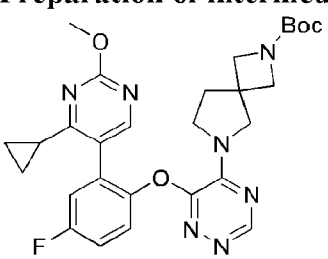
To a solution of intermediate 114 (2.0 g, 8.73 mmol) in 1,4-dioxane (100 mL) were added (5-fluoro-2-hydroxyphenyl)boronic acid (1.6 g, 10.48 mmol), tetrakis(triphenylphosphine)palladium (500 mg, 0.44 mmol) and sodium carbonate solution (17.5 mL, 1 M in water, 17.5 mmol). After stirring for 2 hours at 90 °C, the reaction mixture was cooled to room temperature, quenched with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (Mobile phase: EtOAc/hexane, 2/3). The pure fractions were collected and evaporated to dryness to give 1.4 g (63%) of the desired intermediate 115 as a light yellow solid.

Preparation of intermediate 116:



To a solution of intermediate 115 (1.5 g, 5.76 mmol) in THF (45 mL) were added intermediate 30 (2.1 g, 5.76 mmol) and DBU (877 mg, 5.76 mmol). The resulting solution was stirred for 48 hours at room temperature, then quenched by water and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (Mobile phase: ethyl acetate/hexane: 1/1). The pure fractions were collected and evaporated to dryness to give 3.0 g (78%, 87% purity according to LC/MS) of the desired intermediate 116 as a yellow solid.

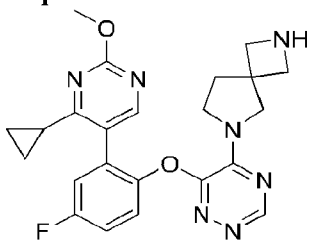
Preparation of intermediate 117:



To a solution of intermediate 116 (2.9 g, 5.0 mmol) in MeOH (175 mL) was added palladium on activated carbon (10% palladium on activated carbon, 67% moisture) (1.6 g, 1.49 mmol). After stirring at room temperature under a hydrogen atmosphere (1 atm.) for 1 h, the resulting mixture was filtered through a diatomite pad. The filtrate was concentrated under reduced pressure to give 2.7 g (96%) of the desired intermediate 117as a yellow solid.

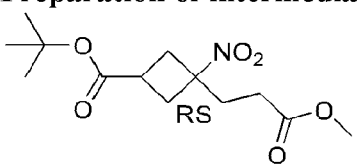
CA 03214746 2023-10-5

Preparation of intermediate 118:



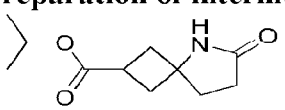
To a solution of intermediate 117 (2.2 g, 4.0 mmol) in DCM (70 mL) was added TFA (24 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduce pressure. The residue was diluted with water and the pH was adjusted to 9 with NaOH solution (1 M in water). The resulting solution was extracted with DCM eight times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered andconcentrated under reduced pressure to give 1.6 g (81%) of desired intermediate 118 as a white solid.

Preparation of intermediate 232:



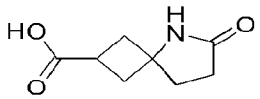
To a solution of *tert*-butyl 3-nitrocyclobutanecarboxylate (1.00 g, 4.72 mmol) (synthesis refer to US20170283406A1) and methyl acrylate (0.840 g, 9.76 mmol) in ACN (10 mL) was added DBU (1.45 g, 9.53 mmol) at 0° C, and the mixture was stirred at the same temperature for 20 min. The reaction was quenched with sat. aq. NH_4Cl solution (20 mL) and the mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude residue was purified by FCC (PE: EA =100: 0 to 80:20) to afford intermediate 232 (0.8 g, 59% yield) as colorless oil

Preparation of intermediate 233:



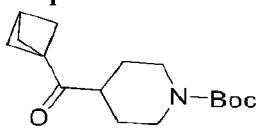
To a mixture of intermediate 232 (1.58 g, 5.50 mmol) and Nickel(II) chloride hexahydrate (1.2 g, 5.05 mmol) in MeOH (40 mL) was slowly added $NaBH_4$ (0.95 g, 25.1 mmol) at -10° C in 3 portions. The mixture was stirred at the same temperature for 3 h. The reaction was quenched with aq. K_2CO_3 solution (0.416 g/mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h and was further stirred at RT for another 2 h. The mixture was passed through a Celite® pad and the filtrate was concentrated *in vacuo* to afford intermediate 233 (0.87 g, crude), which was used directly in next step without further purification.

Preparation of intermediate 234:



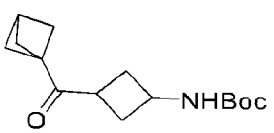
The solution of intermediate 233 (0.5 g, 2.22 mmol) in HCl/dioxane (7 mL, 4M) was stirred at RT for 12 h. The mixture was concentrated *in vacuo* to afford intermediate 234 (350 mg, crude) as a white solid, which was used directly in next step without further purification.

Preparation of intermediate 250:

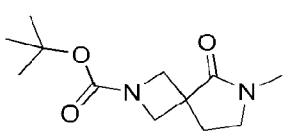


To a mixture of bicyclo[1.1.1]pentane-1-carboxylic acid (1.00 g, 8.92 mmol), *tert*-butyl 4-iodopiperidine-1-carboxylate (4.71 g, 17.8 mmol), 2,2'-bipyridine (696 mg, 4.46 mmol), Nickel(II) acetylacetonate (916 mg, 3.57 mmol), $MgCl_2$ (2.55 g, 26.8 mmol), zinc powder (4.00 g, 61.2 mmol), 4Å MS (10.0 g) and DIEA (4.5 mL, 27.2 mmol) in THF/DMF (100 mL/30 mL) was added Boc_2O (7.79 g, 35.7 mmol) under Ar atmosphere at 25 °C. After addition, the reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was poured into water (150 mL) and extracted with EtOAc (150 mL x 2). The combined layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (EtOAc/PE = 0-15%) to afford intermediate 250 (560 mg, 16% yield) as colorless oil.

The intermediate reported below was prepared following an analogous methodology as described for intermediate 250 starting from the corresponding intermediate:

intermediate 255	 from intermediate 254

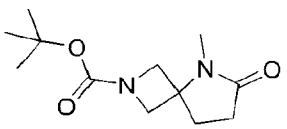
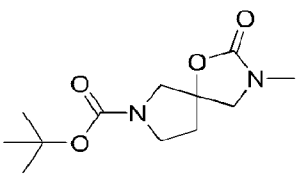
Preparation of intermediate 237:



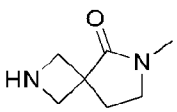
NaH (71 mg, 1.8 mmol, 60% in mineral oil) was added to solution of *tert*-butyl 5-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate (200 mg, 0.884 mmol) in THF (8 mL) cooled at 0 °C under

N_2 atmosphere. The reaction mixture was stirred at this temperature for 1 h. Then, MeI (1.48 g, 10.4 mmol) was added dropwise to the reaction mixture at 0 °C and the mixture was slowly warmed to RT and stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) solution and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to afford intermediate 237 (210 mg, crude) as a brown oil, which was used directly in the next step without further purification.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 237 starting from the corresponding commercial starting materials:

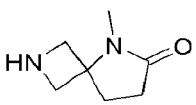
intermediate 239	
intermediate 247	

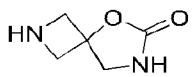
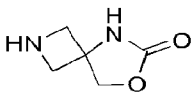
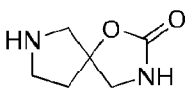
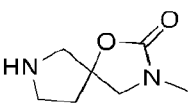
Preparation of intermediate 238:

 TFA salt

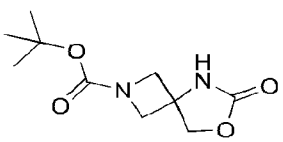
Intermediate 237 (210 mg, 0.874 mmol) was added to a solution TFA (0.5 mL) in DCM (5 mL). The reaction mixture was stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* to afford intermediate 238 (300 mg, crude) as a brown oil, which was used directly in the next step without further purification.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 238 starting from the corresponding intermediates or commercial starting materials:

intermediate 240	 TFA salt from intermediate 239

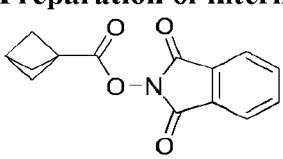
intermediate 241	 TFA salt
intermediate 243	 TFA salt from intermediate 242
intermediate 246	 TFA salt
intermediate 248	 TFA salt from intermediate 247

Preparation of intermediate 242:



To the mixture of *tert*-butyl 3-amino-3-(hydroxymethyl)azetidine-1-carboxylate (500 mg, 2.47 mmol) and TEA (1.0 mL, 7.42 mmol) in THF (15 mL) cooled at 0 °C was added a solution of bis(trichloromethyl) carbonate (800 mg, 2.70 mmol) in THF (5 mL) under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and then stirred at RT for additional 3 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (30 mL) solution and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed *in vacuo* afford intermediate 242 (600 mg, crude) as red solid, which was used directly in next step without further purification.

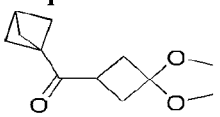
Preparation of intermediate 252:



DIC (5.0 g, 39.6 mmol) was added to a solution of bicyclo[1.1.1]pentane-1-carboxylic acid (4.0 g, 35.7 mmol), 2-hydroxyisoindoline-1,3-dione (6.50 g, 39.8 mmol) and DMAP (450 mg, 3.68 mmol) in DCM (100 mL). The resulting mixture was stirred at 25 °C overnight. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to give

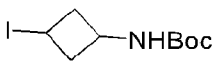
a crude product which was purified by FCC (PE:EtOAc = 10 : 1) to afford intermediate 252 (7.7 g, 84% yield) as white solid.

Preparation of intermediate 253:



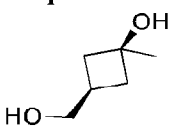
Anhydrous ACN (20 mL) and THF (30 mL) were added to a mixture of intermediate 252 (3.0 g, 11.7 mmol), 3,3-dimethoxycyclobutane-1-carboxylic acid (3.75 g, 23.4 mmol), $Ni(BPhen)Cl_2$•2DMF (710 mg, 1.16 mmol), zinc powder (2.40 g, 36.7 mmol), benzoic anhydride (5.30 g, 23.4 mmol), $MgCl_2$ (1.67 g, 17.7 mmol) and LiBr (1.02 g, 11.7 mmol) using a syringe under N_2 atmosphere. The resulting mixture was stirred at 25 °C overnight. The mixture was diluted with EtOAc (200 mL), washed with 1N NaOH (100 mL x 2) and brine (50 mL x 2), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by FCC (PE:EA = 10:1) to afford intermediate 253 (1.40 g, 57% yield) as colorless oil.

Preparation of intermediate 254:



To a solution of *tert*-butyl (3-hydroxycyclobutyl)carbamate (900 mg, 4.81 mmol), 1*H*-imidazole (982 mg, 14.4 mmol) and Ph_3P (2.52 g, 9.61 mmol) in toluene (15 mL) was added I_2 (1.83 g, 7.21 mmol). The mixture was stirred at 110 °C for 1 h. After cooled to RT, the mixture was diluted with EtOAc (50 mL) and washed with brine (20 mL x 2), further dried over anhydrous Na_2SO_4. After filtration and concentration, the crude residue was purified by FCC (PE : EA = 5 : 1) to afford intermediate 254 (620 mg, 43% yield) as white solid.

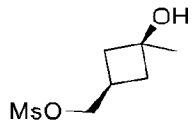
Preparation of intermediate 267:



To a suspension of $LiAlH_4$ (1.17 g, 30.8 mmol) in THF (10 mL) cooled at -10 °C was added a solution of *cis*-3-hydroxy-3-methylcyclobutanecarboxylic acid (1.00 g, 7.68 mmol) in THF (5 mL) dropwise. The resulting mixture was slowly warmed to 25 °C and stirred for 2 h. The reaction was quenched with water (10 mL). The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by FCC over silica gel (PE: EA from 1:0 to 0:1) to afford intermediate 267 (550 mg, 62% yield) as colorless oil.

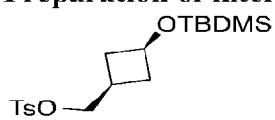
CA 03214746 2023-10-5

Preparation of intermediate 268:



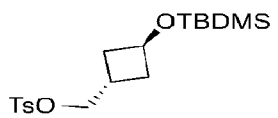
To a solution of intermediate 267 (200 mg, 1.72 mmol) in DCM (10 mL) was added TEA (0.74 mL, 5.3 mmol, 0.73 g/mL) at 0 °C. Then MsCl (750 mg, 6.54 mmol) was dropwise added at 0 °C. The mixture was slowly warmed to 20 °C and stirred for 1 h. The mixture was washed with water (1 mL) and the organic layer was concentrated under reduced pressure. The crude product was purified by FCC over silica gel (PE : EA from 1:0 to 1:2) to afford intermediate 268 (150 mg, 45% yield) as a colorless oil.

Preparation of intermediate 269:

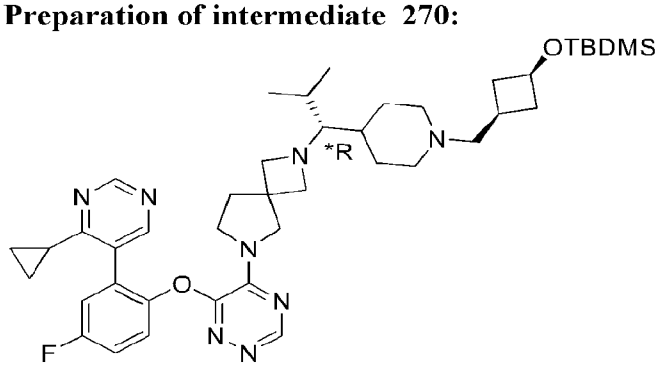


To a solution of *cis*-(3-((*tert*-butyldimethylsilyl)oxy)cyclobutyl)methanol (500 mg, 2.31 mmol), TEA (1 mL, 7 mmol) and DMAP (57 mg, 0.47 mmol) in DCM (10 mL) cooled at 0 °C was added TsCl (500 mg, 2.62 mmol) in portions. The resulting mixture was slowly warmed to RT and stirred for 12 h. The mixture was poured into H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by FCC (PE : EtOAc = 1:0 to 10:1) to afford intermediate 269 (700 mg, 82% yield) as a white solid.

The intermediate reported below was prepared following an analogous methodology as described for intermediate 269 starting from the corresponding commercial starting material:

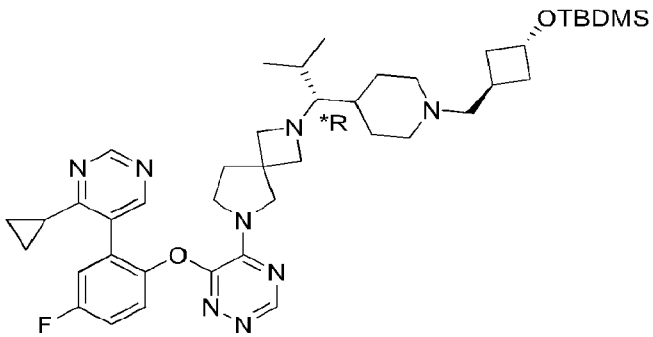
intermediate 271	

Preparation of intermediate 270:

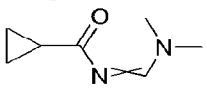


The mixture of compound 3 (600 mg, 1.07 mmol), intermediate 269 (500 mg, 1.35 mmol), K_2CO_3 (230 mg, 1.66 mmol) and KI (36 mg, 0.22 mmol) in ACN (10 mL) was stirred at 90 °C for 16 h. After cooled to RT, the reaction mixture was poured into H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by FCC (DCM : MeOH = 1:0 to 15:1) to afford intermediate 270 (700 mg, 80% yield) as a white solid.

The intermediate reported below was prepared following an analogous methodology as described for intermediate 270 starting from the corresponding intermediates:

intermediate 272	 from compound 3 and intermediate 271

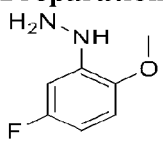
Preparation of intermediate 273:



(mixture E/Z not determined)

To a solution of cyclopropanecarboxamide (3.00 g, 35.3 mmol) in toluene (30 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (8.40 g, 70.5 mmol). The mixture was stirred at 120 °C for 2 h. After cooled to RT, the mixture was concentrated *in vacuo* to afford intermediate 273 (5.0 g, crude) as a yellow solid, which was used directly in next step without further purification.

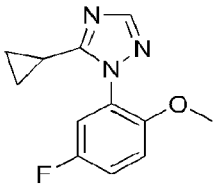
Preparation of intermediate 274:



A solution of 5-fluoro-2-methoxyaniline (10.0 g, 70.9 mmol) in 12 M HCl (30 mL) and H_2O (15 mL) was stirred at 0 °C for 20 min. Then a solution of $NaNO_2$ (6.36 g, 92.2 mmol) in H_2O (15 mL) was slowly added at 0 °C. The resulting mixture was slowly warmed to 25 °C and stirred for 1 h. Then $SnCl_2$ (26.9 g, 142 mmol) in HCl (30 mL) was added at -20 °C and the mixture was stirred at -20 °C for 2 h. The mixture was basified with NaOH (2 M) at -20 °C to adjust the pH value to 12. After slowly warming to RT, the mixture was extracted with DCM

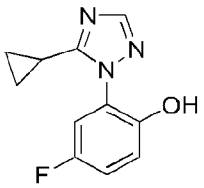
(500 mL) and washed with brine (200 mL x 3), further dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to afford intermediate 274 (7.5 g, crude) as brown oil, which was used directly in next step without further purification.

Preparation of intermediate 275:



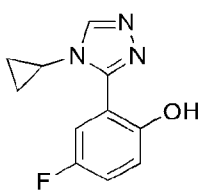
To a solution of intermediate 274 (5.50 g, crude) in AcOH (50 mL) was added intermediate 273 (5.00 g, crude) at 0 °C. The resulting mixture was warmed to RT and stirred for 12 h. The mixture was basified with NaOH (2 M) to adjust the pH value to 12 and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by FCC over silica gel (PE:EA from 1:0 to 2:1) to afford intermediate 275 (3.0 g) as a brown solid.

Preparation of intermediate 276:

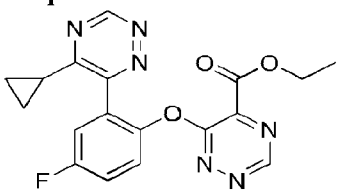


To a solution of intermediate 275 (3.00 g, 12.9 mmol) in DCM (30 mL) was slowly added BBr_3 (3.60 mL, 38.1 mmol) at -78 °C under N_2 atmosphere. The mixture was stirred at -78 °C for 1 h and further stirred at RT for 12 h. The mixture was basified with NaOH (2 M) to adjust the pH value to 12 and extracted with DCM (200 mL). The organic layer was washed with brine (100 mL x 3). The combined aqueous phase was extracted with DCM (100 mL x 3) again and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by FCC over silica gel (PE: EtOAc from 1:0 to 1:1) to afford intermediate 276 (1.90 g, 66% yield) as a brown solid.

The intermediate reported below was prepared following an analogous methodology as described for intermediate 276 starting from the corresponding intermediate:

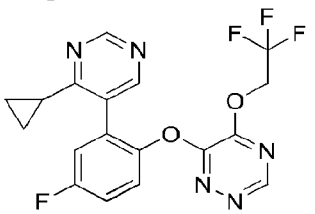
intermediate 288	 from intermediate 287

Preparation of intermediate 280:



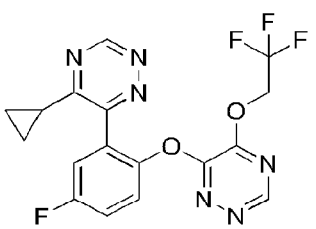
Intermediate 279 (450 mg, 1.13 mmol) was dissolved in THF (15 mL), then isoamyl nitrite (0.55 mL, 4.1 mmol) was added. The reaction was heated at 65 °C for 3 h before it was cooled to RT. The reaction mixture was concentrated *in vacuo* and the crude product was purified by FCC (EA:PE from 1:10 to 1:3) to afford intermediate 280 (200 mg, 46% yield) as yellow oil.

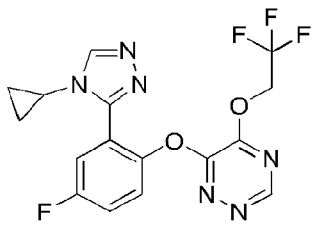
Preparation of intermediate 294:



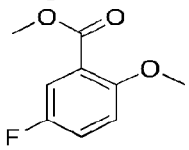
The mixture of intermediate 13 (3.5 g, 9.91 mmol), molecular sieve (6.0 g, 4Å) and 2,2,2-trifluoroethanol (30 mL) was first purged with Ar gas for three times and stirred at 65 °C for 3 h. Then 1,3-dibromo-1,3,5-triazinane-2,4,6-trione (5.69 g, 19.8 mmol) was added to the mixture at 25 °C and the mixture was further stirred at 65 °C for 8 h. After cooled to RT, the mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give the crude product which was purified by FCC (eluent: PE:EA from 1:0 to 3:1) to afford intermediate 294(1.8 g, 45% yield) as a yellow oil.

The intermediates reported below were prepared following an analogous methodology as described for intermediate 294 starting from the corresponding intermediates:

intermediate 282	 from intermediate 281

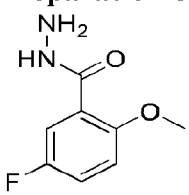
intermediate 291	 from intermediate 290

Preparation of intermediate 285:



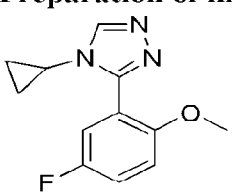
To a solution of 5-fluoro-2-methoxybenzoic acid (10.0 g, 58.8 mmol) in DCM (150 mL) and MeOH (150 mL) cooled at 0 °C was slowly added $TMSCH_2N_2$ (88.0 mL, 176 mmol, 2 M in hexane). The reaction mixture was slowly warmed to RT and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by FCC (PE:EtOAc = 10:1 to 3:1) to afford intermediate 285 (12 g, 89% purity, 99% yield) as a yellow oil.

Preparation of intermediate 286:



The mixture of intermediate 285 (4.00 g, 21.7 mmol) and hydrazine hydrate (2.02 mL, 65.0 mmol) in EtOH (10 mL) was stirred at 90 °C for 16 h. After cooled to RT, the reaction mixture was concentrated *in vacuo* to afford intermediate 286 (2.9 g, crude) as a white solid, which was used directly in next step without further purification.

Preparation of intermediate 287:

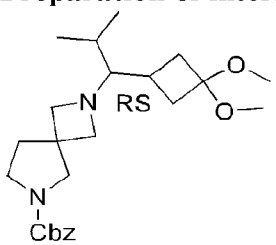


To the solution of intermediate 286 (2.80 g, 15.2 mmol) in ACN (60 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (1.85 mL, 19.8 mmol) and the reaction mixture was stirred at 50 °C for 1 h. Then cyclopropanamine (5.27 mL, 76.0 mmol) in ACN (10 mL) was added to

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above mixture and followed with addition of AcOH (1.74 mL, 30.4 mmol). The reaction mixture was further stirred at 120 °C for 16 h. After cooled to RT, the reaction mixture was concentrated and the residue was purified by preparative HPLC (Welch Xtimate C18 150*40mm*10μm column, eluent: water (0.2% formic acid)-ACN, from 15% ACN to 45% ACN v/v). The desired fractions were collected and lyophilized to afford intermediate 287 (465 mg, 10% yield) as a white solid.

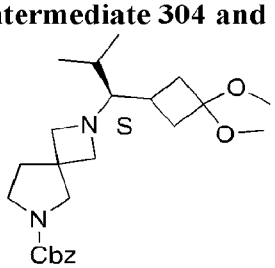
Preparation of intermediate 303



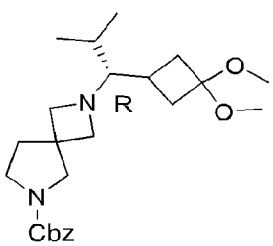
To a stirring solution of intermediate 3 (15 g, 60.900 mmol) in methanol (300 mL) was added intermediate 36 (13.61 g, 73.080 mmol) and acetic acid (4.02 g, 66.990 mmol). After stirring for 0.5 hour at room temperature, sodium cyanoborohydride was added (7.65 g, 121.800 mmol). After stirring overnight at 50°C, the reaction mixture was quenchend with potassium carbonate solution (10% in water) and extracted with ethyl acetate. The combined organic layers were washed brine and dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (EA/PE, 0% EA to 50%) to give 17.8 g (69% yield) of the desired compound as a light yellow oil.

Preparation of intermediate 304 and 305

intermediate 304:



intermediate 305:



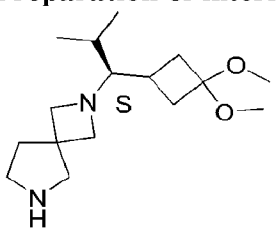
170 g benzyl 2-(1-(3,3-dimethoxycyclobutyl)-2-methylpropyl)-2,6-diazaspiro[3.4] octane-6-carboxylate was purified by SFC with the following conditions: Column: CHIRALPAK IG, 5*25cm,10um; Mobile Phase A:CO_2, Mobile Phase B:EtOH:ACN:DCM=1:1:1; Flow rate:150

mL/min; Gradient:40% B; 220 nm; retention time 1 = 4.45 min; retention time 2 = 5.88 min; Injection Volumn:3.8 ml; Number of Runs:237 to give two fractions.

Fraction A: 67.0 g 39% yield, retention time 1:5.88 min) of intermediate 304 as light yellow oil.

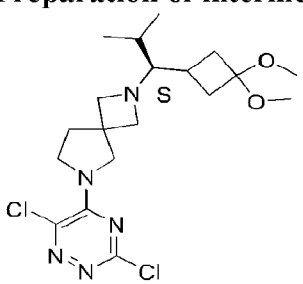
Fraction B: 65 g (38% yield, retention time 2: 4.45 min) of intermediate 305 as light yellow oil.

Preparation of intermediate 306



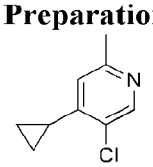
To a solution of intermediate 304 (15 g, 36.010 mmol) in methanol (300 mL) was added palladium on activated carbon (10% palladium) (8g, 7.517 mmol). Then, the mixture was stirred at room temperature for 5 hours under the hydrogen (2-3 atm.). The mixture was diluted with methanol and filtered through a Celite®. The filtrate was evaporated under reduced pressure to give 9.5 g of intermediate 306 as a yellow oil.

Preparation of intermediate 307



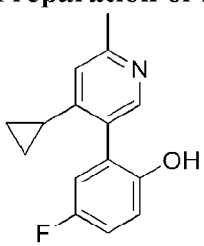
To a solution of 3,5,6-trichloro-1,2,4-triazine (9.4 g, 50.99 mmol) in dichloromethane (100 mL) were added the mixture of intermediate 306 (12.0 g, 42.49 mmol) and triethylamine (12 mL, 84.98 mmol) in dichloromethane (150 mL) under nitrogen at 0 °C. After stirring for 3 hours at room temperature under nitrogen, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure to give 17.3 g (83% yiled) of intermediate 307 as a yellow solid.

Preparation of intermediate 308



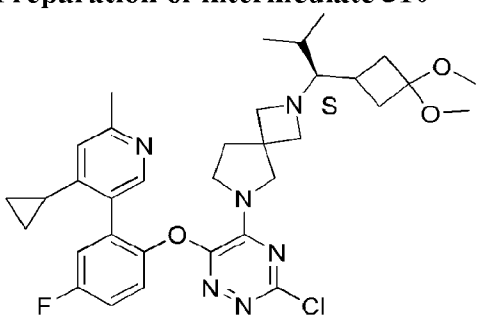
To a solution of 4-bromo-5-chloro-2-methylpyridine (8.8 g, 42.62 mmol) in tetrahydrofuran (90 mL) was added tetrakis(triphenylphosphine)palladium (2.5 g, 2.13 mmol). The resulting mixture was stirred at room temperature for 1 hour under nitrogen atmosphere and, then, cyclopropylzinc(II) bromide (340 mL, 0.5 M in THF) was added. After stirring for 2 hours under nitrogen atmosphere at 65 °C, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 100 g (eluent: petroleum ether-ethyl acetate 75%:25%) to give 7.2 g (97% yield) of intermediate 308 as a yellow solid.

Preparation of intermediate 309



To a stirring solution of intermediate 308 (7.2 g, 42.95 mmol) in 1,4-dioxane (216 mL) were added (5-fluoro-2-hydroxyphenyl)boronic acid (8.0 g, 51.54 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (1.5 g, 2.15 mmol) and sodium carbonate aqueous solution (2M in water, 72 mL). After stirring for 3 hours under nitrogen atmosphere at 100 °C, the reaction mixture was cooled down to room temperature, quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 100 g (eluent: petroleum ether-ethyl acetate 70%:30%) to give 5.8 g (54% yield) of intermediate 309 as a yellow solid.

Preparation of intermediate 310

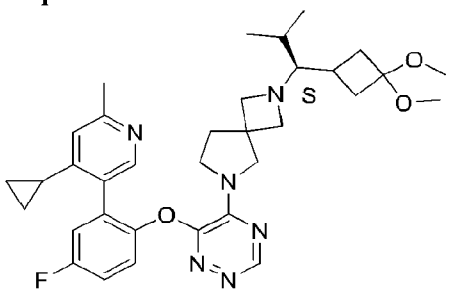


To a solution of intermediate 307 (4.3 g, 9.87 mmol) in tetrahydrofuran (80 mL) were added intermediate 309 (3.0 g, 12.33 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.9 g, 25.90

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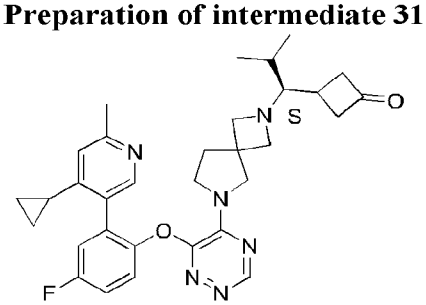
mmol). After stirring at room temperature for 3 days, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers was dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 100 g (eluent: petroleum ether-ethyl acetate 34%:66%) to give 5.0 g (64% yield) of intermediate 310 as a green solid.

Preparation of intermediate 311



To a solution of intermediate 310 (5.3 g, 8.32 mmol) in tetrahydrofuran (100 mL) were added sodium borohydride (535 mg, 14.14 mmol), *N*,*N*,*N*',N'-tetramethylethylenediamine (1.6 g, 14.14 mmol) and 1,1'-bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex (680 mg, 0.83 mmol) under nitrogen atmosphere. After stirring at room temperature overnight under nitrogen atmosphere, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 100 g (eluent: dichloromethane-methanol 93%:7%) to give 4.9 g (88% yield) of intermediate 311 as a brown solid.

Preparation of intermediate 312

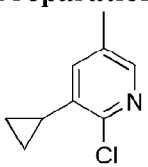


To a solution of intermediate 311 (4.9 g, 8.13 mmol) in acetone (80 mL) were added *p*-toluenesulfonic acid (7.0 g, 40.65 mmol) and water (40 mL). The resulting mixture was stirred at 65 °C overnight. After cooling down to room temperature, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (100 g, eluent: dichloromethane-methanol 98%:2%) to give 4.2 g (88% purity

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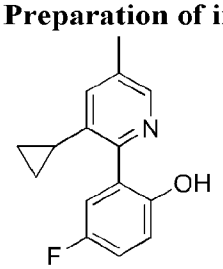
evaluated by LCMS, 81% yield) of intermediate 312 as a yellow solid.

Preparation of intermediate 313



To a solution of 3-bromo-2-chloro-5-methylpyridine (16.0 g, 79.55 mmol) in tetrahydrofuran (160 mL) were added cyclopropylzinc(II) bromide (350.0 mL, 175.000 mmol, 0.5 M in THF) and tetrakis(triphenylphosphine)palladium (4.6 g, 3.98 mmol). After stirring for 10 hours under nitrogen atmosphere at 65°C, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 320 g (eluent: petroleum ether-ethyl acetate/ 0% ~ 10%) to give 12 g (82.8% purity evaluated by LC/MS, 75% yield) of intermediate 313 as a colorless oil.

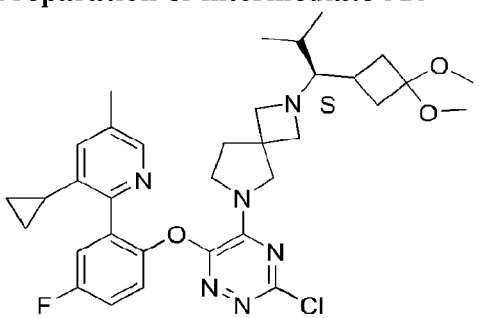
Preparation of intermediate 314



To a solution of intermediate 313 (15.0 g, 89.48 mmol) in 1,4-dioxane (420 mL) and water (140 mL) were added 5-fluoro-2-hydroxyphenylboronic acid (16.74 g, 107.4 mmol)), sodium carbonate (28.45 g, 268.44 mmol) and tetrakis(triphenylphosphine)palladium(0) (10.34 g, 8.95 mmol). The resulting mixture was stirred at 100 °C for 18 hours under nitrogen. After cooling down to room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue obtained was purified by flash chromatography with silica gel 320 g (eluent: petroleum ether-ethyl acetate/ 0% ~ 100%) to afford a crude product. The crude product was triturated in ethyl acetate/petroleum ether in the ratio of 1:10 to afford 18.0 g (82% yield) of intermediate 314 as an off-white solid.

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Preparation of intermediate 315

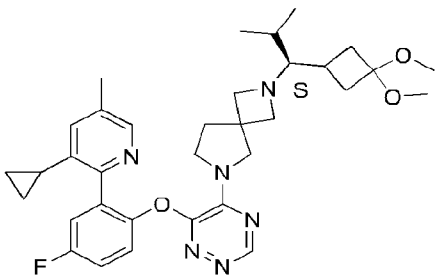


To a solution of intermediate 307 (13.0 g, 30.21 mmol) in tetrahydrofuran (400.0 mL) were added intermediate 314 (8.8 g, 36.25 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (11.0 mL, 75.52 mmol). After stirring at room temperature for 3 days, the reaction mixture was quenched with water and then extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 100 g (eluent: petroleum ether-ethyl acetate/ 0% ~ 100%) to afford two fractions of intermediate 315.

Fraction A: 8.89 g (97.5% purity evaluated by LCMS; 45% yield) as a white solid.

Fraction B: 2.5 g (88.7% purity, 11% yield) as a yellow solid.

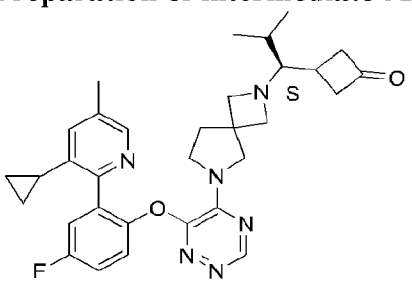
Preparation of intermediate 316



To a solution of intermediate 315 (7.89 g, 12.38 mmol) in tetrahydrofuran (160.0 mL) were added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (506 mg, 0.62 mmol), sodium borohydride (796 mg, 21.05 mmol) and *N,N,N',N'*-tetramethylethylenediamine (3.2 mL, 21.05 mmol). After stirring overnight at room temperature under nitrogen atmosphere, the reaction mixture was quenched with water and then extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel 120 g (eluent: petroleum ether-ethyl acetate: 0% ~ 100%) to afford 6.0 g (81% yield) of intermediate 316 as a yellow solid.

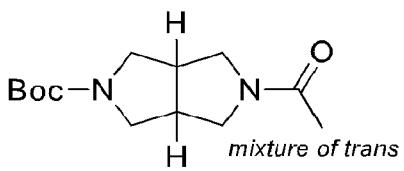
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Preparation of intermediate 317



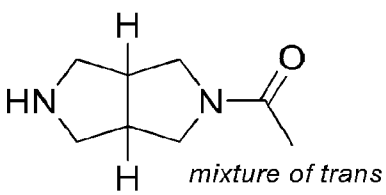
To a solution intermediate 316 (5.4 g, 8.96 mmol) in dichloromethane (26.0 mL) were added trifluoroacetic acid (78.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure. The residue was quenched with saturated sodium bicarbonate solution and then extracted with dichloromethane for three times. The organic layers were combined, washed with brine and dried over sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure to give 4.0 g (80% yield) of intermediate 317 as a yellow solid.

Preparation of intermediate 318



Acetic anhydride (375 mg, 3.67 mmol) was added to a solution consisting of (*trans*)-*tert*-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-carboxylate (750 mg, 2.48 mmol), Et_3N (1.0 g, 9.9 mmol) and DCM (20 mL). The reaction mixture was stirred at room-temperature for 6 hours. The reaction mixture was partitioned between H_2O (30 mL) and DCM (30 mL). The aqueous phase was extracted with DCM (20 mL x 3) and the combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure to afford 600 mg (95% yield) intermediate 318 (mixture of trans) as a yellow solid.

Preparation of intermediate 319

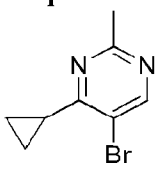


TFA (1.3 mL, 18 mmol) was added to a solution consisting of intermediate 318 (600 mg, 2.36 mmol) in DCM (15 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure to give the crude product as yellow oil which was dissolved in water (20 mL). The pH of the mixture was adjusted to 10 with

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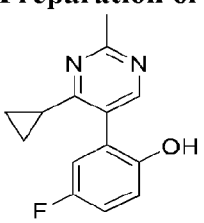
$NH_3•H_2O$ and then, lyophilized to afford to 500 mg (crude) of intermediate 319 (mixture of trans) as a yellow solid which was used for next step without further purification.

Preparation of intermediate 320



A stir bar, 5-bromo-2-methylpyrimidine (36.0 g, 208 mmol) and dry tetrahydrofuran (250 mL) were added to 2 L three-necked round-bottomed flask before the mixture was cooled to 0 °C under ice-water bath and purged with nitrogen for three times. Then, cyclopropyl magnesium bromide (500 mL, 250 mmol, 0.5 M in THF) was added dropwise to the mixture in 2 hours. The reaction mixture was warmed to room temperature gradually and stirred at room temperature for 1.5 hours. The mixture was cooled to 0 °C under ice-water bath again. A solution of DDQ (47.2 g, 208 mmol) in dry tetrahydrofuran (250 mL) was added to the mixture dropwise in 1.5 hours. The reaction mixture was warmed to room temperature gradually and stirred at room temperature for another 16 hours. 400 mL of EtAOc and 50 mL of sat. NH_4Cl were added to the reaction mixture and stirred for 0.5 h. The reaction mixture was filtered through celite® and washed with EtOAc (100 mL x 3). The organic phase was concentrated under reduced pressure. The residue was purified by FCC (eluent: petroleum ether: ethyl acetate = 1:0 to 20:1) to afford the 24.31g (55% yield) of Intermediate 320 as a yellow oil.

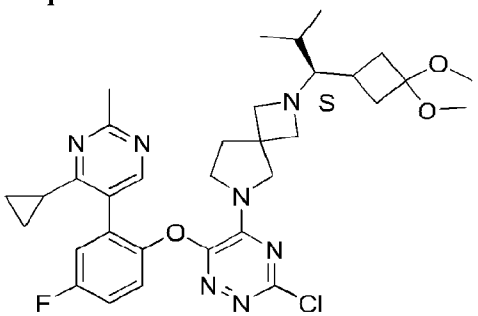
Preparation of intermediate 321



$Pd(dppf)Cl_2$ (4.17 g, 5.70 mmol) was added to a mixture of intermediate 320 (24.3 g, 114 mmol), 5-fluoro-2-hydroxyphenyl)boronic acid (21.3 g, 137 mmol), Na_2CO_3 (24.18 g, 228 mmol) in dioxane (300 mL)/H_2O (60 mL). The mixture was stirred at 90 °C for 16 hours under inert atmosphere. The reaction mixture was cooled to room temperature and filtered through a pad of celite® and washed with EtOAc (50 mL x 2). The filtrate was concentrated in vacuo and the residue was dissolved in EtOAc (300 mL). The mixture was washed with brine (50 mL x 3), dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was dissolved in EtOAc (30 mL), stirred for 30 min, filtered and washed with EtOAc (10 mL x 2). The filter cake was collected and dried to afford 22.3g (78% yield) of intermediate 321 as a pale solid.

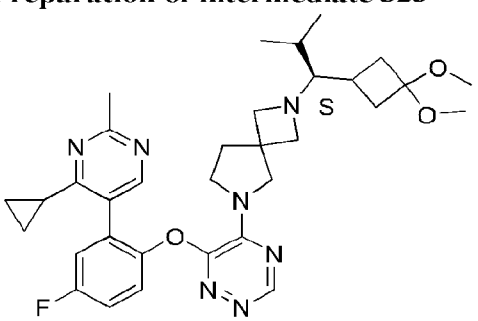
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Preparation of intermediate 322



DBU (2.94 g, 19.3 mmol) was added to a solution consisting of intermediate 307 (7.0 g, 16.3 mmol), intermediate 321 (3.98 g, 16.3 mmol) in THF (200 mL). The reaction mixture was stirred at room-temperature for 16 hours. The reaction mixture was partitioned between H_2O (200 mL) and ethyl acetate (200 mL). The aqueous phase was extracted with ethyl acetate (200 mL x 3) and the combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure to afford a crude product which was mixed with another crude (2g) and purified with by FCC (petroleum ether: ethyl acetate = 1:0 to 0:1) to yield 7.0 g intermediate 322 (53% yield overall yield based on 8 g of intermediate 307) as a yellow solid.

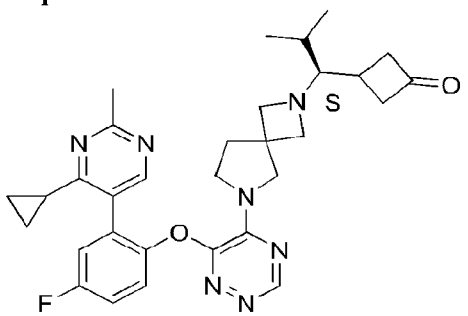
Preparation of intermediate 323



$Pd(dppf)Cl_2$•DCM (540 mg, 0.661 mmol) was added to a solution of intermediate 322 (6.0 g, 9.4 mmol), $NaBH_4$ (620 mg, 16.4 mmol), TMEDA (2.1 g, 18 mmol) and THF (150 mL) under N_2. The reaction mixture was stirred at room-temperature for 4 hours. The reaction mixture was partitioned between H_2O (200 mL) and ethyl acetate (300 mL). The aqueous phase was extracted with ethyl acetate (150 mL x 3) and the combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure to afford a crude product which was mixed with another crude (1.2g) and purified by FCC (petroleum ether: ethyl acetate = 1:0 to 0:1) to yield 4.5g (66% yield overall yield from 7g of intermediate 322) intermediate 323 as a yellow solid.

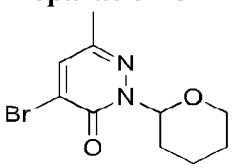
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Preparation of intermediate 324



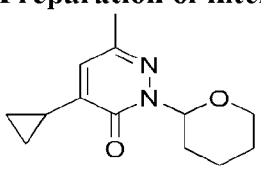
TFA (9.6 mL, 129 mmol) was added to a solution consisting of intermediate 323 (4.0 g, 6.6 mmol) in DCM (100 mL). The reaction mixture was stirred at room-temperature for 4 hours. The mixture was poured into 10% aqueous solution K_2CO_3 (300 mL), and extracted with dichloromethane (200 mL x 3). The combined organic extracts were washed with brine (300 mL), aqueous $NaHCO_3$ (300 mL), H_2O (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford 3.3 g (84% yield) intermediate 324 as a yellow solid which was used in the next step without further purification.

Preparation of intermediate 325



To a solution of 4-bromo-6-methylpyridazin-3(2*H*)-one (5.00 g, 26.45 mmol) in tetrahydrofuran (100 mL) were added 3,4-dihydro-2*H*-pyran (9.65 mL, 105.82 mmol) and *p*-toluenesulfonic acid (455 mg, 2.65 mmol). The resulting mixture was stirred at 70 °C overnight. The reaction was quenched with water and then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel column chromatography (EA/PE, 0% EA to 20%EA) to afford 4.2 g (52% yield, 89.2% purity based on LCMS) of intermediate 325 as a yellow solid.

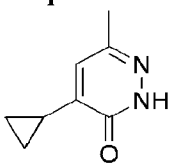
Preparation of intermediate 326



Into a solution of intermediate 325 (8.30 g, 24.62 mmol; 81% purity based on LCMS) in 1,4-dioxane (120 mL) were added cyclopropylboronic acid (2.33 g, 27.08 mmol), Pd(amphos)Cl_2 (871 mg, 1.23 mmol) and sodium carbonate (40 mL, 2 M in water, 80.00 mmol). The resulting mixture was stirred at 90 °C under nitrogen atmosphere overnight. After cooling to room

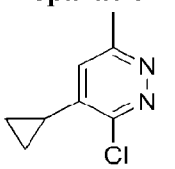
temperature, the reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel column chromatography (EA/PE, 0%EA to 13%EA) to afford 3.4 g (50% yield, 84.7% purity based on LCMS) of intermediate 326 as a yellow oil.

Preparation of intermediate 327



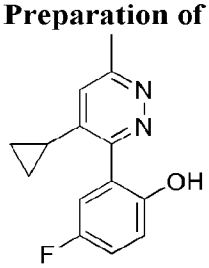
To a solution of intermediate 326 (2.40 g, 8.61 mmol, 84.7% purity based on LCMS) in dichloromethane (30 mL) was added trifluoroacetic acid (10 mL). The resulting mixture was stirred at 50 °C for 1 hour. The resulting mixture was concentrated under reduced pressure. The residue was dissolved with water and adjusted to PH = 7 by ammonium hydroxide (33% in water). The mixture was extracted with dichloromethane for 5 times. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 870 mg (58% yield) of intermediate 327 as a yellow solid.

Preparation of intermediate 328



To a solution of intermediate 327 (2.46 g, 16.38 mmol) in acetonitrile (50 mL) was added $POCl_3$ (7.6 mL, 81.90 mmol). After stirring at 50 °C overnight, the reaction solution was poured into ice water slowly. The resulting solution was adjusted to pH = 7 by a solution of NaOH (2M in water) and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (EA/PE, 0%EA to 30%EA) to give 2.1 g of intermediate 328 as a yellow oil.

Preparation of intermediate 329

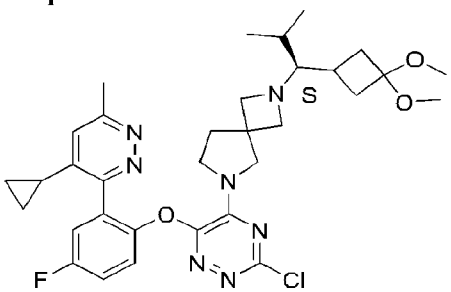


To a mixture of intermediate 328 (5.0 g, 29.65 mmol), 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-

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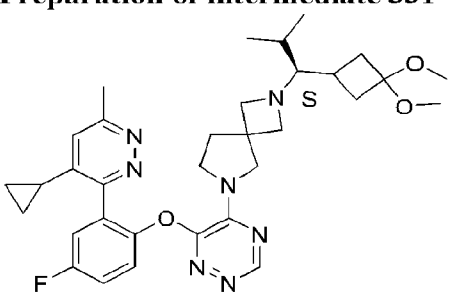
dioxaborolan-2-yl)phenol (7.06 g, 29.65 mmol) and $Pd(PPh_3)_4$ (1.71 g, 1.48 mmol) in 1,4-dioxane (75 mL) was added sodium carbonate solution (25 mL, 2M in water, 50.00 mmol) was stirred 90 °C for 3 hours. After cooling to room temperature, the reaction solution was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (EA/PE, 0%EA to 60%EA) to give 6.0 g of intermediate 329 as a yellow solid.

Preparation of intermediate 330



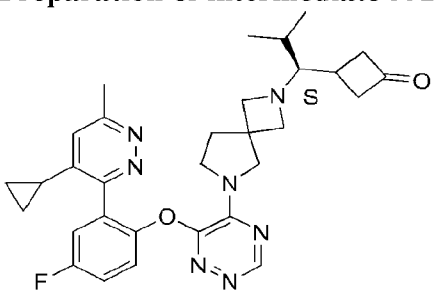
To a solution of intermediate 307 (8 g, 18.6 mmol) in tetrahydrofuran (200 mL) were added intermediate 329 (5.45 g, 22.31 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.94 mL, 46.47 mmol). The resulting mixture was stirred at room temperature overweekend. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel column chromatography (EA/PE, 0%EA to 90%EA) to afford 7.56 g (62% yield) of intermediate 330 as a yellow solid.

Preparation of intermediate 331



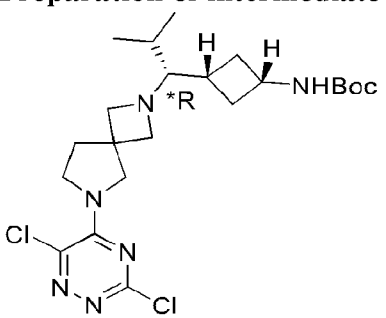
To a solution of intermediate 330 (7.26 g, 10.92 mmol) in THF (140 mL) were added $Pd(dppf)Cl_2$ (446 mg, 0.55 mmol), $NaBH_4$ (702 mg, 18.57 mmol) and TMEDA (2.78 mL, 18.57 mmol). After stirring at room temperature under nitrogen atmosphere overnight, the reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (EA/PE, 0%EA to 91%EA) to afford 416 mg (65% yield) of intermediate 331 as a yellow solid.

Preparation of intermediate 332



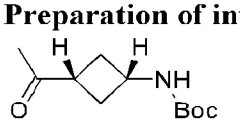
To a solution of intermediate 331 (500 mg, 0.75 mmol) in acetone (7.5 mL) and water (2.5 mL) was added TsOH (649 mg, 3.77 mmol). After stirring at 65 °C overnight, the reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 480 mg (98% yield) of intermediate 332 as a brown solid.

Preparation of intermediate 333



A stir bar, intermediate 283 (2.7 g, 6.58 mmol), 3,5,6-trichloro-1,2,4-triazine (1.21 g, 6.56 mmol) in DCM (100 mL) was stirred at 25 °C for 10 min and added TEA (2.74 mL, 19.7 mmol). The mixture was stirred at 25 °C for 10 h. The mixture was poured into water (100 mL x 2) and extracted with dichloromethane (50 mL x 2). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was puritied by FCC (eluent: dichloromethane : methanol = 1:0 to 10:1) to give intermediate 333 as a yellow soilds (3.32 g, 81.7% yield).

Preparation of intermediate 336

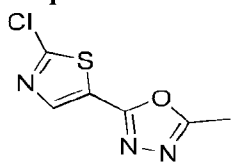


A solution of intermediate 5 (9.91 g, 38.364 mmol) in anhydrous THF (191.8 mL) was cooled to 0 °C. 3.4 M MeMgBr in THF (25.952 mL, 3.4 M, 88.236 mmol) was slowly added. Once the addition was complete, the reaction was allowed to warm to rt and stirred over the weekend. The reaction was quenched by addition of sat. ammonium chloride solution. The water phase was extraced several times with diethyl ether. The organic extracts were combined, dried over

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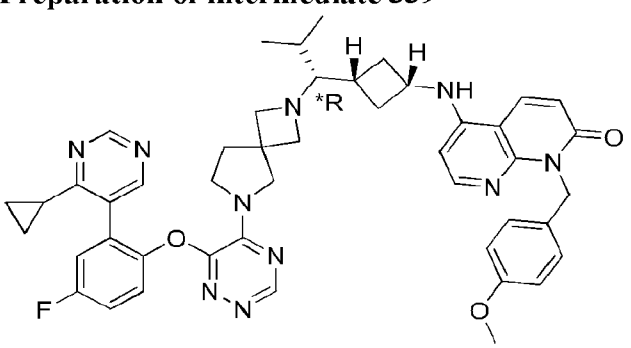
magnesium sulfate, filtered and concentrated to afford the crude material (8 g, yield 97.775%). The material was purified by FCC (silica gel, 10% to 30% EA in n-heptane) to yield Compound 336 (1.16 g, 14.2% yield) as a white powder.

Preparation of intermediate 338



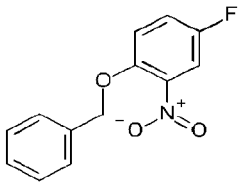
2-chloro-1,3-thiazole-5-carboxylic acid (0.5 g, 3.057 mmol) was dissolved in EtOAc (5.2 mL) and treated with T3P 50% in EtOAc (4.41 mL) and acetohydrazide (226 mg, 3.057 mmol). The resulting solution was stirred over the weekend at 70°C. The reaction mixture was hydrolysed and extracted with ethyl acetate (3x). The combined organic phases were washed with brine. The volatile components were removed at rotavap. The material was analyzed with HPLC and NMR, showing intermediate 338 (240 mg, 39% yield) with T3P impurities. The material was used without further purification.

Preparation of intermediate 339



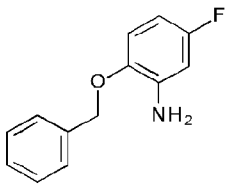
*t*BuXPhos Pd G3 (36.5 mg, 0.046 mmol) was added to a solution of Compound 1a (250 mg, 0.459 mmol), 5-chloro-1-(4-methoxybenzyl)-1,8-naphthyridin-2(1*H*)-one (262 mg, 0.871 mmol) and NaO*t*Bu (132 mg, 1.37 mmol) in 1,4-dioxane (8 mL) under argon atmosphere. The mixture was stirred at 100 °C under microwave for 1 h. The mixture was cooled to room temperature, diluted with dichloromethane (20 mL), washed with H_2O (10 mL) and brine (20 mL). The organic layers were dried over abhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (eluent: dichloromethane : methanol = 1:0 to 10:1) to give intermediate 339 (180 mg, 37.06% yield) as a yellow oil.

Preparation of Intermediate 340 (1-(benzyloxy)-4-fluoro-2-nitrobenzene):



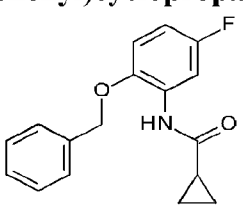
To a solution of 4-fluoro-2-nitro (5 g, 31.827 mmol) and Cs_2CO_3 (20.74 g, 63.653 mmol) in DMF (50 mL) was added benzyl bromide (4 mL, 33.418 mmol) at room temperature for 6 h. Upon completion (TLC), reaction mixture was diluted with EtOAc (100 mL) and washed with water (200 mL). Layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). Combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (0 to 10 % EtOAc in heptane) to afford Intermediate 340 (1-(benzyloxy)-4-fluoro-2-nitrobenzene) (7.85 g, yield 99 %) a thick yellow oil.

Preparation of Intermediate 341 (2-benzyloxy-5-fluoro-aniline):



To a mixture of Intermediate 340 (1 g, 4.045 mmol) and NH_4Cl (2.15 g, 40.196 mmol) in EtOH (30 mL) at ambient temperature was added Zinc powder (2.63 g, 40.208 mmol) and the mixture was then heated to 50 °C overnight. The mixture was diluted with EtOAc and filtered on a pad of Celite® and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and water. Aqueous layer was extracted with EtOAc (2 × 25 mL). Combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$ and rotary evaporated to afford Intermediate 340 (2-benzyloxy-5-fluoro-aniline) (875 mg, yield 99 %) as a brown oil.

Preparation of Intermediate 342 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarboxamide):

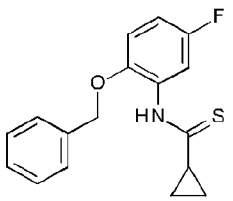


To a solution of Intermediate 341 (2-benzyloxy-5-fluoro-aniline) (1.37 g, 6.306 mmol) and Et_3N (2.64 mL, 19.92 mmol) in anhydrous dichloromethane (20 mL) at 0 ° cyclopropane

carbonyl chloride (0.7 mL, 7.57 mmol) was added, and the reaction mixture was stirred at room temperature for 1h.

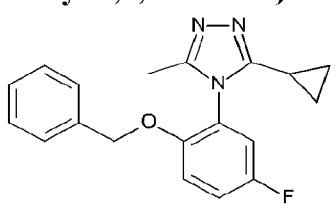
Upon completion (TLC), reaction mixture was diluted with dichloromethane (100 mL) and washed with water (100 mL). Aqueous layer was extracted with dichloromethane (30 mL × 2), combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (0 to 60 % EtOAc in heptane) to afford Intermediate 342 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarboxamide) (1.55 g, yield 86 %) as a colourless solid.

Preparation of Intermediate 343 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarbothioamide):



To a solution of Intermediate 342 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarboxamide) (1 g, 3.505 mmol) in 1,4-dioxane (30 mL), Lawesson's reagent (0.8 g, 1.963 mmol) was added and the resulting mixture was heated to 100 °C for 6 h. Reaction mixture was then concentrated in vacuo and the residue was purified by flash column chromatography (0 to 15 % EtOAc in heptane) to afford Intermediate 343 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarbothioamide) (0.815 g, 77 %) as a pale yellow solid

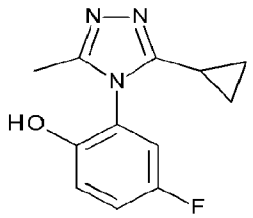
Preparation of Intermediate 344 (4-(2-benzyloxy-5-fluoro-phenyl)-3-cyclopropyl-5-methyl-1,2,4-triazole):



Hydrazine hydrate (0.28 mL, 2.883 mmol) was added dropwise to a stirred solution of Intermediate 343 (*N*-(2-benzyloxy-5-fluoro-phenyl)cyclopropanecarbothioamide) (790 mg, 2.622 mmol) in THF (20 mL) at ambient temperature. After 60 min, the solution was concentrated under reduced pressure and the residue was treated with triethyl orthoacetate (5 mL). The mixture was heated at 80 °C for 30 min, cooled to ambient temperature, and concentrated under reduced pressure. The residue was treated with ice-cold dilute aqueous ammonia (15 mL), water (25 mL) and extracted with EtOAc (70 mL × 3). Combined organic

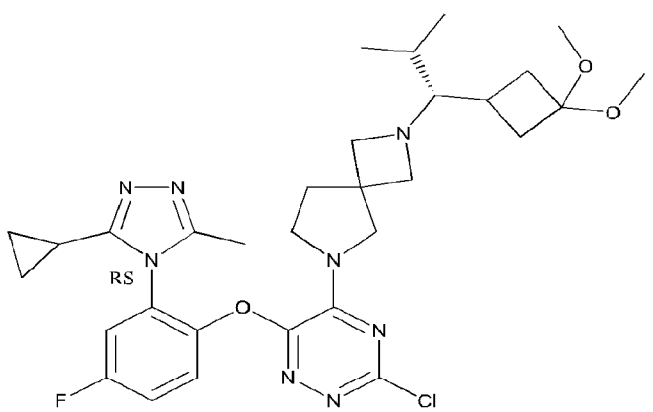
layer was washed with brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The residue was purified by flash column chromatography (0 to 100 % EtOAc in heptane) to afford Intermediate 344 (4-(2-benzyloxy-5-fluoro-phenyl)-3-cyclopropyl-5-methyl-1,2,4-triazole) (530 mg, yield 62 %) as a cream coloured fluffy solid.

Preparation of Intermediate 345 (2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenol):



Pd/C (10%) (27 mg) was added to a solution of Intermediate 344 (4-(2-benzyloxy-5-fluoro-phenyl)-3-cyclopropyl-5-methyl-1,2,4-triazole) (200 mg, 0.62 mmol) in methanol (50 mL) and kept for hydrogenation at ambient temperature overnight. Upon completion (TLC), catalyst was filtered off through a Celite® bed, washed with MeOH several times and combined organic layer was concentrated in vacuo to give Intermediate 345 (2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenol) (135 mg, yield 93 %) as a colourless solid.

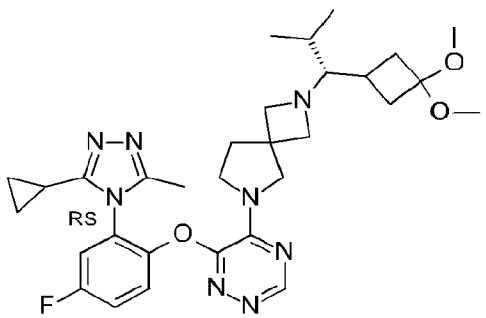
Preparation of Intermediate 346 (7-[3-chloro-6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2-[(1R)-1-(3,3-dimethoxycyclobutyl)-2-methyl-propyl]-2,7-diazaspiro[3.4]octane):



A mixture of intermediate 307 (130 mg, 0.3 mmol), Intermediate 345 (2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenol) (70 mg, 0.3 mmol) and DBU (0.225 mL, 1.5 mmol) in THF (4 mL) was stirred at RT for 48 h. Upon completion, reaction mixture was diluted with EtOAc (30 mL) and washed with water. Layers were separated and aqueous layer was extracted with EtOAc (2 × 50 mL). Combined organic layer was washed with water, brine, dried over

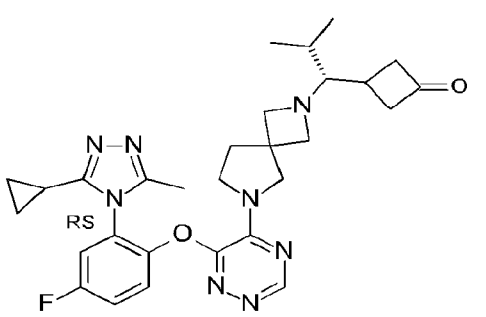
anhydrous $MgSO_4$ and rotary evaporated. The crude compound was purified by flash column chromatography (0 to 70 % n-heptanes in EtOAc) to afford Intermediate 346 (60 mg, yield 31 %) as a colourless oil.

Preparation of Intermediate 347 (7-[6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2-[(1R)-1-(3,3-dimethoxycyclobutyl)-2-methyl-propyl]-2,7-diazaspiro[3.4]octane):



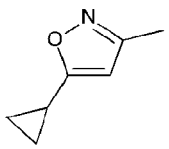
A solution of Intermediate 346 (60 mg, 0.0957 mmol) and *N,N,N',N'*-tetramethylethylenediamine (50 µL, 0.335 mmol) in THF (10 mL) was degassed for 5 min then $Pd(dppf)Cl_2$.DCM (12 mg, 0.0144mmol) and $NaBH_4$ (26 mg, 0.67 mmol) were added and the mixture was purged with nitrogen (3 times) and stirred at room temperature for 18 h. The reaction mixture was quenched with a 10% aqueous solution of K_2CO_3, then extracted with dichloromethane (3 × 25 mL). Combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, evaporated in vacuo and purified by flash column chromatography (0 to 3 % MeOH in dichloromethane as eluents) to afford Intermediate 347 (30 mg, yield 52 %) as a colourless fluffy solid as mixture of atropisomers.

Preparation of Intermediate 348 (3-[(1R)-1-[7-[6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanone):



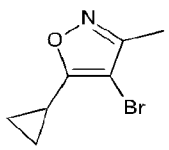
To a solution of Intermediate 347 (252 mg, 0.425 mmol) in anhydrous dichloromethane (3 mL) was added TFA (0.65 mL, 8.5 mmol) and the mixture was stirred at ambient for 2 h. The reaction mixture then diluted with dichloromethane. The organic layer was washed with sat. $NaHCO_3$, then dried over $MgSO_4$, filtered and evaporated in vacuo to give Intermediate 348 (233 mg) as a cream coloured fluffy solid as a mixture of atropisomers.

Preparation of Intermediate 349 (5-cyclopropyl-3-methyl-isoxazole):



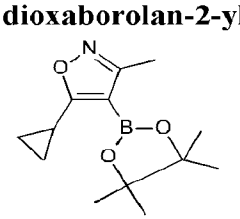
A mixture of 1-cyclopropylbutane-1,3-dione (5 g, 39.634 mmol), $NH_2OH.HCl$ (3.31 g, 47.56 mmol) in EtOH was heated under microwave irradiation at 130°C for 5 min.The mixture was added water (25 mL) and then extracted with EtOAc (3×). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was subjected to flash column purification (0 to 90 % EtOAc in heptane as eluents) to yield 5-cyclopropyl-3-methyl-isoxazole as a major *regio*-isomer (2.4 g, 44 %). The mixture of *regio*-isomers was used in the next step without separation.

Preparation of Intermediate 350 (4-bromo-5-cyclopropyl-3-methyl-isoxazole):



N-bromosuccinimide (1.532 g, 8.607 mmol) was added to a solution of Intermediate 349 (0.5 g, 4.06 mmol) in DMF (8 mL) and stirred at room temperature for 4h
Upon completion (LCMS), water was added to the reaction mixture extracted with diethyl ether (3 × 25 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was subjected to flash column purification (0 to 90 % EtOAc in heptane as eluents) to yield Intermediate 350 as a major regio-isomer 600 mg, 73 %).

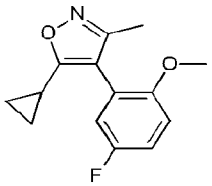
Preparation of Intermediate 351 (5-cyclopropyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole):



Intermediate 350 (6 g, 29.696 mmol) was dissolved in THF (250 mL) and cooled to −78 °C under N_2. *n*-BuLi (2.5 M in hexane) (17.8 mL, 2.5 M, 44.5 mmol) was added slowly to the

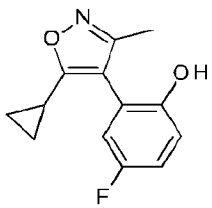
solution, which was then stirred for 30 min at −78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborolane (7.27 mL, 35.635 mmol) was added to the reaction mixture and stirred at −78 °C for an additional 2 h and then it was warmed to rt and stirred overnight. The reaction was quenched by adding NH_4Cl saturated solution. The mixture was then extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (0 to 5 % EtOAc in heptane as eluents) to afford Intermediate 51 (5 g, 67 %) as a regio-isomeric mixture.

Preparation of Intermediate 352 (5-cyclopropyl-4-(5-fluoro-2-methoxy-phenyl)-3-methyl-isoxazole):



To a solution of Intermediate 351 (1.823 g, 7.316 mmol) and 2-bromo-4-fluoro-1-methoxy-benzene (1 g, 4.877 mmol) in dioxane (250 mL), saturated aq. $NaHCO_3$ (50 mL) was added and the mixture was degassed for 10 min. To it, $[Ph_3P]_4Pd$ (1.127 g, 0.975 mmol) was added and the reaction mixture was stirred at 60 °C for 2h. Dichloromethane and water were added to the mixture and layers were separated. Aqueous layer was washed with dichloromethane (2 ×). Combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography (0 to 70 % EtOAc in heptane as eluents) to give 5-cyclopropyl-4-(5-fluoro-2-methoxy-phenyl)-3-methyl-isoxazole (0.65 g, 53 %).

Preparation of Intermediate 353 (2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenol):

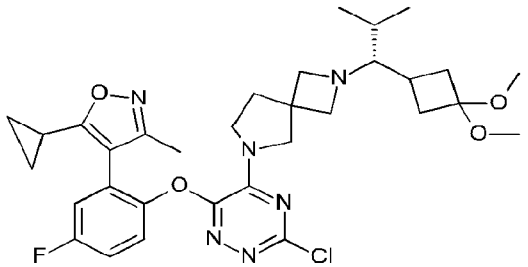


A solution of Intermediate 352 (150 mg, 0.607 mmol) in dichloromethane (10 mL) was cooled to a temperature between 5-10°C. To it, boron tribromide (169 µL, 1.82 mmol) was added dropwise. The resulting reaction mixture was then stirred at 0 °C for 2.5 h. Water (10 mL) was added to the mixture and layers were separated. Aqueous layer was extracted with dichloromethane (2 ×). Combine organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column

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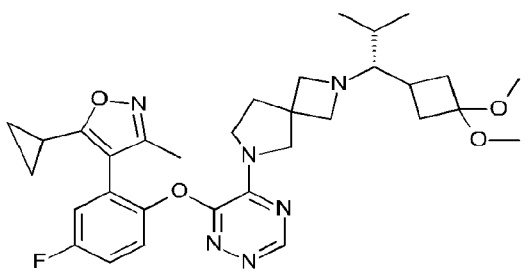
chromatography (0 to 70 % EtOAc in heptanes as eluents) to give Intermediate 353 (70 mg, 49 %).

Preparation of Intermediate 354 (4-[2-[[3-chloro-5-[2-[(1R)-1-(3,3-dimethoxycyclobutyl)-2-methyl-propyl]-2,7-diazaspiro[3.4]octan-7-yl]-1,2,4-triazin-6-yl]oxy]-5-fluoro-phenyl]-5-cyclopropyl-3-methyl-isoxazole):



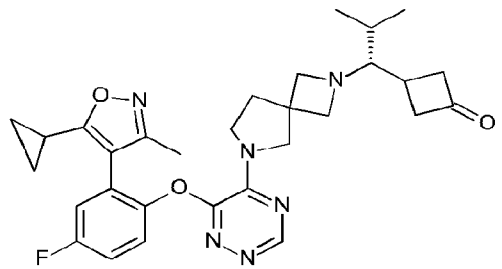
A mixture of intermediate 307 (700 mg, 1.626 mmol), Intermediate 353 (392 mg, 1.678 mmol) and DBU (1.2 mL, 8.13 mmol) in THF (90 mL) was stirred at RT for 72 h. Upon completion, reaction mixture was diluted with dichloromethane (100 mL) and washed with water. Layers were separated and aqueous layer was extracted with dichloromethane (2 × 50 mL). Combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The residue was purified by flash column chromatography (0 to 2 % MeOH in dichloromethane) to afford Intermediate 354 (380 mg, yield 37 %).

Preparation of Intermediate 355 (5-cyclopropyl-4-[5-fluoro-2-[[5-[2-[(1R)-1-(3,3-dimethoxycyclobutyl)-2-methyl-propyl]-2,7-diazaspiro[3.4]octan-7-yl]-1,2,4-triazin-6-yl]oxy]phenyl]-3-methyl-isoxazole):



Pd/C (10%) (45 mg) was added to a solution of afford Intermediate 354 (260 mg, 0.415 mmol) and thiophene (0.10 mL, 0.4 M, 0.041 mmol) in MeOH (50 mL) at ambient temperature and the mixture was stirred under H_2 (1 atm) for 1 h. Upon completion (LCMS), the mixture was filtered over dicalite and the solvent was evaporated under vacuum to give Intermediate 355 (100 mg, 41 %).

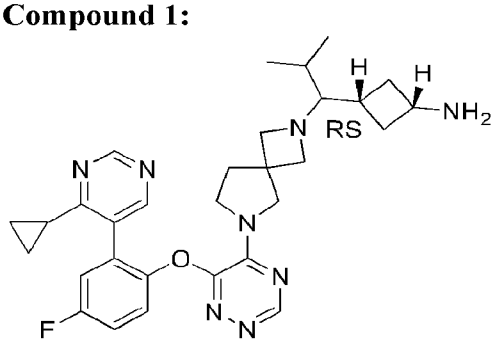
Preparation of Intermediate 356 (3-[(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanone):



To a solution of Intermediate 355 (300 mg, 0.51 mmol) in anhydrous dichloromethane (30 mL) was added trifluoroacetic acid (0.775 mL, 10.123 mmol) and the mixture was stirred at ambient temperature for 2 h. The reaction mixture then diluted with dichloromethane .The organic layer was washed with 10% aqueous solution of Na_2CO_3, then dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford Intermediate 356 in quantitative yield.

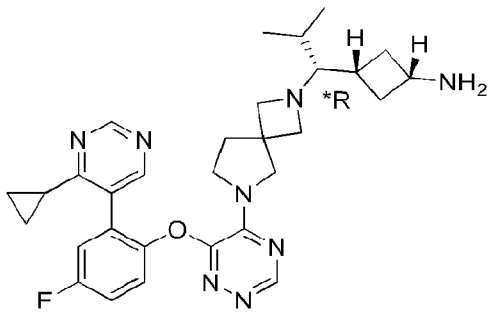
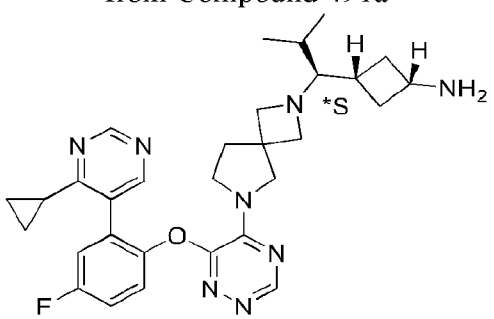
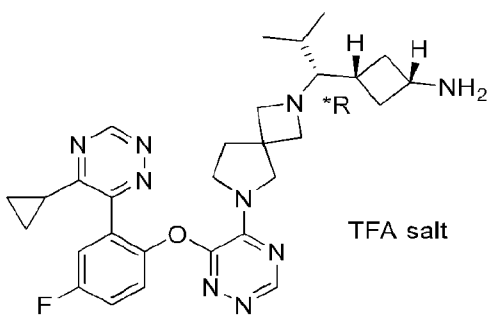
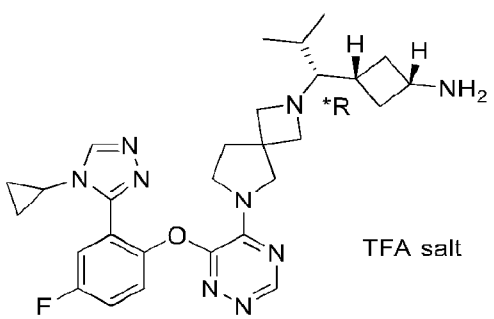
Preparation of Compounds

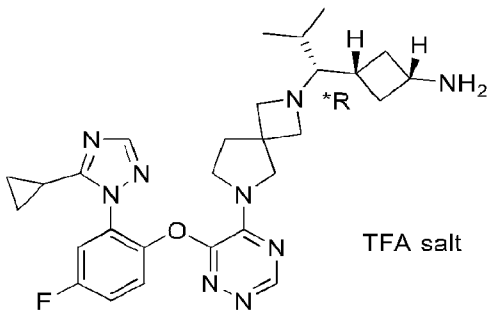
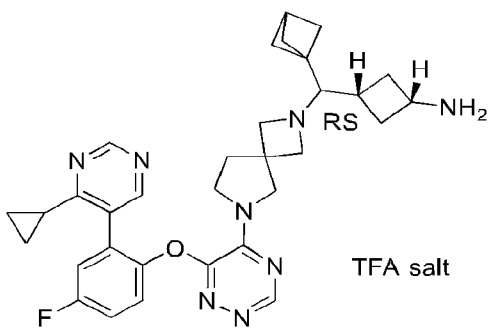
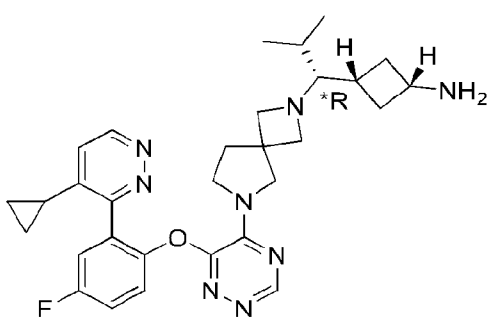
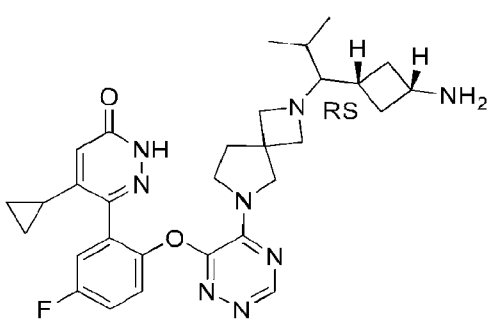
Compound 1:

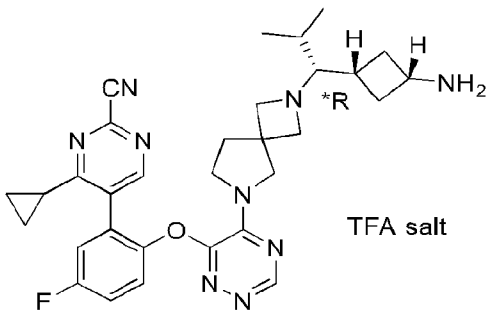
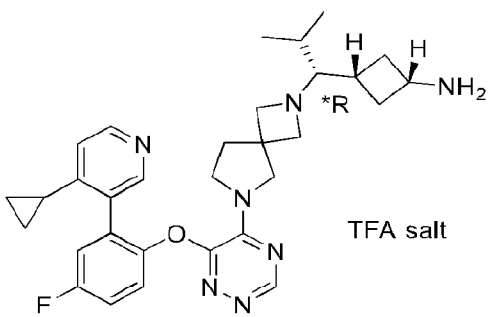
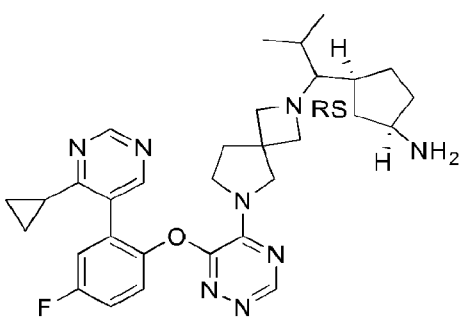


To a solution of Compound 490 (250 mg, 0.388 mmol) in CH_2Cl_2 (3 mL) was added TFA (2.0 mL, 26 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was adjusted to pH=13 with *aq.* NaOH (2 M). Then, the resultant mixture was extracting with CH_2Cl_2 (10 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to yield Compound 1 (185 mg, crude) as a yellow oil, which was used in the next step without additional purification.

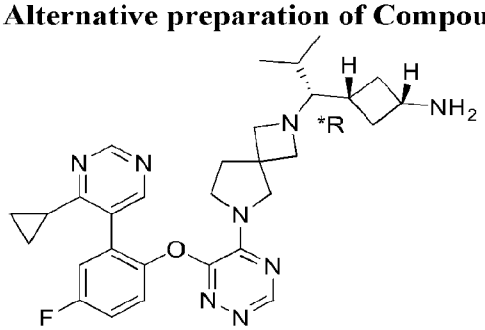
The compounds reported below were prepared following an analogous methodology as described for Compound 1 starting from the corresponding intermediates:

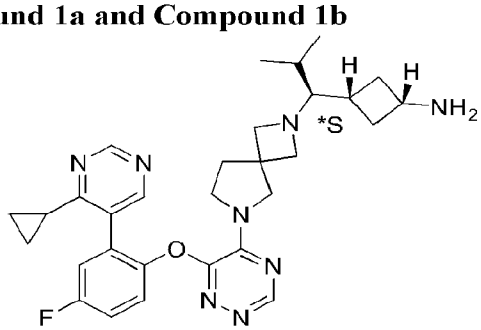
Compound number	Structure
Compound 1a	 from Compound 491a
Compound 1b	 from Compound 491b
Compound 359	 TFA salt from intermediate 284
Compound 360	 TFA salt from intermediate 292

Compound number	Structure
Compound 361	 TFA salt from intermediate 276
Compound 362	 TFA salt from intermediate 33 and intermediate 255
Compound 363	 from intermediate 297
Compound 364	 from intermediate 302

Compound number	Structure
Compound 365	 TFA salt from intermediate 73
Compound 366	 TFA salt from intermediate 77
Compound 369	 from intermediate 33

Alternative preparation of Compound 1a and Compound 1b

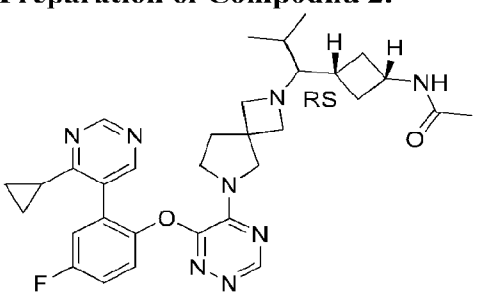




The reaction was performed twice on 6 g of Compound 490. The resulting crude mixtures were combined for the work up and purification.

To a solution of Compound 490 (6 g, 9.4 mmol) in CH_2Cl_2 (150 mL) was added TFA (14 mL, 186 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h. The mixture was adjusted to pH=13 with *aq.* NaOH (2 M). Then, the resultant mixture of both reactions was extracted with CH_2Cl_2 (10 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The residue (10.1 g) was performed via chiral SFC (Stationary phase: Chiralpak IG 5μm 250*30mm, Mobile phase: 60% CO2, 40% mixture of EtOH/iPrOH/DCM 40/40/20 v/v/v (+3.0%$iPrNH_2$)). The pure fractions were collected and the solvent was evaporated under vacuum to give 3.8 g of compound 1a and 3.8 g of compound 1b.

Preparation of Compound 2:



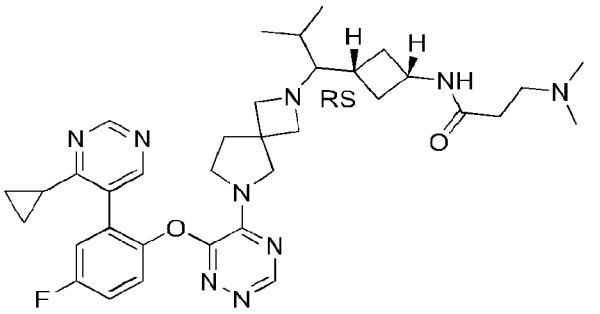
To a solution of Compound 1 (150 mg, crude) and acetic acid (36 μL, 0.63 mmol) in CH_2Cl_2 (5 mL) was added T_3P (403 mg, 0.633 mmol, 50% purity) and DIEA (147 μL, 0.828 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was diluted with CH_2Cl_2 (20 mL). The mixture was washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by preparative HPLC (Column: ACE 5 C18-AR 150*30mm*5μm, Mobile Phase A: water (10mM NH_4HCO_3)-ACN, Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 25% B to 55% B). The pure fractions were collected and the solvent was evaporated under vacuum to give a residue which was partitioned between acetonitrile (2 mL) and water (8 mL). The solution was lyophilized to dryness to yield Compound 2 (60.0 mg) as a white powder.

^1H NMR $CDCl_3$ (Varian_400 MHz): δ 8.93 (br.s., 1H), 8.46 (s, 1H), 8.40 (br.s., 1H), 7.49 -7.31 (m, 1H), 7.26 -7.18 (m, 1H), 7.16 - 7.08 (m, 1H), 6.02 (br.s., 0.2H), 5.60 (br.s., 0.6H), 4.26 - 4.12 (m, 1H), 3.80 - 3.42 (m, 4H), 3.19 - 2.99 (m, 3H), 2.52 - 2.35 (m, 2H), 2.08 - 1.98 (m, 3H), 1.94 (s, 3H), 1.89 - 1.55 (m, 6H), 1.19 - 0.94 (m, 3H), 0.92 - 0.62 (m, 7H)
^{19}F NMR (376 MHz, $CDCl_3$): -115.85 (s, 1F)

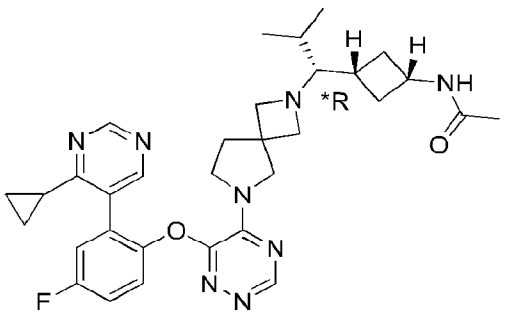
The compound reported below was prepared following an analogous methodology as

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described for Compound 2 starting from Compound 1:

Compound 302	

Preparation of Compound 2a:

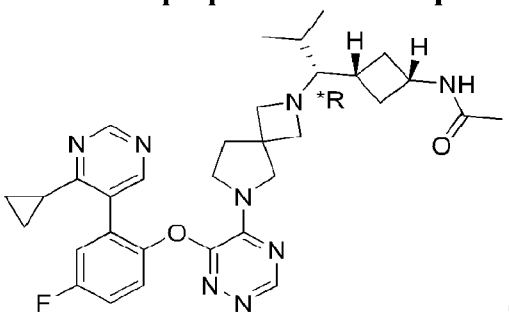


The reaction was performed twice on 1.7 g of compound 1a. The resulting crude mixtures were combined for the work up and purification.

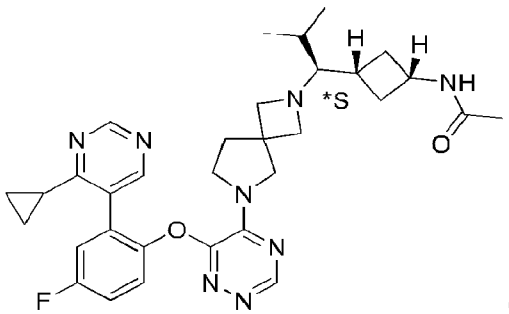
To a solution of compound 1a (1.7 g, 3.12 mmol) and acetic acid (0.4 mL, 7.1 mmol) in DCM (25 mL) was added T_3P (4.3 mL, 7.2 mmol, 50% purity) and DIEA (1.7 mL, 9.4 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was diluted with DCM. The combined mixture of both reactions was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0.1% NH_4OH, 5% MeOH, 95% DCM to 0.1% NH_4OH, 8% MeOH, 92% DCM) . The pure fractions were collected and the solvent was evaporated under vacuum to give a residue which was partitioned between acetonitrile (2 mL) and water (8 mL). The solution was lyophilized to yield compound 2a (1.69 ; 46%) as a white powder.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.80 - 9.02 (m, 1H), 8.41 (br s, 2H), 7.98 (br d, J=7.2 Hz, 1H), 7.52 - 7.63 (m, 1H), 7.39 - 7.50 (m, 2H), 3.95 (dq, J=16.2, 8.2 Hz, 1H), 3.37 - 3.83 (m, 4H), 3.05 (br s, 3H), 2.84 - 2.99 (m, 1H), 2.13 - 2.31 (m, 2H), 1.89 - 2.03 (m, 3H), 1.78 - 1.88 (m, 1H), 1.65 - 1.77 (m, 5H), 1.50 - 1.64 (m, 2H), 0.61 - 1.18 (m, 10H)

Alternative preparation of Compound 2a and Compound 2b:



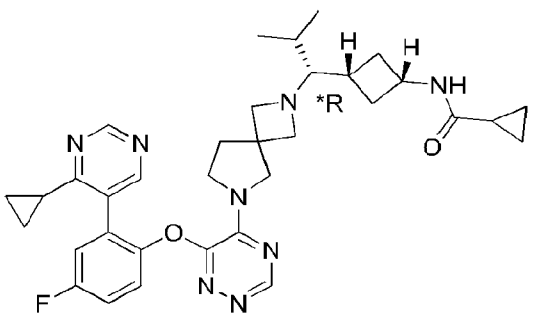
Compound 2a (*R)



Compound 2b (*S)

Compound 2 (30 mg, 0.051 mmol) was separated by SFC (column: DAICEL CHIRALCEL OD-H(250mm*30mm, 5μm), eluent: 30% (v/v) super critical CO_2 in 0.1% NH_3H_2O EtOH, flow rate: 50 mL/min).The desired fractions were collected and the solvent was evaporated *in vacuo*. The residue was redissolved in ACN and water and lyophilized to afford Compound 2a (13 mg, 43 % yield) and Compound 2b (11 mg, 37% yield) both as a white powder.

Preparation of Compound 303:



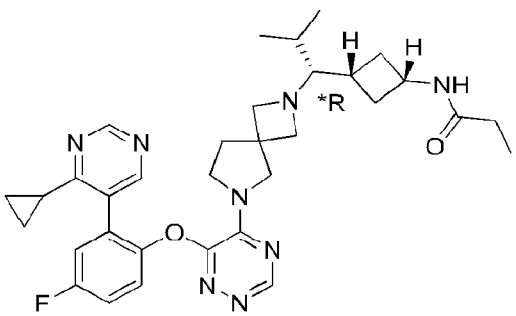
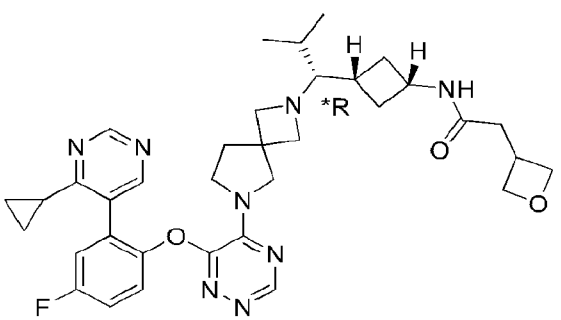
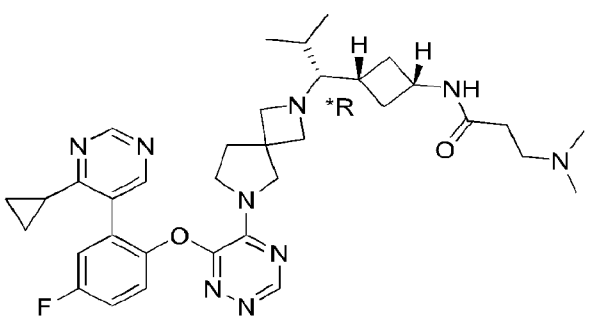
To a solution of Compound 1a (100 mg, 0.184 mmol) and cyclopropanecarboxylic acid (36.2 mg, 0.420 mmol) in DCM (5 mL) were added T3P (268 mg, 0.421 mmol, 50% in EtOAc) and DIEA (118 mg, 0.913 mmol). The resulting mixture was stirred at 25 °C for 12 h. The mixture was diluted with DCM (10 mL) and washed with H_2O (10 mL) and brine (10 mL). After dried over Na_2SO_4, the mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Column: Phenomenex Gemini-NX 150*30mm*5μm, Mobile Phase A: water (0.04% NH_3H_2O+10 mM NH_4HCO_3), Mobile Phase B: ACN, Flow rate: 30 mL/min, gradient condition from 40% B to 70%). The

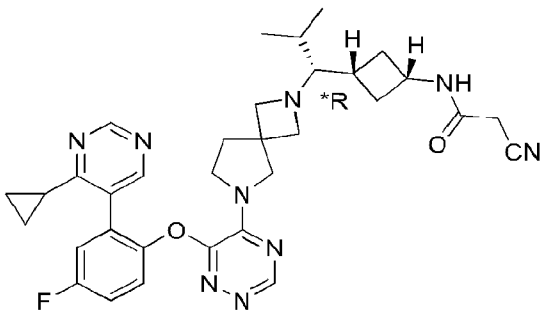
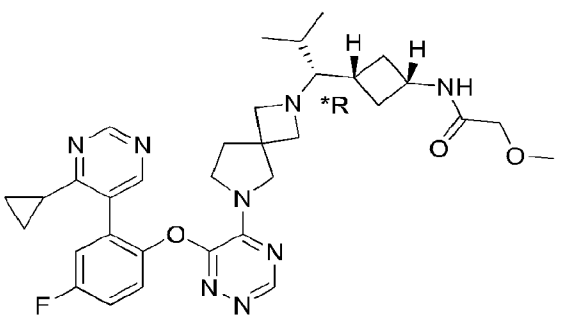
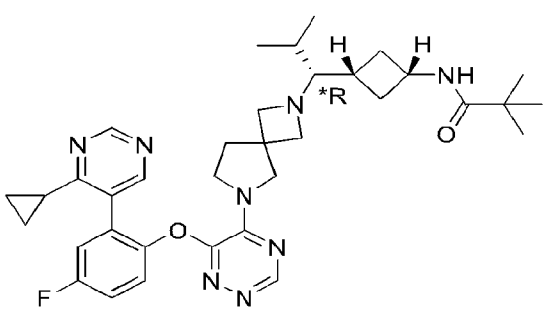
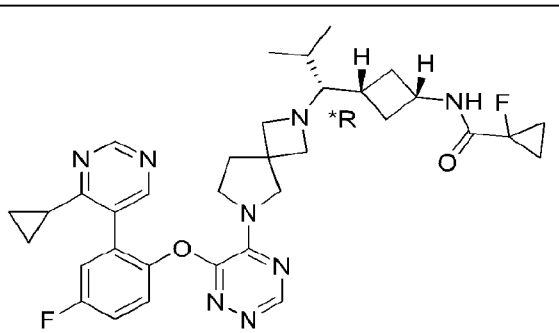
CA 03214746 2023-10-5

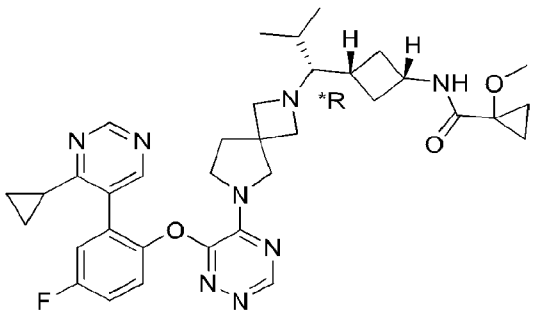
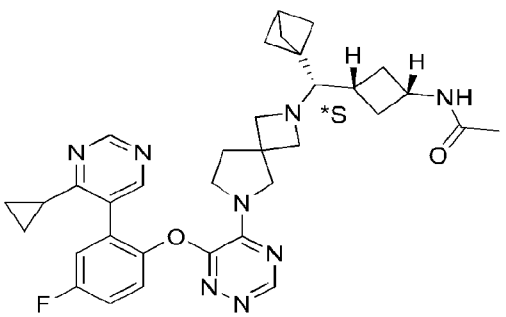
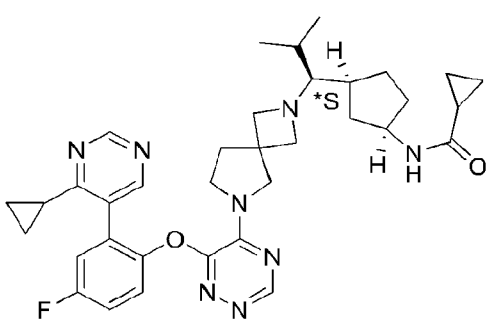
desired fractions were collected and lyophilized to afford Compound 303 (50 mg, 44% yield) as a white powder.

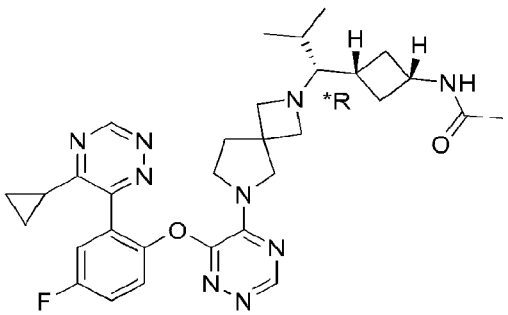
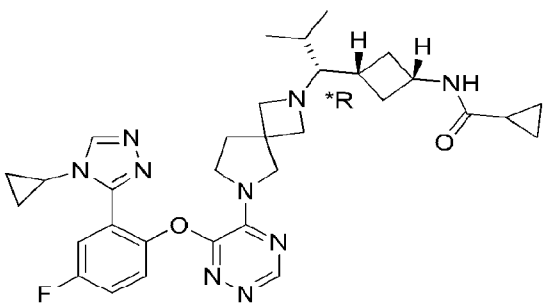
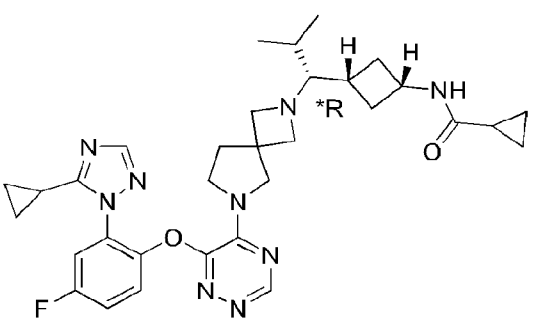
1H NMR $CDCl_3$ (Bruker_400 MHz): δ 8.94 (s, 1H), 8.46 (s, 1H), 8.44 - 8.34 (m, 1H), 7.39 (s, 1H), 7.26 - 7.18 (m, 1H), 7.17 - 7.08 (m, 1H), 6.31 - 5.68 (m, 1H), 4.29 - 4.13 (m, 1H), 3.82 - 3.30 (m, 4H), 3.26 - 2.91 (m, 4H), 2.56 - 2.35 (m, 2H), 2.20 - 1.93 (m, 4H), 1.80 - 1.55 (m, 4H), 1.36 - 1.22 (m, 1H), 1.20 - 1.03 (m, 2H), 1.02 - 0.91 (m, 3H), 0.91 - 0.79 (m, 7H), 0.76 - 0.64 (m, 2H).

The compounds reported below were prepared following an analogous methodology as described for Compound 2a or Compound 303, starting from the appropriate starting materials (e.g. Compound 1a or other appropriate starting materials):

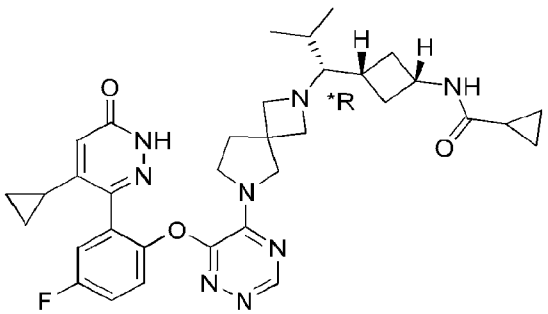
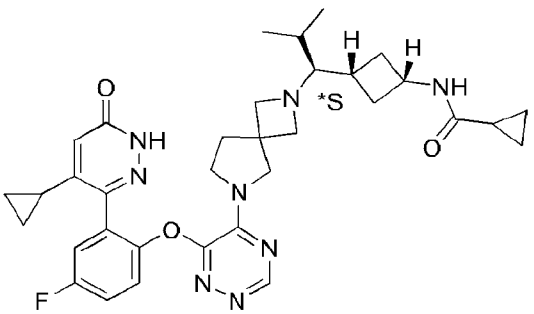
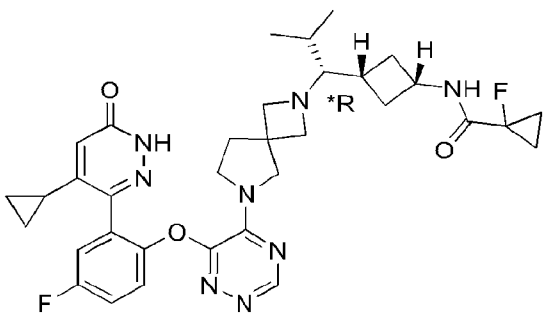
Compound number	Structure
Compound 356	
Compound 296	
Compound 297	

Compound number	Structure
Compound 298	
Compound 299	
Compound 300	
Compound 301	

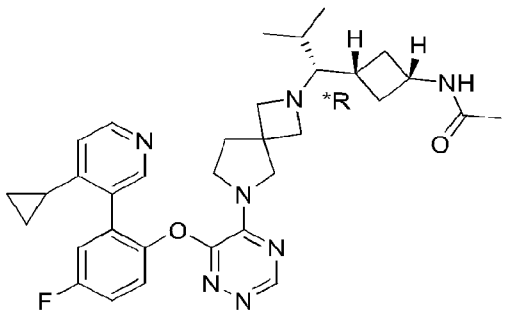
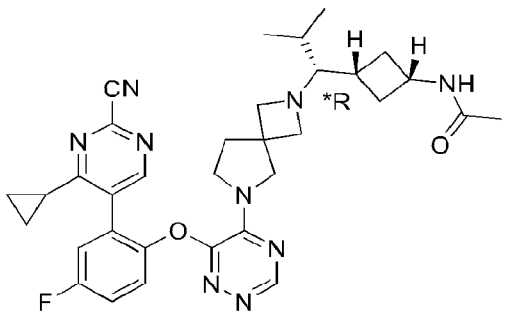
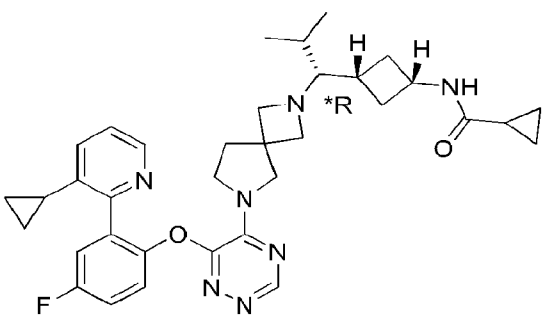
Compound number	Structure
Compound 330	
Compound 342	 from Compound 362, SFC separation: first time, REGIS WHELK-O1 (250mm*30mm, 5um); Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O IPA, A:B =45:55 at 70 mL/min; second time, RDAICEL CHIRALPAK AD-H (250mm*30mm, 5um); Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O IPA, A:B =35:65 at 50 mL/min.
Compound 344	 from Compound 369, SFC separation: DAICEL CHIRALPAK IG (250mm*30mm, 10um); Mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, A:B =65:35 at 50 mL/min

Compound number	Structure
Compound 306	 from Compound 359
Compound 307	 from Compound 360
Compound 308	 from Compound 361

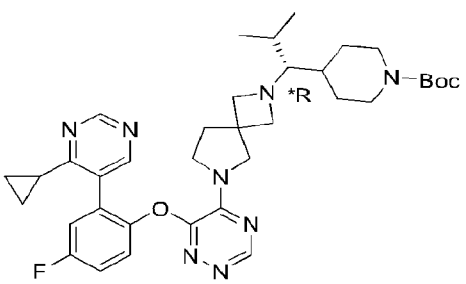
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Compound number	Structure
Compound 309 Compound 310	  from Compound 364, SFC separation: DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O EtOH, A:B=70:30 at 50 mL/min
Compound 311	 from Compound 364, SFC separation: DAICEL CHIRALPAK IG (250mm*30mm, 10um); Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O EtOH, A:B=65:35 at 50 mL/min

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Compound number	Structure
Compound 312	 from Compound 366
Compound 343	 from Compound 365
Compound 27	 from intermediate 50 and intermediate 6

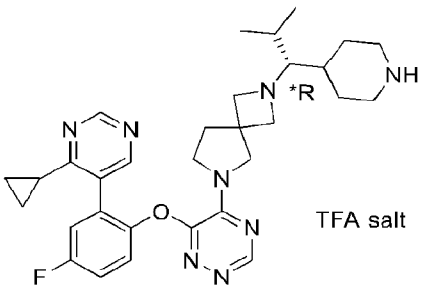
Preparation of Compound 508



To a solution of intermediate 14 (500 mg, 1.54 mmol) in DMF (0.1 mL) in DCM (30 mL), was

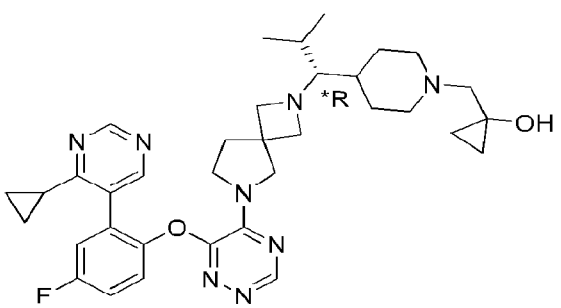
added oxalyl dichloride (1.05 g, 8.27 mmol) at 0°C under N_2 atmosphere. The mixture was stirred at room temperature for 1 hour. Then the mixture was concentrated under reduced pressure (below 35 °C) to give a residue. The residue was dissolved in DCM (30 mL), and TEA (5.0 mL, 35.9 mmol) was added at 0°C under N_2 atmosphere. The mixture was stirred at 0°C for 3 minutes. Intermediate 25 (600 mg, 1.55 mmol) in DCM (2 mL) was added dropwise at 0°C under N_2 atmosphere. The mixture was stirred at r.t. for 1 hour. The reaction mixture was diluted with DCM (50 mL), washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by FCC (PE:EtOAc = 1:3 to 0:1) to yield Compound 508 (260 mg, 18% yield) as a white solid.

Preparation of Compound 3



To a solution of Compound 508 (260 mg, 0.395 mmol) in dioxane (5 mL) was added 4 M HCl/dioxane (3.00 mL, 12 mmol). The mixture was stirred at room temperature for 0.5 hours. The reaction mixture was concentrated to give Compound 3 (240 mg, crude HCl salt) as a light brown solid (no further purification).

Preparation of Compound 4:



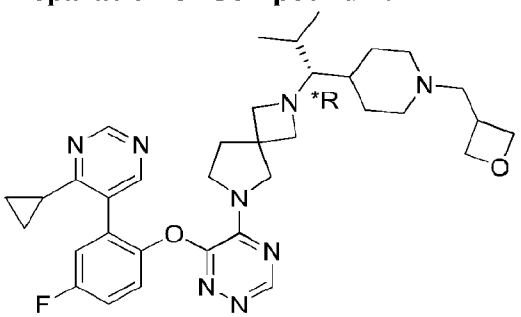
To a solution of intermediate 29 (370 mg, crude) in DCM (3 mL) was added 4 M HCl/dioxane (0.2 mL, 0.8 mmol). The reaction mixture was stirred at r.t. for 0.5 hours. The reaction mixture was concentrated. The resulting residue was first purified by prep-HPLC (Column: Waters Xbridge Prep OBD C18 150*40mm*10um, Mobile Phase A: water(10mM NH_4HCO_3), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 30% B to 80% B), and

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then by prep-HPLC (Column: Boston Prime C18 150*30mm*5um, Mobile Phase A: water(0.04%NH_3H_2O+10mM NH_4HCO_3), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 55% B to 85% B). The pure fractions were collected and lyophilized to yield Compound 4 (8.00 mg, 2% yield) as a white powder.

^{1}H NMR $CDCl_3$ (Bruker-400 MHz): δ 8.93 (s, 1H), 8.46 (s, 1H), 8.38 (s, 1H), 7.38 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 6.4 Hz, 1H), 3.38-3.87 (m, 5H), 2.93-3.27 (m, 6H), 2.44 (s, 2H), 2.01 (d, J = 7.2 Hz, 3H), 1.33-1.91 (m, 11H), 1.11 (br s, 2H), 0.67-0.99 (m, 8H), 0.30-0.40 (m, 2H)

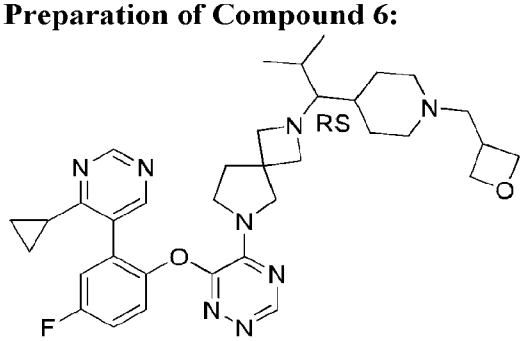
Preparation of Compound 5:



PyBrOP (108 mg, 0.232 mmol) was added to a solution of intermediate 14 (50 mg; 0.15 mmol), intermediate 28 (61 mg, 0.16 mmol), TEA (0.12 mL, 0.88 mmol), and DMF (0.5 mL). The reaction mixture was stirred at r.t. for 0.5 hours. The mixture was purified by preparative high performance liquid chromatography over Phenomenex Gemini-NX 150 x 30mm x 5um (eluent: water (0.04%NH_3H_2O+10mM NH_4HCO_3)/ACN from 65/35 to 41/59 v/v). The pure fractions were collected and lyophilized to dryness to remove the solvent residue completely to yield Compound 5 (7.64 mg), as a white solid.

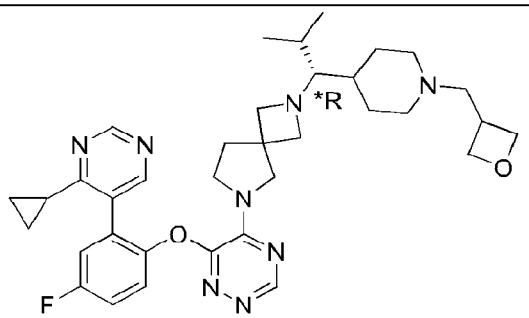
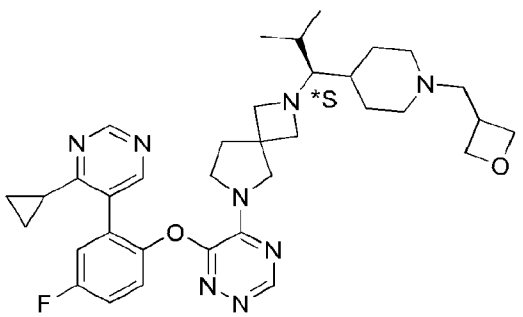
^{1}H NMR $CDCl_3$ (Varian_400 MHz): δ 8.93 (s, 1H), 8.46 (s, 1H), 8.38 (s, 1H), 7.37 (br. s, 1H), 7.25 - 7.18 (m, 1H), 7.15 - 7.09 (m, 1H), 4.83 - 4.73 (m, 2H), 4.40 (t, J = 6.4 Hz, 2H), 3.75 - 3.42 (m, 4H), 3.41 - 3.16 (m, 2H), 3.16 - 3.03 (m, 3H), 3.03 - 2.93 (m, 1H), 2.81 - 2.73 (m, 2H), 2.69 - 2.62 (m, 2H), 2.05 - 1.99 (m, 2H), 1.88 - 1.76 (m, 4H), 1.56 - 1.39 (m, 4H), 1.37 - 1.28 (m, 1H), 1.16 - 1.03 (m, 2H), 0.98 - 0.63 (m, 8H).

Preparation of Compound 6:



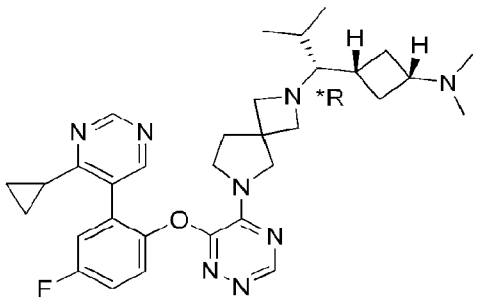
Sodium cyanoborohydride (30 mg; 0.477 mmol) was added to a mixture of intermediate 33 (100 mg; 0.238 mmol), intermediate 34 (107 mg; 0.477 mmol) and acetic acid (14 µL; 0.238 mmol) in MeOH (5 mL) and the reaction mixture was heated at 70°C for 60 h. The reaction mixture was cooled to r.t., diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was decanted, filtered through Chromabond® and evaporated to dryness. The residue (190 mg) was purified by chromatography over silica gel (irregular SiOH, 4g+4g; mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 1% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness yielding 54 mg of material which was freeze dried (10 mL; 20% ACN, 80% water) to afford 52 mg (35% yield) of Compound 6.

The compounds in the table below were prepared by SFC separation of compound 6

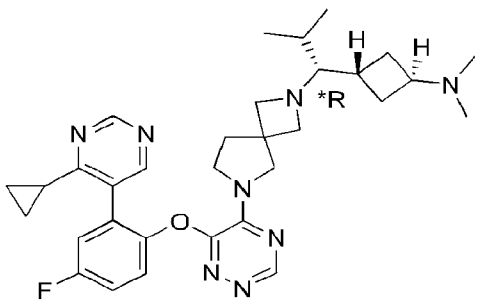
Compound number	Structure
Compound 5	
Compound 29	
	Chiral separation (CHIRALPAK AD-H 5µm 250*30mm; mobile phase: 75% CO2, 25% mixture of iPrOH/ACN 80/20 v/v (+0.3%iPrNH2)

Preparation of Compound 7 and compound 8:

Compound 7:



Compound 8:

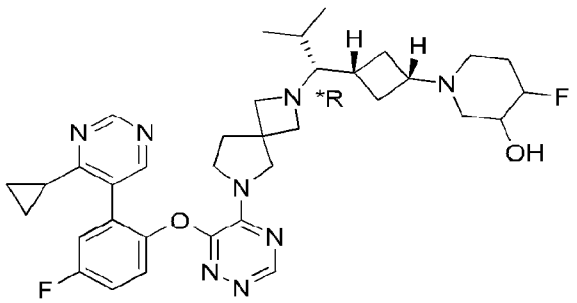
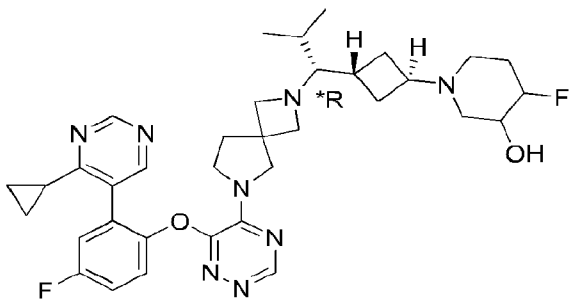
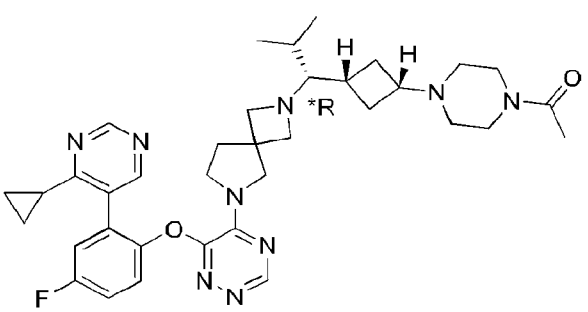
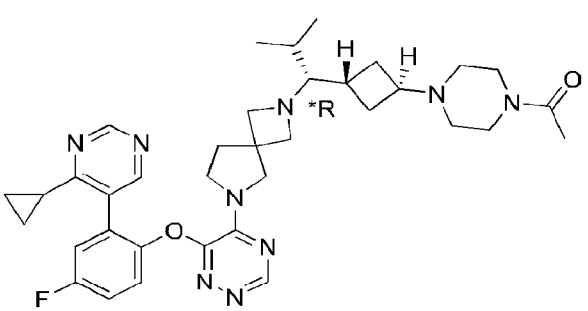


$NaBH_3CN$ (139 mg; 2.21 mmol) was added to a mixture of intermediate 38b (*R) (600 mg; 1.1 mmol), dimethylamine solution (2.76 mL; 5.52 mmol; 2M in THF), AcOH (63 µL; 1.1 mmol) in MeOH (30 mL). Then, the reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 7% MeOH, 93% DCM). The pure fractions were collected and evaporated to dryness. The residue (650 mg) was purified by achiral SFC (CHIRALPAK AD-H 5µm 250*30mm, mobile phase: 82% CO_2, 18% EtOH (0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated to give 425 mg of compound 7 as a white foam and 62 mg of compound 8 as colourless oil. Compound 7 was freeze-dried with water-ACN to give 420 mg (66%) of final compound as a white solid.

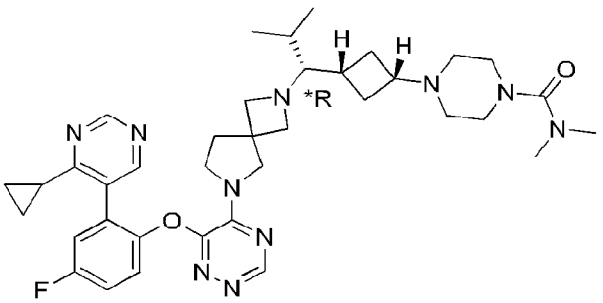
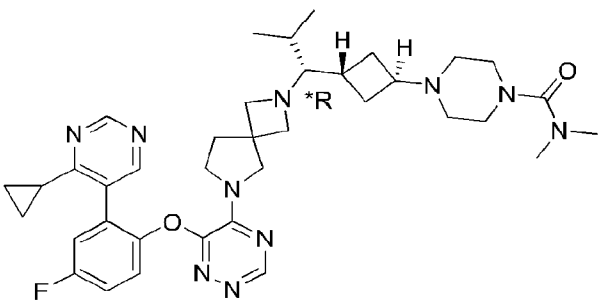
Compound 7

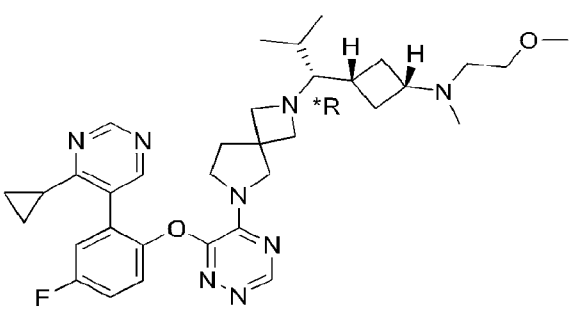
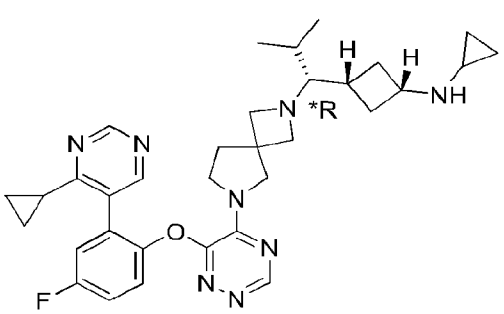
^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.92 (br, 1H) 8.41 (br s, 2H) 7.57 (br s, 1H) 7.46 (br d, J=7.6 Hz, 2H) 3.40 - 3.79 (m, 4H) 2.89 - 3.14 (m, 4H) 2.27 - 2.38 (m, 1H) 2.05 (m, 2H) 1.97 (s, 9H) 1.72 - 1.87 (m, 2H) 1.61 (m, 2H) 1.45 (q, J=9.6 Hz, 1H) 1.01 (m, 3H) 0.82 (br t, J=6.0 Hz, 7H)

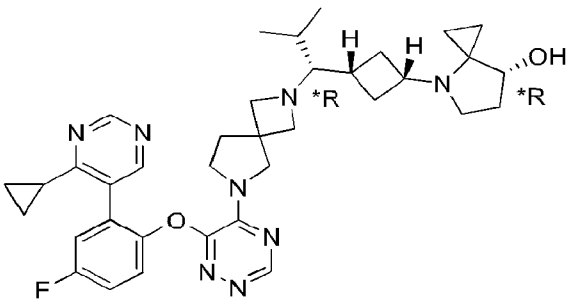
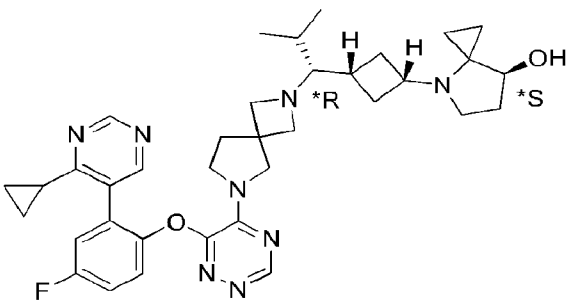
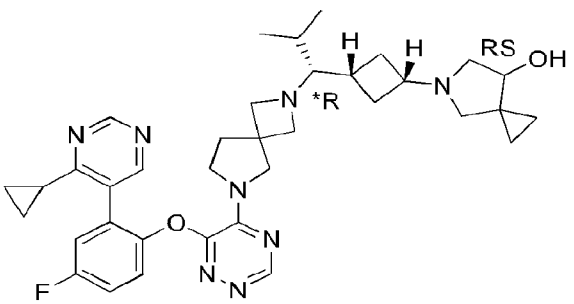
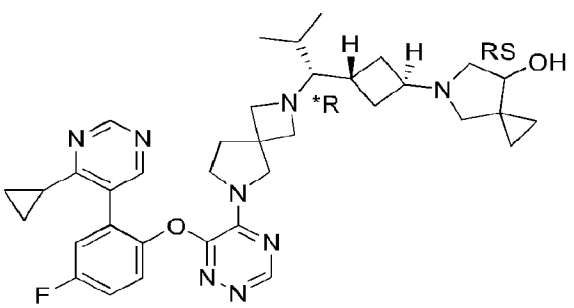
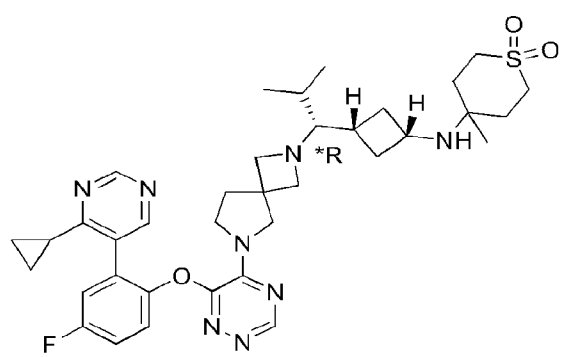
The compounds reported below were prepared following an analogous methodology as reported for the preparation of compound 7 starting from the appropriate starting materials (e.g. intermediate 38 (*R) or other appropriate starting materials):

Compound number	Structure
Compound 30 Compound 31	  In Compounds 30 and 31, the piperidine moiety is one *cis* isomer (undetermined which *cis*)
Compound 34 Compound 35	 

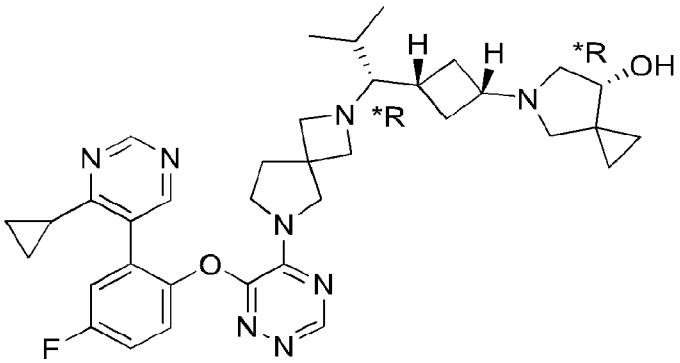
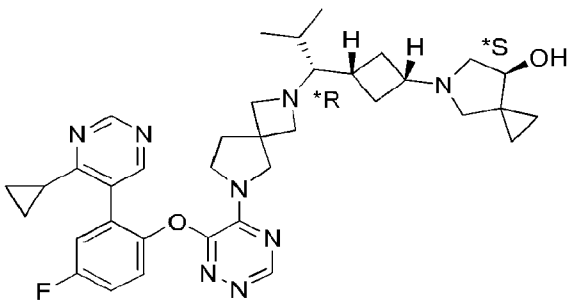
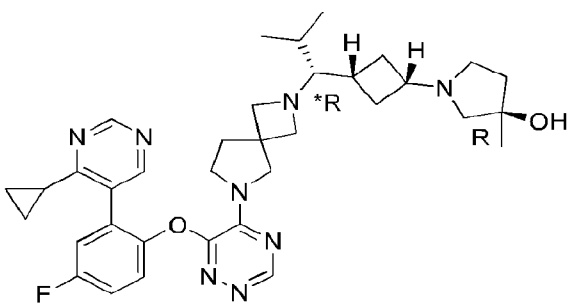
CA 03214746 2023-10-5

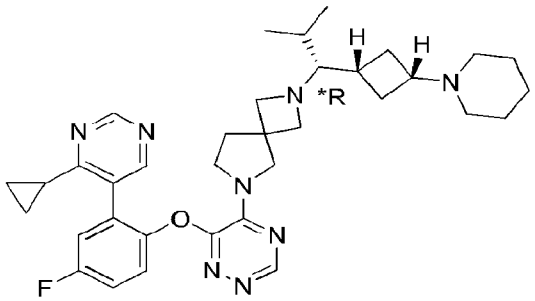
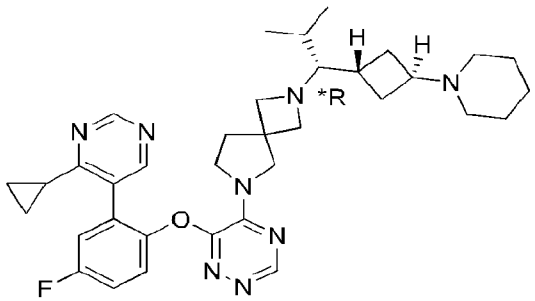
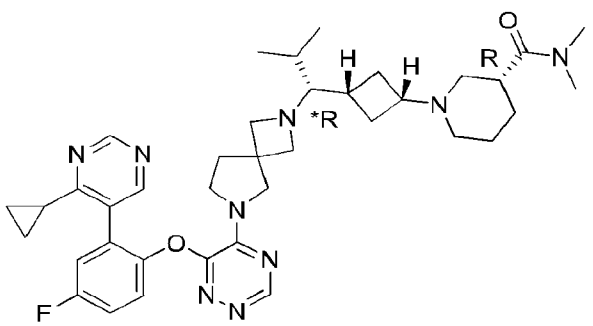
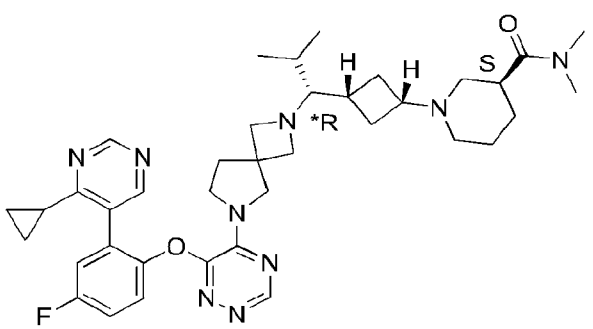
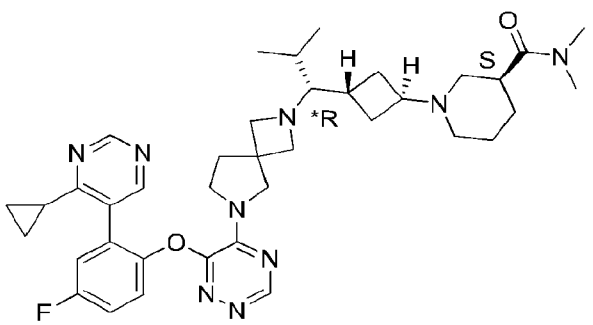
Compound number	Structure
Compound 36	
Compound 37	

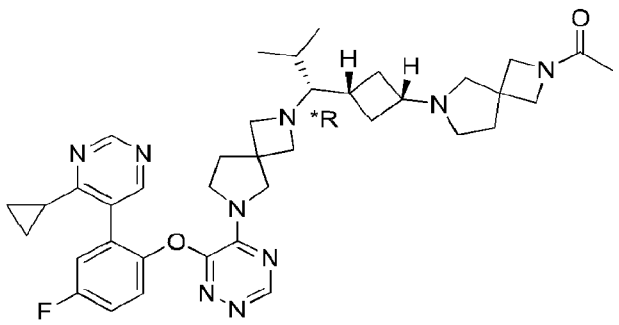
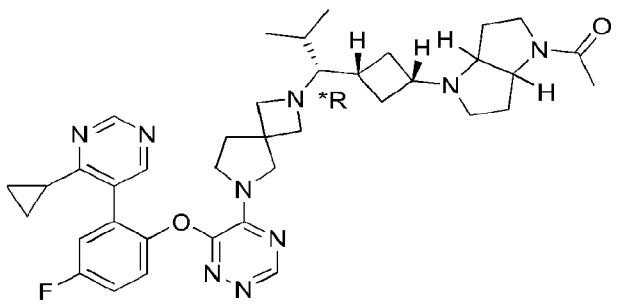
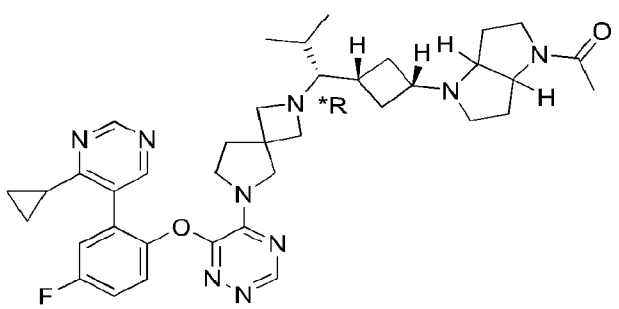
Compound number	Structure
Compound 38	
Compound 39	

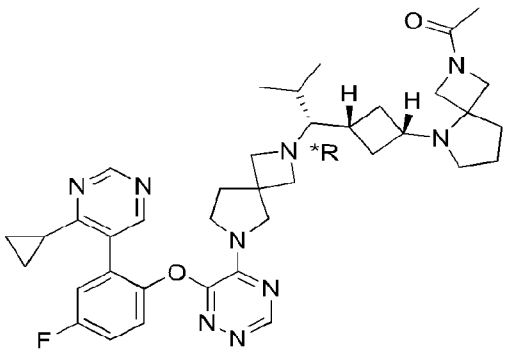
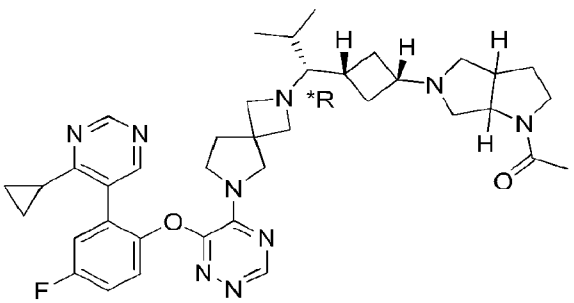
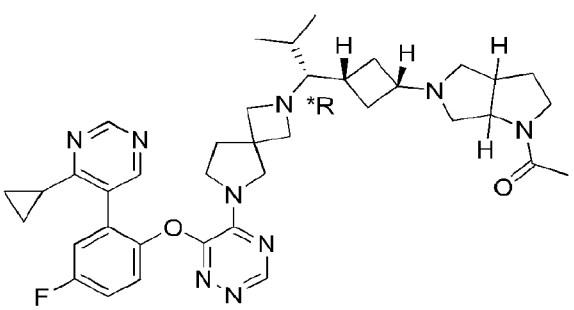
Compound number	Structure
Compound 40	
Compound 41	
Compound 42	
Compound 43	
Compound 44	

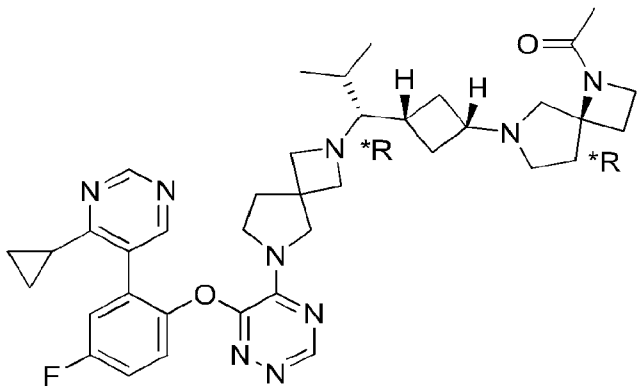
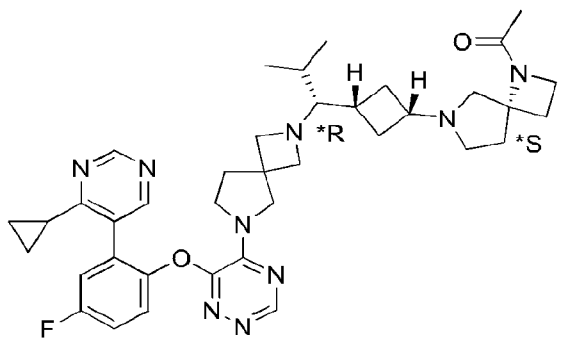
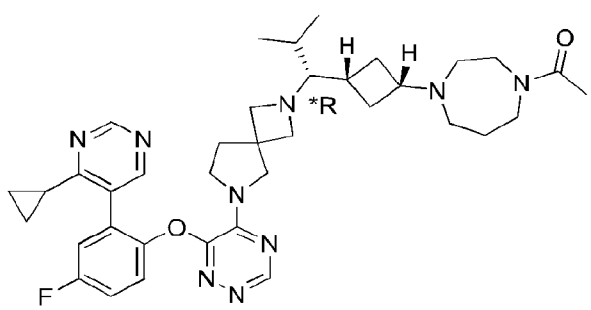
CA 03214746 2023-10-5

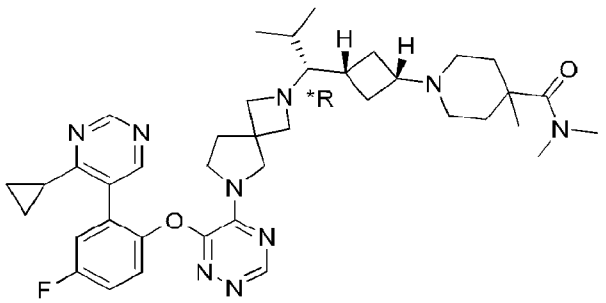
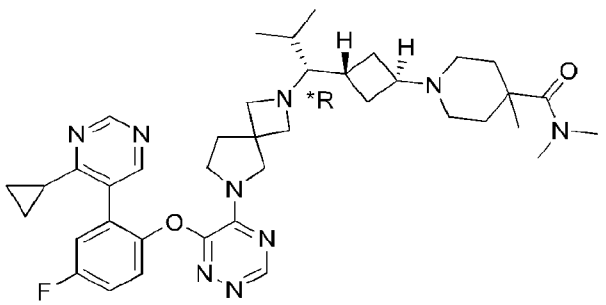
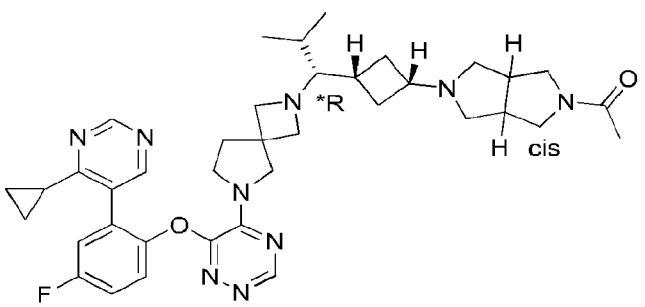
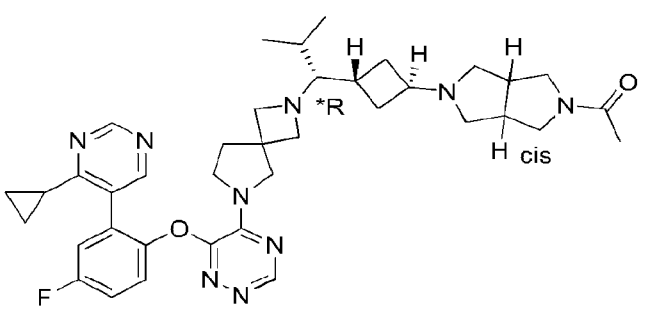
Compound number	Structure
Compound 45	
Compound 46	 Using BH_3.Pyridine as reductive agent
Compound 47	

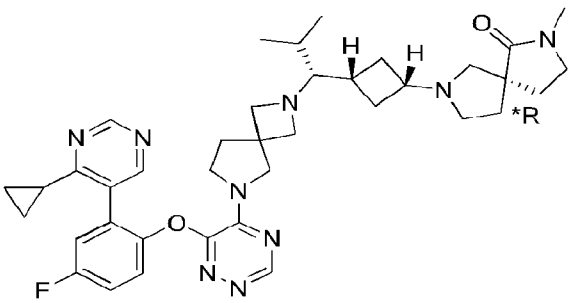
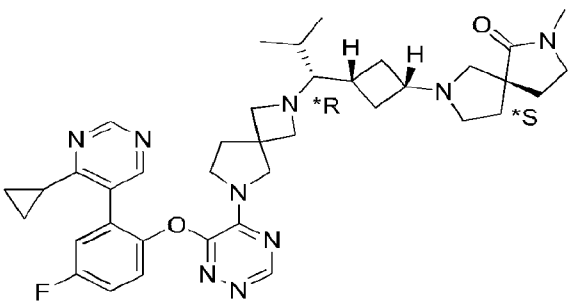
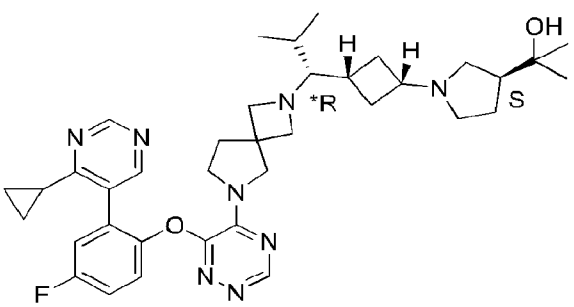
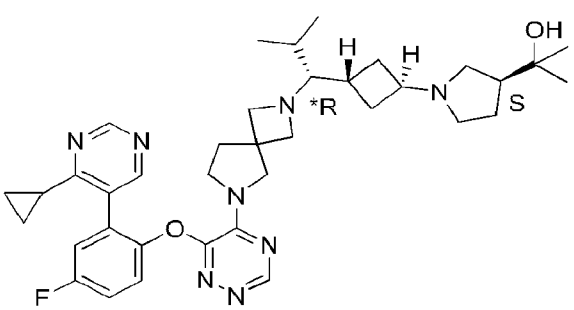
Compound number	Structure
Compound 48	
Compound 49	
Compound 50	
Compound 51	
Compound 52	

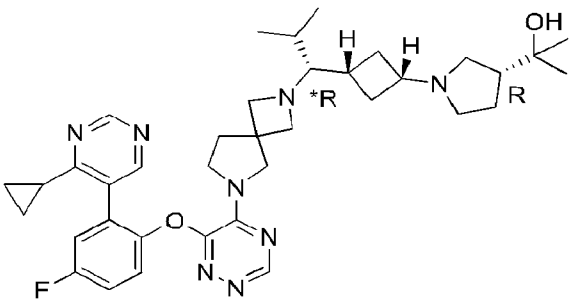
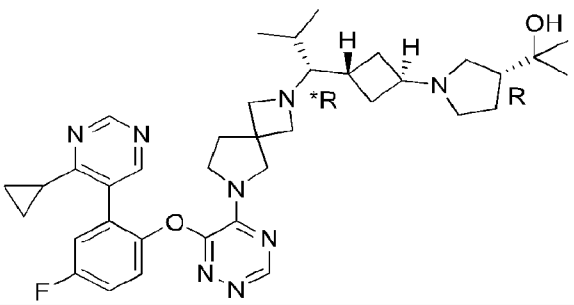
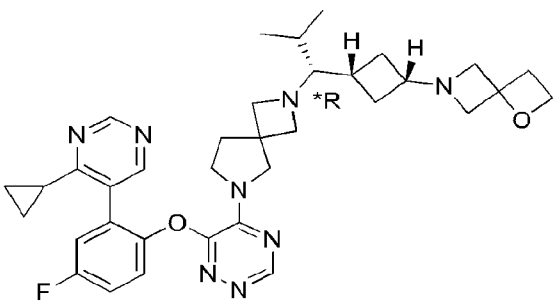
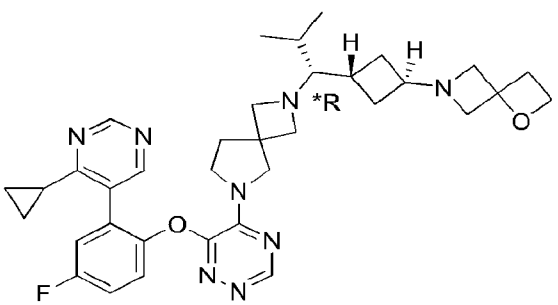
Compound number	Structure
Compound 53	
Compound 54	 Bicyclic moiety is one *cis* isomer. Undetermined which *cis* but the other isomer than Compound 55
Compound 55	 Bicyclic moiety is one *cis* isomer. Undetermined which *cis* but the other isomer than Compound 54

Compound number	Structure
Compound 56	
Compound 57	 Bicyclic moiety is one *cis* isomer. Undetermined which *cis* but the other isomer than Compound 58
Compound 58	 Bicyclic moiety is one *cis* isomer. Undetermined which *cis* but the other isomer than Compound 57

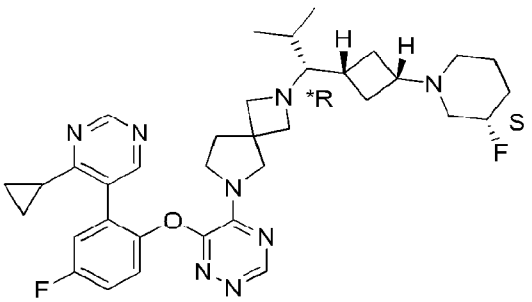
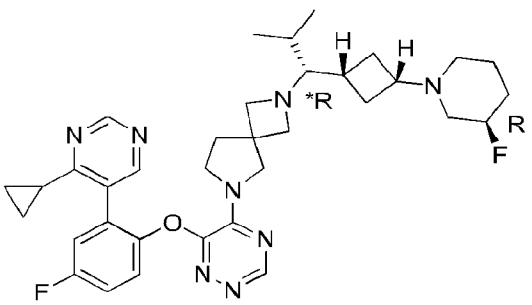
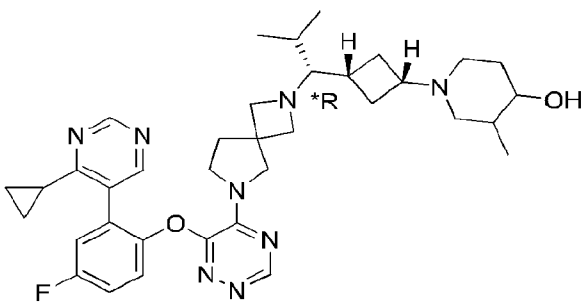
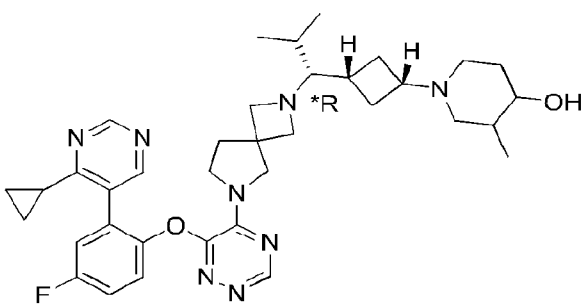
Compound number	Structure
Compound 59	
Compound 60	
Compound 61	

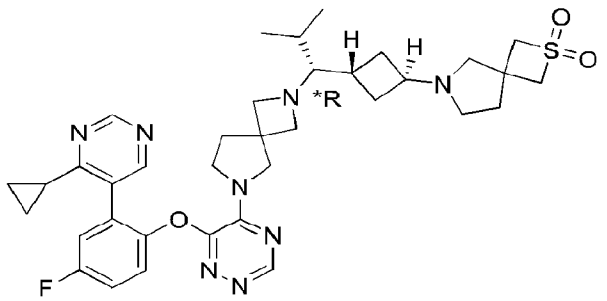
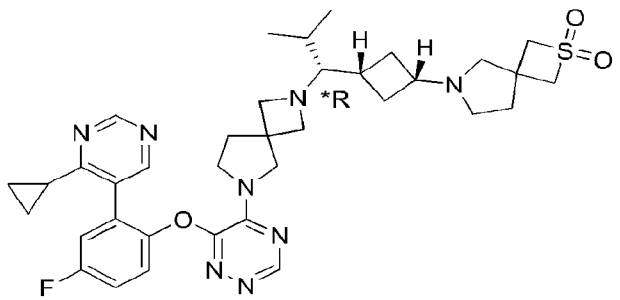
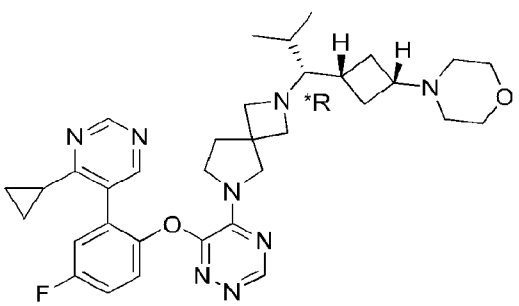
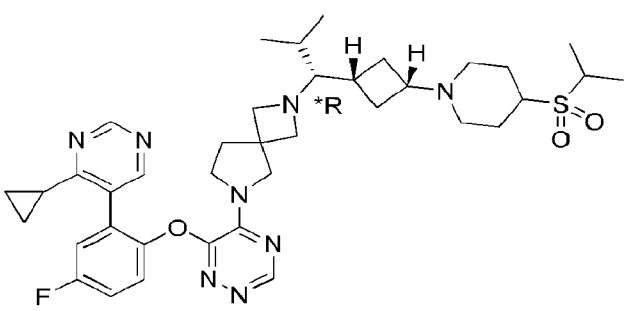
Compound number	Structure
Compound 62	
Compound 63	
Compound 64	
Compound 65	

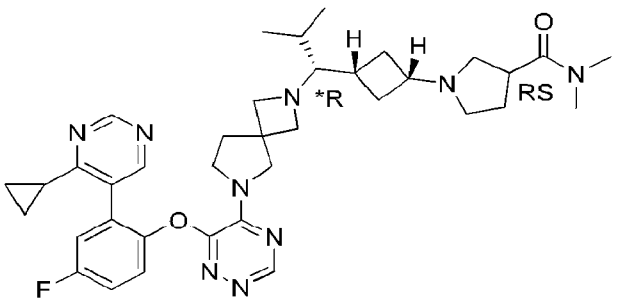
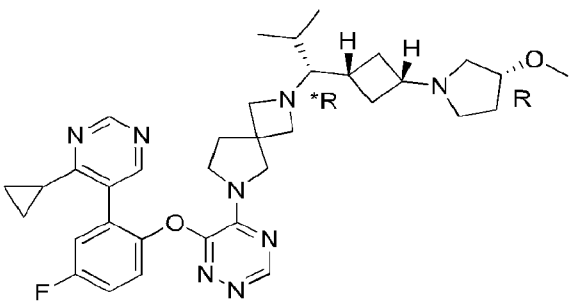
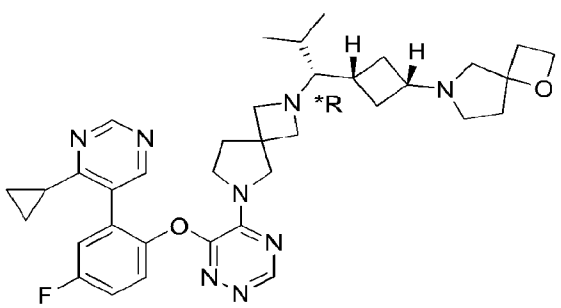
Compound number	Structure
Compound 66	
Compound 67	
Compound 68	
Compound 69	

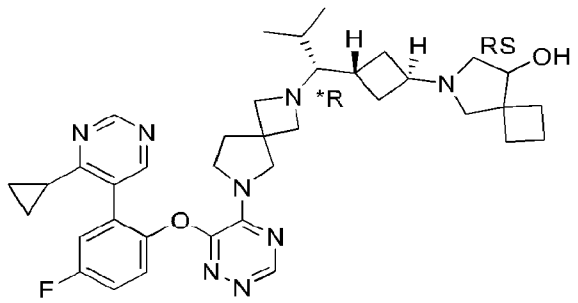
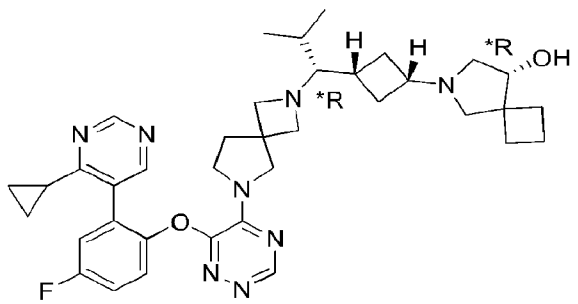
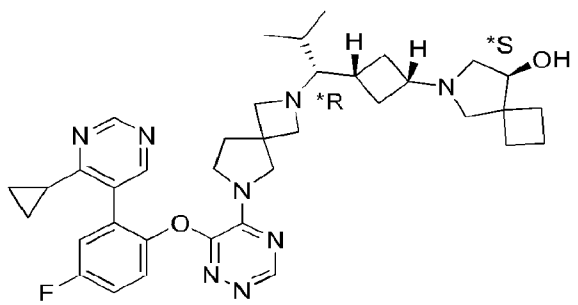
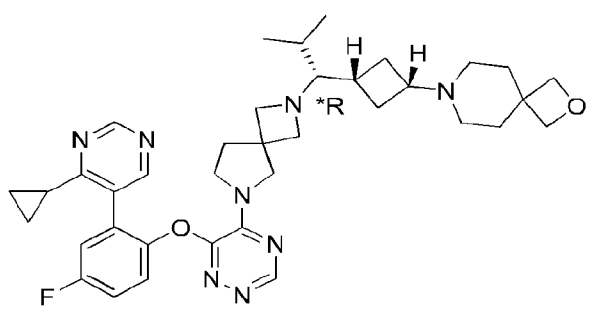
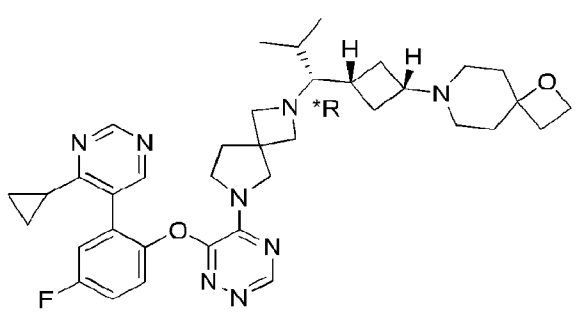
Compound number	Structure
Compound 70	
Compound 71	
Compound 145	
Compound 146	

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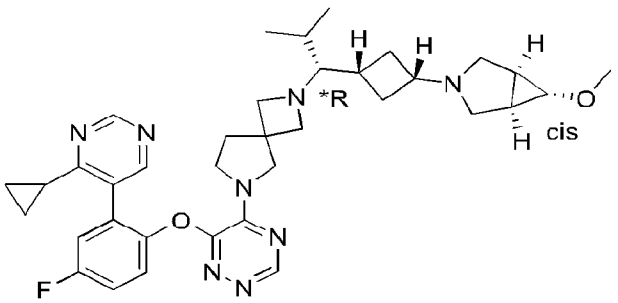
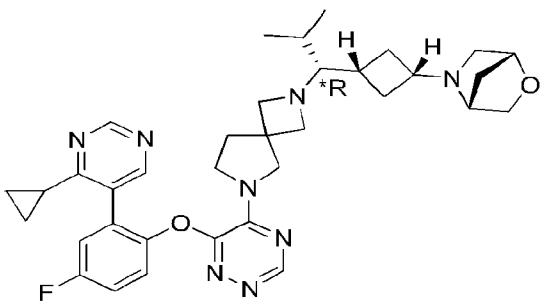
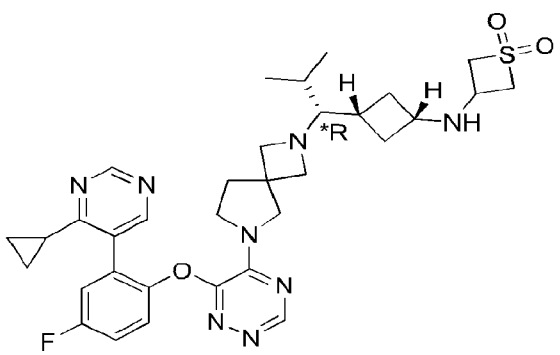
Compound number	Structure
Compound 200	
Compound 206	
Compound 201	 Piperidine moiety is one *cis* isomer (undetermined which *cis*)
Compound 207	 Piperidine moiety is one *trans* isomer (undetermined which *trans*)

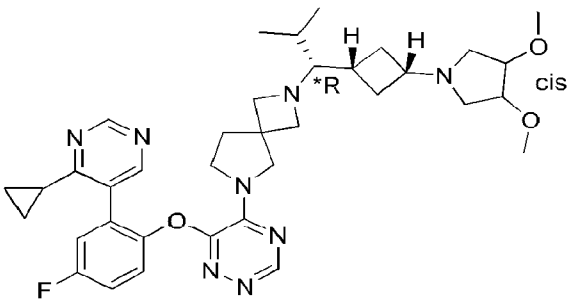
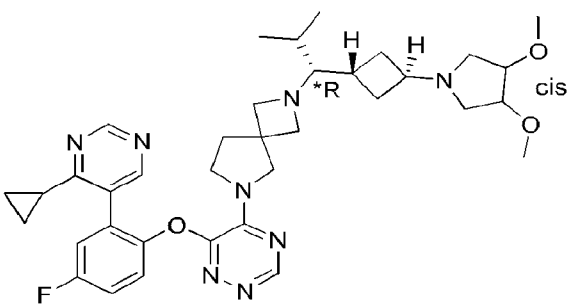
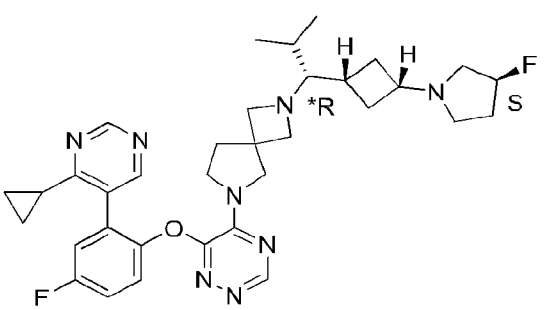
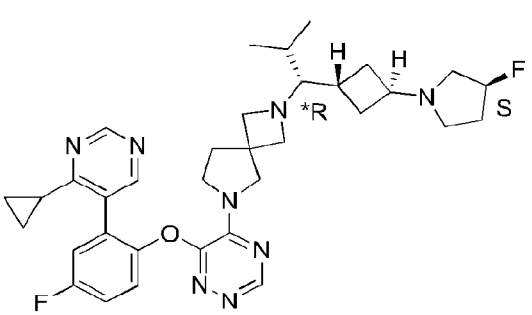
Compound number	Structure
Compound 204	
Compound 205	
Compound 208	
Compound 209	

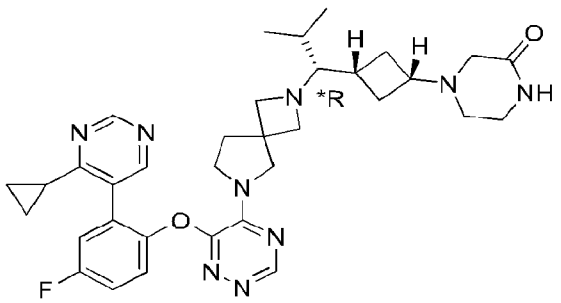
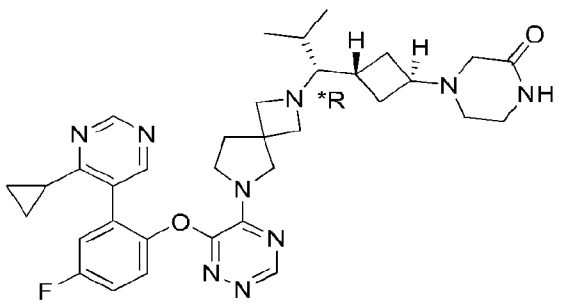
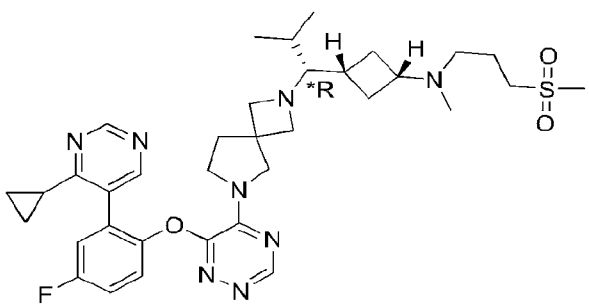
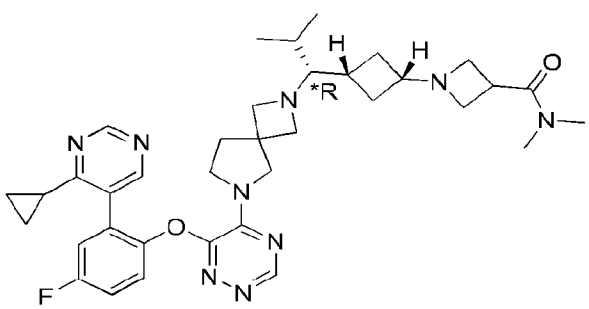
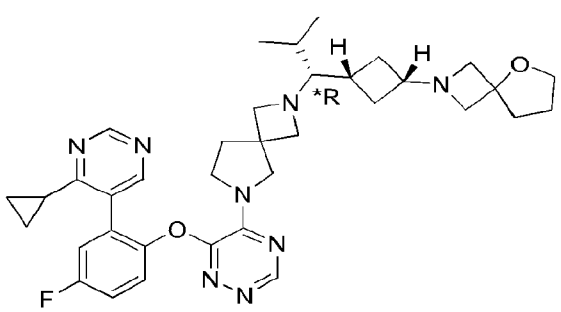
Compound number	Structure
Compound 210	
Compound 211	
Compound 212	

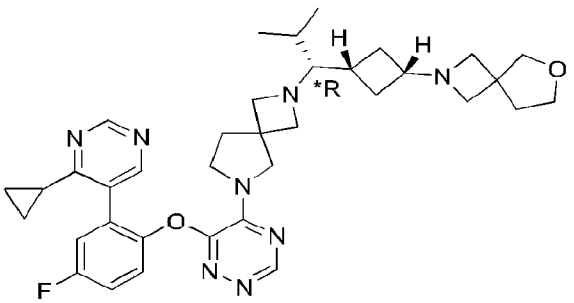
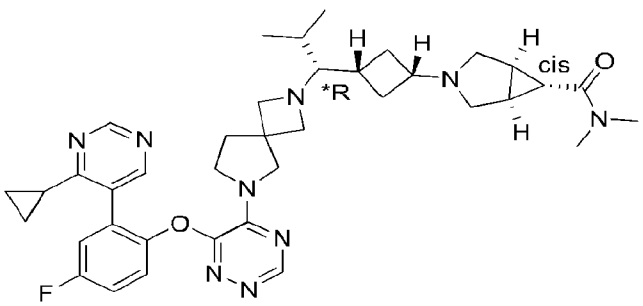
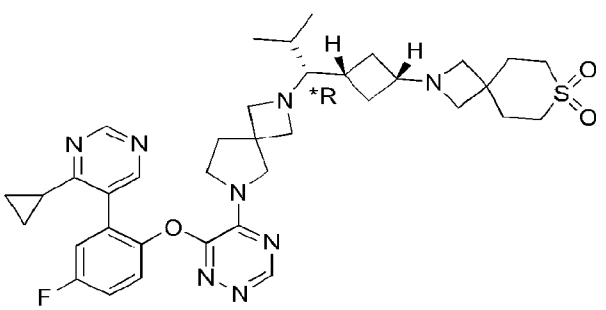
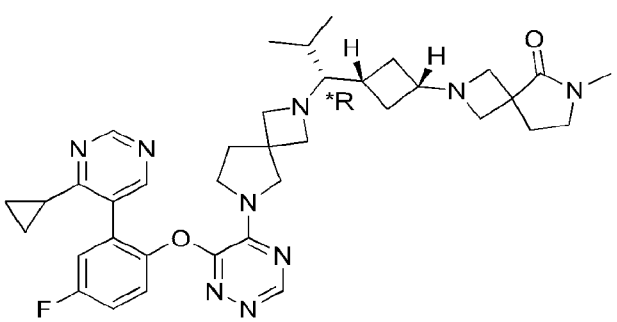
Compound number	Structure
Compound 213	
Compound 214	
Compound 215	
Compound 231	
Compound 232	

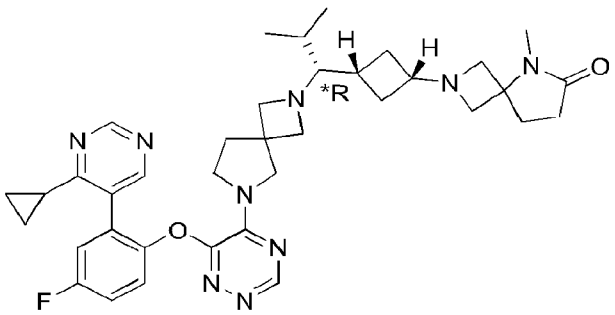
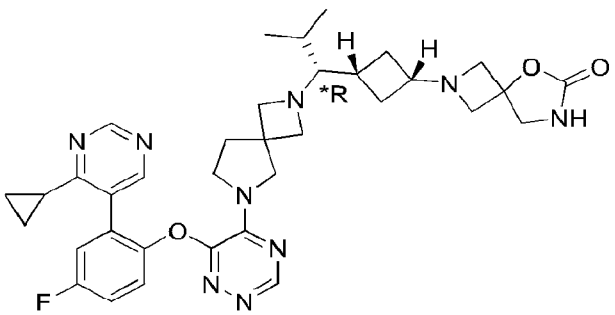
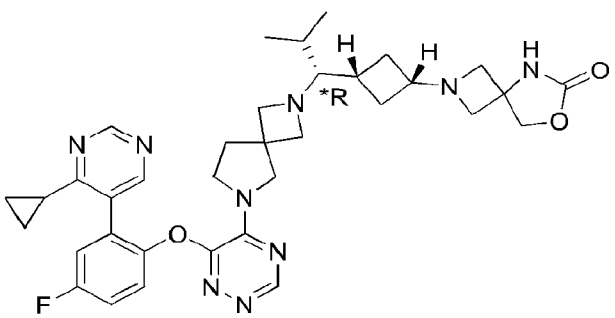
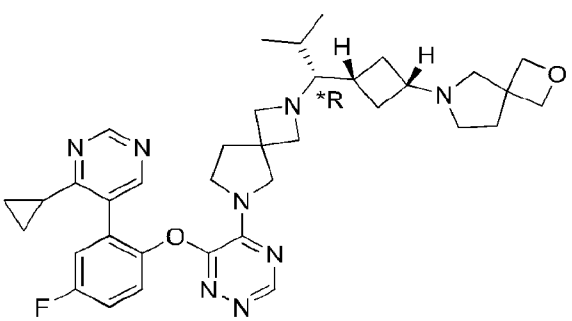
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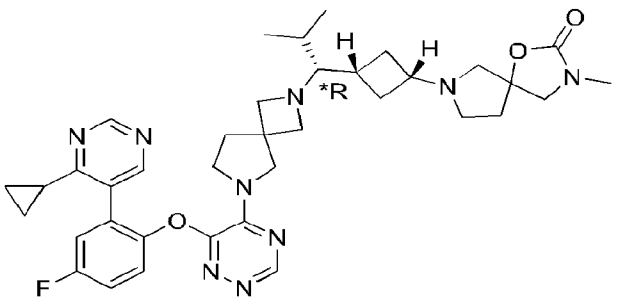
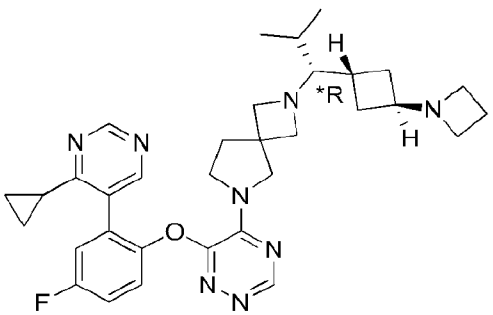
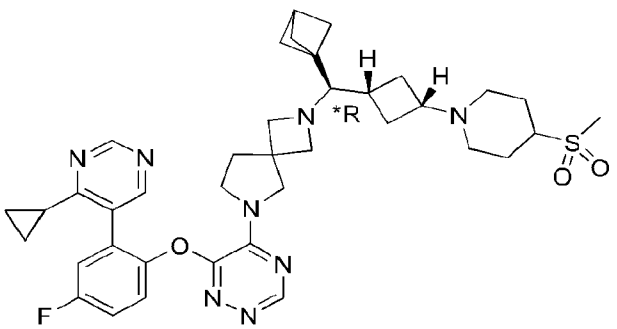
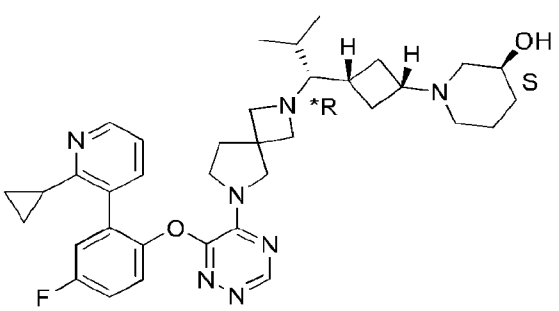
Compound number	Structure
Compound 233	
Compound 234	
Compound 235	

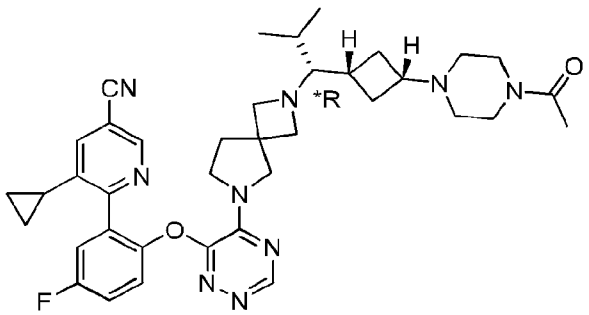
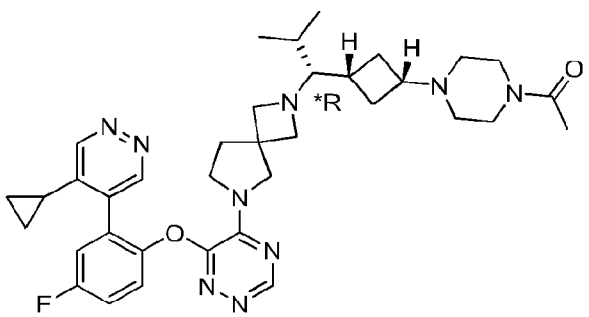
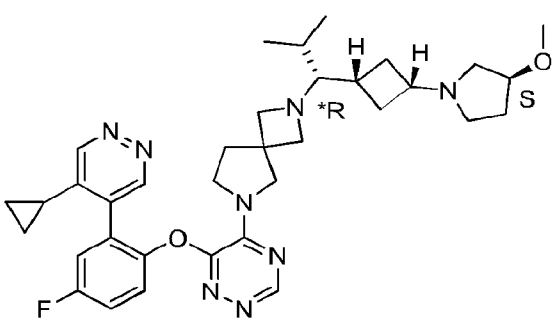
Compound number	Structure
Compound 236	
Compound 237	
Compound 238	
Compound 239	

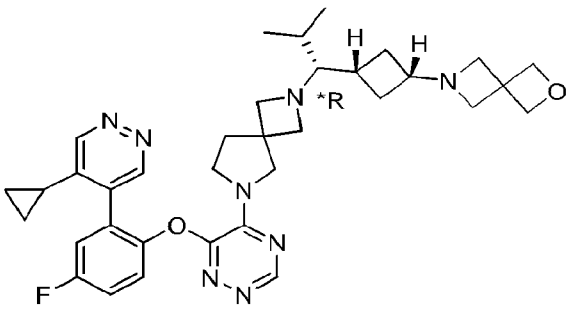
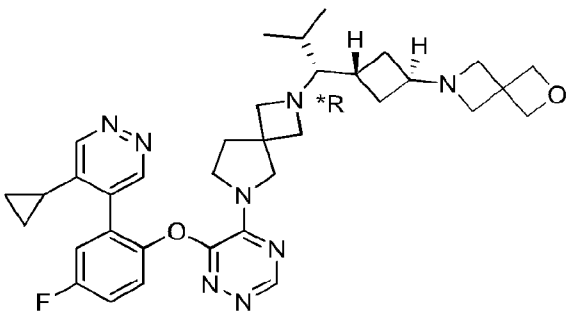
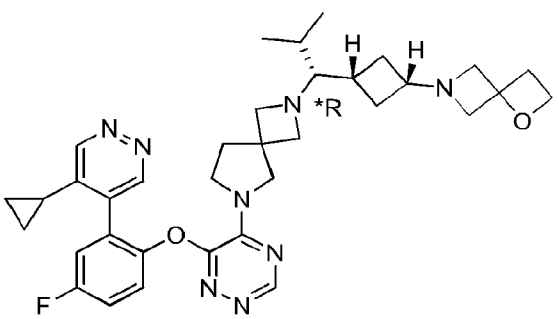
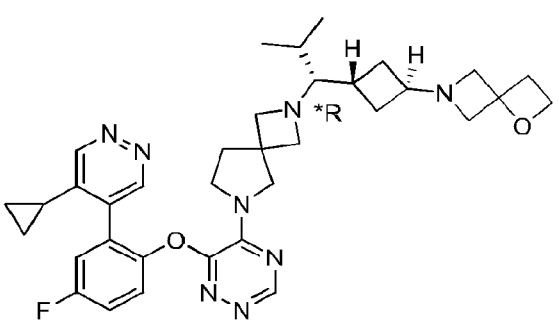
Compound number	Structure
Compound 240	
Compound 241	
Compound 242	
Compound 243	
Compound 246	

Compound number	Structure
Compound 247	
Compound 248	
Compound 249	
Compound 315	 from intermediate 238

Compound number	Structure
Compound 316	 from intermediate 240
Compound 317	 from intermediate 241
Compound 318	 from intermediate 243
Compound 325	

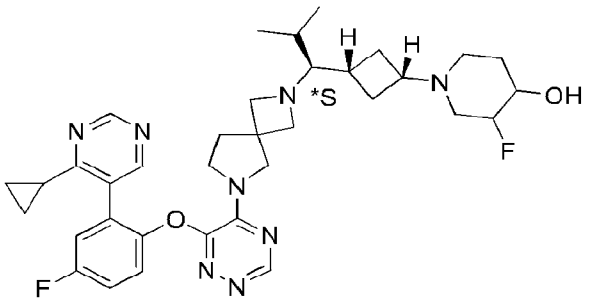
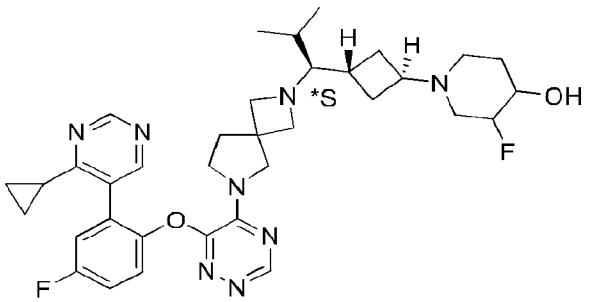
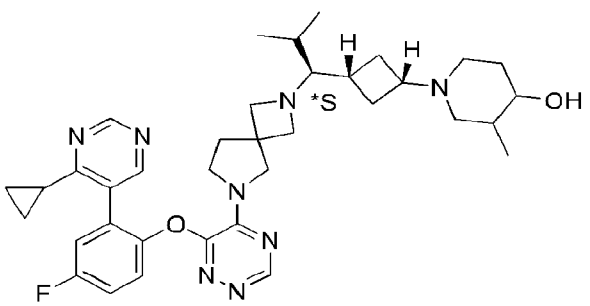
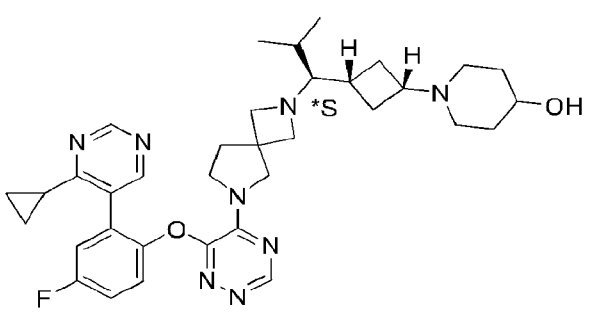
Compound number	Structure
Compound 329	 from intermediate 248
Compound 345	
Compound 341	 from intermediate 295, SFC separation: DAICEL CHIRALPAK IG (250mm x 30mm, 10um), mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: isocratic 60% B v/v, flow rate: 80 mL/min
Compound 78	 from intermediate 46a (*R)

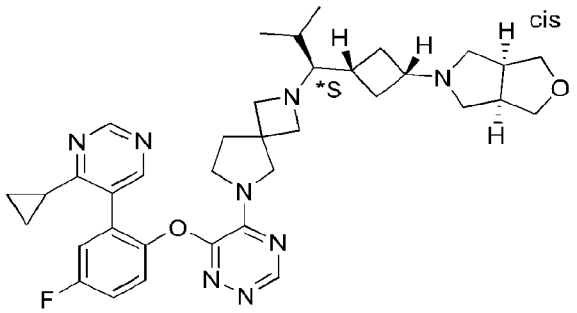
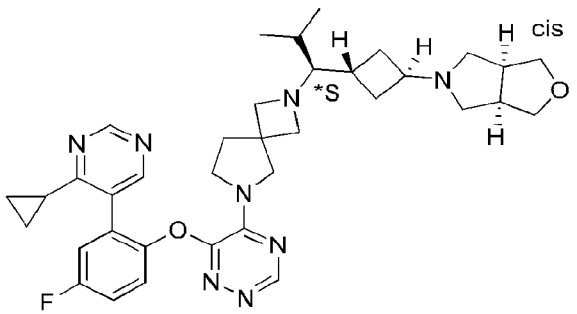
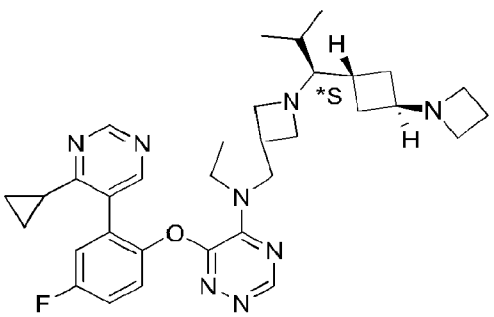
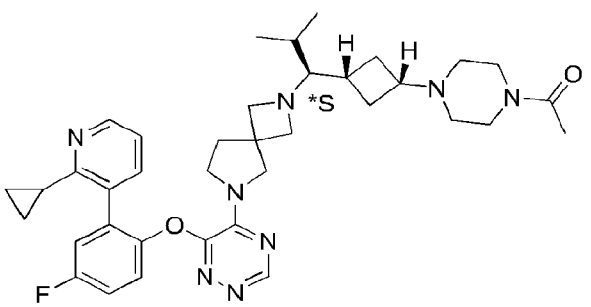
Compound number	Structure
Compound 79	 from intermediate 82
Compound 80	 from intermediate 109
Compound 81	 from intermediate 109

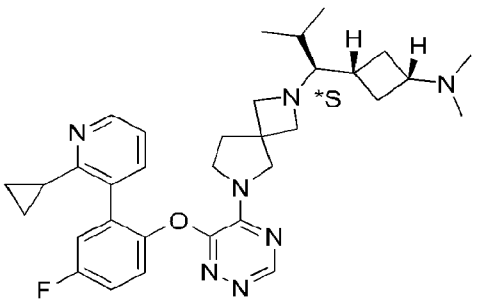
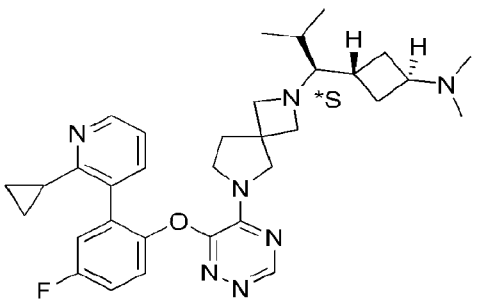
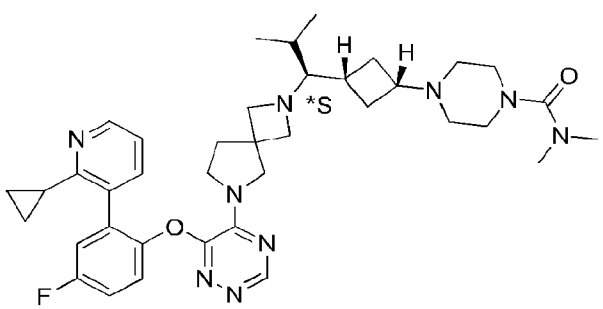
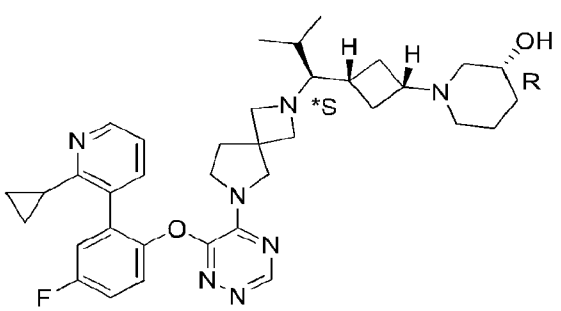
Compound number	Structure
Compound 82	 compound 82
Compound 83	 from intermediate 109
Compound 84	
Compound 84a	 from intermediate 109

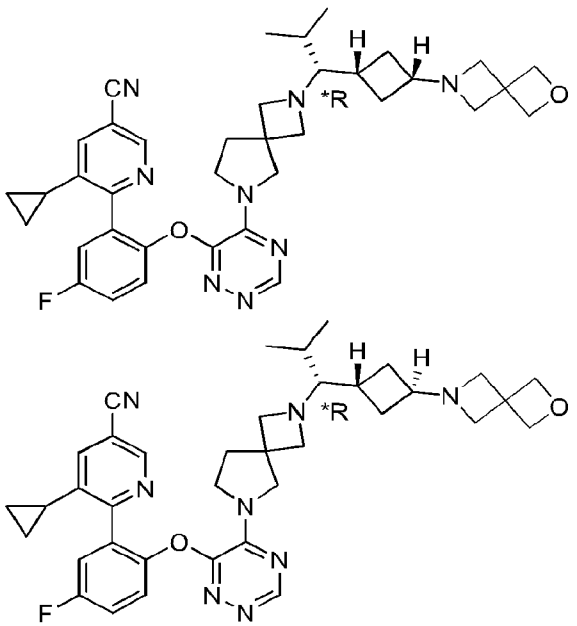
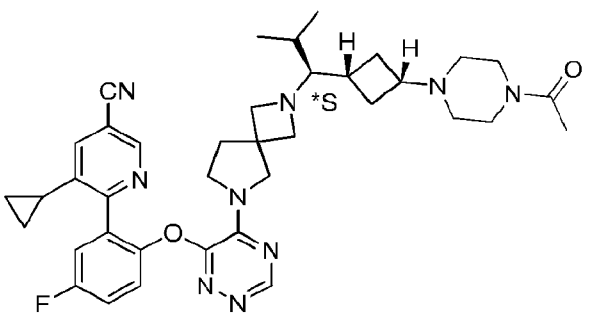
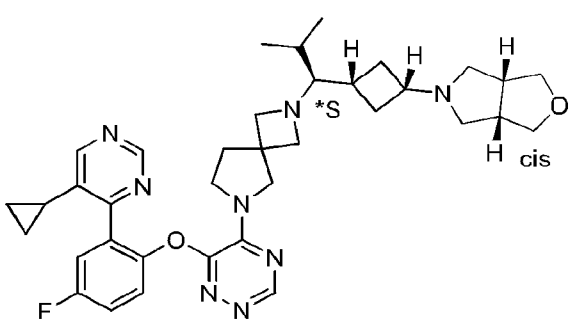
The compounds reported below were prepared following an analogous methodology as reported for the preparation of compound 7, starting from the appropriate starting materials

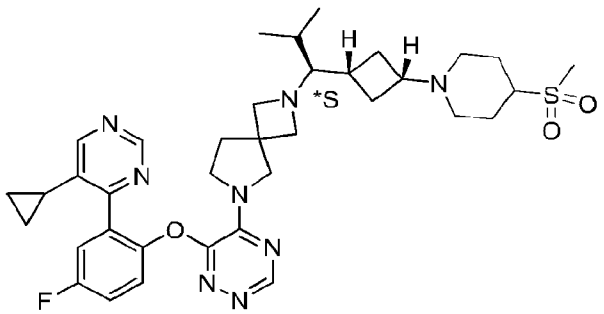
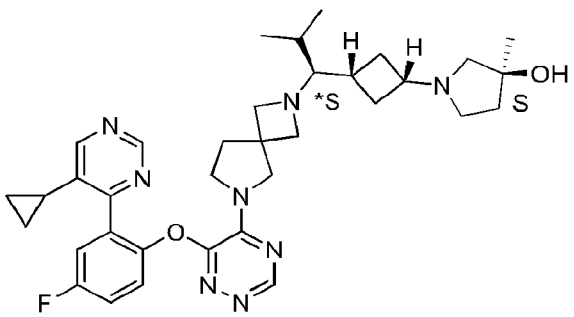
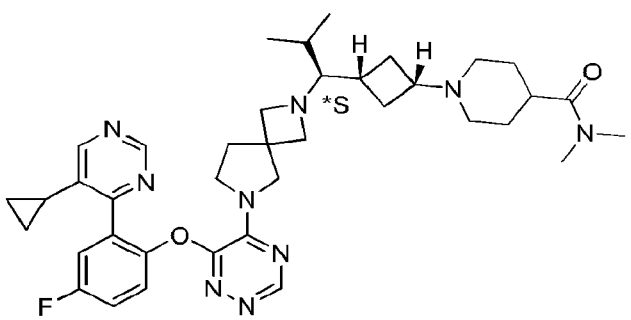
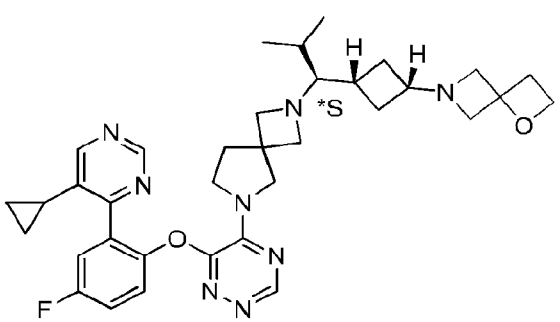
(e.g. intermediate 38a (*S) or other appropriate starting materials):

Compound number	Structure
Compound 85	 Piperidine moiety is one *cis* isomer (undetermined which *cis*)
Compound 86	 Piperidine moiety is one *cis* isomer (undetermined which *cis*)
Compound 87	 Piperidine moiety is one *cis* isomer (undetermined which *cis*)
Compound 88	

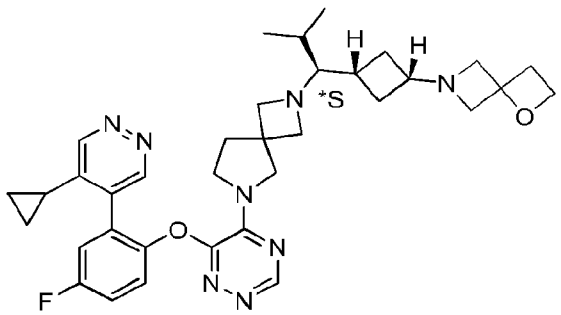
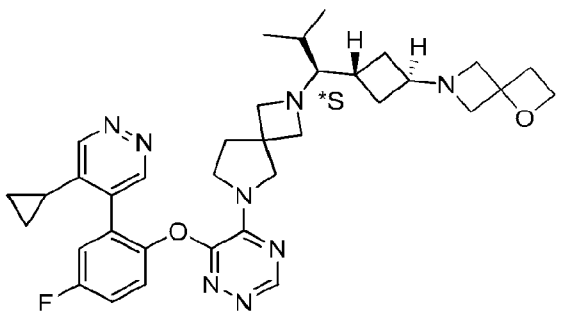
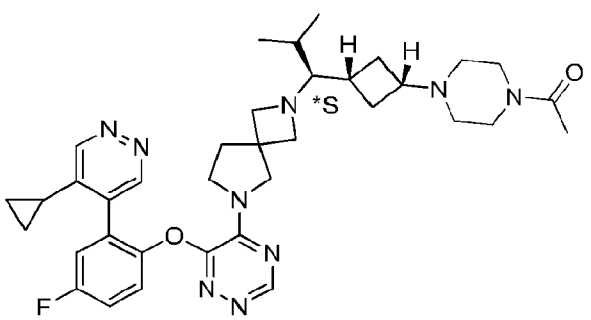
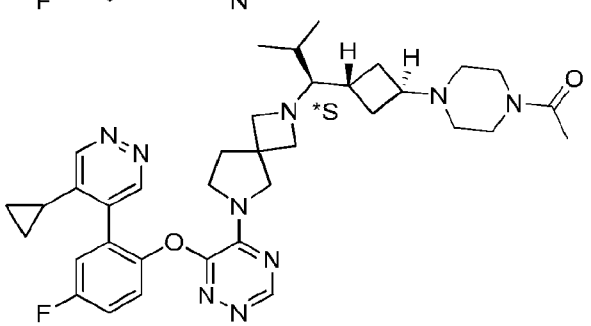
Compound number	Structure
Compound 244	
Compound 245	
Compound 346	
Compound 89	 from intermediate 46b (*S)

Compound number	Structure
Compound 90 Compound 91	  from intermediate 46b (*S)
Compound 92	 from intermediate 46b (*S)
Compound 93	 from intermediate 46b (*S)

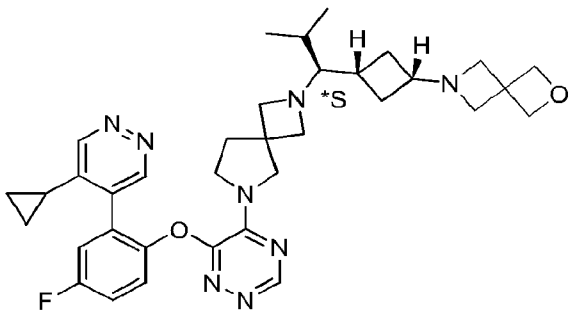
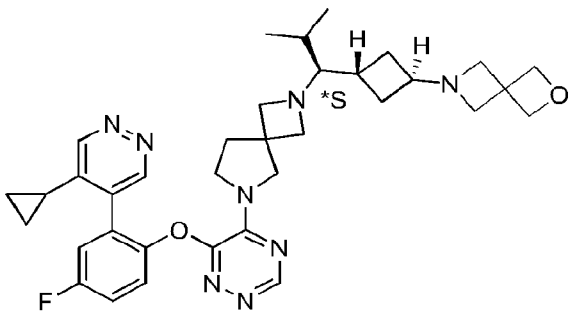
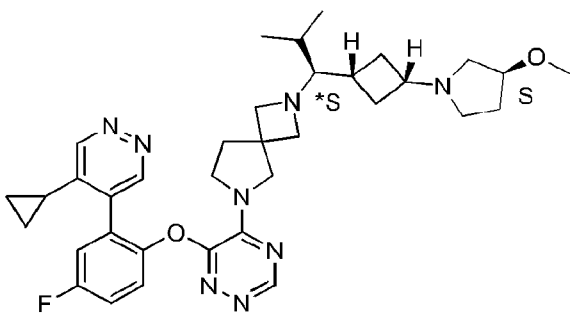
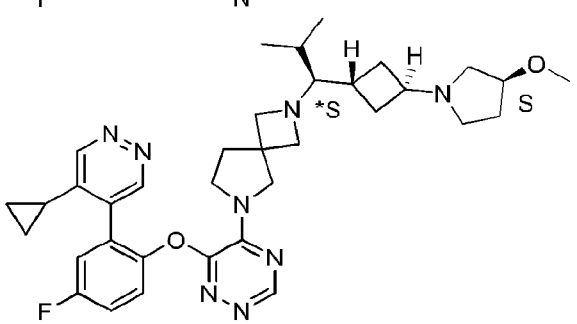
Compound number	Structure
Compound 94 Compound 95	 from intermediate 82
Compound 96	 from intermediate 82
Compound 97	 from intermediate 93

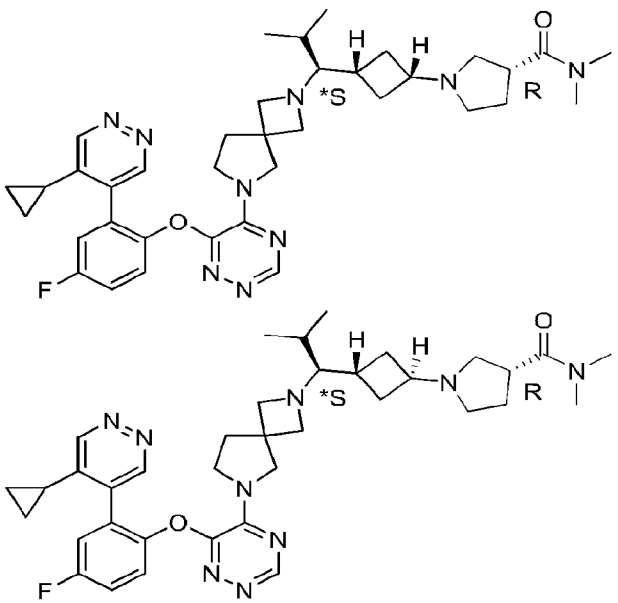
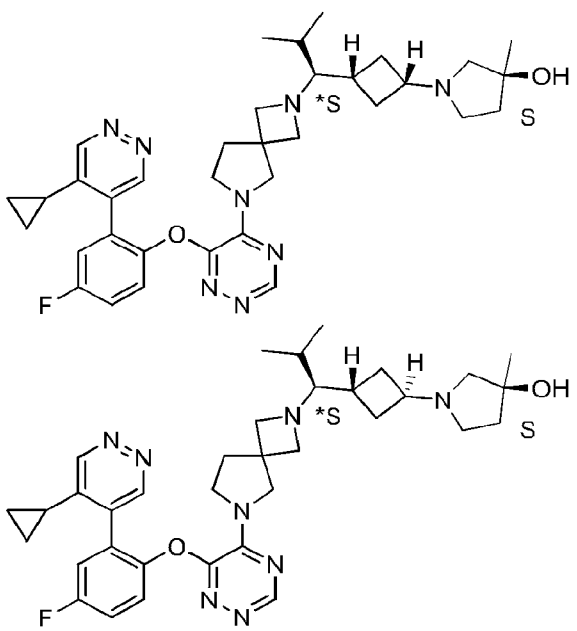
Compound number	Structure
Compound 98	 from intermediate 93
Compound 99	 from intermediate 93
Compound 100	 from intermediate 93
Compound 101	 from intermediate 93

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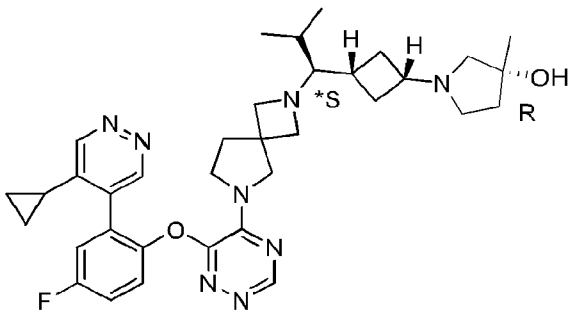
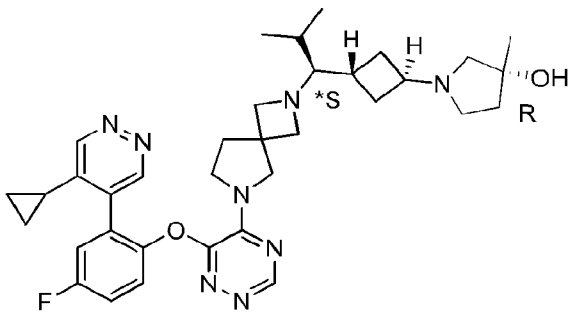
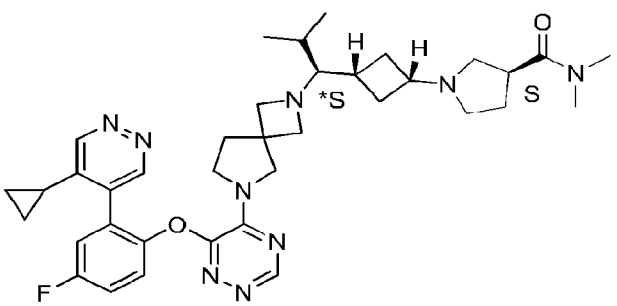
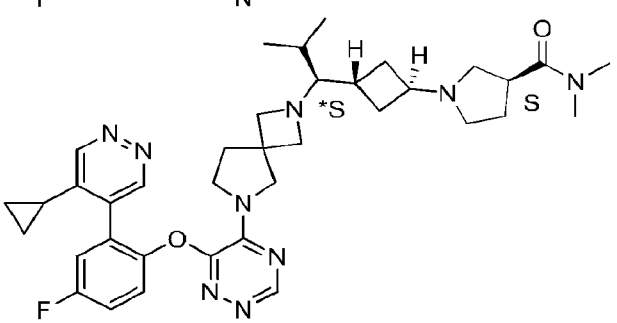
Compound number	Structure
Compound 102	 from intermediate 109
Compound 103	 from intermediate 109
Compound 104	 from intermediate 109
Compound 105	 from intermediate 109

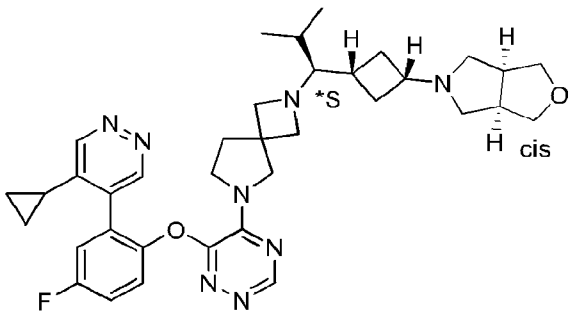
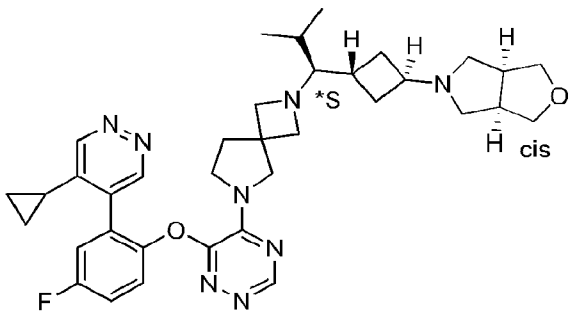
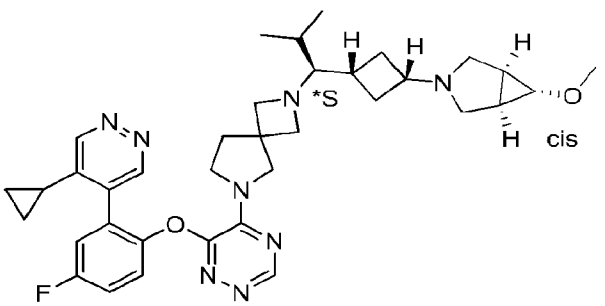
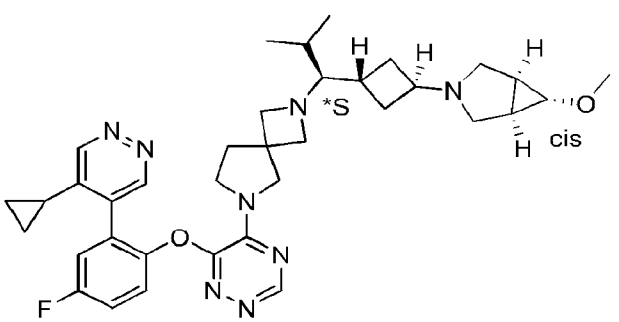
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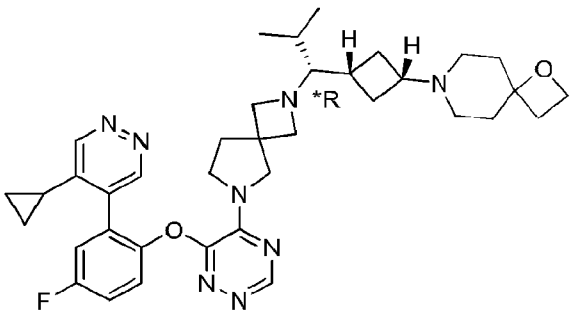
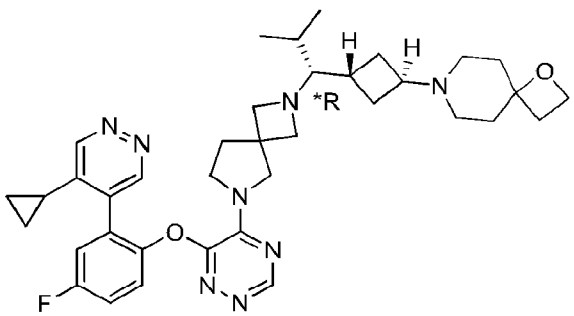
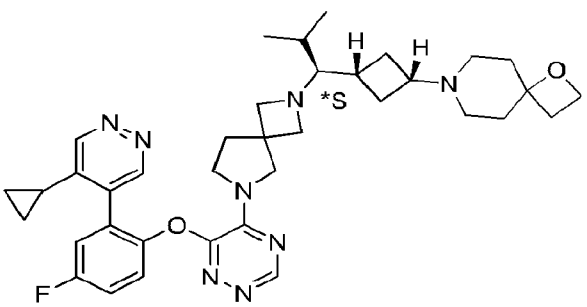
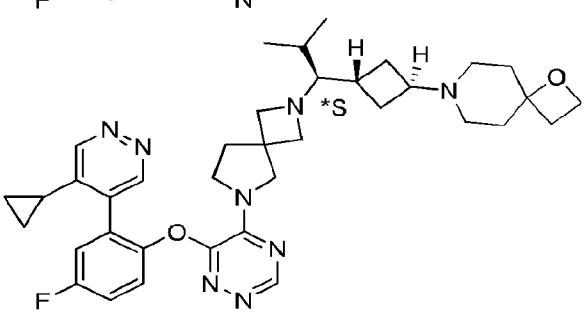
Compound number	Structure
Compound 106	
Compound 107	 from intermediate 109
Compound 108	
Compound 109	 from intermediate 109

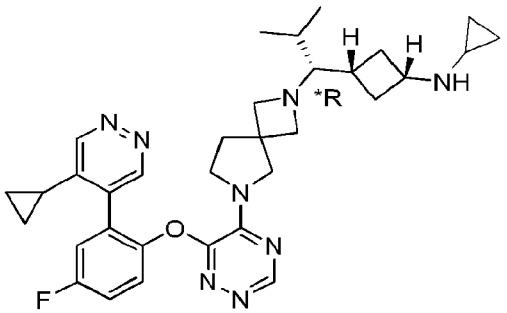
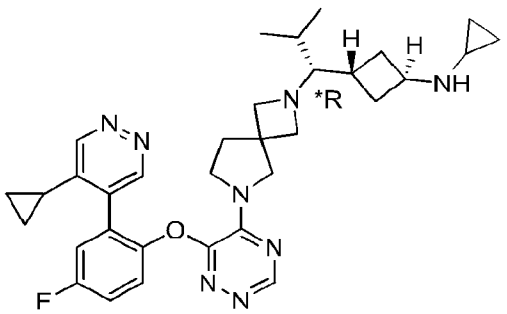
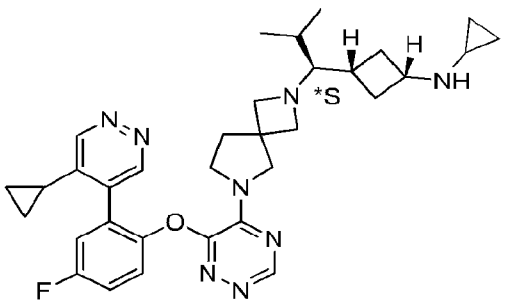
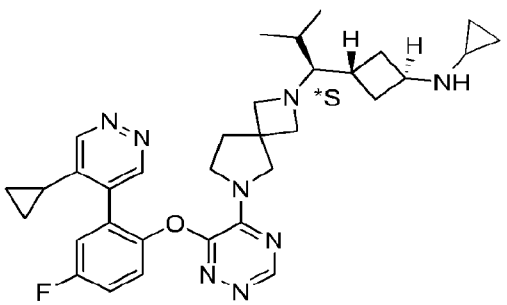
Compound number	Structure
Compound 110 Compound 111	 from intermediate 109
Compound 112 Compound 113	 from intermediate 109

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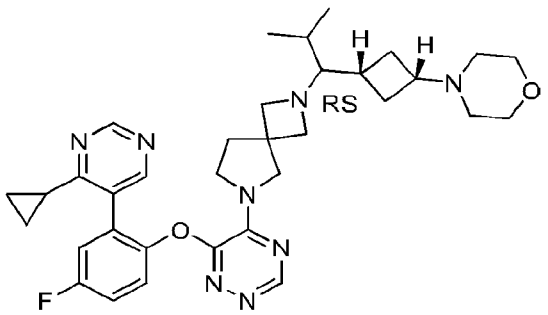
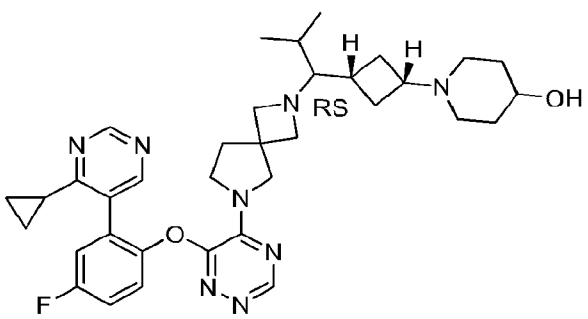
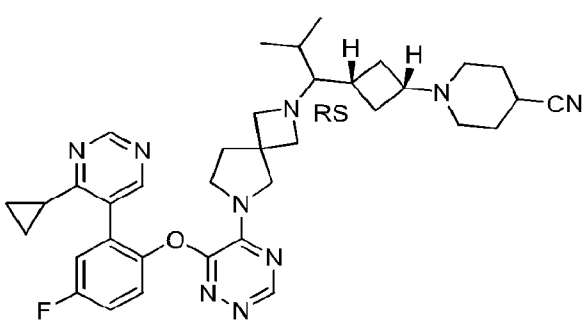
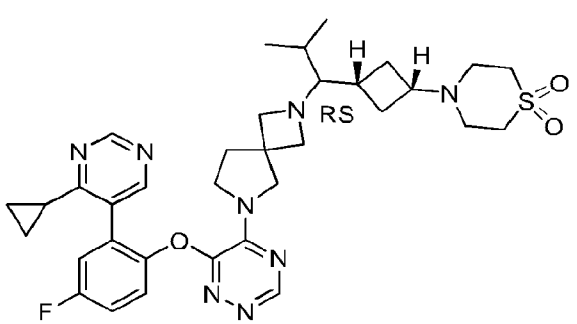
Compound number	Structure
Compound 114	
Compound 115	 from intermediate 109
Compound 116	
Compound 117	 from intermediate 109

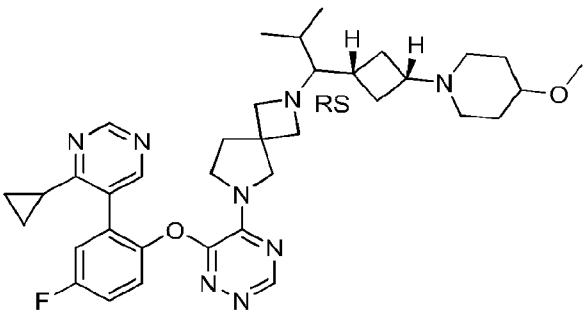
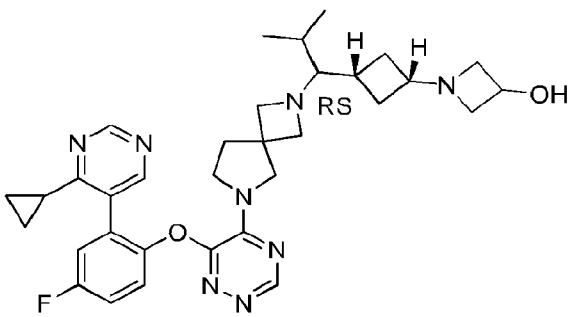
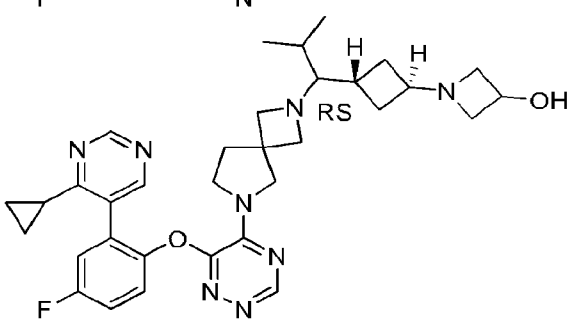
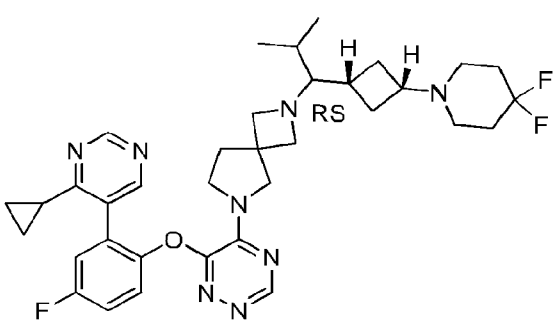
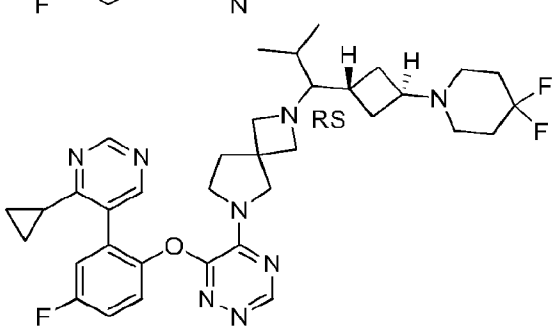
Compound number	Structure
Compound 278	
Compound 279	 from intermediate 109
Compound 282a	
Compound 282b	 from intermediate 109

Compound number	Structure
Compound 280a	
Compound 280b	
Compound 281a	
Compound 281b	
	from intermediate 109

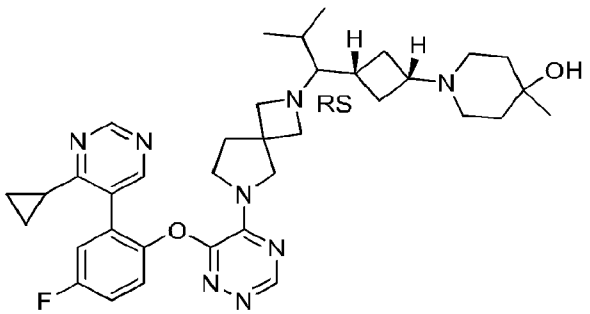
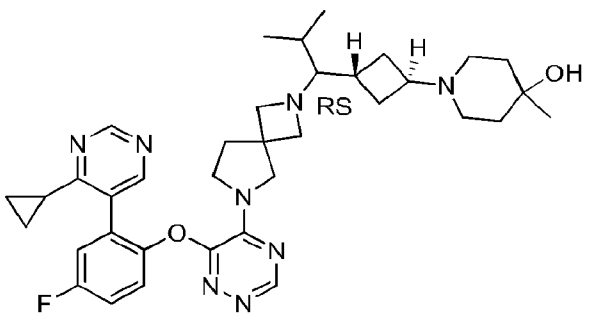
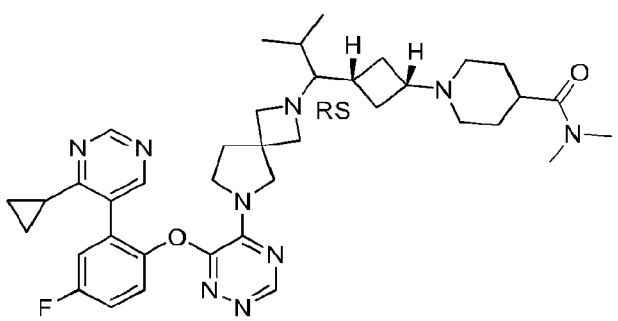
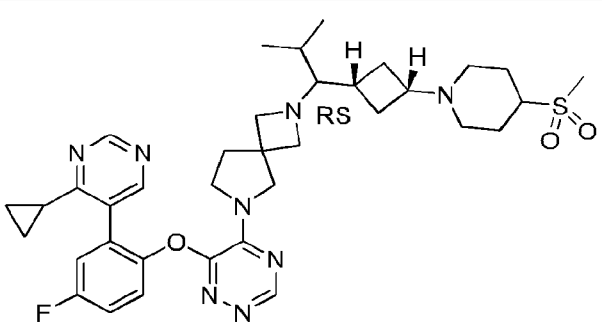
Compound number	Structure
Compound 283a	
Compound 283b	
Compound 284a	
Compound 284b	
	from intermediate 109

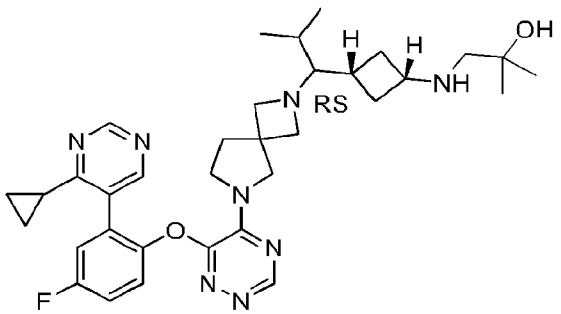
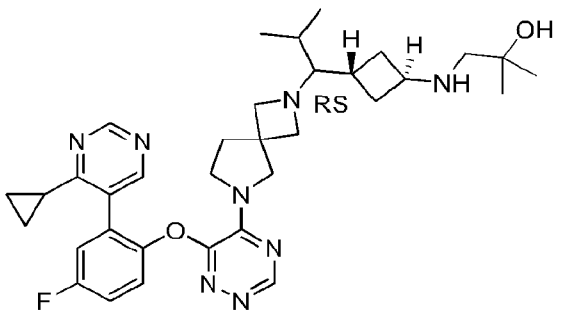
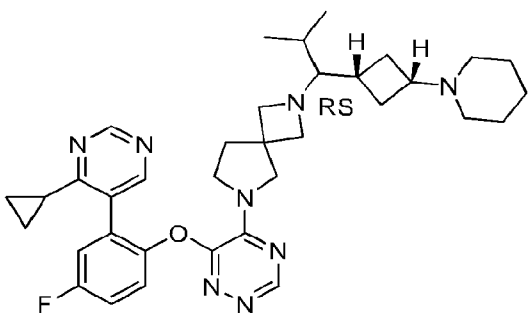
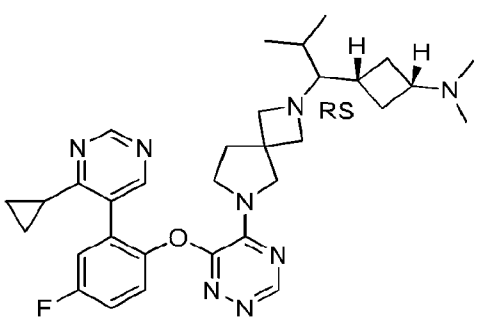
The compounds reported below were prepared following an analogous methodology as reported for the preparation of compound 7 starting from the appropriate starting materials (e.g. intermediate 38b or or other appropriate starting materials). If needed, standard cleavage of protected groups was applied:

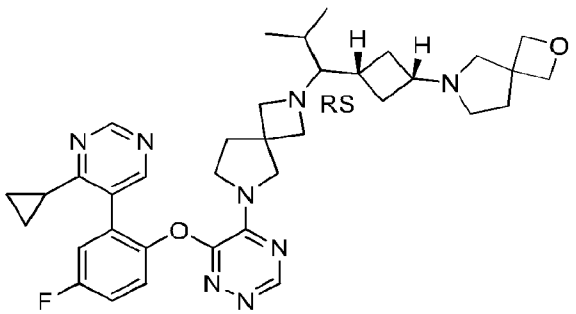
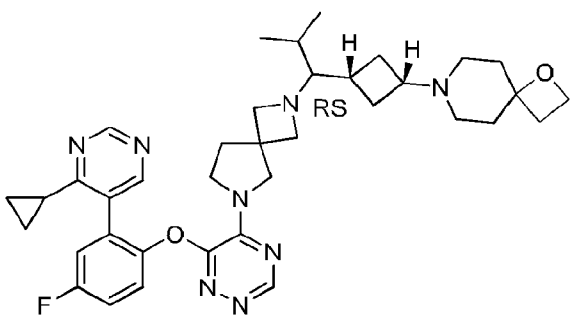
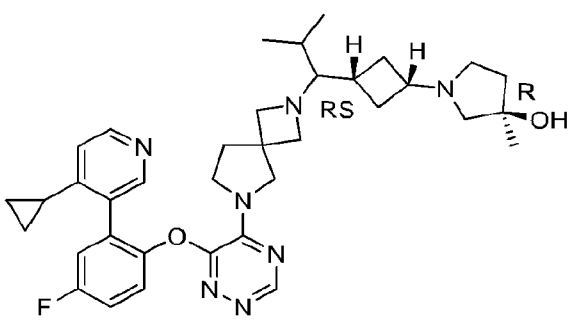
Compound number	Structure
Compound 120	
Compound 121	 Deprotection TBAF 1M (3eq) in THF at RT for 18h.
Compound 122	
Compound 123	

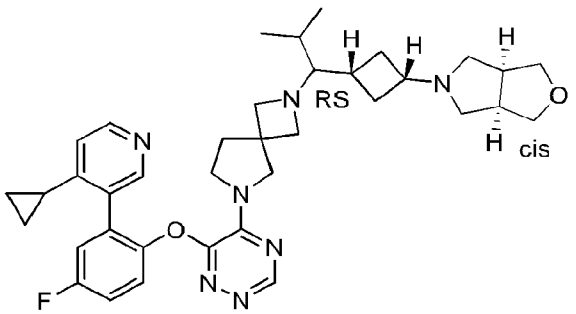
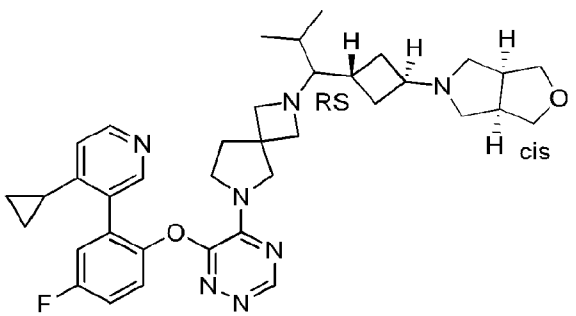
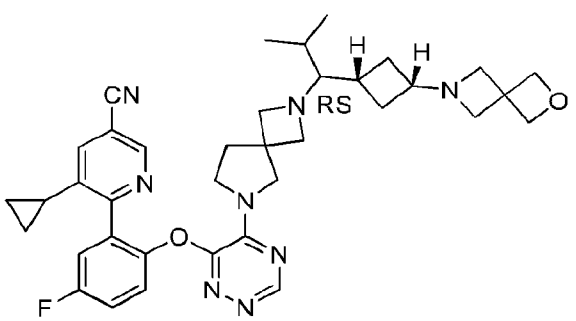
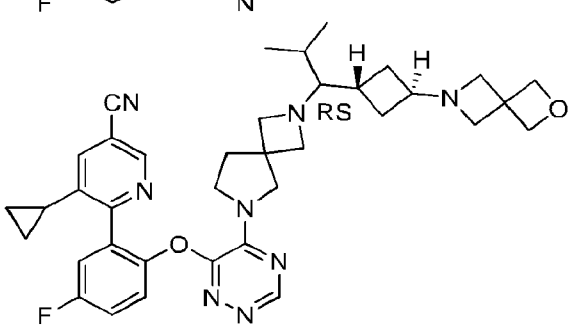
Compound number	Structure
Compound 124	
Compound 125	
Compound 126	
Compound 127	
Compound 128	

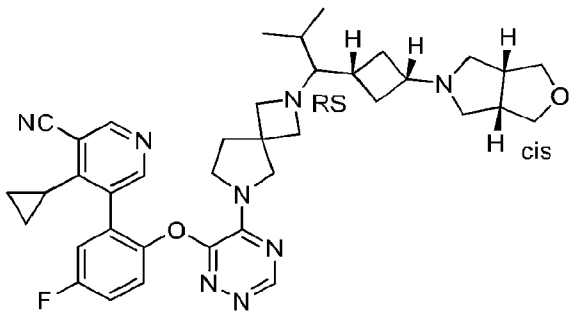
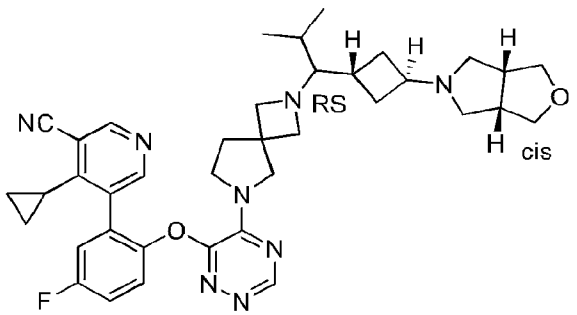
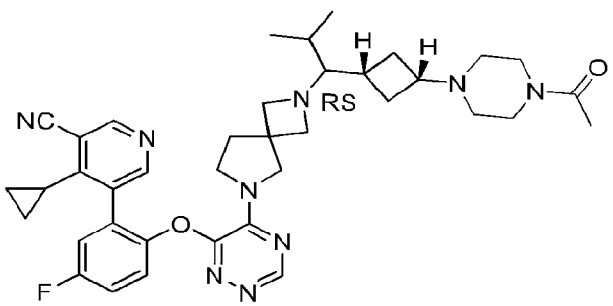
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Compound number	Structure
Compound 129	
Compound 130	
Compound 131	
Compound 132	

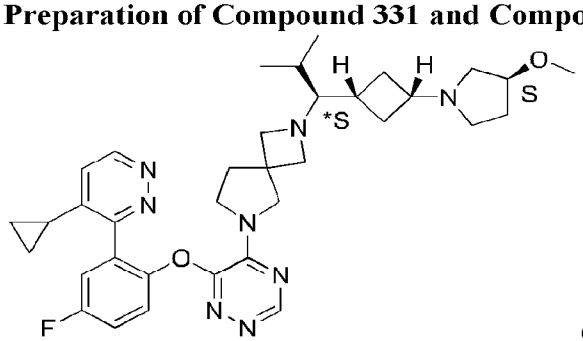
Compound number	Structure
Compound 133	
Compound 134	
Compound 135	
Compound 136	

Compound number	Structure
Compound 326	
Compound 327	
Compound 137	 From intermediate 77

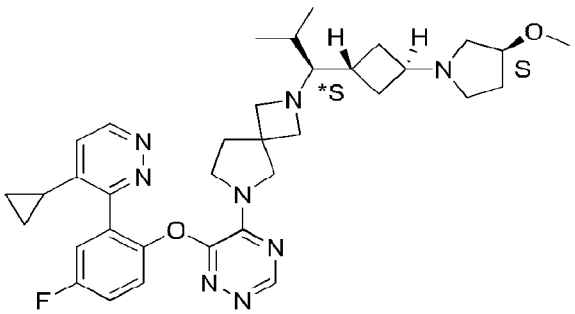
Compound number	Structure
Compound 138	
Compound 139	 From intermediate 77
Compound 140	
Compound 141	 from intermediate 82

Compound number	Structure
Compound 142	
Compound 143	 from intermediate 86
Compound 144	 from intermediate 86

Preparation of Compound 331 and Compound 332:



Compound 331



Compound 332

$NaBH_3CN$ (433 mg, 6.89 mmol) was added to a solution consisting of intermediate 249a (800 mg, 1.38 mmol) and (*S*)-3-methoxypyrrolidine hydrochloride (418 mg, 4.13 mmol), MeOH (10 mL) and AcOH (0.237 mL). The mixture was stirred at 60 °C for 12 h. After cooling to RT, the mixture was adjusted to pH = 8 with NH_3H_2O and purified by preparative HPLC using a Phenomenex Gemini 150 mm x 25 mm x 10 μm column (eluent: 30% to 60% (v/v) ACN and H_2O with 0.05% NH_3H_2O). The desired fractions were collected and lyophilized to afford Compound 331 (321 mg, 36% yield) and Compound 332 (49 mg, 5% yield) as a white solid.

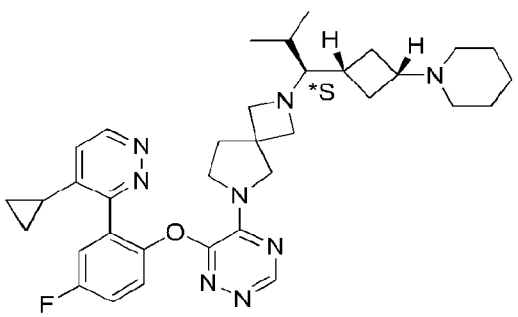
Compound 331:

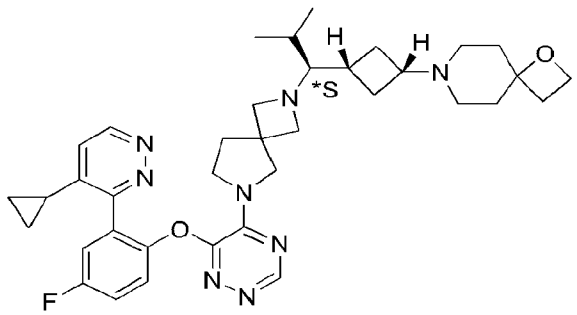
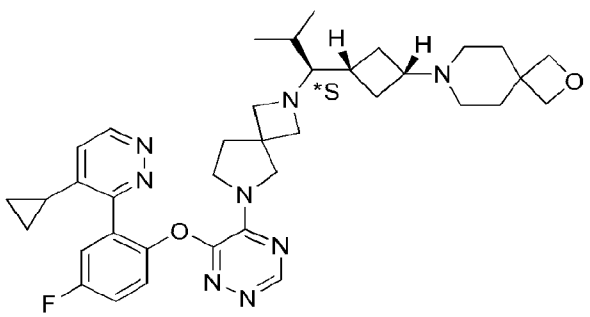
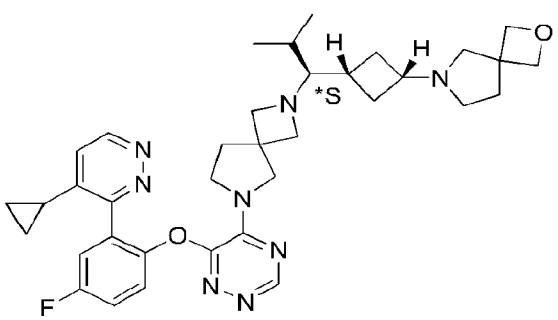
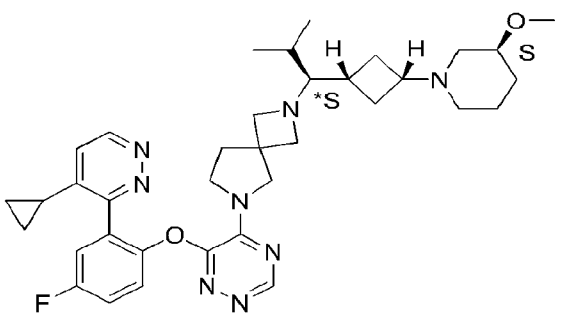
^{1}H NMR Methanol-d_4 (Varian_400 MHz): δ 9.01 - 8.85 (m, 1H), 8.29 (s, 1H), 7.63 - 7.47 (m, 1H), 7.45 - 7.28 (m, 2H), 7.21 - 7.07 (m, 1H), 4.02 - 3.90 (m, 1H), 3.88 - 3.68 (m, 2H), 3.64 - 3.43 (m, 2H), 3.29 - 3.16 (m, 7H), 2.81 - 2.70 (m, 1H), 2.70 - 2.60 (m, 2H), 2.60 - 2.53 (m, 1H), 2.49 - 2.39 (m, 1H), 2.26 - 2.13 (m, 3H), 2.11 - 1.96 (m, 4H), 1.86 - 1.66 (m, 5H), 1.08 - 0.98 (m, 2H), 0.97 - 0.86 (m, 6H), 0.83 - 0.75 (m, 2H).

Compound 332:

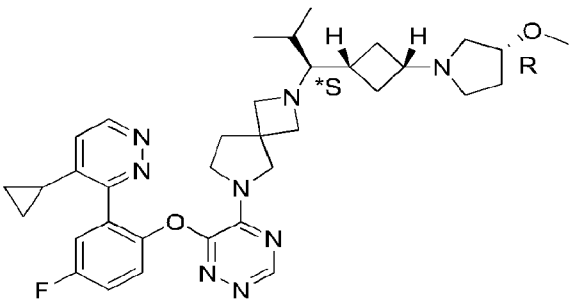
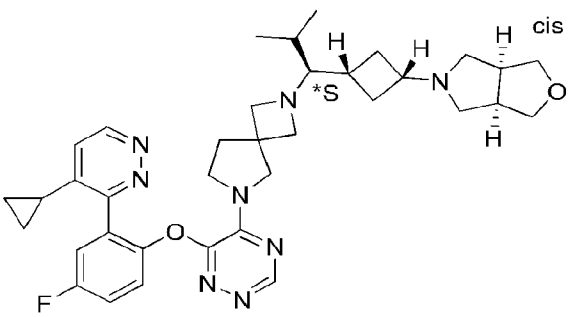
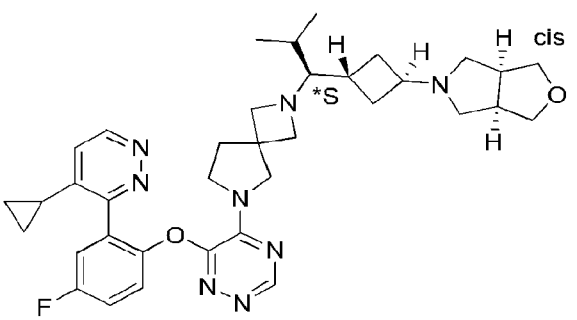
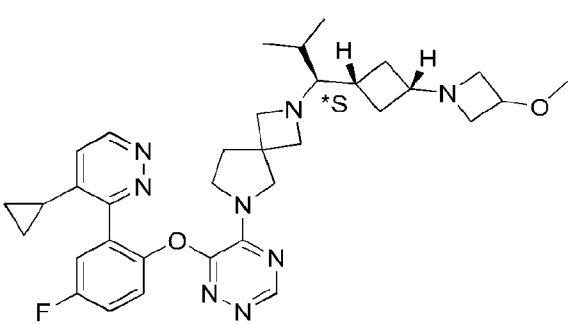
^{1}H NMR Methanol-d_4 (Varian_400 MHz): δ 9.00 - 8.87 (m, 1H), 8.30 (s, 1H), 7.60 - 7.48 (m, 1H), 7.45 - 7.32 (m, 2H), 7.19 - 7.10 (m, 1H), 4.03 - 3.92 (m, 1H), 3.85 - 3.69 (m, 2H), 3.67 - 3.57 (m, 1H), 3.56 - 3.45 (m, 1H), 3.30 - 3.14 (m, 7H), 2.95 - 2.86 (m, 1H), 2.81 - 2.53 (m, 4H), 2.32 - 2.16 (m, 2H), 2.15 - 1.97 (m, 6H), 1.89 - 1.66 (m, 4H), 1.08 - 0.98 (m, 2H), 0.96 - 0.85 (m, 6H), 0.84 - 0.74 (m, 2H).

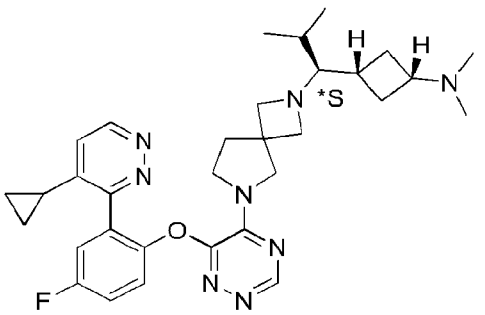
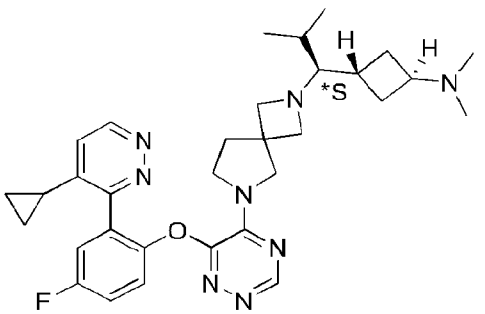
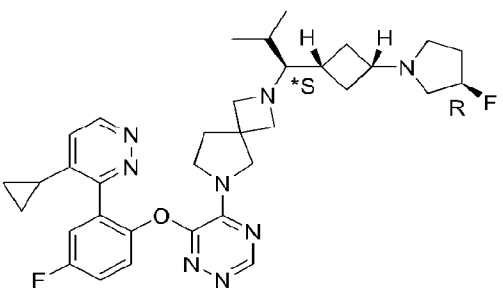
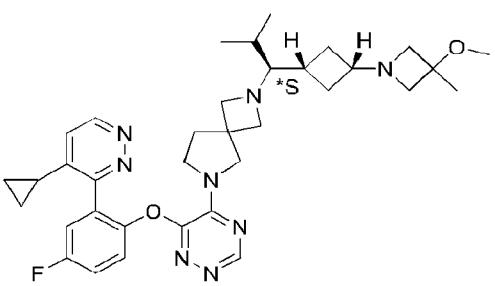
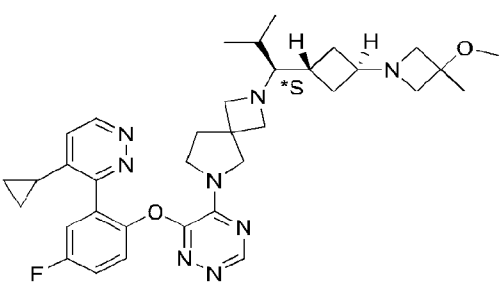
The compounds reported below were prepared following an analogous methodology as described for Compound 331 and Compound 332 starting from the intermediate 249a (*S):

Compound number	Structure
Compound 250	

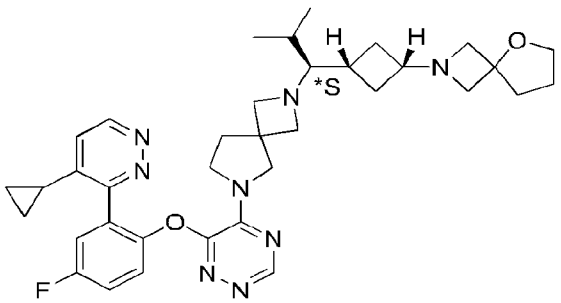
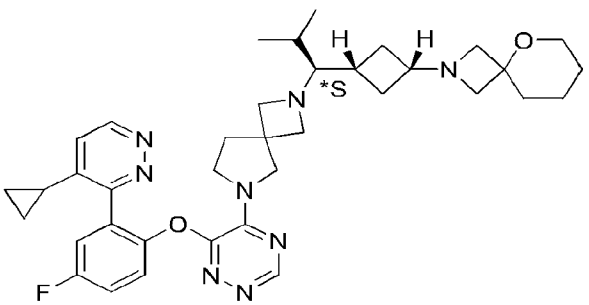
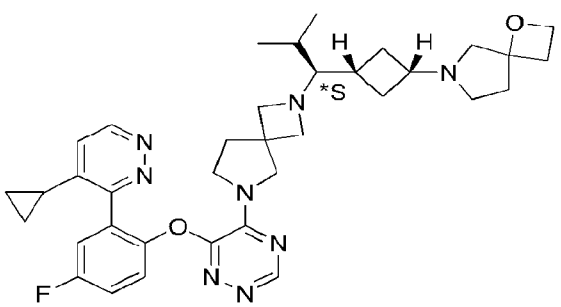
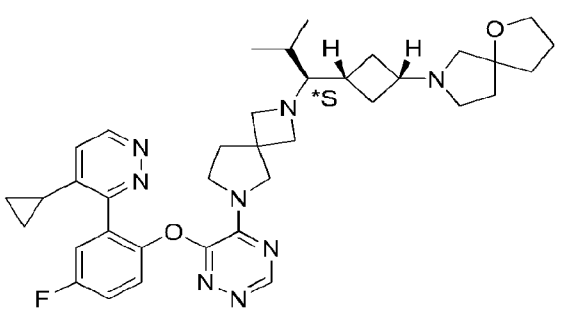
Compound number	Structure
Compound 251	
Compound 253	
Compound 254	
Compound 256	

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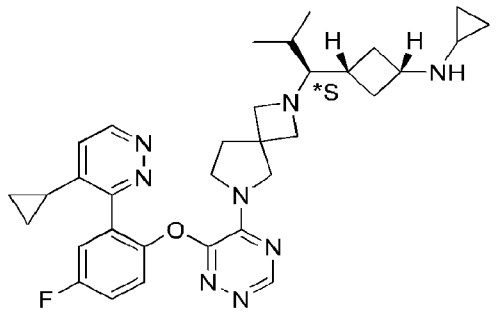
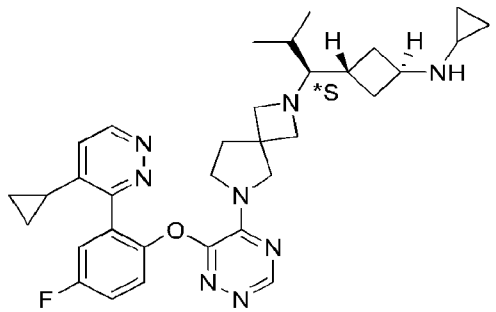
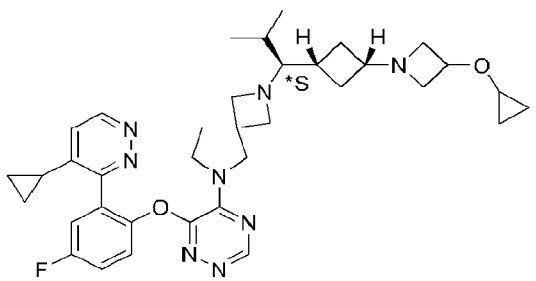
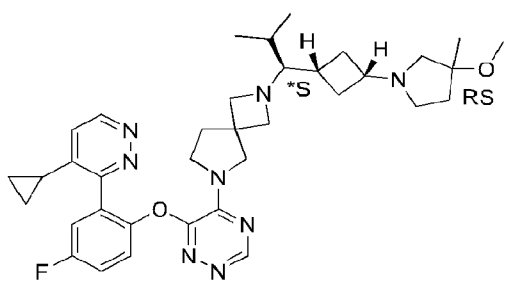
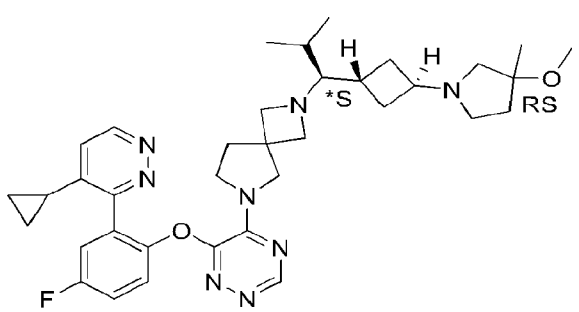
Compound number	Structure
Compound 257	
Compound 258	
Compound 259	
Compound 260	

Compound number	Structure
Compound 261a	
Compound 261b	
Compound 262	
Compound 263	
Compound 264	

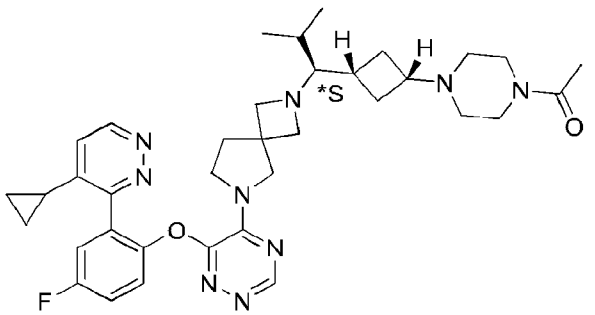
CA 03214746 2023-10-5

Compound number	Structure
Compound 265	
Compound 266	
Compound 268	
Compound 270	

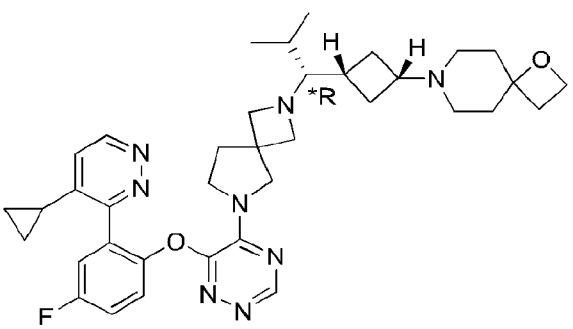
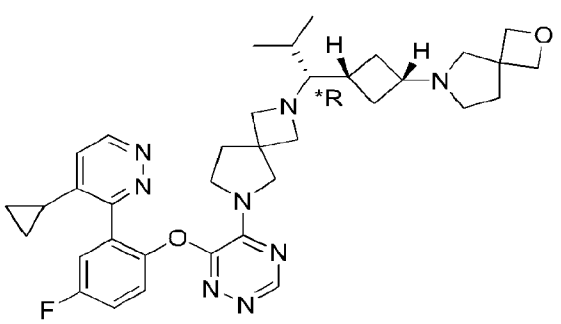
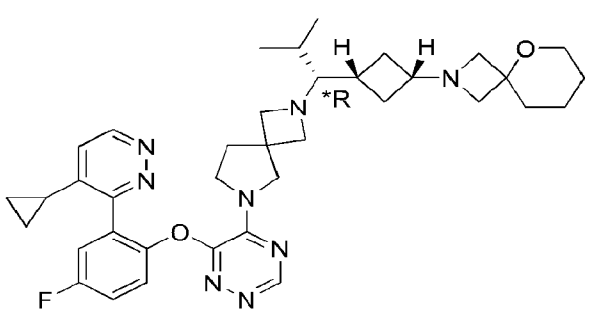
CA 03214746 2023-10-5

Compound number	Structure
Compound 272	
Compound 273	
Compound 274	
Compound 275	
Compound 276	

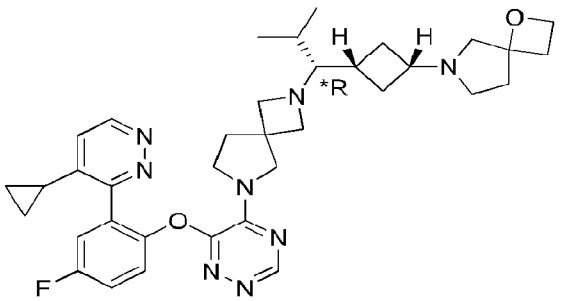
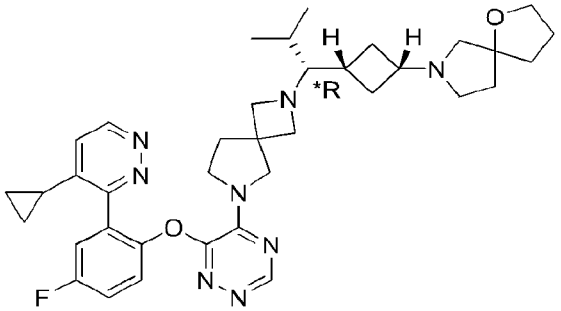
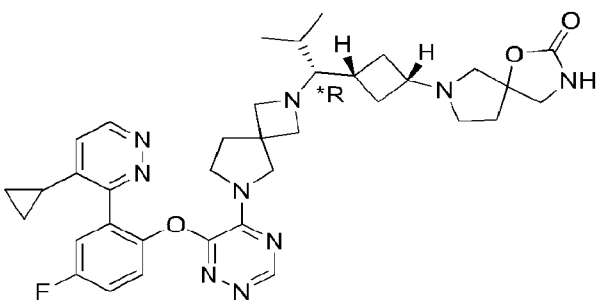
CA 03214746 2023-10-5

Compound number	Structure
Compound 277	

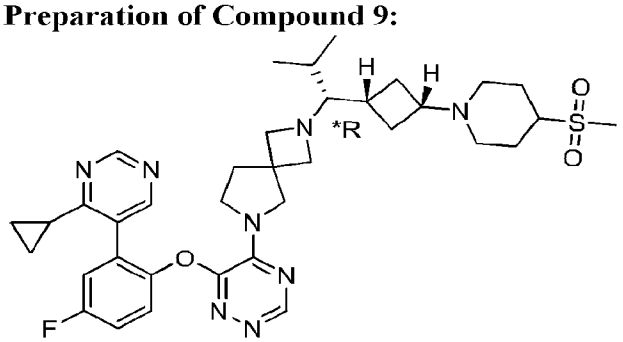
The compounds reported below were prepared following an analogous methodology as described for Compound 331 starting from the intermediate 249b (*R):

Compound number	Structure
Compound 252	
Compound 255	
Compound 267	

CA 03214746 2023-10-5

Compound number	Structure
Compound 269	
Compound 271	
Compound 328	 from intermediate 246

Preparation of Compound 9:



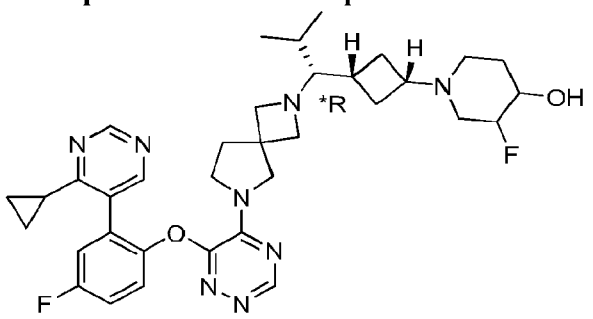
$NaBH_3CN$ (162 mg; 2.58 mmol) was added to a mixture of intermediate 38b (*R) (700 mg; 1.288 mmol), 4-(methylsulfonyl)piperidine (1.05 g; 6.438 mmol), AcOH (74 µL; 1.3 mmol) in MeOH (41 mL). Then, the reaction mixture was heated at 60°C for 24 h. The reaction mixture was cooled to r.t, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The

organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 7% MeOH, 93% DCM). The pure fractions were collected and evaporated to dryness. The residue (684 mg) was freeze-dried with water-ACN to give 655 mg (73%) of final compound 9.

^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.95 (br, 1H) 8.41 (br s, 2H) 7.57 (br d, J=3.4 Hz, 1 H) 7.41 - 7.49 (m, 2H) 3.39 - 3.79 (m, 4H) 2.85 - 3.15 (m, 10H) 2.38 - 2.47 (m, 1H) 2.02 - 2.16 (m, 2H) 1.96 (br d, J=9.8 Hz, 5H) 1.80 - 1.89 (m, 1H) 1.41 - 1.78 (m, 8H) 1.00 (m, 3H) 0.82 (t, J=6.2 Hz, 7H)

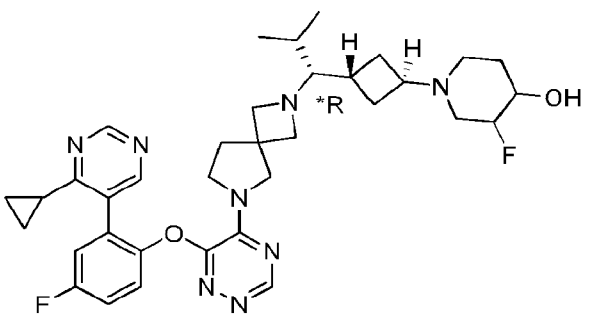
Preparation of Compound 10 and Compound 33:

Compound 10:



piperidine moity is one *cis* isomer (undetermined which *cis*)

Compound 33:



piperidine moity is one *cis* isomer (undetermined which *cis*)

$NaBH_3CN$ (40.7 mg; 0.65 mmol) was added to a mixture of intermediate 38b (*R) (176.1 mg; 0.33 mmol), *cis*-3-fluoropiperidin-4-ol (201.6 mg; 1.30 mmol), AcOH (19 µL; 0.32 mmol) in MeOH (15 mL). Then, the reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 12% MeOH, 88% DCM). The pure fractions were collected and evaporated to dryness. The residue (650 mg) was purified by achiral SFC (CHIRALPAK AD-H 5µm 250*30mm, mobile phase: 80% CO_2, 20% EtOH (0.3%

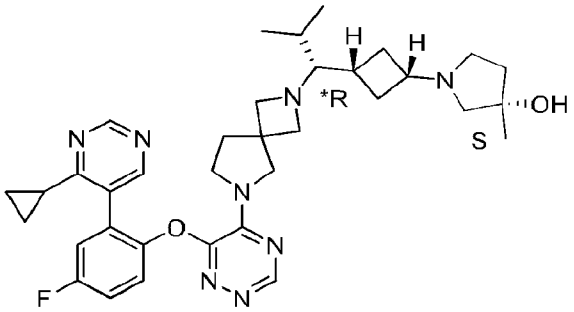
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$iPrNH_2$)). The pure fractions were collected and the solvent was evaporated. After freeze-drying with a mixture of water-ACN, 29 mg (14%) of Compound 10 and 25 mg (12%) of Compound 33.

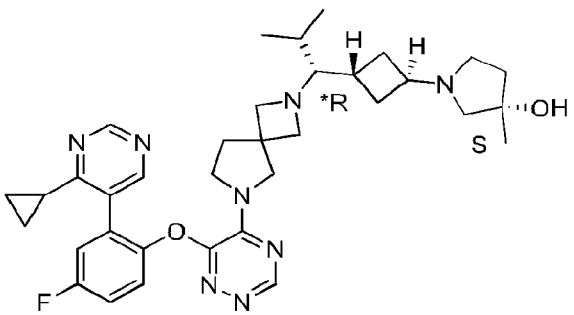
Compound 10: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.88 - 8.97 (m, 1H), 8.41 (br s, 2H), 7.57 (br s, 1H), 7.47 (br d, J=7.5 Hz, 2H), 4.89 (d, J=4.7 Hz, 1H), 4.43 - 4.60 (m, 1H), 3.38 - 3.79 (m, 6H), 2.87 - 3.14 (m, 5H), 1.39 - 2.32 (m, 15H), 1.00 (br d, J=6.9 Hz, 3H), 0.83 (br t, J=5.8 Hz, 7H)

Preparation of Compound 12 and Compound 13:

Compound 12



Compound 13

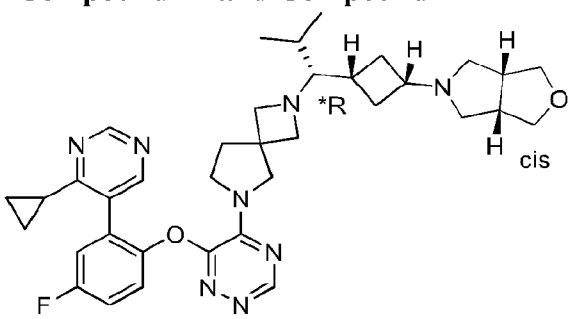


$NaBH_3CN$ (35 mg; 0.55 mmol) was added to a mixture of intermediate 38b (*R) (150 mg; 0.28 mmol), (3*S*)-3-methylpyrrolidin-3-ol (140 mg; 1.38 mmol), AcOH (16 µL; 0.28 mmol) in MeOH (9 mL). Then, the reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0.3% NH_4OH, 3% MeOH, 97% DCM to 1% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to give 130mg of a mixture of compound 12 and compound 13. The residue (130 mg) was purified by reverse phase (mobile phase: gradient from 65% NH_4CO_3 (0.2%), 35% ACN to 25% NH_4CO_3 (0.2%), 75% ACN). The pure fractions were collected and evaporated to dryness which was freeze-dried with water-ACN to give 80 mg (46%) of final compound 12 as a white solid.

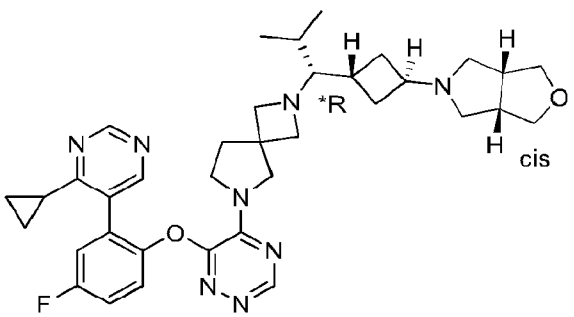
Compound 12

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 - 8.96 (m, 1H), 8.41 (br s, 2H), 7.57 (br d, *J*=2.0 Hz, 1H), 7.41 - 7.51 (m, 2H), 4.45 (s, 1H), 3.38 - 3.77 (m, 4H), 2.88 - 3.20 (m, 4 H), 2.58 - 2.64 (m, 1H), 2.36 - 2.44 (m, 1H), 2.32 (s, 3H), 1.90 - 2.08 (m, 4H), 1.46 - 1.90 (m, 8H), 1.21 (s, 3H), 0.90 - 1.07 (m, 3 H), 0.82 (dd, *J*=6.8, 3.1 Hz, 7H)

Preparation of Compound 14 and Compound 15



Compound 14



Compound 15

$NaBH_3CN$ (35 mg; 0.55 mmol) was added to a mixture of intermediate 38b (*R) (150 mg; 0.28 mmol), hexahydro-1*H*-furo[3,4-C]pyrrole (156 mg; 1.38 mmol), AcOH (16 µL; 0.28 mmol) in MeOH (9 mL). Then, the reaction mixture was heated at 60°C for 48 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0.3% NH_4OH, 3% MeOH, 97% DCM to 0.7% NH_4OH, 7% MeOH, 93% DCM). The pure fractions were collected and evaporated to give 79 mg which were freeze-dried with water-ACN to give 79 mg (44%) of compound 14 as a white solid and 95 mg of a mixture of compound 14 and compound 15 which was not purified further.

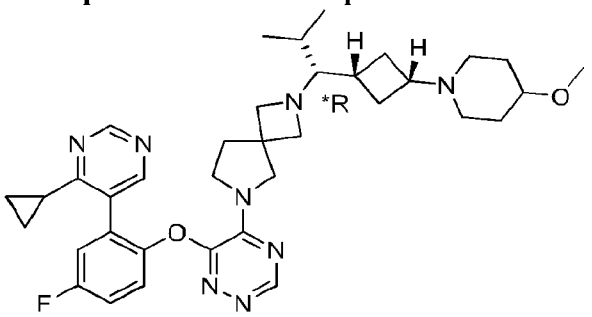
Compound 14

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.88 - 8.98 (m, 1 H), 8.36 - 8.46 (m, 2 H), 7.56 (br d, *J*=4.1 Hz, 1 H), 7.41 - 7.50 (m, 2 H), 3.66 - 3.76 (m, 3 H), 3.39 - 3.63 (m, 4 H), 3.35 (br dd, *J*=8.5, 3.7 Hz, 3 H), 2.88 - 3.16 (m, 4 H), 2.62 - 2.68 (m, 2 H), 2.53 - 2.61 (m, 2 H), 2.34 - 2.48 (m, 4 H), 2.14 - 2.22 (m, 2 H), 1.48 - 2.11 (m, 12 H), 0.91 - 1.05 (m, 3 H), 0.82 (dd, *J*=6.9, 4.9

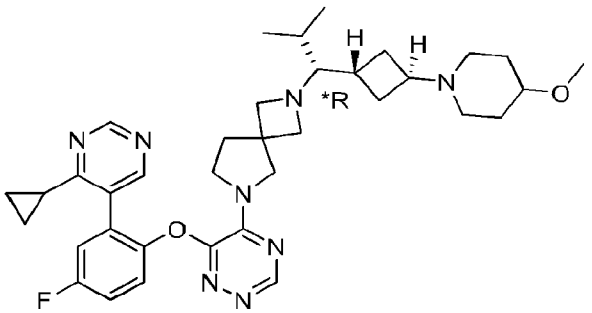
Hz, 7 H)

Preparation of Compound 16 and Compound 17

Compound 16



Compound 17



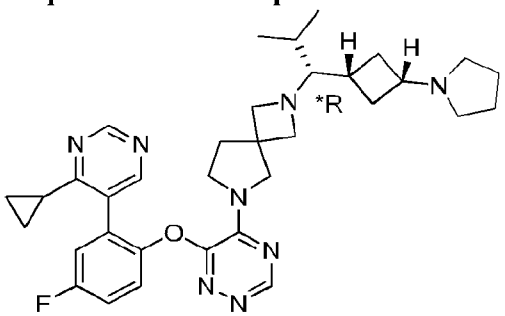
$NaBH_3CN$ (139 mg; 2.21 mmol) was added to a mixture of intermediate 38b (*R) (600 mg; 1.1 mmol), 4-methoxypiperidine (636 mg; 5.52 mmol), AcOH (64 µL; 1.1 mmol) in MeOH (15 mL). Then, the reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 6% MeOH, 94% DCM). The pure fractions were collected and evaporated to dryness to give 355 mg of compound 16 and 155 mg mixture of compound 16 and compound 17. The compound 16 (355 mg) was further purified by reverse phase chromatography(mobile phase: gradient from 40% NH_4CO_3 (0.2%), 60% ACN to 10% NH_4CO_3 (0.2%), 90% ACN). The pure fractions were collected and evaporated to dryness to give 264 mg of compound 16 which was freeze-dried with water-ACN to give 250 mg (35%) of final compound as a white solid.

Compound 16

^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 - 8.98 (m, 1H), 8.41 (br s, 2H), 7.57 (br s, 1H), 7.40 - 7.50 (m, 2H), 3.39 - 3.79 (m, 4H), 3.20 (s, 3H), 2.88 - 3.16 (m, 6H), 2.36 - 2.43 (m, 1H), 2.00 - 2.18 (m, 2H), 1.70 - 2.00 (m, 10H), 1.55 - 1.67 (m, 2H), 1.46 (q, J=9.7 Hz, 1H), 1.29 - 1.40 (m, 2H), 1.00 (br s, 3H), 0.82 (br dd, J=6.9, 3.9 Hz, 7H)

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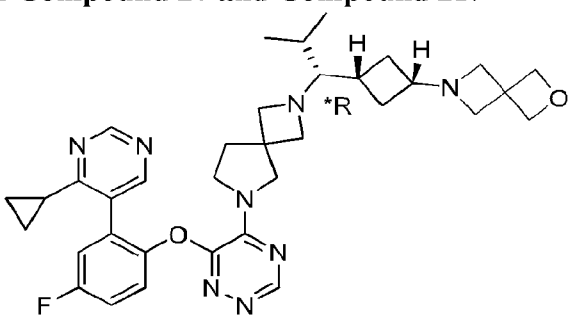
Preparation of Compound 18:



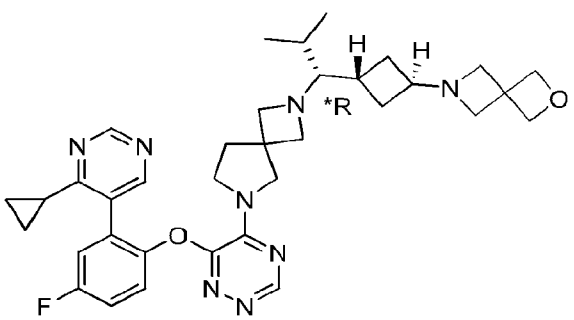
Compound 18 was prepared by an analogous procedure as was used for the synthesis of compound 12 and compound 13 starting from intermediate 38b (*R) and pyrrolidine. 40 mg (36%) of compound 18 was obtained .

Preparation of Compound 20 and Compound 21:

Compound 20



Compound 21

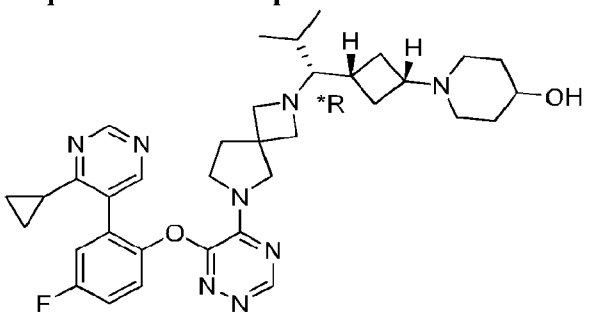


Compound 20 and Compound 21 were prepared by an analogous procedure as was used for the synthesis of Compound 7 and Compound 8 starting from intermediate 38b (*R) and 2-oxa-6-azaspiro[3.3]heptane. 45 mg (26%) of compound 20 and 45 mg (26%) of compound 21 were obtained.

Compound 20

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.93 (br s, 1H), 8.41 (br s, 2H), 7.57 (br s, 1H), 7.37 - 7.49 (m, 2H), 4.56 (s, 4H), 3.39 - 3.82 (m, 4H), 3.13 - 3.23 (m, 4H), 2.85 - 3.12 (m, 4H), 2.71 - 2.83 (m, 1H), 1.84 - 2.07 (m, 5H), 1.68 - 1.83 (m, 2H), 1.51 - 1.67 (m, 2H), 1.42 (q, J=9.8 Hz, 1H), 0.62 - 1.09 (m, 10H)

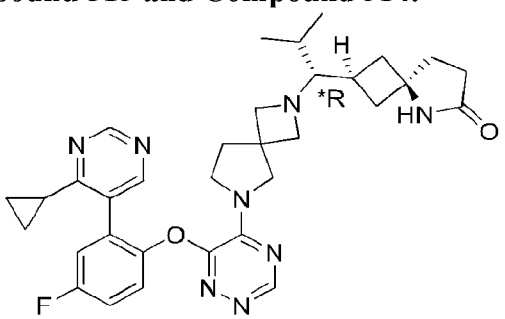
Preparation of Compound 22 :



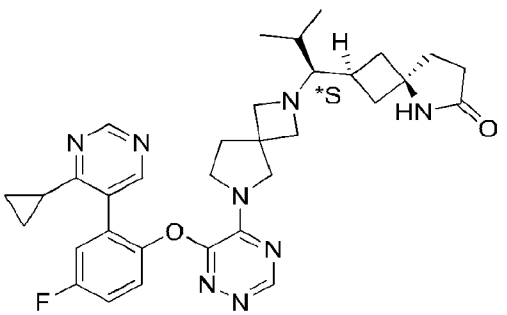
TBAF (11.5 mL; 11.3 mmol; 1M in THF) was added to a solution of intermediate 39 (1.09 g; 1.26 mmol) in MeTHF (25 mL) and the reaction was stirred at RT for 24h. The mixture was poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with EtOAc (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue (1.36 g) was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 7% MeOH, 93% DCM). The pure fractions were collected and evaporated to dryness. The residue (604 mg) was purified by reverse phase phase (mobile phase: gradient from 75% NH_4CO_3 (0.2%), 25% ACN to 35% NH_4CO_3 (0.2%), 65% ACN). The pure fractions were collected and evaporated to dryness which was freeze-dried with water-ACN to give 313 mg (40%) of compound 22 as a white solid.

Preparation of Compound 313 and Compound 314:

Compound 313 (*R):



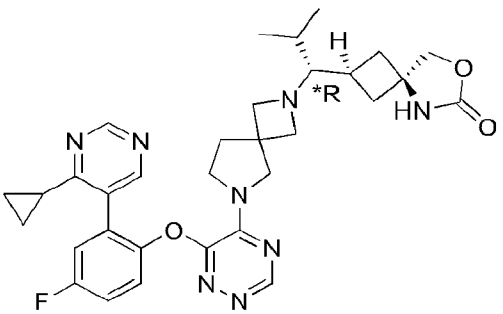
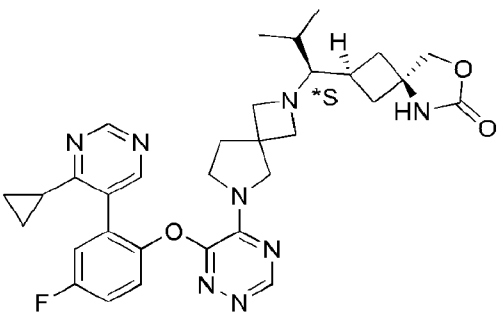
Compound 314 (*S):

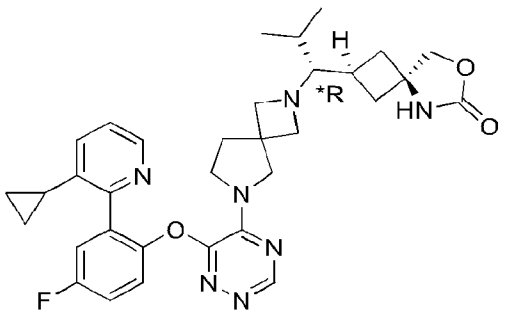
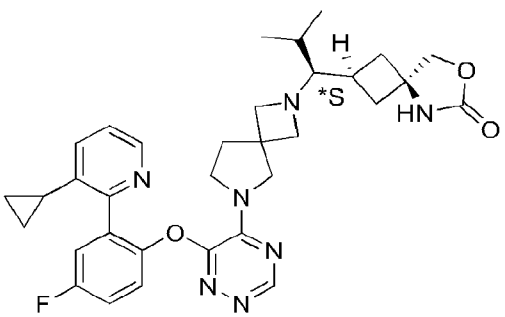
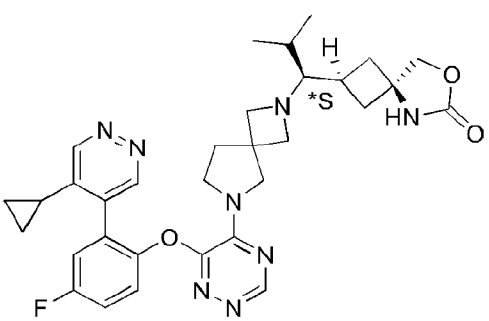


$ZnCl_2$ (450 mg, 3.30 mmol) was added to a solution of intermediate 236 (200 mg, 1.02 mmol) and intermediate 33 (450 mg, 1.07 mmol) in MeOH (10 mL). The mixture was stirred at 70 °C for 2 h. Then, $NaBH_3CN$ (200 mg, 3.18 mmol) was added. The resulting mixture was stirred at 70 °C for additional 2 h. After cooling to RT, the mixture was quenched with water and filtered.

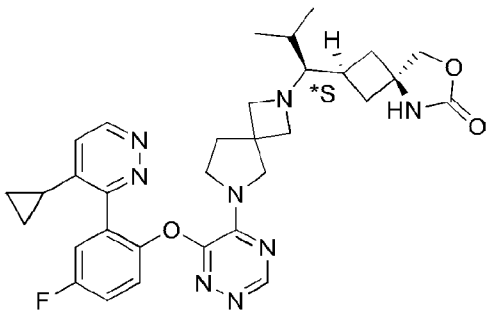
The filtrate was evaporated to give a crude product, which was first purified by preparative HPLC (column: Phenomenex Gemini NX-C18 75*30mm*3um, mobile phase A: H_2O (0.05% NH_3H_2O+10mM NH_4HCO_3), mobile phase B: ACN, gradient condition from 35% B to 65% B). The pure fractions were collected and lyophilized to give a 100 mg residue which was further separated by SFC (DAICEL CHIRALPAK AD-H (250mm*30mm, 10um); mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, A:B=50:50 at 80 mL/min). The desired fractions were collected and the volatiles were removed *in vacuo*. The residue was re-suspended in water (10 mL) and lyophilized to afford Compound 313 (23 mg, 4% yiled) and Compound 314 (30 mg, 5% yield) as a white powder.

The compounds reported below were prepared following an analogous methodology as described for Compound 313 and Compound 314 starting from the appropriate intermediates:

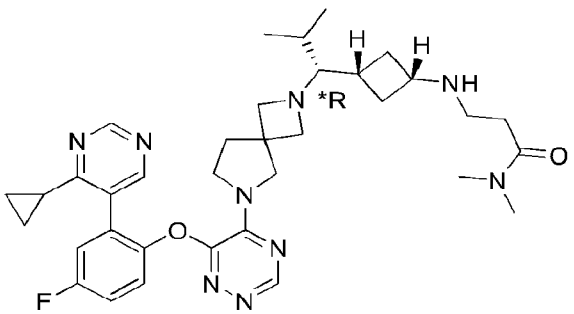
Compound Number	Structure
Compound 319	
Compound 320	
	from intermediate 33 and intermediate 245, SFC separation: DAICEL CHIRALPAK AS (250mm x 30mm, 10um), mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: isocratic 55% B (v/v)

Compound Number	Structure
Compound 321 Compound 322	  from intermediate 50 and intermediate 245, SFC condition: SFC separation: DAICEL CHIRALPAK AS (250mm x 30mm, 10um), mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: isocratic 45% B (v/v)
Compound 323	 from intermediate 296 and intermediate 245, SFC separation: Phenomenex Lux Cellulose-4 (250 x 30mm, 5um), mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: A:B=50:50 at 60 mL/min

CA 03214746 2023-10-5

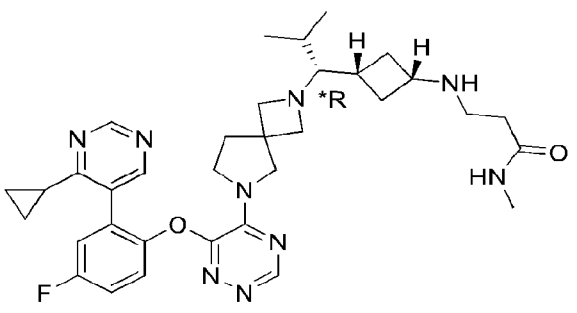
Compound Number	Structure
Compound 324	 from intermediate 297 and intermediate 245, SFC condition: DAICEL CHIRALPAK IG (250mm x 30mm, 10um), mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: A:B=65:35 at 70 mL/min

Preparation of Compound 347:

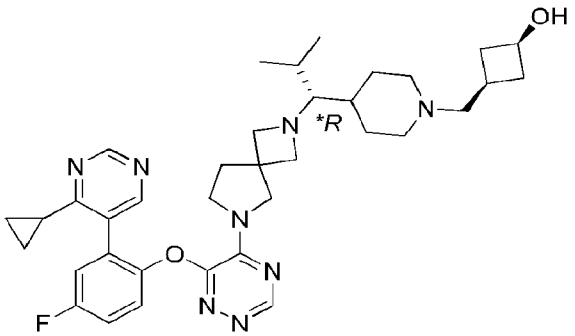


Compound 1a (150 mg, 0.275 mmol), *N,N*-dimethylacrylamide (55 mg, 0.56 mmol) and TEA (110 mg, 1.09 mmol) were added into a 10 mL sealed tube, followed with addition of EtOH (5 mL). The mixture was stirred at 70 °C for 12 h before it was cooled to RT. The reaction mixture was concentrated *in vacuo* to yield Compound 347 (200 mg, crude) as a yellow oil, which was used directly in next step without further purification.

The compound reported below was prepared following an analogous methodology as described for Compound 347 starting from Compound 1a:

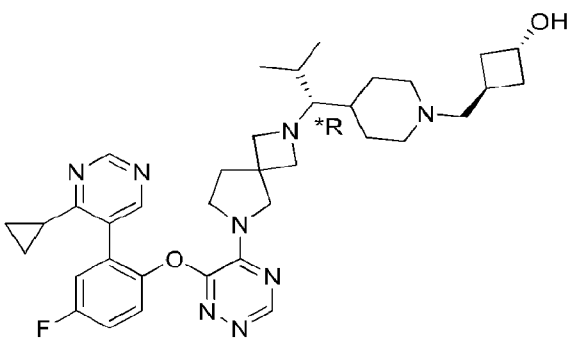
Compound 349	

Preparation of Compund 357:

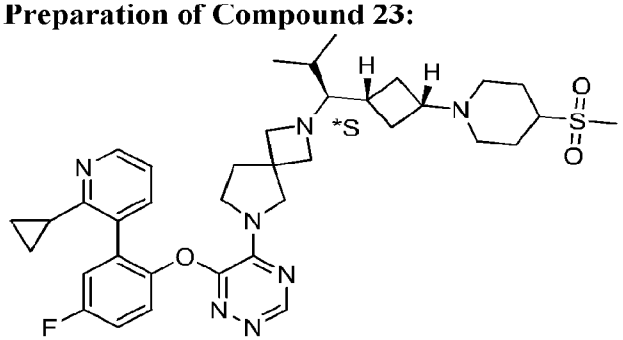


Formic acid (0.2 mL, 5.3 mmol) was added drop-wise to a solution of intermediate 270 (350 mg, 0.462 mmol) in ACN (3 mL) and H_2O (1 mL).The resulting mixture was sitrred at RT for 12 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by preparative HPLC (Welch Xtimate C18 150*30mm*5um, mobile phase A: water with 0.225% formic acid, mobile phase B: ACN, gradient condition: 8% B to 30% B v/v). The desired fractions were collected and lyophilized to afford Compound 357 (305 mg, 87% yield) as a white solid.

The compound reported below was prepared following an analogous methodology as described for Compound 357 starting from the corresponding intermediate:

Compound 358	 from intermediate 272

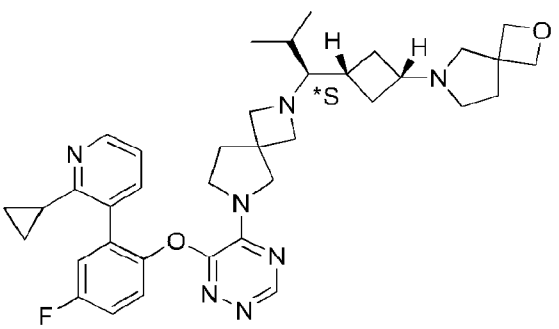
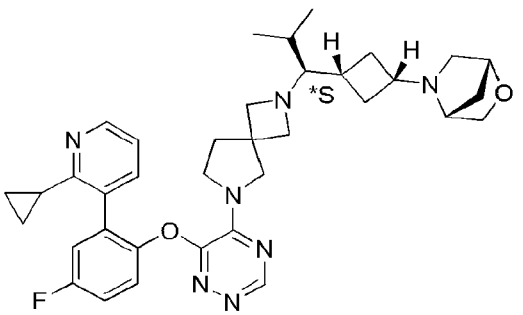
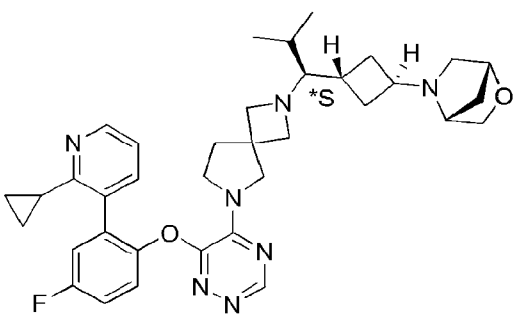
Preparation of Compound 23:



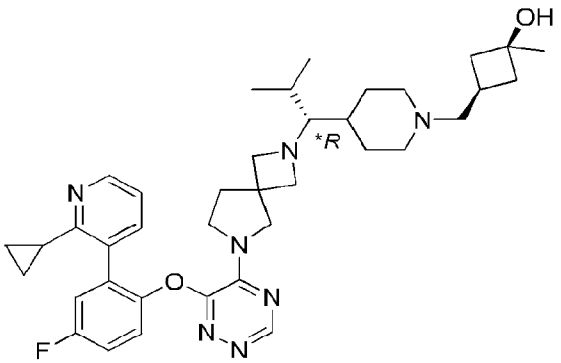
$NaBH_3CN$ (46 mg; 0.74 mmol) was added to a mixture of intermediate 46b (*S) (200 mg; 0.37

mmol), 4-(methylsulfonyl)piperidine (301 mg; 1.84 mmol), AcOH (21 µL; 0.36 mmol) in MeOH (12 mL). Then, the reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0.3% NH_4OH, 3% MeOH, 97% DCM to 0.7% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness. The resulting residue was freeze-dried with water-ACN to give 145 mg (57%) of compound 23 as a white solid.

The compounds reported below were prepared following an analogous methodology as described for Compound 23 starting from intermediate 46b (*S):

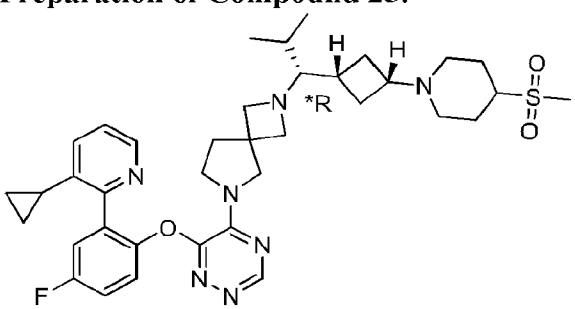
Compound Number	Structure
Compound 289	
Compound 290	
Compound 291	

Preparation of Compound 351:



To a solution of Compound 352 (40 mg, 0.072 mmol) in ACN (3 mL) were added intermediate 268 (35 mg, 0.180 mmol), K_2CO_3 (50 mg, 0.359 mmol) and KI (24 mg, 0.145 mmol). The resulting mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to RT and evaporated under reduced pressure. The resulting residue was partitioned between DCM (8 mL) and H_2O (5 mL). The aqueous layer was extracted with DCM (8 mL x 2). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by preparative HPLC (column: Phenomenex Gemini-NX 80mm x 40mm 3μm, mobile phase A: H_2O (0.05% NH_3H_2O+10mM NH_4HCO_3), mobile phase B: ACN, flow rate: 30 mL/min, gradient condition from 40% B to 70% B). The desired fractions were collected and lyophilized to afford compound 351 (14 mg, 28% yield) as a white powder.

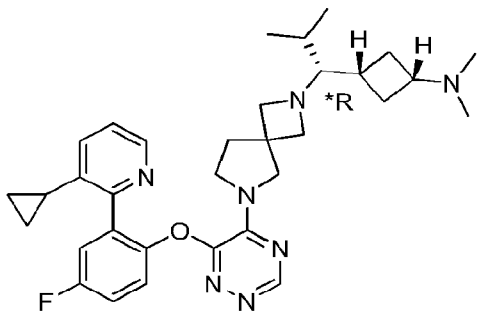
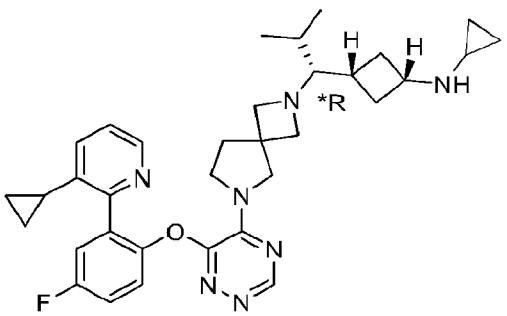
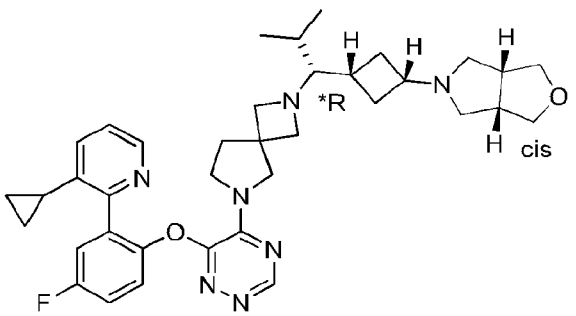
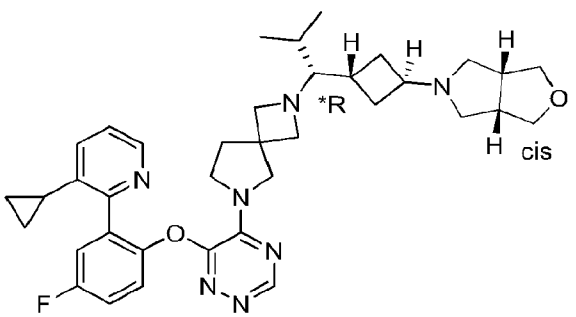
Preparation of Compound 25:

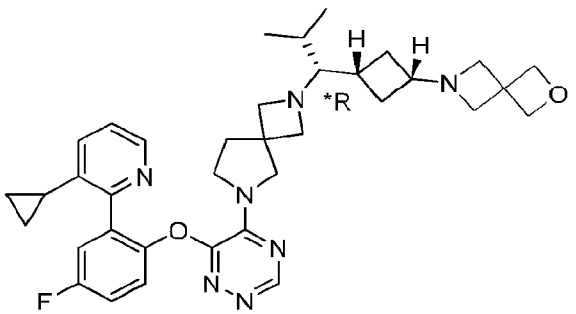
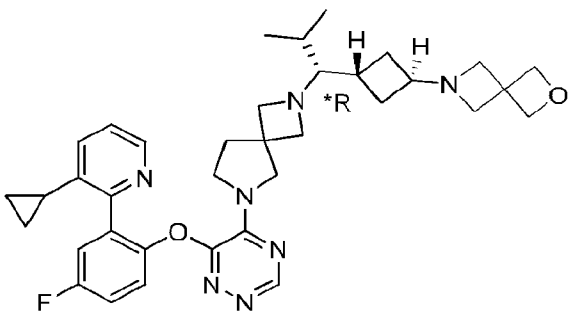
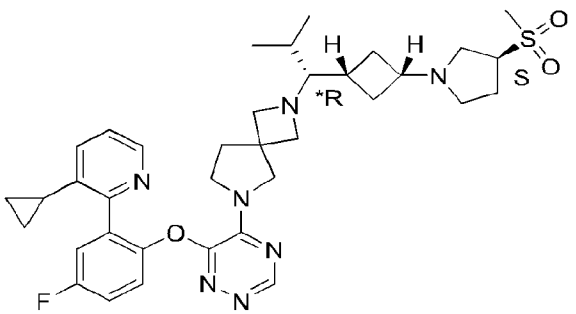
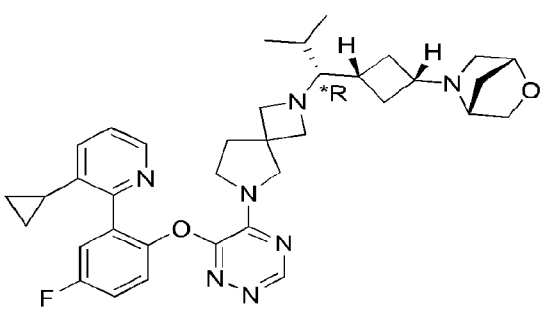


$NaBH_3CN$ (25 mg; 0.41 mmol) was added to a mixture of intermediate 52a (*R) (110 mg; 0.2 mmol), 4-(methylsulfonyl)piperidine (165 mg; 1.01 mmol), AcOH (12 μL; 0.2 mmol) in MeOH (8 mL). Then, the reaction mixture was heated at 60°C for 24 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness. The residue (72 mg) was freeze-dried with water-ACN to give 65 mg (47%) of compound 25 as white solid.

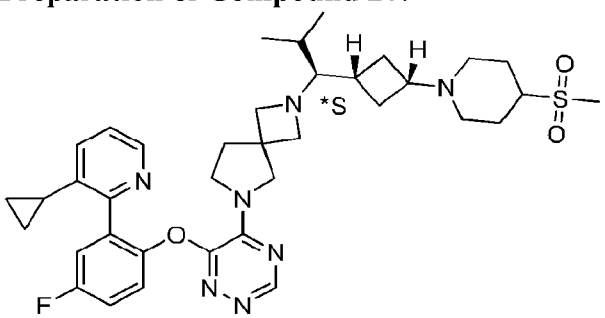
CA 03214746 2023-10-5

The compounds reported below were prepared following an analogous methodology as the one reported for the preparation of compound 25, starting from the appropriate starting materials (e.g. intermediate 52a (*R) or any other relevant intermediates):

Compound Number	Structure
Compound 147	
Compound 148	
Compound 149	
Compound 150	

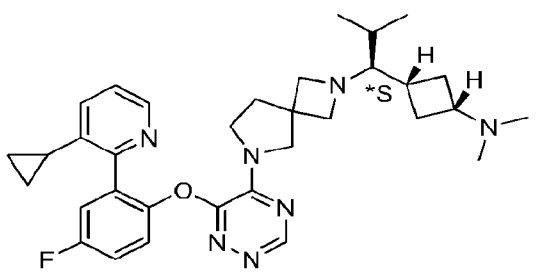
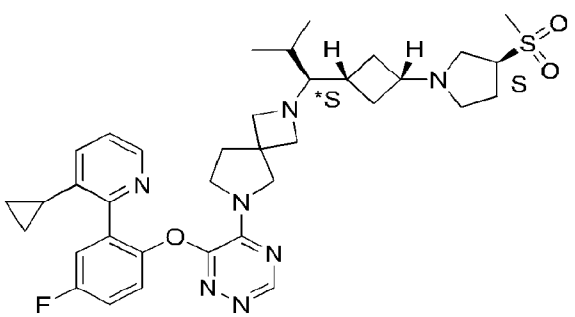
Compound Number	Structure
Compound 151	
Compound 152	
Compound 286	
Compound 288	

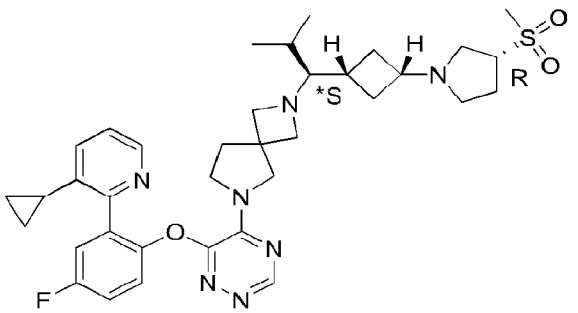
Preparation of Compound 26:



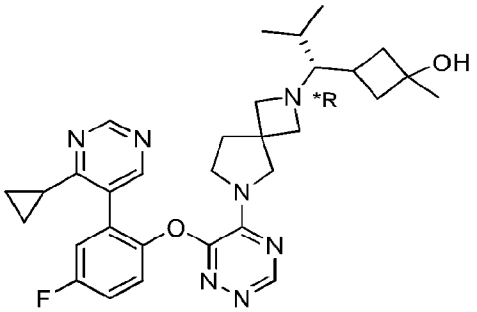
$NaBH_3CN$ (23 mg; 0.37 mmol) was added to a mixture of intermediate 52b (*S) (100 mg; 0.2 mmol), 4-(methylsulfonyl)piperidine (165 mg; 1.01 mmol), AcOH (11 µL; 0.18 mmol) in MeOH (8 mL). Then, the reaction mixture was heated at 60°C for 24 h. The reaction mixture was cooled to RT, diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 5% MeOH, 95% DCM). The pure fractions were collected and evaporated to dryness. The residue (90 mg) was freeze-dried with water-ACN to give 77 mg (61%) of compound 26 as a white solid.

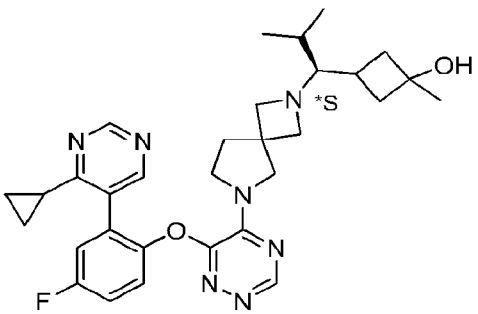
The compounds reported below were prepared following an analogous methodology as the one reported for the preparation of compound 26, starting from the appropriate starting materials (e.g. intermediate 52b (*S) or any other relevant intermediates):

Compound Number	Structure
Compound 153	
Compound 285	

Compound Number	Structure
Compound 287	

Preparation of Compound 159 and Compound 160:

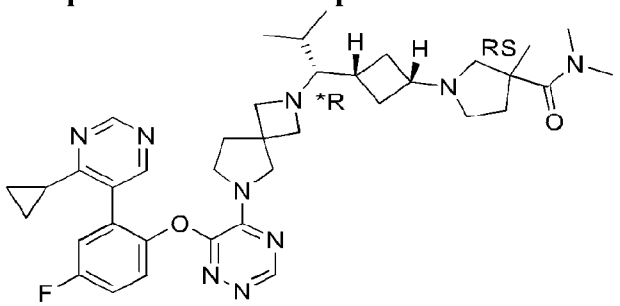
Compound 159: 

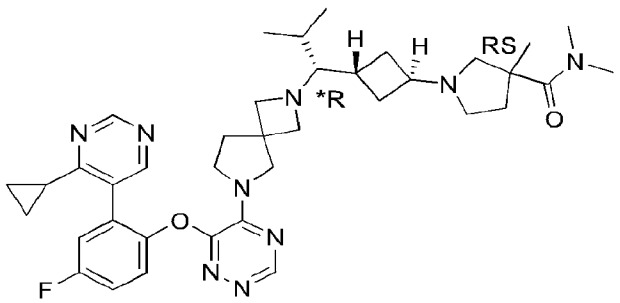
Compound 160: 

A solution of tetrabutylammonium fluoride (0.7 mL, 0.7 mmol, 1M) was added dropwise to a solution of intermediate 5(94 mg, 0.14 mmol) in THF (3 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The mixture was poured into ice water and EtOAc was added. The mixture was basified with a solution of K_2CO_3 10% and the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to give 106 mg of residue. The residue was purified by chromatography over silica gel (Mobile phase: Gradient from 98% DCM, 2% MeOH (+10% NH_4OH) to 90% DCM, 10% MeOH (+10% NH_4OH)). The product containing fractions were collected and evaporated to dryness. The resulting compound (59 mg) was separated by chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*21.2mm, Mobile phase: 75% CO_2, 25% iPOH (0.3% $iPrNH_2$)). The products containing fractions were collected, evaporated to dryness to give 26 mg which

were freeze-dried with water-ACN to give 22mg (28%) of compound 159 and 24 mg which were freeze-dried with water-ACN to give 21 mg (27%) of compound 160 as a white solid.

Preparation of Compound 161 and compound 162:

Compound 161: 

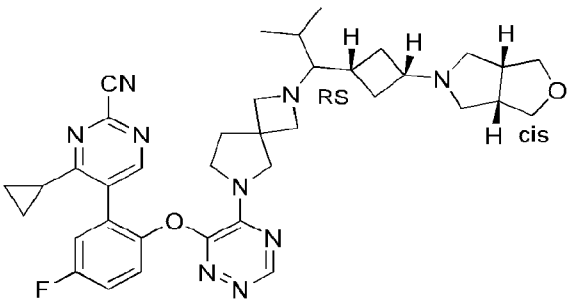
Compound 162: 

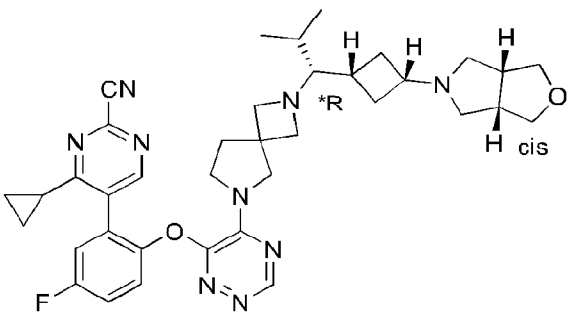
To a solution of intermediate 67 (250 mg, 0.38 mmol) in DMF (15 mL) was added T_3P (0.5 mL, 0.75 mmol, 50% purity) and Et_3N (0.16 mL, 1.13 mmol). The mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc. The mixture was washed with saturated $NaHCO_3$, brine, dried over Mg_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography over silica gel mobile phase: gradient from 0.1% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 10% MeOH, 90% DCM) . The pure fractions were collected and the solvent was evaporated under vacuum. The residue (300 mg) was purified by reverse phase (Stationary phase: YMC-actus Triart C18 10µm 30*150mm, Mobile phase: Gradient from 40% NH_4HCO_3 0.2% pH=9.5, 35% ACN, 70% MeOH to 20% NH_4HCO_3 0.2% pH=10, 40% ACN, 40% MeOH). The pure fractions were collected and the solvent was evaporated under vacuum.

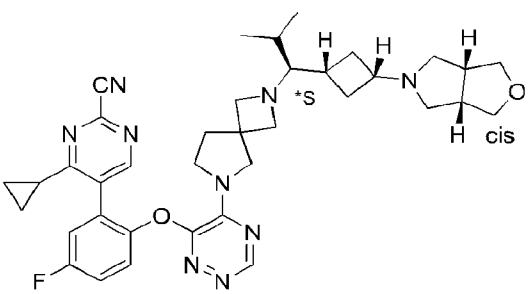
Compound 161 was partitioned between acetonitrile (2 mL) and water (8 mL). The solution was lyophilized to dryness to give 58 mg of compound 161 as a white solid.

Compound 162 was partitioned between acetonitrile (2 mL) and water (8 mL). The solution was lyophilized to dryness to give 14 mg of compound 162 as a white solid.

Preparation of Compound 166, Compound 167 and Compound 168: .

Compound 166: 

Compound 167: 

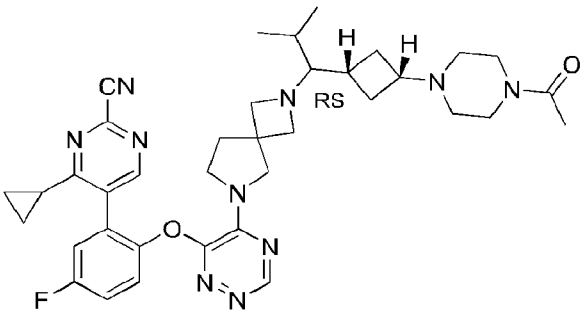
Compound 168: 

$NaBH_3CN$ (92 mg; 1.46 mmol) was added to a mixture of intermediate 75 (414 mg; 0.73 mmol), hexahydro-1*H*-furo[3,4-C]pyrrole (240 µL; 2.19 mmol) and AcOH (41 µL; 0.72 mmol) in MeOH (19 mL). The reaction mixture was stirred at 60°C for 6 hours. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and EtOAc. The mixture was extracted with EtOAc (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue (610 mg) was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.1% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness to give 140 mg of compound 166 and 82mg of an impure fraction.Compound 166 (140mg) was separated via chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*30mm, Mobile phase: 80% CO_2, 20% mixture of EtOH/iPrOH 50/50 v/v(+0.3%$iPrNH_2$)). The pure fractions were collected and evaporated to dryness yielding 12 mg of compound 167 which was freeze-dried with MeCN/water 20/80 to give 11 mg (2 %) of compound 167 as a white powder and 12 mg of compound 168 which was freeze-dried with MeCN/water 20/80 to give 11 mg (2 %) of compound 168 as a white powder.

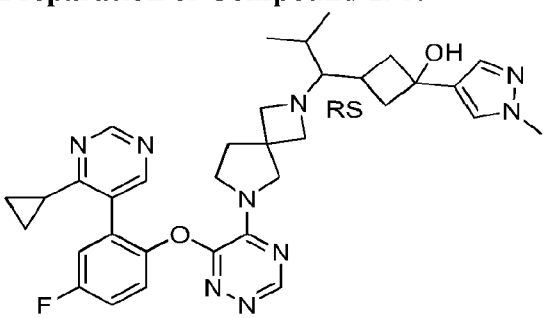
82 mg of the impure fraction of compound 166 were purified by reverse phase (Stationary phase:

YMC-actus Triart C18 10µm 30*150mm, Mobile phase: Gradient from 40% NH_4HCO_3 0.2% pH=9.5, 30% ACN, 30% MeOH to 20% NH_4HCO_3 0.2% pH=9.5, 40% ACN, 40% MeOH). The pure fractions were collected and evaporated to dryness giving additional 4 mg of the compound 166.

The compound reported below was prepared following an analogous methodology as described for compound 167 starting from intermediate 75:

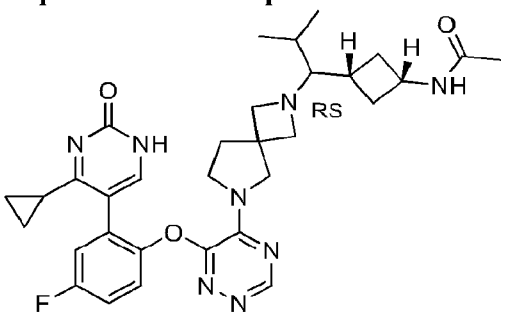
Compound Number	Structure
Compound 169	

Preparation of Compound 195:



To a solution of 4-iodo-1-methyl-*1H*-pyrazole (78 mg; 0.375 mmol) in tetrahydrofuran (2 mL) was added dropwise *n*-butyllithium (2.5M in hexane) (0.16 mL; 0.375 mmol) at -70 °C. After stirring for 20 minutes at -70° C, the reaction solution was added dropwise a solution of intermediate 38 (200 mg; 0.341 mmol, purity 92%) in tetrahydrofuran (2 mL) and stirred for 1 hour at -70°C. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with water then brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by reverse phase chromatography : (SunFire C18 OBD, 5µm, 19x250mm; mobile Phase A : Water (0.1% NH_4CO_3), mobile Phase B : ACN; Flow rate: 20 mL/min; gradient: 15% B to 40% B in 11 min) to afford 9.6 mg (4%) of compound 195 as a light yellow solid.

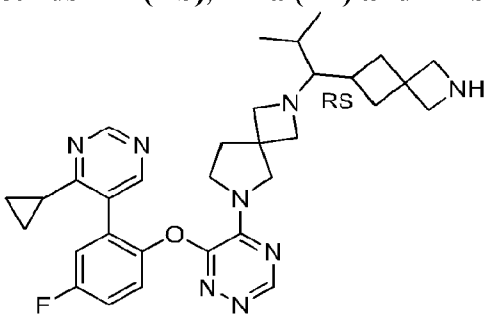
Preparation of Compound 196:



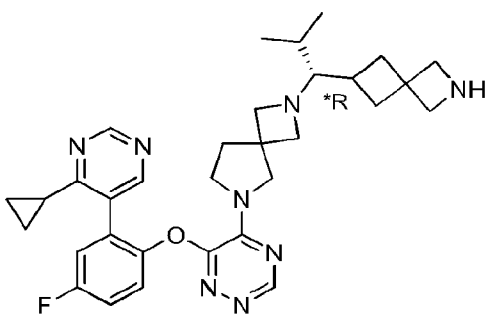
To a solution of Compound 500 (350 mg; 0.568 mmol) in acetonitrile (17 mL) was added TMSI (1.6 g; 11.350 mmol). The reaction mixture was stirred for 2 h at room temperature, quenched with water (20 mL), adjusted to pH 8 - 9 with NaOH solution (1 N) and extracted with 8 x 10 mL of dichloromethane. The organic layers were combined, dried and concentrated under reduced pressure. The resulting crude product was purified by reverse phase chromatography (XBridge Prep OBD C18 Column, 19 x 250mm,5um; mobile phase A: Water (10mmol/L NH_4HCO_3+0.1%NH_4OH), mobile phase B: ACN; Flow rate: 20 mL/min; gradient: 30% B to 36% B in 7.5 min). The product fractions were concentrated and lyophilized to give 95.3 mg (26%) of compound 196 as an off white solid.

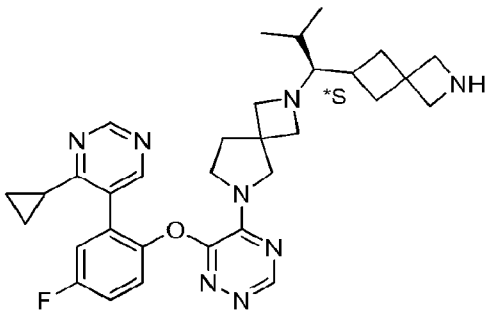
Preparation of compounds 197 (RS), 197a (*R) and 197b (*S):

Compound 197 (RS):



Compound 197a (*R):

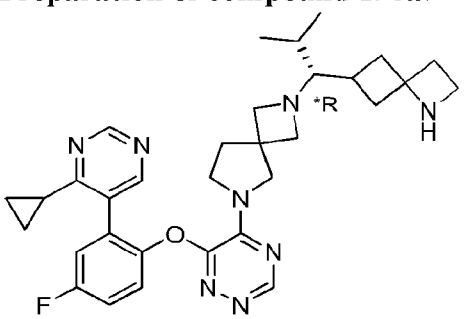




Compound 197b (*S):

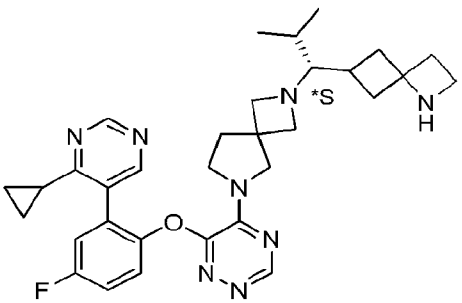
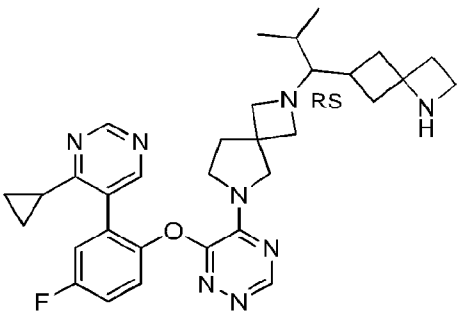
At 0°C, TFA (4.5 mL; 58.1 mmol) was added to a solution of intermediate 63 (1.95 g; 2.9 mmol) in DCM (40 mL). The reaction mixture was stirred overnight at room temperature. The solvents were evaporated and the residue was dissolved in water. Then, the solution was basified with a solution of NaOH 1M until pH=9-10. After stirring for 10 minutes at room temperature, the resulting mixture was extracted with DCM (3x). The combined organics layers were washed with brine and dried over $MgSO_4$, filtered and evaporated till dryness. The residue (2g) was purified by chromatography over silica gel (Mobile phase: Gradient from 95% DCM, 5% MeOH (+10% NH4OH) to 90% DCM, 10% MeOH (+10% NH4OH)). The pure fractions were collected, and the solvent was evaporated. The compound 197 (RS) (1.13g, 68%) was purified by chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*30mm, Mobile phase: 55% CO_2, 45% mixture of ACN/iPrOH 20/80 v/v(+0.3% $iPrNH_2$)). The pure fractions were collected and the solvent was evaporated till dryness to give 405 mg (25%) of compound 197 (*R) and 388 mg (24%) of compound 197b (*S).

Preparation of compound 198a:

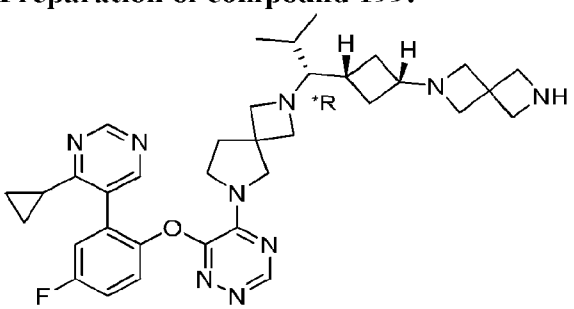


At 0°C, TFA (0.4 mL; 4.2 mmol) was added to a solution of Compound 496a (*R) (143 mg; 0.2 mmol) in DCM (40 mL). The reaction mixture was stirred overnight at room temperature. The solvents were evaporated and the residue was dissolved in water. Then, the solution was basified with a solution of NaOH 1M until pH=9-10. After stirring for 10 minutes at room temperature, The resulting mixture was extracted with DCM (3x). The combined organics layers were washed with brine and dried over $MgSO_4$, filtered and evaporated till dryness. The residue (2g) was purified by chromatography over silica gel (Mobile phase: Gradient from 95% DCM, 5% MeOH (+10% NH_4OH) to 90% DCM, 10% MeOH (+10% NH_4OH)). The pure fractions were collected, and the solvent was evaporated to give 136 mg of compound 198a.

The compounds reported below were prepared following an analogous methodology starting from Compound 496b (*S) :

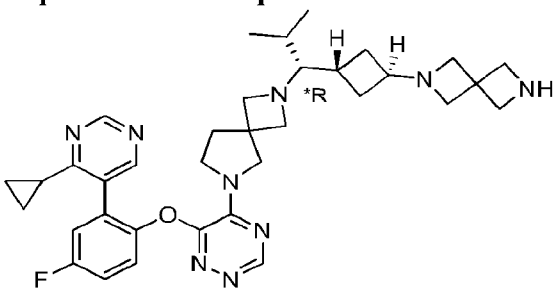
Compound Number	Structure
Compound 198b	
Compound 198	

Preparation of compound 199:



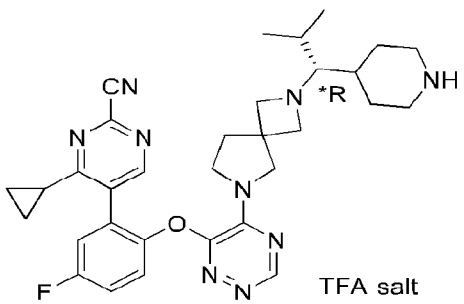
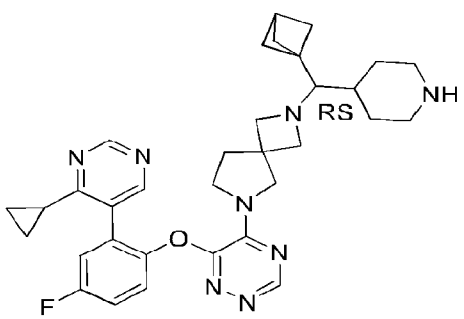
TFA (1.96 mL; 25.62 mmol) was added to a solution of Compound 497 (930 mg; 1.28 mmol) in DCM (25 mL) at 0°C and the reaction mixture was stirred at room temperature for 18h. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1h. The mixture was filtered through Chromabond® and the filtrate was evaporated to give 802 mg of compound 199 (quantitative) as a white foam .

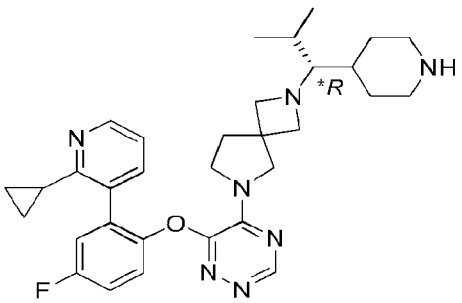
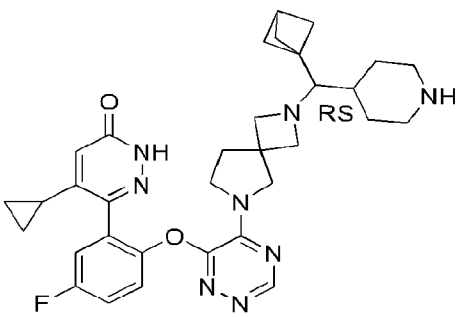
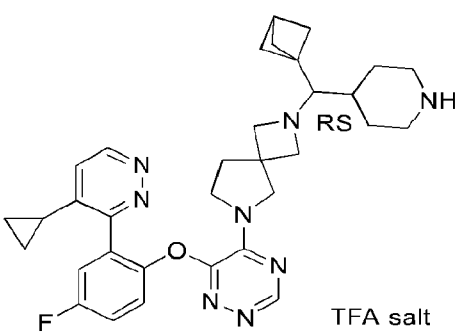
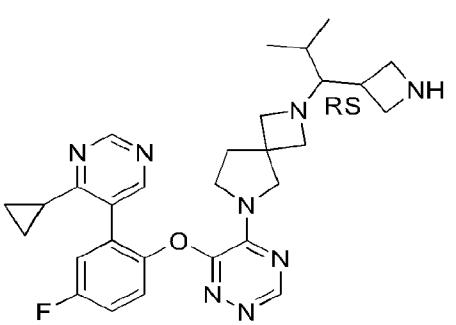
Preparation of compound 199a:



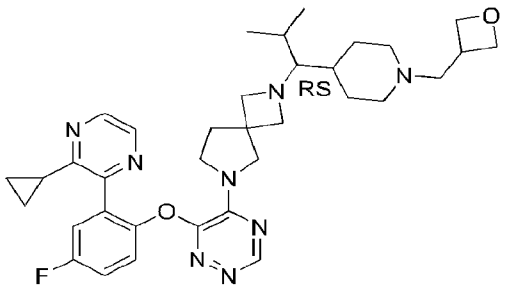
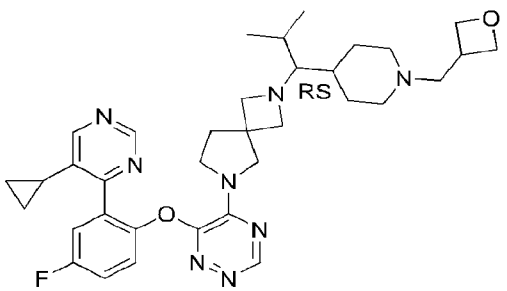
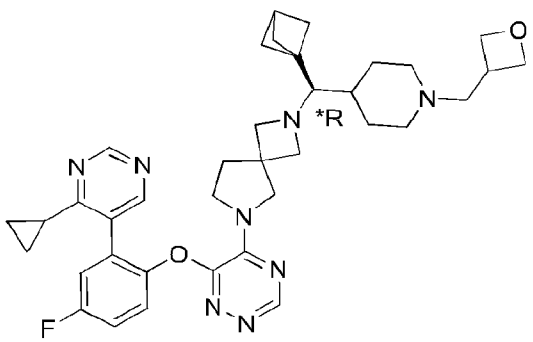
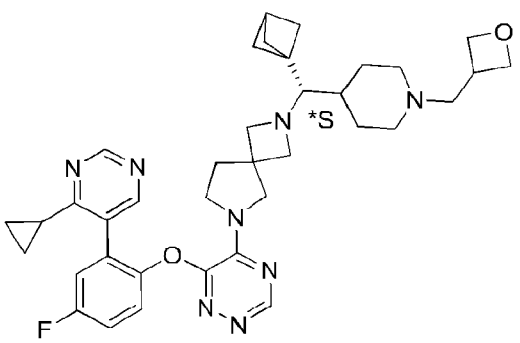
TFA (106 µL; 1.38 mmol) was added to a solution of Compound 498 (50 mg; 0.069 mmol) in DCM (1.5 mL) at 0°C and the reaction mixture was stirred at room temperature for 18h. The residue was dissolved in DCM and basified with a 30% aqueous solution of NH_4OH at 0-5°C. The mixture was stirred at rt for 1h. The mixture was filtered through Chromabond® and the filtrate was evaporated to give 47 mg of compound 199a (quantitative) as a white foam.

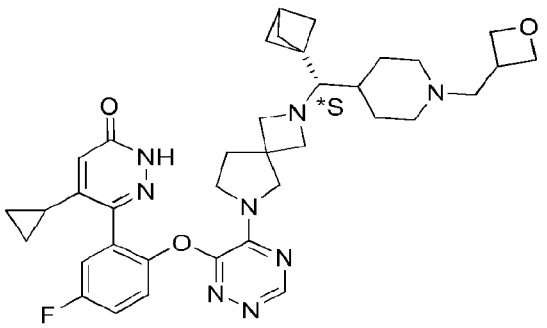
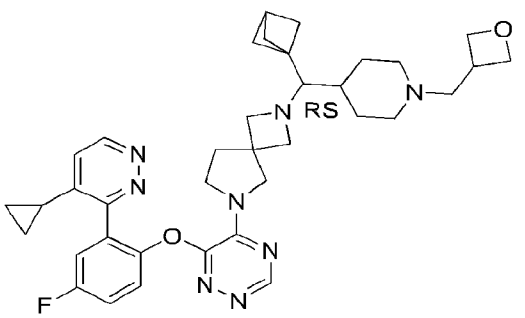
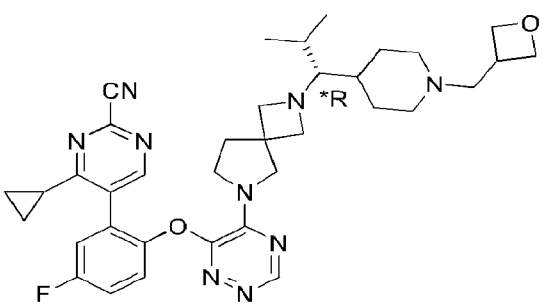
The compounds reported below were prepared following an analogous methodology as described for Compound 199 starting from the corresponding intermediates:

Compound Number	Structure
Compound 334	 TFA salt from intermediate 73
Compound 337	 from intermediate 251

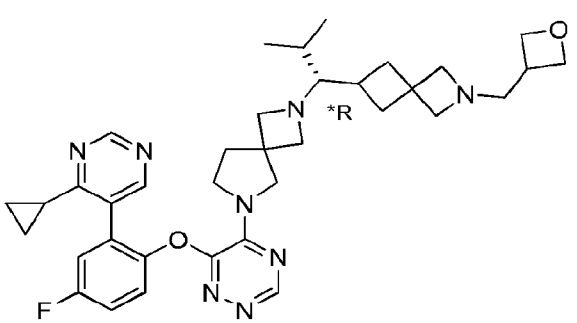
Compound Number	Structure
Compound 352	 from intermediate 44
Compound 367	 from intermediate 302
Compound 368	 from intermediate 297
Compound 355	 from intermediate 33

The compounds in the table below were prepared using an analogous method as described for the preparation of intermediate 29 starting from the corresponding starting materials.

Compound number	Structure
Compound 202	 Using intermediate 88
Compound 203	 Using intermediate 93
Compound 335	
Compound 336	 from Compound 337, SFC separation: DAICEL CHIRALPAK AS-H (250mm x 30mm, 5um); Mobile phase: A: Supercritical CO_2, B: Neu-EtOH, A:B =55:45 at 80 mL/min

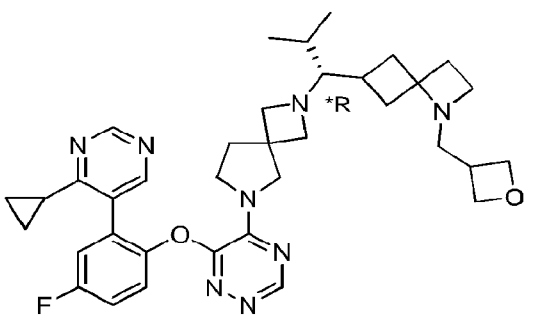
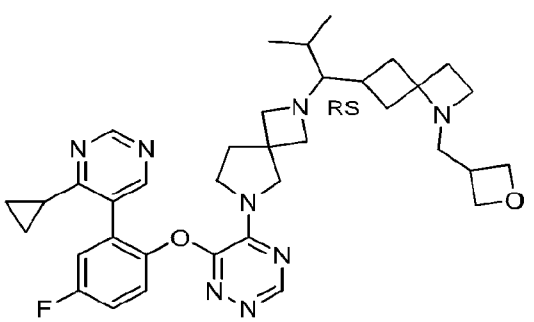
Compound number	Structure
Compound 339	 from Compound 367, SFC separation: DAICEL CHIRALPAK IG (250mm*30mm, 10um); Mobile phase: A: Supercritical CO_2, B: 0.1%NH_3H_2O EtOH, A:B =45:55 at 80 mL/min
Compound 340	 from Compound 368
Compound 333	 from Compound 334

Preparation of Compound 154:

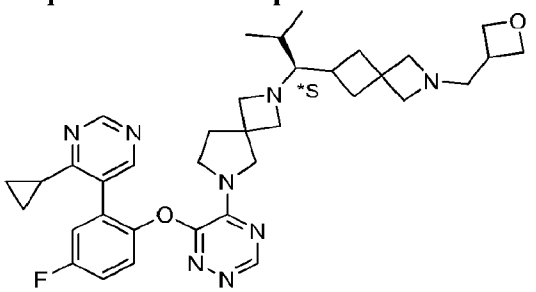


$NaBH_3CN$ (85 mg; 0.4 mmol) was added to a mixture of compound 197a (*R) (152 mg; 0.27 mmol), oxetane-3-carbaldehyde (24 µL; 0.35 mmol; 2M) in MeOH (6 mL). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (177 mg) was purified by chromatography over silica gel (mobile phase: gradient from 0.1% NH_4OH, 5% MeOH, 95% DCM to 0.1% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected, evaporated to dryness and freeze-dried with a mixture of water-ACN to give 75 mg (45%) of compound 154 as a white solid.

The compounds reported below were prepared following an analogous methodology as reported for the preparation of compound 154 starting from the corresponding compounds:

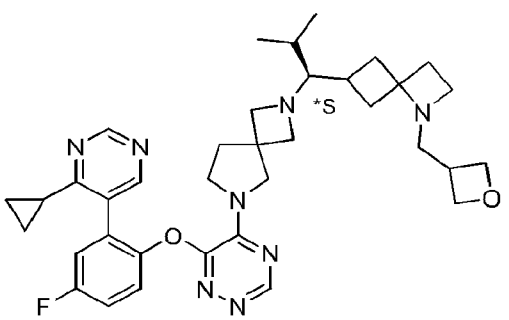
Compound number	Structure
Compound 155	 From compound 198a
Compound 156	 From compound 198

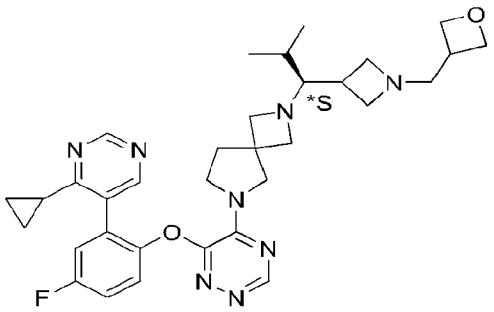
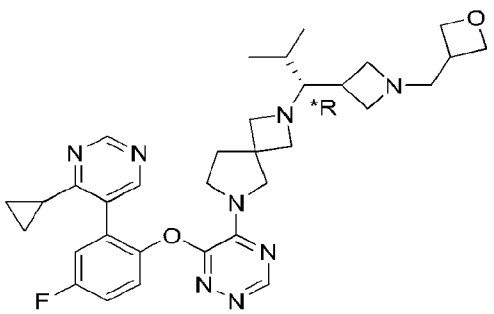
Preparation of Compound 157:



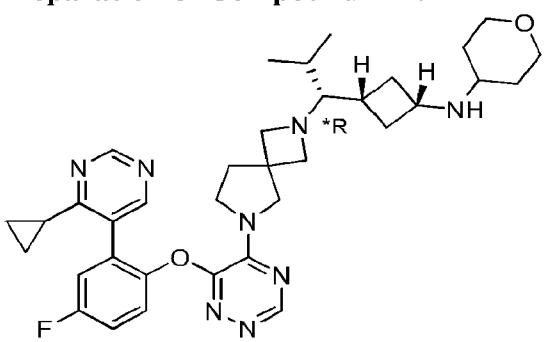
$NaBH_3CN$ (85 mg; 0.4 mmol) was added to a mixture of compound 197b (*S) (152 mg; 0.27 mmol), oxetane-3-carbaldehyde (24 µL; 0.35 mmol; 2M) in MeOH (6 mL). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (175 mg) was purified by chromatography over silica gel (mobile phase: gradient from 0.1% NH_4OH, 5% MeOH, 95% DCM to 0.1% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness. was freeze-dried with a mixture of water-ACN to give 130 mg (76%) of final compound 157 as a white solid.

The compound reported below was prepared following an analogous methodology as decribed for compound 157, starting from the corresponding compounds:

Compound number	Structure
Compound 158	 from compound 198b

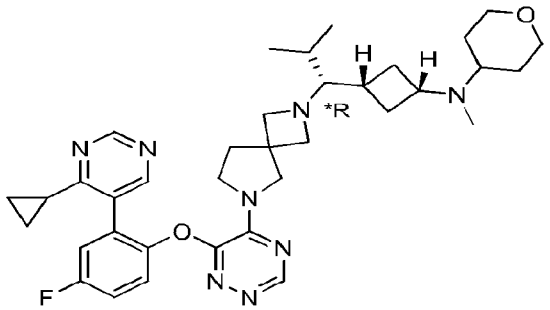
Compound number	Structure
Compound 353	
Compound 354	
	from Compound 355, SFC separation: DAICEL CHIRALPAK AD-H (250mm x 30mm, 5um); mobile phase: A: Supercritical CO_2, B: 0.1% NH_3H_2O EtOH, eluent: A:B=70:30 at 60 mL/min

Preparation of Compound 163:



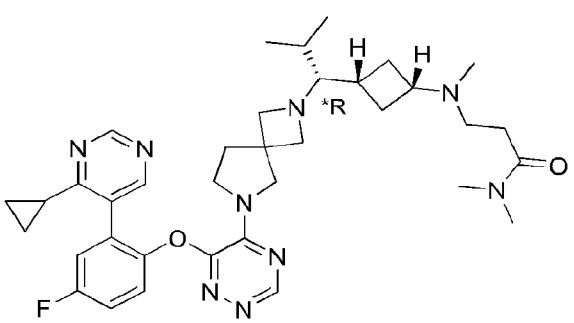
$NaBH(OAc)_3$ (175 mg; 0.83 mmol) was added to a mixture of compound 1a (300 mg; 0.55 mmol), tetrahydro-4*H*-pyran-4-one (60 µL; 0.67 mmol) in DCE (10 mL). Then, the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue (350 mg) was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness to give 230 mg (66%) of compound 163.

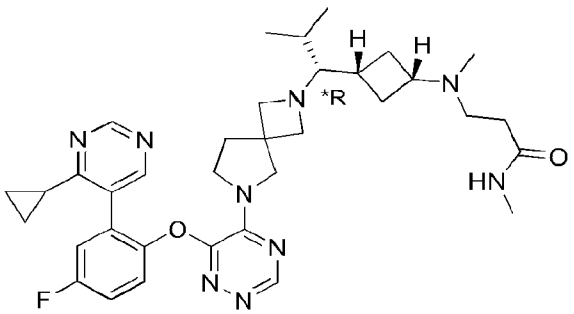
Preparation of Compound 164:



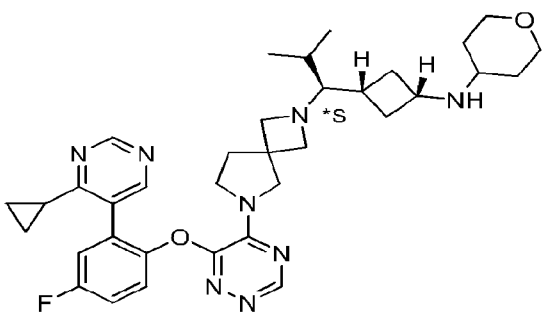
$NaBH(OAc)_3$ (95 mg; 0.45 mmol) was added to a mixture of compound 163 (57 mg; 0.09 mmol), formaldehyde 37% in water (95 µL; 0.94 mmol) and molecular sieves 4 A (60 mg) in DCE (10 mL). Then, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The solution was filtered through a pad of Celite® The organic layer was extracted with DCM, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (44 mg) was purified by reverse phase (Stationary phase: YMC-actus Triart C18 10µm 30*150mm, Mobile phase: Gradient from 45% $NH4HCO_3$ 0.2% , 55% ACN to 25% $NH4HCO_3$ 0.2% , 75% ACN). The pure fractions were collected and evaporated to dryness. Compound 164was partitioned between acetonitrile (2 mL) and water (8 mL). The solution was lyophilized to dryness to give 18 mg (31 %) of compound 164 as a white solid.

The compounds reported below were prepared following an analogous methodology as described for Compound 164, starting from the corresponding compounds:

Compound Number	Structure
Compound 348	 from Compound 347

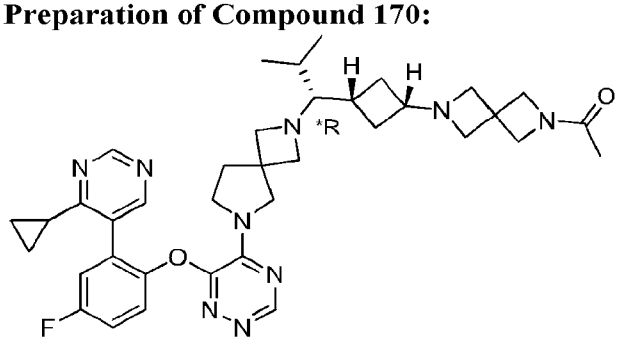
Compound Number	Structure
Compound 350	 from Compound 349

Preparation of Compound 165:



$NaBH(OAc)_3$ (187 mg; 0.89 mmol) was added to a mixture of compound 1b (320 mg; 0.59 mmol), tetrahydro-4H-pyran-4-one (65 µL; 0.71 mmol) in DCE (12 mL). Then, the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with DCM and poured onto a 10% aqueous solution of K_2CO_3. The organic layer was extracted with DCM (3X), dried over $MgSO_4$, filtered and evaporated till dryness. The residue (380 mg) was purified by chromatography over silica gel (mobile phase: gradient from 0% NH_4OH, 0% MeOH, 100% DCM to 0.7% NH_4OH, 10% MeOH, 90% DCM). The pure fractions were collected and evaporated to dryness to give 170 mg (47%) of compound 165.

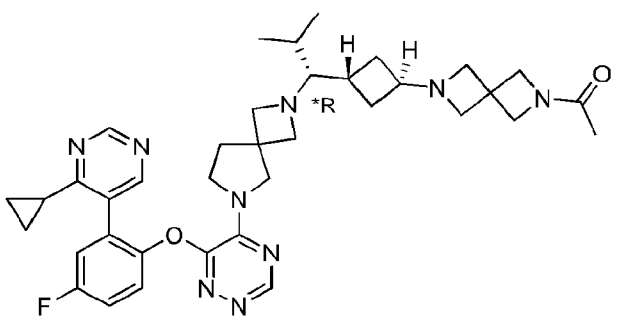
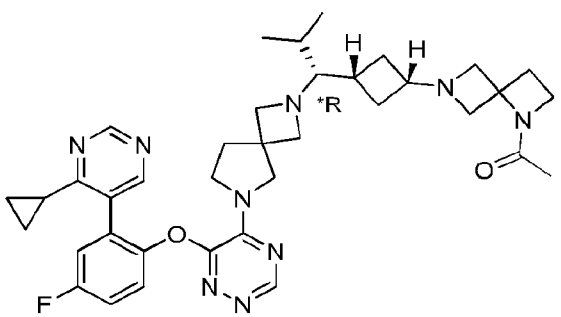
Preparation of Compound 170:

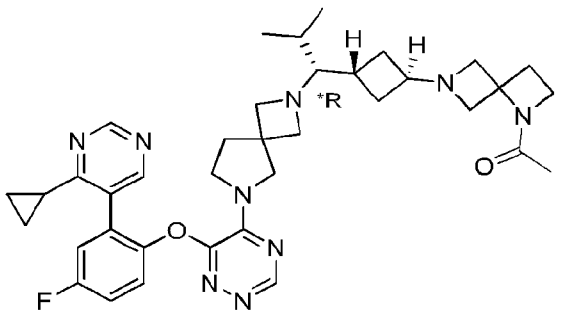
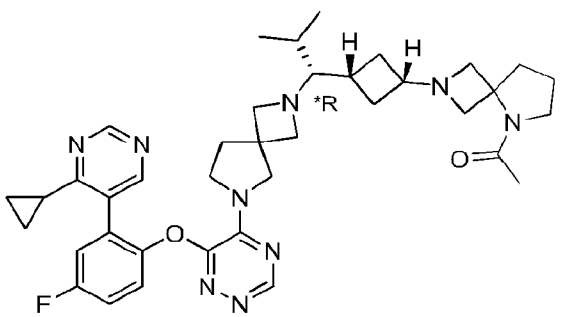
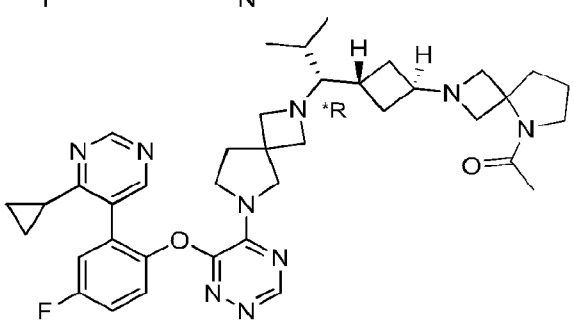


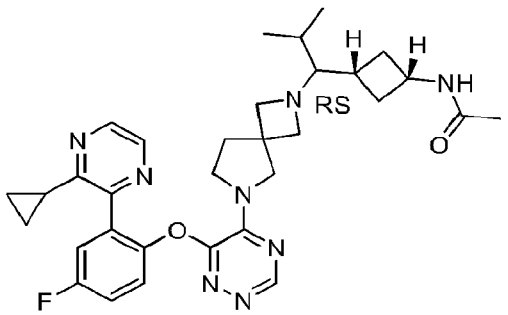
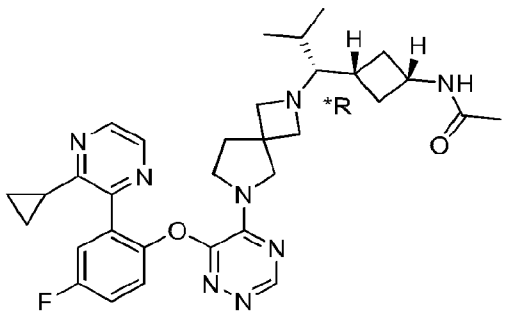
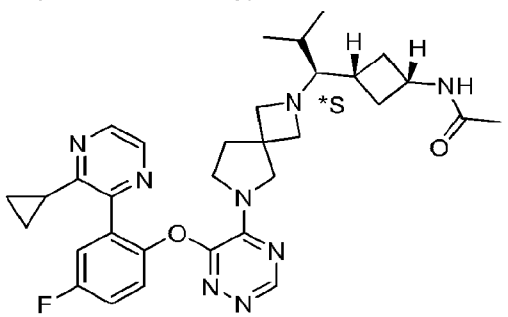
T_3P (1.14 mL; 1.92 mmol) was added to a solution of compound 199 (800 mg; 1.28 mmol), acetic acid (81 µL; 1.41 mmol) and DIPEA (1.10 mL; 6.39 mmol) in DCM (8.4 mL). The reaction mixture was stirred at rt for 18h, poured into a 10% aqueous solution of $NaHCO_3$ and DCM. The mixture was filtered through chromabond® and the filtrate was evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 40 g; mobile phase: gradient from 98% DCM, 2% MeOH to 92% DCM, 8% MeOH). The pure fractions were collected, evaporated to dryness and freeze dried (ACN/water) yielding 145 mg of compound 170 (17%) as a white solid.

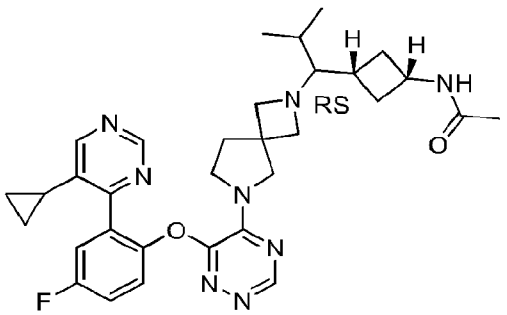
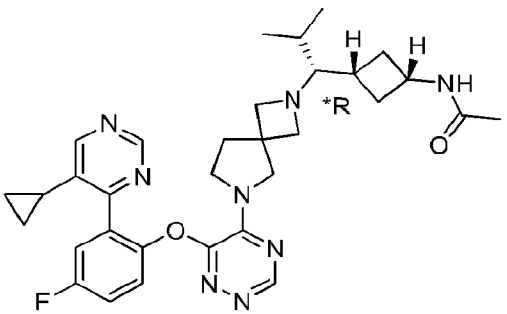
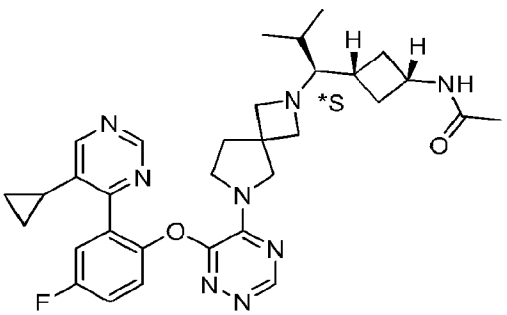
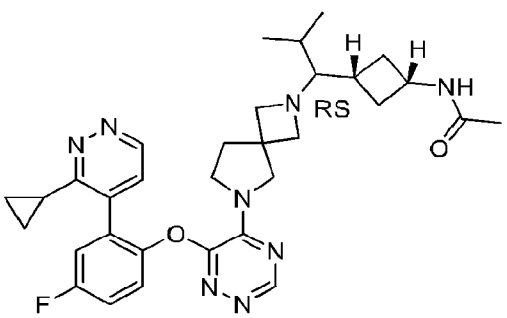
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.93 (br s, 1H), 8.41 (br s, 2H), 7.57 (br s, 1H), 7.38 - 7.50 (m, 2H), 4.12 (s, 2H), 3.84 (s, 2H), 3.40 - 3.75 (m, 4H), 2.85 - 3.21 (m, 8H), 2.74 - 2.84 (m, 1H), 1.86 - 2.02 (m, 5H), 1.73 - 1.84 (m, 2H), 1.71 (s, 3H), 1.55 - 1.66 (m, 2H), 1.44 (q, *J*=9.7 Hz, 1H), 0.65 - 1.10 (m, 10H)

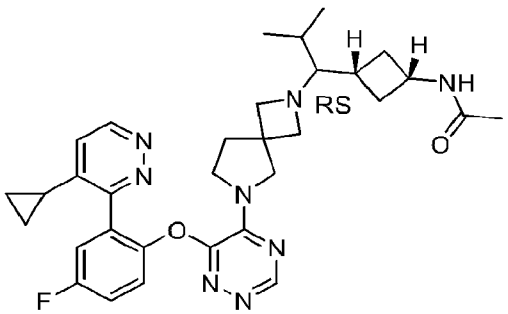
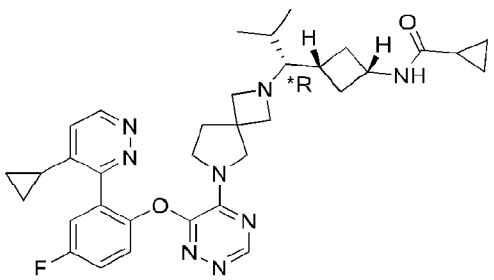
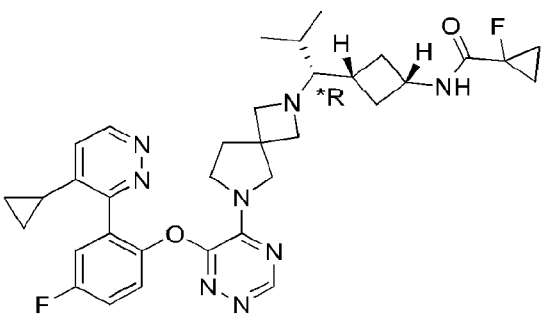
The compounds in the table below were prepared using an analogous method as described for the preparation of compound 170 starting from the corresponding compounds or intermediates.

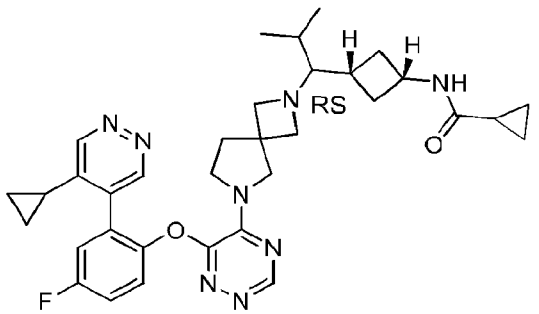
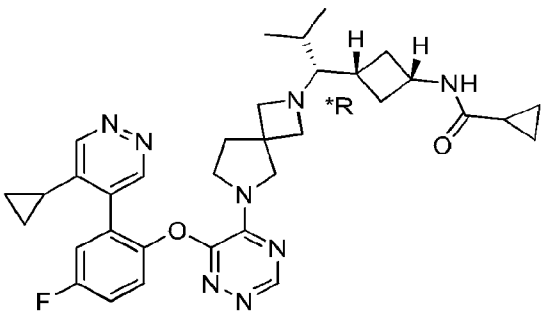
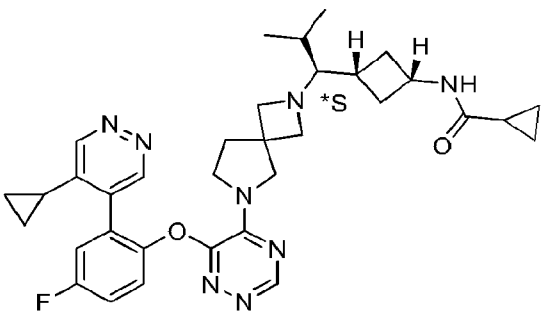
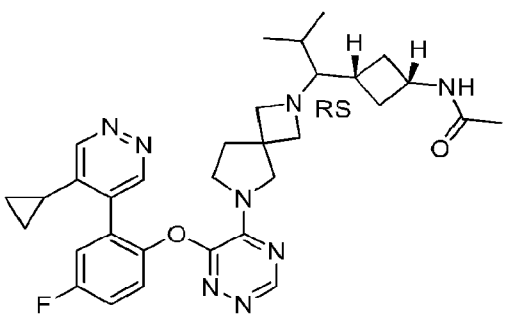
Compound number	Structure
Compound 171	 From compound 199a
Compound 172	 From intermediate 38 doing reductive amination with *tert*-butyl 1,6-diazaspiro[3.3]heptane-1-carboxylate hemioxalate

Compound number	Structure
Compound 173	 From intermediate 38 doing reductive amination with tert-butyl 1,6-diazaspiro[3.3]heptane-1-carboxylate hemioxalate
Compound 174	
Compound 175	 From intermediate 38 doing reductive amination with 2,5-Diazaspiro[3.4]octane-5-carboxylic acid *tert*-butyl ester

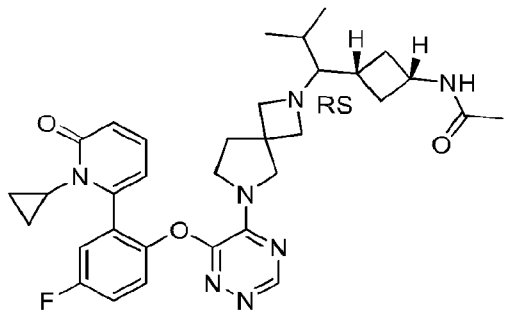
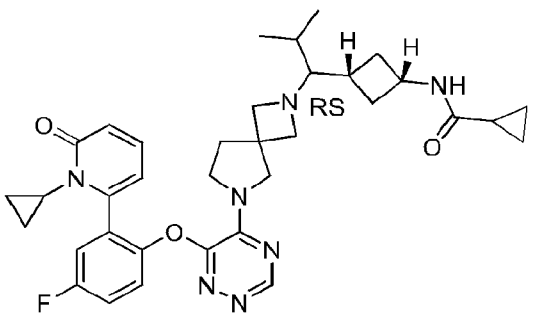
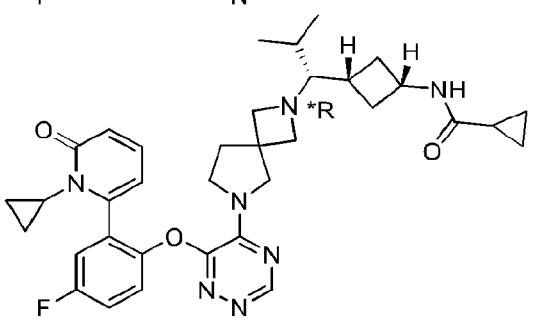
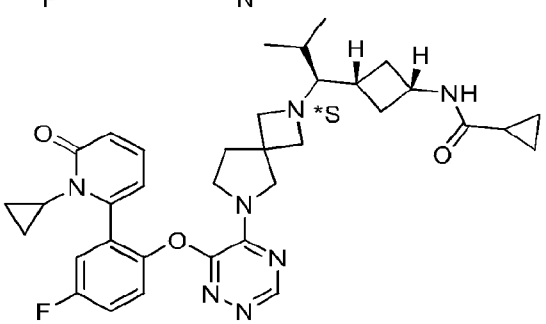
Compound number	Structure
Compound 176	
Compound 177	
Compound 178	
	from intermediate 88 using acetic anhydride as acylating agent. Chiral separation : (R,R)-WHELK-O1-Kromasil(02), 5cm*25cm(5um); mobile Phase A: 10mM NH_3 in methyl tert-butyl ether (MTBE), Mobile Phase B: EtOH; Flow rate:20 mL/min; gradient:20% B for 22 min

Compound number	Structure
Compound 179	
Compound 180	
Compound 181	 from intermediate 93 Chiral separation : (R,R)Whelk-01, 21.1*250mm,5um; mobile phase A:MTBE (10mM NH_3-MeOH), mobile phase B: EtOH; flow rate:20 mL/min; 15% B for 34 min)
Compound 182	 from intermediate 101

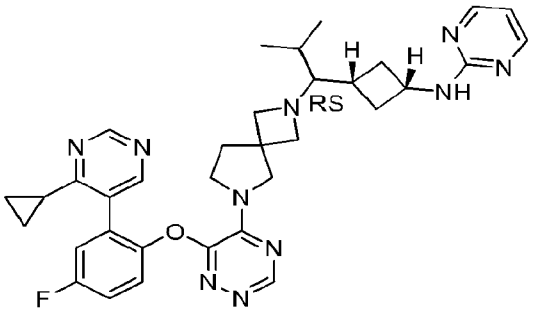
Compound number	Structure
Compound 183	 from intermediate 106
Compound 304	 from intermediate 106
Compound 305	 from intermediate 106

Compound number	Structure
Compound 184 Compound 185 Compound 186	   from intermediate 109 Chiral Prep-HPLC (CHIRAL ART Cellulose-SB, 2 x 25mm,5μm; mobile Phase A:Hex (8 mmol/L NH_3.MeOH), mobile Phase B:EtOH; Flow rate:20 mL/min; 35% B for 13 min)
Compound 187	 from intermediate 109

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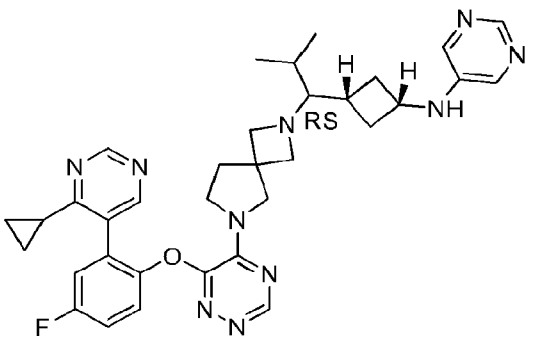
Compound number	Structure
Compound 188	 from intermediate 113
Compound 189	
Compound 190	
Compound 191	 from intermediate 113 Chiral separation ((R,R)-Whelk-01, 2.12*25cm,5um; mobile mhase A: 2mM NH_3 in methyl tert-butyl ether (MTBE), mobile phase B: EtOH; Flow rate:20 mL/min; 20% B for 26 min)

Preparation of compound 192:



To a solution of compound 1 (50 mg; 0.045 mmol) in ethanol (1.0 mL) were added 2-bromopyrimidine (14 mg; 0.09 mmol) and *N,N*-diisopropylethylamine (0.15 mL; 0.90 mmol). The resulting mixture was stirred at 80 °C for 22 hours. The reaction mixture was cooled to RT, quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by reverse phase chromatography (Xbridge prep C18 5um 19*150mm; mobile phase A: 10 mmol/L aqueous NH_4HCO_3, mobile phase B: ACN; Flow rate: 25 ml/min; 44% B). The fractions containing the desired product were combined and lyophilized to give 2.7 mg (10%) of compound 192 as a white solid.

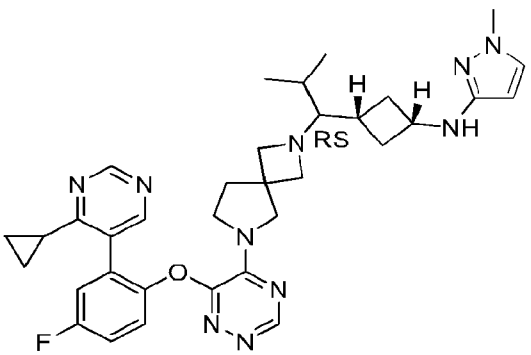
Preparation of Compound 193:



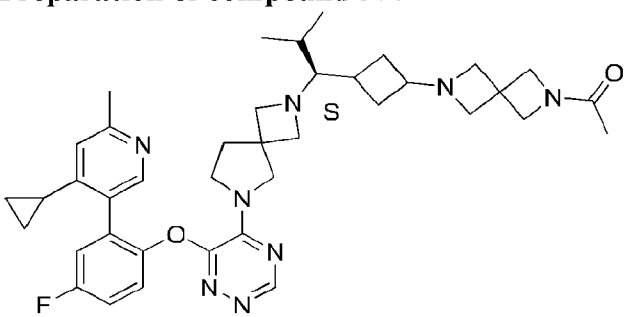
To a solution of compound 1 (300 mg; 0.55 mmol) in toluene (10 mL) were added 5-bromopyrimidine (175 mg; 1.1 mmol), Brettphos (59 mg; 0.11 mmol), BrettPhos-Pd G3 (100 mg; 0.11 mmol) and cesium carbonate (538 mg; 1.65 mmol). The resulting mixture was stirred at 100 °C for 18 hours under nitrogen atmosphere. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by revrese phase chromatography (Xbridge prep C18 5um 19*150mm; mobile phase A: Water (10 mmol NH_4HCO_3), mobile phase B: ACN, Flow rate: 60 ml/min, gradient from 40% B to 55% B in 7 min). The fractions containing the desired product were combined and lyophilized to give 57.7 mg (17%) of Compound 193 as

a white solid.

The compounds in the table below were prepared using an analogous method as described for the preparation of compound 193 starting from the suitable starting materials.

Compound number	Structure
Compound 194	 From compound 1

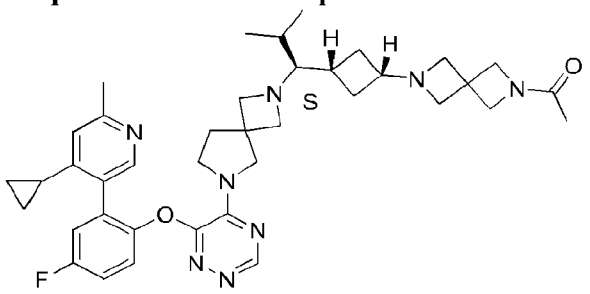
Preparation of compound 370

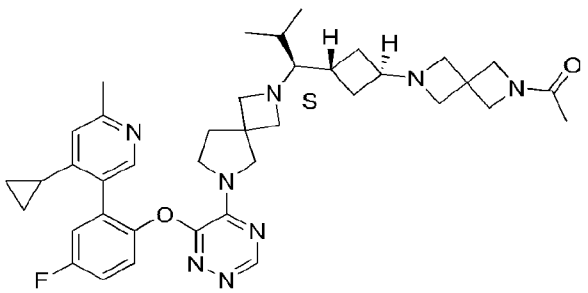


A mixture of intermediate 312 (3.7 g, 14.54 mmol) and 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one 2,2,2-trifluoroacetate (3.1 g, 4.85 mmol) in methanol (40 mL) was stirred at room temperature for 30 minutes, and then sodium cyanoborohydride (244 mg, 3.88 mmol) was added into the mixture. After stirring for 1 hour at room temperature, the reaction mixture was quenched with 10% potassium carbonate solution, adjusted to pH = 10 with 1 M sodium hydroxide solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel 80 g (eluent: dichloromethane-methanol 93%:7%) to afford 2.1 g (60% yield) of compound 370 as an off white solid containing, based on LCMS, a mixture of *cis* and *trans* isomers.

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Preparation of compound 371 and compound 372

Compound 371: 

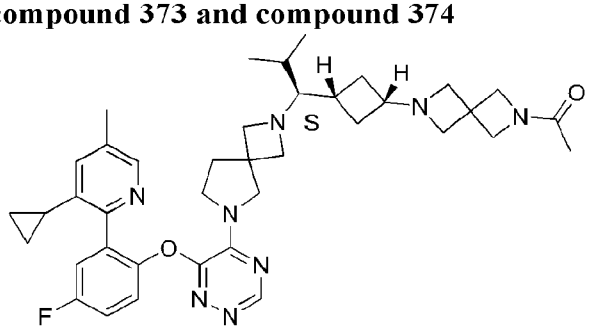
Compound 372: 

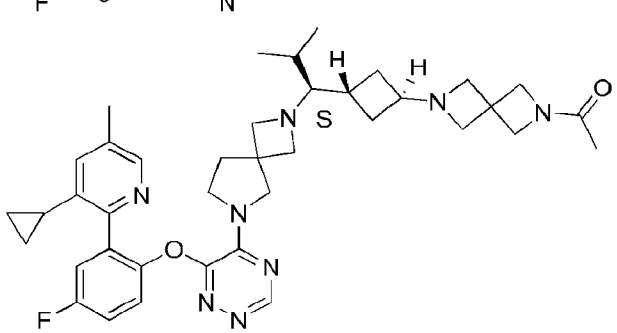
A mixture of *cis/trans* isomers (2.1g) was separated by chiral-HPLC with the following conditions: Column: CHIRALPAK IG, 2*25cm, 5um; Mobile Phase A: Hex: DCM = 3:1(0.5% 2M NH_3-MeOH) - Mobile Phase B:EtOH--HPLC; Flow rate:20 mL/min; Gradient:15 B to 15 B in 16 min; 254/220 nm; Injection Volume:0.5 ml; Number of Runs:9; retention time 1 = 9.57 min; retention time 2 = 12.385 min to afford two fractions.

Fraction A: 580.2 mg (36% yield, retention time 1: 9.57 min) of compound 371.

Fraction B: 498.8 mg (30% yield, retention time: 12.385 min) of compound 372.

Preparation of compound 373 and compound 374

Compound 373: 

Compound 374: 

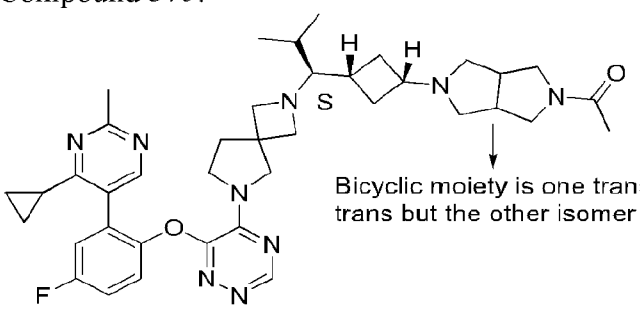
To a solution of intermediate 317 (3.0 g, 5.39 mmol) in methanol (60 mL) was added 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one 2,2,2-trifluoroacetate (4.1 g, 8.92 mmol) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. Then, sodium cyanoborohydride (270 mg, 4.31 mmol) was added to the mixture. The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was quenched with potassium carbonate solution (10% in water) and sodium hydroxide solution (1 M in water) and then, extracted with ethyl acetate for 3 times. The organic layers were combined, washed with brine and dried over sodium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography with silica gel 120 g (eluent: dichloromethane-methanol/ 0% ~ 10%, 8%) to give 1.78 g of a crude product, which was further purified by high pressure revers phase chromatographie with the following conditions: Welch Ultimate XB-C18 50*250 mm,10 um; Mobile Phase A: Water (10 mmolL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 30% B to 60% B in 30 min, 220 nm; retention time 1: 17.5 min; retention time 2: 21.5 min to afford two fractions.

Fraction A: 670 mg (18% yield, retention time 1: 17.5 min) of compound 373 as a white solid.

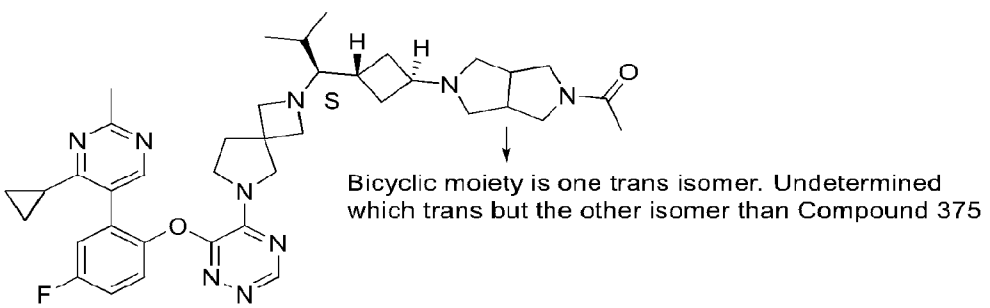
Fraction B: 610 mg (16% yield, retention time 2: 21.5 min) of compound 374 as a white solid.

Preparation of compound 375 and compound 376

Compound 375:



Compound 376



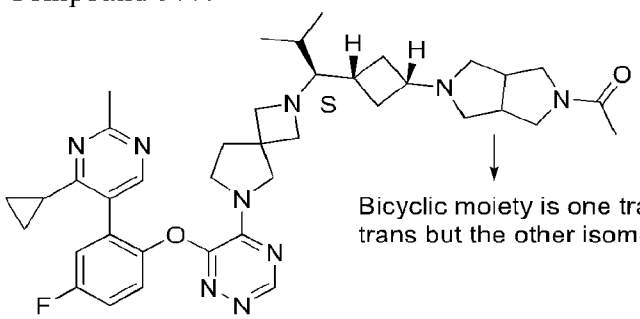
Intermediate 319 (500 mg, crude) was added to a solution consisting of intermediate 324 (600 mg, 1.08 mmol), and MeOH (15 mL). The mixture was stirred at 40 °C for 2 hours. $NaBH_3CN$

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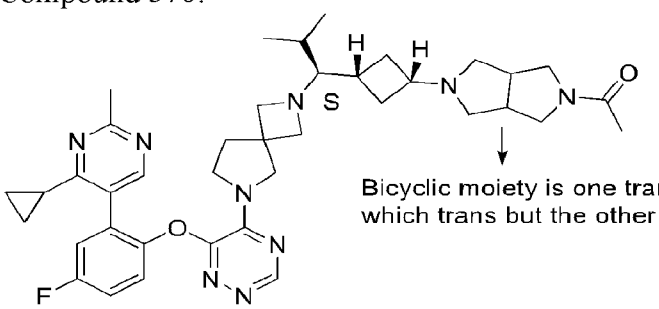
(280 mg, 4.46 mmol) was added to the mixture. Then, the mixture was stirred at 40 °C for 2 hours. The mixture was quenched with H_2O (50 mL) and then, extracted with ethyl acetate (50 mL x 3).The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the crude compound which was purified by high performance liquid chromatography over a Phenomenex Gemini-NX 80 x 40 mm x 3 μm column (eluents: A:water (0.05%NH_3H_2O+10mM NH_4HCO_3)) and B: MeCN; gradient: 34% B to 64% B (v/v) to afford pure product. The product was suspended in water (50 mL). The mixture was frozen using dry ice/ethanol, and then, lyophilized to dryness to afford 300 mg (40% yield) compound 375 and 50 mg (7% yield) of compound 376 as a white solid.

Preparation of compound 377 and compound 378

Compound 377:



Compound 378:



Compound 375 (300 mg, 0.043 mmol) was purified by supercritical fluid chromatography over DAICEL CHIRALPAK AS (250 mm x 30 mm x 10 um) (Condition: solvent A: supercritical CO_2; solvent B: EtOH (0.1% NH_3•H_2O); A:B = 70%: 30%, Flowrate: 80 mL/min). The pure fractions were collected and the volatiles were removed under vacuum. The resulting product was lyophilized to dryness to remove the solvent residue completely. Desired compound 377 (104.9 mg, 97.3% purity, 34% yield) and compound 378 (135.1 mg, 89.4% purity, 40% yield) were obtained as a white solid.

Compound 377

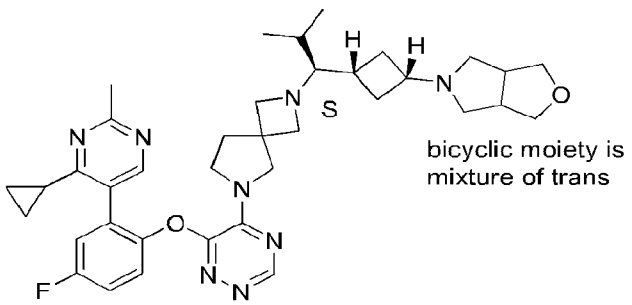
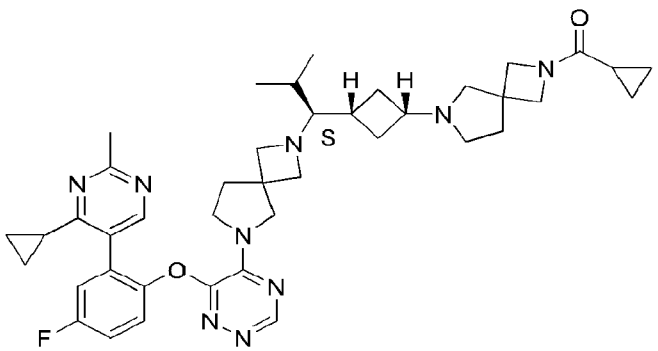
^{1}H NMR CHLOROFORM-*d* (Varian_400 MHz): δ 8.45 (s, 1H), 8.27 (s, 1H), 7.38 - 7.31 (m, 1H), 7.23 - 7.15 (m, 1H), 7.13 - 7.05 (m, 1H), 3.88 - 3.75 (m, 1H), 3.72 - 3.40 (m, 5H), 3.22

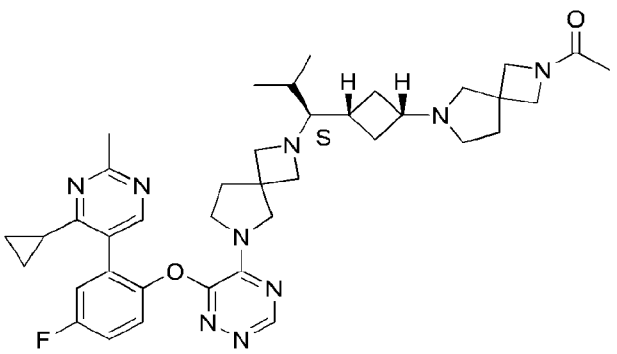
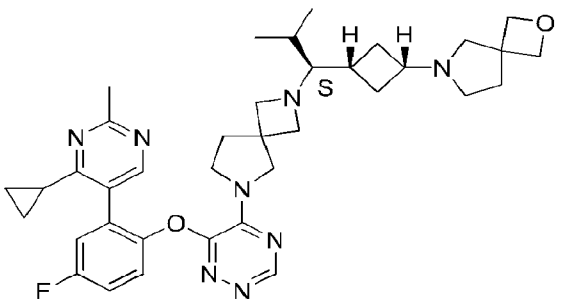
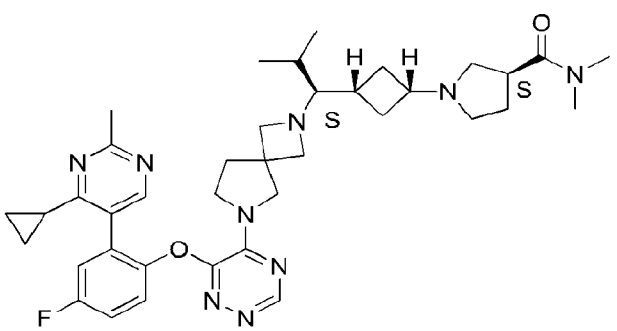
- 3.02 (m, 6H), 2.99 - 2.85 (m, 3H), 2.61 (s, 3H), 2.51 - 2.41 (m, 2H), 2.39 - 2.07 (m, 5H), 2.07 - 1.90 (m, 8H), 1.71 - 1.62 (m, 2H), 1.16 - 1.01 (m, 2H), 0.94 - 0.68 (m, 8H)

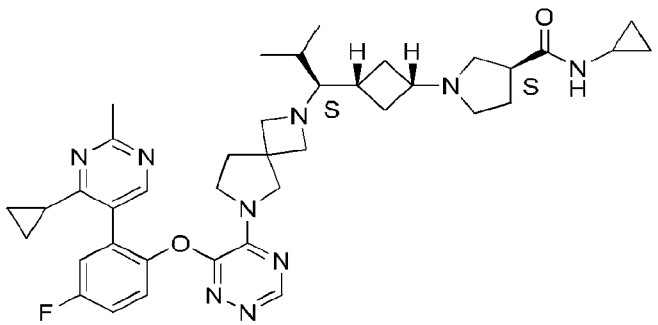
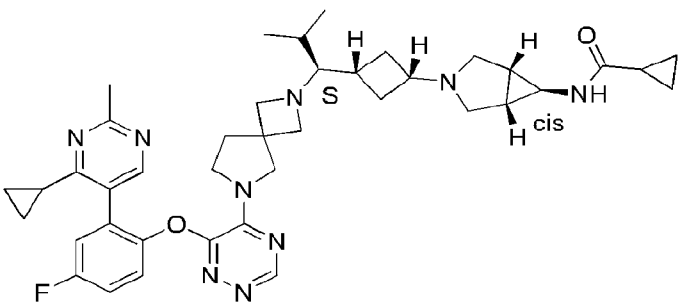
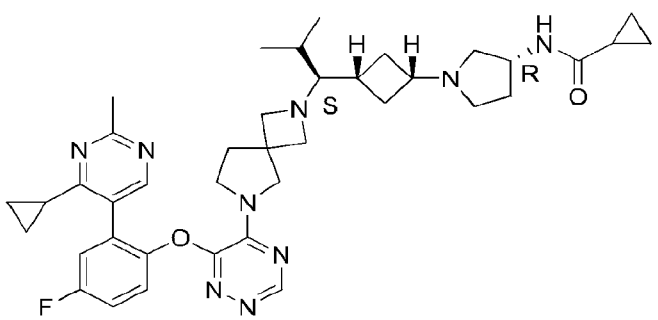
Compound 378

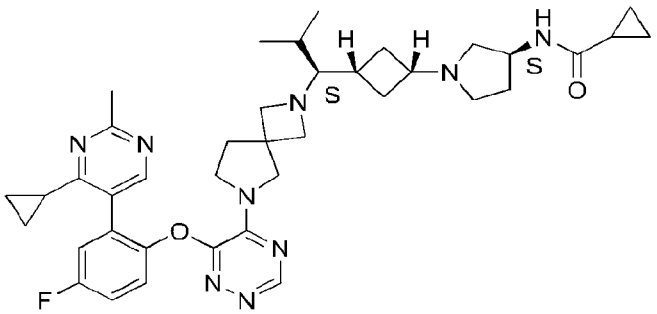
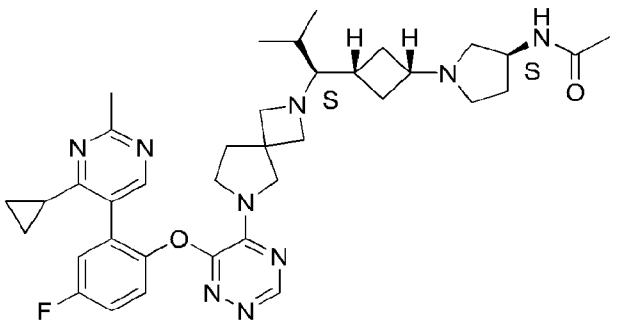
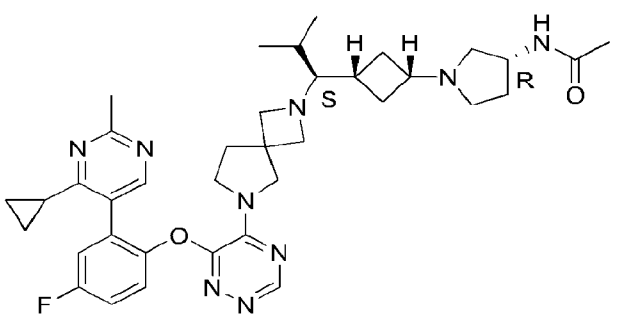
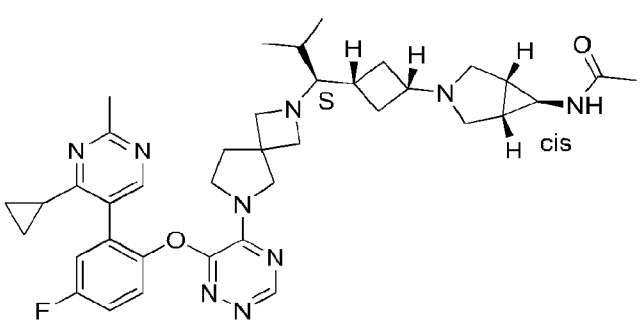
^{1}H NMR CHLOROFORM-*d* (Varian_400 MHz): δ 8.43 (s, 1H), 8.26 (s, 1H), 7.39 - 7.30 (m, 1H), 7.23 - 7.13 (m, 1H), 7.12 - 7.04 (m, 1H), 3.92 - 3.75 (m, 1H), 3.70 - 3.40 (m, 5H), 3.23 - 3.09 (m, 6H), 3.07 - 2.90 (m, 4H), 2.69 - 2.49 (m, 5H), 2.38 - 2.14 (m, 4H), 2.08 - 1.96 (m, 6H), 1.88 - 1.64 (m, 4H), 1.18 - 0.99 (m, 2H), 0.95 - 0.48 (m, 8H)

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of compounds 375 and 376 starting from the corresponding starting materials

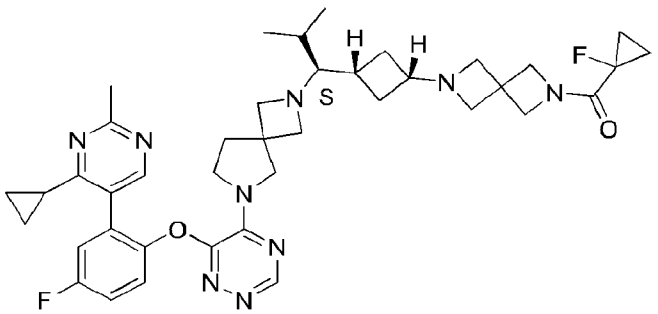
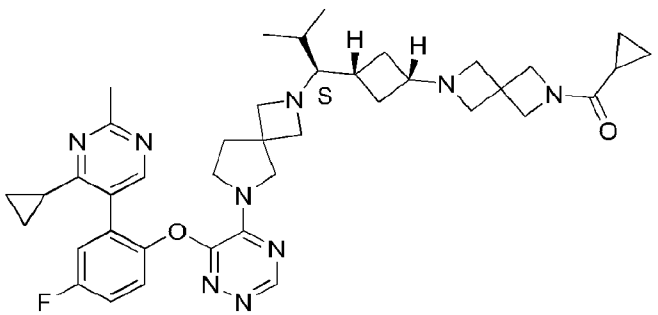
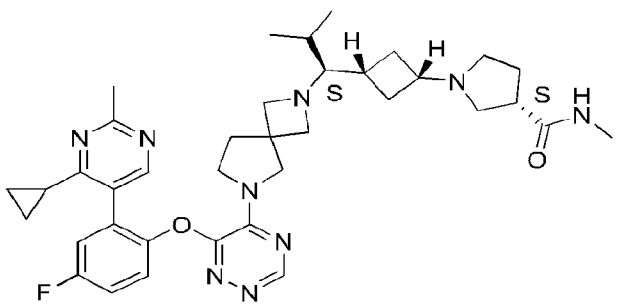
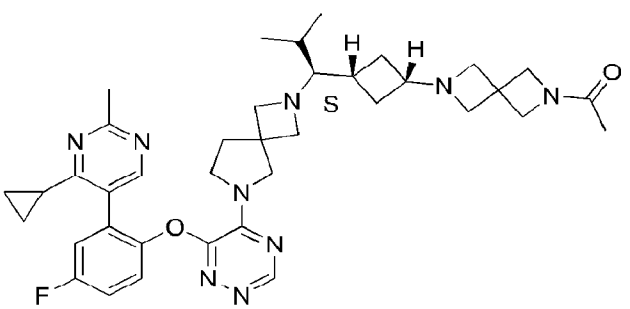
Compound number	Compound structure
379	 From intermediate 324 and 4-(trans)-hexahydro-1*H*-furo[3,4-c]pyrrole
380	 From intermediate 324 and cyclopropyl(2,6-diazaspiro[3.4]octan-2-yl)methanone, TFA salt

381	 From intermediate 324 and 1-(2,6-diazaspiro[3.4]octan-2-yl)ethan-1-one, TFA salt
382	 From intermediate 324 and 2-oxa-6-azaspiro[3.4]octane
383	 From intermediate 324 and (*S*)-*N*,*N*-dimethylpyrrolidine-3-carboxamide, TFA salt

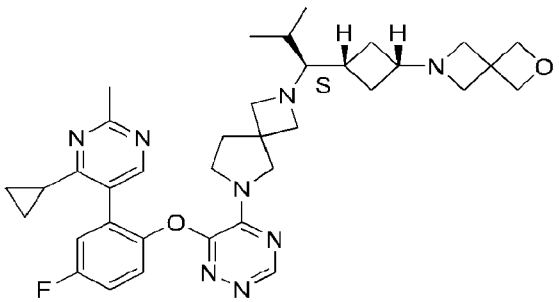
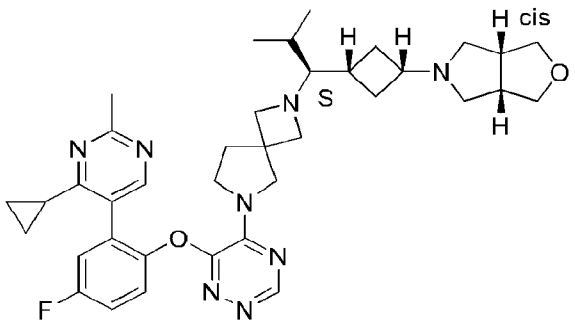
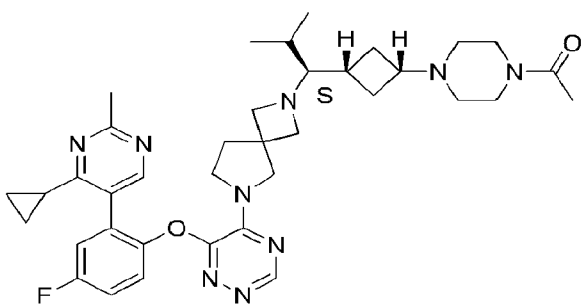
384	 From intermediate 324 and (*S*)-*N*-cyclopropylpyrrolidine-3-carboxamide, TFA salt
385	 From intermediate324 and *exo*-*N*-3-azabicyclo[3.1.0]hexan-6-yl)cyclopropanecarboxamide
386	 From intermediate 324 and (*R*)-*N*-(pyrrolidin-3-yl)cyclopropanecarboxamide, TFA salt

387	 From intermediate 324 and (*S*)-*N*-(pyrrolidin-3-yl)cyclopropanecarboxamide, TFA salt
388	 From intermediate 324 and (*S*)-*N*-(pyrrolidin-3-yl)acetamide
389	 From intermediate 324 and (*R*)-*N*-(pyrrolidin-3-yl)acetamide
390	 From intermediate 324 and exo-*N*-3-azabicyclo[3.1.0]hexan-6-yl)acetamide

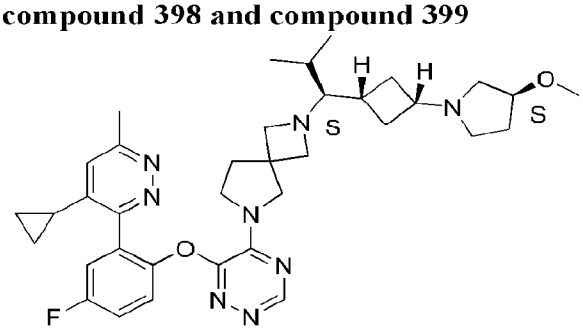
CA 03214746 2023-10-5

391	 From intermediate 324and (1-fluorocyclopropyl)(2,6-diazaspiro[3.3]heptan-2-yl)methanone, TFA salt
392	 From intermediate 324 and cyclopropyl(2,6-diazaspiro[3.3]heptan-2-yl)methanone, TFA salt
393	 From intermediate 324 and (*S*)-*N*-methylpyrrolidine-3-carboxamide, TFA salt
394	 From intermediate 324 and 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one

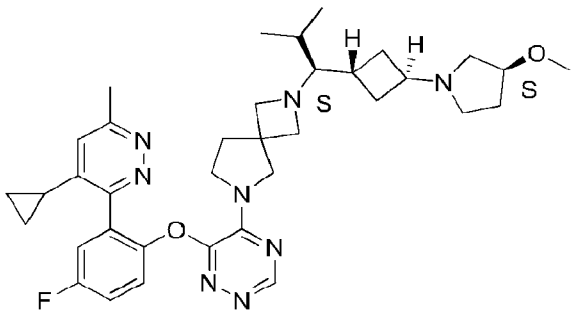
CA 03214746 2023-10-5

395	 From intermediate 324 and 2-oxa-6-azaspiro[3.3]heptane
396	 From intermediate 324 and cis-hexahydro-1*H*-furo[3,4-*c*]pyrrole
397	 From intermediate 324 and 1-(piperazin-1-yl)ethan-1-one

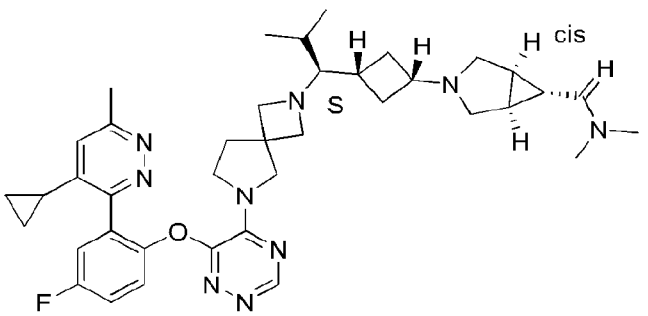
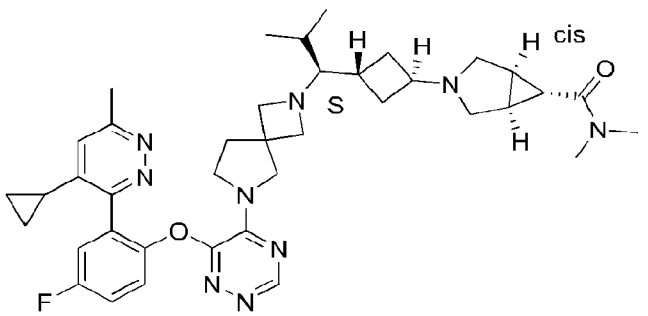
Preparation of compound 398 and compound 399

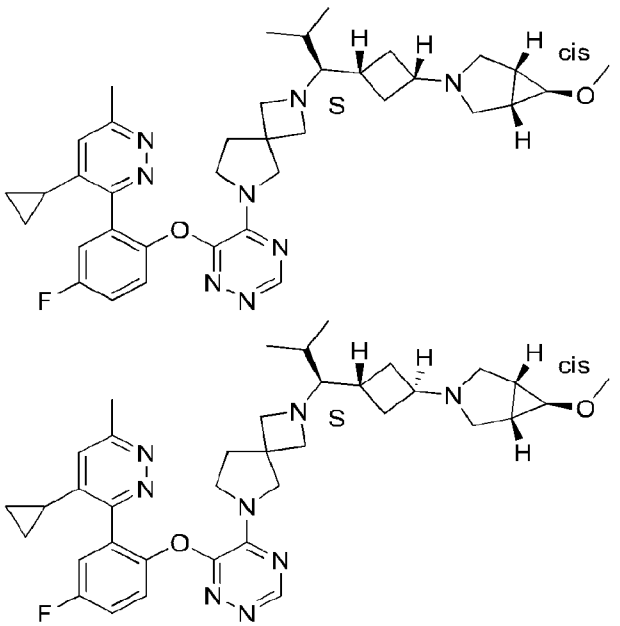
Compound 398: 

CA 03214746 2023-10-5

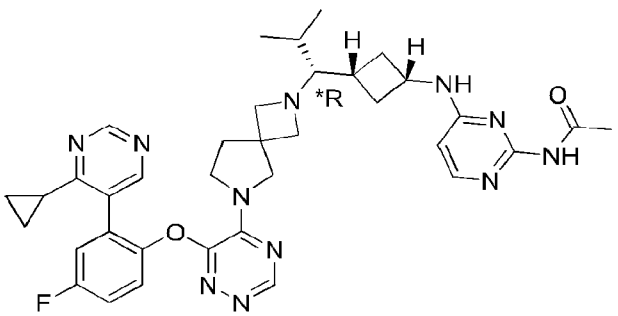
Compound 399: 

To a stirring solution of intermediate 332 (250 mg, 0.39 mmol) in tetrahydrofuran (5 mL) were added (*S*)-3-methoxypyrrolidine hydrochloride (106 mg, 0.77 mmol) and acetic acid (0.5 mL). After strring for 30 minutes at room temperature, sodium triacetoxyborohydride (409 mg, 1.93 mmol) was added. The resulting mixture was stirred at 50 °C for overnight. The reaction mixture were quenched with a solution of potassium carbonate (10% in water) and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC (Column: XBridge Prep C18 OBD Column, 19×150mm 5um; Mobile Phase A:Water(10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B:ACN; Flow rate:25 mL/min; Gradient:30%B to 50%B in 7 min; 220 nm; retention time 1:5.47 min; retention time 2:6.57 min. Mixing the pure fractions following by lyophilization gave 65.5 mg (22% yield, retention time 1: 5.47 min) of compound 398 as a white solid and 59.4 mg (19.4% yield, retention time 2: 6.57 min) of compound 399 as a white solid.

Compound number	Compound structure
400	
401	
	From intermediate 332 and *cis*-*N*,*N*-dimethyl-3-azabicyclo[3.1.0]hexane-6-carboxamide

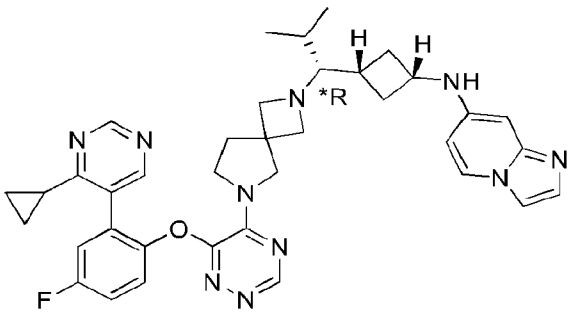
402 403	 From intermediate 332 and *cis*-6-methoxy-3-azabicyclo[3.1.0]hexane

Preparation of Compound 405



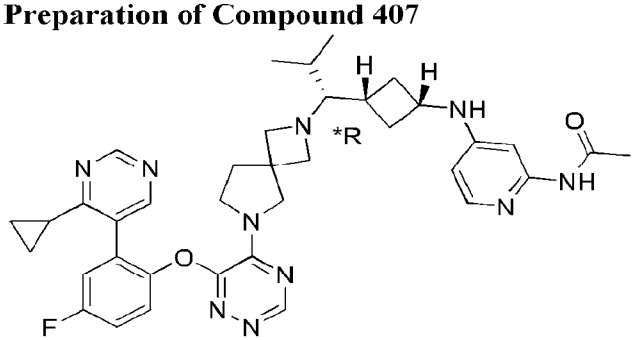
Compound 1a (100 mg, 0.184 mmol), *N*-(4-chloropyrimidin-2-yl)acetamide (60 mg, 0.35 mmol), Cs_2CO_3 (120 mg, 0.368 mmol), KI (6 mg, 0.04 mmol), and DMF (2 mL) were added added to a 10 mL sealed tube. The resultant mixture was stirred at 50°C for 16 hours. The suspension was filtered through a pad of Celite® and the pad washed with dichloromethane (20 mL). The filtrate was concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (Column: Boston Prime C18 150*30mm*5um, Mobile Phase A: water(0.05%NH3H2O)-ACN, Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 36% B to 66%). The pure fractions were collected and the solvent was evaporated under vacuum to give a residue. The residue was partitioned between acetonitrile (2 mL) and water (5 mL). The solution was lyophilized to dryness to give Compound 405 (21.94 mg, 18%) as a white solid.

Preparation of Compound 406



$Ti(OiPr)_4$ (700 mg, 2.46 mmol) was added to a solution consisting of intermediate 38b (300 mg, 0.552 mmol), imidazo[1,2-a]pyridin-7-amine (150 mg, 1.13 mmol) and MeOH (1 mL). The mixture was stirred at 80 °C for 6 hours. $NaBH_3CN$ (140 mg, 2.23 mmol) was added to the mixture. Then the mixture was stirred at 80°C for 5 hours. Aq. $NaHCO_3$ (20 mL) and water (20 mL) was slowly added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to afford the crude product which was purified by high performance liquid chromatography over a Boston Green ODS 150 x 30 mm x 5 μm column (eluent: 10% to 40% (v/v) CH3CN and H2O with 0.225%TFA) to afford pure product. The product was suspended in water (10 mL), the mixture frozen using dry ice/ethanol, and then lyophilized to dryness to afford compound (38 mg) as a white soild which was purified by supercritical fluid chromatography over DAICEL CHIRALPAK AD (250 mm x 30 mm x 10 um) (eluent: supercritical CO2 in EtOH (0.1% v/v ammonia) 50/50, v/v). The pure fractions were collected and the volatiles were removed under vacuum. The resulting product was lyophilized to dryness to remove the solvent residue completely to give Compound 406 (4.65 mg, 1% yield) as a white solid.

Preparation of Compound 407

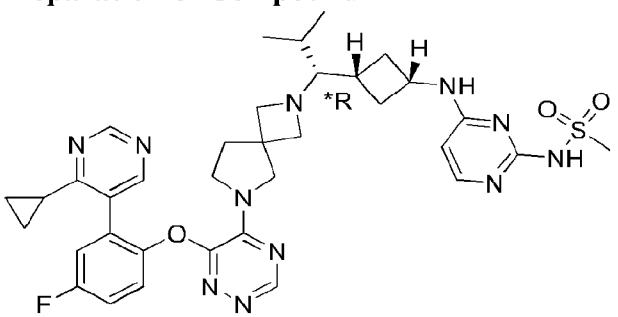


A solution consisting of *N*-(4-fluoropyridin-2-yl)acetamide (100 mg, 0.649 mmol), Compound 1a (20 mg, 0.037 mmol), K_2CO_3 (20.3 mg, 0.147 mmol) and DMF (2 mL) was stirred at 120°C overnight. The crude material was submitted to prep. HPLC for purification and the collected fraction was lyophilized to dryness to afford Compound 407 (5.15 mg, 19.4% yield) as a white

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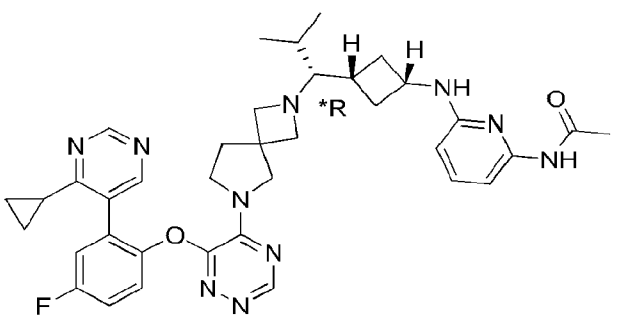
powder.

Preparation of Compound 408



To a solution of *N*-(4-chloropyrimidin-2-yl)methanesulfonamide (52.6 mg, 0.253 mmol) and Compound 1a (115 mg, 0.211 mmol) in EtOH (3 mL) was added TEA (64.1 mg, 0.633 mmol). The mixture was stirred at 90 °C for 16 hours. The reaction mixture was directly purified by pre-HPLC (Column:Phenomenex Gemini-NX C18 75*30mm*3um, Mobile Phase A:water(0.05%NH_3H_2O+10mM NH_4HCO_3), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 33% B to 63% B). The pure fractions were collected and evaporated to give the product as a white solid (99 mg, crude). And then the crude product was further purified by pre-HPLC (Column: Boston Green ODS 150*30mm*5um, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 35 mL/min, gradient condition from 10% B to 40% B). The pure fractions were collected and evaporated to give Compound 408 (53.77 mg, 33% yield) as a white solid.

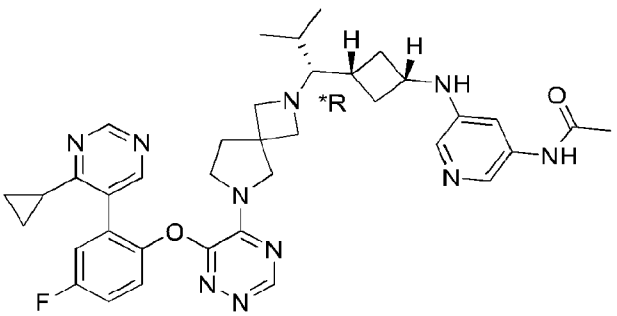
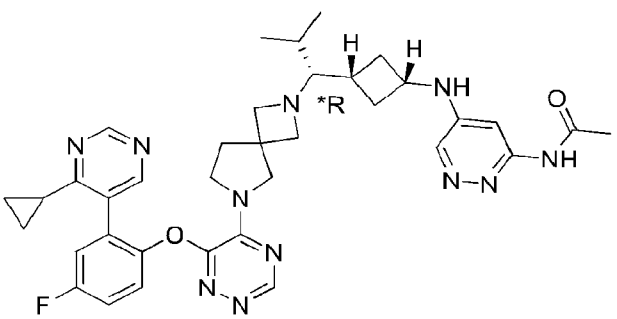
Preparation of Compound 409



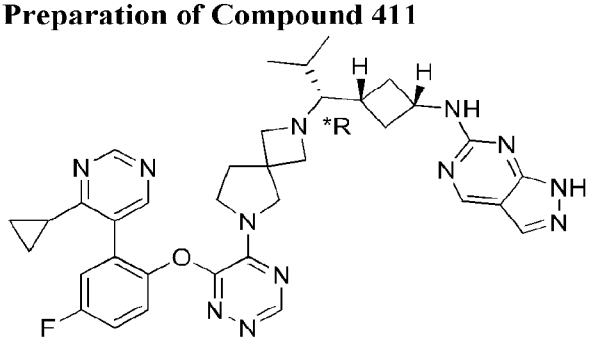
Compound 1a (200 mg, 0.367 mmol), *N*-(6-bromopyridin-2-yl)acetamide (160 mg, 0.774 mmol), Cs_2CO_3 (360 mg, 1.11 mmol) were dissolved in dioxane (10 mL). The resultant mixture was sparged with Ar for 2 minutes and then treated with Brettphos-Pd-G3 (20.0 mg, 0.022 mmol). The resultant mixture was sparged with Ar for another 2 minutes and then stirred at 90°C overnight. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was first purified by prep-HPLC (Column: Welch Xtimate C18 150*25mm*5um, Mobile Phase A: water water(0.2%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 10% B to 40%) and then by prep-HPLC (Column:

Phenomenex Luna C18 150*30mm*5um, Mobile Phase A: water (0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 43% B to 73%). The pure fractions were collected and lyophilized to afford Compound 409 (30.55 mg, 12% yield) as a white powder.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 409 starting from the corresponding starting materials

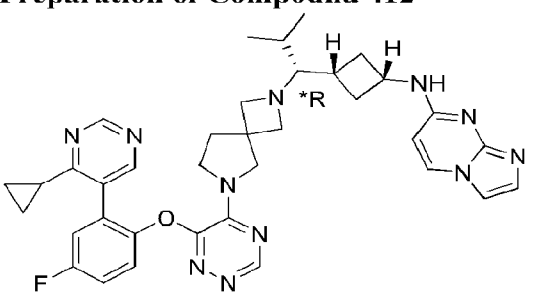
Compound number	Compound structure
410	 From Compound 1a and *N*-(5-bromopyridin-3-yl)acetamide
414	 From Compound 1a and *N*-(5-chloropyridazin-3-yl)acetamide

Preparation of Compound 411



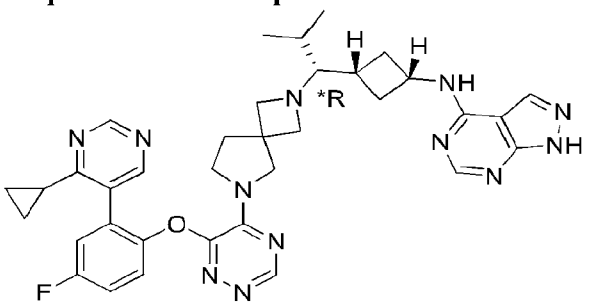
A stir bar, Compound 1a (120 mg, 0.220 mmol), 6-chloro-1*H*-pyrazolo[3,4-d]pyrimidine (35.0 mg, 0.26 mmol), *N*,*N*-diisopropylethylamine (57.0 mg, 0.441 mmol) and acetonitrile (3 mL) were were taken up into a microwave tube. The sealed tube was heated at 90 °C for 1 h under microwave. The mixture was diluted into dichloromethane (30 mL) and washed with water (10 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude which was purified by prep. HPLC (Column: Phenomenex Gemini-NX 80*40mm*3um, Mobile Phase A: water(0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 33% B to 63%). The pure fractions were collected and the solvent was evaporated under vacuum to give a residue. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give Compound 411 (78.88 mg, 53.9% yield) as a white powder.

Preparation of Compound 412



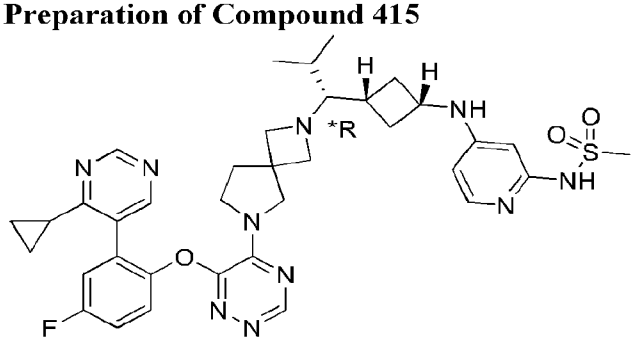
To the solution of intermediate 333 (58.0 mg,0.910 mmol) in ethanol (2 mL) and H_2O (0.35 mL), was added 2-chloroacetaldehyde (35.7 mg, 0.182 mmol) and $NaHCO_3$ (11.5 mg, 0.136 mmol). The mixture was stirred at 70°C overnight. The mixture was purified by SFC over DAICEL CHIRALPAK IG (250mm*30mm, 10um) (eluent: 60% to 60% (v/v) supercritical 0.1%NH_3H_2O ETOH). The pure fractions were collected and the volatiles were removed under reduced pressure. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford the crude material which was further purified by SFC over DAICEL CHIRALPAK AD(250mm*30mm, 10um) (eluent: 50% to 50% (v/v) supercritical 0.1%NH_3H_2O ETOH). The pure fractions were collected and the volatiles were removed under reduced pressure. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford Compound 412 (7.1mg, 11.7% yield) as a white solid.

Preparation of Compound 413



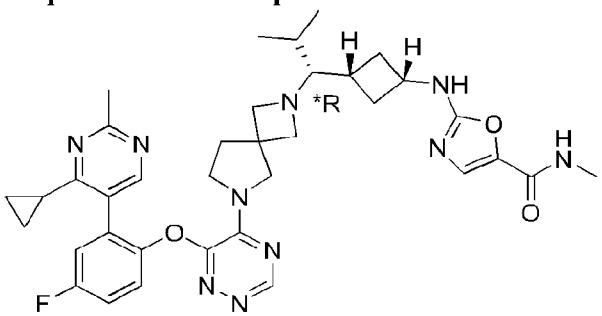
A stir bar, Compound 1a (120 mg, 0.220 mmol), 4-chloro-1*H*-pyrazolo[3,4-d]pyrimidine (34.2 mg, 0.221 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (57.0 mg, 0.441 mmol) and acetonitrile (3 mL) were taken up into a microwave tube. The sealed tube was heated at 90 °C for 1 h under microwave. The mixture was cooled to room temperature, then the mixture was concentrated under reduced pressure to give a residue which was suspended into water (50 mL) and extracted with dichloromethane (30 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a crude, which was purified by prep. HPLC (Column: Phenomenex Gemini-NX 80*40mm*3um, Mobile Phase A: water(0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 28% B to 58%). The pure fractions were collected and the solvent was evaporated under vacuum to give a residue. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give Compound 413 as a white powder (51.8 mg, 35.5% yield).

Preparation of Compound 415



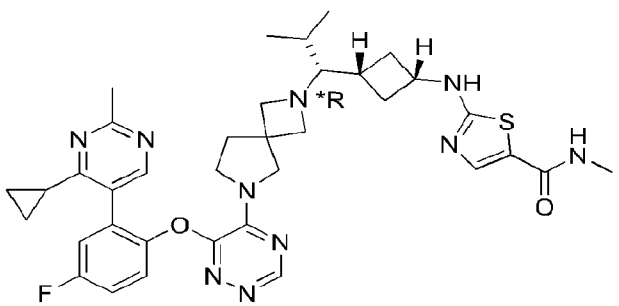
DIPEA (0.03 mL, 0.184 mmol) was added to a solution consisting of Compound 1a (50 mg, 0.092 mmol), *N*-(4-fluoropyridin-2-yl)methanesulfonamide (21 mg, 0.11 mmol) and *i*-PrOH (1 mL). The mixture was stirred at 95 °C for 2 hours. The mixture was concentrated under reduced pressure to give crude product, which was purified by preparative HPLC using a Boston Prime C18 150*30mm*5um column (eluent: 35% to 65% (v/v) CH_3CN and H_2O with 0.05% NH_3) to afford the pure product. The pure fractions were collected and lyophilized to dryness to remove the solvent residue completely to yield Compound 415 (42 mg, 63.2 % yield) as a white solid.

Preparation of Compound 416

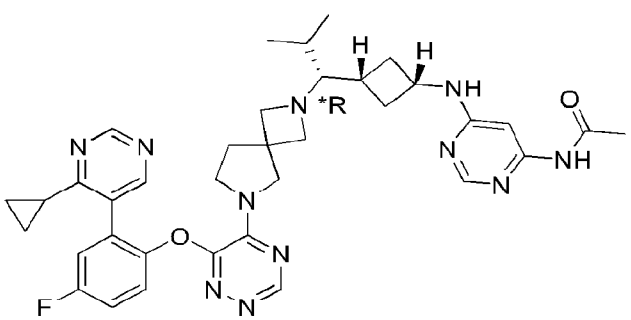


A stir bar, Compound 466 (120 mg, 0.179 mmol), methanamine hydrochloride (60.5 mg, 0.896 mmol), TEA (0.125 mL, 0.896 mmol) in DCM (3 mL) was added T3P (171 mg, 0.269 mmol). The mixture was stirred at 35°C for 10 h. The mixture was purified by prep-HPLC (Column: Phenomenex Gemini-NX 150*30mm*5um, Mobile Phase A: water (0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 34% B to 64%) to give Compound 416 (16.97 mg, 13.5% yield) as a white soilds.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 416 starting from the corresponding starting materials

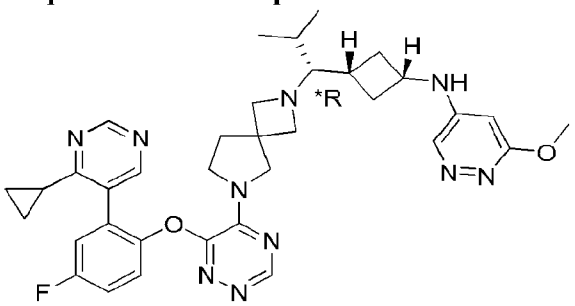
Compound number	Compound structure
417	 From Compound 468

Preparation of Compound 418



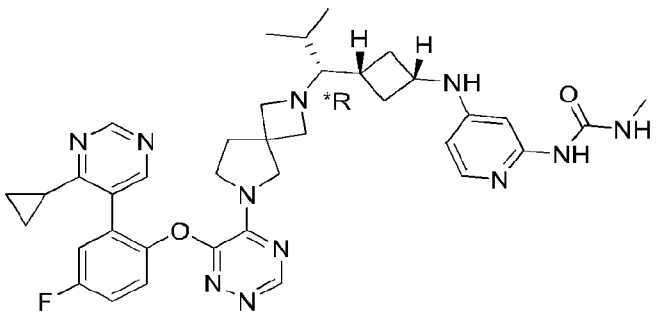
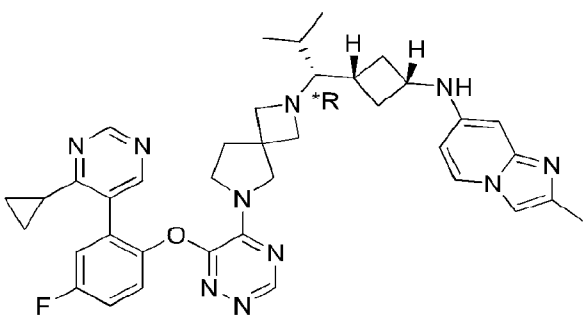
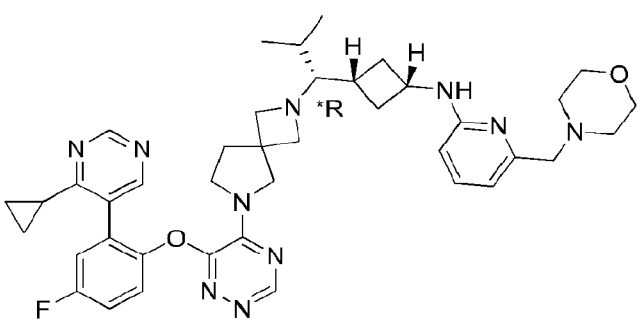
N-(6-bromopyrimidin-4-yl)acetamide (72 mg, 0.33 mmol) was added to a solution consisting of Compound 1a (120 mg, 0.220 mmol), TEA (0.1 mL, 0.72 mmol), and *t*BuOH (5 mL). The mixture was stirred at 120 °C for 16 hours. The mixture was quenched with solution of H_2O (5 mL), and then extracted with EA (10 mL x 3) .The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated invacuo to give the crude product was purified by preparative HPLC using Phenomenex Gemini-NX C18 75 x 30 mm x 3 μm column (eluent: 40% to 70% (v/v) water (0.05% NH_3H_2O+10mM NH_4HCO_3)-ACN) to afford pure product. The product was suspended in water (10 mL), and the mixture frozen using dry ice/ethanol, and then lyophilized to dryness to afford Compound 418 (41.34 mg, 27.53% yield) as a white solid.

Preparation of Compound 419



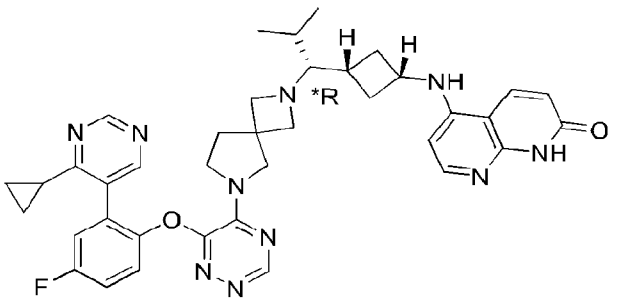
*t*BuXPhos Pd G3 (7.3 mg, 0.009 mmol) was added to a solution of Compound 1a (50 mg, 0.092 mmol), 5-bromo-3-methoxypyridazine (33 mg, 0.175 mmol) and NaO*t*Bu (26.4 mg, 0.275 mmol) in 1,4-dioxane (8 mL) under argon atmosphere. The mixture was stirred at 100°C under microwave for 1 h. The reaction was repeated at the same scale and the combined reaction mixture was cooled to room temperature and concentrated under reduced pressure to give crude product, which was diluted with DCM (20 mL) and was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by preparative HPLC (Column: Phenomenex Gemini-NX C18 75*30mm*3um, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 0% B to 25%). The pure fraction was collected and the solvent was evaporated under vacuum to give a residue, The residue was diluted with H_2O (3 mL), adjusted to pH=8 by the saturated solution of sodium bicarbonate. Then the resultant mixture was extracted with CH_2Cl_2 (10 mL x 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give the product (60 mg, 93.46% purity, 46.79% yield) which was further purified by SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um), eluent: 35% (v/v) super critical CO_2 in 0.1%NH_3H_2O ETOH, flow rate: 70 mL/min), The pure fractions were collected and the volatile solvent was evaporated under vacuum to give the residue which was lyophilized to give Compound 419 (25.44 mg, purity 99.43%, 42.16% yield) as a white powder.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 419 starting from the corresponding starting materials

Compound number	Compound structure
421	 From Compound 1a and 1-(4-bromopyridin-2-yl)-3-methylurea
426	 From Compound 1a and 7-bromo-2-methylimidazo[1,2-a]pyridine
428	 From Compound 1a and 4-((6-bromopyridin-2-yl)methyl)morpholine

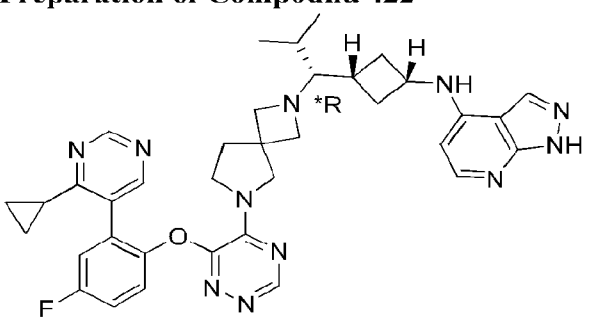
5

Preparation of Compound 420



A solution of Intermediate 339 (150 mg, 0.185 mmol) in TFA (5 mL) was stirred at 75°C for 2 h. The mixture was concentrated under reduced pressure and diluted with CH_2Cl_2 (10 mL), adjusted to pH = 13 with NaOH (2 M). The resultant mixture was extracted with CH_2Cl_2 (10 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to give crude product, which was purified by preparative HPLC (Column: Phenomenex Gemini-NX 80*40mm*3um, Mobile Phase A: water(0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 30% B to 60%). The pure fractions were collected and the volatile solvent was evaporated under vacuum. The resultant aqueous mixture was lyophilized to dryness to give the product (25 mg, purity 99.99%, 19.57% yield) as a white powder (F-NMR showed TFA residual). The product was diluted with CH_2Cl_2 (15 mL), washed with 2 M NaOH (5 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to give a residue. The residue was partitioned between acetonitrile (3 mL) and water (10 mL). The solution was lyophilized to dryness to give Compound 420 (8.86 mg, 6.84% yield) as a white powder.

Preparation of Compound 422

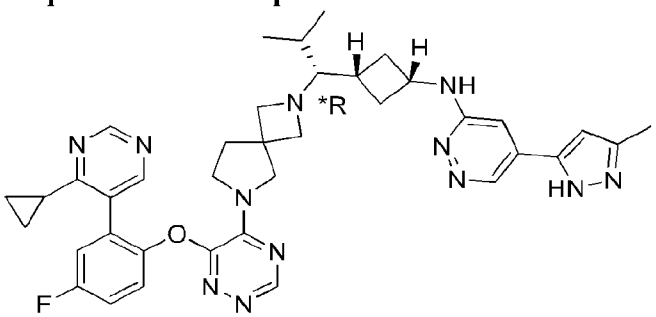


To a solution of Compound 470 (45.0 mg, 0.059 mmol) in anhydrous dichloromethane (2 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by preparative-HPLC over (Column: Boston Prime C18 150*30mm*5um, Mobile Phase A: water(0.05%NH_3H_2O+10mM NH_4HCO_3), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 45% B to 75%). The pure fractions were collected and the solvent was evaporated under vacuum. The residue was partitioned between acetonitrile (2 mL) and water

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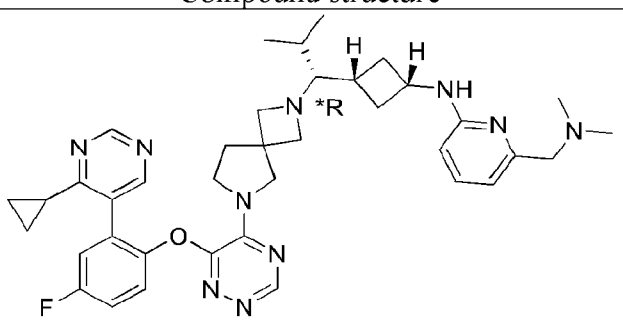
(10 mL). The mixture was lyophilized to dryness to give Compound 422 (10.73 mg, 96.84% purity, 26.6% yield) as a white powder.

Preparation of Compound 423

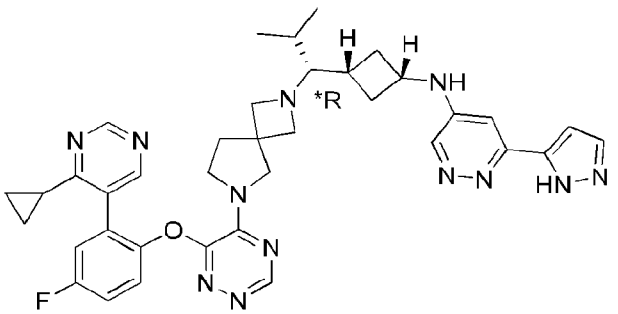


3-chloro-5-(3-methyl-1*H*-pyrazol-5-yl)pyridazine (100 mg, 0.514 mmol), Compound 1a (140 mg, 0.257 mmol), NaO*t*Bu (75 mg, 0.78 mmol) and T-Amyl-OH (5 mL) were added to a 8 mL reaction flask. The resultant mixture was sparged with N_2 for 5 minutes and then treated with t-BuXPhos-Pd-G3 (20 mg, 0.025 mmol). The resultant mixture was sparged with N_2 for another 5 minutes and then the resultant mixture was heated to 130 °C for 12 hours before cooling to room-temperature. The resultant mixture was concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC using a Phenomenex Gemini-NX C18 75*30mm*3um Column (eluent: 40% to 70% (v/v) CH_3CN and water(0.05%NH_3H_2O+10mM NH_4HCO_3)) to afford product. which was purified by preparative HPLC using a Boston Prime C18 150*30mm*5um Column (eluent: 40% to 70% (v/v) CH_3CN and water (0.05%NH_3H_2O+10mM NH_4HCO_3)) to afford product. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford Compound 423 (8.20 mg, 5%) as a white solid.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 423 starting from the corresponding starting materials

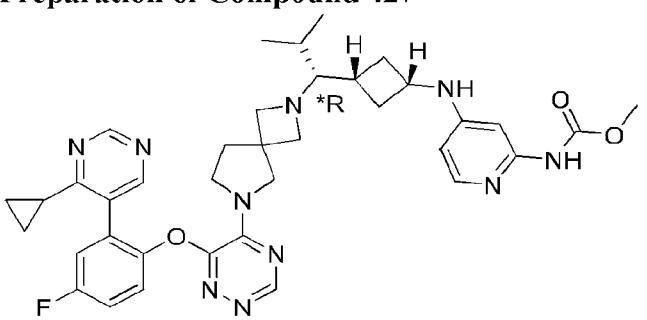
Compound number	Compound structure
425	 From Compound 1a and 1-(6-bromopyridin-2-yl)-*N*,*N*-dimethylmethanamine

Preparation of Compound 424



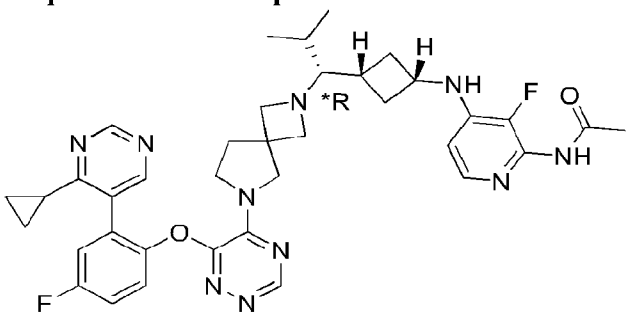
(1*H*-pyrazol-5-yl)boronic acid (15.3 mg, 0.137 mmol), Compound 471 (45 mg, 0.068 mmol) and K_3PO_4 (44 mg, 0.21 mmol) were added to a 10 mL microwave tube and the resulting mixture dissolved in 1,4-dioxane (4 mL) and H_2O (0.5 mL). The resultant mixture was sparged with Ar for 5 minutes and then treated with pd-peppsi(tm)-ipent catalyst (5.5 mg, 0.0070 mmol). The resultant mixture was stirred at 100°C for 12 hours before cooling to room-temperature. The mixture was purified by preparative high performance liquid chromatography over Phenomenex Gemini-NX C18 75*30mm*3um (eluent: 40% to 70% (v/v) CH_3CN and water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN) to afford pure product. The pure fractions were collected and lyophilized to dryness to afford Compound 424 (5.27 mg, 11.27%).

Preparation of Compound 427



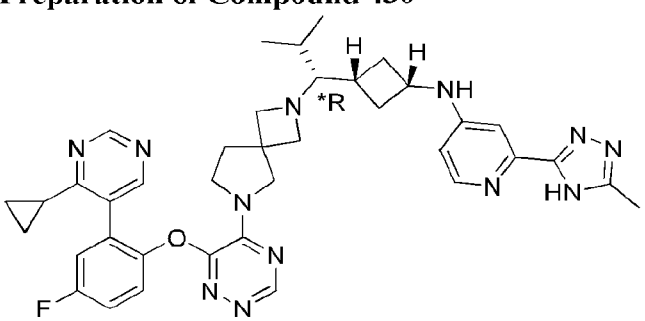
To a solution of Compound 472 (175 mg, 0.267 mmol) in 1,4-dioxane (3 ml) was added methyl carbamate (87 mg, 1.16 mmol), *t*-BuONa (88 mg, 0.916 mmol) and *t*BuXPhos-Pd-G3 (17 mg, 0.021 mmol) with Ar_2 in a microwave apparatus. The mixture was stirred at 110°C for 6 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The compound was further purified by preparative HPLC using a Boston Prime C18 150*30mm*5um (eluent: 50% to 80% (v/v) CH_3CN and water (0.05%NH_3H_2O)-ACN) to afford pure product. The product was lyophilized to dryness to afford Compound 427 (9 mg, 5 % yield) as a white soild.

Preparation of Compound 429



To a suspension of Compound 1a (200 mg, 0.367 mmol) in 1,4-dioxane (3 ml) was added *N*-(3-fluoro-4-iodopyridin-2-yl)acetamide (150 mg, 0.536 mmol), Cs_2CO_3 (390 mg, 1.20 mmol) and BrettPhos-Pd-G3 (20 mg, 0.022 mmol) with Ar in a microwave apparatus. The mixture was stirred at 100 °C for 4 hours. The mixture was filtered and the filtrate was concentrated to give a crude product, which was further purified by preparative HPLC using a Boston Prime C18 150*30mm*5um (eluent: 44% to 74% (v/v) CH_3CN and water (0.05% NH_3H_2O)-ACN) to afford pure product. The product was lyophilized to dryness to afford Compound 429 (37.11 mg, 14% Yield) as a white soild.

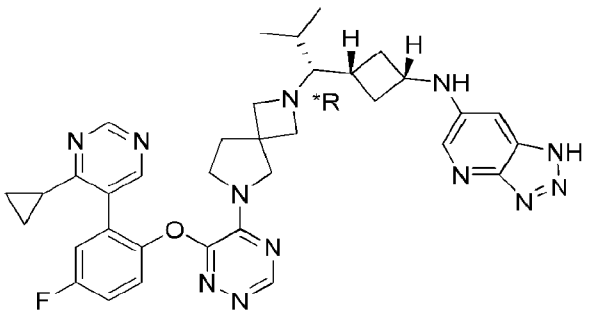
Preparation of Compound 430



To a suspension of Compound 473 (100 mg, 0.155 mmol) in DMSO (4 ml) was added acetimidamide hydrochloride (36 mg, 0.343 mmol, 90% purity), Cs_2CO_3 (152 mg, 0.467 mmol) and CuBr (2.0 mg, 0.014 mmol). The mixture was stirred at 120 °C for 2.5 hours. The mixture was filtered and the filtrate was concentrated to give a crude product. The crude product was duilted with DCM (15 ml) and washed with H_2O (10 ml x 3). The combined organic layers were washed with brine (15 ml), dried over Na_2SO_4, filtered and concentrated to give a crude product. The crude product was purified by FCC (DCM : MeOH = 10 : 1) to afford the crude product, which was further purified by preparative HPLC using a Phenomenex Gemini-NX C18 75*30mm*3um (eluent: 0% to 30% (v/v) CH_3CN and water(0.225%FA)-ACN) to afford pure product. The product was lyophilized to dryness to afford the product (53 mg, crude) as a green soild. HNMR showed the peaks don't split well due to Cu residue. To a solution of the material (53 mg, 0.075 mmol) in MeCN (0.5 mL) and MeOH (0.1 mL) was added $NH_3.H_2O$ (0.5 mL). The resultant mixture was stirred at r.t. for 3 hours. The resultant mixture was purified by

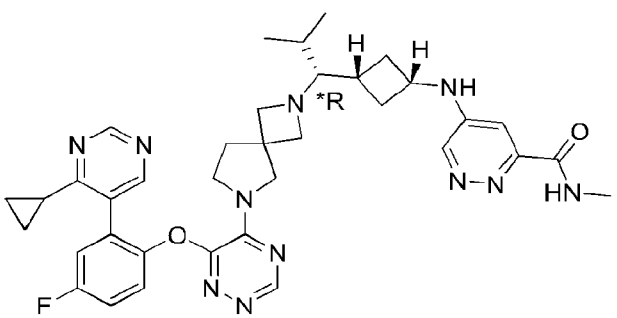
preparative HPLC using a Phenomenex Gemini-NX 80*40mm*3um (eluent: 32% to 62% (v/v) CH_3CN and water (0.05%NH_3H_2O)-ACN) to afford pure product. The product was lyophilized to dryness to afford Compound 430 (22 mg, 41% yield) as a white solid.

Preparation of Compound 431



To a solution of Compound 474 (174 mg, 0.219 mmol) in DCM (5 mL) was added TFA (12 mL). The resultant mixture was stirred at r.t. for 2 hours. The resultant mixture was concentrated under reduced pressure to give a product. The crude product was dissolved in MeCN (1 mL). $NH_3.H_2O$ (0.5 mL) was added and stired at r.t. for 15 min. Then the mixture was purified by preparative HPLC using a Phenomenex Gemini-NX 80*40mm*3um (eluent: 15% to 45% (v/v) CH_3CN and water (0.05%NH_3H_2O)-ACN) to afford pure product. The product was lyophilized to dryness to afford Compound 431 (61 mg, 41% yield) as a white solid.

Preparation of Compound 432

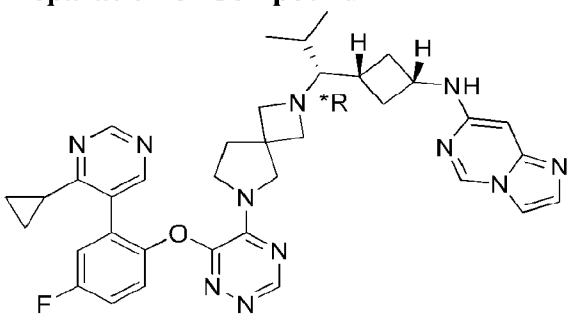


To a mixture of Compound 475 (55.0 mg, 0.081 mmol) and K_2CO_3 (22.0 mg, 0.159 mmol) in THF (1 mL) was added methanamine in EtOH (25.0 mg, 0.241 mmol, 30% w/t). The mixture was stirred for 6 h at rt. The reaction mixture was diluted with DCM (15 mL), washed with brine (5 mL), dried over Na_2SO_4. After filtration and concentration, the crude product was purified by FCC (DCM : MeOH = 10 : 1) to give desired product (16 mg, crude) which was further purified by pre-HPLC (Conditions: Column: Welch Xtimate C18 150*25mm*5um, Mobile Phase A: water (0.2%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 8% B to 38%). The pure fractions were collected and lyophilized to

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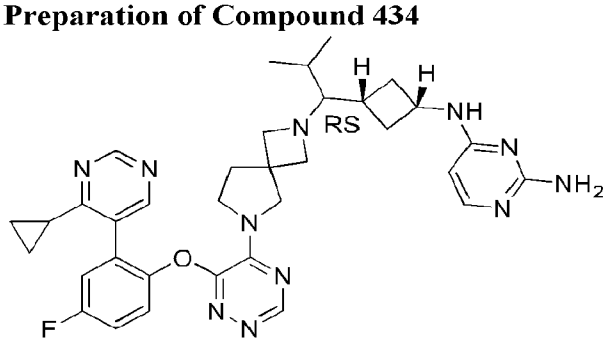
afford Compound 432 (2.82 mg, 4.8% yield) as a white solid.

Preparation of Compound 433



To a solution of Compound 477 (125 mg, 0.20 mmol) in ethanol (4.00 mL), $NaHCO_3$ (25.0 mg, 0.30 mmol), H_2O (0.50 mL) and 2-chloroacetaldehyde (0.18 mL, 1.11 mmol) was added. The mixture was stirred at 70 °C for 65 h. The mixture was cooled to room temperature, concentrated in vacunm and diluted with DCM (15 mL), washed with saturated $NaHCO_3$ aqueous solution (10 mL), saturated brine (10 mL), the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to give the crude which was purified by preparative HPLC (Column: Phenomenex Gemini-NX 80*40mm*3um, Mobile Phase A: water (0.05%NH_3H_2O), Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition from 38% B to 64%). The pure fractions were collected and the solvent was evaporated under vacuum to give a residue. The residue was partitioned between acetonitrile (4 mL) and water (12 mL). The solution was lyophilized to dryness to give Compound 433 (10.77 mg, 92.64% purity, 5.50% yield) as a gray powder.

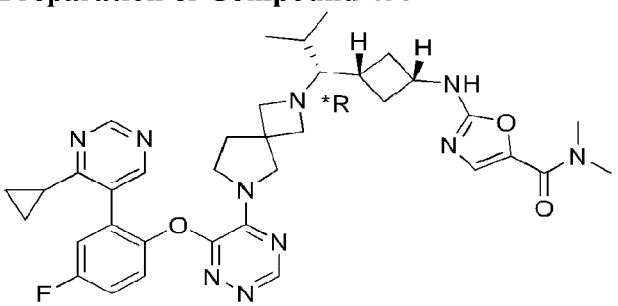
Preparation of Compound 434



To a solution of Compound 1 (200.0 mg, 0.37 mmol) in ethanol (6.0 mL) were added 4-chloropyrimidin-2-amine (95.1 mg, 0.73 mmol) and *N*,*N*-Diisopropylethylamine (1.21 mL, 7.34 mmol). The resulting mixture was stirred at 80°C for 22 hours. After cooling to room temperature, the reaction was quenched with water and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC with the following conditions: Column: Xbridge prep C18 5um 19*150mm; Mobile phase A: Waters (10 mmol/L NH_4HCO_3), Mobile phase B: ACN; Flow rate: 25 ml/min; Gradient: 40% B to 50%

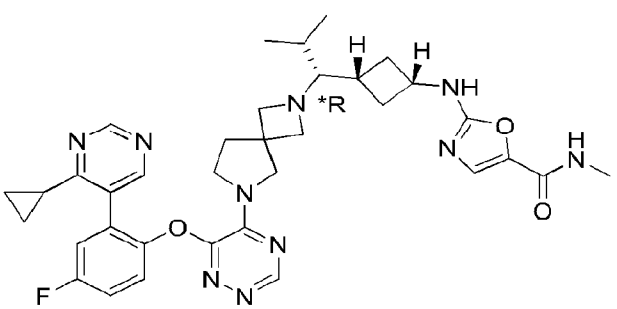
B in 7 min, 254&220nm; t: 6.80 min. The fractions containing the desired product were combined and lyophilized to give Compound 434 (4.6 mg, 98.754% purity, 1.94% yield) as a white solid.

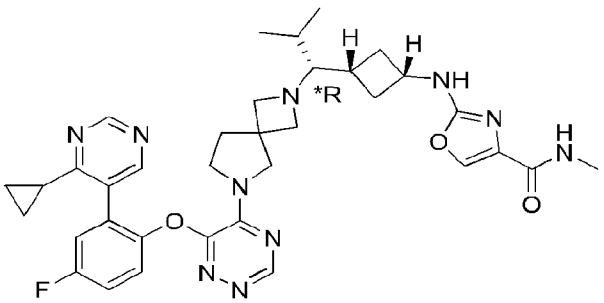
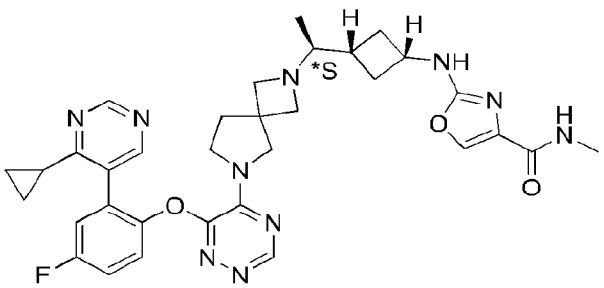
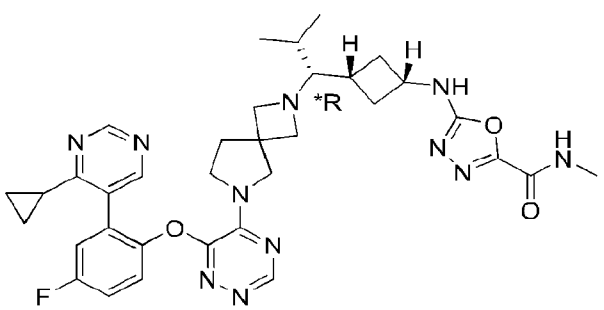
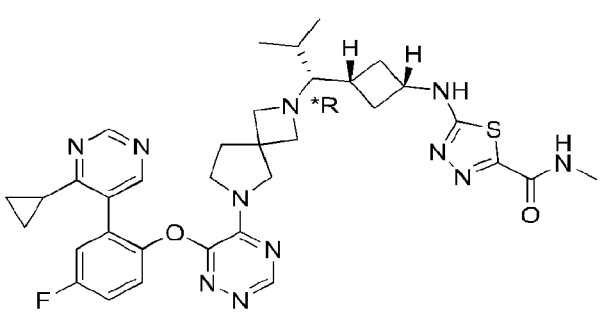
Preparation of Compound 435



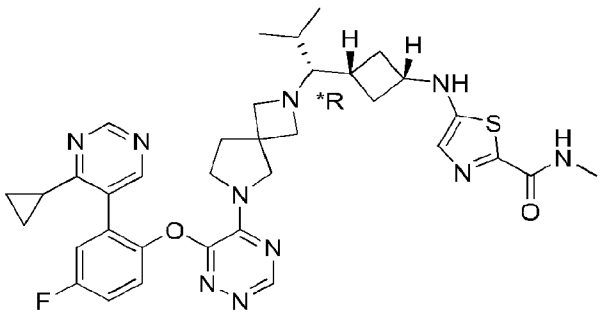
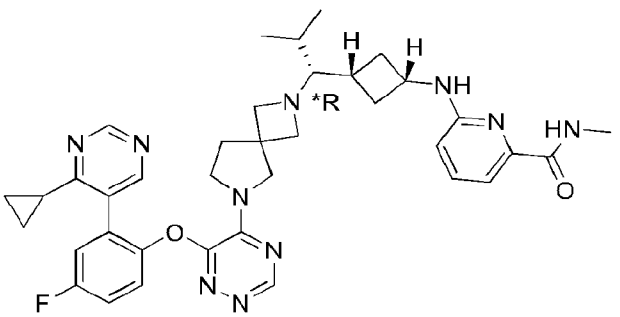
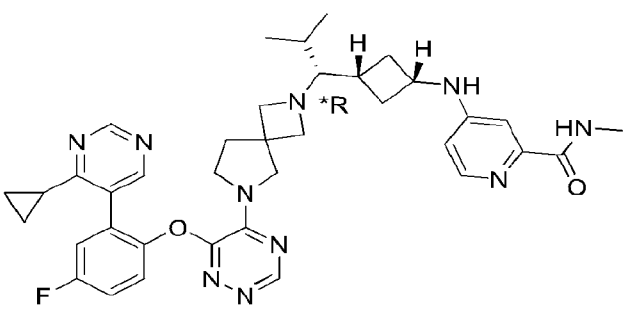
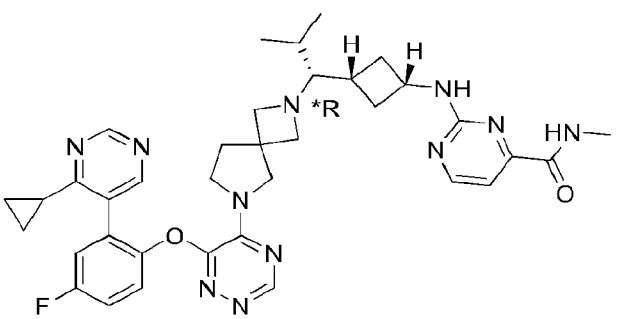
Compound 479 (180 m g, 0.275 mmol) was dissolved in THF (7.2 mL) and treated with dimethylamine (275 uL, 0.549 mmol, 2.0 equiv, 2 M in THF) and triethylamine (83.3 mg, 0.824 mmol, 2.0 equiv). Then T3P (174.7 mg, 0.549 mmol, 2.0 equiv.) was added. The reaction was stirred at room temperature over night. Further 0.2 equiv. of T3P were added and the mixture was stirred for further 2 hours. The reaction was quenched by addition of water and ethyl acetate. The water layer was separated and extracted with ethyl acetate (1 x). The combined organic phases were washed with sat. Na_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. A first purification by column chromatography (silica gel, 0 to 15% MeOH in DCM) was followed by a second purification by Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD- 5µm, 50x250 mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH3CN) to give Compound 435 (35 mg, 0.0513 mmol, 19% yield) as a white solid .

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 435 starting from the corresponding starting materials

Compound number	Compound structure
436	 From Compound 478 and methylamine in MeOH

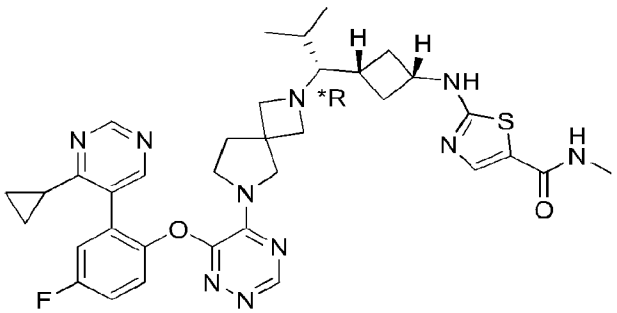
Compound number	Compound structure
438	 From Compound 480 and methylamine in MeOH
461	 From Compound 441, ethyl 2-Cl-oxazole-4-carboxylate and methylamine in MeOH
439	 From Compound 481 and methylamine in MeOH
442	 From Compound 482 and methylamine in MeOH

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Compound number	Compound structure
449	 From Compound 484 and methylamine in MeOH
450	 From Compound 485 and methylamine in MeOH
451	 From Compound 486 and methylamine in MeOH
452	 From Compound 487 and methylamine in MeOH

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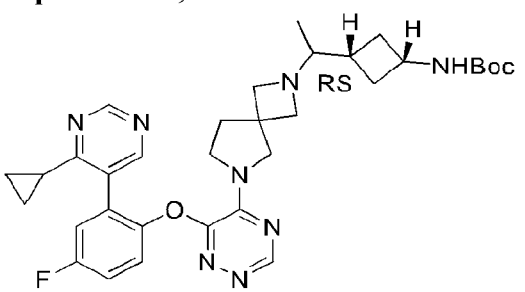
Preparation of Compound 437



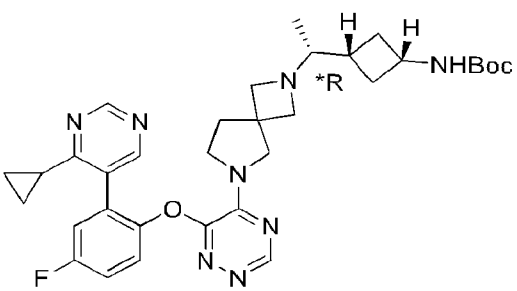
In a closed vial Compound 1a (305 mg, 0.521 mmol) was treated with 2-bromo-*N*-methylthiazole-5-carboxamide (120 mg, 0.521 mmol), and JOSIPHOS SL-J009-1 Pd G3 (48.1 mg, 0.0521 mmol). Then dry DMA (5.2 mL) was added. The dark brown mixture was stirred over night at 70°C. Sat sodium carbonate solution and EtOAc was added. The phases were separated and the water phase was extracted several times with EtOAc. The organic phase was dried with magnesium sulfate and filtered. After evaporation of the solvents, the crude product (410 mg) was obtained as a yellow oil. A purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 437 (121 mg, yield 33.927%) as a white solid.

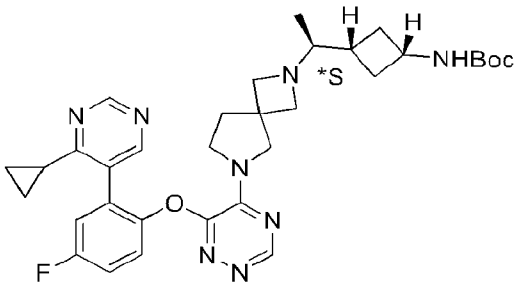
Preparation of Compound 512, 512a & 512b

Compound 512:



Compound 512a:



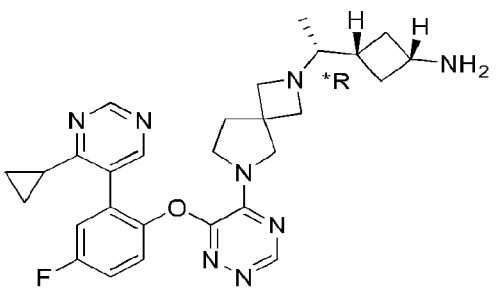


Compound 512b:

To a solution of intermediate 33 (1.59 g, 3.61 mmol), acetic acid (216.8 mg, 3.61 mmol) and intermediate 336 (1.54 g, 7.221 mmol) were dissolved in dry methanol (20 mL). Then sodium cyanoborohydride (907.5 mg, 14.4 mmol) was added. After stirring at 60 °C over night, the methanol was evaporated. Ethyl acetate was added. Then a saturated solution of sodium carbonate was added and the water phase was further basified with 1 N NaOH solution to pH 13. The water phase was extracted with EtOAc and DCM several times. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solid was filtered off. The filtrate was concentrated under reduced pressure. A crude product (2 g) was obtained as light yellow solid and purified by prep CC (silica gel, 2% to 10% MeOH in DCM) to give two fractions of Compound 512 (700 mg, 31.4% yield) and (1000 mg, 44.9% yield) with various amounts of impurities as a white solids.

A purification was performed via Prep SFC (Stationary phase: Chiralpak Daicel IG 20 x 250 mm, Mobile phase: CO_2, EtOH + 0.4 $iPrNH_2$) to give Compound 512a (680 mg, 30.5% yield) and Compound 512b (630 mg, 28.3% yield) were obtained as a colorless oils.

Preparation of Compound 440

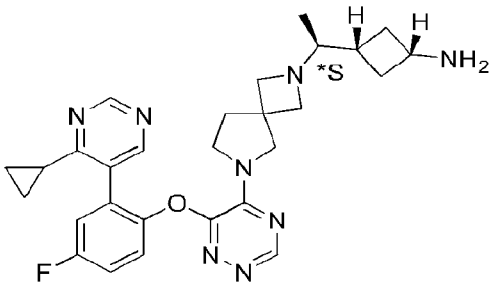


In a flask, Compound 512a (660 mg, 1.07 mmol) was dissolved in DCM (10.3 mL) and treated with TFA (1.31 mL, 17.122 mmol) at 0°C. After stirring over night, thereby the mixture was allowed to come to rt. The mixture was diluted with DCM and sat. sodium carbonate solution. The water was was adjusted to pH 13 with sodium hydroxide solution. The water phase was extracted multiple times with DCM and EtOAc. The combined organic solvents were dried with $MgSO_4$, fiiltrated and evaporated to obtain Compound 440 (550 mg, 99.5% yield) as a white foamy solid. A part of the product (35 mg) was used and a purification was performed via Prep

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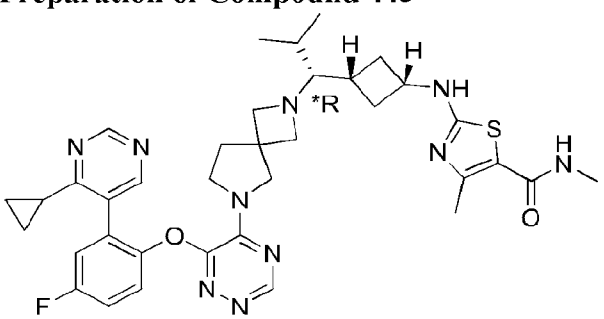
HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm,30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 440 (30 mg) as a white solid.

Preparation of Compound 441



In a flask, Compound 512b (600 mg, 0.973 mmol) was dissolved in DCM (9.4 mL) and treated with TFA (1.19 mL, 15.6 mmol) at 0°C. After stirring over night, thereby the mixture was allowed to come to rt. The mixture was diluted with DCM and sat. sodium carbonate solution. The water was was adjusted to pH 13 with sodium hydroxide solution. The water phase was extracted multiple times with DCM and EA. The combined organic solvents were dried with $MgSO_4$, fiiltrated and evaporated to obtain Compound 441 (530 mg, quant. yield) as a white foamy solid. A part of the product (33 mg) was used and a purification was performed via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm,30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 441 (19.8 mg) as a white solid.

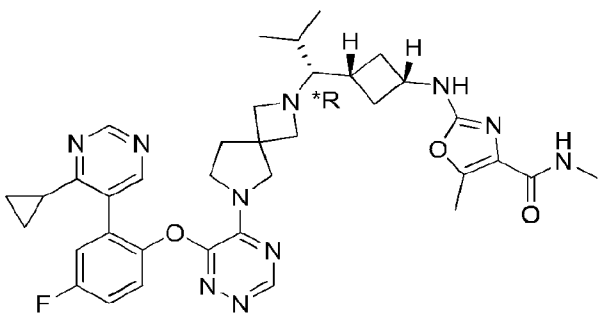
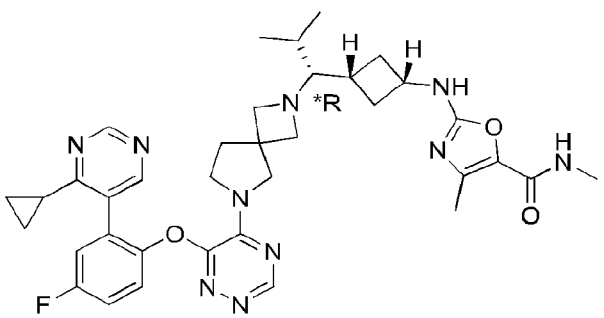
Preparation of Compound 443



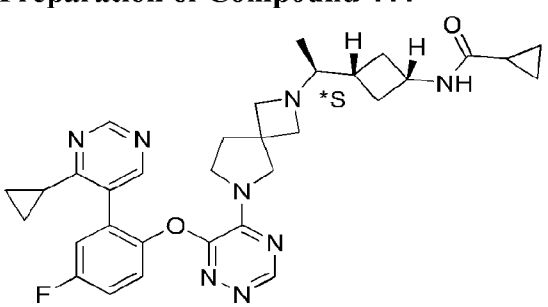
Bis(trimethylaluminium)-1,4-diazabicyclo[2.2.2]octane adduct (0.18 g, 0.71 mmol) was added portionwise to a stirred solution of Compound 482 (130 mg, 0.18 mmol) and methylamine, 2M in THF (0.54 mL, 1.07 mmol) in anhydrous toluene (10 mL). After addition the reaction mixture was stirred at 100°C for 5 hours. The solvents were evaporated using a flow of nitrogen gas while heating at 65°C. The residue was dissolved in dichloromethane and some methanol. The resulting suspension was filtered over a pad of Dicalite. The pad was washed with dichloromethane with some methanol. The solvents of the filtrate were evaporated under reduced pressure at 45°C. The residue was dissolved in dichloromethane and purified over a

SiO_2 column, 12 g, using dichloromethane and methanol as eluens in a gradient starting from 100% dichloromethane and ending with 90% dichloromethane and 10% methanol. The fractions containing product were combined and the solvents were evaporated under reduced pressure at 50°C to give Compound 443 (80 mg, 64% yield).

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 443 starting from the corresponding starting materials

Compound number	Compound structure
459	 From Compound 1a and ethyl 2-bromo-5-methyloxazole-4-carboxylate
460	 From Compound 1a and ethyl 2-bromo-4-methyloxazole-5-carboxylate

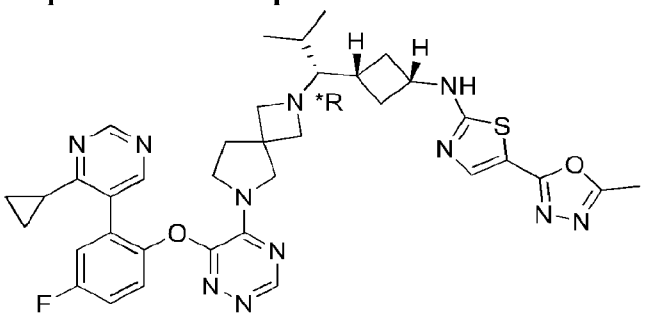
Preparation of Compound 444



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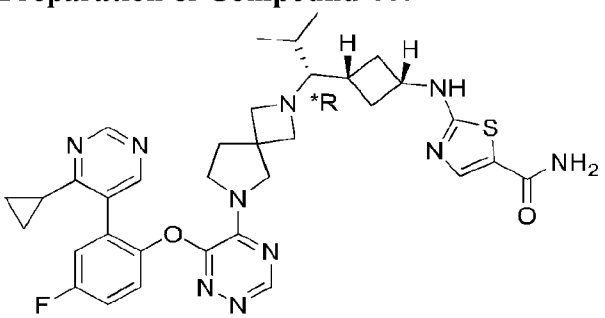
In a small vial, Compound 441 (22 mg, 0.0426 mmol) was dissolved in dry DCM (0.46 mL). Then cyclopropanecarboxylic acid (4.4 mg, 0.0511 mmol), Et_3N (13.0 mg, 0.728 g/mL, 0.128 mmol), and T3P, 50% in ethyl acetate (38.0 mg, 0.0597 mmol) was added. The mixture was stirred over night at rt. The solvents were evaporated and the crude product which was directly subjected to Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH3CN) yielding Compound 444 (12 mg, 48.2% yield) as a white solid.

Preparation of Compound 445



In a flask, Compound 1a (50.0 mg, 0.0918 mmol) was treated with K_2CO_3 (25.4 mg, 0.184 mmol) and intermediate 338 (55.5 mg, 0.138 mmol). Then dry acetonitrile (1.4 mL) was added and and the mixture was heated to 75 °C (red mixture obtained). After stirring over night, a 1:1 mixture of Compound 1a and product was observed. 20 mg more of the base and 20 mg more of intermediate 338 were added. The mixture was stirred for 8 h at 75°C. Nearly no sm was observed anymore in HPLC. After cooling down to RT, the mixture was allowed to stand over 3 days at RT. Water and ethyl acetate were added and the separated water phase was extracted several times with ethyl acetate. The collected organic phases were dried $MgSO_4$, filtered and evaporated at rotavap to give the crude product which was purified by Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD- 5µm, 50x250mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) to afford Compound 445 (15.3 mg, 23.5% yield) as a white solid.

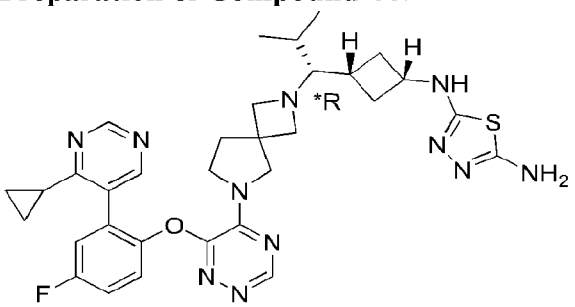
Preparation of Compound 446



In a small vial, Compound 1a (50 mg, 0.0918 mmol) was dissolved in dry MeCN (1.4 mL) and treated with K_2CO_3 (25.4 mg, 0.184 mmol) and 2-bromo thiazole 5-carboxamide (22.8 mg,

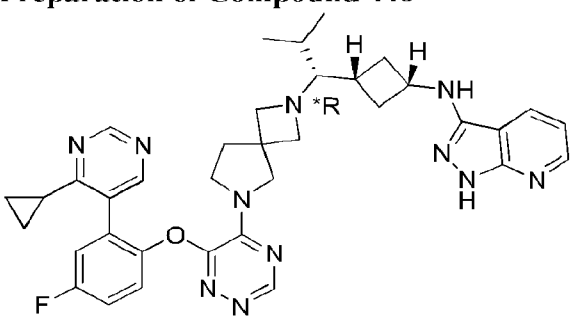
0.11 mmol). The mixture was heated in a closed vial at 70°C for 7 days. The mixture was deep red. HPLC showed full conversion. Sodium carbonate solution (sat.) was added and the water phase was extracted several times with EtOAc. Drying with magnesium sulfate, fillration on evaporation afforded a crude product which was purified by Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 446 (15.3 mg, 24.8% yield) as a white fluffy solid.

Preparation of Compound 447



Compound 1a (40 mg, 0.0734 mmol), 5-bromo-1,3,4-thiadiazol-2-amine (13.221 mg, 0.0734 mmol) and DIPEA (0.0633 mL, 0.75 g/mL, 0.367 mmol) were added to MeCN (4 mL, 0.786 g/mL, 76.585 mmol). The mixture was stirred at 75°C for 2 hours. The solvent was removed and the residue was purified by flash column (C18, CH_3CN:H_2O from 0:100 to 50:50, 0.5% fumarate as buffer) to afford Compound 447 (25 mg, 48% yield).

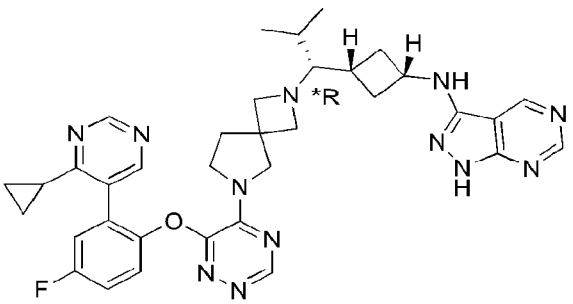
Preparation of Compound 448



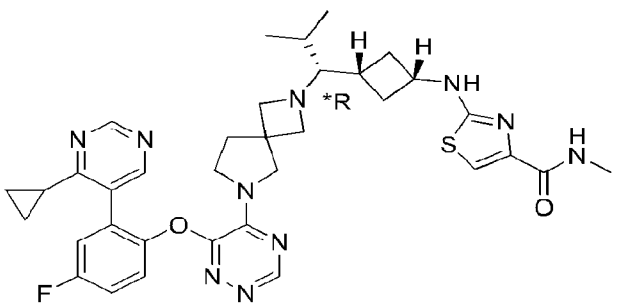
A mixtrure of Compound 1a (200 mg, 0.367 mmol), 3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (241.715 mg, 0.734 mmol), *L*-proline (42.275 mg, 0.367 mmol), CuI (34.966 mg, 0.184 mmol) and K_2CO_3 (152.244 mg, 1.102 mmol) in DMSO (23.676 mL, 1.092 g/mL, 330.894 mmol) was stirred at 115°C overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried, filtered and concentrated to give the crude product. Purification by Biotage (C18, 5-95% MeCN in water with 0.05% formic acid) to afford the THP protected intermediate (130 mg, yield 47.464%), which was treated with TFA and DCM and stirred for 2h, concentrated and purified by Biotage (C18, 5-95% MeCN in water with 0.05% formic acid) to afford Compound 448 (80 mg, 31% yield) as a white solid.

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The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 448 starting from the corresponding starting materials

Compound number	Compound structure
458	 From Compound 1a and 3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine

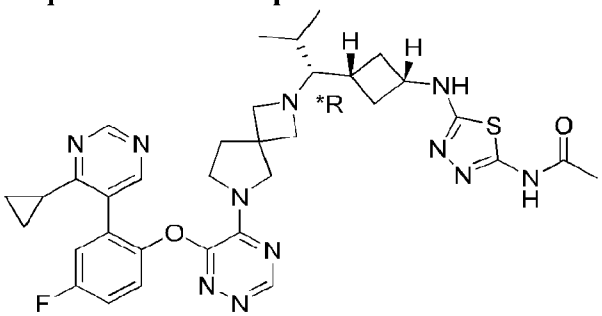
Preparation of Compound 453



In a closed vial, Compound 1a (150 mg, 0.256 mmol) was treated with 2-bromo-*N*-methylthiazole-4-carboxamide (56.6 mg, 0.256 mmol), JOSIPHOS SL-J009-1 Pd G3 (23.7 mg, 0.0256 mmol), and Cs_2CO_3 (250.3 mg, 0.768 mmol). Then dry DMA (2.6 mL) was added. The dark brown mixture was stirred over two days at 70°C. Sat. sodium carbonate solution was added along with EtOAc. The water phase was extracted several times with EtOAc. The organic phase were dried with magnesium sulfate. After filtration and evaporation, the crude product was purified via Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) to obtain Compound 453 (35.6 mg, 20.3% yield) as a white solid.

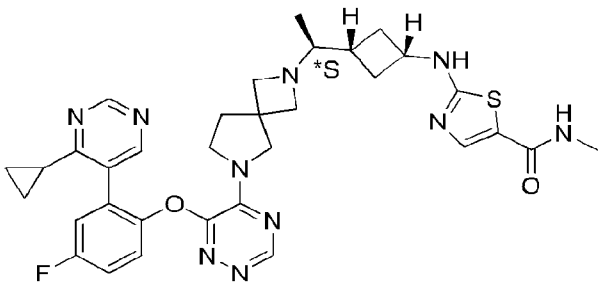
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Preparation of Compound 454



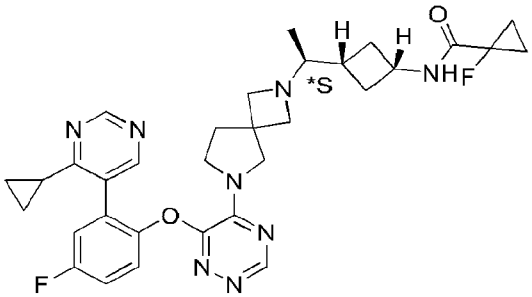
Compound 488 (130 mg, 0.192 mmol) was dissolved in DCM (4.75 mL, 1.326 g/mL, 74.159 mmol). DIEA (0.0496 mL, 0.75 g/mL, 0.288 mmol) and acetic anhyride (23.501 mg, 0.23 mmol) was added to the mixture at 0°C dropwise. The solvent was removed and the residue was purified by flash column(C18, CH_3CN: H_2O from 5:95 to 30:70, HCOOH as buffer) to afford Compound 454 (88 mg, 65% yield).

Preparation of Compound 455



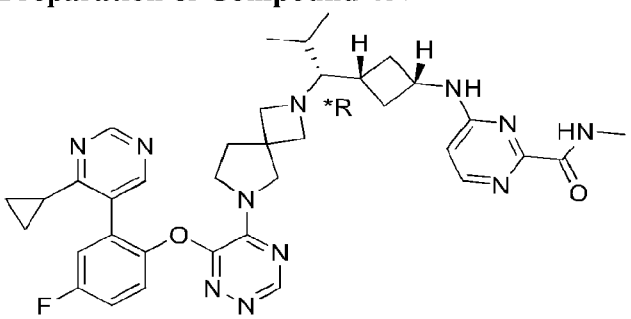
In a closed vial, Compound 441 (94 mg, 0.182 mmol) was treated with 2-bromo-*N*-methylthiazole-5-carboxamide (49.7 mg, 0.2 mmol), JOSIPHOS SL-J009-1 Pd G3 (16.8 mg, 0.0182 mmol), and Cs_2CO_3 (177.9 mg, 0.546 mmol). Then dry DMA (1.8 mL) was added. The dark brown mixture was stirred over night at 7 °C. Sat sodium carbonate solution and EtOAc was added. The phases were separated and the water phase was extracted several times with EtOAc. The organic phase was dried with magnesium sulfate and filtered. After evaporation of the solvents, the crude product was obtained as a yellow solid. A purification was performed FCC (silica gel, 5% to 10% methanol in DCM) to afford the product (33 mg, 93% purity) as white solid, which was further purified by Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD- 5µm, 50x250mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) to give Compound 455 (19 mg, 16% yield).

Preparation of Compound 456



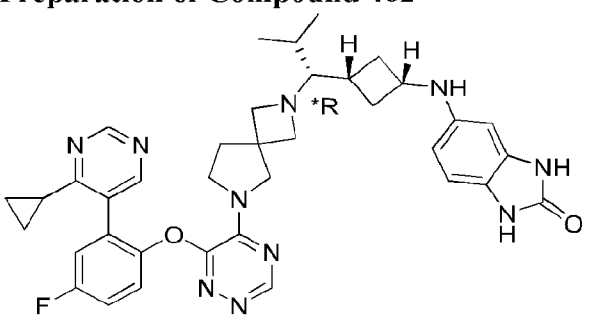
In a small vial, Compound 441 (30 mg, 0.0581 mmol) was dissolved in dry DCM (0.63 mL). Then cyclopropane fluoro carboxylic acid (7.3 mg, 0.0697 mmol), Et_3N (24 µL, 0.728 g/mL, 0.174 mmol), and T3P, 50% in ethyl acetate (51.8 mg, 0.0814 mmol) was added. The mixture was stirred over night at rt. The solvents were evaporated and the solid was directly subjected to Prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm,30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 456 (3.6 mg, 10.3% yield) as a white solid.

Preparation of Compound 457



In a vial, Compound 489 (141 mg, 0.207 mmol) was dissolved in $MeNH_2$ (2M in isopropanol) (4.97 mL, 2 M, 9.941 mmol) and heated at 70°C over night. The solvents were removed at rotavap. The residue was diluted in 18 mL MeCN and subjected to prep HPLC (Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) yielding Compound 457 (73 mg, 51.8% yield) as a white fluffy solid after lyophilzation.

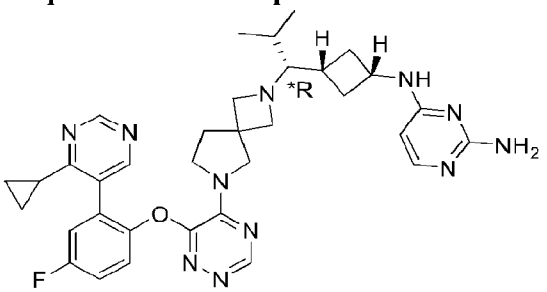
Preparation of Compound 462



A mixture of Compound 38b (100 mg, 0.184 mmol), 5-amino-1,3-dihydro-2h-benzimidazol-2-

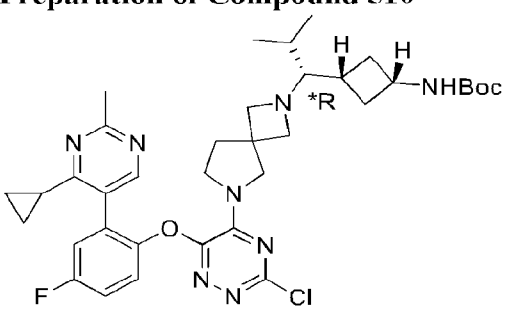
one (54.871 mg, 0.368 mmol), AcOH (0.0211 mL, 1.049 g/mL, 0.368 mmol) in MeOH (3 mL, 0.791 g/mL, 74.059 mmol) was stirred at 50°C for 30 min before the addition of sodium cyanoborohydride (23.119 mg, 0.368 mmol). The mixture was stirred at 50°C for 3hr and concentrated. The crude product was pufiried by ISCO (C18, 5-95% MeCN in water with 0.05% formic acid) to afford Compound 462 (25 mg, 18% yield).

Preparation of Compound 463



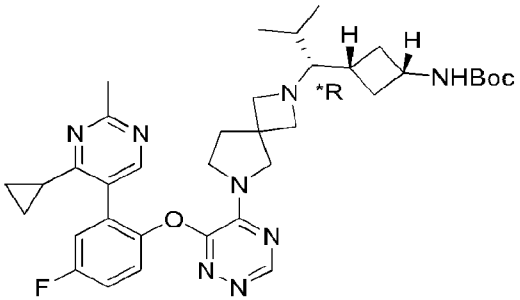
4-chloropyrimidin-2-amine (105 mg, 0.808 mmol) was added to a solution of Compound 1a (200 mg, 0.367 mmol) , TEA (74.3 mg, 0.734 mmol) in propan-2-ol (5 mL). The mixture was stirred at 80°C for overnight. The reaction mixture was concentrated under reduced pressure to afford the crude product which was purified by SFC over DAICEL CHIRALPAK AD (250mm*30mm, 10um) (eluent: 40% to 40% (v/v) supercritical 0.1%NH_3H_2O EtOH). The pure fractions were collected and the volatiles were removed under reduced pressure. The product was suspended in water (5 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford Compound 463 (68 mg, 29. % yield) as a white solid.

Preparation of Compound 510



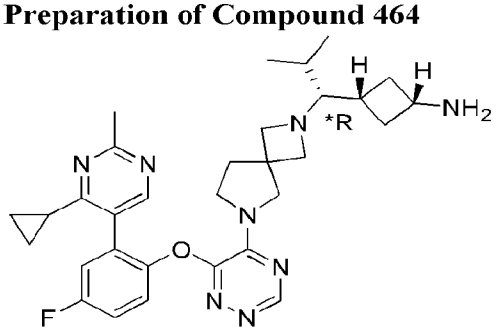
To a solution of intermediate 321 (0.850 g, 3.48 mmol) and intermediate 333 (1.69 g, 3.48 mmol) in dry tetrahydrofuran (30 mL) was added DBU (0.636 g, 4.18 mmol). The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was diluted with dichloromethane (50 mL) and water (50 mL) was added. The mixture was extracted with dichloromethane (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (eluent: DCM: MeOH from 1: 0 to 10: 1) to give Compound 510 (2.50 g, crude) as a yellow solid.

Preparation of Compound 511



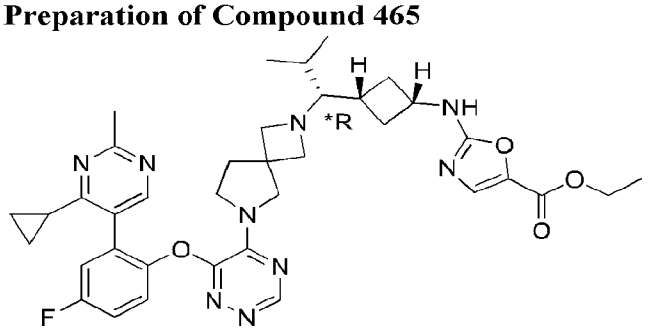
To a solution of Compound 510 (2.50 g, crude) in THF (50 mL) was added TMEDA (0.838 g, 7.21 mmol) and $Pd(dppf)_2Cl_2$ (0.132 g, 0.180 mmol) and $NaBH_4$ (0.408 g, 6.49 mmol). The mixture was stirred at 25 °C for 8 h under N_2. The reaction was quenched with MeOH (50 mL) dropwise, and the mixture was diluted with water (50 mL) and extracted with EtOAc (50 mLX4). The organic layers were dried over Na_2SO_4, filtered and concentrated, and the residue was purified by FCC (from pure DCM to pure DCM/MeOH=10/1) to give Compound 511 (1.30 g, yield: 49.2%) as a yellow solid.

Preparation of Compound 464



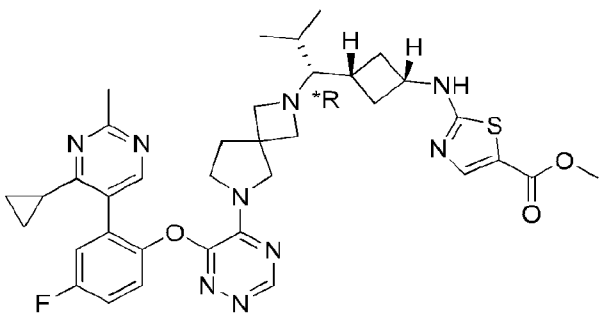
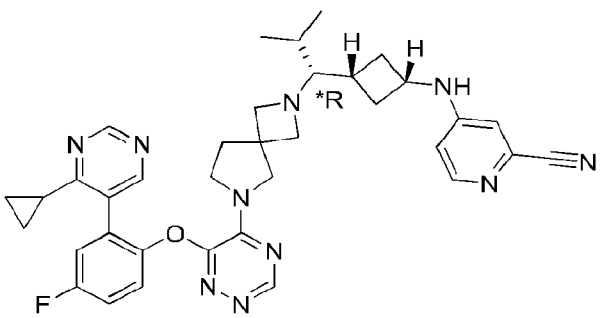
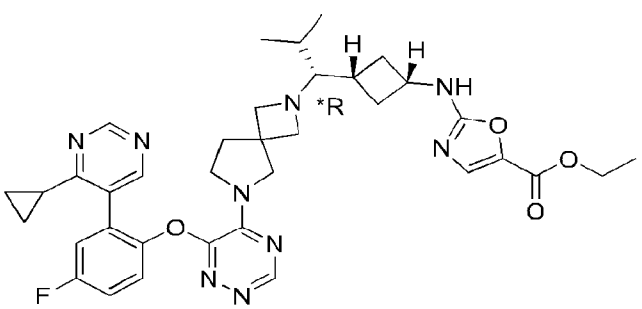
To a solution of Compound 511 (1.30 g, 1.85 mmol) in DCM (6 mL) was added TFA (2 mL, 26.9 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated, the residue was diluted with DCM (20 mL) and neutralized with cold 2M NaOH (14 mL). The mixture was extracted with DCM (25 mLX5) and the organic layers were dried over Na_2SO_4, filtered and concentrated to give Compound 464 (1.1 g, crude) as a yellow solid.

Preparation of Compound 465

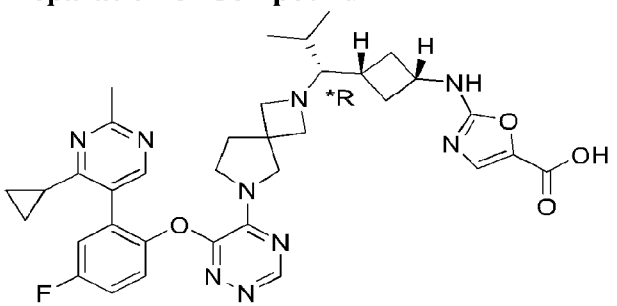


A stir bar, Compound 464 (50 mg, 0.089 mmol), ethyl 2-chlorooxazole-5-carboxylate (17.3 mg, 0.099 mmol), K_2CO_3 (24.7 mg, 0.179 mmol) in ACN (3 mL) were added to a 8 mL round-bottomed flask before the mixture was stirred at rt for 8 h. The solvent was evaporated under reduced pressure to give crude Compound 465 (70 mg, crude) as a brown soild.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 465 starting from the corresponding starting materials

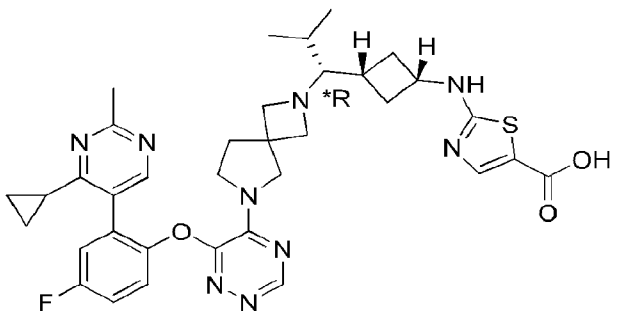
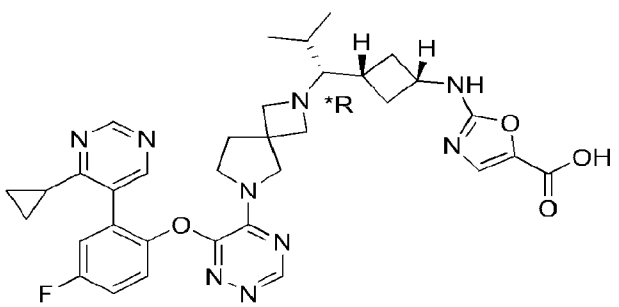
Compound number	Compound structure
467	 From Compound 464 and methyl 2-bromothiazole-5-carboxylate
473	 From Compound 1a and 4-bromopicolinonitrile
478	 From Compound 1a and ethyl 2-chlorooxazole-5-carboxylate

Preparation of Compound 466

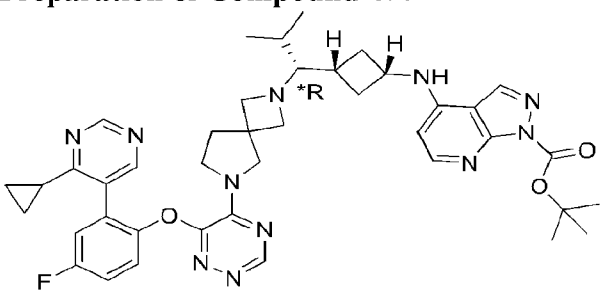


To a solution of Compound 465 (120 mg, 0.17 mmol) in THF/H_2O (4mL/1.5mL) was added $LiOH \cdot H_2O$ (7 mg, 0.17 mmol) and the mixture was stirred at 25°C for 10 h. The residue was basified with HCl (1N aqueous) to pH = 4 and concentrated under reduced pressure to give the crude product as a white solid (120 mg, crude).

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 466 starting from the corresponding starting materials

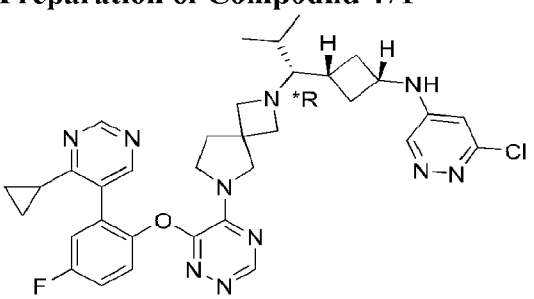
Compound number	Compound structure
468	 From Compound 467
479	 From Compound 478

Preparation of Compound 470



A stir bar, *t*-BuXPhos-Pd-G3 (14.6 mg, 0.018 mmol), *t*-BuXPhos (8.0 mg, 0.019 mmol), Compound 1a (100.0 mg, 0.184 mmol) and *tert*-butyl 4-bromo-1*H*-pyrazolo[3,4-b]pyridine-1-carboxylate (82.1 mg, 0.275 mmol) were added to a 50 mL round-bottomed flask. The resulting mixture was purged with argon for three times, then LiHMDS (0.92 mL, 0.92 mmol, 1 M in THF) and anhydrous tetrahydrofuran (8 mL) were added. The reaction mixture was purged with argon for three times again and heated to 65°C and stirred for 12 hours. The reaction mixture was cooled to room temperature and quenched with HCl (1 M, 3 mL), diluted with ethyl acetate (50 mL) and poured into saturated solution of sodium bicarbonate (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (eluent: dichloromethane: methanol from 1: 0 to 10: 1, TLC: dichloromethane: methanol = 10: 1, Rf = 0.5) to give Compound 470 (45.0 mg, 69.71% purity, 22.4% yield) as a brown solid.

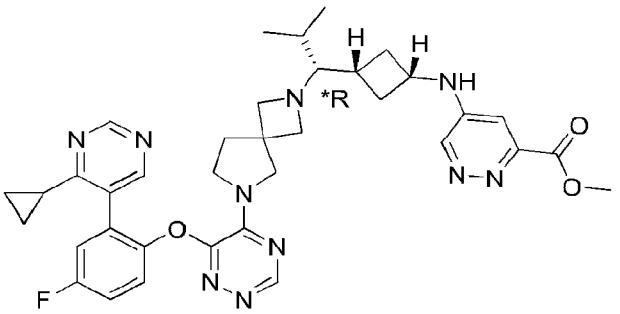
Preparation of Compound 471



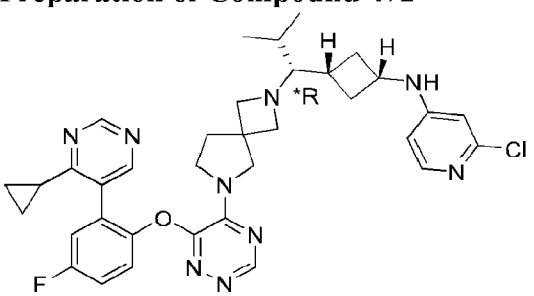
Compound 1a (200 mg,0.367 mmol), 3,5-dichloropyridazine (82 mg, 0.55 mmol), Et_3N (0.16 ml,1.2 mmol), and DMSO (2 mL) were added added to a 10 mL sealed tube. The resultant mixture was stirred at 100°C for 12 hours before cooling to room-temperature. The residue was purified by preparative HPLC using a Phenomenex Gemini-NX 150*30mm*5um (eluent: 41% to 69% (v/v) CH_3CN and water (0.05%NH_3H_2O)-ACN) to afford pure product. The product was suspended in water (4 mL), the mixture frozen using dry ice/EtOH, and then lyophilized to dryness to afford Compound 471 (75 mg, 30.9%) as a yellow solid.

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 471 starting from the corresponding starting

materials

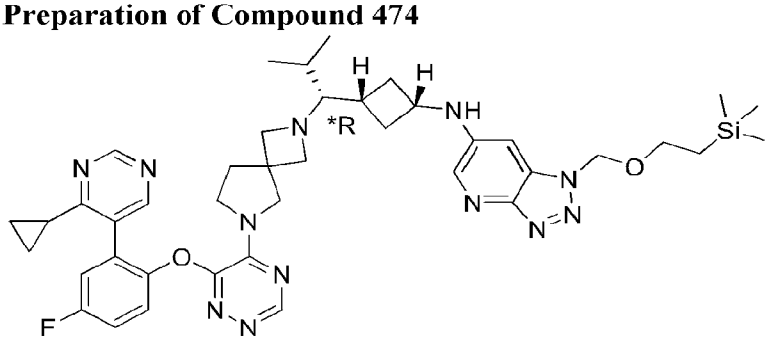
Compound number	Compound structure
475	 From Compound 1a and methyl 5-chloropyridazine-3-carboxylate

Preparation of Compound 472



To a solution of Compound 1a (300 mg, 0.551 mmol) in NMP (3 ml) was added 2-chloro-4-fluoropyridine (150.0 mg, 1.14 mmol) and DIEA (216 mg, 1.671 mmol) in a microwave apparatus. The mixture was stirred at 150 °C for 0.5 hours. The mixture was purified by reverse phase silica gel column (Column:120 g Agela C18 150*25mm*5um, Mobile Phase A: water, Mobile Phase B: acetonitrile, Flow rate: 30 mL/min, gradient condition: from 80% B to 100% B) to afford Compound 472 (350 mg, 90% yield) as a brown soild.

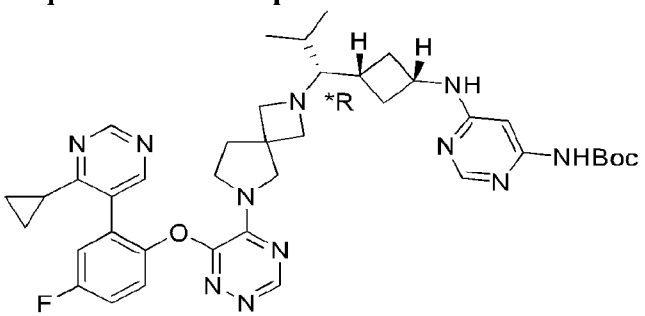
Preparation of Compound 474



To a suspension of Compound 1a (150 mg, 0.275 mmol) in 1,4-dioxane (3 ml) was added 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-[1,2,3]triazolo[4,5-b]pyridine (305 mg, 0.824 mmol), *t*-BuONa (90 mg, 0.936 mmol) and *t*BuXPhos-Pd-G3 (15 mg, 0.019 mmol) with Ar_2 in

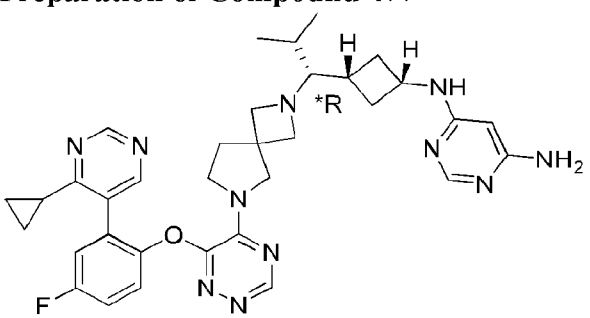
a microwave apparatus. The mixture was stirred at 100 °C for 2 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase silica gel column (Column: 20 g Agela C18 150*25mm*5um, Mobile Phase A: water, Mobile Phase B: acetonitrile, Flow rate: 35 mL/min, gradient condition: from 35% B to 60% B) to afford Compound 474 (174 mg, 80% yield) as a yellow soild.

Preparation of Compound 476



To a mixture of Compound 1a (500 mg, 0.918 mmol), *tert*-butyl (6-chloropyrimidin-4-yl)carbamate (421 mg, 1.83 mmol) in EtOH (8 mL), then DIEA (0.48 mL, 2.76 mmol) was added to the above mixture. The mixture was stirred at 80 °C for 48 hours. The mixture was concentrated in vacuo. The residue was diluted with DCM (20 ml), washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to give the crude which was purified by FCC (eluting with dichloromethane : MeOH = 1:0 to 10:1) to give Compound 476 (226 mg, purity 86.8%, yield 29%) as a yellow solid.

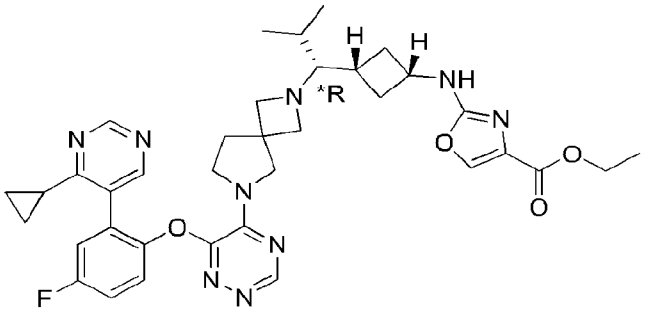
Preparation of Compound 477



To a mixture of Compound 476 (220 mg, 0.298 mmol) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The mixture was stirred for 1 hour at room temperature. The mixture evaporated to remove solvent. The residue was diluted by water (5 mL), besified to pH=12 with NaOH (2 M, 4 mL), extracted with DCM (10 mL x 3). The combined organic dried over Na_2SO_4, filtered, and concentrated to dryness under reduce pressure to afford Compound 477 (173 mg, 91% yield) as a yellow solid.

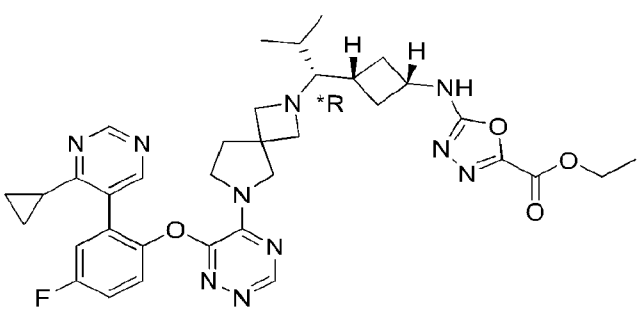
CA 03214746 2023-10-5

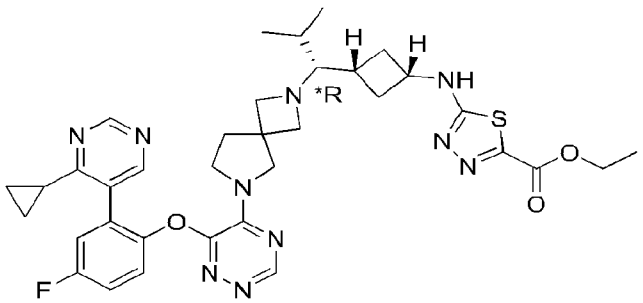
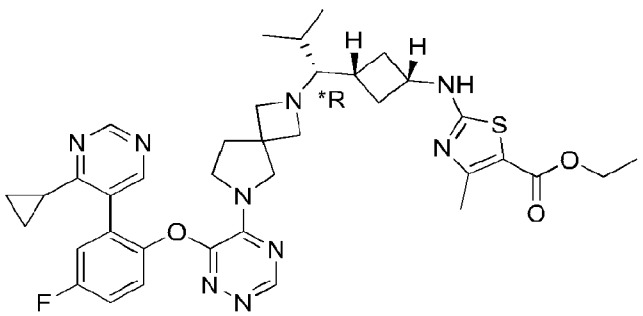
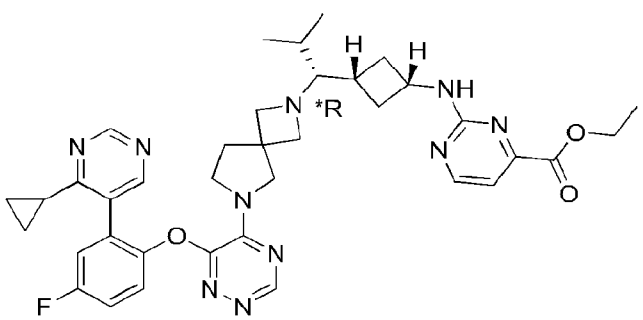
Preparation of Compound 480



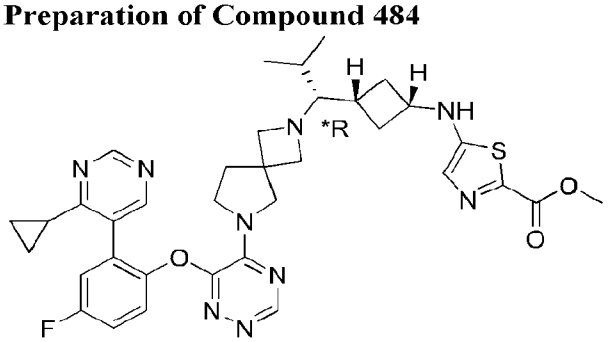
In a vial, ethyl 2-chlorooxazole-4-carboxylate (0.099 g, 0.55 mmol) was added to a stirred mixture of Compound 1a (250 mg, 0.46 mmol) and K_2CO_3 (0.13 g, 0.92 mmol) in DMF (6 mL, 0.94 g/mL, 77.16 mmol) at room temperature. After addition the reaction mixture was stirred at 90°Cfor 4 hours. The reaction mixture was diluted with ethylacetate and then filtered. The filtrate was washed with brine, dried with $MgSO_4$, filtered and the solvents of the filtrate evaporated under reduced pressure at 55°C. The residue was dissolved in dichloromethane and purified over a SiO_2 column, 12 g, using dichloromethane and methanol as eluens in a gradient starting from 100% dichloromethane and ending with 95% dichloromethane and 5% methanol. The fractions containing product were combined and the solvents were evaporated under reduced pressure at 50°C to give Compound 480 (170 mg, 54% yield).

The compounds listed in the table below were prepared following the same procedure as reported for the preparation of Compound 480 starting from the corresponding starting materials

Compound number	Compound structure
481	 From Compound 1a and ethyl 5-bromo-1,3,4-oxadiazole-2-carboxylate

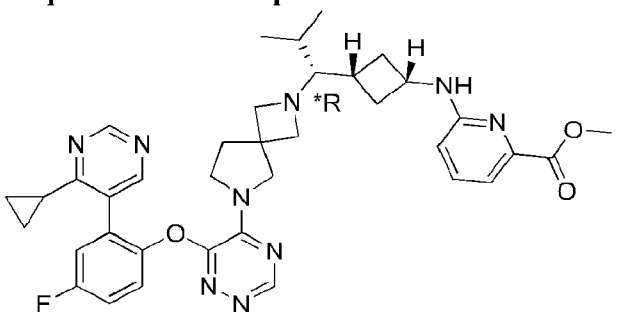
Compound number	Compound structure
482	 From Compound 1a and ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate
483	 From Compound 1a and ethyl 2-bromo-4-methylthiazole-5-carboxylate
487	 From Compound 1a and ethyl 2-bromopyrimidine-4-carboxylate

Preparation of Compound 484



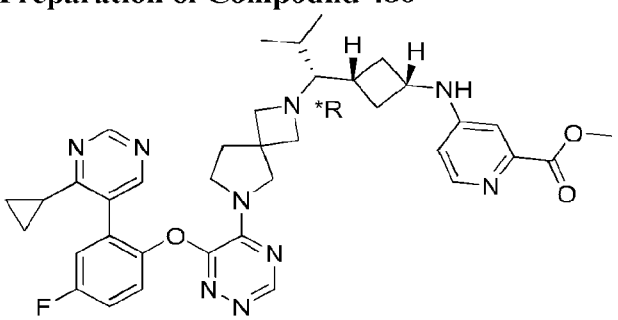
Compound 1a (100 mg, 0.184 mmol), methyl 5-bromothiazole-2-carboxylate (40.77 mg, 0.184 mmol), BrettPhos Pd G3 (16.643 mg, 0.0184 mmol) and Cs_2CO_3 (179.457 mg, 0.551 mmol) were added to toluene (7.5 mL, 0.867 g/mL, 70.572 mmol). The mixture was heated to 110 °C for 16 hours under N_2 protection. Solvent was removed and the residue was purified by flash column (PE:EtOAc from 70:30 to 0:100) to afford Compound 484 (20 mg, 36% yield).

Preparation of Compound 485



A mixture of Compound 1a (250 mg, 0.43 mmol), methyl 6-bromopicolinate (0.18 g, 0.85 mmol) and cesium carbonate (0.42 g, 1.28 mmol) in 1,4-dioxane (3 mL) was flushed through with nitrogen gas. Then, palladium(II) acetate (0.0096 g, 0.043 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.025 g, 0.043 mmol) were added. The reaction mixture was purged with N_2 and heated at 100°C for 18h. The reaction mixture was cooled down to room temperature, diluted with ethylacetate and then filtered. The filtrate was washed with water and brine, dried with $MgSO_4$, filtered and the solvents of the filtrate evaporated under reduced pressure at 45°C. The residue was dissolved in dichloromethane and purified over a SiO_2 column, 12 g, using dichloromethane and methanol as eluens in a gradient starting from 100% dichloromethane and ending with 95% dichloromethane and 5% methanol. The fractions containing product were combined and the solvents were evaporated under reduced pressure at 50°C to give Compound 485 (140 mg, 49% purity, 24% yield) which was used in the next step.

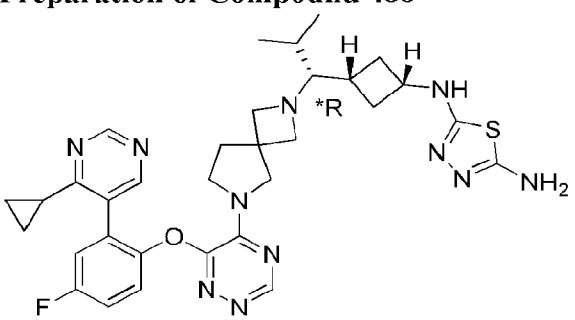
Preparation of Compound 486



A mixture of Compound 1a (250 mg, 0.43 mmol), methyl 4-bromopicolinate (0.18 g, 0.85 mmol) and cesium carbonate (0.42 g, 1.28 mmol) in 1,4-dioxane (3 mL) was degased with N_2. Then,

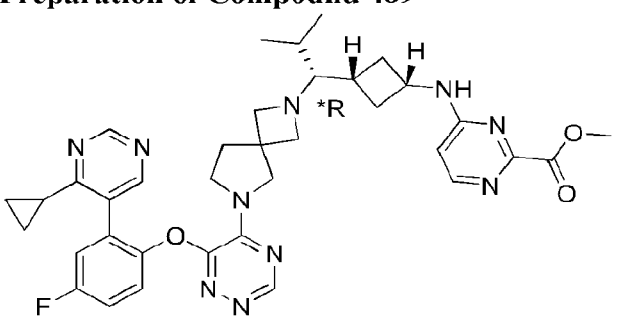
palladium(II) acetate (0.0096 g, 0.043 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.025 g, 0.043 mmol) were added. The reaction mixture was purged with N_2 and heated at 100°C for 18h. An additional amount of methyl 4-bromopicolinate (0.092 g, 0.43 mmol), palladium(II) acetate (0.0096 g, 0.043 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.025 g, 0.043 mmol) was added. The reaction mixture was heated at 100°C for 18h. The reaction mixture was cooled down to room temperature, diluted with ethylacetate and then filtered. The filtrate was washed with water and brine, dried with $MgSO_4$, filtered and the solvents of the filtrate evaporated under reduced pressure at 45°C. The residue was dissolved in dichloromethane and purified over a SiO_2 column, 12 g, using dichloromethane and methanol as eluens in a gradient starting from 100% dichloromethane and ending with 95% dichloromethane and 5% methanol. The fractions containing product were combined and the solvents were evaporated under reduced pressure at 50°C to give Compound 486 (27 mg, 5.5% yield).

Preparation of Compound 488



Compound 1a (150 mg, 0.275 mmol), 5-bromo-1,3,4-thiadiazol-2-amine (49.579 mg, 0.275 mmol) and DIPEA (0.237 mL, 0.75 g/mL, 1.377 mmol) were added to MeCN (15 mL, 0.786 g/mL, 287.193 mmol). The mixture was stirred at 75 °C for 2 hours. The solvent was removed and the residue was purified by flash column (C18, CH_3CN:H_2O from 0:100 to 50:50, 0.5% fumarate as buffer) to afford Compound 488 (140 mg, 75% yield).

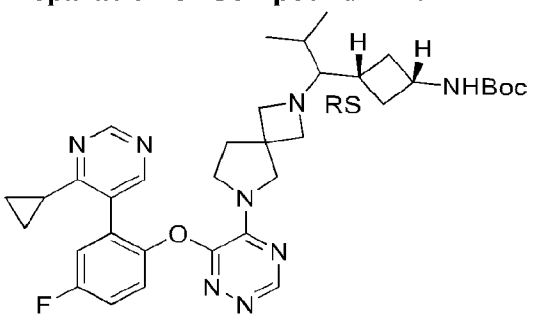
Preparation of Compound 489



In a closed vial, Compound 1a (350 mg, 0.598 mmol) was treated with methyl 4-bromopyrimidine-2-carboxylate (155.6 mg, 0.717 mmol), Cs_2CO_3 (584.1 mg, 1.793 mmol),

and JOSIPHOS SL-J009-1 Pd G3 (55.2 mg, 0.0598 mmol). Then dry DMA (6 mL) was added and the mixture was stirred for 6 h at 70 °C. Then mixture was allowed to stand over the weekend at rt. Then the mixture was heated again over night. The mixture was worked up by addition of sat. sodium carbonate solution and EtOAc. The phases were separated and the water phase was extracted multiple times with EtOAc and DCM. Drying with magnesium sulfate, filtration and evaporation of solvents afforded the crude material which was subjected to FCC (silica gel, 2% to 10% methanol in DCM, evaporation of solvents at 35°C water bath temp) to afford Compound 489 (25 mg, 6.1% yield).

Preparation of Compound 490:



To a solution of intermediate 15 (200 mg, 0.582 mmol) in CH_2Cl_2 (12 mL) was added TEA (1.9 mL, 14 mmol). The mixture was stirred at 20 °C for 3 minutes and intermediate 8 (295 mg, 0.874 mmol) was added. The mixture was stirred at 20 °C for 1 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by FCC (eluting with petroleum ether: ethyl acetate = 100:0 to 0:100) to afford the product (250 mg, yield 66.6 %) as a yellow solid.

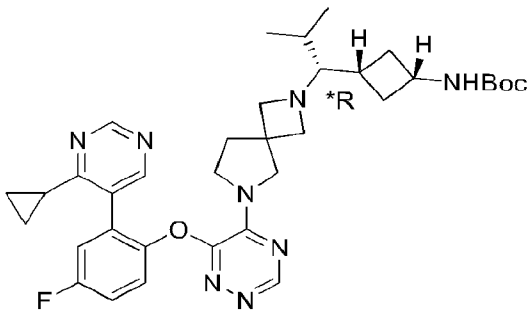
Alternative preparation of Compound 490. The reaction was performed twice on 5 g of intermediate 33. The resulting crude mixtures were combined for the work up and purification.

A mixture of intermediate 33 (5 g; 11.9 mmol), intermediate 6 (4.3 g; 17.8 mmol), AcOH (1.4 mL; 23.7 mmol) and $NaBH_3CN$ (2.3 g; 35.6 mmol) in MeOH (190 mL) was stirred at 50°C overnight. This reaction was performed twice and the two reaction mixtures were combined and poured onto a 10% aqueous solution of K_2CO_3, DCM was added. The layers were separated and then, the aqueous layer was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (mobile phase: 96% DCM, 4% MeOH, 0.1% NH_4OH). The pure fractions were collected and the solvent was evaporated to afford 12 g (78%) of Compound 490.

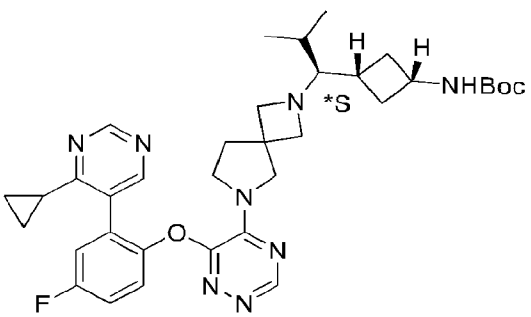
CA 03214746 2023-10-5

Preparation of Compound 491a & 491b:

Compound 491a (*R)

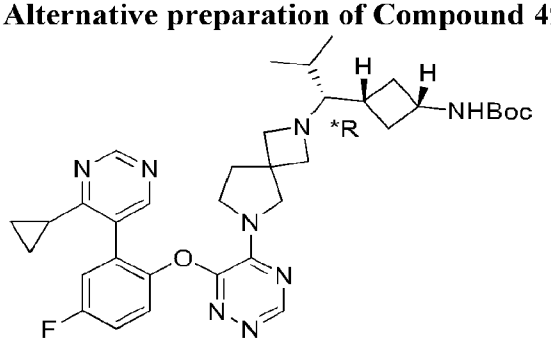


Compound 491b (*S)



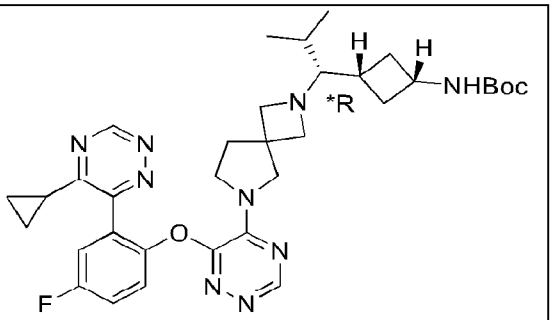
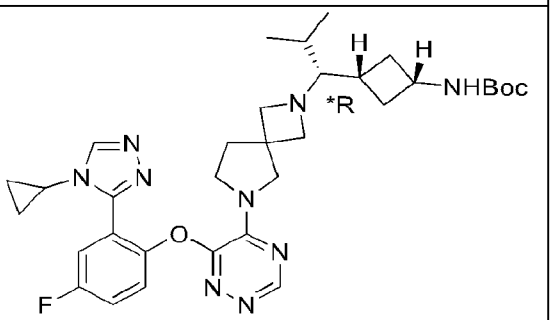
Compound 490 (230 mg, 0.357 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD-H (250 mm*30 mm, 5 μm), eluent: 35% (v/v) super critical CO_2 in 0.1% NH_3H_2O IPA, flow rate: 60 mL/min) to afford Compound 491a (90 mg, 39% yield) and Compound 491b (90 mg, 39% yield) both as a yellow solid.

Alternative preparation of Compound 491a:

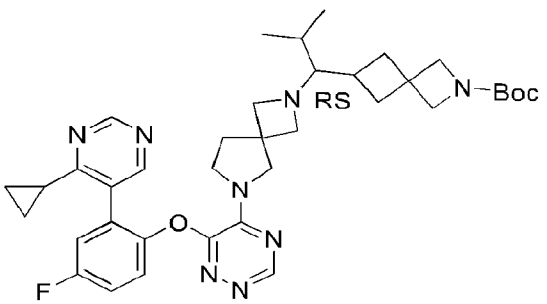


DBU (4.0 mL, 27 mmol) was added into a solution of intermediate 294 (1.60 g, 3.93 mmol) and intermediate 283 (1.94 g, 4.73 mmol) in ACN (20 mL). The reaction was stirred at RT for 2 h. The mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL x3). The combined organic layers were concentrated and purified by FCC (DCM:MeOH = 1:0 to 10:1) to afford Compound 491a (1.705 g, 67% yiedl) as a white solid.

The compounds reported below were prepared following an analogous methodology as reported for the alternative preparation of Compound 491a starting from the corresponding intermediates:

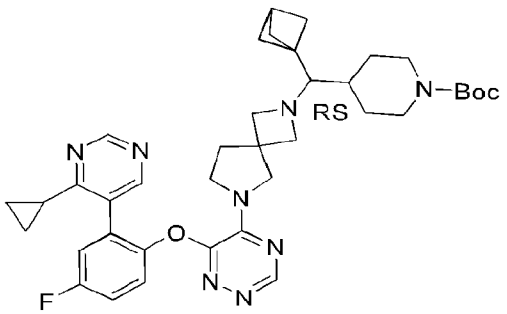
Compound 492	 from intermediates 282 and 283
Compound 493	 from intermediates 291 and 283

Preparation of Compound 494:

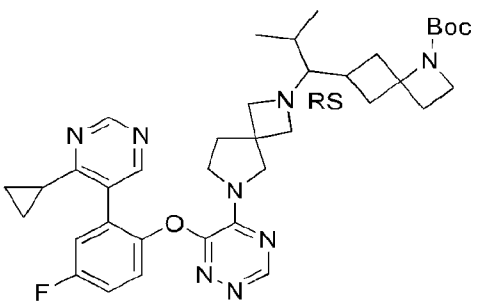


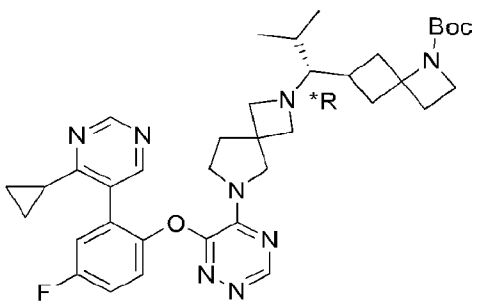
A mixture of intermediate 33 (1.78 g; 4.3 mmol), intermediate 61 (1.47 g; 5.5 mmol), AcOH (242 µL; 4.3 mmol) and $NaBH_3CN$ (798 mg; 12.7 mmol) in MeOH (36 mL) was stirred at 50°C overnight. The reaction mixture was poured onto a saturated solution of $NaHCO_3$ and DCM was added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product (3.1 g) was purified by chromatography over silica gel (Mobile phase: Gradient from 99% DCM, 1% MeOH (+10% NH_4OH) to 95% DCM, 5% MeOH (+10% NH_4OH)). The pure fractions were collected and the solvent was evaporated to give 1.95 g (70%) of Compound 494.

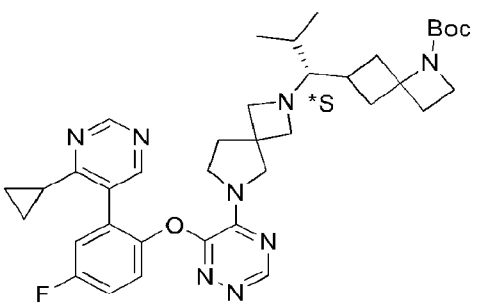
The intermediate reported below was prepared following an analogous methodology as described for Compound 494 starting from the corresponding intermediates:

Compound 495	 **from intermediate 33 and intermediate 250**

Preparation of Compound 496 (RS), 496a (*R) and 496b (*S):

Compound 496: 

Compound 496a (*R): 

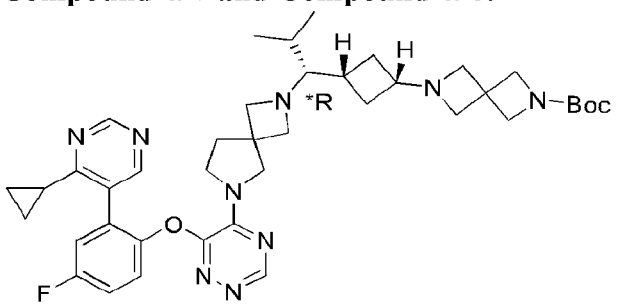
Compound 496b (*S): 

A mixture of intermediate 33 (367 mg; 0.9 mmol), intermediate 62 (304 mg; 1.2 mmol), AcOH (50 µL; 0.9 mmol) and $NaBH_3CN$ (165 mg; 2.7 mmol) in MeOH (8 mL) was stirred at 50°C overnight. The reaction mixture was poured onto a saturated solution of $NaHCO_3$ and DCM was added. The mixture was extracted with DCM (3X). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product (614 mg) was purified by

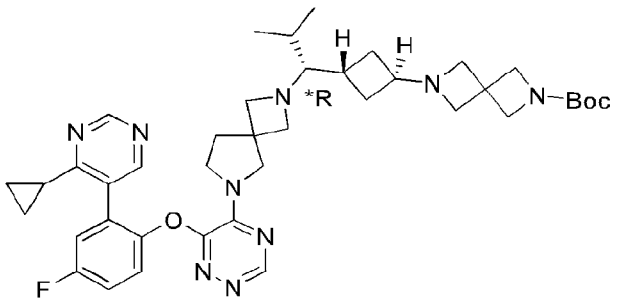
chromatography over silica gel (Mobile phase: Gradient from 99% DCM, 1% MeOH (+10% NH_4OH) to 95% DCM, 5% MeOH (+10% NH_4OH)). The pure fractions were collected and the solvent was evaporated. The Compound 496 (420 mg, 72%) was purified by chiral SFC (Stationary phase: CHIRALPAK AD-H 5µm 250*30mm, Mobile phase: 80% CO_2, 20% iPrOH (+0.3%*i*PrNH$_2$)). The pure fractions were collected and the solvent was evaporated till dryness to give 143 mg (24%) of Compound 496a (*R) and 147 mg (25%) of Compound 496b (*S).

Preparation of Compound 497 and Compound 498:

Compound 497:

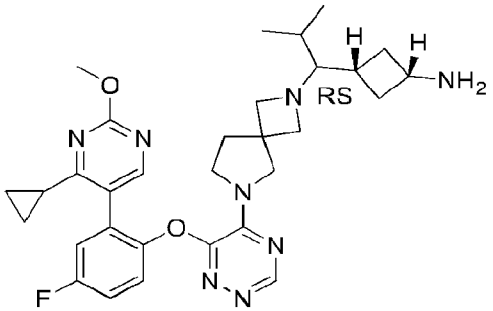


Compound 498:



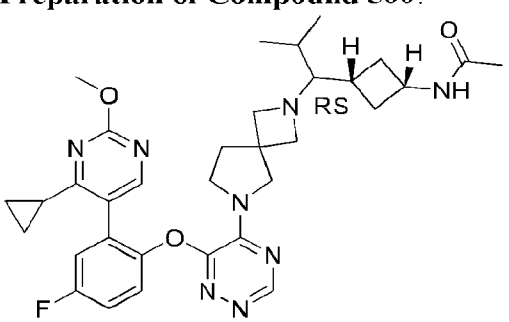
$NaBH_3CN$ (462 mg; 7.36 mmol) was added to a mixture of intermediate 38b (2 g; 3.68 mmol), 2,6-diazaspiro[3.3]heptane-2-carboxylic acid *tert*-butyl ester hemioxalate (2.24 g; 9.20 mmol) and acetic acid (211 µL; 3.68 mmol) in MeOH (100 mL) and the reaction mixture was stirred at 60°C for 18h. The reaction mixture was cooled to rt, poured onto a 10% aqueous solution of K_2CO_3 and DCM. The mixture was filtered through Chromabond® and the filtrate was evaporated to dryness. The residue (5g) was purified by chromatography over silica gel (irregular SiOH, 80 g; mobile phase: 0.7% NH_4OH, 93% DCM, 7% MeOH). The pure fractions were collected and evaporated to dryness. Then, The residue (2.1g) was purified by reverse phase chromatography (YMC-actus Triart C18 10µm 30*150mm; mobile phase: gradient from 40% NH_4HCO_3 0.2% pH=9.5, 30% MeOH, 30% ACN to 10% NH_4HCO_3 0.2% pH=9.5, 45% MeOH, 45% ACN). The pure fractions were collected and evaporated to dryness yielding 930 mg of Compound 497 (35%) as a white foam and 750 mg of Compound 498 (28%) as a white foam.

Preparation of Compound 499:



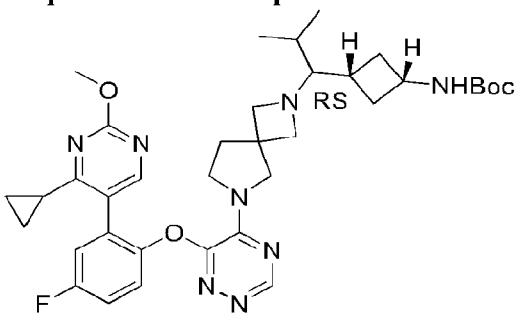
To a solution of Compound 501 (1.0 g, 1.48 mmol) in DCM (30 mL) was added TFA (10 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduce pressure. The residue was diluted with water, and then, the pH was adjusted to 9 with NaOH solution (1 M in water). The resulting solution was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 860 mg (92%) of the desired Compound 499 as a white solid.

Preparation of Compound 500:



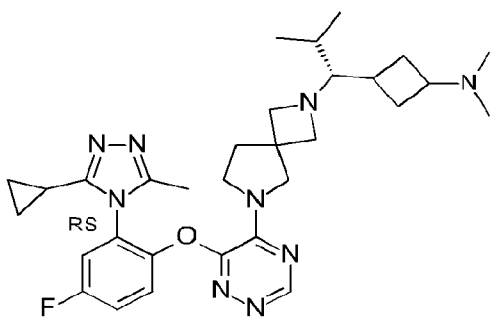
To a solution of Compound 499 (210 mg, 0.37 mmol) in DCM (8 mL) were added Et_3N (0.8 mL) and acetic anhydride (0.8 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was quenched with $NaHCO_3$ aqueous solution and extracted with DCM. The combined organic layers were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude product was purified by prep-HPLC (Column: XBridge C18 OBD Prep Column, 100Å, 5 μm, 19 mm x 250 mm; Mobile Phase A: Water (10MMOL/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate:25 mL/min; Gradient: 40% B to 50% B). The pure fractions were collected and the solvent was evaporated. Then, the resulting residue was lyophilized to give 50.3 mg (21%) of the desired Compound 500 as a white solid.

Preparation of Compound 501:



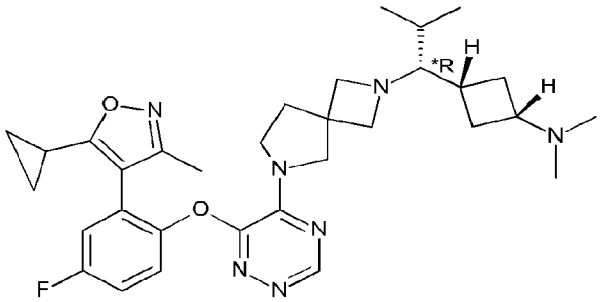
To a solution of intermediate118 (1.0 g, 2.23 mmol) in MeOH (40 mL) was added intermediate 6 (1.1 g, 4.45 mmol). After stirring for 30 minutes at room temperature, $NaBH_3CN$ (700 mg, 11.12 mmol) was added to the reaction mixture. The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (MeOH/DCM: 1/10). The pure fractions were collected and evaporated to dryness to give 1.05 g (64%) of desired Compound 501 as a white solid.

Preparation of Compound 502 (N,N-dimethyl-3-[(1R)-1-[7-[6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanamine):



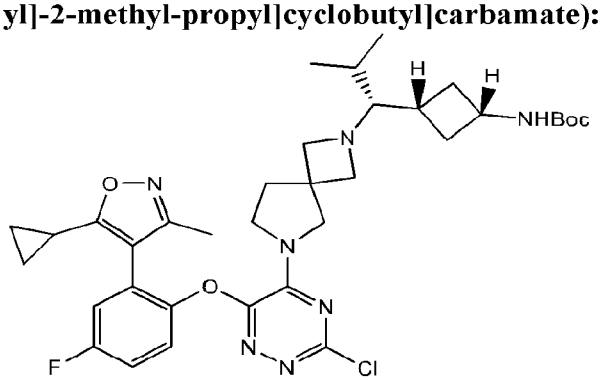
Sodium cyanoborohydride (25 mg, 0.384 mmol) was added to 3-[rac-(1R)-1-[7-[6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanone (105 mg, 0.192 mmol), dimethyl amine (2 M in THF, 0.48 mL, 0.96 mmol) and acetic acid (11 µL, 0.192 mmol) in MeOH (6 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured onto a 10% aqueous solution of K_2CO_3 and dichloromethane. The mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to give N,N-dimethyl-3-[rac-(1R)-1-[7-[6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanamine (98 mg) as a mixture of atropisomers.

Preparation of Compound 503 (N,N-dimethyl-3-[(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanamine):



Sodium cyanoborohydride (56 mg, 0.878 mmol) was added to a mixture of 3-[rac-(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanone (240 mg, 0.439 mmol), dimethyl amine (1.1 mL, 2 M in THF, 2.195 mmol) and acetic acid (26 µL, 0.439 mmol) in MeOH (15 mL) and the reaction mixture was stirred at ambient temperature for 2h. The reaction mixture was then poured onto a 10 % aqueous solution of K_2CO_3 and dichloromethane. The mixture was extracted with dichloromethane (3 ×). Combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by flash column chromatography (0 to 2 % 7N MeOH-NH_3 in dichloromethane as eluents) to give *N,N*-dimethyl-3-[rac-(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutanamine (14 mg, 16 %).

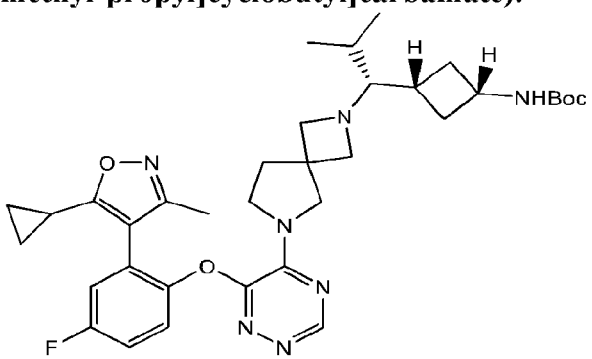
Preparation of Compound 506 (tert-butyl N-[3-[(1R)-1-[7-[3-chloro-6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutyl]carbamate):



A mixture of intermediate 333 (230 mg, 0.474 mmol), 2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenol (111 mg, 0.474 mmol) and Cs_2CO_3 (186 mg, 0.569 mmol) in anhydrous

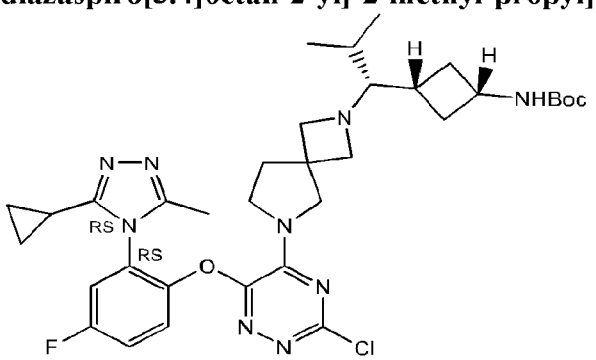
DMF (10 mL) was stirred at RT for 18 h. Upon completion, reaction mixture was diluted with dichloromethane (30 mL) and washed with water. Layers were separated and aqueous layer was extracted with dichloromethane (2 × 25 mL). Combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The residue was purified by flash column chromatography (0 to 2 % MeOH in dichloromethane) to give Compound 506 (225 mg, yield 69 %).

Preparation of Compound 504 (tert-butyl N-[3-[(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutyl]carbamate):



Pd/C (10%) (25 mg) was added to a solution of Compound 506 (160 mg, 0.235 mmol) and thiophene (0.06 mL, 0.4 M, 0.0235 mmol) in MeOH (20 mL) at ambient temperature and the mixture was stirred under H_2 (1 atm) for 1 h. Upon completion (LCMS), the mixture was filtered over dicalite and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography (0 to 2 % 7N MeOH-NH_3 in dichloromethane as eluents) to give Compound 504 (40 mg, 26 %).

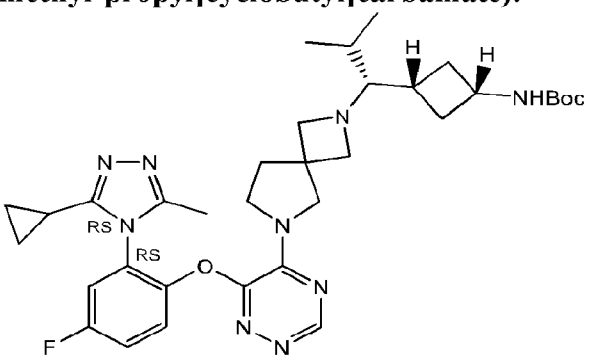
Preparation of Compound 507 (tert-butyl N-[3-[(1R)-1-[7-[3-chloro-6-[2-(3-cyclopropyl-5-methyl-1,2,4-triazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutyl]carbamate):



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A mixture of intermediate 333 (1 g, 2.06 mmol), Intermediate 345 (481 mg, 2.06 mmol) and Cs_2CO_3 (806 mg, 2.472 mmol) in anhydrous DMF (60 mL) was stirred at RT for 18 h. Upon completion, reaction mixture concentrated to dryness and diluted with dichloromethane (100 mL) and washed with water. Layers were separated and aqueous layer was extracted with dichloromethane (2 × 50 mL). Combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The residue was purified by flash column chromatography (0 to 2 % MeOH in dichloromethane) to afford Compound 507 (1 g, yield 71 %).

Preparation of Compound 505 (tert-butyl N-[3-[(1R)-1-[7-[6-[2-(5-cyclopropyl-3-methyl-isoxazol-4-yl)-4-fluoro-phenoxy]-1,2,4-triazin-5-yl]-2,7-diazaspiro[3.4]octan-2-yl]-2-methyl-propyl]cyclobutyl]carbamate):



Pd/C (10%) (141 mg) was added to a solution of Compound 507 (900 mg, 1.319 mmol) and thiophene (0.33 mL, 0.4 M, 0.132 mmol) in MeOH (100 mL) at ambient temperature and the mixture was stirred under H_2 (1 atm) for 1 h. Upon completion (LCMS), the mixture was filtered over dicalite and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography (0 to 3 % MeOH-NH_3 in dichloromethane as eluents) to give Compound 505 (420 mg, 49 %).

ANALYTICAL METHODS

The analytical information in the Examples above or in the Tables below, was generated by using the analytical methods described below.

NMR-Methods

Some NMR experiments were carried out using a Bruker Avance III 400 spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with BBO 400MHz S1 5 mm probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are

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expressed in Hz.

Some NMR experiments were carried out using a Varian 400-MR spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with Varian 400 4NUC PFG probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

Some NMR experiments were carried out using a Varian 400-VNMRS spectrometer at ambient temperature (298.6 K), using internal deuterium lock and equipped with Varian 400 ASW PFG probe head with z gradients and operating at 400 MHz for the proton and 100MHz for carbon. Chemical shifts (δ) are reported in parts per million (ppm). J values are expressed in Hz.

LCMS (Liquid chromatography/Mass spectrometry)

General procedure

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector.

Table 1a: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes). "TFA" means trifluoroacetic acid; "FA" means formic acid

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
1	Waters: Acquity UPLC® - DAD and Quattro Micro™	Waters: BEH C18 (1.7µm, 2.1x100 mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343 ---------- 40	6.2
2	Agilent	Xtimate C18 2.1*30mm,3 um	A: water(4L)+ TFA(1.5mL); mobile phase, B: acetonitrile (4L) + TFA (0.75mL)	A gradient from 100% A to 40% A is applied in 6 minutes, and hold at these conditions for 0.5 minutes, to 100% A and 0 % B in 0.01 minutes and reequilibrate with 100% A for 0.49 minutes. A	0.8 --------- 50	7
3	Agilent	Xbrige Shield RP-18,5um,2.1* 50mm	A:water(1L)+ NH_3H_2O (0.2mL); mobile phase B:aceto-nitrile	From 90 % A to 20 % A, 80% B in 6 minutes, and hold at these conditions for 0.5 minutes, to 90% A and 10 % B in 0.01 minutes and reequilibrate with 90% A for 0.49 minutes	0.8 --------- 30	7
4	Agilent	Waters XBridge Shield RP18 column (50*2.1mm 5µm)	mobile phase A: water with 0.05% $NH_3.H_2O$; mobile phase B: acetonitrile	First, 100 % A was hold for 1 minute. Then a gradient was applied to 40 % A and 60 % B in 4 minutes and then to 5% A and 95 % B in 2.5 minutes. Finally return to 100% A in 2 minutes and hold for 0.5 minute. Post Time is 0.5minute	0.8 --------- 40	10
5	Shimadzu LCMS-2020	Luna Qmega	ACN-Water-0.1% FA	0.0 min 5 % B -> 2.8 min 40% B -> 3.6 min 95% B-> 4.1 min 95%B	1.5 ---------- 40	4.50

Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
6	Shimadzu LCMS-2020	Poroshell HPH-C18	ACN-Water-0.03% NH_3H_2O	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.2 --------- 40	3.00
7	Shimadzu LCMS-2020	Poroshell HPH-C18	ACN-Water-5mM NH_4HCO_3	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.2 --------- 40	3.00
8	Shimadzu LCMS-2020	Luna Omega	ACN-Water-0.1% FA	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.5 --------- 40	3.00
9	Shimadzu LCMS-2020	Kinetex EVO	ACN-Water-5mM NH_4HCO_3	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.2 --------- 40	3.00
10	Shimadzu LCMS-2020	Poroshell HPH-C18	ACN-Water-0.04% NH_3H_2O	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.2 -------- - 40	3.00
11	Shimadzu LCMS-2020	Shim-pack XR-ODS	ACN-Water-0.05%TFA	0.0 min 5 % B -> 2.0 min 100% B -> 2.7 min 100% B	1.5 -------- - 40	3.00

Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
12	Shimadzu LCMS-2020	XBridge BEH C18	ACN-Water-5mM NH_4HCO_3	0.0 min 5 % B -> 2.0 min 95% B -> 2.7 min 95% B	1.2 -------- - 40	3.00
13	Shimadzu LCMS-2020	Poroshell HPH-C18	ACN-Water-5mM NH_4HCO_3	0.0 min 30 % B -> 3.0 min 70% B -> 3.2 min 95% B-> 4.2 min 95% B	1.2 -------- 40	4.50
14	Shimadzu LCMS-2020	Ascentis Express C18	ACN-Water-0.05% TFA	0.0 min 5 % B -> 2.0 min 100% B -> 2.7 min 100% B	1.5 -------- 40	3.00
15	Shimadzu LCMS-2020	HALO	ACN-Water-0.05% TFA	0.0 min 5 % B -> 0.3 min 5 % B ->2.2 min 100% B -> 2.7 min 100% B	1.2 -------- 40	3.00
16	Waters: Acquity UPLC® H-Class - DAD and QDa	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	From 85% A to 10% A in 2.1min, held for 2min, back to 85% A in 0.8min, held for 0.7min.	0.35 ------ 40	6.1
17	Waters: Acquity UPLC® H-Class - DAD and QDa	Waters BEH®-C18 (1.7µm, 2.1x100mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	95% A to 5% A in 1min, held for 1.6min, back to 95% A in 0.2min, held for 0.5min.	0.5 ------- 40	3.3

Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
18	Waters: Acquity UPLC® H-Class - DAD and SQD 2	Waters BEH®C18 (1.7µm, 2.1x50mm)	A: 95% CH_3COONH_4 7mM / 5% CH_3CN, B: CH_3CN	From 95% A to 5% A in 1min, held for 1.6min, back to 95% A in 0.2min, held for 0.5min.	0.5 -------- 40	3.3
19	Agilent	Waters Xbridge-C18 2.1*50 mm, 5 um	A: water with 0.04 % TFA; mobile phase, B: acetonitrile with 0.02 % TFA	100%A was hold for 1 minute, A gradient from 100% A to 40% A is applied in 4 minutes, and 40%A down to 15%A in 2.5 minutes. And then return to 100% A in 2 minutes and hold for 0.5 minutes .The post time is 0.5min.	0.8 ---- 50	10
20	Agilent	Waters Xbridge-C18 2.1*50 mm, 5 um	mobile phase A: water with 0.04 % TFA; mobile phase B: acetonitrile with 0.02 % TFA	First, 90 % A was hold for 0.8 minute. Then a gradient was applied to 20 % A and 80 % B in 3.7 minutes and hold for 3 minutes. And then return to 90% A in 2 minutes and hold for 0.5 minutes. The post time is 0.5min.	0.8 ---- 50	10

Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
21	Agilent	XBridge ShieldRP18, 50*2.1mm 5μm	mobile phase A: H_2O (0.05% $NH_3.H_2O$); mobile phase B: acetonitrile	First, 100 % A was hold for 1 minute. Then a gradient was applied to 40 % A and 60 % B in 4 minutes and then to 5% A and 95 % B in 2.5 minutes. 95% B was hold for 2.0 minute.Finally return to 100% A and hold for 0.5 minute. Post Time is 1.5minute.	0.8 ---- 40	10
22	SHIMADZU LC20-MS2020	Xbridge Shield RP-18,5um,2.1*50mm	mobile phase A: water(4L)+ $NH_3.H_2O$ (2mL); mobile phase B: acetonitrile	from 90 % A to 20 % A, 80% B in 6 minutes, and hold at these conditions for 0.5minutes, to 90% A and 10% B in 0.01 minutes and reequilibrate with 90% A for 0.49 minutes.	0.8 ---- 50	7
23	SHIMADZU LC20-MS2020	Xbridge Shield RP-18,5um,2.1*50mm	mobile phase A: water(4L)+ $NH_3·H_2O$ (0.8mL); mobile phase B: acetonitrile	10% to 80% (mobile phase B) over 2 minutes and holding at 80% for 0.48minutes	1 ---- 50	3

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
24	Agilent	Xtimate C18 2.1*30mm ,3um	mobile phase A: water(4L)+ TFA (1.5mL); mobile phase B: acetonitrile (4L)+ TFA (0.75mL)	10% to 80% (mobile phase B) over 0.9 minutes and holding at 80% for 0.6 minutes	1.2 ---- 50	2
25	Agilent 6120 LC/MS	Waters: Sunfire C18 (2.5µm, 3.0x30 mm)	A: H_2O 0.1% FA, B: ACN	95% A to 5% A in 2.5min, held for 1.0 min	1 ------- 40	3.5
26	Shimadzu LCMS2020, LC30AD	Shim-pack Velox SP-C18 (3.0*30 mm, 2.7 µ)	A: H_2O 0.05% TFA B: ACN 0.05% TFA	5% B to 100% B in 1.1min, hold for 0.6 min. Then, to 5%B in 0.3 mn	1.5 ------- 40	2
27	Shimadzu LCMS2020, LC30AD	Shim-pack Velox SP-C18 (3.0*30 mm, 2.7 µ)	A: H_2O 0.05% TFA B: ACN 0.05% TFA	2% B to 100% B in 2 min, then 100% B for 0.7 m. then to 2% B in 0.3 mn,	0.5 ------- 40	3

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
28	Shimadzu LCMS2020, LC30AD	Shim-pack Velox SP-C18 (3.0*30 mm, 2.7 μ)	A: H_2O 0.05% TFA B: ACN 0.05% TFA	2% B to 100% B in 2 min, then 100% B for 0.7 mn then to 5% B in 0.3 mn	0.5 ------- 40	3
29	SHIMADZU LC20-MS2010	Xtimate C18 2.1*30mm,3um	mobile phase A: A:water(4L)+ TFA(1.5mL) mobile phase B: B:acetonitrile (4L)+ TFA(0.75mL)	a gradient condition from 100 % A to 40 % A, 60% B in 6 minutes, and hold at these conditions for 0.5 minutes, then to 100% A and 0% B in 0.1 min and held for 0.49 min.	0.8 ---- 50	7
30	Shimadzu LCMS-2020	kinetex EVO-C18	ACN-Water-6.5 mM NH_4HCO_3+ NH_3H_2O	0.0 min 10 % B -> 2.0 min 95 % B ->2.7 min 95% B -> 2.75 min 10% B->3.00 min Controller	1.2 ------- 40	3.00
31	Shimadzu LCMS-2020	Poroshell HPH C18	ACN-Water-5 mM NH_4HCO_3	0.0 min 10 % B -> 2.0 min 95% B -> 2.7 min 95% B-> 2.75 min 10% B-> 2.85 min Controller	1.2 ------- 40	2.85

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
32	Agilent	Agilent Poroshell 120 EC-C18 1.9um 3.0*30mm	mobile phase A: A:water(4L)+TFA(1.5mL) mobile phase B: B:acetonitrile (4L)+TFA(0.75mL)	A gradient condition from 95 % A to 20 % A, 80% B in 1.2 minutes, then to 5% A and 95% B in 1.3 min. Then return to 95%A in 0.1 min and held for 0.49 min.	1 ---- 50	3
33	Waters: Acquity® UPLC® - DAD and SQD	Waters : BEH C18 (1.7µm, 2.1*50mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 95% A to 5% A in 1.3min, held for 0.7 min	0.8 ------- 55	2
34	Waters: Acquity® UPLC® - DAD and SQD	Waters :BEH (1.8µm, 2.1*100mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 2.10min, to 0% A in 0.9min	0.6 ------- 55	3.5
35	Waters: Acquity® UPLC® - DAD and SQD	Waters :BEH (1.8µm, 2.1*50mm)	A: 0.1% NH_4HCO_3 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 1.3 min, hold 0.7min	0.8 ------- 55	2.0
36	Waters: Acquity® UPLC® - DAD and SQD	Waters :BEH (1.8µm, 2.1*100mm)	A: 10mM NH_4HCO_3 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 2.10min, to 0% A in 0.9min	0.6 ------- 55	3.5

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
37	Agilent: 1260 Infinity and 6120 Quadrupole LC/MS	Waters: Sunfire C18 (2.5µm, 3.0x30mm)	A:0.1% FA solution in water B: CH_3CN	Gradient start from 5% of B increase to 95% within 2.5 min and keep at 95% till 3.5 min	1.2 ------- - 50	3.5
38	Waters: Acquity® UPLC® - DAD and SQD	Waters :BEH (1.8µm, 2.1*100mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 2.00min, to 0% A in0.9min,	0.6 ------- 55	3.5
39	Shimadzu LCMS-2020	Luna Omega	ACN-Water-0.1%FA	0.0 min 5 % B -> 2.0 min 95 % B ->2.6 min 95% B -> 2.7 min 5% B->3.00 min Controller	1.5 ------ 40	3.0
40	Waters: Acquity® UPLC® - DAD and SQD	Waters :BEH (1.7µm, 2.1*100mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 2.10min, to 0% A in 0.9min, to 5% A in 0.5min	0.6 ------- 55	3.5
41	Shimadzu LC20-MS2010	MERCK, RP-18e 25-2mm	A:water(4L)+ TFA(1.5mL) B:acetonitrile (4L)+TFA(0.75mL)	a gradient condition from 95% A, 5% B to 5% A, 95% B in 0.7 minutes, hold at these conditions for 0.4 minutes, and then to 95% A, 5% B in 0.01 min and held for 0.49 min.	1.5 ---- 50	1.5

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Method code	Instrument	Column	Mobile phase	Gradient	Flow -(ml/mn) ---- Column T (°C)	Run time (min)
42	Waters: Acquity® H-Class - DAD and SQD2™	Waters BEH® C18 (1.7µm, 2.1x50mm)	A: CH_3COONH_4 7mM 95%/ CH_3CN 5%, B: CH_3CN	From 95% A/5% B to 5% A in 1min, held for 1.6min, back to 95% A/5% B in 0.2min, held for 0.5min.	0.5 ------ - 40	3.5
43	Shimadzu LCMS-2020	Kinetex EVO (2.6µm, 3.0x50 mm)	A: Water-5mM NH_4HCO_3, B: ACN	95% A to 5% A in 1.10 min, held for 0.50 min, back to 95 % A in 0.05 min, held for 0.15 min	1.2 ------- -- 40	1.80
44	Shimadzu LCMS-2020	Ascentis Express C18 (2.7µm, 3.0x50 mm)	A: Water-0.05% TFA, B: ACN	95 % A to 5% A in 1.20 min, held for 1.50 min, back to 95% A in 0.1 min, held for 0.20 min	1.5 ------- -- 40	3.00
45	Shimadzu LCMS-2020	Xtimate C18 2.1*30mm,3um	A: water(4L)+TFA(1.5mL) B: acetonitrile(4L)+TFA(0.75mL	a gradient condition from 100% A, 00% B to 40% A, 60% B in 0.9 minutes, hold at these conditions for 0.6 minutes, and then to 100% A, 00% B in 0.01 min and held for 0.49 min.	1 ---- 50	2

Table 1b: LCMS and melting point data. Co. No. means compound number; R_t means retention time in min.

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
6	2.46	629.6	687.7	1
4	2.44	629.4		2
5	4.24	629.4		3
2	4.13	587.2		4

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
7	2.25	573.7	631.8	1
8	2.39	573.1	631.7	1
9	2.39	691.8	749.9	1
10	2.30	647.7	705.6	1
12	2.24	629.8	687.8	1
14	2.42	641.8	699.8	1
16	2.46	643.7	701.7	1
18	2.30	599.7	657.6	1
20	2.28	627.8	685.7	1
21	2.43	627.9	685.8	1
22	2.22	629.7	687.8	1
23	2.59	690.8	748.8	1
25	2.30	690.4	748.5	1
26	2.29	690.4	748.5	1
163	2.26	629.6	687.5	1
165	2.26	629.6	687.8	1
200	2.92	631.7	690.0	1
87	2.34	643.7	701.9	1
201	2.32	643.8	701.8	1
206	2.91	631.7	689.7	1
86	2.28	647.8	705.6	1
85	2.27	647.8	706.2	1
27	2.54	612.7	670.7	1
207	2.37	663.9	705.7	1
145	2.35	627.8	685.7	1
146	2.49	627.7	685.8	1
147	2.35	571.3	630.4	1
153	2.36	572.7	630.3	1
33	2.31	647.7	706.5	1
30	2.36	647.6	705.8	1
31	2.43	647.7	705.7	1
148	2.63	584.7	642.7	1
149	2.51	640.7	698.7	1
151	2.38	626.7	684.4	1
152	2.53	626.7	684.7	1
150	2.63	640.7	698.7	1
161	2.51	684.8	742.7	1
162	2.55	684.8	742.7	1
159	2.40	560.5	618.5	1
160	2.40	560.5	618.6	1

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
154	2.32	641.7	699.7	1
157	2.34	641.7	699.8	1
155	2.36	641.6	699.7	1
158	2.36	641.6	699.7	1
156	2.43	641.6	699.7	1
198	2.24	571.5	629.6	1
198a	1.02	571.4	629.3	17
135	2.45	613.8	671.8	1
136	2.30	573.7	631.9	1
208	2.54	615.7	673.8	1
209	2.66	719.9	778.8	1
210	2.32	670.8	728.8	1
2a	2.29	587.6	645.7	1
169	2.66	681.7	739.7	1
166	2.76	666.7	724.7	1
167	2.75	666.7	724.8	1
168	2.76	666.7	724.6	1
211	2.27	629.4		16
34	2.17	656.4	714.6	16
35	2.27	656.4	714.6	16
36	2.48	685.8	743.8	1
37	2.62	685.8	743.8	1
212	2.49	641.7	699.6	1
106	2.14	627.7	685.8	1
213	2.50	655.6	713.6	1
214	2.63	655.6	713.6	1
215	2.63	655.6	713.6	1
164	2.38	643.7	701.8	1
192	1.884	623.40		5
193	1.600	623.10		6
195	1.428	626.45		7
176	0.923	587.45		8
177	1.456	587.20		7
178	1.455	587.25		7
179	1.363	587.25		9
182	1.349	587.25		7
183	1.350	587.05		10
196	1.223	603.25		7
184	0.944	613.50		8
185	1.020	613.25		1

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
186	1.027	613.25		11
189	0.948	628.50		8
190	1.476	628.35		12
191	1.473	628.35		12
180	1.354	587.25		7
181	1.351	587.25		7
194	0.975	625.45		8
202	1.689	628.80		13
131	2.657	684.35		13
132	1.529	691.30		7
203	1.518	629.30		7
133	1.398	617.35		7
134	1.475	617.35		7
187	0.814	587.55		14
188	0.891	602.50		8
108	1.046	629.35		7
109	1.083	629.35		7
68	0.807	657.60		8
69	1.012	657.35		15
70	0.824	657.60		8
71	0.835	657.60		8
110	0.786	670.60		8
111	0.802	670.60		8
112	0.752	629.55		8
113	0.782	629.55		8
114	0.768	629.55		8
115	0.758	629.55		8
116	0.791	670.60		8
117	1.443	670.35		7
138	2.50	640.6	698.7	1
139	2.65	640.6	698.7	1
120	2.49	615.6	673.7	1
121	2.20	629.6	687.7	1
122	2.67	638.7	696.9	1
123	2.50	663.8	721.7	1
38	2.41	617.8	675.8	1
39	2.49	585.7	643.7	1
40	2.32	641.8	699.9	1
42	2.34	641.7	699.6	1
43	2.46	641.7	699.7	1

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
41	2.37	641.7	699.7	1
44	2.55	691.8	749.7	1
137	2.31	628.7	686.6	1
45	2.29	641.7	699.8	1
46	2.30	641.7	699.8	1
72	2.34	626.7	684.6	1
73	2.47	626.7	684.6	1
174	2.31	682.8	740.7	1
175	2.38	682.7	740.7	1
47	2.24	629.8	688.2	1
29	2.51	629.6	687.7	1
124	2.49	643.8	701.8	1
125	2.21	601.7	659.8	1
126	2.30	601.7	659.7	1
127	3.09	649.8	707.9	1
128	3.19	649.8	707.7	1
129	2.27	643.8	701.9	1
130	2.37	643.8	701.7	1
88	2.19	629.8	687.8	1
48	2.44	613.8	671.8	1
49	2.57	613.7	671.8	1
172	2.27	668.8	726.8	1
170	2.25	668.7	726.7	1
173	2.35	668.8	726.6	1
171	2.35	668.8	726.8	1
50	2.39	684.8	742.9	1
51	2.34	684.8	742.8	1
52	2.47	684.8	742.8	1
140	2.50	651.7	709.8	1
142	2.57	665.7	723.7	1
143	2.67	665.7	723.7	1
97	2.37	641.7	699.7	1
144	2.44	680.7	738.7	1
80	2.20	656.7	714.7	1
74	2.29	572.4	-	16
75	2.42	572.4	-	16
76	2.34	683.4	-	16
78	2.34	628.4	686.5	16
98	2.35	691.7	749.9	1
99	2.19	629.7	687.8	1

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
100	2.31	684.8	742.8	1
102	2.22	627.6	685.7	1
103	2.34	627.7	685.6	1
53	2.27	682.8	740.8	1
54	2.37	682.8	740.8	1
55	2.35	682.8	740.8	1
56	2.40	682.7	740.7	1
57	2.36	682.7	740.7	1
58	2.39	682.7	740.8	1
59	2.31	682.8	740.8	1
60	2.30	682.8	740.9	1
61	2.35	670.8	728.8	1
81	2.25	629.7	687.8	1
141	2.61	651.7	709.8	1
82	2.17	627.7	685.8	1
83	2.29	627.7	685.7	1
84	2.24	627.7	685.8	1
84a	2.33	627.7	685.8	1
101	2.32	627.7	685.8	1
104	2.18	656.7	714.8	1
105	2.26	656.7	714.7	1
89	2.40	655.4	713.6	16
62	2.37	698.8	756.7	1
63	2.49	698.8	756.8	1
64	2.28	682.8	740.8	1
65	2.39	682.8	740.8	1
95	2.66	651.8	709.8	1
96	2.48	680.7	738.7	1
66	2.32	682.7	740.7	1
67	2.32	682.7	740.7	1
107	2.29	627.6	685.6	1
91	2.42	572.4	-	16
92	2.34	683.4	-	16
93	2.52	628.8	686.8	1
79	2.49	680.8	738.9	1
90	2.29	572.4	-	16
94	2.52	651.6	709.6	1
199	1.13	626.5	684.8	18
205	2.62	689.4	747.5	16
204	2.41	689.3	747.5	16

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
231	3.404	655.3		19
232	4.633	655.3		4
233	3.065	641.3		19
234	2.99	627.4		19
235	4.414	649.2		4
236	3.063	659.3		19
237	3.062	659.3		19
238	3.007	617.3		19
239	3.003	617.3		19
240	4.472	628.4		4
241	4.291	628.3		4
242	4.551	679.2		4
243	4.394	656.1		4
244	3.047	641.3		19
245	3.07	641.2		19
246	5.156	641.5		4
247	2.274	641.3		19
248	4.691	682.2		4
249	4.486	703.2		4
250	2.994	613.3		19
251	2.816	655.3		19
252	2.909	655.3		19
253	2.915	655.3		19
254	2.873	641.3		19
255	2.882	641.4		19
256	2.894	643.3		19
257	2.931	629.3		19
258	2.828	641.3		19
259	4.726	641.3		4
260	2.911	615.4		19
261a	2.830	573.3		19
261b	2.827	573.3		19
262	4.55	617.3		4
263	3.268	629.4		19
264	3.285	629.4		19
265	3.317	641.4		19
266	4.869	655.3		4
267	4.969	655.3		4
268	4.489	641.3		4
269	4.618	641.3		4

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
270	2.987	655.4		19
271	5.388	655.3		4
272	2.102	585.3		19
273	2.118	585.1		19
274	3.052	641.3		19
275	4.69	643.2		4
276	4.878	643.2		4
277	4.061	656.2		4
278	4.685	641.3		4
279	4.856	641.4		4
280a	2.998	655.2		19
280b	3.005	655.2		19
281a	4.476	655.6		21
281b	4.623	655.6		21
282a	3.012	641.2		19
282b	3.006	641.3		19
283a	4.662	585.2		4
283b	4.774	585.2		4
284a	5.065	585.4		21
284b	4.733	585.3		21
285	3.101	676.4		19
286	2.955	676.3		19
287	2.221	676.2		19
288	3.011	626.3		19
289	3.005	640.2		19
290	2.992	626.3		19
291	2.993	626.3		19
1a	3.134	545.2		19
1b	3.145	545.2		19
2b	3.349	587.4		19
296	4.413	643.3		4
297	0.815	644.4		24
298	3.48	612.2		19
299	3.488	617.3		19
300	3.725	629.3		19
301	4.787	631.2		4
302	3.169	644.3		4
303	3.488	613.7		19
304	3.185	613.3		19
305	3.352	631.3		19

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
306	3.235	588.3		19
307	4.162	602.3		4
308	3.135	602.3		19
309	3.247	629.2		19
310	3.177	629.3		19
311	3.655	647.3		19
312	4.348	586.3		4
313	4.264	599.3		4
314	4.304	599.3		4
315	4.714	668.4		4
316	4.281	668.1		4
317	3.118	656.4		19
318	2.251	656.2		19
319	3.283	601.2		19
320	3.274	601.2		19
321	4.702	600.3		4
322	4.702	600.3		4
323	4.146	601.2		4
324	3.059	601.3		19
325	3.042	641.3		19
326	3.055	641.3		19
327	3.116	655.4		19
328	4.638	670.3		4
329	3.077	684.1		19
330	4.692	643.3		4
331	2.919	629.4		19
332	2.869	629.3		19
333	3.323	654.3		19
335	3.319	653.3		19
336	3.318	653.3		19
339	2.148	669.1		19
340	2.919	653.3		4
341	4.52	715		4
342	3.411	611.3		19
343	4.806	612.3		4
344	3.483	627.4		19
345	3.011	585.3		19
346	2.994	585.2		19
348	3.199	658.5		19
350	4.342	644.3		4

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
351	1.872	656.3		20
353	3.564	601.6		22
354	3.564	601.9		22
356	1.821	601.4		25
357	3.156	643.3		19
358	3.083	643.4		19
371	0.423	681.30		26
372	0.423	681.35		26
373	0.699	681.3		27
374	0.698	681.3		28
377	2.685	696.4		29
378	3.196	696.4		19
385	2.225	708.3		20
390	3.162	682.3		19
391	3.352	726.3		19
392	3.275	708.3		19
393	4.740	670.3		21
375	3.147	696.4		19
394	4.515	682.3		21
379	1.630	655.3		25
380	1.669	722.3		25
381	1.651	696.3		25
382	1.712	655.3		25
383	1.671	684.3		25
384	1.656	696.3		25
386	1.664	696.3		25
387	1.656	696.3		25
388	1.607	670.2		25
389	1.591	670.3		25
395	2.42	670.8	728.8	1
396	2.58	655.7	713.8	1
397	2.44	641.8	699.8	1
376	4.846	696.3		4
398	1.458	643.30		30
399	1.538	643.30		30
402	1.637	655.55		31
403	1.732	655.40		31
400	1.470	696.45		31
401	1.547	696.50		31
405	4.484	680.3		4

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
406	1.236	661.4		32
407	4.731	679.3		4
408	3.523	716.4		19
409	4.985	679.3		4
410	3.211	679.4		19
411	3.354	663.3		19
412	4.610	662.3		4
413	3.179	663.3		19
414	3.152	680.3		19
415	3.296	715.3		19
416	3.408	683.3		19
417	3.432	699.3		19
418	3.212	680.3		19
419	3.205	653.4		19
420	3.194	689.3		19
421	3.268	694.3		19
422	4.806	662.3		4
423	4.652	703.3		4
424	3.471	689.3		19
425	3.220	679.3		19
426	3.301	675.3		19
427	3.333	695.3		19
428	3.277	721.3		19
429	3.193	697.3		19
430	4.586	703.6		4
431	3.405	663.3		19
432	3.272	680.3		19
433	4.672	662.5		4
434	0.80	638.4		39
435	1.72	683.5		38
436	0.82	669.4		1
437	0.86	685.3		33
438	1.73	669		34
439	0.82	670		33
440	0.76	517.4		35
441	0.77	517.4		35
442	1.85	686		36
443	1.75	699		34
444	0.77	585.3		33
445	0.96	710.3		33

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
446	0.82	671.3		33
447	1.82	644.2		37
448	2.29	662.4		37
449	2.10	685.2		37
450	1.94	679		34
451	1.85	679		34
452	1.79	680		34
453	1.08	685.5		35
454	2.64	686.2		37
455	0.86	657.5		35
456	0.97	603.5		35
457	1.00	680.5		35
458	2.16	663.2		37
459	1.98	683.5		36
460	1.84	683.5		36
461	1.64	641		36
462	1.75	677.2		37
502	3.48	576		40
503	1.78	576		33
504	1.19	648		33
505	0.94	648		33
506	1.31	682		33
507	1.05	682		33
508	2.5	658.4	717	40
510	0.85	693.1		41
511	0.8	659.2		41
512a	1.88	617		40
512b	1.87	617		40
463	0.63	638.3		41
464	0.70	559.2		41
465	2.13	698.4		23
466	1.25	670.3		23
467	2.17	700.3		23
468	1.04	686.4		45
470	3.49	762.6		29
471	0.7	658.4		41
472	0.65	656.3		41
473	0.71	647.4		41
474	0.26	793.1		41
475	1.85	681.3		23

Co. No.	Rt	$[M+H]^+$	$[M+CH_3COO]^-$	LCMS
476	0.89	738.5		24
477	0.79	638.5		24
478	2.09	684		36
479	1.38	656.5		38
480	2.08	684		36
481	2.05	685.3		40
482	2.1	701		36
483	2.21	714		40
485	2.14	680		36
486	1.97	680		36
487	2.05	695		40
488	1.8	644.3		37
489	0.9	681.4		33
491a	0.82	645.3		41
491b	0.85	645.4		41
492	0.70	646.4		41
493	0.70	634.4		41
494	1.57	671.4	729.6	42
495	0.72	683.4		41
496	1.53	671.5		18
497	1.26	726.5		42
498	1.32	726.5		42
499	1.13	575.3		43
500	0.766	617.55		44
501	1.337	675.30		43

PHARMACOLOGICAL PART

1) Menin/MLL homogenous time-resolved fluorescence (HTRF) assay

To an untreated, white 384-well microtiter plate was added 40 nL 200X test compound in DMSO and 4 µL 2X terbium chelate-labeled menin (vide infra for preparation) in assay buffer (40 mM Tris·HCl, pH 7.5, 50 mM NaCl, 1 mM DTT (dithiothreitol) and 0.05% Pluronic F-127). After incubation of test compound and terbium chelate-labeled menin for 30 min at ambient temperature, 4 µL 2X FITC-MBM1 peptide (FITC-β-alanine-SARWRFPARPGT-NH_2) ("FITC" means fluorescein isothiocyanate) in assay buffer was added, the microtiter plate centrifuged at 1000 rpm for 1 min and the assay mixtures incubated for 15 min at ambient temperature. The relative amount of menin·FITC-MBM1 complex present in an assay mixture is determined by measuring the homogenous time-resolved fluorescence (HTRF) of the terbium/FITC donor /acceptor fluorphore pair using an EnVision microplate reader (ex. 337 nm/terbium em. 490 nm/FITC em. 520 nm) at ambient temperature. The

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degree of fluorescence resonance energy transfer (the HTRF value) is expressed as the ratio of the fluorescence emission intensities of the FITC and terbium fluorophores (F^{em} 520 nm/F^{em} 490 nm). The final concentrations of reagents in the binding assay are 200 pM terbium chelate-labeled menin, 75 nM FITC-MBM1 peptide and 0.5% DMSO in assay buffer. Dose-response titrations of test compounds are conducted using an 11 point, four-fold serial dilution scheme, starting typically at 10 μM.

Compound potencies were determined by first calculating % inhibition at each compound concentration according to equation 1:

$$\% \text{ inhibition} = ((HC - LC) - (HTRF^{compound} - LC)) / (HC - LC)) * 100 \quad (Eqn\ 1)$$

Where LC and HC are the HTRF values of the assay in the presence or absence of a saturating concentration of a compound that competes with FITC-MBM1 for binding to menin, and $HTRF^{compound}$ is the measured HTRF value in the presence of the test compound. HC and LC HTRF values represent an average of at least 10 replicates per plate. For each test compound, % inhibition values were plotted *vs.* the logarithm of the test compound concentration, and the IC_{50} value derived from fitting these data to equation 2:

$$\% \text{ inhibition} = \text{Bottom} + (\text{Top-Bottom})/(1+10\text{^}((\log IC_{50}-\log[\text{cmpd}])*h)) \quad (Eqn\ 2)$$

Where Bottom and Top are the lower and upper asymptotes of the dose-response curve, respectively, IC_{50} is the concentration of compound that yields 50% inhibition of signal and h is the Hill coefficient. IC_{50} values below 0.1 nM in the HTRF assay were reported as 0.1 nM in the Table below (detection limit).

Preparation of Terbium cryptate labeling of Menin: Menin (a.a 1-610-6xhis tag, 2.3 mg/mL in 20mM Hepes (2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethane sulfonic acid), 80 mM NaCl, 5mM DTT (Dithiothreitol), pH 7.5) was labeled with terbium cryptate as follows. 200 μg of Menin was buffer exchanged into 1x Hepes buffer. 6.67 μM Menin was incubated with 8-fold molar excess NHS (N-hydroxysuccinimide)-terbium cryptate for 40 minutes at room temperature. Half of the labeled protein was purified away from free label by running the reaction over a NAP5 column with elution buffer (0.1M Hepes, pH 7 + 0.1% BSA (bovine serum albumin)). The other half was eluted with 0.1M phosphate buffered saline (PBS), pH7. 400 μl of eluent was collected for each, aliquoted and frozen at -80°C. The final concentration of terbium-labeled Menin protein was 115 μg/mL in Hepes buffer and 85 μg/mL in PBS buffer, respectively.

MENIN Protein Sequence (SEQ ID NO: 1):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPELT
FQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKKVSDV
IWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSEDHAWVVF
GPNGEQTAEVTWHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKMEVAFMVCAINPSID

LHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGRPDPLTLYHKGIASAK
TYYRDEHIYPYMYLAGYHCRNRNVREALQAWADTATVIQDYNYCREDEEIYKEFFEVANDVI
PNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPECFAHLLRFYDGICKWEEGSPTPVLHV
GWATFLVQSLGRFEGQVRQKVRIVSREAEAAEAEEPWGEEAREGRRRGPRRESKPEEPPPPK
KPALDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTAQVPAPAASPPPEGPVLTFQSEKM
KGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTLSFLKRQRKGLHHHHHH

2) Proliferation assay

The anti-proliferative effect of menin/MLL protein/protein interaction inhibitor test compounds was assessed in human leukemia cell lines. The cell line MOLM14 harbors a MLL translocation and expresses the MLL fusion proteins MLL-AF9, respectively, as well as the wildtype protein from the second allele. MLL rearranged cell lines (e.g. MOLM14) exhibit stem cell-like HOXA/MEIS1 gene expression signatures. KO-52 was used as a control cell line containing two *MLL (KMT2A)* wildtype alleles in order to exclude compounds that display general cytotoxic effects.

MOLM14 cells were cultured in RPMI-1640 (Sigma Aldrich) supplemented with 10% heat-inactivated fetal bovine serum (HyClone), 2 mM L-glutamine (Sigma Aldrich) and 50µg/ml gentamycin (Gibco). KO-52 cell lines were propagated in alpha-MEM (Sigma Aldrich) supplemented with 20% heat-inactivated fetal bovine serum (HyClone), 2 mM L-glutamine (Sigma Aldrich) and 50µg/ml gentamycin (Gibco). Cells were kept at 0.3 – 2.5 million cells per ml during culturing and passage numbers did not exceed 20.

In order to assess the anti-proliferative effects, 200 MOLM14 cells, or 300 KO-52 cells were seeded in 200µl media per well in 96-well round bottom, ultra-low attachment plates (Costar, catalogue number 7007). Cell seeding numbers were chosen based on growth curves to ensure linear growth throughout the experiment. Test compounds were added at different concentrations and the DMSO content was normalized to 0.3%. Cells were incubated for 8 days at 37°C and 5% CO_2. Spheroid like growth was measured in real-time by live-cell imaging (IncuCyteZOOM, Essenbio, 4x objective) acquiring images at day 8. Confluence (%) as a measure of spheroid size was determined using an integrated analysis tool.

In order to determine the effect of the test compounds over time, the confluence in each well as a measure of spheroid size, was calculated. Confluence of the highest dose of a reference compound was used as baseline for the LC (Low control) and the confluence of DMSO treated cells was used as 0% cytotoxicity (High Control, HC).

Absolute IC_{50} values were calculated as percent change in confluence as follows:

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LC = Low Control: cells treated with e.g. 1 μM of the cytotoxic agent staurosporin, or e.g. cells treated with a high concentration of an alternative reference compound

HC = High Control: Mean confluence (%) (DMSO treated cells)

% Effect = 100 - (100*(Sample-LC)/(HC-LC))

GraphPad Prism (version 7.00) was used to calculate the IC_{50}. Dose-response equation was used for the plot of % Effect vs Log10 compound concentration with a variable slope and fixing the maximum to 100% and the minimum to 0%.

Table 3. Biological data

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
2	0.4	0.029	9.04
4	0.3	0.066	7.73
5	0.2	0.120	9.31
6	0.3	0.280	6.47
7	0.1	0.004	5.04
8	0.3	0.052	10.21
9	0.1	0.021	7.16
10	0.4	0.017	5.09
12		0.002	>15
14	0.1	0.002	2.11
16	0.1	0.004	1.88
18	0.1	0.002	0.81
20	0.1	0.005	4.30
21	0.1	0.052	4.61
22	0.1	0.003	10.77
23	0.3	0.009	1.06

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
25	0.1	0.085	5.57
26	6.2	>0.94	>15
27	0.1	0.036	5.56
29	1.8	0.220	>15
30	0.3	0.029	2.58
31	0.3	0.007	2.41
33	0.3	0.007	2.49
34	0.5	0.036	5.14
35	1.3	0.340	>15
36	0.2	0.010	3.05
38	0.2	0.006	>15
39	0.1	0.007	1.48
40	0.2	0.010	0.50
41	0.2	0.012	>15
42	0.1	0.004	2.12
43	0.1	0.042	9.96
44	0.1	0.027	
45	0.2	<0.002	6.33
46	0.1	0.002	5.93
47	0.2	0.003	4.36
48	0.3	0.004	1.06
49	0.6	0.027	2.13
50	0.1	<0.002	>15
51	0.1	0.014	14.44
52	0.4	0.210	14.03

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
53	0.2	0.005	9.28
54	0.3	0.028	4.96
55	0.5	0.095	6.43
56	0.4	0.350	>15
57	0.1	0.008	7.54
58	0.1	0.019	>15
59	0.1	0.024	5.01
60	0.2	0.007	3.37
61	0.2	0.023	
62	0.1	0.004	6.26
63		0.057	>15
64	0.1	0.002	>15
65	0.2	0.130	11.83
66	0.1	0.006	>15
67	0.1	0.007	>15
68	0.1	0.005	4.41
69	0.1	0.039	14.03
70	0.1	0.004	5.15
71	0.1	0.060	9.73
72	0.1	0.005	1.62
73	0.2	0.040	7.05
74	1.3	0.580	2.79
75	0.5	0.690	4.00
76	8.0	>0.94	5.69
78	2.9	0.630	4.64

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
79	0.3	0.240	3.66
80	43.2	>0.94	>15
81	2.0	0.280	>15
82	0.4	0.300	>15
83	1.6	0.980	>15
84	5.5	0.220	>15
85	25.4	1.560	>15
86	17.2	0.650	>15
87	1.9	0.820	>15
88	2.3	0.410	>15
89	0.2	0.020	6.18
90	0.1	0.002	0.54
91	0.1	0.026	1.03
92	0.1	0.007	0.78
93	0.1	0.003	0.49
94	0.1	0.025	3.39
95	0.1	0.210	11.35
96	153.1	>0.94	>15
97	0.1	0.003	0.31
98	0.4	0.058	4.35
99	0.1	0.002	2.00
100	0.1	0.033	9.81
101	0.1	0.010	1.07
102	0.1	0.012	8.47
103	0.1	0.100	12.21

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
104	0.2	0.073	11.80
105	1.0		
106	0.1	0.011	4.99
107	0.1	0.076	>15
108	0.2	0.001	2.65
109	0.1	0.053	>15
110	0.1	0.012	6.84
111	0.2	0.120	>15
112	0.1	0.006	10.14
113	0.2	0.200	>15
114	0.1	0.008	14.22
115	0.2	0.430	>15
116	0.1	0.007	8.89
117	0.1	0.170	>15
120	0.3	0.073	>15
121	0.1	0.007	2.78
122	0.2	0.055	>15
123	5.4	1.910	>15
124	0.2	0.012	2.52
125	0.1	0.012	5.30
126	0.4	0.150	14.90
127	0.5	0.160	4.66
128	1.3	0.450	7.89
129	0.2	0.011	3.39
130		0.120	>15

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
131	0.2	0.050	6.20
132	0.3	0.076	8.10
133	0.1	0.021	7.38
134		0.130	13.20
135	0.3	0.008	1.00
136	0.1	0.008	7.07
137	0.2	0.007	
138	0.1	0.002	0.46
139	0.1	0.041	1.31
140	0.5	0.042	
141		0.260	12.37
142	0.1	0.007	1.35
143	0.1	0.027	1.53
144	0.8	0.200	12.31
145	0.2	0.006	3.58
146	0.2	0.160	6.60
147	0.1	0.004	0.39
148	0.2	0.003	0.61
149	0.1	<0.002	0.51
150	0.1	0.120	3.14
151	0.1	0.004	2.03
152	0.2	0.049	3.96
153	5.3	0.730	4.83
154	0.4	0.230	9.08
155	2.3	0.570	>15

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
156	0.8	0.100	7.96
157	0.2	0.120	7.77
158	0.8	0.480	>15
159	0.3	0.110	1.10
160	23.2	>3.75	>15
161	0.1	0.004	3.36
162	0.1	0.110	6.40
163	0.1	0.011	4.37
164	0.1	0.010	1.41
165	0.8	0.200	9.91
166		0.003	1.53
167	0.1	<0.002	4.11
168	0.6	0.053	2.59
169	0.5	0.051	
170	0.1	0.005	8.68
171	0.1	0.031	>15
172	0.1	0.022	10.09
173	0.2	0.150	>15
174	0.1	0.009	7.40
175	0.1	0.110	>15
176	0.5	0.080	10.43
177	0.2	0.037	8.87
178	108.4	>0.94	>15
179	0.4	0.073	12.61
180	0.3	0.062	10.14

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
181	96.9	>0.94	>15
182	0.6		
183	0.4	0.160	
184	0.2	0.010	0.60
185	0.1	0.006	6.04
186	5.4	>0.94	7.05
187	0.8	0.065	>15
188	0.2	0.520	>15
189	0.4	0.140	>15
190		0.076	14.79
191		>0.94	>15
192	4.8	1.040	
193	0.2	0.050	>15
194	0.9	0.450	>15
195	1.3	0.510	>15
196	13.6	>0.94	>15
198	0.3	0.250	>15
200	0.1	0.016	9.71
201	0.2	0.006	4.24
202	0.7		
203	0.8	0.300	1.86
204	0.3	0.190	>15
205	0.1	0.039	8.47
206	0.2	0.009	7.95
207	0.2	0.033	3.23

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
208	0.3	0.029	9.13
209	0.3	0.016	5.26
210	0.1	0.005	
211	0.1	0.003	>15
212	0.2	0.008	
213	0.1	0.041	3.91
214	0.1	<0.002	3.63
215	0.1	0.002	7.94
231	0.1	0.007	5.52
232	0.1	0.007	1.80
233	0.1	0.002	0.84
234	0.1	0.009	6.28
235	0.5	0.003	
236	0.2	0.004	2.25
237	0.2	0.036	7.90
238	0.1	0.002	7.17
239	0.3	0.016	2.81
240	1.9	0.270	
241	2.1	0.510	
242	0.1	0.008	12.15
243	2.5	0.580	>15
244	1.6	0.130	
245	0.6	0.460	8.94
246	0.3	0.180	
247	0.1	0.009	

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
248	0.1	0.004	1.46
249	0.1	0.009	
250	0.1	0.008	0.94
251	0.2	0.007	1.24
252	12.7	0.270	>15
253	0.1	0.010	1.62
254	0.1	0.016	>15
255	4.7	0.920	>15
256	0.2	0.005	>15
257	0.1	0.006	>15
258	0.1	0.004	0.49
259	0.4	0.094	4.76
260	0.1	0.006	3.25
261a	0.16	0.019	>15
261b	0.3	0.083	3.07
262	0.1	0.005	1.28
263	0.2	0.009	
264	0.8	0.170	14.39
265	0.1	0.011	
266	0.1	<0.002	
267	1.3	0.180	
268	0.1	0.006	
269	5.6	>0.94	
270	0.2	0.002	
271	2.4	0.260	>15

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
272	0.1	0.021	
273	0.3	0.110	>15
274	0.1	0.002	3.56
275	0.1	0.007	
276	0.8	0.082	>15
277	0.9	0.250	
278	0.1	0.002	
279	0.1	0.020	5.99
280a	5.0	>0.94	
280b	2.4	0.740	>15
281a	0.17	0.010	
281b	0.31	0.083	
282a	2.4	0.280	
282b	0.5	0.380	11.48
283	0.5	0.200	14.40
284	0.3	0.320	7.33
285	23.3	>0.94	>15
286	0.3	0.120	12.24
287	70.3	>0.94	>15
288	0.1	0.017	12.06
289	0.1	0.002	0.31
290	0.1	0.005	1.08
291	0.2	0.024	1.07
1a	0.1	0.020	>15
1b	0.4	0.200	>15

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
2b	16.6	1.310	>15
296	0.2	0.010	>15
297	0.1	0.010	10.60
298	0.1	0.006	9.32
299	0.2	0.034	8.35
300	0.3	0.170	8.19
301	0.2	0.033	2.50
302	0.1	0.021	14.14
303	0.3	0.007	4.53
304	0.1	0.032	12.13
305	0.2	0.017	5.78
306	0.3	0.056	6.46
307	0.7	>0.94	>15
308	0.2	0.070	4.57
309	0.2	0.022	7.39
310	24.2	>0.94	
311	0.3	0.052	9.99
312	0.2	0.005	1.27
313	43.4	>0.94	>15
314	0.2	0.120	5.87
315	0.1	0.018	1.96
316	4.9		
317	0.3	0.060	
318	0.1	0.026	6.90
319	23.7	>0.94	>15

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
320	0.1	0.028	4.60
321	91.1	>0.94	>15
322	0.3	0.030	>15
323	0.2	0.053	
324	117.1	>0.94	>15
325	0.1	0.004	4.98
326	0.2	0.032	9.18
327	0.2	0.005	>15
328	0.1	0.033	
329	0.3	0.032	
330	0.4	0.130	5.90
331	0.2	0.003	2.85
332	0.7	0.037	
333	0.1	0.038	0.82
335	0.2	0.030	3.24
336	0.6	0.180	7.65
339	0.4	>0.94	>15
340		0.170	11.40
341	3.0	>0.94	>15
342	0.3	0.082	5.84
343	0.2	0.015	1.14
344	0.1	0.054	1.59
345	1.0	0.055	7.40
346	2.3	0.700	>15
348	0.2	0.004	10.18

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
350	0.1	0.010	
351	0.1	0.020	1.10
353	0.5		
354	7.4	2.430	>15
356	0.3	0.011	>15
357	0.1	0.045	9.79
358	0.1	0.023	2.21
2a	0.2	0.022	7.00
84a	21.5	0.850	>15
371	0.15	0.003	10.06
372	0.2	0.018	
373	0.77	0.0076	5.41
374	0.19	0.14	
375	0.055	0.004	
376	0.62	0.10	
377	0.137	0.0027	4.84
378	0.106	0.0016	
379	0.11	0.0019	
380	0.16	0.0037	
381	0.14	0.0081	
382	0.08	0.007	
383	0.04	0.0023	
384	0.085	0.0007	
385	0.026	<0.0018	
386	0.059	<0.0018	

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
387	0.026	<0.0018	
388	0.027	<0.0018	
389	0.046	0.002	
390	0.18	0.004	
391	0.057	<0.0018	
392	0.11	0.002	
393	0.13	<0.0018	
394	0.083	0.003	
395	0.071	0.007	
396	0.059	<0.0018	
397	1.31	0.044	
398	0.144	0.0064	
399	0.92	0.20	
400	0.26	0.021	
401	0.52	0.26	
402	0.17	0.009	
403	0.59	0.23	
405	0.22	0.003	7.57
406	0.30	0.042	
407	0.11	<0.0018	
408	0.14	0.22	
409	0.14	0.008	
410	0.11	0.019	
411	0.15	0.01	
412	0.16	<0.0018	

Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
413	0.08	0.026	
414	0.10	0.021	
415	0.13	0.13	
416	0.17	0.0089	
417	0.05	0.0018	
418	0.07	0.009	
419	0.14	0.005	
420	~0.39	0.29	
421	0.13	<0.0018	
422	~0.27	0.088	
423	0.18	0.009	
424	0.17	0.004	
425	0.03	0.006	
426	0.09	<0.0018	
427	~0.11	<0.0018	
428	0.09	0.016	
429	0.17	0.0033	
430	0.11	0.0034	
431	0.54	0.079	
432	0.17	0.022	
433	0.15	0.002	
434	0.08	0.0029	2
435	0.17	0.003	2.47
436	0.36	0.0099	5.97
437	0.05	0.0033	4.7

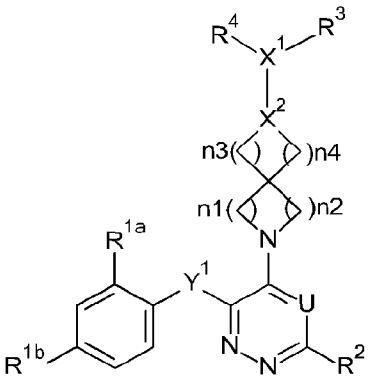
Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
438	0.16	0.004	
439	0.39	0.025	
440	13.68		
441	0.92	0.68	
442	0.21	0.004	
443	0.08	0.004	
444	0.16		
445	0.19	0.006	
446	~0.1	0.007	
447	0.15	0.004	
448	0.18	0.0046	
449	0.09	0.0084	
450	0.08	0.007	
451	0.15	0.011	
452	0.11	0.02	
453	0.05	0.006	
454	0.17	0.013	
455	0.14	0.024	
456	0.53		
457	0.29		
458	0.16	0.027	
459	0.06		
460	0.07	0.011	
461	0.20	0.063	
462	0.27	0.089	

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Co. No.	HTRF-30min incubation IC50(nM)	spheroid assay_OneTime MOLM14 IC50(μM)	spheroid assay_OneTime KO-52 IC50(μM)
463	0.082	0.029	
478	0.29	0.012	1.25
479	1.77	0.53	>15
480	0.15	0.006	
481	0.14	>0.94	
482	0.18	0.015	
483	0.07	0.017	
488	0.15	0.004	
489	0.22		
491a	0.13	0.0049	
500	0.30	0.035	10.21
502	0.12	0.032	
503	0.18		
504	0.58		
505	0.54		
512a	29.7577	0.04 (1)	0.31
512b	0.589115	>0.94 (1)	5.81

CLAIMS

1. A compound of Formula (I)



(I)

,

or a tautomer or a stereoisomeric form thereof, wherein

R^{1a} represents Het;

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O-, -S-, or $-NR^{5c}-$;

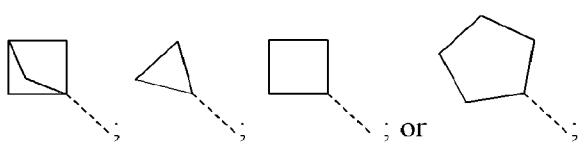
R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents C_{1-5}alkyl;



R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of Het^1, Het^2, Cy^2 and -C_{1-6}alkyl-$NR^{xc}R^{xd}$;

R^{xc} represents Cy^1; Het^5; -C_{1-6}alkyl-Cy^1; -C_{1-6}alkyl-Het^3; -C_{1-6}alkyl-Het^4; or -C_{1-6}alkyl-phenyl;

R^{xd} represents hydrogen; C_{1-4}alkyl; or C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

or R^{xc} and R^{xd} are taken together to form together with the N-atom to which they are attached a 4- to 7-membered monocyclic fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6, -C(=O)-Cy^1, and -C(=O)-R^8; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, C_{1-4}alkyl, oxo, -$NR^{9a}R^{9b}$ and -OH;

Het^2 represents C-linked pyrazolyl or triazolyl; which may be optionally substituted on one nitrogen atom with R^{6a};

R^6 and R^{6a} are each independently selected from the group consisting of
Het^3; Het^4; -C(=O)-NH-Cy^1; -C(=O)-NH-R^8;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl-C_{3-6}cycloalkyl, -C(=O)-OH, -$NR^{11a}R^{11b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl; and
C_{3-6}cycloalkyl optionally substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, -O-C_{1-4}alkyl, -C(=O)-NH-C_{1-4}alkyl and -NH-$S(=O)_2$-C_{1-4}alkyl;

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R^8 represents -O-C_{1-6}alkyl, C_{1-6}alkyl; or C_{1-6}alkyl substituted with one, two or three substituents each independently selected from -OH, halo, cyano, -$NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

Het^3, Het^{3a}, Het^5 and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -OH, -$NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two, three or four heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl or –(C=O)-O-C_{1-4}alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, C_{1-4}alkyl,
-O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, C_{1-4}alkyl-$NR^{11a}R^{11b}$, -NH-C(=O)-C_{1-4}alkyl, cyano, -COOH,
-NH-C(=O)-O-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -NH-C(=O)-$NR^{10a}R^{10b}$, –(C=O)-O-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, Het^{8a}, -C_{1-4}alkyl- Het^{8a}, Het^{8b}, Het^9, and -C(=O)-$NR^{10a}R^{10b}$;

Het^{6a}, Het^8 and Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo,
-NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl,
-$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl, -C_{1-4}alkyl-OH, -O-C_{1-4}alkyl, -O-(C=O)-$NR^{10a}R^{10b}$, and -O-(C=O)-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and -(C=O)-$NR^{10a}R^{10b}$;

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Het^{6b} and Het^{8b} each independently represent a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, $-(C=O)-NR^{10a}R^{10b}$, $-NH-C(=O)-C_{1-4}$alkyl, $-NH-C(=O)-Cy^3$, and $-O-C_{1-4}$alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of $-C(=O)-C_{1-4}$alkyl, $-C(=O)-Cy^3$, $-(C=O)-C_{1-4}$alkyl-OH, $-C(=O)-C_{1-4}$alkyl-$O-C_{1-4}$alkyl, $-C(=O)-C_{1-4}$alkyl-$NR^{11a}R^{11b}$, and C_{1-4}alkyl;

Het^9 represents a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, and C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH, $-NH-C(=O)-C_{1-4}$alkyl, C_{1-4}alkyl, $-NH-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-C_{1-4}$alkyl, and $-O-C_{1-4}$alkyl;
Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, $-NR^{9a}R^{9b}$, -OH, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or two substituents each independently selected from the group consisting of Het^{3a}, Het^{6a}, Het^{6b}, and $-NR^{9a}R^{9b}$;

Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; $-C(=O)-C_{1-4}$alkyl; $-C(=O)-C_{3-6}$cycloalkyl; $-S(=O)_2-C_{1-4}$alkyl; Het^5; Het^7; $-C_{1-4}$alkyl-R^{16}; $-C(=O)-C_{1-4}$alkyl-Het^{3a}; $-C(=O)-R^{14}$;
C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, $-O-C_{1-4}$alkyl, $-NR^{11a}R^{11b}$, and cyano; and
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, $-O-C_{1-4}$alkyl, $-NR^{11a}R^{11b}$, and cyano;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{15a}, R^{15b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents Het^{5a}; Het^{7}; Het^{8a}; -O-C_{1-4}alkyl; -C(=O)$NR^{15a}R^{15b}$; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl and halo; or
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl, $-NR^{13a}R^{13b}$, halo, cyano, -OH, Het^{8a}, and Cy^{1};

R^{16} represents -C(=O)-$NR^{17a}R^{17b}$, -S(=O)$_2$-C_{1-4}alkyl, Het^{5}, Het^{7}, or Het^{8};

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, wherein

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of C_{3-6}cycloalkyl, cyano, and C_{1-4}alkyl;

R^{2} is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and -$NR^{7a}R^{7b}$;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{3} is selected from the group consisting of Het^{1}, Het^{2}, Cy^{2} and -C_{1-6}alkyl-$NR^{xc}R^{xd}$;

R^{xc} represents Cy^{1}; Het^{5}; -C_{1-6}alkyl-Cy^{1}; -C_{1-6}alkyl-Het^{3}; -C_{1-6}alkyl-Het^{4}; or -C_{1-6}alkyl-phenyl;
R^{xd} represents hydrogen; C_{1-4}alkyl; or C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;
or R^{xc} and R^{xd} are taken together to form together with the N-atom to which they are attached a 4- to 7-membered monocyclic fully saturated heterocyclyl containing one N-atom and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or S(=O)$_2$; wherein said heterocyclyl is optionally substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, and cyano;

Het^{1} represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl

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containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6 and $-C(=O)-R^8$; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, R^6, Het^{6a}, Het^{6b}, C_{1-4}alkyl, oxo, $-NR^{9a}R^{9b}$ and -OH;

Het^2 represents C-linked pyrazolyl or triazolyl; which is substituted on one nitrogen atom with R^{6a};

R^6 is selected from the group consisting of
Het^3; $-C(=O)-NH-R^8$;
C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from the group consisting of Het^3, Het^4, Het^{6a}, Het^{6b}, Cy^1, -CN, -OH, $-O-C_{1-4}$alkyl, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-NH-C_{1-4}$alkyl-C_{3-6}cycloalkyl,
$-C(=O)-OH$, $-NR^{11a}R^{11b}$, and $-NH-S(=O)_2-C_{1-4}$alkyl; and
C_{3-6}cycloalkyl optionally substituted by one or two substituents each independently selected from the group consisting of -CN, -OH, $-O-C_{1-4}$alkyl, $-C(=O)-NH-C_{1-4}$alkyl, $-NH-S(=O)_2-C_{1-4}$alkyl, and C_{1-4}alkyl optionally substituted with one substituent selected from the group consisting of OH, $-O-C_{1-4}$alkyl, $-C(=O)-NH-C_{1-4}$alkyl and $-NH-S(=O)_2-C_{1-4}$alkyl;

R^{6a} represents C_{1-6}alkyl substituted with one substituent selected from the group consisting of $-NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

R^8 represents C_{1-6}alkyl optionally substituted with one, two or three substituents each independently selected from -OH, halo, cyano, $-NR^{11a}R^{11b}$, Het^{3a}, and Het^{6a};

Het^3 and Het^5 each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -

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OH, -$NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^{3a} and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom, and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom, and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl, halo, -OH, -$NR^{11a}R^{11b}$, or oxo; and wherein said heterocyclyl is optionally substituted on one nitrogen atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said 5-membered aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl; and wherein said 5- or 6-membered aromatic ring is optionally substituted on one carbon atom with -OH;

Het^{6a} and Het^8 each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl, -$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl, -C_{1-4}alkyl-OH, -O-C_{1-4}alkyl, -O-(C=O)-$NR^{10a}R^{10b}$, and -O-(C=O)-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and -(C=O)-$NR^{10a}R^{10b}$;

Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing two N-atoms and optionally one additional heteroatom selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl, -$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl,

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C_{1-4}alkyl-OH, -O-C_{1-4}alkyl, -O-(C=O)-$NR^{10a}R^{10b}$, and -O-(C=O)-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and -(C=O)-$NR^{10a}R^{10b}$;

Het^{6b} represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl, -C(=O)-Cy^3, -(C=O)-C_{1-4}alkyl-OH, -C(=O)-C_{1-4}alkyl-O-C_{1-4}alkyl, -C(=O)-C_{1-4}alkyl-$NR^{11a}R^{11b}$, and C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH, -NH-C(=O)-C_{1-4}alkyl, C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, and -O-C_{1-4}alkyl;
Cy^2 represents C_{3-7}cycloalkyl substituted with one or two substituents each independently selected from the group consisting of -$NR^{9a}R^{9b}$; Het^{6a}; Het^{6b}; and C_{1-6}alkyl substituted with one or two substituents each independently selected from the group consisting of Het^{3a}, Het^{6a}, Het^{6b}, and -$NR^{9a}R^{9b}$; and said C_{3-7}cycloalkyl is optionally substituted with one or two additional substituents each independently selected from the group consisting of halo, R^6, C_{1-4}alkyl, and -OH;
Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; Het^5; -C_{1-4}alkyl-R^{16}; -C(=O)-C_{1-4}alkyl-Het^{3a}; -C(=O)-R^{14}; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano; and C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, and cyano;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{15a}, R^{15b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

R^{14} represents Het^{5a}; Het^{8a}; or
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of

$-NR^{13a}R^{13b}$ and Het^{8a};

R^{16} represents $-C(=O)-NR^{17a}R^{17b}$, $-S(=O)_2-C_{1-4}$alkyl, Het^5, Het^7, or Het^8.

3. The compound according to claim 1, wherein

Het represents a monocyclic 5- or 6-membered aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said monocyclic 5- or 6-membered aromatic ring is substituted with one C_{3-6}cycloalkyl and wherein said monocyclic 5- or 6-membered aromatic ring is optionally substituted with one or two additional substituents selected from the group consisting of cyano, and C_{1-4}alkyl;

R^{1b} represents F;

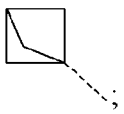
Y^1 represents -O-;

R^2 represents hydrogen;

U represents N;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

R^4 represents C_{1-5}alkyl; or



R^3 is selected from the group consisting of Het^1 and Cy^2;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; or a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of R^6 and $-C(=O)-R^8$; and wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of oxo and -OH;

R^6 and R^{6a} are each independently selected from the group consisting of Het^4; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected

from the group consisting of Het^3, Het^{6a}, and Cy^1; and C_{3-6}cycloalkyl;

R^8 represents -O-C_{1-6}alkyl;

Het^3, Het^{3a}, Het^5 and Het^{5a} each independently represent a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$;
wherein said heterocyclyl is optionally substituted on one carbon atom with C_{1-4}alkyl;

Het^4 and Het^7 each independently represent a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N, or a fused bicyclic C-linked 9- or 10-membered aromatic ring containing one, two, three or four heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one nitrogen atom with C_{1-4}alkyl or –(C=O)-O-C_{1-4}alkyl; and wherein said aromatic ring is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of -OH, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, -$NR^{11a}R^{11b}$, C_{1-4}alkyl-$NR^{11a}R^{11b}$, -NH-C(=O)-C_{1-4}alkyl, cyano, -COOH, -NH-C(=O)-O-C_{1-4}alkyl, -NH-C(=O)-$NR^{10a}R^{10b}$, –(C=O)-O-C_{1-4}alkyl, -NH-$S(=O)_2$-C_{1-4}alkyl, Het^{8a}, -C_{1-4}alkyl- Het^{8a}, Het^{8b}, Het^9, and -C(=O)-$NR^{10a}R^{10b}$;

Het^{6a}, Het^8 and Het^{8a} each independently represent a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one, two, three or four substituents each independently selected from the group consisting of halo, -OH, oxo, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, -(C=O)-$NR^{10a}R^{10b}$, -O-C_{3-6}cycloalkyl, -$S(=O)_2$-C_{1-4}alkyl, cyano, C_{1-4}alkyl, -C_{1-4}alkyl-OH, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl and -(C=O)-$NR^{10a}R^{10b}$;

Het^{6b} and Het^{8b} each independently represent a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two additional

heteroatoms each independently selected from O, S, and N, wherein said S-atom might be substituted to form S(=O) or $S(=O)_2$; wherein said heterocyclyl is optionally substituted on one or two carbon atoms with in total one or two substituents each independently selected from the group consisting of C_{1-4}alkyl, -OH, oxo, -(C=O)-$NR^{10a}R^{10b}$, -NH-C(=O)-C_{1-4}alkyl, -NH-C(=O)-Cy^3, and -O-C_{1-4}alkyl; and wherein said heterocyclyl is optionally substituted on one nitrogen with a substituent selected from the group consisting of -C(=O)-C_{1-4}alkyl, -C(=O)-Cy^3, and C_{1-4}alkyl;

Het^9 represents a monocyclic C-linked 5- or 6-membered aromatic ring containing one, two or three heteroatoms each independently selected from O, S, and N; wherein said aromatic ring is optionally substituted on one or two carbon atoms with C_{1-4}alkyl;

Cy^1 represents C_{3-6}cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of -OH and C_{1-4}alkyl;
Cy^2 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of R^6, Het^{6a}, Het^{6b},
-$NR^{9a}R^{9b}$, -OH, and C_{1-4}alkyl;

Cy^3 represents C_{3-7}cycloalkyl; wherein said C_{3-7}cycloalkyl is optionally substituted with one, two or three halo substituents;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-C_{3-6}cycloalkyl; Het^5; Het^7; -C_{1-4}alkyl-R^{16}; -C(=O)-C_{1-4}alkyl-Het^{3a}; -C(=O)-R^{14}; and
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of halo, -OH, and -O-C_{1-4}alkyl;

R^{11a}, R^{11b}, R^{13a}, R^{13b}, R^{17a}, and R^{17b} are each independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and C_{3-6}cycloalkyl;

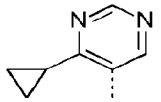
R^{14} represents -O-C_{1-4}alkyl; C_{3-6}cycloalkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl and halo; or
C_{1-4}alkyl substituted with one, two or three substituents selected from the group consisting of -O-C_{1-4}alkyl, -$NR^{13a}R^{13b}$, and cyano;

R^{16} represents -C(=O)-$NR^{17a}R^{17b}$ or -$S(=O)_2$-C_{1-4}alkyl.

4. The compound according to claim 1, wherein

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Het represents



5. The compound according to claim 1, wherein U represents N.

6. The compound according to claim 1, wherein
Y^1 represents -O-.

7. The compound according to claim 1, wherein
R^{1b} represents F.

8. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 and a pharmaceutically acceptable carrier or diluent.

9. A process for preparing a pharmaceutical composition as defined in claim 8 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 7.

10. A compound as claimed in any one of claims 1 to 7 or a pharmaceutical composition as claimed in claim 8 for use as a medicament.

11. A compound as claimed in any one of claims 1 to 7 or a pharmaceutical composition as claimed in claim 8 for use in the prevention or treatment of cancer, myelodysplastic syndrome (MDS) and diabetes.

12. The compound or a pharmaceutical composition for use according to claim 11, wherein cancer is selected from leukemias, myeloma or a solid tumor cancer such as prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma.

13. The compound or a pharmaceutical composition for use according to claim 12, wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell

prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, and leukemias exhibiting *HOX/MEIS1* gene expression signatures.

14. A method of treating or preventing a disorder selected from cancer, myelodysplastic syndrome (MDS) and diabetes comprising administering to a subject in need thereof, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 7 or a pharmaceutical composition as claimed in claim 8.

15. The method according to claim 13 wherein the disorder is cancer.